AN INVESTIGATION INTO THE UTILITY OF SELF-REPORTED PAIN AND QUALITY OF LIFE FOR PATIENTS WITH PANCREATITIS.

by

Megan Leigh Marshall

BS, The Pennsylvania State University, 2004

Submitted to the Graduate Faculty of

The Graduate School of Public Health in partial fulfillment

of the requirements for the degree of

Master of Science

University of Pittsburgh

2006

UNIVERSITY OF PITTSBURGH

GRADUATE SCHOOL OF PUBLIC HEALTH

This thesis was presented

by

Megan Leigh Marshall

It was defended on

April 6, 2006

and approved by

Thesis Advisor

M. Michael Barmada, PhD
Associate Professor
Department of Human Genetics
Graduate School of Public Health
University of Pittsburgh

Committee Members

David C Whitcomb, MD, PhD
Professor
Department of Gastroenterology, Hepatology, and Nutrition
Department of Human Genetics
University of Pittsburgh

John W Wilson, PhD
Associate Professor
Department of Biostatistics
Graduate School of Public Health
University of Pittsburgh

Erin Fink, MS
Genetic Counselor/ Research Coordinator
Hereditary Pancreatitis Study
Hillman Cancer Center
University of Pittsburgh

M Michael Barmada, PhD

AN INVESTIGATION INTO THE UTILITY OF SELF-REPORTED PAIN AND QUALITY OF LIFE FOR PATIENTS WITH PANCREATITIS.

Megan L Marshall, MS

University of Pittsburgh, 2006

Hereditary pancreatitis is characterized by episodes of pancreatic inflammation accompanied by unrelenting abdominal pain, usually beginning in childhood. Therefore, this emerging population of individuals is affected with a chronic pain condition affecting global quality of life. A multidisciplinary approach, including psychosocial and behavioral factors, is necessary to elicit responses to and treat chronic pain. Improving overall quality of life is an important outcome of interventions for chronic conditions. Health-related quality of life reflects an individual's physical and mental well-being. This study documents the pain levels and quality of life of individuals with both hereditary and sporadic pancreatitis. Data from 73 individuals with hereditary pancreatitis and 271 individuals with sporadic pancreatitis who participated in the Hereditary Pancreatitis Study and the North American Pancreatitis Study 2 were examined for this study. The questionnaires addressed each subjects' report of quality of life, severity and duration of pain, alcohol use, tobacco use, and diagnosis of diabetes. Patient responses were analyzed using a battery of comparative analyses. The SF-12® health survey was analyzed using an algorithm for standardizing and weighting the physical and mental health scores. Pain and quality of life measures were compared to each other, as well as to several commonly measured environmental influences on health using correlation analysis, regression

analysis, and the Mann-Whitney U test. As hypothesized, individuals with familial pancreatitis reported worse pain and poorer overall quality of life than individuals with sporadic pancreatitis. Factors influencing the measure of pain include the duration, severity, frequency, and character. Other findings include correlations between (a) physical quality of life and gender, smoking, and alcohol, (b) pain and age, and (c) pain frequency and tobacco and alcohol use. This study will provide public health significance because the information can potentially assist health care professionals who work with individuals with pancreatitis and chronic pain, and who are assessing the necessity of psychosocial intervention or support services.

TABLE OF CONTENTS

PREFACE ..... **xii**

1.0 INTRODUCTION **1**

1.1 SPECIFIC AIMS **3**

1.2 BACKGROUND AND SIGNIFICANCE **4**

1.2.1 Pancreatitis Studies **4**

1.2.2 Features of Pancreatitis **5**

1.2.3 Features of Hereditary Pancreatitis **5**

1.2.3.1 Risk Factors and Causes of Pancreatitis **6**

1.2.3.2 Clinical Presentation and Diagnosis **8**

1.2.3.3 Genetics of Hereditary Pancreatitis **9**

1.2.3.4 Genetic Testing **11**

1.2.3.5 Management and Treatment of Hereditary Pancreatitis" **12**

1.2.4 Chronic Pain **13**

1.2.5 The Short-Form 12® Health Survey (Version 1) **15**

1.2.6 Support Groups **15**

1.2.6.1 History of Self-Help and Support Groups in the United States **15**

1.2.6.2 Genetic Support Groups **17**

2.0 EXPERIMENTAL DESIGN AND METHODS **18**

2.1 QUESTIONNAIRES 18

2.2 DATA ANALYSIS 19

3.0 RESULTS 21

3.1 DEMOGRAPHICS 21

3.2 ASSIGNED VARIABLES FOR ANALYSIS 23

3.3 SPECIFIC AIM 1 24

3.3.1 Combined Pain Index 24

3.3.2 SF-12® v1 Analysis 27

3.3.3 Impact of Pain on Quality of Life 30

3.3.4 Impact of Pain Duration and Severity on Quality of Life 33

3.3.5 Correlation of Pain and Quality of Life 38

3.4 SPECIFIC AIM 2 40

3.4.1 Comparison of Covariates 40

3.4.2 Regression with Environmental Covariates 42

4.0 DISCUSSION 47

4.1 SPECIFIC AIM 1 47

4.2 SPECIFIC AIM 2 52

4.2.1 Patient Interest 55

4.3 LIMITATIONS 57

5.0 FUTURE RESEARCH OPPORTUNITIES 60

APPENDIX A 63

TABLES CORRESPONDING TO TEXT

APPENDIX B 64

FIGURES CORRESPONDING TO TEXT

APPENDIX C 65

INFORMED CONSENT FOR NAPS2 STUDY

APPENDIX D 76

NAPS2 QUESTIONNAIRE

APPENDIX E 88

INFORMED CONSENT FOR HP STUDY

APPENDIX F 103

HP QUESTIONNAIRE

BIBLIOGRAPHY 121

LIST OF TABLES

Table 1. Demographic Information..... 22

Table 2. Assigned Variables 23

Table 3. Combined Pain Rank Scores..... 24

Table 4. Pain Scores Based on Severity and Duration..... 33

Table 5. Counts of all Covariates by Combined Pain Rank Score 38

Table 6. Total Pairwise Correlation of Pain and QOL..... 38

Table 7. Total Pairwise Correlation of QOL, Pain, and Covariates 39

Table 8. Total Population Comparison of Covariates..... 40

Table 9. Total Population Quality of Life compared with Severity and Duration of Pain 40

Table 10. Familial Quality of Life compared with Severity and Duration of Pain 41

Table 11. Non-Familial Quality of Life compared with Severity and Duration of Pain 41

Table 12. Familial Comparisons of Covariates..... 42

Table 13. Non-Familial Comparisons of Covariates 42

Table 14. Regression Analysis of Pain Measure and Binary Variables 43

Table 15. Regression Analysis of Physical Health Score with Binary Variables and Genotype . 44

Table 16. Regression Analysis of Physical Health Score with Binary Variables..... 44

Table 17. Regression Analysis of Mental Health Score with Binary Variables and Genotype.... 45

Table 18. Regression Analysis of Physical Health Scores with Binary Variables 45

Table 19. Regression Analysis of Total QOL Scores with Binary Variables and Genotype 46

Table 20. Regression Analysis of Total Quality of Life Scores with Binary Variables 46

Table 21. Quality of Life Indexes for Common Diseases 49

Table 22. SF-12® Mean Scores- 1990 General Population 63

LIST OF FIGURES

Figure 1. Total Pain Measure 25

Figure 2. Genotype Distribution 26

Figure 3. Total Combined Pain Rank Stratified by Genotype 26

Figure 4. Total Physical Quality of Life 27

Figure 5. Total Mental Quality of Life 28

Figure 6. Familial QOL Outcomes 28

Figure 7. Non-Familial QOL Outcomes 29

Figure 8. TotalQuality of Life Outcomes 29

Figure 9. Familial versus Non-Familial Quality of Life 30

Figure 10. Total Physical QOL Versus Combined Pain Rank 31

Figure 11. Total Physical Quality of Life Stratified by Type of Pain 31

Figure 12. Total Mental QOL Versus Combined Pain Rank 32

Figure 13. Total Mental Quality of Life Stratified by Type of Pain 33

Figure 14. Total Physical Quality of Life Stratified by Pain Severity 34

Figure 15. Familial Mental QOL Stratified by Pain Severity 34

Figure 16. Non-Familial Mental QOL Stratified by Pain Severity 35

Figure 17. Total Mental QOL Stratified by Pain Duration 35

Figure 18. Familial Mental QOL Stratified by Pain Duration 36

Figure 19. Familial Physical QOL Stratified by Pain Duration 36

Figure 20. Non-Familial Mental QOL Stratified by Pain Duration 37

Figure 21. Non-Familial Physical QOL Stratified by Pain Duration 37

Figure 22. Trypsin Molecule 64

PREFACE

I would first like to acknowledge Dr. Michael Barmada, my thesis advisor and chair, for his hard work, patience, and guidance with this research project. Thank you for helping me mold my original ideas to make them an interesting and meaningful topic for the pancreatitis community.

I would also like to thank my thesis committee for your support and assistance with this project, and all of the members of the NAPS2 and HP study research teams for searching for data, help with data entry, and their thoughts and input regarding my project.

Lastly, I would like to thank all of the participants of the North American Pancreatitis Study and Hereditary Pancreatitis for your time and participation in research on pancreatitis.

1.0 INTRODUCTION

This investigation was undertaken to examine the factors influencing the perception of pain and the effect on quality of life in individuals with pancreatitis, with an eventual goal of identifying individuals who might benefit from involvement with a support group. Hereditary pancreatitis (HP) is an autosomal dominant condition characterized by acute episodes of pancreatic inflammation, which can progress to chronic pancreatitis. It is estimated that at least 1,000 individuals in the United States are affected with hereditary pancreatitis.[1] Most pancreatitis is caused by alcohol, gallstones, or unknown factors. However, hereditary pancreatitis is caused by an abnormal form of trypsin which often is activated in the pancreas. Generally, individuals with a hereditary form of pancreatitis begin experiencing recurrent attacks in childhood.[2] As a result, there is a population of individuals who are affected with a chronic pain condition that affects their general quality of life. As with all genetic diseases, a hereditary pancreatitis predisposition has implications for other family members. Therefore, these families also have to deal with issues such as the communication of genetic information to at-risk family members, the possibility of having transmitted the predisposition to children, and the guilt that may be associated with discovering that other family members also have an increased risk of pancreatitis, and subsequently pancreatic cancer.

The features of pancreatitis are varied and include acute attacks of pain ranging from mild abdominal discomfort to life-threatening episodes of pancreatic necrosis and intractable

pain.[3] A multidisciplinary approach comprised of psychosocial and behavioral factors that might influence the responses to chronic pain seems necessary in order to treat chronic pain successfully.[4] Health-related quality of life is a multidimensional theoretical construct reflecting an individual's global physical and mental well-being.[5] The impact of chronic pain and its effect on emotional, physical and social functioning are addressed in quality of life surveys. Improving overall quality of life is an important outcome of interventions, particularly for persons suffering from pain related to hereditary pancreatitis. Support groups are one available intervention.[6] Although support groups, in general, are widely available for a variety of hereditary diseases, groups tailored to individuals with a hereditary predisposition to pancreatitis are rare.

Major aims of support groups are to improve physical function, coping skills, and quality of life in patients suffering from chronic pain. Group approaches offered to chronic pain patients are common and give several benefits, such as mutual support, feedback, and active participation.[29, 31] In summary, there may be a need for support services that are specific to this population of individuals.

More research efforts are needed to clarify further whether individuals with chronic pain report a quality of life that necessitates intervention services. This study was designed to document the level of patient reported pain and patient reported quality of life from individuals with pancreatitis. The association of these two factors will allow researchers to explore whether intervention in this population is warranted, as well as eventually to develop a protocol for targeting patients who would benefit based on these variables. It was expected that Hereditary Pancreatitis patients would report a severe level of chronic pain and a poor overall quality of life to support the need for a psychosocial and behavioral intervention in the form of a support group.

1.1 SPECIFIC AIMS

Specific Aim 1:	To document the levels of patient reported pain and patient reported quality of life (using the Short Form-12® Quality of Life survey) for individuals with pancreatitis.
Hypothesis:	Patients with Hereditary Pancreatitis will report high levels of chronic pain and poor quality of life in both physical and mental subsets.
Plan:	HP study and NAPS2 study participants filled out a questionnaire; patients are required to assess their pattern of pain based on level of severity and frequency. Questions assessing physical and mental well-being are also included. Patient-reported pain will be compared between those who reported hereditary pancreatitis versus non-hereditary pancreatitis. Pain level and patient genotype will also be compared.
Specific Aim 2:	To explore whether the need for intervention services such as the implementation of a support group for patients with Pancreatitis exists.
Hypothesis:	Patients with chronic pain attributed to HP would benefit from psychosocial and behavioral treatment in the context of a support system.

Plan: The responses to thirteen questions involving pain and the SF-12® Version 1 survey will be analyzed to see if measures are severe enough to warrant additional support.

1.2 BACKGROUND AND SIGNIFICANCE

1.2.1 Pancreatitis Studies

The Hereditary Pancreatitis Study was initiated by David C. Whitcomb, MD, PhD in 1995 at the University of Pittsburgh. The study's original aim was to evaluate the distribution of HP in the United States and to determine the major gene mutation that causes HP. Families were recruited through referrals from collaborating centers, other physicians, and self-referral of patients. Family histories were constructed, questionnaires completed and blood samples drawn for each proband and participating family members. Over 200 families have been recruited to date. Following studies have looked at new approaches to prevention and therapy.[7]

The North American Pancreatitis Study II is a multi-site collaborative study consisting of 20 study centers across the United States. The NAPS2 study was initiated in 2002 in order to determine the genetic and environmental factors contributing to pancreatitis. Participants were recruited from collaborating centers. The study has enrolled over 1,000 patients with acute or chronic pancreatitis.[8]

1.2.2 Features of Pancreatitis

Acute pancreatitis is a potentially life-threatening condition presenting with severe abdominal pain. Acute pancreatitis is initiated with injury to the pancreas, followed by an acute inflammatory response and associated complications. When a person has acute pancreatitis the amounts of amylase and lipase in the blood are often elevated. With pancreatic rest, IV fluids, and pain medications recovery occurs within approximately a week. After acute pancreatitis the pancreas typically returns to normal, but scarring may occur. Patients with recurrent acute pancreatitis are at risk of developing chronic pancreatitis. Individuals with chronic pancreatitis are at increased risk of developing pancreatic cancer. The risk of pancreatic cancer in hereditary cases of pancreatitis is greater than 50 times the general population risk.[17]

Chronic pancreatitis occurs following persistent attacks of acute pancreatitis. Chronic pancreatitis is characterized by irreversible scarring of the pancreas with a permanent loss of pancreatic function and is often associated with unrelenting abdominal pain.[16] The permanent structural changes in the pancreas lead to impairment of exocrine and endocrine function. When the pancreas has a considerable amount of scarring, individuals are unable to digest food properly (exocrine insufficiency) due to acinar cell loss and have trouble controlling their blood sugar (diabetes mellitus) due to islet cell loss. [16]

1.2.3 Features of Hereditary Pancreatitis

Hereditary pancreatitis (HP) is a rare and unusual form of acute and chronic pancreatitis. HP accounts for only 2-3% of all cases of chronic pancreatitis. It is estimated that at least 1,000

individuals in the United States are affected with hereditary pancreatitis. Onset of attacks can begin at any age, but typically begin within the first two decades of life, with pain being one of the most distressing symptoms. Various options are available for treatment of pain, but they provide limited relief for short periods of time.

1.2.3.1 Risk Factors and Causes of Pancreatitis

The pathogenesis of pancreatitis appears to be multifactorial, meaning that the risk to develop pancreatitis is heavily influenced and dependent on the interaction of hereditary and environmental exposures.

Acute pancreatitis can occur secondary to several different factors. A long history of alcohol use (usually 10 to 20 years) is the most frequently observed cause of acute pancreatitis. Individuals who have undergone surgery or who have had trauma to the abdominal area may develop acute pancreatitis. Also, acute pancreatitis can be drug-induced. Some individuals who are on certain medications are at higher-risk for developing pancreatitis, including: patients with AIDS on DDI, with Crohn's disease on 6-mercaptopurine, or on ACE inhibitors with a history of angioedema. In addition, individuals who have prior episodes of biliary colic and/or cholangitis are at increased risk for developing gallstones and in turn pancreatitis. Finally, individuals with familial hypertriglyceridemia or sporadic hypertriglyceridemia are at an increased risk of developing acute pancreatitis.[9] In about 15% of cases, the cause of acute pancreatitis is unknown.

The TIGAR-O risk factor classification system lists several major factors associated with chronic pancreatitis.[10] These risk factors are categorized into six groups.

- Toxic-Metabolic
    - Alcohol abuse[11] (Alcohol abuse is the cause of 70-80% of pancreatitis cases.)

    - Chronic smoking[12]
    - Hypercalcemia
    - Hyperlipidemia
    - Chronic renal failure
    - Medications
    - Toxins
- Idiopathic
    - Early/late onset
    - Tropical
- Obstructive
    - Panreatic Divisum
    - Sphincter of Oddi disorders
    - Duct Obstruction
    - Preampullary duodenal wall cysts
    - Posttraumatic pancreatic duct scars
- Systemic disease (lupus erythematosus, cystic fibrosis, and hyperparathyroidism)
- Autoimmune
    - Sjogren's syndrome
    - Primary biliary cirrhosis
    - Isolated autoimmune chronic pancreatitis[13]
- Recurrent and severe acute pancreatitis
    - Postnecrotic
    - Recurrent acute pancreatitis
    - Vascular diseases/ischemic
    - Postirradiation
- Genetic
    - Autosomal Dominant (*PRSS1*)
    - Autosomal Recessive (*SPINK1*/CFTR)

All of these risk factors for the development of chronic pancreatitis are therefore risk factors for pancreatic cancer. Approximately 32,180 patients are diagnosed with pancreatic adenocarcinoma each year; it is the fourth leading cause of cancer deaths among Americans.[14] Generally, pancreatic cancer is rare before the age of 45, but hereditary factors can predispose an individual to pancreatic cancer with a 40% lifetime risk to developing pancreatic cancer. Pancreatic cancer also aggregates in some families without hereditary pancreatitis, but with some other underlying hereditary cause.

1.2.3.2 Clinical Presentation and Diagnosis[15,16,17]

Pancreatitis causes structural changes in the pancreas, which lead to a disruption of endocrine and exocrine function. The three primary clinical manifestations of chronic pancreatitis are abdominal pain, diabetes and pancreatic insufficiency, though other health problems result as well.

Abdominal pain is the hallmark feature of chronic pancreatitis. The pain is usually epigastric and radiates to the back. Abdominal pain due to pancreatitis has been described by patients as stabbing, boring, burning, sharp, and gnawing. Fever, nausea, vomiting, and marked elevation of serum amylase often accompany the abdominal pain. The pain is typically the worst in the 15-30 minutes directly following eating. It may occur in attacks, but as pancreatitis progresses, individuals usually experience continuous pain.[18]

The type and pattern of pain varies from patient to patient. Most individuals fall within two patterns of pain. Some experience episodes of pain that last several days. Between these episodes are periods without pain that span several months to a few years. The second pattern of pain is characterized by prolonged periods of pain occurring on a daily basis with episodes of

severe pain. Not all patients affected by pancreatitis experience pain, although it is the most common clinical complaint.

