# HEREDITARY PANCREATITIS: OUTCOMES AND RISKS

by

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## ABSTRACT

Pancreatitis is an inflammatory disease of the pancreas that was first identified in the 1600s. Symptoms for pancreatitis include intense abdominal pain, nausea, and malnutrition. Hereditary pancreatitis (HP) is a genetic condition in which recurrent acute attacks can progress to chronic pancreatitis, typically beginning in adolescence. Mutations in the *PRSS1* gene cause autosomal dominant HP. The 1996 discovery of a *PRSS1* mutation causative for hereditary pancreatitis was in direct contrast to much of the medical community's long-held beliefs that pancreatitis is primarily caused by alcoholism and gallstones. HP strongly impacts quality of life and is a risk factor for pancreatic cancer, making it a public health concern. Our understanding of HP is still limited, and chronic pancreatitis remains a serious disease for which significant treatment options are lacking. Questions remain regarding the exact mechanism of cancer development and risk factors in families with HP. Furthermore, HP has unpredictable duration, severity, complications, and outcomes. It is often accompanied by systemic diseases and complications, such as diabetes mellitus. Therefore, research is needed to further define the natural history of HP, its psychosocial implications, and its interactions with other risk factors. The overall goal of this research is to improve quality of life, patient care, and treatment options for individuals with this debilitating disease by understanding more about the natural history of the condition and collecting information on attitudes, concerns, and perspectives. The Hereditary Pancreatitis Study at the University of Pittsburgh has collected genetic, medical, and environmental data from hundreds of American

families with pancreatitis since the mid-1990s. I have described the natural history of HP in this American cohort, analyzed risks for pancreatic cancer and diabetes based on family history, and assessed large HP pedigrees with pancreatic cancer. My analysis indicates that this American cohort is similar to published studies on the French, Danish, and other European populations. I also created a follow-up questionnaire for these participants to gather information on attitudes, risks for pancreatic cancer, and views on a pancreatic center of excellence and its services. Data from this questionnaire will be relevant to improving patient care in future studies.

## TABLE OF CONTENTS

## LIST OF TABLES

## LIST OF FIGURES

# PREFACE

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# 1.0 INTRODUCTION

## 1.1 BACKGROUND

### 1.1.1 Basic Pancreas Physiology

The pancreas is a gland organ that is a part of the human digestive system. It is located in the abdominal cavity in a position both posterior and inferior to the stomach. Within the pancreas is the pancreatic duct, which joins the common bile duct to empty into the duodenum. The pancreas can further be divided into the exocrine pancreas and the endocrine pancreas (Das et al., 2014).

The majority of pancreatic cells are exocrine cells, comprising over 95% of its mass (Das et al., 2014). The purpose of the exocrine pancreas is to secrete precursor digestive enzymes to digest the carbohydrates, proteins, and lipids found in the chyme. The exocrine pancreas is composed of acini, or clusters of acinar cells that surround a saclike cavity, or acinar lumen (Pandiri, 2014). Acinar cells secrete zymogens into this lumen, which travel through intralobular ducts into the main pancreatic duct. The zymogens secreted by acinar cells include trypsinogen, chymotrypsinogen, pancreatic lipase, and amylase (Pandiri, 2014). Ductal cells secrete bicarbonate through the CFTR membrane protein, which flushes zymogens through the ducts and

into the duodenum (Choi et al., 2001; Pandiri, 2014). Once in the duodenum, bicarbonate neutralizes the acidic chyme and the zymogens are activated.

The endocrine pancreas secretes hormones directly into the blood vessels to regulate blood glucose levels. It is composed of cells called the islets of Langerhans, which are classified into four major types according to their secretions. Alpha cells secrete glucagon, and beta cells secrete insulin, which increase and decrease blood glucose levels, respectively. Somatostatin is secreted by delta cells, and pancreatic polypeptide by gamma cells. The endocrine and exocrine functions of the pancreas make it a vital organ for digestion and blood glucose regulation.

### 1.1.2 Pancreatitis Overview

#### 1.1.2.1 Classification

Pancreatitis is the inflammation of the pancreas, for which major symptoms include intense abdominal pain, nausea, and vomiting. There are multiple forms of pancreatitis that are defined according to the frequency, severity, and length of a pancreatic attack. These major categories of pancreatitis are acute pancreatitis (AP), recurrent acute pancreatitis (RAP), and chronic pancreatitis (CP).

Acute pancreatitis is defined as a sudden inflammation of the pancreas, which is believed to have been first described by the Dutch anatomist Nicholaes Tulp in 1652 (Pannala, Kidd, & Modlin, 2009; Tulp, 1652). It is diagnosed in the presence of two out of three of the following features: a pattern of abdominal pain consistent with the disease, serum lipase or amylase activity that is increased by a factor of three, and specific findings on contrast enhanced computed tomography

(CECT), magnetic resonance imaging (MRI) or transabdominal ultrasonography (Banks et al., 2013; Working Group, 2013). It can be further sub classified according to severity into mild AP, moderately severe AP, and severe AP (Banks et al., 2013; Petrov & Windsor, 2010; Vege et al., 2009). Individuals who have had one or more acute pancreatic attacks are at risk to develop recurrent acute pancreatitis and chronic pancreatitis, particularly in the presence of alcohol and tobacco exposure (Yadav, O'Connell, & Papachristou, 2012).

Recurrent acute pancreatitis refers to the occurrence of more than one acute pancreatic attack in an individual (Chari & Singer, 1994; Sarles et al., 1965). Some classifications, particularly the revised Marseille and Marseille-Rome classifications have removed the term RAP due to the difficulty of distinguishing it from chronic pancreatitis (Sarles et al., 1989; Singer, Gyr, & Sarles, 1985; Testoni, 2014).

Chronic pancreatitis is a progressive disease involving inflammation of the pancreas. It results in permanent morphologic changes to the pancreas (fibrosis), typically resulting in both endocrine and exocrine insufficiency (Lankisch, Lohr-Happe, Otto, & Creutzfeldt, 1993; Steer, Waxman, & Freedman, 1995). Symptoms of CP include frequent or persistent abdominal pain, nausea, diarrhea and bloating. Loss of pancreatic function leads to an impairment in the production of digestive enzymes, which leads to steatorrhea (presence of excess fat in stool), weight loss, and malnutrition if not treated. These diseases are interrelated, and individuals with AP and RAP have an increased risk for CP, especially in the presence of environmental and/or genetic risk factors (Mounzer & Whitcomb, 2013; Nojgaard et al., 2011).

Pancreatitis can also be classified as idiopathic sporadic, familial, or hereditary based on an individual's family history and/or mutation status. Idiopathic sporadic pancreatitis is defined as pancreatitis in an individual without a family history or a known etiology. Familial pancreatitis is the occurrence of pancreatitis in a family that is greater than expected by chance alone. Hereditary pancreatitis (HP) is a sub-type of familial pancreatitis. HP is diagnosed by meeting one of two criteria: (1) pancreatitis in two or more related individuals in two or more generations of a family; (2) an identified pathogenic germline mutation (Whitcomb DC, 2010).

#### 1.1.2.2 Risk Factors

Historically, the primary causes of pancreatitis were believed to be gallstones for acute pancreatitis and alcoholism for chronic pancreatitis. While this is not always the case, they remain major contributors to this disease. About 30% of AP cases in the United States are caused by alcoholism (Yang, Vadhavkar, Singh, & Omary, 2008). Gallstones are another major cause of AP, being responsible for 35 – 40% of cases worldwide (Forsmark, Baillie, Practice, Economics, & Board, 2007). Additional known causes for pancreatitis include other obstructions, smoking, hypercalcemia, hypertriglyceridemia, drugs, infections, toxins, complications from endoscopic retrograde cholangiopancreatography (ERCP), autoimmune disease, genetic mutations, and trauma (Yadav & Lowenfels, 2013).

### 1.1.3 Hereditary Pancreatitis

#### 1.1.3.1 Description and Clinical Course

Hereditary pancreatitis is a genetic condition characterized by an onset of acute pancreatitis, typically in childhood. This acute pancreatitis then progresses to recurrent acute pancreatitis, with

the development chronic pancreatitis usually by early adulthood. Clinical course and symptoms are variable among patients, and the average age of symptom onset is twelve years (Howes et al., 2004).

#### 1.1.3.2 Symptoms and complications

The symptoms and complications of hereditary pancreatitis are similar to those seen in patients with chronic pancreatitis of non-genetic etiology. Pain is a common symptom, but difficult to treat, and quality of life is significantly impacted by pain in individuals with HP that develop chronic pancreatitis (Mullady et al., 2011). Constant pain, independent of severity, in patients with CP is associated with increased rates of disability, use of analgesics, and hospitalizations (Mullady et al., 2011).

Damage to the pancreas from chronic pancreatitis typically results in exocrine insufficiency, or the inability of the pancreas to release sufficient amounts of digestive enzymes. The primary symptom of exocrine insufficiency is fat malabsorption, resulting in steatorrhea, or excess fat and oil in the stool (Pezzilli, 2009). Other symptoms of maldigestion include weight loss, gastrointestinal distress (e.g. gas, pain, and diarrhea), and nutritional deficiency of fat-soluble vitamins (A, D, E, K) (Pezzilli, 2009). The cumulative risk for pancreatic exocrine insufficiency in association with hereditary pancreatitis at 50 years of age is estimated to be 37.2% (Howes et al., 2004).

Diabetes mellitus is frequently seen in association with hereditary pancreatitis (Howes et al., 2004; Rebours, Boutron-Ruault, Schnee, et al., 2009). A distinct type of diabetes mellitus, type 3c, arises from loss of pancreatic tissue from CP, surgery, or other diseases (American Diabetes, 2011). Type 3c differs from type 1 diabetes because there is loss of both insulin (beta cells) and glucagon

(alpha cells), creating a risk for hypoglycemia and pancreatic cancer (Cui & Andersen, 2011). The cumulative risk for diabetes at 50 years of age in patients with hereditary pancreatitis is close to 50% (Howes et al., 2004).

It is well known that inflammation is a risk factor for cancer (Weiss, 2014). A study on the French population found that HP is associated with an increased risk of pancreatic adenocarcinoma (standardized incidence ratio = 87) (Rebours et al., 2008). In contrast, patients with alcoholic CP have 16 – 27 times the relative risk of pancreatic adenocarcinoma compared to the general population (Lowenfels et al., 1993; Malka et al., 2002; Rebours et al., 2008). Pancreatic cancer is an aggressive and difficult to treat cancer with a 6.7% five-year survival rate (Howlader N, 2014).

Lifespan does not appear to be reduced in individuals with hereditary pancreatitis who do not develop pancreatic cancer (Rebours, Boutron-Ruault, Jooste, et al., 2009). However, quality of life is significantly reduced by the disease and its associated symptoms beginning at an early age.

#### 1.1.3.3 Molecular Genetics – *PRSS1*- related Hereditary Pancreatitis

Comfort and Steinburg (1952) were the first to report a pedigree of a family with hereditary pancreatitis (Comfort & Steinberg, 1952). However, it wasn't until 1996 that a gene for hereditary pancreatitis was mapped to chromosome 7q (Le Bodic et al., 1996; Whitcomb, Preston, et al., 1996). In the same year, Whitcomb *et al*. (1996) identified a missense mutation in the cationic trypsinogen gene (*PRSS1*) in a large family (Whitcomb, Gorry, et al., 1996). Since this discovery, we know that hereditary pancreatitis is most often caused by gain of function mutations in the *PRSS1* gene.

*PRSS1*-related hereditary pancreatitis is an autosomal dominant condition. The *PRSS1* gene encodes trypsinogen, which is the zymogen for trypsin-1, a serine protease. Trypsinogen is secreted by acinar cells in the exocrine pancreas and washed through the pancreatic duct into the small intestine (Pandiri, 2014). Once in the duodenum, trypsinogen is activated by enterokinase into its active form – trypsin-1. Trypsin-1 is a major digestive enzyme and activates other pancreatic zymogens in the small intestine.

Pathogenic *PRSS1* mutations can be divided into two types – mutations that result in a form of trypsinogen that is prematurely activated in the pancreas and mutations that prevent trypsin degradation (Gorry et al., 1997; Mounzer & Whitcomb, 2013). Still, both types of mutations result in elevated trypsin levels within the pancreas. Trypsin activity leads to damage of the pancreatic tissue, as well as inflammation by triggering an immune system response (Singhi et al., 2014). Histologic findings include pancreatic atrophy, fibrosis, and replacement of peripheral tissue with adipose (Pandiri, 2014). Of individuals with a mutation in *PRSS1,* about 90% have the mutation R122H or N29I (Howes et al., 2004; Rebours, Boutron-Ruault, Schnee, et al., 2009). Less commonly seen mutations include A16V, R122C, N29T, D22G, and K23R (Howes et al., 2004). About 65 – 100% of families with hereditary pancreatitis have a mutation in the *PRSS1* gene, and *PRSS1*-related pancreatitis is estimated to have a penetrance of about 80% (Howes et al., 2004). Copy number variations of the *PRSS1-PRSS2* (anionic trypsinogen) locus have also been associated with chronic pancreatitis (J. M. Chen, Masson, Le Marechal, & Ferec, 2008).

#### 1.1.3.4 Molecular Genetics – Other Genes

There are a number of genes in addition to *PRSS1* in which pathogenic variants have been linked to pancreatitis, particularly *SPINK1, CFTR,* and *CTRC* (J. M. Chen & Ferec, 2009, 2012;

Rosendahl et al., 2013; Whitcomb, 2013). Additional risk genes include *CASR*, *UBR1* (Zenker et al., 2005), SBDS (Boocock et al., 2003), CEL (Raeder et al., 2006), *CTSB*, *CLDN2*, *CPA1*, *GGT1*, *MMP1*, and *MTHFR* (Shelton & Whitcomb, 2014). Disease mechanisms for many of these genes are complex, and gene-gene and gene-environment interactions are not fully defined (LaRusch, Barmada, Solomon, & Whitcomb, 2012).

The *SPINK1* gene encodes serine protease inhibitor, Kazel-type 1. In the pancreas, SPINK1 functions as an important inhibitor of trypsin, inhibiting as much as 20% of trypsin activity to defend the pancreas (Laskowski & Kato, 1980; Rinderknecht, 1986). Loss-of-function mutations in the *SPINK1* gene were found to be associated with chronic pancreatitis in 2000 and are found in about 2% of the population (Pfutzer et al., 2000; Witt et al., 2000). Biallelic loss-of-function mutations in *SPINK1* may lead to autosomal recessive pancreatitis. Pathogenic variants in *SPINK1* can act as disease modifiers for individuals with pancreatitis, and compound heterozygosity for pathogenic variants in *SPINK1*/*PRSS1* and *SPINK1*/*CFTR* in patients with pancreatitis have been identified (Rosendahl et al., 2013).

*CFTR* encodes the cystic fibrosis transmembrane conductance protein, an anionic channel that conducts chloride ions in the lungs and intestines, and bicarbonate in the pancreas (Schneider et al., 2011). Cystic fibrosis can be separated into two distinct diseases depending on whether chloride conductance is impaired or preserved. The traditional form of cystic fibrosis is caused by severe biallelic *CFTR* (*CFTR*$^{SEV}$) mutations, which impair both bicarbonate and chloride conductance through the CFTR channel (Rosendahl et al., 2013). This traditional form of cystic fibrosis is characterized by thick mucus leading to respiratory system damage and susceptibility to

infection. Other major symptoms include pancreatic dysfunction, male infertility, and intestinal damage. The second form of cystic fibrosis is caused by mutations in *CFTR* that prevent its transformation into a bicarbonate-specific channel (*CFTR*$^{BD}$) (LaRusch et al., 2014). *CFTR*$^{BD}$ mutations lead to an inability to fully flush zymogens out of the pancreatic ducts and into the common bile duct. These zymogens remain in the pancreas and can become active, damaging the pancreatic tissue. Sufficient digestion of the pancreas leads to pancreatic attacks.

The *CTRC* gene encodes the $Ca^{2+}$-dependent serine protease chymotrypsinogen C. Chymotrypsin C acts as the primary regulator of trypsin. In the $Ca^{2+}$-rich environment of the duodenum, chymotrypsin C participates in the activation of trypsinogen (Szmola & Sahin-Toth, 2007). However, in the pancreas and lower intestines, chymotrypsin C degrades trypsin, defending against pancreatitis (Szmola & Sahin-Toth, 2007). Variants in *CTRC* that impair the function and/or secretion of chymotrypsinogen C have been associated with pancreatitis (Masson, Chen, Scotet, Le Marechal, & Ferec, 2008; Rosendahl et al., 2008). The c.180T>G variant in *CTRC* is common and significantly increases the risk of progression from RAP to CP, particularly in the presence of other risk factors such as alcohol and smoking (LaRusch et al., 2015; Masson et al., 2008).

More information is available on pancreatitis genetics in the article "Shelton CA, Whitcomb DC. Genetics and treatment options for recurrent acute and chronic pancreatitis. Curr Treat Options Gastroenterol. 2014;12(3):359-71" found in **Appendix C**.

#### 1.1.3.5 Population Data

Hereditary pancreatitis is considered a rare genetic condition. Population-based studies have been performed in France, Denmark, and across 14 European countries (Howes et al., 2004; Joergensen,

Brusgaard, Cruger, Gerdes, & Schaffalitzky de Muckadell, 2010; Rebours, Boutron-Ruault, Schnee, et al., 2009). A study on the French population estimates a prevalence for *PRSS1*-related hereditary pancreatitis of at least 0.3/100,000 (Rebours, Boutron-Ruault, Schnee, et al., 2009). This study also found *PRSS1* gene mutations in about 2/3 of individuals with hereditary pancreatitis, with a penetrance of 93% (Rebours, Boutron-Ruault, Schnee, et al., 2009). A similar penetrance (96% at 50 years of age) was identified in a registry representing 14 European countries (Howes et al., 2004). In the Danish population, about 1% of all patients with pancreatitis have been identified to have hereditary pancreatitis (Joergensen et al., 2010). Studies on the prevalence of HP in the Japanese population are similar to the prevalence seen in Western countries.

#### 1.1.3.6 Genetic Counseling and Testing

The indications to offer genetic testing of *PRSS1* in a symptomatic patient are (1) unexplained RAP; (2) unexplained CP; (3) family history of pancreatitis in a first or second-degree relative; and/or (4) unexplained episode of pancreatitis in a child requiring hospitalization (Ellis, Lerch, Whitcomb, & Consensus Committees of the European Registry of Hereditary Pancreatic Diseases, 2001). Predictive molecular genetic testing is recommended for only patients over 16 years of age with a first-degree relative with an identified HP-related mutation (Ellis et al., 2001).

Testing should begin with a targeted mutation analysis of exons 2 and 3 or complete sequence analysis of the *PRSS1* coding regions. Deletion/duplication analysis can be considered if a mutation is not identified. Genes offered on commercial chronic pancreatitis next-generation and Sanger sequencing panels include *CASR*, *CFTR*, *CPA1*, *CTRC*, *PRSS1*, and *SPINK1*. Prenatal testing is also available but may be controversial given that this disease is not 100% penetrant.

Assessment of a family medical history should include at least a three-generation pedigree, including family history of pancreatitis, age of onset, ages of diagnosis for multiple pancreatic attacks, and pancreatic cancer (Solomon & Whitcomb, 2012). Other valuable family history information includes smoking, alcohol use, diabetes, exocrine insufficiency, male infertility, cystic fibrosis, chronic sinusitis, and nasal polyps (Solomon & Whitcomb, 2012). Recurrence risk is dependent on genotype and exposure environmental risk factors (Solomon & Whitcomb, 2012).

A 2001 study on motivations and concerns with regard to genetic testing for hereditary pancreatitis found that the largest concern for genetic testing was insurance discrimination (Applebaum-Shapiro, Peters, O'Connell, Aston, & Whitcomb, 2001). Furthermore, the major motivation to participate in research for hereditary pancreatitis was to help current family members and future generations (Applebaum-Shapiro et al., 2001). Helping future generations was second only to "the disturbance of seeing affected relatives" as the primary motivation for genetic testing (Applebaum-Shapiro et al., 2001). The results also suggested that symptomatic patients are highly motivated to confirm their clinical diagnosis through genetic testing (Applebaum-Shapiro et al., 2001). About 85% responded that genetic testing results were not important for making reproductive decisions (Applebaum-Shapiro et al., 2001).

#### 1.1.3.7 Treatment

Treatment options for chronic pancreatitis are similar for individuals with and without hereditary pancreatitis. There is no cure, and available options focus on improving quality of life by reducing pain and malnutrition, and by removing any environmental risk factors (e.g. smoking, alcohol). Evaluation of pancreatic exocrine and endocrine function are important for determining the extent of disease and evaluate appropriate treatment options.

For individuals who are known to have or be at risk for hereditary pancreatitis, early preventative measures can delay and potentially prevent AP attacks. Recommended measures beginning in childhood include eating a low-fat diet, eating multiple small meals a day, staying hydrated, and taking antioxidants (Uomo, Talamini, & Rabitti, 2001).

Maldigestion is treated with pancreatic enzyme replacement therapy. This therapy is orally administered during meals and snacks with a dose corresponding to the fat content of the meal (Lindkvist, 2013). For patients who develop diabetes, insulin therapy and antidiabetic agents, particularly metformin, may be beneficial (Decensi et al., 2010).

Pain is a common symptom of pancreatitis and can sometimes be managed by pancreatic enzyme replacement therapy (Burton et al., 2011; Whitcomb et al., 2010). If pain persists, analgesics are used to treat pain. Antioxidants have also been suggested to reduce pain in hereditary pancreatitis (Uomo et al., 2001).

Endoscopic retrograde cholangiopancreatography (ERCP) is an endoscopic procedure that can be used to visualize and remove obstructions or calcifications blocking the pancreatic ducts. When there is a blockage, this procedure can significantly reduce pain, hospitalizations, and the recurrence of pancreatic attacks in patients with HP (Dever, Irani, Brandabur, Traverso, & Kozarek, 2010).

Surgery can be considered for patients in whom therapy has not been successful in relieving symptoms. For chronic pancreatitis, surgical approaches include decompression/drainage, pancreatic resection, and denervation of afferent nerves originating from the pancreas to reduce pain and/or remove inflammation. Pancreatic resection in individuals with HP is less successful because it is unlikely to end inflammation and results in the removal of precious islet cells. Total pancreatectomy with islet cell auto-transplantation (TPIAT) is a newer option as a last-resort to reduce uncontrolled pain, improve quality of life, and prevent pancreatic cancer and type 3c diabetes mellitus (Bellin, Freeman, et al., 2014; Bellin, Gelrud, et al., 2014; Bellin et al., 2015). This surgery first involves the removal of the pancreas. The pancreatic tissue is then digested to isolate islet cells, which are subsequently re-implanted into another site, such as the liver or abdomen. However, this procedure restricts patients to life-long pancreatic enzyme replacement therapy and can cause major gastrointestinal motility issues.

### 1.1.4 Pancreatic Cancer Genetics

The most common form of pancreatic cancer is pancreatic ductal adenocarcinoma, which comprises about 90% of cases of pancreatic cancer cases. It is difficult to treat, and typically fatal, being the 4$^{th}$ leading cause of death from cancer in the United States (Lewis, Frost, & Venne, 2009). Pancreatic cancer is typically sporadic, but as many as 10% of cases can be attributed to a hereditary predisposition (Brand et al., 2007). However, it is likely that there is a larger genetic contribution in the development of pancreatic cancer, particularly through common risk variants and complex gene-gene and gene-environment interactions (Solomon, Das, Brand, & Whitcomb, 2012).

Major genes in which variants have been associated with inherited cancer syndromes and increased risk for pancreatic cancer are *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CDKN2A*, *APC*, *MLH1*, *MSH2*, *MSH6*, *PMS2*, *TP53*, *PRSS2*, and *STK11* (Solomon et al., 2012; Syngal et al., 2015). Familial pancreatic cancer is defined as pancreatic cancer in two or more first degree relatives who do not meet criteria for a known cancer syndrome associated with pancreatic cancer (Brand et al., 2007; Syngal et al., 2015). A risk variant in the *PALLD* gene was found to be associated with familial pancreatic cancer in a large family, but has not been identified in other cases (Pogue-Geile et al., 2006). The majority of cases of familial pancreatic cancer do not have an identified genetic cause, and a responsible genetic mutation has only been identified in about 20% of cases (Syngal et al., 2015). Furthermore, it is unknown why some families with hereditary pancreatitis have higher incidences of pancreatic cancer than other families. It has likely that other risk variants and complex interactions are influencing the development of pancreatic cancer in these families.

## 1.2 SPECIFIC AIMS

### 1.2.1 Specific Aim 1

To provide a description of the current HP Study Cohort in order to determine if participants with hereditary pancreatitis in this American cohort differ from previous studies in the US and Europe.

### 1.2.2 Specific Aim 2

To describe and analyze families with pancreatic cancer and diabetes mellitus by:

a. Comparing risks for chronic pancreatitis, diabetes mellitus, and pancreatic cancer based on family history and HP status

b. Describing large pedigrees with pancreatic cancer

### 1.2.3 Specific Aim 3

To create and implement a valuable follow-up questionnaire for this cohort to answer new questions on QOL, attitudes, concerns, and perceptions in participants with HP to provide UPMC/The University of Pittsburgh with information on how to improve care in a pancreatic center of excellence.

## 1.3 SIGNIFICANCE

### 1.3.1 Specific Aim 1

The Hereditary Pancreatitis Cohort is a valuable resource to study the natural history of hereditary pancreatitis in the United States. Comparison of this American cohort to other studies on populations in Europe is valuable to understanding the disease and its course. Furthermore, the availability of DNA samples allows for comparisons between different genotype groups.

### 1.3.2 Specific Aim 2

Familial risk for pancreatic cancer and diabetes mellitus is incompletely defined in families with hereditary pancreatitis. Furthermore, it is unknown why some families have greater incidence of pancreatic cancer and diabetes than other families. It is expected that many risk variants and environmental factors play a role in the development of these outcomes. By understanding the correlation between a family history of pancreatitis, diabetes mellitus, pancreatic cancer, and HP status, this familial risk can further be defined. This information is valuable for personalized care and risk assessment by genetic counselors.

### 1.3.3 Specific Aim 3

The HP Cohort provides a valuable resource to gather attitudes, concerns, and perceptions, as well as follow-up medical and family information for further analysis. Understanding emotional health

and quality of life for individuals with hereditary pancreatitis and their families is critical toward understanding the psychosocial implications of this disease. Gathering information on concerns, perceptions and experiences regarding genetic testing and genetic counseling will inform the genetic counseling process for hereditary pancreatitis. Concerns and perceptions regarding the medical, surgical, and financial aspects of this disease will help inform care for patients with HP. Furthermore, information about attitudes regarding a Pancreas Center of Excellence and experiences with total pancreatectomy with islet autotransplantation (TPIAT), a new procedure, will be useful to improve the care provided by the Pancreas Center of Excellence at the University of Pittsburgh Medical Center.

# 2.0 MATERIALS AND METHODS

The Hereditary Pancreatitis Genetic Linkage Study (ID: PRO07090243) is currently approved by the University of Pittsburgh's Institutional Review Board (**Appendix A**). A modification of this study to include a new follow-up survey was reviewed by the University of Pittsburgh Institutional Review Board and approved on February 3, 2015 (**Appendix B**).

## 2.1 DATA SOURCE

The Hereditary Pancreatitis Study at the University of Pittsburgh began in 1994. It has collected genetic, medical, and environmental data from hundreds of families with pancreatitis. Data is participant-reported through medical history questionnaires, and consenting participants provided DNA samples for genetic analysis. Medical histories were validated from medical records when made available. Participants met inclusion criteria for this study if they were age 3 months up to 100 years ***and*** met *at least **one** of the following criteria*:

- Diagnosis of pancreatitis at age < 60
- Diagnosis of pancreatitis at any age and at least one other 1st or 2nd degree relative with a diagnosis of pancreatitis or pancreatic cancer
- Diagnosis of pancreatic cancer and a 1st or 2nd degree relative with pancreatic cancer or pancreatitis
- Diagnosis of pancreatic insufficiency or maldigestion that improves with pancreatic enzyme replacement

- Close family member of subjects who meet the above criteria

This study does not have any specific exclusion criteria. The initial goal of this study was to enroll patients with possible familial or hereditary pancreatitis and their families to examine genes that may serve as a potential resource for genetic linkage. It was started after several large families with pancreatitis were identified and recruited. This study has expanded to include over 700 individuals from over 200 families. From this study came the discovery of mutations in the cationic trypsinogen gene (*PRSS1*) as a major cause of hereditary pancreatitis. Follow-up studies on this cohort have been performed to gather updates on personal and family history, as well as obtain new blood samples. This study remains open for enrollment.

## 2.2 INCLUSION CRITERIA FOR SPECIFIC AIM 1A

For specific aim 1, participants from the Hereditary Pancreatitis Genetic Linkage study were included in the analysis if they reported a physician diagnosis of hereditary pancreatitis ***and*** provided a three-generation pedigree. This criteria was used to make this cohort comparable to studies on European populations.

## 2.3 ANALYTICAL METHODS FOR SPECIFIC AIM 1A

The general cohort statistics were included as counts and percentages, or mean and range. The cohort was split into two groups: (1) participants with an identified *PRSS1* mutation; (2)

participants without an identified PRSS1 mutation, which includes individuals for which testing was not completed. Comparisons between the groups were made using the Kruskal-Wallis test for continuous data. The $\chi^2$ test was used for categorical data except when $n \leq 5$ for a cell, in which case Fisher's exact test was used.

## 2.4 SPECIFIC AIM 1B – SURVIVAL ANALYSIS

Deceased status was obtained through the free Social Security Death Index (SSDI) database search at Ancestry.com (Ancestry.com, 2011). The SSDI is a database of deaths that were reported to the Social Security Administration (Social_Security_Administration). Information is available from 1962 to March of 2014. Information is not currently available for deaths after March 2014 due to new legislative rules requiring that records only become available after a three year period. First name, middle name, last name, date of birth (DOB), and social security number (SSN) for HP cases were entered into the Ancestry.com SSDI search engine. Deceased individuals that matched the name and exact DOB were confirmed as the participant by SSN and/or location of birth and death.

The survival of the cohort was estimated using the Kaplan-Meier non-parametric method with right censoring. The log-rank test was used to determine the significance of survival differences according to gender, mutation status, smoking habits, diabetes, and pancreatic enzyme therapy. The end point used was date of death or March 1, 2014 according to the timeframe available from the SSDI. Analyses were performed using Minitab® 16 statistical software with a critical level of significance of $P < 0.05$.

## 2.5 DATA SOURCE FOR SPECIFIC AIM 2A

Specific aim 2A was completed using two cohorts: HP and NAPS2/CV. See Section 2.1 for a description of the HP Cohort.

The North American Pancreatitis Study 2 (NAPS2) ascertained 1,000 subjects with RAP or CP and 695 controls across twenty centers in the United States between 2000 and 2006 (Whitcomb et al., 2008). Participants and their physicians completes questionnaires, and blood was obtained for genetic and biomarker studies. The NAPS2-Continuation and Validation (CV) began in 2008 to continue the study and ascertain a validation group for genome-wide association studies (GWAS).

## 2.6 ANALYTICAL METHODS FOR SPECIFIC AIM 2A

Statistics were reported as counts and percent values. Confidence intervals were obtained using standard error. Significance was determined using a two-tailed test of two binomial proportions, except when $n \leq 5$ for a cell, in which case Fisher's exact test was used.

## 2.7 PEDIGREE ASSESSMENT (SPECIFIC AIM 2B)

Pedigrees were selected from the HP cohort for assessment of pancreatic cancer outcomes. These pedigrees were selected because they met the following criteria: (1) Extensive number of participants in the study for which medical history, smoking status, and alcohol exposure is

available; (2) Case(s) of pancreatic cancer; and (3) an identified *PRSS1* mutation. Two pedigrees met this criteria and were chosen for a case series. In each kindred, the following were assessed: (1) age or age at death; (2) smoking history; (3) alcohol exposure; (4) pancreatic cancer diagnosis and age at diagnosis; (5) *PRSS1* mutation status; and (6) HP symptoms.

## 2.8 QUESTIONNAIRE DESIGN (SPECIFIC AIM 3)

Two questionnaires were created – one for cases and one for controls. Cases are defined as individuals in the Hereditary Pancreatitis Genetic Linkage Study who report a physician diagnosis of hereditary pancreatitis. Controls are defined as the participants without a physician diagnosis of hereditary pancreatitis. The questionnaire was written to gather information from six categories: (1) Risk and State, (2) Emotional Health, (3) Quality of Life, (4) Concerns and Perceptions, (5), Genetic Testing, and (6) Genetic Counseling.

The Risk and State section of the questionnaire includes questions regarding alcohol and tobacco exposure, current height and weight, and pain. The alcohol and tobacco questions were designed to match the questions used in the North American Pancreatitis Study 2 (NAPS2) for a direct comparison.

The Emotional Health section of the questionnaire asks questions directly related to anxiety, depression, and problems caused by hereditary pancreatitis. The anxiety and depression questions are adapted from the Patient Reported Outcomes Measurement Information System (PROMIS®)

short forms 1.0 Anxiety 4a and Depression 4a. These short forms were chosen because they are validated measures of anxiety and depression.