Pancreatic insufficiency is the second major clinical feature of pancreatitis. Proper digestion of complex foods is dependent on adequate pancreatic exocrine function. Individuals with pancreatitis may have severe exocrine dysfunction. Clinically significant symptoms of exocrine dysfunction do not typically occur until the majority, approximately 90%, of pancreatic function is lost.[19] As a result of exocrine insufficiency, fat malabsorption causes loose, greasy, foul smelling stools that are difficult to flush.

Intolerance to glucose progressing to diabetes mellitus occurs frequently in pancreatitis. Most patients eventually require treatment with insulin. The difference between diabetes mellitus associated with HP and type 1 diabetes is an increased risk of hypoglycemia due to the affected pancreatic alpha cells that still produce glucagon.

Other health complications of pancreatitis include bile duct or duodenal obstruction, pseudocyst formation, pancreatic ascites or pleural effusion, pseudoaneurysms, and splenic vein thrombosis.

Differentiation between hereditary pancreatitis and familial paroxysmal peritonitis (familial mediterranean fever characterized by paroxysmal attacks of fever and inflammation.) is difficult except for the occurrence of an elevation in serum amylase associated with pancreatitis.[18] However, Mediterranean fever is rare in the United States.

1.2.3.3 Genetics of Hereditary Pancreatitis[20,21, 22, 23]

Hereditary pancreatitis is an autosomal dominant genetic disorder; the symptoms of HP are caused by a change in a specific gene that is passed through a family. Sixty to seventy percent of hereditary pancreatitis families have been found to have a mutation in a single gene. The

cationic trypsinogen gene (*PRSS1*) has been localized to chromosome 7q35 and produces the cationic trypsinogen enzyme, which breaks down the protein in food. Currently, two common mutations and six more uncommon mutations that are associated with hereditary pancreatitis have been identified. The known common mutations are R117H and N291. It is thought that some individuals with hereditary pancreatitis do not have a mutation in this gene; thus, there are most likely additional genes and mutations that cause HP. There is a great deal of variety in the frequency and severity of pancreatic attacks for people who inherit a mutation in the *PRSS1* gene, with some individuals never developing symptoms. Individuals who have inherited either of the common mutations have an 80% risk of developing clinical symptoms of HP by age 20 years. Mutations in the serine protease inhibitor, Kazal type, 1 (*SPINK1*), a pancreatic trypsin inhibitor, have also been identified in HP patients.[24]

Trypsin plays an important role in digestion. The enzyme trypsinogen is made in the pancreas in an inactive form. Trypsinogen is activated to trypsin in the intestine and in turn activates all other digestive enzymes (Figure 23- Appendix B). If trypsinogen is activated in the pancreas (trypsin), activation of other digestive enzymes can cause the pancreas to begin digesting itself. Normally, active trypsin destroys itself by cutting at R122 (arginine 122); thus, splitting trypsin and inactivating it. In hereditary pancreatitis, R122 is mutated to H122 (histidine 122) blocking the splice site and, therefore trypsin cannot be inactivated. This leads to acute pancreatitis. The other known trypsin mutation, N291 is a substitution in the trypsin molecule. This mutation facilitates pancreatitis by causing early activation.

SPINK1 is a protective measure that acts as a trypsin inhibitor that neutralizes about 20% of pancreatic trypsin activity. *SPINK1* codes for pancreatic secretory trypsin inhibitor (PSTI), which is a serine protease inhibitor that inhibits premature activation of trypsin in the pancreas.

Mutations in these inhibitory mechanisms are associated with juvenile chronic hereditary pancreatitis, and are also associated with a complex autosomal recessive pattern of inheritance.

Prior to the discovery of genes associated with hereditary pancreatitis, the cystic fibrosis transmembrane conductance regulator (CFTR) gene was identified as being associated with acute and chronic idiopathic pancreatitis. Many groups have identified and confirmed this association between mutations in the CFTR gene and recurrent pancreatitis.[25] THE CFTR mutations prevent water from entering the pancreas due to osmosis. Thus, the enzymes are not flushed from the pancreas to the intestine. Trypsinogen is then activated while still in the pancreas causing digestion.

Proteinase Activated Receptors (*PAR*) are cell surface receptors that are known to play a critical role in pancreas inflammation. The proteinase-activated receptors are a family of four G-protein-coupled receptors that are activated by trypsin. PAR is expressed in the pancreas and small intestine and plays a role in inflammation. PAR has been shown to be involved with the activation of nociceptive neurons in the thoracic dorsal root ganglia. Mutations in the PAR gene induce a pain response in the pancreas. Therefore, PAR plays in important part of the pathogenesis of pancreatic pain.[26, 27]

1.2.3.4 Genetic Testing

Genetic testing for hereditary pancreatitis is very important because it is clinically indistinguishable from other causes of pancreatitis. Genetic testing, in additiona to other tests, can also help differentiate possible diagnoses of abdominal pain including: cystic fibrosis, hyperlipidemia, familial hyperchylomicronemia, homocystinuria, hyperparathyroidism, and familial hypocalciuric hypercalcemia. Site specific genetic testing for mutations in the cationic trypsinogen gene (*PRSS1*) is based on polymerase chain reaction (PCR) amplification of two

exons followed by restriction-enzyme digestion of the products. In the majority of cases, hereditary pancreatitis can be attributed to severe mutations such as R122H and N291. Not all individuals with early onset severe disease have a corresponding genotype.

Genetic testing is available through Ambry Genetics. To account for all genetic variations in the major pancreatic enzyme *PRSS1* gene, analysis of the entire coding region is performed. In addition to analysis of the *PRSS1* gene, Ambry provides complete sequencing of CFTR and *SPINK1* because they have been identified as risk factors in chronic pancreatitis. The comprehensive genetic test for pancreatitis is capable of detecting greater than 98% of all (greater than 1,300) known mutations in the CFTR gene, as well as providing complete sequencing of *PRSS1* and *SPINK1*.[28]

Genetic testing is indicated when individuals have recurrent attacks of acute pancreatitis with no explanation, unexplained chronic pancreatitis, a family history of pancreatitis, and/or an unexplained episode of pancreatitis in childhood. Genetic testing guidelines for hereditary pancreatitis are published by The National Guideline Clearinghouse.[29]

1.2.3.5 Management and Treatment of Hereditary Pancreatitis[30,31,32]

Most therapies and treatments for pancreatitis are aimed at relief of pain, correction of pancreatic endocrine and exocrine insufficiency, and management of resulting complications. Control of abdominal pain can prove difficult due to the wide spectrum of presentation. The heterogeneity of the population, subjective nature of pain, and poor understanding of pathophysiology are all obstacles in studying the effectiveness of pain management. In general, pain management should proceed in a stepwise approach including: establishing a secure diagnosis, pancreatic enzyme supplementation, and analgesics administration. Pancreatic enzymes such as Creon, Pancrease, and Violiase are helpful in improving digestion and reducing diarrhea and pain for

patients with more advanced disease.[33] Dietary treatment is also used to help control pain with digestion including the consumption of small meals that are high in carbohydrates and low in protein and fat. Patients with persistent symptoms can be treated with more invasive options in specialized centers. Furthermore, many centers use interdisciplinary approaches to cover all aspects of pain management. Some available modalities include: medical management, acupuncture, radiographically guided injections, relaxation training and imagery, intravenous infusions, neuromodulation, and implantable technologies. Although there is no established standard of care, the American Gastroenterological Association (AGA) has set forth management guidelines in the form of an algorithm (Figure 24-Appendix B) on the treatment of pain in chronic pancreatitis.

1.2.4 Chronic Pain

Managing patients with chronic pain is a challenge to health professionals. Roughly 7-11% of the general population is affected by chronic pain. Generally, multiple interventions are required to reduce pain level.[34] Previous studies on chronic pain have showed that pain has a profound effect on the lives of those with chronic conditions. Many people with chronic pain believe that it affects their emotional well being. People in pain generally experience feelings of depression, anxiety, anger, helplessness and/or hopelessness. These effects of pain can interact with and exacerbate an already difficult situation by increasing pain.[21] Patients report that they feel they are not believed about their chronic pain condition and its impact on their lives. Individuals with chronic pain are often unaware of what support services and treatments exist. Participants found it helpful to attend group sessions with health care professionals to learn how to cope with chronic pain. Coping is defined as the intentional and effortful attempt to adapt pain.[35] Part of

the coping process is the recognition that a cure for chronic pain is very unlikely and the need to focus on non-pain aspects of life rather than pain aspects.[36] The level and severity of pain may control the effectiveness of coping strategies.

Patients with mild to moderate pain rather than high-intensity pain have greater feelings of control that allow for better social functioning. The acceptance of pain has a contribution to mental well-being beyond the effect of pain severity. Ilse et. al. found that high levels of mental and physical health were related to lower levels of pain severity when evaluated by the SF-36® health survey. The study also showed that greater acceptance of pain was associated with better mental health.

Herrmann et. al. conducted a study investigating the coping skills of HP patients. The study concluded that patients with HP are more likely to use passive coping strategies than active coping strategies. Passive coping strategies do not require effort (such as worrying). Active coping strategies do require effort and focus, such as engaging in activities. People who use active coping strategies feel more control over situations where they have no control, for example pain. This approach to coping with pain improves overall daily functioning. Increased emotional tension, as a result of the level of pain combined with the management of everyday stressors (for example: school, work, children), interferes with the ability to use active coping methods. The stressors are too physically, mentally, and emotionally taxing, which hinder attempts at active coping strategies. Overall, Herrmann found that an outlet such as a support group or therapy would allow these patients to learn how to cope with a chronic illness.[37]

1.2.5 The Short-Form 12® Health Survey (Version 1)

The SF-36® survey is a brief, comprehensive measure of general health status designed for use in clinical practice and research, evaluation of health policy, and general population surveys. The SF-12® Health Survey is a subset of the SF-36® designed at The Health Institute in 1994. The survey was designed to measure general health status, including physical, social, and emotional functioning from the patient's point of view. This subset provides only physical and mental health subscores, not individual domain scores.[38] The reliability and validity of the subset version is slightly lower than that of the SF-36®, but when used with large sample size and an objective to monitor overall physical and mental health outcomes, the SF-12® Health Survey is a satisfactory alternative. The survey includes eight concepts commonly represented in health surveys: physical functioning, role functioning physical, bodily pain, general health, vitality, social functioning, role functioning emotional, and mental health.[39] Each dimension of the survey is scored on a scale from 0 to 100, with higher scores indicating better health.[40] The SF-12® can apply in any context of age or disease and is therefore a useful tool for surveying the general population. The general health survey has been used to analyze quality of life in many contexts. In cases of chronic conditions and postoperative patients this tool has been able to show marked improvement in the patient's quality of life.[41]

1.2.6 Support Groups

1.2.6.1 History of Self-Help and Support Groups in the United States

Support groups are often comprised of individuals who share experiences or who face the same issues. A support group is a group that meets for the purpose of exchanging information or

advice, and providing emotional support. Support groups focus on the support and education of the group as a whole. The group is typically led by a health professional and is likely to be linked to a larger, formal organization, although groups can be led and organized by its members.[42] Aspects of the group's focus include personal growth or change. Such groups provide many benefits: a chance to learn from others' experience, suggestions about coping, support and encouragement, friendship, and reduction of guilt.

Dating back to the 1800's, immigrants arriving to the United States sought out others that shared common backgrounds for support.[43] These groups joined to address many issues such as language and religion problems and feelings of intolerance and isolation.

The majority of documented support groups deal with substance-related addiction. Over time, substance control self-help groups have been established to cater to different subgroups of people, and different problem areas. With the establishment of Alcoholics Anonymous in 1935, self-help groups gained increasing popularity. Health care professionals began to play an important role in the formation of self-help or support groups. Many health care fields attempted to use these groups to offer non-directive services to patients. Using this theory, these services began to allow patients to their own advocates in health management. These changes led to the increased and ever growing availability of support groups for patients.

Many research studies have been conducted analyzing the effectiveness of chronic illness support groups; most studies have shown that members benefit from participation.[44] Group participants reported decreased psychological problems, a more positive outlook on life, greater satisfaction with their medical care, increased self-esteem, and decreased feelings of shame. One study conducted on a chronic illness support group for pain reported that members experienced significantly less disability and that the support group helped them in their daily lives. In

addition to benefits previously cited, members reported learning about coping strategies, learning increased motivation, and learning to adapt to life with pain.[23]

1.2.6.2 Genetic Support Groups

Following the evolution of support groups, a large number of organizations were formed to deal with the issues accompanying genetic diseases. The occurrence of genetic disease may have a strong impact on an individual because they usually affect a person throughout his/her life, have implications for more than one family member, involve complex scientific concepts, and have no cure. The effects of a genetic disease on an entire family system may include powerful feelings of guilt, shame, fear, and blame. Often, individuals with a genetic disease experience feelings of social isolation. The development of genetic support groups helps to reduce some of these feelings among individuals and families, as well as aiding in teaching and providing information surrounding medical management. In this way, genetic support groups play a vital role in the health care of affected individuals and their families. Directors and healthcare professionals in these groups provide a wide range of support services to individuals with genetic diseases. Today many networks of support services exist, including The National Organization for Rare Disorders (NORD). The NORD's Organizational Database provides information on more than 2,000 disease-specific support groups, registries, agencies, and organizations that serve the needs of rare diseases.[45]

Current literature reports few supportive medical services for individuals with Hereditary Pancreatitis. The extensive database of the NORD does not include a support group for individuals with Hereditary Pancreatitis. One self-help organization for pancreatitis was identified in the United Kingdom: Pancreatitis Supporters Network. Recently the National Pancreas Foundation has created on on-line email list for patients with pancreatitis.

2.0 EXPERIMENTAL DESIGN AND METHODS

2.1 QUESTIONNAIRES

The questionnaires used for this study were created by investigators of the North American Pancreatitis Study II (NAPS2) and the Hereditary Pancreatitis (HP) study at the University of Pittsburgh (Division of Gastroenterology, Hepatology, and Nutrition), and approved for research purposes by the Institutional Review Board of the University of Pittsburgh in Pittsburgh, Pennsylvania. Informed consent for participation in the studies was obtained from participants prior to filling out the questionnaires. The NAPS2 survey (Appendix C) included 76 multiple-choice and short answer questions for the subjects. The HP survey (Appendix E) also included 76 multiple-choice and short answer questions. Multiple opportunities exist throughout both questionnaires for respondents to elaborate on their answers and provide personal comments. The NAPS2 study questionnaire was distributed to participants through twenty study centers throughout North America. Study centers were recruited from the Mid-Atlantic Pancreatitis Study.

Questions and data used for this study were extracted from the two questionnaires. In total, 13 multiple-choice questions were used for this study. Of these, twelve questions are from the SF-12® Health Survey (Version 1), and the last is a two-part question regarding pain. The

data from 73 subjects from the two studies who reported a family history of pancreatitis were used in this study.

For the first question, the respondents were asked to categorize their pattern of pain. In addition to the pattern of pain, questions regarding respondent's views about their general health, with respect to how they feel and how well they are able to do usual daily activities, were presented (SF-12®). All responses and family history information were entered into a computerized database, Progeny Version 5.0. Pertinent questions were then queried and extracted from the database.

2.2 DATA ANALYSIS

The SF-12® physical and mental health scales are scored using norm-based methods. The scoring involves four steps. The first step is to convert each item response choice category into an indicator variable (0-5). The indicator variables are weighted (using physical and mental regression weights from the 1990 general U.S. population) and aggregated. The 1998 constant (regression intercept) is then added so that the aggregate scores are standardized to have the same mean as SF-36® versions in the general U.S. population.

Results of the SF-12® were expressed in terms of two meta-scores: the Physical Component Summary (PCS) and the Mental Component Summary (MCS). To calculate the PCS and MCS scores, test items were scored and normalized in a complex algorithm. Scores ranging from 0 to 100 were designed to have a mean score of 50 and a standard deviation of 10 in a representative sample of the 1990 US population (Table 22- Appendix A).

Relationships between reported pain or quality of life and environmental factors (study, family history, age, gender, smoking, alcohol, and diabetes) were analyzed by box and whisker plots. Comparisons between the familial and non-familial groups were carried out using Mann-Whitney U test or, if the outcomes were normally distributed, 2-sample t-tests. Combined rank scores were subdivided by severity and duration based on preliminary trends seen with the combined pain scores. Ranks for severity and duration were combined into two levels. The severity group was separated into a mild to moderate pain group and a severe pain group. For duration, responses were divided by episodes and constant pain. To incorporate all aspects of pain (frequency, duration, character, and severity) a pain measure variable was calculated. Each variable is weighted with the average. The comprehensive pain measure was calculated using the formula:

Pain Measure = ((# episodes per month – average # episodes per month)/standard deviation of episodes per month)) + (Combined Pain Score-2.5) + (Pain Severity – 0.5) + (Pain Duration – 0.5)

Data analysis also consisted of pairwise correlations between SF-12® scores and combined rank pain scores. Regression analysis was also performed with the covariates for the total population, familial subpopulation, and non-familial subpopulation. Statistical analyses were performed using the statistical software package Stata Version 7.0.

3.0 RESULTS

3.1 DEMOGRAPHICS

Data from 73 patients that reported having hereditary pancreatitis were used in this study. Of these, 28 patients were from the HP study and 45 from the NAPS2 study. Data from 271 non-familial patients from the NAPS2 study were also used. Table 1 illustrates the characteristics of the participants by several categories including: gender, age, age at first diagnosis, smoking, alcoholism, and type of pancreatitis. In both the familial and non-familial groups a higher proportion of patients were female than male. Two hundred and eleven (61.34%) subjects reported being diagnosed with both acute and chronic pancreatitis. The proportion of individuals who reported a history of smoking and alcohol abuse was higher in the NAPS2 study than the HP study, but non-familial subjects were more likely to use tobacco than alcohol. The age of study participants ranged from 9 to 79, with a mean age of 44.8 years. The age at first diagnosis of study participants ranged from 2 to 74, with a mean age at first diagnosis of 29.9 years. The age of non-familial subjects ranged from 8 to 91, with a mean age of 48.48 years. The age at first diagnosis of non-familial subjects ranged from 4 to 77, with a mean age at first diagnosis of 41.11 years.