The Quality of Life section of the questionnaire contains the 12-Item Short Form Survey from the RAND Medical Outcomes Study (SF-12® Health Survey). This Short Form survey was designed to measure eight health domains: Physical Functioning, Role-Physical, Bodily Pain, Vitality, Social Functioning, Role-Emotional, and Mental Health. It uses the standard 4-week recall period. The SF-12® was chosen over the SF-36® because of its lower respondent burden and for comparison purposes.

Section 4, Concerns and Perceptions, can be further broken down into four categories: Medical, Surgical, Financial, and Pancreas Center of Excellence (COE). The Medical section asks about concern regarding medical problems related to pancreatitis and perception of pancreatic cancer risk. These questions were chosen to garner patient concerns about their disease and outcomes. The Surgical section focuses on one procedure – total pancreatectomy with islet autotransplantation (TPIAT). This section asks for opinions and experiences with this newer surgical procedure – particularly regarding the benefits and drawbacks. The Surgical section also has questions regarding TPIAT outcomes and satisfaction, which were created at the University of Minnesota (Sutherland et al., 2012). The Financial section asks about the financial burdens of HP, and the Pancreas COE section asks about opinions on the characteristics of a pancreas COE. This section is particularly relevant for the Pancreas COE at the University of Pittsburgh Medical Center.

The Genetic Testing section is designed to gather information on the benefits and drawbacks of genetic testing for HP, as well as participant experiences with genetic testing. It incorporates motivators and concerns for genetic testing that have been previously surveyed in this HP cohort (Applebaum-Shapiro et al., 2001). This section will allow for an analysis of changes in attitudes and concerns over the past fourteen or more years.

The final section of the questionnaire asks about experiences and perceptions regarding genetic counseling for Hereditary Pancreatitis. This section is expected to be useful to inform genetic counseling for HP. The questionnaires for HP cases and controls can be found in **Appendix D** and **Appendix E**, respectively. The results from this questionnaire will not be reported in this document; rather, it was developed for future studies.

# 3.0 RESULTS

## 3.1 SPECIFIC AIM 1

### 3.1.1 Demographics

Out of 757 participants in the Hereditary Pancreatitis Genetic Linkage Study, 254 participants were found to meet the following criteria:

(1) A physician diagnosis of hereditary pancreatitis, **AND**

(2) Provision of a 3-generation family history

All results for specific aim 1, with the exception of the survival analysis, include only these 254 participants for the purpose of comparison to previously described cohorts in Europe. These participants comprised 93 three-generation families. Out of the 254 participants, 114 (45.6%) were male, and the median age at enrollment was 29 years (range 0 – 77) **(Table 1).** Of these individuals, 78 (30.7%) were minors (≤ 17 years) at the time they were enrolled. Participants were asked to identify their ethnicity/race. 238 participants (93.7%) indicated their ethnicity/race as Caucasian/white, making up the majority of all participants. Other represented ethnicities included African American (0.4%), American Indian (0.4%), Hispanic/Latino (0.4%), and Asian (0.8%). Eleven participants did not specify their race/ethnicity.

**Table 1 Enrollment data and demographics**

| | N | % of total |
|---|---|---|
| **Participants that meet criteria** | 254 | |
| **Families ( ≥ 3 generations)** | 93 | |
| **Sex** | | |
| Male | 114 | 45.9% |
| Female | 140 | 55.1% |
| **Median age at enrollment (years)** (md = 4) | 29 (Range 0 – 77) | |
| **Race/Ethnicity** | | |
| Caucasian/White | 238 | 93.7% |
| Asian | 2 | 0.8% |
| African American/Black | 1 | 0.4% |
| American Indian | 1 | 0.4% |
| Hispanic/Latino | 1 | 0.4% |
| Unknown (Not specified) | 11 | 4.3% |

md = missing data

### 3.1.2 Characteristics

The percentage of ever smokers in this cohort was 28% **(Table 2)**. Chronic alcohol consumption, defined here as greater than 3 drinks per day for women and 4 drinks per day for men, was detected in 3.15% of participants. *PRSS1* mutations were detected in 74.4% of participants (R122H 83.1%, N29I 13.8%, R112C 1.1%, A16V 1.1%, R116C 1.1%). *SPINK1* and *CFTR* mutations were identified in 11% and 1.2% of participants, respectively. There were no statistically significant differences in number of men, number of smokers, chronic alcohol consumption, or age at enrollment between individuals with an identified mutation and those without.

**Table 2 Characteristics**

| Characteristic | All participants (n = 254) | Patients with *PRSS1* mutations (n= 189) | Patients without a detected *PRSS1* mutation* (n = 65) | *P* value† |
|---|---|---|---|---|
| Age at enrollment (md=4)‡ | 29 years (0 - 77) | 30 years (0 - 76) | 28 years (5 - 77) | 0.959 |
| Number of men | 114 (45.6%) | 88 | 26 | 0.359 |
| Number of families (≥ 3 generations) | 93 families | 64 families | 29 families | - |
| Number of ever smokers | 71 (28%) | 55 | 15 | 0.352 |
| Chronic Alcohol Consumption§ | 8 (3.15%) | 5 | 3 | 0.426 |
| **PRSS1 mutations (n)** | 189 | 189 | - | - |
| R122H | - | 157 | - | - |
| N29I | - | 26 | - | - |
| R122C | - | 2 | - | - |
| K23R | - | 0 | - | - |
| A16V | - | 2 | - | - |
| R116C | - | 2 | - | - |
| *SPINK1* mutations (md = 86) | 28 (11%) | 19 | 9 | - |
| *CFTR* mutations (md = 241) | 3 (1.2%) | 0 | 3 | - |

* Includes 44 participants with incomplete *PRSS1* testing
† The Kruskall-Wallis test was used for continuous data; Chi-squared was used for categorical data when n > 5. When n ≤ 5 for any cell in a two-way table, Fisher's exact test was used. Calculations were made using Minitab®.
‡ Median (range)
§ Chronic alcohol consumption is defined here as > 4 drinks per day for men and > 3 drinks per day for women
md = missing data

### 3.1.3 Clinical and Biochemical Features

The median age (and range) for diagnosis of any pancreatitis and at HP diagnosis was 7 years (0 – 73) and 13 years (1 – 66) respectively **(Table 3)**. There was no significant difference in age at first diagnosis with pancreatitis between HP participants with and without identified *PRSS1* mutations **(Figure 1).** Penetrance of any pancreatitis for a known-pathogenic *PRSS1* mutation was 87% for this cohort. When the disease definition is expanded to include endocrine insufficiency, exocrine insufficiency, and pancreatic calcifications, the penetrance increased to 93.3%. 84.6% of participants reported a diagnosis of acute pancreatitis, and 117/237 (49.4%) reported a diagnosis

of chronic pancreatitis. Four individuals reported a diagnosis of CP in the absence of previous acute pancreatic attacks, none of which had an identified mutation. 69 (27.2%) of participants report a diagnosis of diabetes and 19 (7.5%) report having gallstones. The median age at endocrine failure was 31 years. Exocrine failure was reported by the use of pancreatic enzymes and found in 37% of participants. Pancreatic cancer was identified in 3 participants and diagnosed at an average age of 72 years. Cumulative rates of diagnosis with any pancreatitis, endocrine insufficiency, and pancreatic cancer are represented in **Figure 2**.

**Table 3 Clinical Features**

| **Characteristic** | **All patients (n=254)** | **Patients with *PRSS1* mutations (n= 189)** | **Patients without a detected *PRSS1* mutation[*] (n = 65)** | ***P* value[†]** |
|---|---|---|---|---|
| Age at first diagnosis of pancreatitis[‡] (md = 9) | 7 years (0 - 73) | 7 years (0.17 - 73) | 11 years (0 - 55) | 0.544 |
| Age at diagnosis with HP[‡] (md = 175) | 13 years (1 - 66) | 13 (1 - 66) | 20 (11-21) | 0.489 |
| Acute pancreatitis (md = 1) | 214 (84.6%) | 159 | 55 | 0.376 |
| Chronic pancreatitis (md = 19) | 117 (46.1%) | 81 | 36 | 0.080 |
| CP without prior AP | 4 (0.02%) | 0 | 4 | **0.04** |
| Admission in intensive care unit (md = 186) | 11 (12.8%) | 7 | 4 | 0.755 |
| Diabetes Mellitus | 69 (27.2%) | 49 | 20 | 0.449 |
| Age at diabetes mellitus diagnosis[‡] (md = 25) | 31 years | 35 years | 28 years | 0.427 |
| Use of pancreatic enzymes | 94 (37%) | 75 | 19 | 0.298 |
| Gallstones | 19 (7.5%) | 14 | 5 | 1.00 |

[*] Includes 44 participants with incomplete *PRSS1* testing

[†] The Kruskall-Wallis test was used for continuous data; Chi-squared was used for categorical data when $n > 5$. When $n \leq 5$ for any cell in a two-way table, Fisher's exact test was used. Calculations were made using Minitab®.

[‡] Median (range)

md = missing data

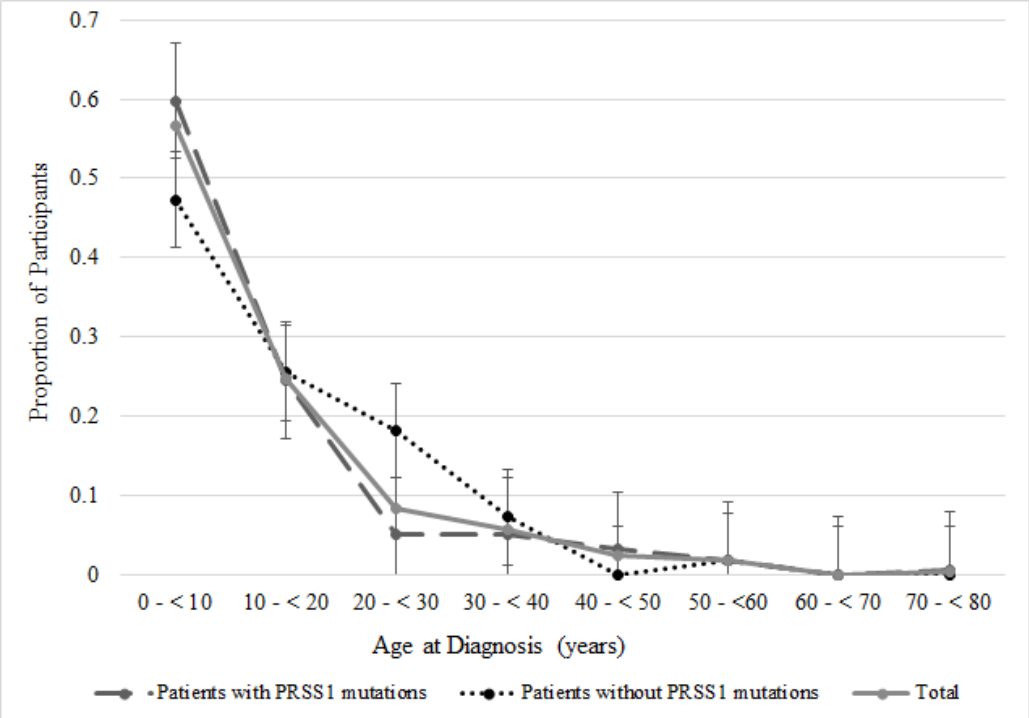


**Figure 1 Distribution by age at first diagnosis with pancreatitis**

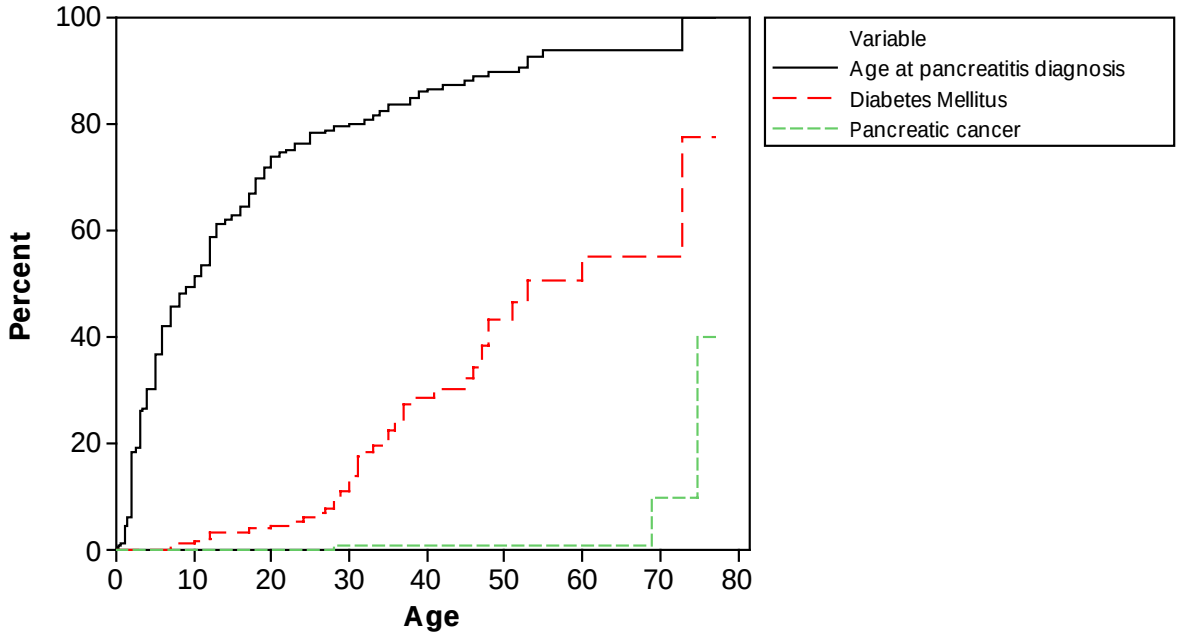


**Figure 2 Time to Diagnosis and Symptom Development**

### 3.1.4 Morphological Features

12.9% of participants reported pancreatic calcifications, and 9.4% reported the diagnosis of pseudocysts **(Table 4)**. There were no statistically significant differences in the morphologic features of pancreatic calcifications and pseudocysts in patients with and without an identified mutation.

**Table 4 Morphological Features**

| Characteristic | All patients (n=254) | Patients with *PRSS1* mutations (n= 189) | Patients without a detected *PRSS1* mutation (n = 65)* | *P* value† |
|---|---|---|---|---|
| Pancreatic calcifications | 33 (12.9%) | 26 | 7 | 0.537 |
| Pseudocysts | 24 (9.4%) | 16 | 8 | 0.402 |

* Includes 44 participants with incomplete *PRSS1* testing
† Chi-squared test was used and calculations were made using Minitab®.

### 3.1.5 Treatment

Treatments for these participants included analgesics, endoscopic treatment, and surgical interventions **(Table 5)**. 113/117 (96.6%) used analgesics at any point, with 41/89 (46.1%) reporting a chronic use of analgesics to treat pain. 48/170 (57.1%) reported endoscopic treatment, and 49/224 (21%) reported one or more pancreatic surgical treatments. Pancreatic surgical treatments included Puestow (18/49; 36.7%), Whipple (6/49; 12.2%), draining procedures (3/49; 6.1%), and pancreatectomy (partial or full) (15/49; 30.1%) **(Table 6)**.

**Table 5 Treatment**

| Treatment | All patients (n=254) | Patients with *PRSS1* mutations (n = 189) | Patients without a detected *PRSS1* mutation (n = 65)* | *P* value† |
|---|---|---|---|---|
| Use of analgesics ever (md = 137) | 113 (96.6%) | 93 | 20 | 1.000 |
| Chronic use of analgesics (md = 165) | 41 (46.1%) | 35 | 7 | 0.430 |
| Endoscopic treatment (md = 84) | 48 (57.1%) | 35 | 13 | 0.084 |
| Surgical treatment (md = 30) | 49 (21%) | 39 | 10 | 0.225 |
| Hepaticojejunostomy/other biliary bypass | 2 (0.01%) | 1 | 1 | 0.447 |
| Cholecystectomy | 47 (18.5%) | 36 | 11 | 0.704 |

* Includes 44 participants with incomplete *PRSS1* testing
† Chi-squared test was used and calculations were made using Minitab®.
md = missing data

**Table 6 Surgical Interventions**

| Surgical Intervention | All patients (n=49) | | Patients with PRSS1 mutations (n = 39) | | Patients without detected PRSS1 mutation* (n = 10) | | *P* value† |
|---|---|---|---|---|---|---|---|
| | N (%) | Mean Age (yrs) | N (%) | Mean Age (yrs) | N (%) | Mean Age (yrs) | |
| Puestow | 18 (36.7%) | 26.81 years (md=2) | 13 (33.3%) | 25.27 years | 5 (50%) | 30.20 years | 0.465 |
| Whipple | 6 (12.2%) | 29.17 years | 5 (7.7%) | 28.8 years | 1 (10%) | 31 years | 1.000 |
| Draining Procedure | 3 (6.1%) | 20.5 years (md=2) | 2 (5.1%) | 20.5 years | 1 (10%) | - (md=1) | 0.504 |
| Pancreatectomy (total or partial) | 15 (30.6%) | 31.9 years (md=5) | 12 (30.%) | 29.89 years | 3 (30%) | 50 years | 1.000 |

* Includes 44 participants with incomplete *PRSS1* testing
† Chi-squared test was used and calculations were made using Minitab®.
md = missing data

### 3.1.6 Survival Analysis

For survival analysis, all participants who reported a physician diagnosis of hereditary pancreatitis (n=271) were included. A total of 25 (9.2%) participants were identified as deceased through the Social Security Death Index (SSDI). The average age of death for deceased participants was 57 years, with a range of 17 years to 85 years. Median overall survival for the entire cohort was 85 years, with a mean of 77.93years (CI 95%: 75 – 81) **(Figure 3)**. Mean survival for ever smokers and never smokers was 74.2 and 79.2 years, respectively **(Figure 4)**. Mean survival for males and females was 76.4 and 78.8 years, respectively. Survival by mutation status was obtained for the following categories: *PRSS1* R122H, *PRSS1* N29I, and no *PRSS1* mutation identified. Mean survival rates for these groups were 77.6, 75.9, and 78.5 years, respectively **(Figure 5)**. For endocrine insufficiency, mean survival was 74.3 years for participants with diabetes and 81 years for participants without diabetes **(Figure 6)**. For exocrine insufficiency, mean survival was 81.9 years for participants taking digestive enzymes and 75.3 years for participants who were not treated with enzyme therapy **(Figure 7)**. Smoking habits, gender, and mutation status were not associated with significant differences in survival **(Table 7)**. Diabetes was identified as a risk factor of mortality ($p = 0.031$). Furthermore, lack of treatment with digestive enzymes was significantly associated with increased mortality ($p = 0.022$). However, exocrine failure was not directly measured.

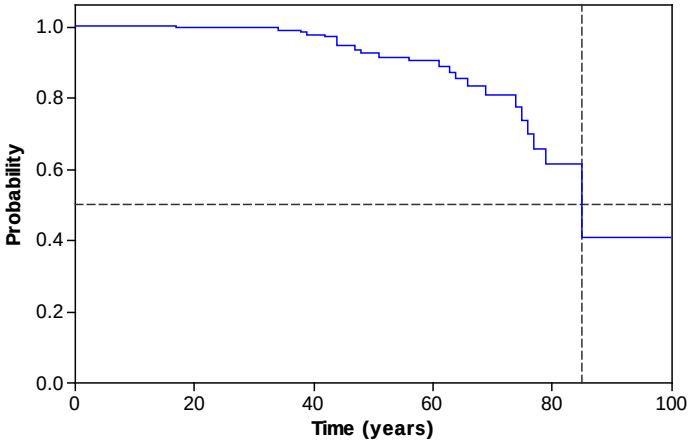


**Figure 3 Overall HP Survival Plot**

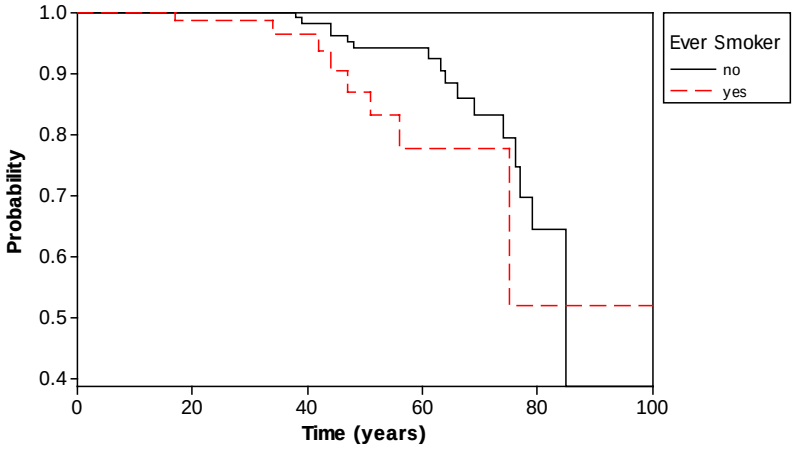


**Figure 4 HP Survival Plot by Smoking Status**

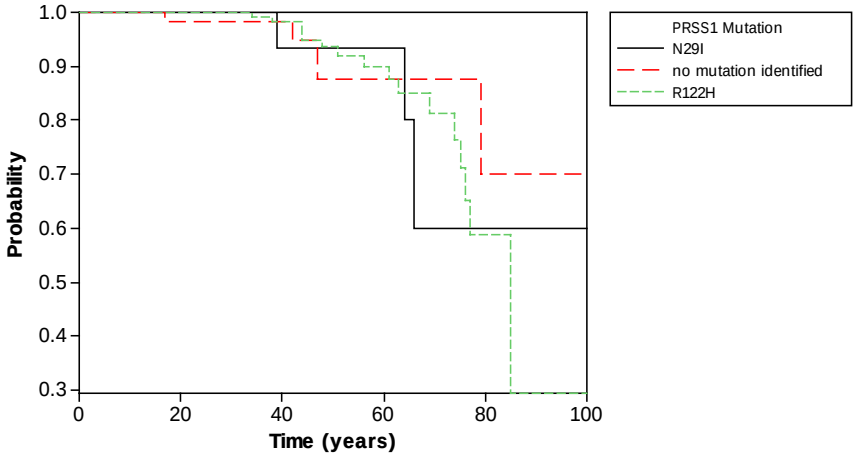


**Figure 5 HP Survival Plot by *PRSS1* Mutation**

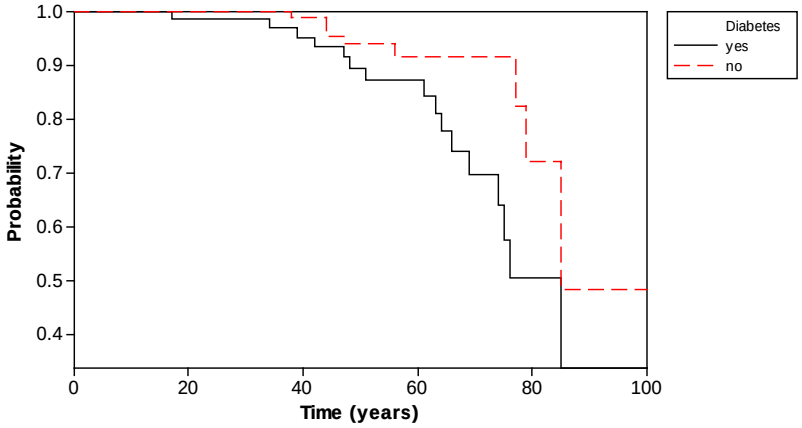


**Figure 6 HP Survival Plot by Diabetes Status**

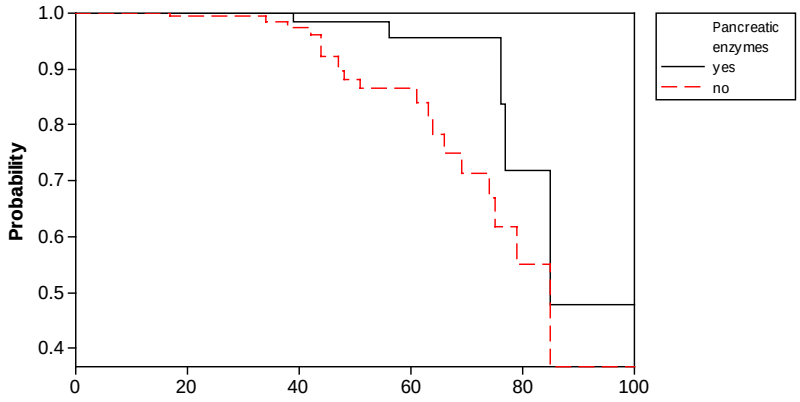


**Figure 7 HP Survival Plot by Pancreatic Enzyme Therapy Status**

**Table 7 Log-Rank Test of Survival**

| Category | Variables | | | P-Value |
|---|---|---|---|---|
| Sex | Male | Female | | 0.476 |
| Smoking Status | Ever-Smoker | Never-smoker | | 0.065 |
| Exocrine Failure | Digestive enzymes | No digestive enzymes | | **0.022** |
| Endocrine Failure | Diabetes | No diabetes | | **0.031** |
| *PRSS1* Mutation Status | R122H | N29I | No mutation identified | 0.926 |

## 3.2 SPECIFIC AIM 2

### 3.2.1 Family History Risk Analysis

#### 3.2.1.1 Demographics

The NAPS2 and NAPS2 CV cohorts were found to have similar ethnic backgrounds as the HP cohort, with the majority of participants being Caucasian **(Table 8)**. Caucasian participants comprised 85.7% of all NAPS2/CV participants (including cases and controls) and 93.7% of the 254 HP participants with family history information included in specific aim 1. Both cohorts are from the North American population. Fisher's exact test was used to determine if the proportion of Caucasians in the HP cohort of cases is significantly different than the proportion of Caucasians in the NAPS2 and NAPS2 CV cohort. A p-value of 0.008 was identified, resulting in a rejection of the null hypothesis and the conclusion that there is a significant difference in the proportion of Caucasians between the HP cases and the NAPS2/CV cohort. The HP cases were more likely to be Caucasian than the NAPS2/CV participants (OR= 1.88). However, this odds ratio corresponds to a Cohen's effect size (*d*) value of between 0.2 and 0.5, indicating low practical effect (H. Chen, Cohen, & Chen, 2010). Therefore, these groups were deemed comparable for this analysis.

**Table 8 Demographics for NAPS2, NAPS2 CV, and HP Cohorts**

| | Race/Ethnicity | AA | Asian | Caucasian | Other | Unknown | Total (n) |
|---|---|---|---|---|---|---|---|
| NAPS2 and NAPS2 CV Studies | Total | 7.7% | 1.0% | 87.6% | 2.9% | 0.8% | 2567 |
| | Controls (all) | 4.9% | 1.5% | 89.5% | 4.0% | 0.2% | 570 |
| | Related Controls | 5.0% | 0.0% | 86.6% | 7.9% | 0.5% | 202 |
| | Unrelated Controls | 4.8% | 1.9% | 90.4% | 2.8% | 0.1% | 684 |
| | CP Cases | 11.1% | 0.5% | 84.4% | 2.3% | 1.6% | 1111 |
| | RAP Cases | 5.4% | 1.2% | 90.7% | 2.5% | 0.2% | 570 |
| HP Study | HP Cases | 0.4% | 0.7% | 93% | 1.1% | 4.8% | 271 |
| Total | | 7.0% | 1.0% | 88.1% | 2.7% | 1.4% | 2821 |

#### 3.2.1.2 Risks for CP, DM, and PDAC

Proportions of chronic pancreatitis (CP), diabetes mellitus (DM) and pancreatic cancer (PDAC) outcomes were compared between HP cases and individuals from the NAPS2/CV cohort with a family history of AP, CP, DM or PDAC. No significant difference in the percentage of CP outcomes were found between HP cases and individuals with a family history of AP and/or CP from the NAPS2/CV cohorts **(Table 9)**. The lack of significant differences in CP outcomes between these cohorts makes them comparable for further analyses regarding other outcomes.

A significantly higher proportion of the HP cohort had diabetes mellitus compared to the NAPS2/CV family history groups **(Table 10)**. This result confirms that diabetes mellitus is an outcome related to hereditary pancreatitis, and suggests that a diagnosis of HP is a higher risk factor for diabetes than a family history of pancreatitis, DM, or PDAC amongst these cohorts.

A significant difference ($p=0.003$) in the proportion of pancreatic cancer outcomes was identified between the HP cases and participants in the NAPS2/CV cohort with a family history of diabetes mellitus groups **(Table 11)**. This data suggests that a family history of diabetes mellitus is not as strong a risk factor for pancreatic cancer as a diagnosis of hereditary pancreatitis amongst these cohorts. Overall, this analysis supports higher risks for diabetes and pancreatic cancer in individuals with HP, potentially higher than the risks for these outcomes associated with a family history of pancreatitis, diabetes, or pancreatic cancer even in higher-risk populations.

**Table 9 HP v. Family History: Risks for Chronic Pancreatitis**

| Cohort | Category* | Total (n) | Number with CP (n) | Percentage with CP | P-Value† |
|---|---|---|---|---|---|
| HP Cohort | Diagnosis of HP | 271 | 129 | 47.6% | - |
| NAPS2/CV Cohorts | Any FHx AP‡ | 221 | 93 | 42.1% | 0.221 |
| | Any FHx CP‡ | 233 | 103 | 44.2% | 0.446 |
| | FHx AP (excluding FHx CP)‡ | 122 | 63 | 51.6% | 0.459 |

* HP cases and individuals with a family history of HP excluded from FHx categories from the NAPS2/CV cohorts
† Two-tailed test of binomial proportions was used except where $n \leq 5$, in which case Fisher's exact test was performed. P-values represent a comparison to the HP group.
‡ RAP cases excluded because RAP was not measured as an outcome for HP
FHx = Family history; DM = Diabetes mellitus; PDAC = Pancreatic ductal adenocarcinoma

**Table 10 HP v. Family History: Risks for Diabetes Mellitus**

| Cohort | Category* | Total (n) | Number with DM (n) | Percentage with DM | P-Value† |
|---|---|---|---|---|---|
| HP Cohort | Diagnosis of HP | 271 | 69 | 25.5% | - |
| NAPS2/CV Cohorts | Any FHx AP | 274 | 33 | 12.0% | **0.000** |
| | Any FHx CP | 269 | 26 | 9.7% | **0.000** |
| | FHx AP (excluding FHx CP) | 159 | 23 | 14.5% | **0.007** |
| | FHx DM | 1370 | 232 | 16.9% | **0.001** |
| | FHx PDAC | 204 | 34 | 16.7% | **0.021** |

* HP cases and individuals with a family history of HP excluded from FHx categories from the NAPS2/CV cohorts
† Two-tailed test of binomial proportions was used except where $n \leq 5$, in which case Fisher's exact test was performed. P-values represent a comparison to the HP group.
‡ RAP cases excluded because RAP was not measured as an outcome for HP
FHx = Family history; DM = Diabetes mellitus; PDAC = Pancreatic ductal adenocarcinoma

**Table 11 HP v. Family History: Risks for Pancreatic Cancer**

| Cohort | Category* | Total (n) | Number with PDAC (n) | Percentage with PDAC | P-Value† |
|---|---|---|---|---|---|
| HP Cohort | Diagnosis of HP | 271 | 4 | 1.5% | - |
| NAPS2/CV Cohorts | Any FHx AP | 274 | 0 | 0.0% | 0.060 |
| | Any FHx CP | 269 | 0 | 0.0% | 0.124 |
| | FHx AP (excluding FHx CP) | 159 | 0 | 0.0% | 0.302 |
| | FHx DM | 1370 | 1 | 0.1% | **0.003** |
| | FHx PDAC | 204 | 0 | 0.0% | 0.138 |

* HP cases and individuals with a family history of HP excluded from FHx categories from the NAPS2/CV cohorts
† Two-tailed test of binomial proportions was used except where $n \leq 5$, in which case Fisher's exact test was performed. P-values represent a comparison to the HP group.
‡ RAP cases excluded because RAP was not measured as an outcome for HP
FHx = Family history; DM = Diabetes mellitus; PDAC = Pancreatic ductal adenocarcinoma

### 3.2.2 Pancreatic Cancer Pedigree Case Series

In a single family with autosomal dominant *PRSS1*-related hereditary pancreatitis, four cases of pancreatic cancer were reported over 2 generations **(Figure 8).** Three of these cases were among first degree relatives. Genetic testing identified the R122H *PRSS1* mutation in this family. Smoking and alcohol status is only known for one of the cases of pancreatic cancer (III-19), and this individual was an ex-smoker and never-drinker. Median age at diagnosis with pancreatic cancer in this family was age 53. One case of pancreatic cancer was found in an individual with genetically confirmed hereditary pancreatitis (II-19), and another case was found in an obligate carrier (III-15). The observation of multiple individuals affected with pancreatic cancer with and without hereditary pancreatitis suggest that other genetic risk factors are involved in the development of pancreatic cancer in this family.

Pedigree 2 represents a family with one case of pancreatic cancer in an individual (II-1) who was a never drinker and never smoker **(Figure 9)**. However, other individuals in the family with HP were exposed to both alcohol and tobacco did not develop pancreatic cancer. For example, individual IV-19 is a 3$^{rd}$ degree relative of II-1 with HP who reports drinking an average of 5 drinks per day and smoking > 1 pack per day. Individual II-12 is a sibling of II-1 with HP who reports smoking > 1 pack per day. The lack of pancreatic cancer in these individuals and other adult family members with major environmental risk factors suggests the presence of risk and/or protective variants in this family.