Table 1. Demographic Information

	HP Study	NAPS2 Study	Non-familial	Total
Gender				
Male	12 (42.86%)	17 (37.78%)	145 (53.51%)	174 (50.58%)
Female	16 (57.14%)	28 (62.22%)	126 (46.49%	170 (49.42%)
Age				
<20	7 (25.00%)	1 (2.22%)	6 (2.21%)	14 (4.07)
20-29	3 (10.71%)	2 (4.44%)	25 (3.23%)	14 (4.07%)
30-39	2 (7.14%)	13 (28.89%)	40 (14.76%)	55 (15.99%)
40-49	5 (17.86%)	9 (20.00%)	68 (25.09)	82 (23.84%)
50-59	5 (17.86%)	10 (22.22%)	69 (25.46%)	84 (24.42%)
60-69	3 (10.71%)	7 (15.56%)	43 (15.87%)	53 (15.41%)
70-79	3 (10.71%)	3 (6.67%)	15 (5.54%)	21 (6.10%)
≥ 80	0 (0%)	0 (0%)	4 (1.48%)**	4 (1.16%)
Age at First Diagnosis				
<20	16 (57.14%)	6 (13.33%)	20(7.38%)	22 (30.14%)
20-29	5 (17.86%)	8 (17.78%)	52 (19.19%)	13 (17.81%)
30-39	1 (3.57%)	9 (20.00%)	51 (18.82%)	10 (13.70%)
40-49	3 (10.71%)	10 (22.22%)	65 (23.99%)	13 (17.81%)
50-59	2 (7.14%)	7 (15.56%)	46 (16.97%)	9 (12.33%)
60-69	0 (0%)	3 (6.67%)	22 (8.12%)	3 (4.11%)
70-79	0 (0%)	2 (4.44%)	12 (4.43%)	2 (2.74%)
≥ 80	0 (0%)*	0 (0%)	1 (0.37%)***	0 (0%)
Smoking				
No	19 (67.86%)	15 (20.54%)	111 (40.96%)	145 (42.15%)
Yes	9 (32.14%)	30 (41.10%)	154 (56.83%)*[4]	193 (56.10%)
Alcoholism				
No	20 (71.43%)	28 (62.22%)	166 (61.25%)	214 (62.21%)
Yes	8 (28.57%)	17 (37.77%)	103 (38.01%)*[5]	128 (37.21%)
Type of Pancreatitis				
Chronic	4 (14.29%)	9 (20.0%)	54 (19.93%)	67 (19.48%)
Acute	11 (39.3%)	12 (26.7%)	43 (15.87%)	66 (19.19%)
C & A	13 (46.43%)	24 (53.3%)	174 (46.43%)	211 (61.34%)

*One patient did not report age at diagnosis.
** A date of birth was not available for one patient.
*** Two patients did not report age at diagnosis.
*[4] Six patients did not report tobacco use.
*[5] Two patients did not report alcohol consumption.

3.2 ASSIGNED VARIABLES FOR ANALYSIS

For all statistical analysis (performed using Stata Version 7.0), text variables were converted into the numerical responses listed in Table 2.

Table 2. Assigned Variables

COVARIATES	ASSIGNED VARIABLES
Study	HP = 0 NAPS2 = 1
Hereditary	Familial = 0 Non-familial = 1
Genotype	Normal Allele = 0 Mutated Allele = 1
Gender	Male = 0 Female = 1
Smoking	No = 0 Yes = 1
Alcoholism	No = 0 Yes = 1
Diabetes	No = 0 Yes = 1
Pain Severity	Mild to moderate = 0 Severe = 1
Pain Duration	Episodes = 0 Constant = 1

3.3 SPECIFIC AIM 1

3.3.1 Combined Pain Index

Study participants were asked to rank their level of pain on a scale from "mild to moderate episodes of pain" to "severe constant pain." In order to describe the patients' reported pain level across both studies a combined ranking score based on severity and duration of pain was designed. Table 3 displays the combined scores. The description of pain are the responses available to participants in the questionnaire. The pain index simply gives each response a numerical counterpart.

Table 3. Combined Pain Rank Scores

COMBINED PAIN INDEX	DESCRIPTION OF PAIN (by Severity and Duration)	FAMILIAL	NON-FAMILIAL
0	No pain	5 (6.85%)	0 (0%)
1	Mild-moderate episodes of pain	6 (8.22%)	35 (12.92%)
2	Constant mild-moderate pain	2 (2.74%)	22 (8.12%)
3	Severe episodes of pain	18 (24.66%)	106 (39.11%)
4	Constant mild pain, and episodes of severe pain	27 (36.99%)	89 (32.84%)
5	Constant severe pain	7 (9.59%)*	19 (7.01%)

* Eight (10.96%) subjects did not report their level of pain.

Therefore, a combined rank of 1 is the mildest form of pain with the shortest duration period, and a combined rank of 5 is the most severe level of pain with the longest duration.

Combined pain index scores were also analyzed by comparison to several environmental factors and exposures for both pancreatitis groups collectively. The total pain ranks were compared to patient responses of tobacco use, alcohol use, gender, and diagnosis of diabetes.

Each environmental exposure was also evaluated within each group, familial and non-familial. No significant trends were found in this analysis.

In addition to scoring their level of pain, subjects who reported a severe level of pain were required to quantify the frequency of severe episodes per month and per year. Because many different measures of pain were extrapolated from the questionnaires, an overall pain measure was calculated to capture all pain descriptions. Four pain measures- frequency, character, severity, and duration- were weighted and combined for each individual. The distribution of the pain measure for the total population is shown in Figure 1, and is approximately normal.

Total Pain Measure

Figure 1. Total Pain Measure

In addition to examining pain responses by study and environmental exposures, pain was compared with genotype. Genotypes for forty-five patients existed, representing the PAR, *SPINK1*, and *PRSS1* genes. Several patients were found to have mutations in more than one tested gene, and six subjects tested negative for all three genes. These proportions of patients have atleast one mutation in the indicated gene (except for the negatives). This distribution is shown in Figure 2.

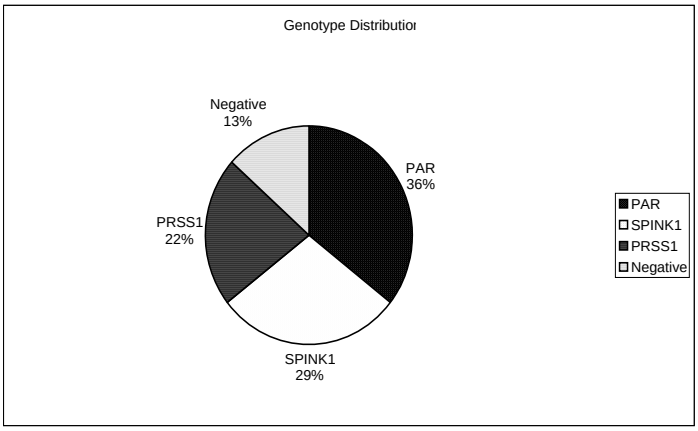

Figure 2. Genotype Distribution

Genotype variables were assigned as shown in Table 2, and were grouped by mutated and normal alleles. The mutant alleles were scored as 1, and the normal as 0. For individuals who were found to have a PAR mutation, as shown above, 75% were carriers, and 25% homozygous for the risk allele. Genotypes were compared against the combined pain scores, pain severity, and pain duration. Figure 3 shows the combined pain rank scores for each of the three genes.

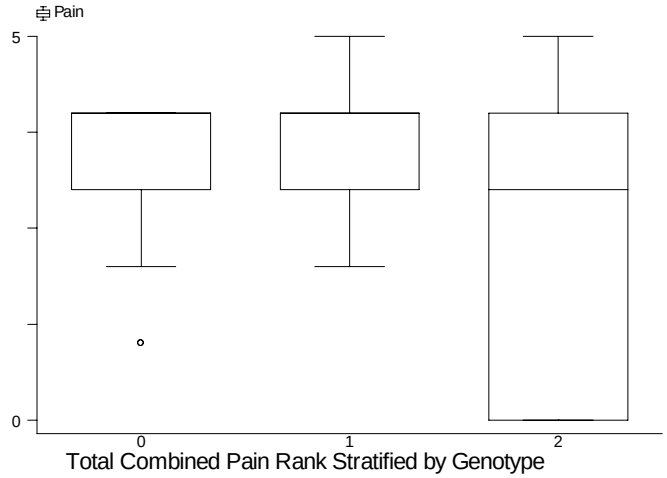

Figure 3. Total Combined Pain Rank Stratified by Genotype

No significant difference appear to be seen between the genotypes in terms of the combined pain scale.

3.3.2 SF-12® v1 Analysis

The SF-12® analysis consisted of a complex algorithm based on population data from 1990. The outcomes for each measure were added to a 1996 constant (based on general population responses) to obtain the final Physical and Mental Weight scores. Higher scores equate to a better quality of life. Scores for the familial and non-familial physical component ranged from 4.34 to 59.45 and 10.05 to 72.26, respectively. The familial mental score range was -11.10 to 58.87 and the non-familial mental score range was -10.38 to -52.10. The values for the total physical quality of life are shown in Figure 4.

Total Physical Quality of Life Measure

Figure 4. Total Physical Quality of Life

Figure 5 below shows the distribution of the mental quality of life outcomes, which also appear to be normally distributed for the total population.

Total Mental Quality of Life Measure

Figure 5. Total Mental Quality of Life

Figures 6 and 7 show the physical and mental quality of life measures for the familial population and non-familial population, respectively.

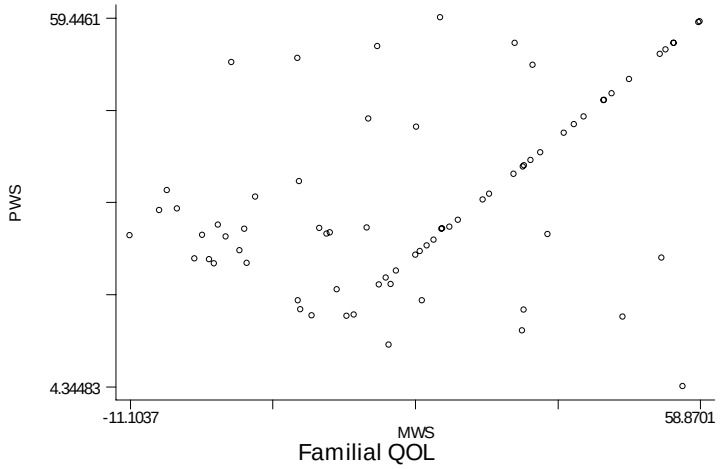

Figure 6. Familial QOL Outcomes

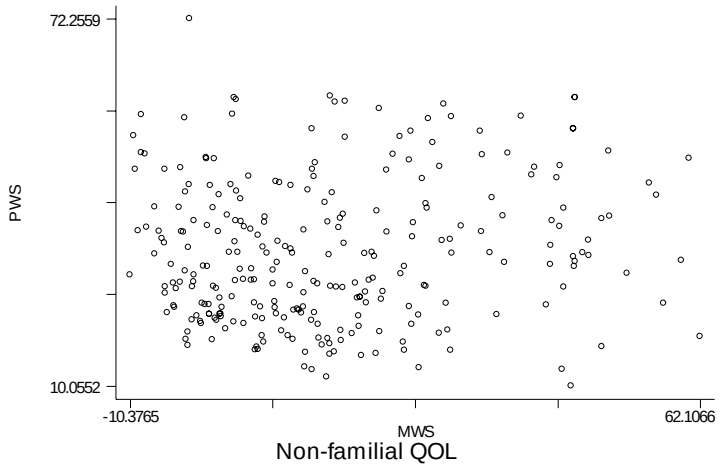

Figure 7. Non-Familial QOL Outcomes

Figure 8 shows the physical and mental quality of life measures for the familial versus non-familial subpopulations.

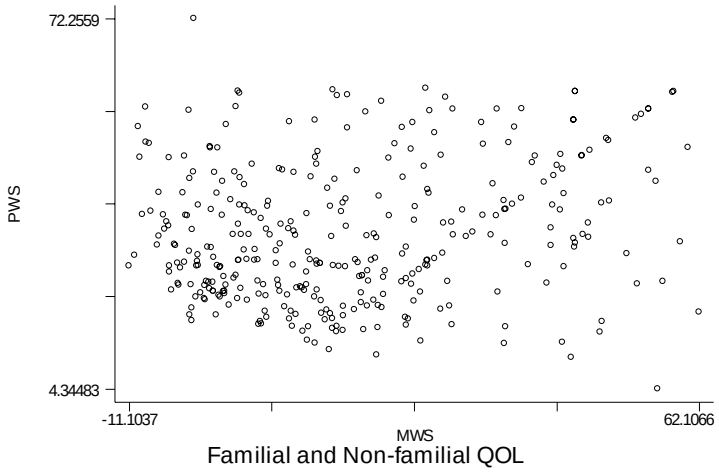

Figure 8. TotalQuality of Life Outcomes

Although outcomes varied greatly, a subtle trend can be seen between physical and mental weight scores as quality of life increases. Familial (0) physical and mental health compared with non-familial (1) physical and mental health showed a significant difference ($p = 0.000$ and $p =$

0.000 respectively).

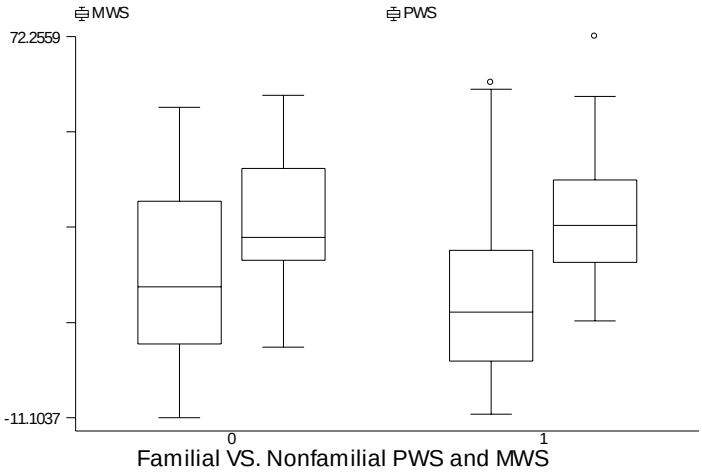

Figure 9. Familial versus Non-Familial Quality of Life

In both subgroups physical health was reported to be better than mental health. (In Figure 9, MWS is the left box-and-whisker plot for each subgroup)

Quality of life was also assessed by comparison with other patient specific environmental factors including gender, diabetes, alcohol consumption and tobacco use. These exposures were compared within the whole population and by subpopulation (familial, non-familial) independently to assess whether they had a significant impact on quality of life. Outcomes are available in Tables 7-8 and 12-13.

3.3.3 Impact of Pain on Quality of Life

In order to determine the impact of chronic pain associated with pancreatitis on quality of life a variety of analyses were performed. Each quality of life outcome was assessed based on type of

pain categorized by the combined rank. A trend in responses is apparent; those with pain categories including moderate to severe pain reported a lower physical quality of life (Figure 10).

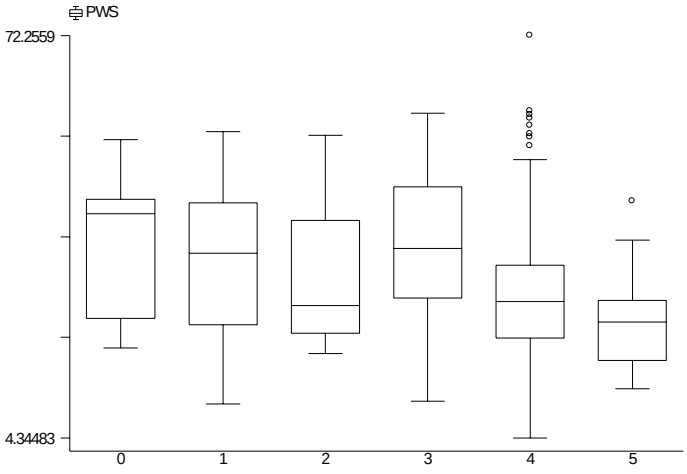

Figure 10. Total Physical QOL Versus Combined Pain Rank

The distribution of quality of life measure combined with the pain characterization is displayed in Figure 11.

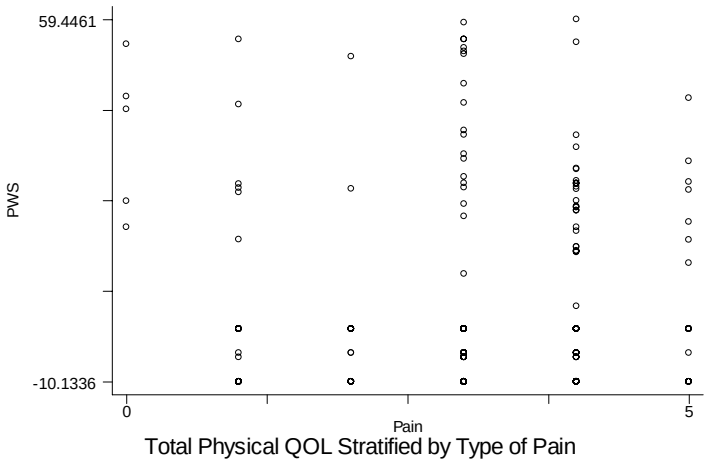

Figure 11. Total Physical Quality of Life Stratified by Type of Pain

Figure 12 shows the mental health scores for each pain category.

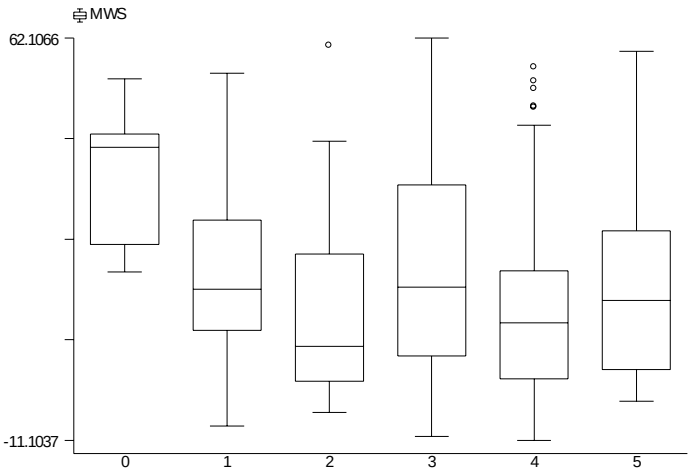

Figure 12. Total Mental QOL Versus Combined Pain Rank

Individuals with no pain reported the best mental health, although there was not a significant difference between the other measures of pain. Individuals with constant pain, regardless of severity reported lower mental quality of life. Figure 13 shows the distribution the pain character with mental quality of life outcomes.

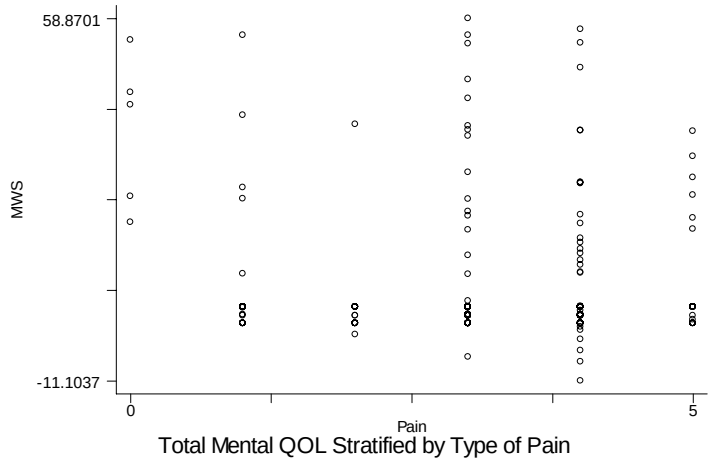

Figure 13. Total Mental Quality of Life Stratified by Type of Pain

3.3.4 Impact of Pain Duration and Severity on Quality of Life

As a result of the trends obtained from pain outcomes, the pain categories were further subdivided by duration and severity.

Table 4. Pain Scores Based on Severity and Duration

GROUPED RANK	PAIN SEVERITY	PAIN DURATION
0	0,1,2,3	0,1,3
1	4,5	2,4,5

Combined pain ranks included in the mild to moderate pain severity grouping were 0, 1, 2, and 3; the severe pain grouping consisted of 4 and 5. Combined pain ranks of 0, 1, and 3 were joined to make the episodic pain group; 2, 4, and 5 compose the constant pain group (Table 4).

Figure 14 shows the groups based on severity of pain (mild to moderate and severe). Those with

severe pain report a statistically significant (p = 0.0007) lower physical quality of life within the familial group, and difference in severity was seen in the non-familial group.

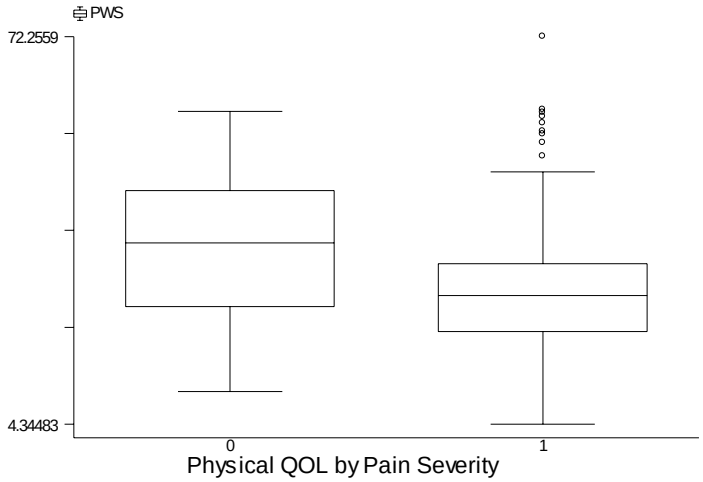

Figure 14. Total Physical Quality of Life Stratified by Pain Severity

Familial mental QOL was also significantly different between pain severity groups with a p-value of 0.0194 (Figure 15).

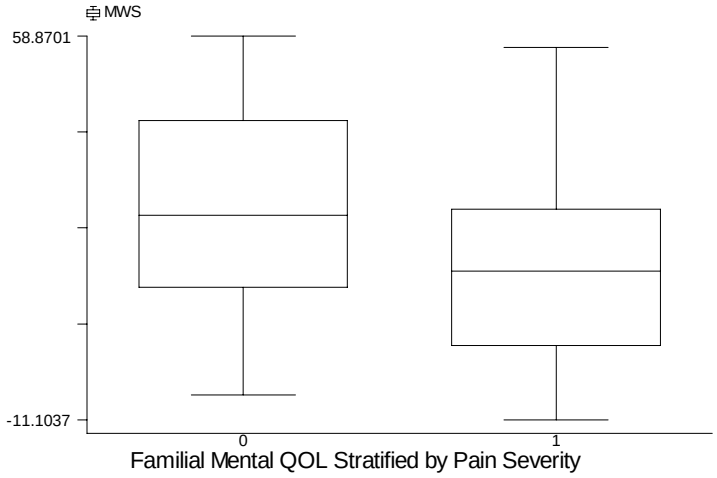

Figure 15. Familial Mental QOL Stratified by Pain Severity

Figure 16 shows the non-familial mental QOL stratified by pain severity.

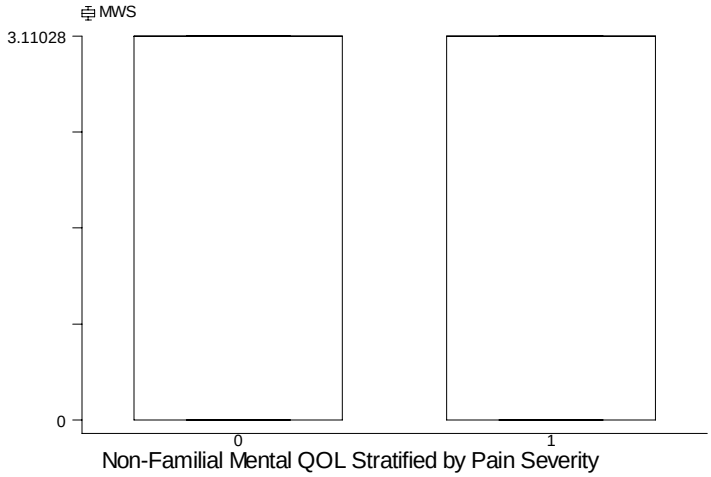

Figure 16. Non-Familial Mental QOL Stratified by Pain Severity

Those study participants with constant pain rather than episodes of pain reported lower levels of mental health. The difference between mental quality of life between pain duration groups for the total population did not appear to be significant (Figure 17).

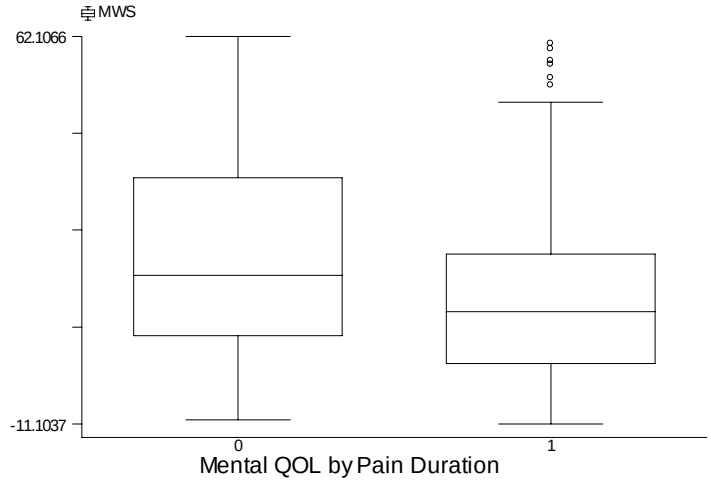

Figure 17. Total Mental QOL Stratified by Pain Duration

When subdivided into familial subjects, the difference between mental (Figure 18) and physical

(Figure 19) quality of life between pain duration groups was also evident (p = 0.0141 and p = 0.0007 respectively).

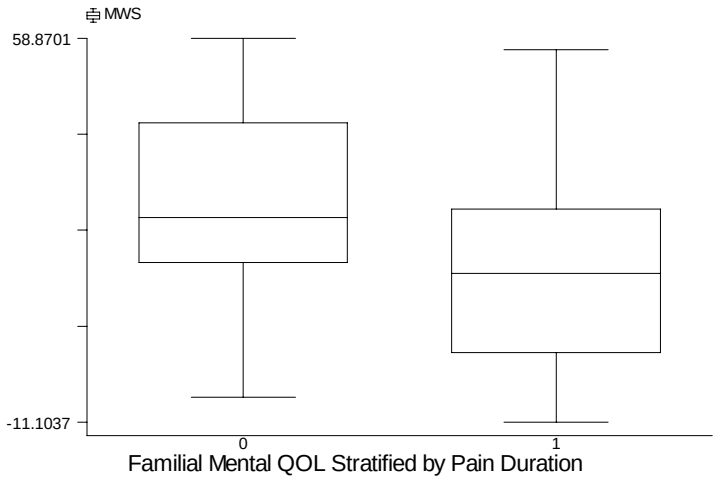

Figure 18. Familial Mental QOL Stratified by Pain Duration

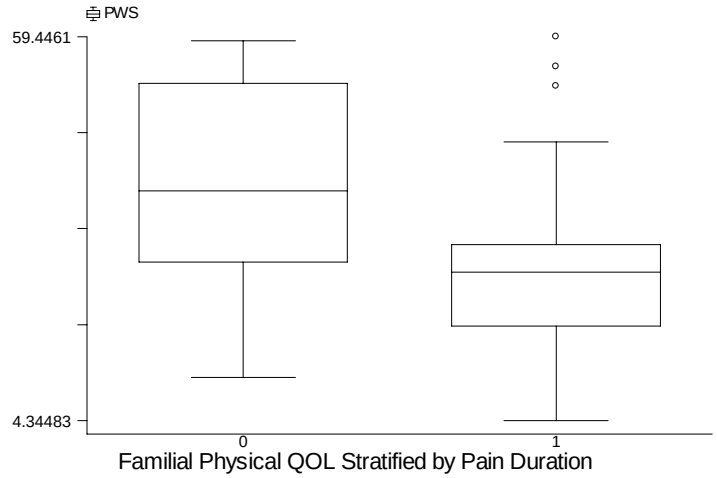

Figure 19. Familial Physical QOL Stratified by Pain Duration

When subdivided into non-familial subgroups the difference between mental and physical quality of life and pain duration was not significant (Figures 20 and 21).

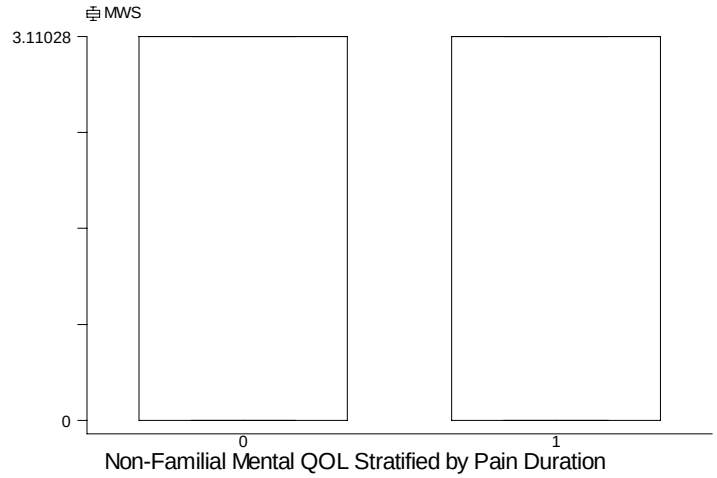

Figure 20. Non-Familial Mental QOL Stratified by Pain Duration

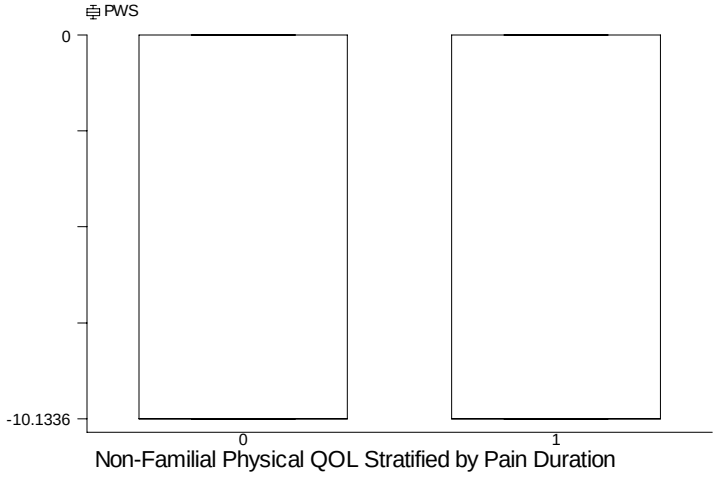

Figure 21. Non-Familial Physical QOL Stratified by Pain Duration

In addition to assessing pain with quality of life outcomes, comparisons were made with common environmental influences. Counts for each group according to the pain index are shown in Table 5. The physical and mental summary scores and frequency of pain in a month are represented as averages. The standard deviation of the physical and mental quality of life measures are 17.686 and 12.8886, respectively. The standard deviation for the frequency of pain per month is 8.9197.

Table 5. Counts of all Covariates by Combined Pain Rank Score

Pain Index	0	1	2	3	4	5	Blank
Total Count	5	41	24	123	117	26	8
Males	2	18	16	65	53	12	-
Females	3	23	8	58	64	14	-
Familial	5	6	2	18	27	7	8
Non-Familial	-	35	22	105	90	19	-
Smokers	4	14	7	58	45	11	6
Non-Smokers	1	25	17	64	69	15	2
Alcoholics	4	30	9	77	72	17	5
Non-Alcoholics	1	11	15	45	44	9	3
Severe Pain	-	-	-	-	117	26	-
Mild-Mod Pain	5	41	24	123	-	-	8
PWS	17.689	26.209	37.045	33.814	47.303	-15.84	-
MWS	17.689	26.209	-5.295	27.757	34.059	-15.84	-
Pain in Months	0	0.333	0	0.833	-3.5	0	-

3.3.5 Correlation of Pain and Quality of Life

A pairwise correlation study was performed to examine the impact of pain on physical and mental quality of life (Table 6). A negative correlation existed between pain and physical weight ($r = -0.2064$), and between pain and mental weight ($r = -0.1408$).

Table 6. Total Pairwise Correlation of Pain and QOL

	PAIN	PWS	MWS
Pain	1.0000		
PWS	-0.2064	1.0000	
MWS	-0.1408	0.1569	1.0000

Similarly, correlation studies were also undertaken to determine the relationship between pain, quality of life, and environmental factors reported by the patients in the questionnaire (Table 7). Again, pain and quality of life showed a negative correlation. Pain was also negatively correlated with age (r = -0.1055). A slight negative correlation was found between physical quality of life and gender (r = -0.1023), smoking (r = -0.0765), and alcohol use (r = -0.0768), though these were not significant. Mental quality of life was also negatively correlated with smoking and alcohol use.

Table 7. Total Pairwise Correlation of QOL, Pain, and Covariates

	Pain Index	PWS	MWS	Age	Gender	Smoking	Alcoholism	Familiarity	Pain Duration	Pain Severity
Pain	1.0000									
PWS	-0.2134	1.0000								
MWS	-0.1461	0.1433	1.0000							
Age	-0.1055	0.0035	0.0234	1.0000						
Gender	0.0234	-0.1023	0.0596	-0.0811	1.0000					
Smoking	0.0038	-0.0765	-0.1251	0.1344	-0.1635	1.0000				
Alcoholism	0.0436	-0.0768	-0.1840	0.0643	-0.3194	0.3856	1.0000			
Familiarity	-0.0156	-0.8990	-0.7023	0.0377	-0.1741	0.0083	0.0443	1.000		
Pain Duration	0.6211	-0.0133	-0.0591	-0.0927	0.0213	0.0774	0.0755	-0.0549	1.000	
Pain Severity	0.775	0.0099	-0.0214	-0.0674	0.0712	0.0392	0.0047	-0.0979	0.8633	1.000

3.4 SPECIFIC AIM 2

3.4.1 Comparison of Covariates

All covariates, pain measures, and quality of life scores were compared against each other within the total population, familial population, and non-familial population. These measures were compared using box-and-whiskers plots followed by the Mann-Whitney U test giving a p-value. For the quality of life measures a student's t-test for equal variances was used due to the normal distribution of the measure. Table 8 illustrates the p-values for the comparisons within the total population.

Table 8. Total Population Comparison of Covariates.

	PWS	MWS	Pain	Pain Severity	Pain Duration	Pain In Months
Familiarity	**0.0000**	**0.0000**	0.2440	0.0772	0.4742	0.5578
Gender	0.0932	0.3115	0.3806	0.2132	0.7428	0.9281
Diabetes	0.1106	0.2022	0.7787	0.5367	0.3373	0.6696
Alcoholism	0.8309	0.1934	0.9392	0.9738	0.1847	**0.0459**
Smoking	0.6440	0.2934	0.8964	0.5036	0.1759	**0.0536**

Alcohol and smoking both had an impact on frequency of pain per month. A table including the p-values for the quality of life scores and pain scores by severity and duration only within the entire population is shown below.

Table 9. Total Population Quality of Life compared with Severity and Duration of Pain

	PWS	MWS
Pain Severity	0.5059	0.8396
Pain Duration	0.5745	0.4315

P-values for comparisons between all covariates were also made within the subpopulations. Again, these 2-way comparisons were divided between the environmental exposures with pain and quality of life measures (Familial -Table 11; Non-Familial-Table 12) and quality of life compared to pain severity and pain duration (Familial-Table 10).

Table 10. Familial Quality of Life compared with Severity and Duration of Pain

	PWS	**MWS**
Pain Severity	**0.018**	**0.0194**
Pain Duration	**0.0015**	**0.0141**

P-values obtained from the standard t-test with equal variances for comparison of pain severity and duration classifications with quality of life showed significant trends within the familial population.

Table 11. Non-Familial Quality of Life compared with Severity and Duration of Pain

	PWS	**MWS**
Pain Severity	0.6342	0.6344
Pain Duration	0.8647	0.8665

P-values obtained from the t-test with equal variances for comparison of pain severity and duration classifications with quality of life did not show any significant trends within the non-familial population.

Table 12. Familial Comparisons of Covariates

	Pain	PWS	MWS	Pain Severity	Pain Duration	Pain In Months
Gender	0.3802	0.2321	0.6119	0.6039	0.3879	0.5946
Diabetes	0.5024	0.9815	0.4711	0.5953	0.3680	0.0779
Alcoholism	0.8043	0.8433	0.1666	0.7915	0.5354	0.5939
Smoking	0.7121	0.2785	**0.0397**	0.8602	0.8056	0.1627

A significant trend was seen when smoking and mental qualities of life were compared within the familial population.

Table 13. Non-Familial Comparisons of Covariates

	Pain	PWS	MWS	Pain Severity	Pain Duration	Pain in Months
Diabetes	0.8830	0.7114	0.7114	0.4495	0.1396	0.6028
Alcohol	0.9250	0.3048	0.3048	0.8688	0.0704	**0.0460**
Smoking	0.7954	0.7601	0.7601	0.3884	0.0999	0.1291
Gender	0.7386	0.7217	0.7217	0.4103	0.8252	0.7506

Within the non-familial subgroup a significant trend was seen between alcohol use and frequency of pain per month.

3.4.2 Regression with Environmental Covariates

Regression studies were also performed to examine the relationship between two random variables. Regression analysis was performed on pain and quality of life with multiple variables

answered by the study participants. Five separate regression analyses were performed. For all analyses each alleles for each gene were counted as a variable. For each allele a mutant allele was scored as 1 and a normal allele scored as 0. For *PRSS1* and *SPINK1* no heterozygotes exist, therefore these allele variables were combined. Thus, PAR(1) is allele one of the PAR gene and PAR(2) is the second allele of the PAR gene, etc.