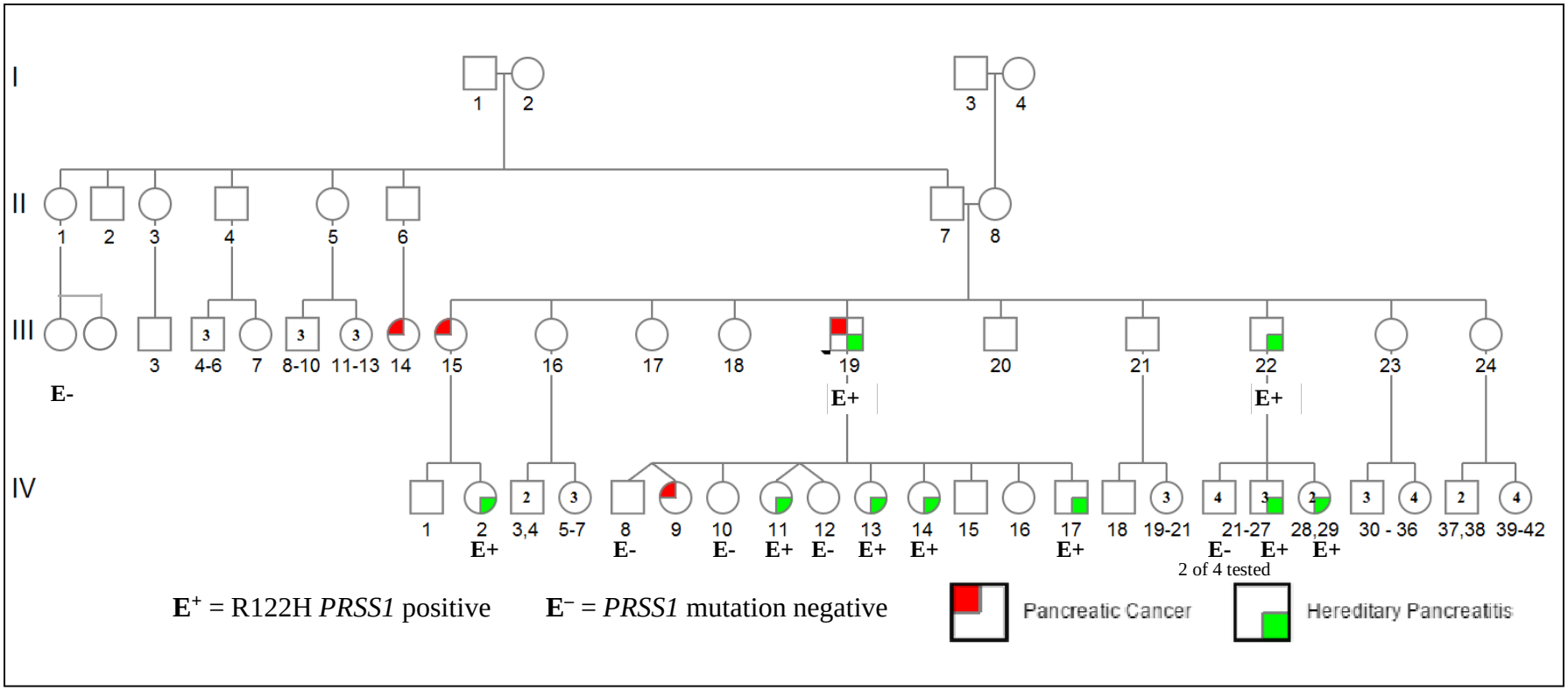


**Figure 8 Pedigree 1**

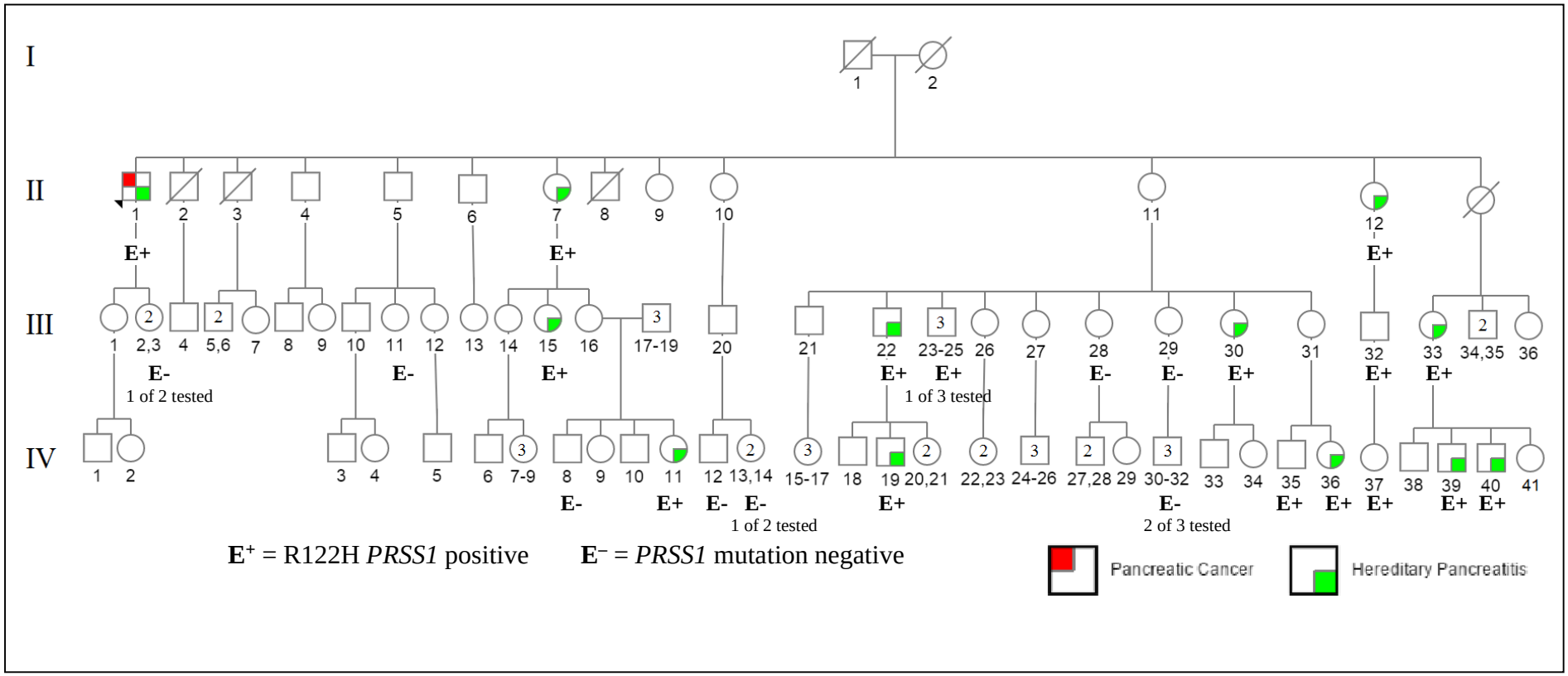


**Figure 9 Pedigree 2**

## 3.3 SPECIFIC AIM 3

Two questionnaires – cases (**Appendix D**) and controls (**Appendix E**) – were created as described in **Section 2.7**. This questionnaire has been approved by the University of Pittsburgh Institutional Review Board **(Appendix B)**. An online version has also been created through the University of Pittsburgh IRB-approved Qualtrics web-based survey software. The link to the questionnaire and paper versions of the survey will be mailed to current HP Study participants for a follow-up study and to obtain new information and attitudes, concerns, and perceptions as a future study.

# 4.0 DISCUSSION

Hereditary pancreatitis is a rare disorder, and published literature on the natural history of HP is limited. While there are many reports on clinical features in the form of case reports or small case series, few studies have been performed on larger scales. Particularly, the natural history of HP has not been well described in the North American population. This study represents a description of the cohort that has been ascertained in the United States and provides information regarding risks for pancreatic cancer and diabetes mellitus according to family history.

The first aim of this study was to describe the HP cohort that has been obtained by the University of Pittsburgh. In this HP cohort, a mutation in the *PRSS1* gene was detected in 74.4% of cases, with a penetrance of 87% for any pancreatitis in an individual with a known pathogenic *PRSS1* mutation. There was nearly a 4.5 year gap between the mean age of pancreatitis onset and diagnosis with hereditary pancreatitis, indicating a need for better recognition of this disease, particularly in pediatric patients. As anticipated according to previous studies (Gorry et al., 1997; Whitcomb, Gorry, et al., 1996), the most common *PRSS1* mutation identified was R122H, confirming that this is the most common mutation associated with *PRSS1*-related hereditary pancreatitis. No statistically significant differences were found in clinical, biochemical, or morphological features between individuals with and without an identified mutation, with the exception of the occurrence of CP without prior AP favoring individuals without an identified mutation. However, the potential of response bias and the small number of individuals who report a diagnosis of CP without prior AP (n = 4) suggest that this result has low practical significance.

The characteristics of this HP cohort are similar to the characteristics described in the French, Danish, and larger European Cohorts (Howes et al., 2004; Joergensen et al., 2010; Rebours, Boutron-Ruault, Schnee, et al., 2009). Therefore, the natural history of patients with HP in the United States is unlikely to be substantially different from the natural history of HP in the European populations. However, the percentage of individuals with HP in which *PRSS1* mutations were identified is higher in this cohort than seen in the Danish and French studies (Howes et al., 2004; Joergensen et al., 2010; Rebours, Boutron-Ruault, Schnee, et al., 2009), but comparable to the EUROPAC study (Howes et al., 2004). Furthermore, rates of exocrine and endocrine insufficiency are higher in this population than seen in the Danish study, but similar to the French study (Joergensen et al., 2010; Rebours, Boutron-Ruault, Schnee, et al., 2009). As seen in other studies, there is a gap of many years between symptom onset and diagnosis with HP.

The mean overall survival for this HP cohort (77.93 years) is consistent with the mean survival of the French cohort (CI 95%: 71 – 79) (Rebours, et al. 2009), indicating that HP survival rates are comparable between these populations. However, survival was likely overestimated in this case due to the limitations of the SSDI and the low number of participants who were greater than 60 years of age at the time of this study. Furthermore, participants were living at the time of ascertainment, which may have created a bias in the survival analysis. In contrast to the French studies, diabetes and lack of pancreatic enzyme therapy were found to be risk factors of mortality in this cohort. However, exocrine insufficiency was not directly measured. Therefore, there may be confounding variables, such as death prior to beginning enzyme therapy, non-adherence in participants who do not report enzyme therapy, pancreatic resection/removal in enzyme users that is protective against other outcomes, and lack of therapy for individuals that would benefit. Further

studies are needed to identify this correlation of diabetes and lack of enzyme therapy with lower rates of survival. Furthermore, it will be valuable to compare cause of death between the 19 deceased participants in the French cohort and the 25 deceased participants in this cohort.

The family history risk analysis and case series supports the presence of complex risk variants that influence the development of pancreatic cancer. Understanding and identifying these risk variants will help improve detection of higher-risk and lower-risk individuals, as well as help clarify the mechanisms behind pancreatic cancer development in families with hereditary pancreatitis.

## 4.1 LIMITATIONS

Limitations exist in the ascertainment of patient information in the HP Cohort. Patient medical history is patient reported, though many reports have been verified by medical records. Furthermore, there is much missing data in this cohort. Prevalence cannot be calculated from this study unlike studies on the French population because it is not based on a complete national series of patients. As with all data, errors may exist from transferring from paper files to electronic systems.

The Social Security Death Index is a database created from the Social Security Administration's Death Master File. It contains information on deceased individuals with social security numbers whose deaths were reported to the Social Security Administration. The Social Security Administration cannot guarantee the accuracy of the SSDI, and missing and incorrect information

may exist. Therefore, some errors may exist in the data retrieved for the survival analysis on the HP cohort.

## 4.2 FUTURE STUDIES

This study supports the value of this HP cohort and confirms its similarity to cohorts described in European populations. As an ongoing study, it will be valuable to continue follow-up with these participants to further and more accurately define the natural history of HP. Furthermore, identifying cause of death for deceased participants will be valuable for understanding this condition in the American population.

Analysis of risks for chronic pancreatitis, diabetes mellitus, and pancreatic cancer based on HP status and family history support the influence of other genes leading to these outcomes. Further studies are needed to identify genetic risk factors, modifiers, and other environmental factors that play a role in the development of these conditions.

Finally, the survey developed for Aim 3 will be important for understanding perceptions and concerns of individuals with HP. Results with inform healthcare providers and genetic counselors to improve care and counseling for this complex disease, particularly in a Pancreas Center of Excellence.

# 5.0 CONCLUSION

This is the first study describing the natural history of hereditary pancreatitis in the United States on a large scale. The similarity of this cohort to cohorts described in the European population makes this a good cohort for further studies on hereditary pancreatitis that may be applicable across populations. This study contributes to the understanding of hereditary pancreatitis and its disease course, which is an important step toward improving patient care and awareness for individuals with this disease. Analysis of risks for chronic pancreatitis, diabetes, and pancreatic cancer based on family history provided further evidence for the influence of risk genes on the development and inheritance of these conditions apart from HP. This is further supported by the identification of HP families with a higher incidence of pancreatic cancer than expected due to HP alone. Further research will define how other risk genes (or environmental risk factors) influence the outcomes associated with hereditary pancreatitis.

## APPENDIX A: UNIVERSITY OF PITTSBURGH IRB RENEWAL LETTER

**University of Pittsburgh**
***Institutional Review Board***

3500 Fifth Avenue
Pittsburgh, PA 15213
(412) 383-1480
(412) 383-1508 (fax)
http://www.irb.pitt.edu

**Memorandum**

To: David Whitcomb, MD, PhD
From: Margaret Hsieh, MD, Vice Chair
Date: 12/22/2014
IRB#: REN14120023 / PRO07090243
Subject: Genetic Linkage Study for Hereditary Pancreatitis

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At its full board meeting on 12/9/2014, the University of Pittsburgh Institutional Review Board, Committee B, reviewed the Renewal for the above referenced research study and approved it pending minor modifications. Your responses to these comments have been reviewed and the research submission, in its currently modified form, adequately addresses the concerns of the IRB and is therefore approved.

The risk level designation is Greater Than Minimal Risk .

Please note the following information:

Approval Date: 12/19/2014
Expiration Date: 12/8/2015

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

**Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.**

## APPENDIX B: UNIVERSITY OF PITTSBURGH IRB MODIFICATION APPROVAL

**University of Pittsburgh**
***Institutional Review Board***

3500 Fifth Avenue
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Pittsburgh, PA 15213
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http://www.irb.pitt.edu

**Memorandum**

To: David Whitcomb, MD
From: IRB Office
Date: 2/2/2015
IRB#: MOD07090243-17 / PRO07090243
Subject: Genetic Linkage Study for Hereditary Pancreatitis

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The University of Pittsburgh Institutional Review Board reviewed and approved the requested modifications by expedited review procedure authorized under 45 CFR 46.110 and 21 CFR 56.110.

Modification Approval Date: 2/2/2015
Expiration Date: 12/8/2015

For studies being conducted in UPMC facilities, no clinical activities that are impacted by the modifications can be undertaken by investigators until they have received approval from the UPMC Fiscal Review Office.

Please note that it is the investigator's responsibility to report to the IRB any unanticipated problems involving risks to subjects or others [see 45 CFR 46.103(b)(5) and 21 CFR 56.108(b)]. Refer to the IRB Policy and Procedure Manual regarding the reporting requirements for unanticipated problems which include, but are not limited to, adverse events. If you have any questions about this process, please contact the Adverse Events Coordinator at 412-383-1480.

The protocol and consent forms, along with a brief progress report must be resubmitted at least one month prior to the renewal date noted above as required by FWA00006790 (University of Pittsburgh), FWA00006735 (University of Pittsburgh Medical Center), FWA00000600 (Children's Hospital of Pittsburgh), FWA00003567 (Magee-Womens Health Corporation), FWA00003338 (University of Pittsburgh Medical Center Cancer Institute).