Table 13. Regression Analysis of Pain Measure and Binary Variables Including Genotype

Pain Measure	Coef	Std. Err	z	P>z	[95% Conf. Interval]
Smoking	.253957	.2928588	0.87	0.386	(-.3200357, .8279498)
Alcoholism	.3277014	.3096957	1.06	0.290	(-.2792911, .9346938)
Diabetes	-.265623	.31194	-0.85	0.394	(-.8770142, .3457682)
Familiarity	.2336664	.3927836	0.59	0.552	(-.5361753, 1.003508)
Gender	.4104061	.275691	1.49	0.137	(-.1299384, .9507505)
PAR(1)	-.4970362	1.393123	-0.36	0.721	(-3.227508, 2.233435)
PAR(2)	.9454356	.7773508	1.22	0.224	(-.578144, 2.469015)
***SPINK1*(1/2)**	.6658422	.7338226	0.91	0.364	(-.7724236, 2.104108)
***PRSS1*(1/2)**	-2.020095	.846289	-2.39	**0.017**	(-3.678791, -.3613989)

The first regression (Table 13) used the comprehensive pain measure with all binary variables. Alleles one and two of the *PRSS1* gene showed a relationship with measure of pain. The other variables did not show a linear relation to pain measure (Table 14).

Table 14. Regression Analysis of Pain Measure and Binary Variables

Pain Measure	Coef	Std. Err	z	P>z	[95% Conf. Interval]
Smoking	.23006	.2865218	0.80	0.422	(-.3315075, .7916374)
Alcoholism	.0344157	.2953159	0.12	0.907	(-.5443928, .6132241)
Diabetes	-.7028933	.3103272	-2.27	0.024	(-1.311123, .0946631)
Familiarity	.497739	.320971	1.55	0.121	(-.1313526,1.126831)
Gender	-.2707278	.2754921	-.98	0.326	(-.8106823, .2692268)

Table 15. Regression Analysis of Physical Health Score with Binary Variables and Genotype

PWS	COEF.	STD ERR.	Z	P>Z	[95% CONF INTERVAL]
Smoking	-1.271828	.8870957	-1.43	0.152	(-3.010503, .4668479)
Alcoholism	.9811537	.9380962	1.05	0.296	(-.8574811, 2.819788)
Diabetes	-.2050867	.9448945	0.828	0.828	(-2.057046, 1.646872)
Familiarity	-41.71774	1.189777	-35.06	**0.000**	(-44.04966, -39.38582)
Gender	-.4744655	.8350929	-0.57	0.570	(-2.111218, 1.162287)
PAR(1)	10.43738	4.219896	4.219896	2.47	2.166536, 18.70823
PAR(2)	-8.957851	2.354666	2.354666	**-3.80**	(-13.57291, -4.342791)
***SPINK1*(1/2)**	-9.201247	2.222815	2.222815	**-4.14**	(-13.55788, -4.844611)
***PRSS1*(1/2)**	3.223526	2.563486	2.563486	1.26	(-1.800813, 8.247866)

Table 15 shows a comparison of the binary variables with physical quality of life. Relationships with physical quality of life were seen with heredity as a variable (individuals who report familial pancreatitis versus non-familial pancreatitis), the second allele of the PAR gene, and both alleles of the *SPINK1* gene. Table 16 shows the same analysis, but without the genotypes to limit the number. Again, familiarity and physical quality of life were extremely related.

Table 16. Regression Analysis of Physical Health Score with Binary Variables

PWS	COEF.	STD. ERR.	Z	P>Z	[95% CONF. INTERVAL]
Smoking	-1.131037	.913685	-1.24	0.216	(-2.921827, .6597522)
Alcoholism	.8002285	.9417281	0.85	0.395	(-1.045525, 2.645982)
Diabetes	-.0393467	.9895976	-0.04	0.968	(-1.978922, 1.900229)
Familiarity	-39.16699	1.023539	-38.27	**0.000**	(-41.17309, -37.16089)
Gender	-.7471892	.8785124	-0.85	0.395	(-2.469042, .9746635)

Table 17. Regression Analysis of Mental Health Score with Binary Variables and Genotype

MWS	COEF.	STD. ERR.	Z	P>Z	[95% CONF. INTERVAL]
Smoking	-1.249885	1.049999	-1.19	0.234	(-3.307845, .8080752)
Alcoholism	-.4263546	1.110365	-.38	0.701	(-2.60263, 1.74992)
Diabetes	.0265401	1.118412	0.02	0.981	(-2.165506, 2.218586)
Familiarity	-22.19885	1.408263	-15.76	**0.000**	(-24.95899, -19.4387)
Gender	.5398056	.9884464	0.55	0.585	(-1.397514, 2.477125)
PAR(1)	-4.777239	4.994822	-0.96	0.339	(-14.56691, 5.012434)
PAR(2)	-4.870557	.7870683	-1.75	0.081	(-10.33311, .5919963)
***SPINK1*(1/2)**	-1.086303	2.631004	-0.41	0.680	(-6.242977, 4.070371)
***PRSS1*(1/2)**	14.13769	3.034235	4.66	**0.000**	(8.190702, 20.08469)

Similar to the previous comparison, mental quality of life shows a linear relationship with heredity and both alleles of the *PRSS1* gene as shown in Table 17. The regression analysis was also performed excluding genotype as a variable (Table 18). Familiarity and smoking were both related to mental health when genotype was not used as a limiting variable.

Table 18. Regression Analysis of Physical Health Scores with Binary Variables

MWS	COEF.	STD. ERR.	Z	P>Z	[95% CONF. INTERVAL]
Smoking	-1.826019	1.068309	-1.71	**0.087**	(-3.919866, .2678284)
Alcoholism	-.4783335	1.101098	-0.43	0.664	(-2.636446, 1.679779)
Diabetes	-.687093	1.157068	-0.59	0.553	(-2.954905, 1.580719)
Familiarity	-22.92194	1.196754	-19.15	**0.000**	(-25.26754, -20.57635)
Gender	.0041497	1.027184	0.00	0.997	(-2.009094, 2.017394)

Table 19. Regression Analysis of Total QOL Scores with Binary Variables and Genotype

PWS + MWS	COEF.	STD. ERR.	Z	P>Z	[95% CONF INTERVAL]
Smoking	-2.476634	1.491082	-1.66	0.097	(-5.399101, .4458334)
Alcoholism	.472683	1.523025	0.31	0.756	(-2.512392, 3.457758)
Diabetes	-.1745279	1.619846	-0.11	0.914	(-3.349368, 3.000312)
Familiarity	-63.92128	2.039314	-31.34	**0.000**	(-67.91827, -59.9243)
Gender	.0453707	1.426229	0.975	0.434	(-2.749987, 2.840729)
PAR(1)	5.657721	7.232864	0.78	**0.001**	(-8.518431, 19.83387)
PAR(2)	-13.82754	4.035857	-3.43	**0.007**	(-21.73768, -5.917407)
***SPINK*(1/2)**	-10.27499	3.808883	-2.70	**0.000**	(-17.74026, -2.809717)
***PRSS1*(1/2)**	17.37376	4.393172	3.95	0.65417	(8.763301, 25.98422)

When physical and mental health scores are combined to give overall quality of life (Table 19) multiple variables are related. Again, relationships between heredity and multiple alleles of several genes (PAR and *SPINK1*) exist. The same outcome was not observed without genotype as a variable. Diabetes showed a strong relationship with total quality of life (Table 20).

Table 20. Regression Analysis of Total Quality of Life Scores with Binary Variables

PWS + MWS	COEF.	STD. ERR.	Z	P>Z	[95% CONF. INTERVAL]
Smoking	2.303185	3.181197	0.72	0.469	(-3.931846, 8.538217)
Diabetes	7.301242	3.702236	1.97	**0.049**	(.0449924, 14.55749)
Familiarity	-.6722528	3.830624	-0.18	0.861	(-8.180138, 6.835632)
Gender	-.0165831	3.153617	-0.01	0.996	(-6.19755, 6.164392)

4.0 DISCUSSION

4.1 SPECIFIC AIM 1

Aim:

To document the levels of patient reported pain and patient reported quality of life (using the Short Form-12® Quality of Life survey) for individuals with pancreatitis.

Hypothesis:

Patients with Hereditary Pancreatitis will report high levels of chronic pain and poor quality of life in both physical and mental subsets.

Outcome:

Patients from the Hereditary Pancreatitis and NAPS2 studies were categorized based on multiple demographic variables, level of pain, genotype, and quality of life.

The majority of subjects in both the familial and non-familial pancreatitis subgroups reported severe and constant pain. When classified according to the combined pain rank 36.05% of subjects reported constant mild to moderate pain. Approximately 1/3 (33.7%) of patients reported constant mild pain with severe episodes. Over half of the individuals used in this study reported pain levels in these two categories. Contrary to the original hypothesis, this finding shows that all individuals with pancreatitis report a high level of pain according to the combined pain rank. Pain can be described using many facets, and

was therefore described based on duration, severity, frequency, and character. These qualities were combined to form the total pain measure, which ranged from -4.04 to 8.69. Quality of life measures were described using the SF-12® health survey. Physical summary outcomes ranged from 4.34 to 72.26. Mental summary scores ranged from -11.10 to 58.87. Scores above 50 represent above average health status. All scores above and below 50 are above and below the average for both the physical and mental component summaries. Each one point difference in scores has a direct interpretation; a one-point difference is one-tenth of a standard deviation**.** Those with a score of 40 function at a level lower than 84% of the population (one standard deviation). People with scores lower than 30 function at a level lower than approximately 98% of the population (two standard deviations). The average physical score was 43.9086, and the average mental score was 43.90865.

Average quality of life indexes for other common diseases are listed in Table 21.[46] These scores, however, are outcomes from Version 2.0 of the health survey, thus may not berepresentative of an exact comparison with Version 1.0 used in this study. Patients with pancreatitis have similar physical health to individuals with stomach ulcers or disease. Physical health is reported to be better than individuals who have cancer, diabetes, kidney disease, and congestive heart failure. The mental health of individuals with pancreatitis is comparable to those with anemia. The only mental health score that is lower than that found for pancreatitis is that found for depression. Therefore, the reported mental health of individuals with pancreatitis is lower than that of all the surveyed common diseases except one.

Table 21. Quality of Life Indexes for Common Diseases

CONDITION	PHYSICAL SCORE	MENTAL SCORE
"Healthy" Adults	54.41	52.36
Pancreatitis	**43.91**	**43.91**
Allergies (Chronic)	47.56	47.43
Anemia	44.25	43.78
Back Pain/Sciatica	46.10	47.23
Cancer (Except Skin)	40.93	47.48
Congestive Heart Failure	40.02	51.15
Depression	45.77	36.85
Dermatitis	48.48	47.36
Diabetes	41.92	48.13
Hearing Impairment	44.79	48.08
Heart Disease	39.16	47.00
Hypertension	44.44	48.95
Kidney Disease	40.84	44.61
Liver Disease	39.95	45.44
Limited Use of Arms/Legs	39.14	46.00
Lung Disease	38.14	45.59
Myocardial Infarction	42.34	51.52
Osteoarthritis/Degenerative	38.70	47.48
Rheumatoid Arthritis	39.60	46.82
Ulcer/Stomach Disease	43.09	45.11
Vision Impairment	44.29	46.42

The advantage of standardizing the SF-12® outcome scores is that each result can be compared to the other summary score and have a direct interpretation in relation to the distribution scores in the general U.S. population.[5] The statistical differences for the SF-12® analysis were judged significant when $p < 0.05$.[12] A trend was seen when mental and physical scores were compared with each other, showing that as one measure increased in this population the other measure also increased. Therefore, for pancreatitis patients factors contributing to quality of life have an impact on both physical and mental health.

When familiarity was used as a parameter of quality of life, a significant difference was evident. As hypothesized, individuals who reported familial pancreatitis reported lower physical and mental quality of life than non-familial individuals. This conclusion was supported by a p-value equal to 0.000.

When the distribution of quality of life scores was compared to pain level, using the combined pain rank, a significant trend was noted between certain qualities of pain in association with the quality of life measures. Combined ranks involving more severe pain showed poorer overall physical health. Ranks based on duration, specifically those with constant pain, corresponded to lower mental health. This trend was further evaluated and found to be significant when the combined pain rank scores were subdivided by these two aspects of pain. However, this was not a solitary trend. Severe pain (instead of mild to moderate pain) showed a significant impact on both physical and mental health ($p = 0.0007$ and $p = 0.0194$, respectively). Likewise, constant pain (instead of episodic pain) showed a significant impact on both physical and mental health ($p = 0.0007$ and $p = 0.0141$).

Finally, to document pain and quality of life measures correlation studies were performed. Variables with correlation coefficients, "r", that were close to 1.0 or –1.0 are closely related. When r is negative, one variable gets larger as the other variable gets smaller. Pain was found to be negatively correlated to both physical and mental health scores as was hypothesized. As pain increased quality of life decreased. Approximately 4.26% of the variation in pain is related to the variation in physical health ($r = -0.2064$). A negative correlation was also seen between mental health and pain with an r value equal to -0.1023, meaning that 1.98% of the variation in pain is related to the variation in

mental health. Slight negative correlations were also discovered between (a) pain and age (r = -0.1055), (b) physical health and gender (r = -0.1023), smoking (r = -0.0765), and alcohol (r = -0.0768), (c) mental health and smoking (r = -0.1251) and alcohol (r = -0.1840).

Implications:

The documentation of the quality of life summary measures and pain levels of patients with pancreatitis hopefully provides insight for the implementation of the ultimate goal of psychosocial support for individuals with pancreatitis. Ideally, these measures will be used to target individuals who would benefit from additional support.

In general, hereditary conditions have an earlier age of onset, more severe phenotypic effects, and additional mental and psychological factors (such as guilt, fear, and anxiety) than their sporadic forms. The significant difference found between familial and non-familial subgroups in this study supports this theory, as well as the hypothesis that familial individuals report more severe pain and worse quality of life than their counterparts. However, the hereditary component of such conditions typically provides a built-in support system in families members who share similar experiences. These results did not support this theory.

These findings mean that individuals who reported severe and constant pain have lower quality of life than those who had mild or moderate pain. As previously mentioned, the majority of the pancreatitis population reported pain levels that were both constant and severe to some degree. The overall quality of life measures also fell below the average of the general population. Within the familial subset of the population the higher level of pain had a greater impact on quality of life. Therefore, these results support the

hypothesis that individuals with pancreatitis report a low quality of life and high level of pain that may be significant enough to warrant psychosocial intervention.

In this case, quality of life is a useful tool for identifying patients who are in need of more intense support because this population experiences a considerable decline in quality of life compared with the general population. The quality of life health outcome survey evaluates emotions and other mental health components that enables researchers to understand patient's perception of health.[47] The trends found in the quality of life measures obtained from the pancreatitis population suggest a need for more intense support. Although, these findings are only exploratory and need to be repeated in a larger sample and in different population.

4.2 SPECIFIC AIM 2

Aim:

To explore whether there is a need for a pancreatitis support group.

Hypothesis:

Patients with chronic pain attributed to HP would benefit from psychosocial and behavioral treatment in the context of a support system.

Outcome:

Scores and descriptions of pain and quality of life were compared to each other and a series of other variables commonly measured by medical professionals. Tables of two-way comparisons show the outcomes of the Mann-Whitney U test and Student's t-test.

Alcohol and smoking were found to have a slight impact on the frequency of severe pain episodes per month ($p = 0.0459$ and $p = 0.0536$, respectively). Of more significance, when the total population was scored based on familiarity the relation to quality of life was evident ($p = 0.000$). This finding supports the previous finding that quality of life was significantly lower in the familial population than non-familial. A significant relationship was again found between mental health and smoking ($p = 0.0397$), which confirms this finding from the correlation study. Also supporting the findings of correlation studies, physical and mental summary scores were associated with pain severity and duration. This finding was previously reported and described in the first aim of the study.

Regression analysis also further supported the previous findings. P-values of all relations between heredity and pain/quality of life, however combined to form one measure, were significant ($p = 0.000$ for each measure). Of significance, allele variation for each gene (genotype) also had an influence on pain and quality of life. *PRSS1* variables influenced pain ($p = 0.017$) and mental health ($p = 0.000$). *SPINK1* allele variables influenced physical health ($p = -4.14$) and total quality of life ($p = 0.000$). Total quality of life and physical health by itself were both impacted by mutations in the PAR gene ($p = 0.007$ and $p = -3.80$).

Implications:

The findings of the two-way comparisons of all individuals, familial individuals, and non-familial individuals and regression analysis confirmed the findings of aim 1. The relationship of pain, quality of life, and genotype confirm the need for additional support for these patients. This information may help medical care professionals target

individuals who would benefit from additional psychosocial support using commonly measured variables. Again, this was an exploratory study, which needs to be confirmed in a larger sample and a different study population.

Studies have found that chronic pancreatitis and its associated complications have a considerable impact on quality of life, but that overall research in this area is insufficient. These data are thought to provide insight into the impact of pancreatitis on patient's functional status and well-being.[48] According to findings in the literature, little data exists documenting whether patients achieve satisfactory quality of life following disease-associated complications such as hospital stays.[49] Researchers who have examined chronic pain and psychological and phenomenological perspectives for dealing with pain have found that control and coping contribute to pain. Individuals that experience a lack of control and inefficiently cope with internal and external demands have more significant pain. By identifying individuals with significant pain, medical professionals dealing with pancreatitis can identify those individuals that need additional assistance in coping with the demands that effect pain. Programs can be developed to promote pain understanding. After implementation of a pain program, Haugli et. al. found a trend towards less pain and a significant effect on how well patients felt they were coping with life demands.[40]

Studies have also examined the benefit of counseling intervention in addition to general medical practice. Counseling intervention is thought to have a profound effect on mental health.[50] Therefore, in the pancreatitis population psychological factors are likely linked to quality of life in terms of mental health. Nettleton et. al. also reported that a great need exists to find effective ways of promoting mental health through general practice.[44]

Well-being scores following psychological support showed significant improvement. Given these results, the results of this study appear to support the hypothesis that similar outcomes following psychological support would be found in the pancreatitis population. The effectiveness of support groups has also been investigated and reported in the literature. Most research studies of self-help groups have found important benefits of participation. Chronic illness groups benefited by decreased depression, a more positive outlook on life, satisfaction with medical care, and reduced feelings of shame.[51] For chronic pain specific support groups, participants reported less functional disability as a result of participation in a support system.

4.2.1 Patient Interest

Interest in psychosocial intervention from patients within the Hereditary Pancreatitis population has already been shown and verifies the results of this study. After contact with one patient, the desire and need for a support system was evident for this population of individuals who are affected with a chronic condition.