**Please be advised that your research study may be audited periodically by the University of Pittsburgh Research Conduct and Compliance Office.**

## APPENDIX C: PUBLISHED PAPER

Current Treatment Options in Gastroenterology
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Pancreas (T Stevens, Section Editor)

# Genetics and Treatment Options for Recurrent Acute and Chronic Pancreatitis

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**Keywords** Acute pancreatitis · Chronic pancreatitis · Cystic fibrosis · CFTR-related disorders · Genetics · Genetic testing · Genetic counseling · Genetic counselor · Genomics · Direct-to-consumer genetic testing · *PRSS1* · *SPINK1* · *CFTR* · *CTRC* · *CASR* · *CLDN2* · *GGT1* · Genomic counseling · Complex disease · Personalized medicine · Genomic medicine · Pancreas

## Opinion statement

Worldwide research efforts demonstrate a major role of gene-environment interactions for the risk, development, and progression of most pancreatic diseases, including recurrent acute and chronic pancreatitis. New findings of pancreas disease-associated risk variants have been reported in the *CPA1*, *GGT1*, *CLDN2*, *MMP1*, *MTHFR*, and other genes. These risk genes and their regulatory regions must be added to the known pathogenic variants in the *PRSS1*, *SPINK1*, *CFTR*, *CTRC*, *CASR*, *UBR1*, *SBDS*, *CEL*, and *CTSB* genes. This new knowledge promises to improve disease management and prevention through personalized medicine. At the same time, however, knowledge of an increasing number of pathogenic variants, and their complicated effects when present in combination, results in increasing difficulty in interpretation and development of recommendations. Direct-to-consumer marketing of genetic testing results also adds complexity to disease management paradigms, especially without interpretation and, in many cases, proven accuracy. While improvements in the ability to rapidly and accurately interpret complex genetic tests are clearly needed, some results, such as pathogenic *CFTR* variants, including a new class of bicarbonate-defective mutations, and *PRSS1* variants have immediate implications that direct management. In addition, discovery of pancreatitis-associated genetic variants in patients with glucose intolerance may suggest underlying type 3c diabetes, which also has implications for treatment and disease management.

## Introduction

Historically, it was assumed that acute pancreatitis was almost always caused by gallstones, and chronic pancreatitis by alcoholism. These simple, concrete causations exemplify the germ theory of disease, where a single factor causes a complex disease syndrome. In practice, however, it is clear that gallstones and alcohol are not always the proximal cause of pancreatitis. Furthermore, the clinical syndrome has unpredictable severity, duration, complications, and outcomes. Although studies have identified additional factors in the development of pancreatitis, it is clear that there are missing variables. Given that multiple variables affect each individual patient, how can the care and management of individual patients be accomplished?

Genetic susceptibility to pancreatitis and modification of the disease course by other genetic and environmental interactions plays a major role in the onset, severity, complexity, and outcome of human pancreatic disease. Genetic tests differ from common medical tests used to evaluate pancreatic disease, such as measuring biomarkers (e.g., amylase, lipase), biopsies, or abdominal imaging tests. Such tests reveal structural changes or measure variable processes that are evaluated as indicators of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention [1]. Alternatively, genetic tests provide insights into the cellular blueprint that determines the molecular components that will be available for use under normal and abnormal conditions, as well as their functional qualities.

In most cases, adult pancreatic disease is not the result of abnormal pancreatic development. Rather, it is a disruption of the normal state of physiological function by stress or injury, with or without a failure to fully return to the normal state. For a given amount of stress or injury, pathogenic genetic variants disrupt optimal adaptation to stress, response to injury, regeneration, and/or post-injury return to the normal state. Thus, in pancreatic disease, biomarkers are most useful in determining the current state of function or dysfunction. On the other hand, genetics is useful in determining which underlying molecules or pathways are likely to function normally or abnormally in the current context as well as predicting which systems are most likely to respond normally or abnormally in the future. As such, optimal care must go beyond excluding gallstones and alcohol as the causative factor. Attention must be given to risk of recurrent acute pancreatitis (RAP), complications of altered anatomy (e.g., pancreatic necrosis, fluid collections), pathogenic persistence of inflammation and consequent fibrosis, atrophy, pain syndromes, diabetes mellitus (Type 3c) [2••], altered metabolism and nutrition, and cancer risk, all of which define chronic pancreatitis (CP).

As the conceptual framework and new methods of evaluating complex pancreatic diseases are being developed, there are economic, legal, and political forces that are changing the way complex medical conditions such as RAP and CP are evaluated and managed. Repeated use of abdominal imaging and function testing to diagnose and manage pancreatic diseases is expensive, potentially dangerous (ERCP, EUS with biopsy, radiation exposure) or insensitive, and provides information on severity of damage rather than etiology and prognosis. Large pancreatitis cohort studies such as the North American Pancreatitis Study II (NAPS2) [3] have established the complexity of RAP and progression to CP through the interaction of multiple genetic and environmental factors [4, 5]. The challenge is that complex genetics is complex, and busy physicians cannot easily keep up with all of the nuances and implications of various combinations of factors, their implications for other family members, and their prognostic implications for medical decision-making. Furthermore, the cost of genetic testing can be high, and insurance companies often refuse coverage of established tests by considering them "experimental." In the case of individuals who wish to obtain genetic testing without a health professional intermediary, there have been restrictions placed on direct-to-consumer (DTC) genetic testing in some instances due to lack of proven analytic validity and concern for improper or potentially harmful self-care.

While it is clear that genetic evaluation of patients with early pancreatic disease will become increasingly important, the methods of obtaining the required genetic data and interpreting individual results have not been adequately defined. What is the state of the field, and what will be important in the future?

*CFTR*$^{BD}$ variants increased the risk for both rhinosinusitis (OR 2.3, $p<0.005$) and male infertility (OR 395, $p<0.0001$). However, there was no increase in lung disease. Since the evaluation and management of CF has been led by pulmonary physicians, it is likely that the scope and impact of the *CFTR*$^{BD}$ variants will be increasingly recognized as they are evaluated by pediatricians, internists, and gastroenterologists.

These findings underscore the fact that new paradigms and new approaches will be needed to integrate the expanding realm of genetic factors into clinical practice and personalized medicine [5, 26••]. The opportunities for better management of pancreatic diseases are significant. Limitations to implementing therapeutic changes for pancreatic diseases include issues surrounding genetic testing, interpretation of genetic results, and developing new treatment plans that are aimed at both targeting defects and avoiding potential complications.

## Genetic Testing Controversies

While genetic testing has the power to reveal lifelong potentially pathogenic variants, this utility is linked to potential dangers. These dangers are not necessarily associated with immediate physical injury but with underlying mechanisms. There can be long-term implications to a patient's self-concept as well as future health implications – an area of concern for health insurance, life insurance, employment, and other relationships. In some cases, such as the expanded trinucleotide repeat for glutamine in the Huntington's disease gene (*HTT*), the results of genetic testing predict a horrible death at a young age, with no good treatment options [27, 28]. In pancreatic diseases, knowledge of gain-of-function mutations in the cationic trypsinogen gene (*PRSS1*) indicating hereditary pancreatitis [29, 30], or two severe mutations in the cystic fibrosis transmembrane conductance regulator gene (*CFTR*) indicating cystic fibrosis [31–33], have important and immediate implications for disease. However, knowledge of other genetic variants – especially common ones that may or may not play a role in various pancreatic diseases as a complex genotype or modifier- is difficult or impossible to interpret outside a well-defined context [5, 26••].

In the examples above of mutations in the Huntington's disease gene, *PRSS1*, and *CFTR*, some genetic results provide clear, significant risk implications based on single-gene genotyping. Other pancreatic disease variants in genes such as *CTRC* [7•] or the *CLDN2* locus [14••] confer risk in combination with other pathogenic gene variants or strong environmental factors, and therefore have lower gene-specific risk. We believe that the knowledge of variants in the second group of genes alone, independent of the clinical context, has minimal predictive utility and therefore confers little risk.

The calculus that goes into genetic testing integrates the rights and needs of multiple stakeholders and becomes more complicated when the potential results of extensive genotyping span the range of genetic risk profiles from minimal to life-changing. Years of experience have led to well-defined approaches to genetic tests of simple rare diseases [34]. This process includes careful pre-test counseling, as well as post-test disclosure and education that typically involve specialty-trained physicians, genetic counselors, and special

resources. Consensus guidelines and expert guidance have been published for pancreatic disease such as hereditary pancreatitis [35–37, 38•, 39]. The wide availability of accurate and inexpensive single-nucleotide polymorphism (SNP) testing on a chip and massively parallel next-generation sequencing (NGS) technologies now puts huge amounts of information into the hands of "everyone." When, where, and how should this new and complex data be used, and by whom and for whom?

## Direct-to-consumer genotyping

Given the high cost of detailed genetic sequencing obtained through healthcare channels, genetic testing companies, which provide individuals with the opportunity to obtain genetic results directly, may be an attractive alternative for patients motivated by curiosity and a desire learn about themselves without having to share such information with their health provider. Physicians should be aware of direct-to-consumer genetic testing and its controversies so that they are able to provide an optimal course of action for patients that divulge such results.

23andMe, founded in 2006, was among the first of the "direct-to-consumer" (DTC) personalized genetic testing companies in the United States. The company was highly successful, genotyping over 650,000 individuals [40]. Cost was controlled by the use of SNP chips, which initially allowed analysis of close to 600,000 polymorphisms [41]. The danger of reporting very high-impact and potentially serious results, such as Lynch syndrome, FAP, and other familial cancer syndrome-associated genetic variants, was avoided by not placing critical SNPs on the chip, and instead selecting tag SNPs that had proven associations with common disorders such as cardiovascular disease, diabetes, and obesity. In most of cases, the "risk" was relatively low because the relative risk of the disease was low or the impact of the results was self-evident (e.g., obesity).

The problem was that many of the conditions, such as risk of autoimmune disease, were distressing to individuals, especially those who had friends or family with complications of the particular disorder [42]. Additionally, although 23andMe marketed their testing as providing both medically meaningful and potentially actionable health reports, this marketing strategy was not approved by the FDA, as the company failed to prove the analytical validity and clinical utility of each SNP used to provide health information. Other major concerns from DTC genetic testing include inappropriate risk interpretation by consumers and incorrect or unwarranted health management decisions based upon DTC genetic testing reports. The magnitude of this problem was such that on November 13, 2013, the FDA ordered 23andMe to cease and desist from marketing and testing for health-related information. Consumers ordering testing on or after November 22, 2013 would not receive health information, but would still receive ancestry information and "uninterpreted raw genetic data."

We believe that the stance of the FDA toward DTC genetic testing companies is warranted given that such testing typically is presymptomatic, provides results that are difficult to interpret, and does not involve a healthcare professional intermediary to provide guidance for the decision to test and results disclosure. The most important pathogenic variants are also excluded,

possibly providing individuals with false assurance. Furthermore, consumers are not required to seek genetic counseling with the disclosure of their test results. As such, individuals who undergo such DTC testing may incorrectly perceive predictive genetic testing results that prompt inappropriate and potentially harmful medical decisions.

DTC genetic testing companies may provide health information that individuals do not want to obtain through their healthcare provider because of huge price markups and required copays (i.e., financial barrier). Others may want to know their results prior to deciding if they want the results as part of their healthcare record (i.e., fear of genetic discrimination). Whether companies like 23andMe can align the "individual's right to know" with FDA standards and provide both accurate and clinically useful results within an acceptable context has not been resolved.

In summary, there is reasonable concern that the general population is not capable of fully understanding the risks and implications of complex genetic test results. DTC genetic testing may drive unreasonable and unnecessary healthcare actions, and increase rather than alleviate anxiety and stress. Perhaps integrating DTC results with counseling will improve these outcomes [43•]. On the other hand, the question of whether an individual has the right to know details about their own body remains an important moral, ethical, legal, and social debate. Gastroenterologists should consider these points when faced with patients arriving with DTC genetic testing results for known genes involved in pancreatic disease, or patients expressing a desire to undergo DTC genetic testing for health-related information.

## Pre-existing Conditions

A major non-medical risk of genetic variant information is the potential penalty of having a "pre-existing condition" resulting in genetic discrimination. This is clearly one of the major concerns of patients, including those with risk for pancreatic disease [44]. The Genetic Information Nondiscrimination Act of 2008 (GINA, Pub. L, 110–233) made it illegal to use genetic test results in consideration of health insurance rates or employment. However, patients are still concerned, and rightfully so, about life insurance, mortgages, and other potential areas of discrimination. The issue of discrimination also raises moral, ethical, social, and legal issues surrounding patient disclosure of DTC test results to their doctor, health plan, employer, and others, as noted above. Likewise, there are questions as to whether all genetic information from broad genome-wide sequencing tests by physicians and healthcare providers could be collected without disclosing all of the results to the patient. The American College of Medical Genetics (ACMG) currently recommends that their minimal list of medically-actionable findings be disclosed [45]. Implications of findings from any comprehensive genetic testing performed for pancreatic disease, therefore, may supersede issues specific to pancreatic disease.

## Genetic Testing for Complex Disorders

Most of the debate highlighted above revolves around genetic testing for simple Mendelian disorders or presymptomatic testing of a wide spectrum of

common disorders with independently informative SNPs. There has been less debate and discussion on genetic testing for complex disorders, since there are very few well-defined disorders in which multiple genes and environmental factors are integrated into disease models that provide utility for managing these disorders. Should the same rules and guidelines apply for complex disorders? Who should own the results? How can they be interpreted by the physician and patient?

It is the authors' opinion that genetic testing is critical for understanding and managing complex disorders. It is the cornerstone of personalized medicine. It is central to predictive modeling for many conditions and disorders, such as pancreatic diseases, and many genes and regulator SNPs must be considered simultaneously to make accurate predictions in complex diseases. The field may become even more complex as epigenetics, regulatory elements, functional genomics, expression profiling, and the "omics" technologies enter the mix and must be interpreted [46, 47].

The greatest issue is that most physicians are not – and cannot be – adequately trained to interpret complex genetic data sets during a busy clinical session, especially when complex clinical and environmental factors contribute to variable risk and outcomes. With increasing focus on patient turnover and productivity, there is just not enough time to stay up to date on all of the important genetic factors and nuances of interpretation. However, there must be someone able to evaluate genetic data within the context of a clinical question or problem and to communicate the appropriate information in understandable terms to the healthcare provider and/or patient.

## Pancreatitis Genetics and their Implications

Given the anatomical and functional simplicity of the pancreas as compared to other organs, and its relative protection from environmental factors, the pancreas provides an outstanding model for understanding complex disease [5, 26••]. The first observation is that the clinical features of acute, recurrent acute, and chronic pancreatitis center on the signs and symptoms of inflammation, regardless of etiology. Management and prevention of recurrence necessitates addressing the underlying etiologies and patient-specific risk. Since the pancreas is protected from direct exposure to the environment, and because its function is to synthesize digestive enzymes and hormones rather than eliminate toxic metabolites or xenobiotics, the risk of injury and inflammation are largely linked to genetic variants. Appropriate genetic testing will provide information-rich data regarding these factors – but the key will be the interpretation of the data.

The second observation is that genetic risk factors for pancreatitis susceptibility and complications have different implications, and thus require individualized management. Autosomal dominant *PRSS1*-related hereditary pancreatitis provides a model for interpreting, counseling, and managing probands and families with a Mendelian disorder [39]. Likewise, cystic fibrosis, a recessive disorder of severe *CFTR* mutations, provides a model of a multi-system genetic syndrome with specific implications and treatments [48, 49]. Complex genotypes are common with variants in *CFTR*, *SPINK1*, *CTRC*, and other genes, both within and outside the context of smoking and drinking. Interpretation of the genes, variants, and context can be critical in

immediately defining the reason for pancreatitis susceptibility and recurrence of progression, thereby limiting continued expensive and invasive evaluations or preventive procedures. The framework for understanding the effects and consequences of common and rare variants continues to evolve [6, 7, 38•, 49]. The work that has been done in identifying subsets of patients that are phenotypically similar to patients with single-gene pancreatic diseases [37, 50], but with more intricate genotypes, has made it possible to begin developing genetic counseling models for complex diseases as one option for managing complex genetic results [50].

## Treatment Options

There are several goals in genetic testing for pancreatic disease. The first is to identify a mechanistic etiology. It is important to compare the cost of a traditional evaluation comprising multiple office visits, biomarker studies, abdominal imaging tests, and procedures to determine etiology, with the cost of genetic testing. Of note, with the exception of very high levels of ionized calcium, IgG4, and triglycerides, most biomarkers are not linked with etiology. The issue with genetic testing early in the evaluation of pancreatitis without an obvious cause, such as gallstones, is that it is not a "medical necessity." However, it does provide both diagnostic expedience and cost savings, and a positive genetic test eliminates the need for additional diagnostic testing and transitions the care plan to disease management and avoidance of complications.

Discovery of genetic syndromes such as CF, secondary forms of CF (e.g., *CFTR*$^{BD}$ syndrome), or atypical CF have immediate implications for disease management as well as consideration of dysfunction of other organs. Treatment approaches for CF disease, for example, are well-established and may involve a referral to a CF center for full evaluation [48]. The new *CFTR* enhancers or correctors are intriguing, but have not been tested in predominantly pancreatic disease forms of CF and are prohibitively expensive.

A preliminary study was published on the use of amlodipine for management of hereditary pancreatitis from *PRSS1* gain-of-function mutations [51]. Use of this calcium channel blocker appeared to be safe, and trends toward benefit were observed. Additional trials have not been reported, but the author has received positive anecdotal reports. It is clear that prospective randomized double-blinded clinical treatment trials are needed to determine the most effective therapies for specific problems.