Living with pancreatitis for a lifetime (often without having an official diagnosis for a significant portion of that time) can be extremely difficult for patients to the point of being devastating. For this individual, finding others who understood and acknowledged the condition was difficult. Feelings of loneliness and frustration drove her to seek out methods of coping beyond traditional medical treatments, though it was difficult to make contacts. She found the lack of information on her condition frustrating, even when researching medical documentation and articles. Having a chronic condition involving unbearable pain was also a significant factor

in her desire to find support. She stated that she was not believed when telling others of her condition because she looks normal and healthy. Others do not understand that lethargy is a side effect of medications and pain associated with pancreatitis. For this reason, individuals with pancreatitis are often labeled as "lazy." This is not uncommon in hereditary conditions, and often leads to feeling like others don't understand or have the knowledge to provide ample support. Therefore, although families are one system of support that individuals with pancreatitis can turn to who are knowledgeable about the condition, they might not be able to adequately calm patient's fears and anxieties. These aspects of disease not only have a role in patient's physical health, but also in their relationships with others and emotional state. These patients have several additional obstacles to overcome on a daily basis as a result of the condition.

As a result of these reasons and feelings, individuals with pancreatitis feel the need to seek out others that truly know how they feel and what they deal with. Having emotional support in the context of a support group provides individuals with pancreatitis an outlet and someone to talk to. One patient stated that "having a contact who was my same age, in the same stage of life as me, and who understood what I was going through would be so beneficial." Having a psychosocial support system or contact would allow these patients to converse with others about the variety of issues that accompany a diagnosis of pancreatitis.

In addition to the demands and suffering patients personally encounter with pancreatitis, having a hereditary condition poses other issues. Having children is difficult for someone with pancreatitis, because of the risk (50%) of passing it on to future generations (with involvement of *PRSS1*). Individuals who are affected by the condition don't want their children to suffer in the same way. After living with a chronic condition that changes who a person is, the decision to

begin a family is difficult. This situation can be extremely difficult for families, and the availability of support to discuss such topics would be beneficial so that others don't have to go through it alone.

After having a discussion with one driven and proactive hereditary pancreatitis patient, the goals of this study were proven to be a necessary component of the multi-disciplinary system of care for patients who have pancreatitis.

In summary, as hypothesized, individuals with pancreatitis report a severe and constant pain level that negatively influences quality of life. Given this correlation, participants should benefit from intervention in the form of psychosocial support. Individuals with pancreatitis would benefit from discussing with other individuals, gaining knowledge about pancreatitis, adapting to life with pain, learning alternative coping strategies, having a sense of belonging, making new friendships, and helping others in the process. This study provides information that can potentially help health care professionals who work with individuals with pancreatitis and who are assessing patient's quality of life and pain measures as an indicator of who to target for psychosocial intervention in addition to general medical practice.

4.3 LIMITATIONS

The primary limitation of this study was the generality of the questions elicited from the Hereditary Pancreatitis and NAPS2 studies. The questions used in the SF-12® analysis were aimed at global quality of life. To adapt the quality of life portion of this study to the target audience additional questions concerning quality of life could be investigated.

Another limitation of this study was the usage of subjects from two different populations. Extracting data from both the HP and NAPS2 study allowed for other differences in the study. The questionnaires filled out by these two groups were not identical (Appendix D and Appendix F). The slight difference in the wording of the questions presented in each of these questionnaires may have prompted slightly different understanding of the questions and in turn responses. Therefore, a potential limitation of this study exists in that individuals might have interpreted questions differently. Also, there are a small number of individuals who are enrolled in both the HP and NAPS2 study. Investigation into whether any of the patients used in this study were actually enrolled into both studies was not performed.

In regards to the questionnaires, many individuals from the studies did not answer the pain and quality of life questions entirely, which reduced the overall sample size used in this study. The sample population (73 individuals) used in this study did not equal the number of sporadic pancreatitis patients (271 individuals) obtained from the NAPS2 study. To increase participant numbers, patients could have been contacted through the study site that they were enrolled to fill in the information that was missed in the initial completion of the questionnaires. Study centers that consistently submitted incomplete questionnaires could also be contacted to correct this problem. In addition, the selection of subjects for this study was limited to individuals that responded positively to the question "Does pancreatitis run in your family." This question may have been interpreted incorrectly, or subjects may not have been aware of other members in their extended family that have pancreatitis. Therefore, this discrepancy in numbers may have influenced or biased the results obtained in this study.

All of the information obtained from the questionnaires was input into the Progeny database by hand. Therefore, another source of error could be in the data entry process when transferring responses from paper to computer.

Lastly, the questions posed in the HP and NAPS2 questionnaires were retrospective. The information obtained for use in this study is all patient report and was not confirmed by medical record or physician documentation. This study required subjects to recollect information and feelings about their health. Individuals may not have accurately reported their pain and quality of life over the last several years. These responses may also be influenced by the patient's current health status. Therefore, this aspect of the study may be confounded by patient recall bias.

5.0 FUTURE RESEARCH OPPORTUNITIES

Given the results of this study, many opportunities for future research exist. It would be useful to investigate questions regarding the subject's current methods of coping with pain. This would provide additional insight into the necessity for and utility of psychosocial intervention. Inquiring about subject's use of alternative pain management techniques would also be interesting to assess options outside of medication and psychosocial support as pain intervention. In addition, questioning the participant's current system of support would be important to examine. Support systems already in place would influence the responses to quality of life and level of pain obtained in this study. It would also be useful to look at patient's response to their current employment status as in indicator for how pancreatitis effects a normal aspect of everyday life. Employment status would also give insight as to whether the pain associated with pancreatitis is severe enough that affected individuals cannot work at all. In addition, how many days of work or school the individuals with pancreatitis miss would be useful for assessing their quality of life with respect to pain and pancreatitis.

As the first step in the protocol for organization and initiation of a support system for individuals with pancreatitis, an interest survey could be assembled. A variety of items can be addressed in the survey including questions regarding patient satisfaction with information provided by their physician, and details surrounding the formation of a support group. Potential participants should be asked whether they felt they were provided with enough medical

information at the time of genetic testing or their diagnosis of pancreatitis. In addition to questions concerning medical information, inquiring about satisfaction with the amount of information given to them about emotional support options, as well as their interest in speaking to other individuals who have pancreatitis, should be a point in the interest survey.

The interest survey can also obtain opinions of potential participants and topics surrounding the details of a support group. Various systems and organization set-ups exist for support groups. The questionnaire can ask the patient their preference for a face-to-face group meeting (at a pancreatitis study site or care center) or an online message board. Other preferences to consider in implementing a support group would include whom to include in the group or limit the group to (age, type of pancreatitis, etc.), possible topics of discussion, support for family members or support persons in addition and separately from those with a diagnosis of pancreatitis, how often the group should meet, the location of the meetings, and what time of day (these details would be different according to each center).

Following the receipt of the interest survey, the information can be compiled and used to form a support group or an alternative for psychosocial intervention as well as patient's interest in additional support. Based on the interest expressed in the survey, study participants could be recruited to participate in the study with an explanation of the purpose, and informed consent obtained and documented.

Given the small population of hereditary patients that is spread throughout the country, a face-to-face support group would not be feasible. Support groups for pancreatitis in general (hereditary and sporadic) could be formed at study sites or pancreatitis centers. Alternative forms of support can be investigated including a contact list and online message board.

Following a predetermined length of time for the intervention in place, a post-support questionnaire comprised of questions involving pain and quality of life can be administered to compare pre- and post-intervention attitudes. The benefit of comparing patient's quality of life before and after intervention would allow researchers to assess whether patients were benefiting from these services. This comparison would also confirm the findings of this study, which based on patients' report of pain level and quality of life psychosocial intervention is warranted.

APPENDIX A

TABLES CORRESPONDING TO TEXT

Table 22. SF-12® Mean Scores- 1990 General Population

AGE	PCS	MCS
45-54	50	50
55-64	47	51
65-74	44	52
>75	39	50

APPENDIX B

FIGURES CORRESPONDING TO TEXT

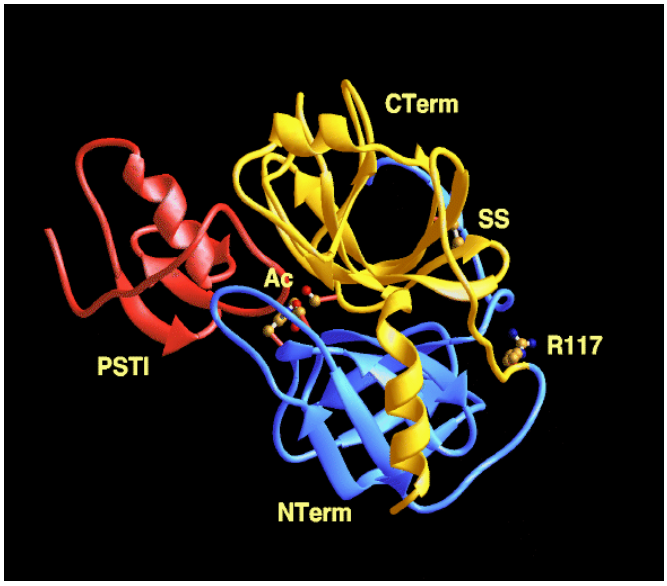

Figure 22. Trypsin Molecule

APPENDIX C

INFORMED CONSENT FOR NAPS2 STUDY

University of Pittsburgh

School of Medicine
Department of Medicine
Division of Gastroenterology, Hepatology, and Nutrition

Mezzanine Level, C-Wing
UPMC Presbyterian
200 Lothrop Street
Pittsburgh, PA 15213-2582
412-648-9115
Fax: 412-648-9378

Approval Date: August 30, 2005
Renewal Date: March 28, 2006
University of Pittsburgh
Institutional Review Board #000537

Name: _____
Please Print

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

TITLE: North American Pancreatitis Study II Molecular Epidemiology of Chronic Pancreatitis in the United States

PRINCIPAL INVESTIGATOR:

David C. Whitcomb, M.D., Ph.D.
Professor of Medicine, Cell Biology and Physiology and Human Genetics
University of Pittsburgh
412 648-7218

CO INVESTIGATORS:

Asif Khalid, M.D.
Kevin McGrath, M.D.
Robert Schoen, M.D., M.P.H.
Adam Slivka, M.D., Ph.D.
Klaus Bielefeldt, M.D., Ph.D.
M2, C Wing
Presbyterian University Hospital
412 648-9115

Beth Elinoff, RN, MPH
Kathy Bauer, RN
576 Scaife Hall, 3550 Terrace Street
Pittsburgh, PA 15261
412-623-4124

Kenneth Lee, M.D.
Arthur J. Moser, M.D.
4th Floor, A Wing, Scaife Hall
3550 Terrace Street
Pittsburgh, PA 15261

Ihsan M. Salloum, MD, MPH
Jeanine Hayes, MSN
9th Floor Oxford Building
3811 O'Hara Street
Pittsburgh, PA 15213
412/282-2005

Mark Lowe, MD, PhD
Leena Kandula, MD
Division of Pediatric Gastroenterology
Children's Hospital of Pittsburgh
412-692-5180

SOURCES OF SUPPORT: **NIH** (National Institutes of Health) **RO1- DK 61451**

Description:
You / your child are being asked to participate in a multicentered genetic research study because you / your child have been identified as having recurrent acute pancreatitis or chronic pancreatitis. The purpose of this study is to determine the genetic and environmental factors that cause these forms of pancreatitis. Pancreatitis is an inflammation of the pancreas. Sudden attacks of inflammation are called acute pancreatitis. More than one attack of acute pancreatitis is called recurrent acute pancreatitis. Chronic pancreatitis is an inflammatory process leading to irreversible destruction of the pancreas, often for unknown reasons. This study will investigate several genes and other factors measured in the blood that may cause recurrent acute pancreatitis and chronic pancreatitis; and may help us to better understand how genes and environmental factors may work together to cause recurrent acute pancreatitis and chronic pancreatitis. This will be done by collecting and storing plasma and DNA which will be obtained from the blood samples and health related information from questionnaires to test for causes and effects of pancreatitis. If you have a biopsy or surgery on your pancreas, waste tissue (tissue that would normally be thrown away) will be collected.

Techniques have been developed which allow for the evaluation of inherited factors called genes, as well as of the genetic make-up of cells, called DNA. By studying material obtained from your blood and tissue sample, researchers might identify the gene(s) that carry the trait(s) of recurrent acute pancreatitis and chronic pancreatitis.

The blood and tissue sample will be used for research on pancreatitis. The blood will be tested for variations in DNA (deoxyribonucleic acid). These are similarities and differences found in an individual's blood. Once the sample is received, it will be given a unique code number and will

no longer contain your / your child's name to help keep information about you / your child confidential. Neither you nor your doctor will be able to find out your / your child's specific results.

If you / your child agree to participate in this study, you / your child will be one of 1000 cases to be recruited from major medical centers located throughout the United States, and one of about 300 subjects recruited from the University of Pittsburgh. Subjects will range in age from 3 months (since this is the age at which pancreatitis is usually first diagnosed) to 100 years of age, and both male and female subjects will be included. Participation in this study will require one visit. Study participants will be requested to fill out a questionnaire. The questionnaire will ask questions about your / your child's age, your / your child's family history of pancreatic disease, your / your child's personal history of pancreatic disease (including the age that symptoms first occurred, the type of symptoms, and any treatments), your history of alcohol and tobacco use, and current medications. It will take approximately 30 minutes for you to complete the questionnaire and approximately 15 minutes for you to get your blood drawn, and you may be called to review the questionnaire with a trained individual. You will also be contacted every year for the duration of the study (10 years), by mail or by phone, to update your health and family history information. This follow-up contact will take approximately 30 minutes. You / your child will also provide 30-40cc (3 tablespoons) of blood. For children who weigh less than 20kg (45 pounds), no more than 2ml/kg (about 1ml/pound) will be obtained. You/your child will only be asked to provide a blood sample once. The questionnaire and blood will be sent to the Genomics and Proteomics Core Laboratories at the University of Pittsburgh and/or the laboratory of Dr. David Whitcomb (the study director) for processing. The blood samples will have your name and date of birth on them when they arrive at the laboratory. Once the samples have been processed, your name and date of birth will be removed and replaced by an ID number. This ID number can only be linked to your name by the study coordinator. You will also be asked to sign a consent form releasing medical records relevant to your / your child's diagnosis of pancreatitis and related conditions.

If you have surgery or a biopsy done, you should notify the study coordinator in advance so that arrangements can be made for getting a sample of tissue.

If you / your child agree to participate in this study you will be encouraged to ask your spouse, or 5 friends of a similar age (within 5 years) and ethnicity to participate in this study as an unaffected control subject (someone without the disease being studied). You / Your child will also be encouraged to ask other family members who may or may not have pancreatitis to participate as a family unit.

This research will not have an effect on your care, therefore, you, your family, or your doctor will not receive results of these studies, and the results will not become a part of your medical record. Because this is a research study, any results of testing are of unknown significance. These results are not confirmed in a certified clinical laboratory, therefore, the results cannot be used for clinical decision-making or family planning, nor can the results be released to you.

Subject's Initials
Revised 8/16/05

The samples will be stored in the Genomics and Proteomics Core Laboratories at the University of Pittsburgh or in the laboratory of Dr. Whitcomb until the samples are used up. Samples collected as part of this study will be controlled by Dr. Whitcomb. At the end of this study, samples of your/ your child's blood will be destroyed unless you agree to make them available for other studies. You may also request in writing, at any time, to have your/your child's sample destroyed. Once this written request is received by the laboratory your/your child's sample will be destroyed immediately.

If you / your child agree to participate in this research project, the blood sample and genetic material you/your child provided will become the property of the University of Pittsburgh and the use of your / your child's biological material will be under the control of the principal investigator of this research project. If you agree, your/your child's biological material will be made available to other investigators associated with this study, with identifying information, for other research related to pancreatitis.

Risks/Benefits:
The only physical risk of participating in this study is that associated with the blood draw. The blood draw may cause discomfort, bleeding and/or bruising from the insertion of the needle, fainting (infrequent, expected to occur in 1-10% of people) and infection at the needle stick site (rare, expected to occur in less than 1% of people). There is the possibility that if the results of the research studies involving you/your child's genetic material were to become generally known, this information could affect your ability to be insured, employed or influence plans for children or have a negative impact on family relationships, and/or result in paternity suits or stigmatization.

There is no direct benefit to you /your child from participating in this study. The information provided by you/your child may help the investigators to better understand the causes of recurrent acute pancreatitis and chronic pancreatitis and add to the knowledge of genetic conditions in general.

New Information:
Individual results of this research study will not be provided to you / your child. You / your child will be promptly notified if any other general information about this research study develops during the course of the study which may cause you / your child to change your mind about continuing to participate.

Costs and Payments:
There are no costs to you / your child for participation in this study. You / Your child will be compensated $25 for participating in this study. You will be compensated when the consent forms, questionnaires and blood samples have all been received by the Genomics and Proteomics Core Laboratories or the laboratory of Dr. Whitcomb at the University of Pittsburgh. Neither you / your child nor your / your child's insurance carrier will be billed for either the preparation of your biologic samples, or the genetic material or the shipping and handling of these samples.

Compensation

The University of Pittsburgh investigators and their associates who provide services at the UPMC Health System (UPMC HS) recognize the importance of your voluntary participation to their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research. If you believe that you / your child have been injured as the result of the research procedures being performed, please contact immediately the Principal Investigator listed on the cover sheet of this form (Dr. Whitcomb) or one of the co-investigators listed on the first page of this form.

Emergency medical treatment for injuries solely and directly relating to your participation in this research will be provided to you by hospitals of the UPMC HS. It is possible that the UPMC HS may bill your insurance provide for the costs of this emergency treatment, but none of these cost will be charged directly to you. If you / your child's research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. You / your child will not receive monetary payment for, or associated with, any injury that you suffer in relation to this research.

Confidentiality:
This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other health care provider (e.g., physician office) records. The information that will be recorded will be limited to information concerning your Pancreatitis and/or other gastrointestinal problems. This information will be used for the purpose of evaluating your Pancreatitis before and during the study.

All records related to your involvement in this research study will be stored in a locked file cabinet. Your identity on these records will be indicated by a case number rather than by your name, and the information linking these case numbers with your identity will be kept separate from the research records. In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study:

> Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical record information) for the purpose of monitoring the appropriate conduct of this research study.

The fact that you are participating in a research study and that you are undergoing certain research procedures (but not the results of the procedures) may also be made known to individuals involved in insurance billing and/or other administrative activities associated with the conduct of the study.

Authorized representatives of the UPMC Health System hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2)

addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical record information) related to your participation in this research study for at least 5 years after the study is completed.

To further help to protect your / your child's privacy, the investigators have obtained a Confidentiality Certificate from the U.S. Department of Health and Human Services (DHHS). With this federal Certificate, the investigators cannot be forced (for example, by court order) to disclose information that may identify you in any federal, state, or local court; administrative; legislative; or other proceeding. Disclosure will be necessary, however, upon the request of the DHHS (for example, for audit or program evaluation purposes).

You should understand that this federal Certificate does not prevent you or a member of your family from voluntarily releasing information about yourself or your involvement in this research study. Note, however, that if an insurer or employer learns about your study participation and obtains your consent to receive your identifiable research information, then the investigators may not use the Certificate to withhold this information from the insurer or employer. This means that you or your family must also actively protect your privacy. Finally, you should also understand that this federal Certificate does not prevent investigators from taking steps, including reporting to appropriate authorities, to prevent serious harm to yourself or others.