Genetic testing results may also have important implications for the treatment of diabetes mellitus. Chronic pancreatitis from any cause, including genetic, may result in type 3c diabetes mellitus, in which insufficient insulin production due to pancreatic disease or surgery diminishes the number of islets [2••, 52]. A definitive diagnosis of CP is difficult unless there is severe RAP, significant morphologic distortions of the pancreas, or pancreatic calcifications. Diagnosis of CP based on steatorrhea, weight loss, or malnutrition is also an issue, as these signs and symptoms occur late in the disease when the exocrine pancreas is almost completely destroyed. Even with signs and symptoms that are obvious to a gastroenterologist, CP may not be appreciated by most endocrinologists, who are managing the glucose intolerance rather than pancreatic disease. Indeed, up to 9 % of patients with

diabetes may have unrecognized type 3c DM [53–55].

From a treatment standpoint, a correct diagnosis of type 3c diabetes is important for several reasons [2••, 52, 56–58]. First, type 3c DM is associated with the loss of all islet cells, not just the beta cells. Therefore, these patients lack counterregulatory hormones such as glucagon and pancreatic polypeptide, and are thus susceptible to hypoglycemia and other metabolic dysfunctions. Second, there may be asynchrony between the ingestion of a meal, delivery of exogenous insulin, and nutrient absorption following meal digestion if there is a lack of pancreatic digestive enzymes (e.g., pancreatic exocrine insufficiency) and a significant delay in digestion. In this case, it seems reasonable to provide pancreatic enzyme supplements with meals to improve meal digestion and absorption in synchrony with the effects of insulin on clearance of glucose and fats from the bloodstream. Third, the use of incretins (GLP-1 agonists, DPP-4 inhibitors) to manage type 2 DM may be ineffective in type 3c DM, since levels of natural GLP-1 may already be high [59]. Fourth, there appears to be an increased risk of pancreatic ductal adenocarcinoma (PDAC) in patients with CP, and the risk of PDAC in DM may be linked to undiagnosed CP. Therefore, the use of genetic testing to assess the risk of RAP and CP in patients with DM and equivocal histories of episodes of RAP or CP should be considered.

The ultimate treatment for persistent, severe, or disabling CP with the threat of impending type 3c DM is total pancreatectomy with islet autotransplantation (TPIAT). This procedure, which was available at only two facilities a few years ago, is now conducted at over 20 medical centers. TPIAT involves the early removal of the pancreas before the number of islets is completely diminished, digestion of the pancreatic parenchyma and isolation of the islets, and reimplantation of the islets into the liver, abdomen, or other sites. The procedure, which is associated with significant dangers, exchanges one problem for another. Since the TPIAT alters gastrointestinal anatomy, some patients have major post-procedure motility problems, and all are committed to lifetime full-dose pancreatic enzyme replacement therapy with each meal and each snack. However, TPIAT typically provides relief from the severe abdominal pain associated with pancreatitis and may prevent the development of diabetes. Guidelines for the evaluation and management of patients being considered for or who have undergone the procedure have recently been published [60].

## Summary and Conclusions

The low cost and wide availability of human genotyping offers new opportunities for rapid advances in personalized medicine. The hope is that the technology will lead to much better care and much lower costs. The reality is that the technology is far ahead of the ability to interpret the results, as witnessed in the controversy surrounding DTC genotyping by 23andMe. While the involved nature of complex disorders is aptly illustrated in pancreatic diseases, the simplicity of the pancreas provides the opportunity to model the management of a complex disorder by utilizing genetic information. However, it also reveals the challenge of interpreting large and complex data sets by busy physicians, which is likely functionally impossible. For the

subset of data with clear implications, course of treatment is guided by the results. In some cases, management and care for patients with pancreatic disease should be coordinated with CF centers. Clinical trials are needed to determine the most useful therapies for specific disorders and genotypes. Recognition of CP in patients with DM is also important, as the management of type 3c DM is drastically different from that of type 2 DM, and may require TPIAT to save remaining islets and prevent brittle DM and other consequences of prolonged CP, such as PDAC.

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## Compliance with Ethics Guidelines

**Conflict of Interest**
Celeste A. Shelton was supported off of a gift account from AbbVie to develop a pancreas center of excellence. The gift was to the University of Pittsburgh Medical.
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**Human and Animal Rights and Informed Consent**
This article does not contain any studies with human or animal subjects performed by any of the authors.

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## **APPENDIX D**: QUESTIONNAIRE – CASES (CONDENSED)

Date Consent Signed: __ __ / __ __ / __ __ __ __ Confirmed (Initials: _____ )

**1. Risk and State** **HP Cases**

**1.1 Do you have hereditary pancreatitis?**

☐( 1 ) Yes → *advance to question 1.2*
☐( 0 ) No → please complete the questionnaire for participants without hereditary pancreatitis
☐( - 3 ) Unknown → please complete the questionnaire for participants without hereditary pancreatitis

**1.2 Alcohol consumption:**

***NOTE: one shot of liquor, a mixed drink, one glass of wine or one beer is considered one drink.***

Was there ever a time when you drank beer, wine, wine coolers, liquor, or mixed drinks?

☐ (1) Yes ☐ (0) No (less than 20 drinks in your life) → *Advance to question 1.3*

**1.2.1** How many years did you drink alcohol in your life **(this could be consecutive or non-consecutive periods of time)?** ____ years

**Think about the period of life when you were drinking the most in your lifetime (this could be consecutive or non-consecutive periods of time). The next 4 questions are related to this period of your life:**

**1.2.2** How old were you when you began drinking **the most alcohol** in your life? ____

**1.2.3** On the **AVERAGE** about how many drinks would you have **on a drinking day**? ____

**1.2.4** How many **days per month** did you drink **at this level**? _____

**1.2.5** How long did you drink alcohol at the heaviest level? _____ years or _____ months

**1.2.6** Do you currently drink alcohol?

☐ (1)Yes ☐ (0)No → advance to question *1.3*

**1.2.6.1** On the AVERAGE about how many drinks would you have on a drinking day? _____ drinks

**1.2.6.2** How many days per month did you drink at this level? _____ days per month

**1.3 Tobacco use:**

Have you ever smoked cigarettes?

☐ (1) Yes ☐ (0) Never (less than 100 cigarettes in your life) → advance to question *1.4*

**1.3.1** What age did you start smoking? ____ years

**1.3.2** Do you currently smoke? ☐ (1) Yes → advance to question *1.3.4* ☐ (0) No

**1.3.2.1** What age did you quit smoking? ____ years

**1.3.3** On the average, how many cigarettes do / did you smoke per day? ____

**1.4 Current Height and weight**

Height: _____ feet, _____ inches

Usual Weight: _____ pounds.

Current Weight: _____ pounds.

Weight change over the past 6 months: ____pounds → ☐ increase in weight ☐ decrease in weight

**1.5 Do you have abdominal pain from pancreatitis?**

☐( 1 ) Yes ☐( 0 ) No → *advance to question 2.1* ☐( - 3 ) Unknown → *advance to question 2.1*

↓

**1.5.1 What type of pain pattern do you have? (check one)**

☐( 1 ) usually **pain free**, but episodes of **mild to moderate pain**
☐( 2 ) constant **mild to moderate pain**
☐( 3 ) usually **free of abdominal pain**, but episodes of **severe pain**
☐( 4 ) constant **mild to moderate** pain ***plus*** episodes of **severe** pain
☐( 5 ) **constant severe** pain

## 2. Emotional Health

This section asks about the status of your emotional health related to hereditary pancreatitis, particularly feelings related to anxiety and depression. We recognize that hereditary pancreatitis affects both a person's physical and emotional health. If you feel that you identify with any of the statements below, please let your physician know. You are not alone, and it may be useful for you to speak to a counselor and/or join a support group.

**Please respond to each question or statement by marking one box per row.**

### 2.1 Anxiety

**2.1.1 With regard to my hereditary pancreatitis, in the past 7 days…**

| | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I felt fearful…….. | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I found it hard to focus on anything other than my anxiety…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| My worries overwhelmed me…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I felt uneasy…….. | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |

### 2.2 Depression

**2.2.1 With regard to my hereditary pancreatitis, in the past 7 days…**

| | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I felt worthless…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I felt helpless…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I felt depressed…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I felt hopeless…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |

### 2.3 Most important problems caused by hereditary pancreatitis:

**2.3.1 What is the most difficult problem for you to deal with because of hereditary pancreatitis in you or your family?**

**2.3.2 Why is the problem noted in the previous question the most important problem?**

## 3. Quality of Life

This survey asks for your views about your health. This information will help you keep track of how you feel and how you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

3.1 In general, would you say your health is:

Excellent (4) ☐ Very good (3) ☐ Good (2) ☐ Fair (1) ☐ Poor (0) ☐

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

| | Yes limited a lot (2) | Yes limited a little (1) | No not limited at all (0) |
|---|---|---|---|
| 3.2 Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ☐ | ☐ | ☐ |
| 3.3 Climbing several flights of stairs | ☐ | ☐ | ☐ |

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

| | Yes (1) | No (2) |
|---|---|---|
| 3.4 Accomplished less than you would like | ☐ | ☐ |
| 3.5 Were limited in the kind of work or other activities | ☐ | ☐ |

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

| | Yes (1) | No (0) |
|---|---|---|
| 3.6 Accomplished less than you would like | ☐ | ☐ |
| 3.7 Did work or other activities less carefully than usual | ☐ | ☐ |

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

3.8 Not at all (0) ☐ A little bit (1) ☐ Moderately (2) ☐ Quite a bit (3) ☐ Extremely (4) ☐

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

| | All of the time (4) | Most of the time (3) | Some of the time (2) | A little of the time (1) | None of the time (0) |
|---|---|---|---|---|---|
| **3.9** Have you felt calm and peaceful? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **3.10** Did you have a lot of energy? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **3.11** Have you felt downhearted and blue? | ☐ | ☐ | ☐ | ☐ | ☐ |

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

| All of the time (4) | Most of the time (3) | Some of the time (2) | A little of the time (1) | None of the time (0) |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

## 4. Concerns and Perceptions

sections that ask about your perspectives on the medical, surgical, and financial aspects of hereditary pancreatitis, as well as your views on the characteristics of a Pancreas Center of Excellence (described below). Your concerns and perceptions are important to us to understand so that we can improve care for individuals with hereditary pancreatitis. The sub-categories in this section are as follows:

**A. Medical**
**B. Surgical**
**C. Financial**
**D. Pancreas Center of Excellence**

**Please respond to each question or statement by marking one box per row.**

### A. Medical

**4.1.1 Prior to today, how have you felt about the following medical problems related to pancreatitis?**

| | Not at all concerned | Slightly concerned | Somewhat concerned | Moderately concerned | Extremely concerned |
|---|---|---|---|---|---|
| Malnutrition | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Continuous Pain | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Narcotic Addiction | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Getting Adequate Treatment | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Diabetes | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Pancreatic Cancer | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**4.1.2 Please describe any concerns for pancreatitis that are not listed above.**

**4.1.3 How would you describe your chances to develop pancreatic cancer?**

| Extremely unlikely | Unlikely | Neutral | Likely | Extremely Likely |
|---|---|---|---|---|
| ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**4.1.4 Have you been counseled on your risks to develop cancer?**

☐(1) Yes ☐(2)No ☐(3)Unknown

## B. Surgical

A total pancreatectomy is a newer procedure that involves the removal of the entire pancreas. The decision to have a total pancreatectomy is dependent on a number of risks and benefits. We are looking to further understand the benefits, drawbacks, and outcomes of a total pancreatectomy, and this section asks for your opinions and experiences with this surgical procedure.

**4.2.1 Have you had or considered a total pancreatectomy with islet autotransplantation (TPIAT)?**

☐ Yes(1) ☐ No(0) → *go to question 4.3*

↓

**4.2.1.1 How important to you are the following benefits and drawbacks of a total pancreatectomy?**

| | Not at all important | Slightly important | Somewhat important | Moderately important | Extremely important |
|---|---|---|---|---|---|
| Lifetime enzymatic replacement therapy | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Reduction of abdominal pain | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Reduced risk for pancreatic cancer | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Preventing diabetes | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Acquiring diabetes | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Risks of undergoing surgery | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Financial costs | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**4.2.2 Have you had a total pancreatectomy with islet autotransplantation (TPIAT)?**

☐ Yes(1) ☐ No(0) → *advance to question 4.3*

↓

**4.2.2.1 Please describe your reason for getting a total pancreatectomy and your experiences as compared to your expectations. (short answer)**

**4.2.2.2 The following questions ask about your experiences with a total pancreatectomy. Please check <u>one</u> box per question.**

a. <u>Compared to the time before your pancreatectomy and islet auto-transplantation</u>, how would you rate your health in general <u>now</u>?

1 ☐ Much better now
2 ☐ Somewhat better now
3 ☐ About the same
4 ☐ Somewhat worse now
5 ☐ Much worse now

b. Compared to the time before your pancreatectomy and islet auto-transplantation, how would you rate your level of pain now?

1 ☐ Much better now
2 ☐ Somewhat better now
3 ☐ About the same
4 ☐ Somewhat worse now
5 ☐ Much worse now

c. Would you recommend pancreatectomy and islet auto-transplantation to your family or friends if they needed care for a similar problem?

1 ☐ Definitely not
2 ☐ Probably not
3 ☐ Not sure
4 ☐ Probably yes
5 ☐ Definitely yes

d. How would rate the overall results of your pancreatectomy and islet auto-transplantation?

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

**C. Financial**

**4.3 How important to you are the following financial burdens of having hereditary pancreatitis?**

| | Not at all important | Slightly important | Somewhat important | Moderately important | Extremely important |
|---|---|---|---|---|---|
| Cost of medical treatment | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Costs of surgery | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| School or work limitations | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Requiring caretaker(s) | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**D. Pancreas Center of Excellence**

A Center of Excellence is an academic center that provides leadership, research, and the most up-to-date services in a given field. At the University of Pittsburgh, we are developing a Pancreas Center of Excellence that strives to provide leadership, quality patient education, and advanced care and services for pancreatic diseases, including hereditary pancreatitis. A Pancreas Center of Excellence also aims to research and develop new therapies and treatments. In order to provide the best possible care to our patients in this center, we are asking your opinions on the characteristics of a pancreatic center of excellence.

**4.4 How important to you are the following characteristics of an academic multidisciplinary pancreatic center of excellence?**

| | Not at all important | Slightly important | Somewhat important | Moderately important | Extremely important |
|---|---|---|---|---|---|
| Expert providers | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Nearby location | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Low financial costs | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Advanced treatment options | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| New research studies | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

## 5. Genetic Testing

The decision to pursue genetic testing for hereditary pancreatitis is a personal decision. There are a number of factors that motivate individuals to pursue genetic testing, as well as reasons that individuals choose not to get genetic testing. If you have not had genetic testing for hereditary pancreatitis and you are interested, we suggest that you speak with your physician and/or genetic counselor.

**Please respond to each question or statement by marking <u>one</u> box per row.**

**5.1 The following are reasons to pursue genetic testing for hereditary pancreatitis.**

| | Strongly disagree | Somewhat disagree | Neutral | Somewhat agree | Strongly agree |
|---|---|---|---|---|---|
| To help one's future generations | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| To learn more about yourself | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| To help others through research | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Improvement of personal medical care | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Presymptomatic testing to reduce uncertainty or anxiety | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Pressure from relatives | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| The disturbing emotions prompted by witnessing a relative afflicted with hereditary pancreatitis | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**5.2 How important to you are the following possible reasons to <u>NOT</u> get genetic testing for hereditary pancreatitis?**

| | Not at all important | Slightly important | Somewhat important | Moderately important | Extremely important |
|---|---|---|---|---|---|
| Health insurance discrimination | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Employment discrimination | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Being treated differently by family and friends | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Not wanting to know | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Testing is not useful | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Financial costs | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**5.3 Have you had genetic testing for your hereditary pancreatitis <u>and</u> were told the results of the genetic test(s)?**

☐ Yes(1) continue ☐ No(0) → *advance to question 5.3.5*

↓

**5.3.1 Was your genetic testing before or after you began to have physical symptoms of pancreatitis?**

- ☐ Before (1)
- ☐ After
- ☐ Not applicable

**5.3.2 Which of the following reasons to GET genetic testing was most important in your decision to test?**

**(Drop Down)**

- ☐ To help one's future generations
- ☐ To learn more about yourself
- ☐ To help others through research
- ☐ Improvement of personal medical care
- ☐ Presymptomatic testing to reduce uncertainty or anxiety
- ☐ Pressure from relatives
- ☐ The disturbing emotions prompted by witnessing a relative afflicted with HP
- ☐ None of the above

**5.3.3 Who recommended genetic testing to you? (please check <u>all</u> that apply)**

- ☐ Yourself
- ☐ A family member
- ☐ Your physician
- ☐ Other → If you selected other, please specify:

**5.3.4 Please describe the questions you had and the information, if any, that you were lacking after you were given your genetic test results.**

**5.3.5 What do you believe the chances are for a parent to pass on hereditary pancreatitis to his or her children?**

- ☐ 100%
- ☐ 50% (1 in 2)
- ☐ 25% (1 in 4)
- ☐ 0% (no chance)
- ☐ Unknown

## 6. Genetic Counseling

Genetic counselors are professionals trained to discuss testing options to determine if a person has a genetic disorder, as well as the chances that a genetic disorder can be passed on to a person's children. Genetic counselors also address the physical, mental, social and emotional impacts of a genetic condition. This section asks you about your experiences and perceptions on genetic counseling for hereditary pancreatitis.