Your / your child's biological material used in this study may contribute to a new invention or discovery. In some instances, these inventions or discoveries may be of commercial use and my be sold, patented, or licensed by the investigator at the University of Pittsburgh for use in other research or the development of new products related to recurrent acute pancreatitis or chronic pancreatitis. If you / your child agree to participate in this research study, you voluntarily and freely provide your blood to the investigator and the University of Pittsburgh. You / your child will not retain any property rights to this blood nor will you share in any money or other benefits that the investigator, the University of Pittsburgh or their agents may realize from the biological sample or their use in this research study. You retain the right to have your / your child's biological sample destroyed if you / your child decide to withdraw from the study.

Right to Withdraw

Your / your child's participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no affect on your current or future medical care at a UPMC Health System hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

Your / your child's doctor is involved as an investigator in this research study. As both your doctor and a research investigator, s/he is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical record information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no affect on your current or future medical care at a UPMC Health System hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

It is possible that you may be removed from the research study by the researchers for example if your diagnosis of pancreatitis cannot be confirmed; your biological specimen becomes contaminated, used up, or lost; the origin of your biological specimen is uncertain; or the entire study has been terminated.

_____
Subject's Initials
Revised 8/16/05

****

Voluntary Consent

The above information has been explained to me and all of my questions have been answered. I understand that any future questions I have about this research will be answered by the investigator(s) listed on the first page of this consent document at the telephone numbers given. I also understand that I may always request that my questions be answered by a physician involved in this research study. Any questions I/my child have about rights as a research subject will be answered by the Human Subject Protection Advocate, IRB Office, University of Pittsburgh (1-866-212-2668). By signing this form, I agree to participate in this research study.

A copy of this consent form will be given to me.

1. I give my permission to use my biological sample or genetic material, with personal identifiers, in other research projects involving the study of pancreatitis.

   YES_____ NO_____

2. I give my permission to be re-contacted to obtain my consent if there is a desire to use my biological sample or genetic material, with personal identifiers, in other research projects involving the study of different diseases or conditions (i.e., diseases or conditions other than those specified in the Description section of this consent form).

   YES_____ NO_____

_____ _____
Participant Date

_____ _____
Witness (if appropriate) Date

For children under the age of 18:

_____
Participant's (child's) name (print)

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____ _____
Parent's or Guardian's name (Print) Relationship to participant (child)

_____ _____
Parent's or Guardian's signature Date

_____ _____
Parent's or Guardian's name (Print) Relationship to participant (child)

_____ _____
Parent's or Guardian's signature Date

ASSENT:
I certify that I have carefully explained the purpose and nature of this research study to the child subject in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e. assent) to participate in this study.

_____ _____
Investigator's Signature Date

_____
Investigator's Printed Name

For children ages 14 – 17 or children able to sign their name:
This research has been explained to me, and I agree to participate.

_____ _____
Signature of Child-Subject Date

_____
Printed Name of Child-Subject

Certification of Informed Consent

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the above individual and that any questions about this information have been answered.

_____ _____

Investigator's Signature Date

APPENDIX D

NAPS2 QUESTIONNAIRE

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

Thank you for taking the time to carefully fill out the following questions. It is very important to be as accurate as possible. If needed, you can update some of the questions that you are unsure about during the next two weeks by contacting the person helping you fill out this form, or by calling our toll free number (1-888-PITT-DNA; 1-888-748- 8362). A few of the questions may be of a personal nature, such as past drinking habits. Again, it is important to be as accurate as possible and all information will be kept CONFIDENTIAL as part of this study. Thank you for your complete cooperation.

1. Demographics and Family History

1.1 Sex: ☐ Male ☐ Female

1.2 Height: ☐ ft ☐☐ inches

1.3 Current Weight: ☐☐☐ lbs.

1.4 Greatest Weight: ☐☐☐ lbs.

1.5 Race/Ethnicity (If you are bi- or multiracial, please check all that apply):

☐ White ☐ Black ☐ Asian ☐ Hispanic ☐ American Indian ☐ Other

please specify:_____

1.6 Are you of Ashkenazi Jewish heritage? ☐ No ☐ One parent ☐ Both parents ☐ I don't know

1.7 Please name the countries from where your ancestors originated. Be as specific as possible, add region or city, if you know: for example Germany (Bavaria); or Italy (Rome): _____

_____

2. Family History

	living	deceased
2.1 How many **brothers and sisters** do you have?	☐☐	☐☐
2.2 How many **children** do you have?	☐☐	☐☐

2.3 Does pancreatitis run in your family? ☐ No ☐ Yes

2.4 Does pancreatic cancer run in your family? ☐ No ☐ Yes

2.5 If either pancreatitis or pancreatic cancer run in your family, would you like to be contacted about other studies related to these problems? ☐ No ☐ Yes (sign here)_____

Form 012704

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

2.6 How many of your family members were diagnosed with one or more of the following diseases? (Enter the actual number, to the best of your memory.)

	Me	Father / Mother	Brother / Sister	Children	Grandparents	Aunt / Uncle	Cousins
Example: ---------->	1	1	2		2	1	
Chronic Pancreatitis	☐	☐	☐	☐	☐	☐	☐
Acute Pancreatitis	☐	☐	☐	☐	☐	☐	☐
Hereditary Pancreatitis	☐	☐	☐	☐	☐	☐	☐
Asthma or hay fever	☐	☐	☐	☐	☐	☐	☐
Liver disease or cirrhosis	☐	☐	☐	☐	☐	☐	☐
Gall stones / Gallbladder removal	☐	☐	☐	☐	☐	☐	☐
High Triglycerides	☐	☐	☐	☐	☐	☐	☐
High Cholesterol	☐	☐	☐	☐	☐	☐	☐
Diabetes (treated by diet/pills)	☐	☐	☐	☐	☐	☐	☐
Diabetes (treated by insulin)	☐	☐	☐	☐	☐	☐	☐
Cystic fibrosis	☐	☐	☐	☐	☐	☐	☐
Male Infertility	☐	☐	☐	☐	☐	☐	☐
Chronic sinusitis	☐	☐	☐	☐	☐	☐	☐
Renal (kidney) disease or failure (dialysis)	☐	☐	☐	☐	☐	☐	☐
Heart attack or stroke	☐	☐	☐	☐	☐	☐	☐
Pancreatic cancer	☐	☐	☐	☐	☐	☐	☐
Cancer of the liver	☐	☐	☐	☐	☐	☐	☐
Colon cancer	☐	☐	☐	☐	☐	☐	☐
Breast cancer	☐	☐	☐	☐	☐	☐	☐
Ovarian cancer	☐	☐	☐	☐	☐	☐	☐
Endometrial cancer	☐	☐	☐	☐	☐	☐	☐
Any other form of cancer (specify:) _____	☐	☐	☐	☐	☐	☐	☐
Other _____	☐	☐	☐	☐	☐	☐	☐

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

3. Diet and Lifestyle

Tobacco Use

3.1 Smoking – did you ever smoke cigarettes?

- ☐ never (less than 100 cigarettes in your life) *->go to question 3.3*
- ☐ started (month/year) ☐☐/☐☐☐☐
- ☐ quit (month/year) ☐☐/☐☐☐☐

3.2 On the average, how many cigarettes do / did you smoke per day? ☐☐

Alcohol consumption

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

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

☐ Yes. ☐ No (less than 20 drinks in a lifetime) *go to question 4.1.*

3.4 In the months *before* getting pancreatitis, OR if no history of pancreatitis, in general,

3.4.1) How many drinks were you able to consume in a day? ☐☐

3.4.2) Did close friends or relatives worry or complain about your drinking? ☐ Yes ☐ No

3.4.3) Did you sometimes take a drink in the morning when you first got up? ☐ Yes ☐ No

3.4.4) Did a friend or family member ever tell you about things you said or did while you were drinking that you could not remember? ☐ Yes ☐ No

3.4.5) Did you feel the need to cut down on your drinking other than to prevent attacks of pancreatitis? ☐ Yes ☐ No

3.5 How old were you when you **began drinking** at least once per month? ☐☐

3.6 How old were you when you began drinking **the most alcohol** in your life? ☐☐

3.7 On the AVERAGE about how many drinks would you have on a drinking day? ☐☐

3.8 How many days per month did you drink at this level? ☐☐

3.9 What is the MOST number of drinks you would have in any one day? ☐☐

3.10 What type of beverage would you consume in an average month of heaviest drinking?

Beer ☐☐☐ Wine ☐☐☐ Mixed Drinks ☐☐☐

3.11 How long did you drink alcohol at the heaviest level (in months ☐☐ or years ☐☐)?

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

Drinking Patterns

Drinking patterns often change after an event such as college, marriage, loss of a spouse, unemployment, religious reasons, development of pancreatitis or other health problem. The following chart is for questions 3.12-3.16.

Drinking patterns during an average month

1. Abstinent (none)
2. Occasionally (less than 15 drinks per month on average – no binges)
3. Weekend drinker (up to 6 drinks per day for up to 2 days per week)
4. Moderate drinking (15 drinks per month up to two drinks per day)
5. Heavier drinking (more than two drinks per day)
6. Binge drinking (at least 3 days in a row of heavy drinking of more than 6 drinks per day)

3.12 From the list above, rate your usual style of drinking when you **began** drinking (1 to 6) ☐

3.13 Was there an event that caused you to change your drinking habits? ☐No (go to question 3.16)

☐ Yes, event _____, Your age ☐☐

New drinking pattern ☐

Average number of drinks per day on an average day ☐☐

3.14 Was there another event causing you to change your drinking habits? ☐No (go to question 3.16)

☐ Yes, event _____, Your age ☐☐

New drinking pattern ☐

Average number of drinks per day on an average day ☐☐

3.15 Was there another event causing you to change your drinking habits? ☐No (go to question 3.16)

☐ Yes, event _____, Your age ☐☐

New drinking pattern ☐

Average number of drinks per day on an average day ☐☐

3.16 Do you currently drink alcohol? ☐No

☐ Yes, the age you started the present pattern ☐☐

Current drinking pattern ☐

Average number of drinks per day on an average day ☐☐

What type(s) of beverage do you consume on an average day?

Beer ☐☐ Wine ☐☐ Mixed Drinks ☐☐

Thank you for answering these questions honestly. The results will be kept confidential, and protected by a Certificate of Confidentiality. Please feel free to return to this section and updated it at any time.

Form 012704

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

4. Acute Pancreatitis

Note: Acute pancreatitis is defined as sudden-onset of abdominal pain due to inflammation of the pancreas. It causes high blood amylase and/or lipase(3 times upper limits of normal) and may require hospitalization (overnight stay in a hospital), pain-medication and withholding of food

4.1 Have you ever had **acute** pancreatitis?

☐ No (go to question 5.1)

☐ Yes

When was your **first medically proven** acute pancreatitis attack?

☐☐/☐☐☐☐ (month/year)

4.2 Have you been **hospitalized** (at least overnight) for acute pancreatitis?

☐ No (go to next question)

☐ Yes

Date of your **first** hospitalization for pancreatitis ☐☐/☐☐☐☐ (month/year)

Duration of your **first** hospitalization for pancreatitis ☐☐☐ days

4.3 Have you had **more than one** attack of acute pancreatitis?

☐ No (go to next question)

☐ Yes

Number of attacks ☐☐☐

Number of hospitalizations ☐☐☐

4.4 **How long** does an attack of **acute pancreatitis** usually last?

☐☐ hours or ☐☐ days

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

5. Chronic Pancreatitis / Abdominal Pain

Note: Chronic pancreatitis is defined as irreversible scaring of the pancreas that can be seen on a CT scan, ultrasound or by special testing. Symptoms, such as pain, must last 6 months or longer.

5.1 When did you **first have pain** that you **believe** came from your pancreas? ☐☐/☐☐☐☐

5.2 Have you been **diagnosed** with chronic pancreatitis? ☐ Yes ☐ No (*go question 5.12*)

5.3 **When** was the diagnosis of chronic pancreatitis made? ☐☐/☐☐☐☐ (mm/yyyy)

5.4 **How** was the diagnosis of chronic pancreatitis made? (Check all that apply)

☐ CT Scan ☐ Transabdominal Ultrasound ☐ EUS ☐ Abdominal X-ray

☐ Tube (secretin) test ☐ Fecal Elastase ☐ Abdominal pain

☐ Other _____ ☐ I am not sure

5.5 What do you believe **caused** your pancreatitis? _____

5.6 Several **patterns of pain** have been described in chronic pancreatitis. In this question, please identify the type of pain that best fits your condition.

☐ A) I have **episodes of mild to moderate** pain, usually controlled by the medicines noted above.

☐ B) I have **constant mild to moderate** pain, usually controlled by medicines noted above.

☐ C) I am usually free of abdominal pain, but I have **episodes of severe** pain.

☐ D) I have **constant mild** pain that is controlled (as above), plus **episodes of severe** pain.

☐ E) I have **constant severe** pain that does not change.

If you have marked answers C) or D):

5.6b How many **episodes of severe pain** do you have in a month / in a year?

☐☐☐ bouts of severe pain in a **month**

☐☐☐ bouts of severe pain in a **year**

Form 012704

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

5.7 How many times have you been hospitalized (overnight or longer) for **severe abdominal pain?**

☐☐☐ times in my whole life ☐☐☐ times in the last 12 months

5.8 How many work days or school days have you lost in the last month due to pain? ☐☐ ☐N A

5.9 Are you on disability or unemployed because of your pain? ☐Yes ☐No

5.10 What **triggers** a painful episode of pancreatitis or abdominal pain? (check all that apply)

☐ Alcohol ☐ Emotional stress ☐ Spicy meals ☐ Fatty meals ☐ Menstrual period

☐ Other _____

☐ There seems to be no specific trigger

5.11 Do you have one or more of the following pancreatitis-associated **diseases**?

☐ diabetes (high blood sugar) starting in: ☐☐/☐☐☐☐ (month/year)

☐ diarrhea (controlled with enzymes) starting in: ☐☐/☐☐☐☐ (month/year)

☐ Other (_____) starting in: ☐☐/☐☐☐☐ (month/year)

5.12 Do you use **pain medication on a regular basis**? ☐ Yes ☐ No (go to next question)

Please circle the type of pain medicine you regularly use from the list below.

ASPIRIN-TYPE MEDICATIONS			IBUPROFEN-TYPE MEDICATIONS			
Acuprin	Excederin		Advil	Feldene	Meclomen	Ponstel
Anacin	Fiorinal		Aleve	Fenoprofen	Mefanamic Acid	Piroxicam
Ascriptin	Halfprin		Anaprox	Flurbiprofen	Midol 200	Relafen
Axotol	Lortab		Ansaid	Haltran	Motrin	Sulindac
Azdone	Norgesic		Cataflam	Ibuprofen	Nalfon	Tolectin
Bufferin	Percodan		Clinoril	Indocin	Nambumeton	Tolmetin
Damason	Roxiprin		Daypro	Indomethacin	Naprosyn	Toradol
Easprin	Soma Cmpd.		Diclofenac	Ketoprofen	Naproxen Sodium	Trendar
Ecotrin	Synalgos		Diflunisal	Lodine	Nuprin	Voltaren
Empirin	Talwin		Dolobid	Medipren	Orudis	
Equagesic			Etodolac	Meclofenamate	Oruvail	

How many of these pills do you take per day? ☐☐

5.13 Do you use **acetaminophen**-containing medication (for example, Tylenol)? ☐yes ☐no

5.14 Are there any medicines not listed above that work for pain?

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

6. Medications

Please list all your current medication(s). Include over-the-counter (OTC) medicine you take on a regular basis (vitamins, antioxidants, etc), when you started taking them, and if you are taking them for your pancreas. If you do not have a complete list, please ask the person helping you to give you another sheet to be returned within *one week*. If you need more space, please use the back of this sheet.

6.1 Pancreatic Enzymes:

Name:	Dose per meal:	No. of meals/day:	Started (month/year):
_____	_____	_____	☐☐/☐☐☐☐
	Dose per snack:	No. of snacks/day:	
	_____	_____	

6.2 Insulin:

Name:	Units per day:	Started (month/year):
_____	_____	☐☐/☐☐☐☐
_____	_____	☐☐/☐☐☐☐

6.3 Other Prescription Medication:

Name:	Dose Size:	Doses per day:	Started (month/year):
_____	_____	_____	☐☐/☐☐☐☐
_____	_____	_____	☐☐/☐☐☐☐
_____	_____	_____	☐☐/☐☐☐☐
_____	_____	_____	☐☐/☐☐☐☐
_____	_____	_____	☐☐/☐☐☐☐
_____	_____	_____	☐☐/☐☐☐☐
_____	_____	_____	☐☐/☐☐☐☐

6.4 Over-the-counter (OTC) Medications: (check the first box if this is for the pancreas)

☐	_____	_____	_____	☐☐/☐☐☐☐
☐	_____	_____	_____	☐☐/☐☐☐☐
☐	_____	_____	_____	☐☐/☐☐☐☐
☐	_____	_____	_____	☐☐/☐☐☐☐

☐ **Check if continued on back.**

Form 012704

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

7.9 Have you ever been forced to find a bathroom urgently because you had to have a bowel movement within 30-60 minutes after eating or drinking something?

- ☐ No (go to next question)
- ☐ Yes
  - ☐ May be unpredictable, sometimes with food, spices, or stress
  - ☐ Only after coffee/tea
  - ☐ Only with possible food poisoning
  - ☐ Only after being prescribed a drug (specify drug): _____

7.10 Have you ever had frequent bowel movements and abdominal surgery?

- ☐ No (go to next question)
- ☐ Yes, I had problems with my bowels before surgery
- ☐ Yes, the change with my bowel movement frequency started only after having surgery

If yes, what surgery did you have? _____

If yes, what bowel changes did you have with the surgery? _____

_____

7.11 Do you have to be careful about eating in general or avoid certain foods or liquids because they cause you to have abdominal pain and/or cramping, and results in a change in your usual bowel habits?

- ☐ No
- ☐ Yes, what foods _____

_____

7.12 Have you ever had or thought you had symptoms of irritable bowel syndrome or spastic colon at any time in your life?

- ☐ No
- ☐ Yes, why? _____

_____

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

8. General Health Survey (SF-12)

This survey asks for your views about your general health. This information will help you keep track of how you feel and how well 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.

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

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

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	Yes limited a little	No not limited at all
2. Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
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	No
4. Accomplished less than you would like	☐	☐
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	No
6. Accomplished less than you would like	☐	☐
7. Didn't do work or other activities as carefully as usual	☐	☐

---

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

Form 012704

☐☐-☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Center Initials Patient ID Date of Birth (Month/Date/Year)

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

How much of the time during the *past 4 weeks*...

		All of the time	Most of the time	A good bit of the time	Some of the time	A little the time	None of the time
9.	Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
10.	Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
11.	Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

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	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

********** **END OF QUESTIONAIRE** **********

Thank you for completing the questionnaire portion of this study. The information will be kept confidential and coordinated with the answers of over 2000 other people. Although the specific results of your test will not be available, you will be kept informed of the general findings of this study if you so choose. If you would like to be placed on our mailing list, please check the box below.