**6.1 Have you spoken to a genetic counselor regarding hereditary pancreatitis?**

☐ Yes(1) continue ☐ No(0) → *advance to question 6.2*

↓

**6.1.1 Please describe the most useful aspects, if any, of your experience speaking with a genetic counselor.**

**6.1.2 Please describe the least useful aspects, if any, of your experience speaking with a genetic counselor.**

**6.2 Please describe the information, if any, that you think should be provided by a genetic counselor regarding hereditary pancreatitis.**

**6.3 Which of the following provided the most useful information to you about hereditary pancreatitis?**

- ☐ Yourself (researched disease on own)
- ☐ A family member
- ☐ A physician
- ☐ A genetic counselor
- ☐ Not applicable
- ☐ Other → If you selected other, please specify:

# APPENDIX E: QUESTIONNAIRE – CONTROLS (CONDENSED)

Date Consent Signed: __ __ / __ __ / __ __ __ __ Confirmed (Initials: _____ )

## 1. Risk and State Controls

**1.1 Do you have hereditary pancreatitis?**

☐( 1 ) Yes → please complete the questionnaire for participants with hereditary pancreatitis
☐( 0 ) No → *advance to question 1.2* ☐( - 3 ) Unknown → *advance to question 1. 2*

**1.2 Alcohol consumption:**

***NOTE: one shot of liquor, a mixed drink, one glass of wine or one beer is considered one drink.***

Was there ever a time when you drank beer, wine, wine coolers, liquor, or mixed drinks?

☐ (1) Yes ☐ (0) No (less than 20 drinks in your life) → *Advance to question 1.3*

**1.2.1** How many years did you drink alcohol in your life **(this could be consecutive or non-consecutive periods of time)?** ____ years

**Think about the period of life when you were drinking the most in your lifetime (this could be consecutive or non-consecutive periods of time). The next 4 questions are related to this period of your life:**

**1.2.2** How old were you when you began drinking **the most alcohol** in your life? ____

**1.2.3** On the **AVERAGE** about how many drinks would you have **on a drinking day**? ____

**1.2.4** How many **days per month** did you drink **at this level**? _____

**1.2.5** How long did you drink alcohol at the heaviest level? _____ years or _____ months

**1.2.6** Do you currently drink alcohol?

☐ (1)Yes ☐ (0)No → advance to question *1.3*

**1.2.6.1** On the AVERAGE about how many drinks would you have on a drinking day? _____ drinks

**1.2.6.2** How many days per month did you drink at this level? _____ days per month

**1.3 Tobacco use:**

Have you ever smoked cigarettes?

☐ (1) Yes ☐ (0) Never (less than 100 cigarettes in your life) → advance to question *1.4*

**1.3.1** What age did you start smoking? ____ years

**1.3.2** Do you currently smoke? ☐ (1) Yes → advance to question *1.3.3* ☐ (0) No

**1.3.2.3** What age did you quit smoking? ____ years

**1.3.3** On the average, how many cigarettes do / did you smoke per day? ____

**1.4 Current Height and weight**

Height: _____ feet, _____ inches

Usual Weight: _____ pounds.

Current Weight: _____ pounds.

Weight change over the past 6 months: ____pounds → ☐ increase in weight ☐ decrease in weight

**1.5 Have you been diagnosed with pancreatitis?**

☐( 1 ) Yes ☐( 0 ) No → *advance to question 2.1* ☐( - 3 ) Unknown → *advance to question 2.1*

↓

**1.5.1 Do you have abdominal pain from pancreatitis?**

☐( 1 ) Yes ☐( 0 ) No → *advance to question 2.1* ☐( - 3 ) Unknown → *advance to question 2.1*

↓

**1.5.1.1 What type of pain pattern do you have? (check <u>one</u>)**

☐( 1 ) usually **pain free**, but episodes of **mild to moderate pain**

☐( 2 ) constant **mild to moderate pain**

☐( 3 ) usually **free of abdominal pain**, but episodes of **severe pain**

☐( 4 ) constant **mild to moderate** pain ***plus*** episodes of **severe** pain

☐( 5 ) **constant severe** pain

## 2. Emotional Health

This section asks about the status of your emotional health, particularly feelings related to anxiety and depression. If you feel that you identify with any of the statements below, please let your physician know. You are not alone, and it may be useful for you to speak to a counselor and/or join a support group.

**Please respond to each question or statement by marking <u>one</u> box per row.**

### 2.1 Anxiety

**2.1.1 With regard to my health, in the past 7 days…**

| | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I felt fearful…….. | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I found it hard to focus on anything other than my anxiety…….. | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| My worries overwhelmed me…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I felt uneasy…….. | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |

### 2.2 Depression

**2.2.1 With regard to my health, in the past 7 days…**

| | Never | Rarely | Sometimes | Often | Always |
|---|---|---|---|---|---|
| I felt worthless…….. | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I felt helpless…….. | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I felt depressed…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |
| I felt hopeless…… | ☐ (1) | ☐ (2) | ☐ (3) | ☐ (4) | ☐ (5) |

## 2.3 Most important problems caused by hereditary pancreatitis:

**2.3.1 What is the most difficult problem for you to deal with because of hereditary pancreatitis in you or your family?**

**2.3.2 Why is the problem noted in the previous question the most important problem?**



### 3. Quality of Life

This survey asks for your views about your health. This information will help you keep track of how you feel and how you are able to do your usual activities. Answer every question by selecting the answer as indicated. If you are unsure about how to answer a question, please give the best answer you can.

3.1 In general, would you say your health is:

| Excellent (4) | Very good (3) | Good (2) | Fair (1) | Poor (0) |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

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

| | Yes limited a lot (2) | Yes limited a little (1) | No not limited at all (0) |
|---|---|---|---|
| 3.2 Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf | ☐ | ☐ | ☐ |
| 3.3 Climbing several flights of stairs | ☐ | ☐ | ☐ |

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

| | Yes (1) | No (2) |
|---|---|---|
| 3.4 Accomplished less than you would like | ☐ | ☐ |
| 3.5 Were limited in the kind of work or other activities | ☐ | ☐ |

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

| | Yes (1) | No (0) |
|---|---|---|
| 3.6 Accomplished less than you would like | ☐ | ☐ |
| 3.7 Did work or other activities less carefully than usual | ☐ | ☐ |

During the past 4 weeks, how much did pain interfere with your normal work (including both work outside the home and housework)?

3.8 Not at all (0) ☐ A little bit (1) ☐ Moderately (2) ☐ Quite a bit (3) ☐ Extremely (4) ☐

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

| | All of the time (4) | Most of the time (3) | Some of the time (2) | A little of the time (1) | None of the time (0) |
|---|---|---|---|---|---|
| **3.9** Have you felt calm and peaceful? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **3.10** Did you have a lot of energy? | ☐ | ☐ | ☐ | ☐ | ☐ |
| **3.11** Have you felt downhearted and blue? | ☐ | ☐ | ☐ | ☐ | ☐ |

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

| All of the time (4) | Most of the time (3) | Some of the time (2) | A little of the time (1) | None of the time (0) |
|---|---|---|---|---|
| ☐ | ☐ | ☐ | ☐ | ☐ |

## 4. Concerns and Perceptions

This sections asks about your concerns and perceptions related to hereditary pancreatitis. It is composed of four sections that ask about your perspectives on the medical, surgical, and financial aspects of hereditary pancreatitis, as well as your views on the characteristics of a Pancreas Center of Excellence (described below). Your concerns and perceptions are important to us to understand so that we can improve care for individuals with hereditary pancreatitis. The sub-categories in this section are as follows:

**A. Medical**

**B. Surgical**

**C. Financial**

**D. Pancreas Center of Excellence**

**Please respond to each question or statement by marking one box per row.**

**A. Medical**

**Please complete the following section only if you have been diagnosed with pancreatitis. If you have not been diagnosed with pancreatitis, please skip to section 4C (Financial).**

**4.1.1 Prior to today, how have you felt about the following medical problems related to pancreatitis?**

| | Not at all concerned | Slightly concerned | Somewhat concerned | Moderately concerned | Extremely concerned |
|---|---|---|---|---|---|
| Malnutrition | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Continuous Pain | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Narcotic Addiction | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Getting Adequate Treatment | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Diabetes | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Pancreatic Cancer | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**4.1.2 Please describe any concerns for pancreatitis that are not listed above.**

**4.1.3 How would you describe your chances to develop pancreatic cancer?**

| Extremely unlikely | Unlikely | Neutral | Likely | Extremely Likely |
|---|---|---|---|---|
| ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**4.1.4 Have you been counseled on your risks to develop cancer?**

☐**(1) Yes** ☐**(2) No** ☐**(3) Unknown**

## B. Surgical

**Please complete the following section if you have been diagnosed with pancreatitis. If you have not been diagnosed with pancreatitis, please skip to section 4C (Financial).**

A total pancreatectomy is a newer procedure that involves the removal of the entire pancreas. The decision to have a total pancreatectomy is dependent on a number of risks and benefits. We are looking to further understand the benefits, drawbacks, and outcomes of a total pancreatectomy, and this section asks for your opinions and experiences with this surgical procedure.

**4.2.1 Have you had or considered a total pancreatectomy with islet autotransplantation (TPIAT)?**

☐ Yes(1) ☐ No(0) → *go to question 4.3*

↓

**4.2.1.1 How important to you are the following benefits and drawbacks of a total pancreatectomy?**

| | Not at all important | Slightly important | Somewhat important | Moderately important | Extremely important |
|---|---|---|---|---|---|
| Lifetime enzymatic replacement therapy | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Reduction of abdominal pain | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Reduced risk for pancreatic cancer | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Preventing diabetes | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Acquiring diabetes | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Risks of undergoing surgery | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Financial costs | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**4.2.2 Have you had a total pancreatectomy with islet autotransplantation?**

☐ Yes(1) ☐ No(0) → *advance to question 4.3*

↓

**4.2.2.1 Please describe your reason for getting a total pancreatectomy and your experiences as compared to your expectations. (short answer)**

**4.2.2.2 The following questions ask about your experiences with a total pancreatectomy. Please check <u>one</u> box per question.**

a. <u>Compared to the time before your pancreatectomy and islet auto-transplantation</u>, how would you rate your health in general <u>now</u>?

1 ☐ Much better now
2 ☐ Somewhat better now
3 ☐ About the same
4 ☐ Somewhat worse now
5 ☐ Much worse now

b. <u>Compared to the time before your pancreatectomy and islet auto-transplantation</u>, how would you rate your level of pain <u>now</u>?

1 ☐ Much better now
2 ☐ Somewhat better now
3 ☐ About the same
4 ☐ Somewhat worse now
5 ☐ Much worse now

c. Would you recommend pancreatectomy and islet auto-transplantation to your family or friends if they needed care for a similar problem?

1 ☐ Definitely not
2 ☐ Probably not
3 ☐ Not sure
4 ☐ Probably yes
5 ☐ Definitely yes

d. How would rate the overall results of your pancreatectomy and islet auto-transplantation?

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

**C. Financial**

**4.3 How important to you and your family are the following financial burdens of hereditary pancreatitis?**

| | Not at all important | Slightly important | Somewhat important | Moderately important | Extremely important |
|---|---|---|---|---|---|
| Cost of medical treatment | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Costs of surgery | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| School or work limitations | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Requiring caretaker(s) | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**D. Pancreas Center of Excellence**

A Center of Excellence is an academic center that provides leadership, research, and the most up-to-date services in a given field. At the University of Pittsburgh, we are developing a Pancreas Center of Excellence that strives to provide leadership, quality patient education, and advanced care and services for pancreatic diseases, including hereditary pancreatitis. A Pancreas Center of Excellence also aims to research and develop new therapies and treatments. In order to provide the best possible care to our patients in this center, we are asking your opinions on the characteristics of a pancreatic center of excellence.

**4.4 How important to you are the following characteristics of an academic multidisciplinary pancreatic center of excellence?**

| | Not at all important | Slightly important | Somewhat important | Moderately important | Extremely important |
|---|---|---|---|---|---|
| Expert providers | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Nearby location | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Low financial costs | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Advanced treatment options | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| New research studies | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

## 5. Genetic Testing

The decision to pursue genetic testing for hereditary pancreatitis is a personal decision. There are a number of factors that motivate individuals to pursue genetic testing, as well as reasons that individuals choose not to get genetic testing. If you have not had genetic testing for hereditary pancreatitis and you are interested, we suggest that you speak with your physician and/or genetic counselor.

**Please respond to each question or statement by marking <u>one</u> box per row.**

**5.1 The following are reasons to pursue genetic testing for hereditary pancreatitis.**

| | Strongly disagree | Somewhat disagree | Neutral | Somewhat agree | Strongly agree |
|---|---|---|---|---|---|
| To help one's future generations | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| To learn more about yourself | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| To help others through research | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Improvement of personal medical care | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Presymptomatic testing to reduce uncertainty or anxiety | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Pressure from relatives | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| The disturbing emotions prompted by witnessing a relative afflicted with hereditary pancreatitis | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**5.2 How important to you are the following possible reasons to <u>NOT</u> get genetic testing for hereditary pancreatitis?**

| | Not at all important | Slightly important | Somewhat important | Moderately important | Extremely important |
|---|---|---|---|---|---|
| Health insurance discrimination | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Employment discrimination | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Being treated differently by family and friends | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Not wanting to know | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Testing is not useful | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |
| Financial costs | ☐(1) | ☐(2) | ☐(3) | ☐(4) | ☐(5) |

**5.3 Have you had genetic testing for your hereditary pancreatitis <u>and</u> were told the results of the genetic test(s)?**

☐ Yes(1) continue ☐ No(0) → *advance to question 5.3.5*

↓

**5.3.1 Was your genetic testing before or after you began to have physical symptoms of pancreatitis?**

- ☐ Before (1)
- ☐ After
- ☐ Not applicable

**5.3.2 Which of the following reasons to GET genetic testing was most important in your decision to test?**

**(Drop Down)**

- ☐ To help one's future generations
- ☐ To learn more about yourself
- ☐ To help others through research
- ☐ Improvement of personal medical care
- ☐ Presymptomatic testing to reduce uncertainty or anxiety
- ☐ Pressure from relatives
- ☐ The disturbing emotions prompted by witnessing a relative afflicted with HP
- ☐ None of the above

**5.3.3 Who recommended genetic testing to you? (please check <u>all</u> that apply)**

- ☐ Yourself
- ☐ A family member
- ☐ Your physician
- ☐ Other → If you selected other, please specify: ☐

**5.3.4 Please describe the questions you had and the information, if any, that you were lacking after you were given your genetic test results.**

**5.3.5 What do you believe the chances are for a parent to pass on hereditary pancreatitis to his or her children?**

- ☐ 100%
- ☐ 50% (1 in 2)
- ☐ 25% (1 in 4)
- ☐ 0% (no chance)
- ☐ Unknown

## 6. Genetic Counseling

Genetic counselors are professionals trained to discuss testing options to determine if a person has a genetic disorder, as well as the chances that a genetic disorder can be passed on to a person's children. Genetic counselors also address the physical, mental, social and emotional impacts of a genetic condition. This section asks you about your experiences and perceptions on genetic counseling for hereditary pancreatitis.

**6.1 Have you spoken to a genetic counselor regarding hereditary pancreatitis?**

☐ Yes(1) continue ☐ No(0) → *advance to question 6.2*

↓

**6.1.1 Please describe the most useful aspects, if any, of your experience speaking with a genetic counselor.**

**6.1.2 Please describe the least useful aspects, if any, of your experience speaking with a genetic counselor.**

**6.2 Please describe the information, if any, that you think should be provided by a genetic counselor regarding hereditary pancreatitis.**

**6.3 Which of the following provided the most useful information to you about hereditary pancreatitis?**

- ☐ Yourself (researched disease on own)
- ☐ A family member
- ☐ A physician
- ☐ A genetic counselor
- ☐ Not applicable
- ☐ Other → If you selected other, please specify:

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