☐ Yes, I would like to be placed on the mailing list

☐ No, not at this time.

Comments about the study or questionnaire:

Updates of the study will also be posted on our web sites.

http://www.pancreas.org. or http://www.pancreatitis.org

Form 012704

APPENDIX E

INFORMED CONSENT FOR HP STUDY

University of Pittsburgh

School of Medicine
Department of Medicine
Division of Gastroenterology, Hepatology, and Nutrition

Mezzanine Level, C-Wing
UPMC Presbyterian
200 Lothrop Street
Pittsburgh, PA 15213-2582
412-648-9115
Fax: 412-648-9378

University of Pittsburgh
Institutional Review Board
Approval Date: Oct 18, 2005
Renewal Date: Oct 17, 2006
IRB #0311032

Subject's Name:_____

Consent To Act As A Subject In An Experimental Study

Title: **Genetic Linkage Study For Hereditary Pancreatitis**

Investigator
David Whitcomb, M.D., Ph.D.
Principal Investigator
Professor of Medicine, Cell Biology and Physiology and Human Genetics
University of Pittsburgh
200 Lothrop St.
Mezzanine 2, C Wing
Pittsburgh, PA 15213
412 648-9016

Co- Investigators
Véronique Morinville, MD
M. Michael Barmada, PhD
Beth Elinoff, RN, MPH
Erin Fink, MS
University of Pittsburgh
5115 Centre Avenue
Pittsburgh, PA 15232
1-888-PITT-DNA

Mary Money, MD
354 Mill Street
Hagerstown, Maryland 21740
301-797-0210

Sources Of Support
Research Funds, Division of Gastroenterology and Hepatology
NIH Grant RO1-DK54709

_____
Subject's Initials

Description:

The purpose of this research study is to collect and store information and blood samples for a genetic research study (genetic bank) related to Hereditary Pancreatitis (HP). By studying material obtained from your blood sample, researchers may be able to identify the gene(s) that are related to HP.

You are being asked to participate in a research study because you or a close relative (parent, brother, sister, spouse or child) has been diagnosed with pancreatitis or pancreatic cancer that may be due to hereditary pancreatitis or if you have pancreatic insufficiency/maldigestion that improves with taking pancreatic enzymes. Hereditary pancreatitis (inflammation of the pancreas) is a genetic condition (passed on from parents to children), the cause of which is not completely known. Hereditary pancreatitis is associated with a 30-40% incidence of pancreatic cancer. The purpose of this study is to search for the cause of this condition by comparing the DNA obtained from blood from family members with and without pancreatitis and/or pancreatic cancer. We have currently identified the gene responsible for the most common form of HP, and are working to identify other genetic factors responsible for this condition.

If you have pancreatitis or pancreatic cancer, you will be asked to identify currently living biological relatives (e.g. mother, father, grandparents, brothers and sisters). You will be requested to discuss this research study with these relatives and ask them if they will agree to contact the investigators to discuss obtaining their consent to participate in the study.

If you agree to participate in this study you will be asked to sign this consent form. If you have any questions about this consent form, you can call the toll-free number listed on the first page, and your questions will be answered by one of the investigators. When this signed consent form is received by the study center, a questionnaire and sample kit will be sent to you. You may arrange for the blood sample to be drawn at a location of your own choosing such as your doctor's office, a hospital lab or independent lab. You will be asked to call the research center at 1-888 PITT DNA (1-888-748-3362) prior to scheduling the blood draw so that arrangements can be made for payment to the phlebotomy (blood drawing) center. You should return the questionnaire and the samples in the approved kit.

We anticipate that approximately 2000 subjects, male and female, between the ages of 3 months and 100 years, will be asked to participate in this study.

If you/your child agree to participate in this study, approximately 2 tablespoons of blood will be drawn from a vein in your arm. Dr. Whitcomb will try to identify differences which may be related to the presence of hereditary pancreatitis. If consistent differences can be found, these may give us a clue as to the cause of this condition. If you are not able to give a blood sample, you will be given a container to spit in to along with directions, so that your DNA can be collected from your saliva (spit). About ½ teaspoon of saliva will be collected. The saliva samples will be stored in the same way as the blood samples.

You will also be requested to fill out a questionnaire related to HP. This will take approximately 30 minutes.

You/your child will only be asked to provide a blood sample once. The questionnaire and blood will be sent to the Genomics and Proteomics Core Laboratories at the University of Pittsburgh and/or the laboratory of Dr. David Whitcomb (the study director) for processing and storage. The Principal Investigator, Dr. David Whitcomb, will have control over the blood sample. The blood samples will have your name and date of birth on them when they arrive at the laboratory. Once the samples have been processed, your name and date of birth will be removed and replaced by an ID number. This ID number can only be linked to your name by the study coordinator. If you or your child has pancreatitis, you will also be asked to sign a consent form releasing medical records relevant to your / your child's diagnosis of pancreatitis and related conditions to the research study. Specifically, medical information confirming your diagnosis of pancreatitis and/or pancreatic cancer, such as pathology reports (results from your biopsies) and diagnostic tests, will be requested from your doctor to verify your / your child's diagnosis.

New research may identify other genes that may be involved in the development of HP, and if so, we would like to examine these genes. Thus, we will save part of your blood sample for future testing of genes that may be involved in HP. After 10 years or at the completion of this study on HP, samples of your blood and DNA will be destroyed unless you agree to make such samples available to investigators associated with this study, with identifying information, for other studies of pancreatitis. Your informed consent will be re-obtained for the use of these samples in any studies not involving HP.

If you agree to participate in this research project, use of your biological sample and genetic material will be under the control of the principal investigator of this research project.

Risks and Benefits

The risks of participating in this study are the following: The blood collection may result in some discomfort, bruising, bleeding, fainting, and rarely infection at the site of the needle stick. There is the possibility that if the results of the research studies involving you/your child's genetic material were to become generally known, this information could affect your ability to be insured, employed or influence plans for children or have a negative impact on family relationships, and/or result in paternity suits or stigmatization. There may also be psychological stress if one is found to have a marker for hereditary pancreatitis.

There is no direct benefit to you from participating in this study. Information from the study of you and/or your family may help the investigator to understand the cause of hereditary pancreatitis and add to the knowledge of genetic conditions in general.

Since the genetic testing for this study is done by a research laboratory, results from this study laboratory cannot be released. However, Genetic test results are available for those who choose to have their blood tested by Molecular Diagnostics, a licensed clinical laboratory at the University of Pittsburgh. If you wish to have your test results confirmed by this laboratory, you will need to mark your choice at the end of this consent form allowing the study center to release a small amount of your blood to Molecular Diagnostics. Then your DNA sample will be identified using an anonymous unique coding system. Because genetic information may result in psychological, legal, health insurance discrimination or other risk, you will be offered genetic

_____
Subject's Initials

counseling before and after genetic information is provided. After test results have been confirmed, they will be released directly to you (or parent/legal guardian) over the telephone by a trained genetic counselor. Following a telephone discussion of the results, a copy of your genetic test report will be mailed to you for your personal records. However, definite answers may not be available to you until this, and subsequent studies have been completed. This may delay the communication of results. If you choose to have your results confirmed by the clinical laboratory, you will be charged a fee for the clinical testing. This charge will be discussed with you by the study coordinator.

New Information
We will continue to provide you with new and current information during the course of the study via our newsletter and our World Wide Web page. You or your representative will be promptly notified if any other information about this research study develops during the course of the study which may cause you to change your mind about continuing to participate.

Costs and Payments
Your blood kit will be shipped to you and returned to us at no cost to you. We will pay for any fees associated with having your blood drawn for this research study. The blood analysis for this research study will be performed in our laboratory at no cost to you. You will be charged a fee if you decide to have your test results confirmed by Molecular Diagnostics. This charge should be discussed with the study coordinator. There will be no payment made to you for your participation.

Your biological sample or genetic material may lead, in the future, to new inventions or products. If the research investigators are able to develop new products from the use of your biological sample or genetic material, there are currently no plans to share with you any money or other rewards that may result from the development of the new product.

Compensation for Injury
The University of Pittsburgh researchers and their associates who provide services at UPMC recognize the importance of your voluntary participation to their research studies. These individuals and their staffs will make reasonable efforts to minimize, control, and treat any injuries that may arise as a result of this research.

If you believe that your are injured as the result of the research procedures being performed, please contact immediately the Principal Investigator or one of the co-investigators listed on the first page of this form.

Emergency medical treatment for injuries solely and directly relating to your participation in this research will be provided to you by hospitals of the UPMC. It is possible that the UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form.

_____
Subject's Initials

Confidentiality

This research study will involve the recording of current and/or future identifiable medical information from your/your child's hospital and/or other health care provider (e.g., physician office) records. The information that will be recorded will be limited to information concerning your / your child's pancreatitis and/or other gastrointestinal problems. This information will be used for the purpose of evaluating your/your child's pancreatitis during the study.

All records related to your/your child's involvement in this research study will be stored in a locked file cabinet. Your/your child's identity on these records will be indicated by a case number rather than by your/your child's name, and the information linking these case numbers with your/your child's identity will be kept separate from the research records. Your/your child's research results will not be put in your/your child's medical record. If you choose to have the genetic testing confirmed, results from the clinical laboratory will not be put in your/your child's medical record. In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable information (which may include your/your child's identifiable medical record information) related to your participation in this research study:

> Authorized representatives of the University of Pittsburgh Research Conduct and Compliance Office may review your identifiable research information (which may include your identifiable medical record information) for the purpose of monitoring the appropriate conduct of this research study.

The fact that you are participating in a research study and that you are undergoing certain research procedures (but not the results of the procedures) may also be made known to individuals involved in insurance billing and/or other administrative activities associated with the conduct of the study.

Authorized representatives of the UPMC hospitals or other affiliated health care providers may have access to identifiable information (which may include your identifiable medical record information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospital and health care services (e.g., laboratory tests, diagnostic procedures) associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical record information) related to your participation in this research study for at least 5 years after the study is completed.

Your biological material used in this study may contribute to a new invention or discovery. In some instances, these inventions or discoveries may be of commercial use and my be sold, patented, or licensed by the investigator at the University of Pittsburgh for use in other research or the development of new products related to pancreatic cancer. If you agree to participate in this research study, you voluntarily and freely provide your blood to the investigator and the

_____
Subject's Initials

University of Pittsburgh. You will not retain any property rights to this blood nor will you share in any money or other benefits that the investigator, the University of Pittsburgh or their agents may realize from the biological sample or their use in this research study. You retain the right to have your biological sample destroyed if you / your child decide to withdraw from the study.

Right to Participate or Withdraw

Your / your child's participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no affect on your current or future medical care at a UPMC Health System hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical record information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above.

To formally withdraw your consent for participation in this research study you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no affect on your current or future relationship with the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no affect on your current or future medical care at a UPMC hospital or affiliated health care provider or your current or future relationship with a health care insurance provider.

It is possible that you may be removed from the research study by the researchers for example if your diagnosis of pancreatitis cannot be confirmed; your biological specimen becomes contaminated, used up, or lost; the origin of your biological specimen is uncertain; or the entire study has been terminated.

Length of the study

The linkage study will continue for up to 10 years allowing for the comparison of the various forms of hereditary pancreatitis worldwide. At the termination of the study, the samples will be destroyed along with any personal identifiers.

_____
Subject's Initials

****

Voluntary Consent
The above information has been explained to me and all of my questions have been answered. I understand that any future questions I have about this research will be answered by the investigator(s) listed on the first page of this consent document at the telephone numbers given. I also understand that I may always request that my questions be answered by a physician involved in this research study. Any questions I/my child have about rights as a research subject will be answered by the Human Subject Protection Advocate, IRB Office, University of Pittsburgh (1-866-212-2668). By signing this form, I agree to participate in this research study.

A copy of this consent form will be given to me.

1. I give my permission to use my biological sample or genetic material, with personal identifiers, in other research projects involving the study of pancreatitis.

   YES_____ NO_____

2. I give my permission to be re-contacted to obtain my consent if there is a desire to use my biological sample or genetic material, with personal identifiers, in other research projects involving the study of different diseases or conditions (i.e., diseases or conditions other than those specified in the Description section of this consent form).

   YES_____ NO_____

For those who choose to have clinical testing:

3. I give my permission to the Hereditary Pancreatitis Study Center to release a small amount of my biological sample to Molecular Diagnostics for clinical confirmatory testing.

   YES_____ NO_____

_____ _____
Participant Date

_____ _____
Witness (if appropriate) Date

University of Pittsburgh
Institutional Review Board
Approval Date: Oct 18, 2005
Renewal Date: Oct 17, 2006
IRB #0311032

For children under the age of 18:

_____
Participant's (child's) name (print)

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____ _____
Parent's or Guardian's name (Print) Relationship to participant (child)

_____ _____
Parent's or Guardian's signature Date

_____ _____
Parent's or Guardian's name (Print) Relationship to participant (child)

_____ _____
Parent's or Guardian's signature Date

ASSENT:
I certify that I have carefully explained the purpose and nature of this research study to the child subject in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e. assent) to participate in this study.

_____ _____
Investigator's Signature Date

_____
Investigator's Printed Name

For children ages 14 – 17 or children able to sign their name:
This research has been explained to me, and I agree to participate.

_____ _____
Signature of Child-Subject Date

_____
Printed Name of Child-Subject

University of Pittsburgh
Institutional Review Board
Approval Date: Oct 18, 2005
Renewal Date: Oct 17, 2006
IRB #0311032

Certification of Informed Consent

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the above individual and that any questions about this information have been answered.

_____ _____

Investigator's Signature Date

Approval Date: Oct 18, 2005
Renewal Date: Oct 17, 2006
University of Pittsburgh
Institutional Review Board #0311032

Name: _____
Please Print

ADDENDUM

CONSENT TO ACT AS A PARTICIPANT IN A RESEARCH STUDY

TITLE: Genetic Linkage Study for Hereditary Pancreatitis

PRINCIPAL INVESTIGATOR: David C. Whitcomb, M.D., Ph.D.
Professor of Medicine, Cell Biology and Physiology and Human Genetics
University of Pittsburgh
412 648-7218

CO INVESTIGATORS:
Véronique Morinville, MD
M. Michael Barmada, PhD
Beth Elinoff, RN, MPH
Erin Fink, MS
University of Pittsburgh
5115 Centre Avenue
Pittsburgh, PA 15232
1-888-PITT-DNA

Mary Money, MD
354 Mill Street
Hagerstown, Maryland 21740
301-797-0210

Sources Of Support
Research Funds, Division of Gastroenterology and Hepatology
NIH Grant RO1-DK54709

NEW INFORMATION:
You / your child has participated in the Hereditary Pancreatitis research study in the past, which included filling out a questionnaire and giving a small amount (less than 2 tablespoons) of blood.

_____
Subject's Initials
Revised 10/27/05

The questionnaire for this study has been changed, and asks more questions than the old one. In order to get the same information on everyone, you / your child is being asked to fill out the new questionnaire. This questionnaire will take about 30 minutes to complete.

In addition, the blood of some people has been either used up or very little remains. If you / your child are one of these people (one of the investigators will tell you), you will also be asked to give another 2 tablespoons of blood. If you / your child would decide to participate in this new part of the study, you / your child will be asked to sign this addendum consent form and fill out the questionnaire. If your / your child's previous blood sample is low or used up, you / your child will give about 15 cc of blood (about 1 tablespoon). You may arrange for the blood sample to be drawn at a location of your own choosing such as your doctor's office, a hospital lab or independent lab. You will be asked to call the research center at 1-888 PITT DNA (1-888-748-3362) prior to scheduling the blood draw so that arrangements can be made for payment to the phlebotomy (blood drawing) center. The blood will go to the laboratory of Dr. David Whitcomb (the study director) for processing. The blood samples will have your study ID number on it. Your / your child's name will not be on the sample. The ID number can only be linked to your name by the study coordinator. The new blood samples will be stored in the laboratory of Dr. Whitcomb until the samples are used up. If you are not able to give a blood sample, you will be given a container to spit in to along with directions, so that your DNA can be collected from your saliva (spit). About ½ teaspoon of saliva will be collected. The saliva samples will be stored in the same way as the blood samples. Samples collected as part of this study will be controlled by Dr. Whitcomb. At the end of this study, samples of your/ your child's blood will be destroyed unless you agree to make them available for other studies. You may also request in writing, at any time, to have your/your child's sample destroyed. Once this written request is received by the laboratory your/your child's sample will be destroyed immediately.

You should return the questionnaire and if you are giving a DNA sample (either blood or saliva), the sample in the approved kit.

Risks

The only physical risk of participating in this part of the study is the blood draw. The blood collection may result in some discomfort, bruising, bleeding, fainting, and rarely infection at the site of the needle stick.

****

_____
Subject's Initials
Revised 10/27/05

Voluntary Consent
The above information has been explained to me and all of my questions have been answered. I understand that any future questions I have about this research will be answered by the investigator(s) listed on the first page of this consent document at the telephone numbers given. I also understand that I may always request that my questions be answered by a physician involved in this research study. Any questions I/my child have about rights as a research subject will be answered by the Human Subject Protection Advocate, IRB Office, University of Pittsburgh (1-866-212-2668). By signing this form, I agree to participate in this research study.

A copy of this consent form will be given to me.

1. I agree to complete the updated questionnaire.

   YES_____ NO_____

2. I agree to give the additional blood sample requested.

   YES_____ NO_____ N/A (not requested)_____

_____ _____
Participant Date

_____ _____
Witness (if appropriate) Date

Approval Date: Oct 18, 2005
Renewal Date: Oct 17, 2006
University of Pittsburgh
Institutional Review Board #0311032

For children under the age of 18:

_____
Participant's (child's) name (print)

I understand that, as a minor (age less than 18 years), the above-named child is not permitted to participate in this research study without my consent. Therefore, by signing this form, I give my consent for his/her participation in this research study.

_____ _____
Parent's or Guardian's name (Print) Relationship to participant (child)

_____ _____
Parent's or Guardian's signature Date

_____ _____
Parent's or Guardian's name (Print) Relationship to participant (child)

_____ _____
Parent's or Guardian's signature Date

ASSENT:
I certify that I have carefully explained the purpose and nature of this research study to the child subject in age appropriate language. He/she has had an opportunity to discuss it with me in detail. I have answered all his/her questions and he/she has provided affirmative agreement (i.e. assent) to participate in this study.

_____ _____
Investigator's Signature Date

_____
Investigator's Printed Name

For children ages 14 – 17 or children able to sign their name:
This research has been explained to me, and I agree to participate.

_____ _____
Signature of Child-Subject Date

_____
Printed Name of Child-Subject

Approval Date: Oct 18, 2005
Renewal Date: Oct 17, 2006
University of Pittsburgh
Institutional Review Board #0311032

Certification of Informed Consent

I certify that the nature and purpose, the potential benefits, and possible risks associated with participation in this research study have been explained to the above individual and that any questions about this information have been answered.

_____ _____

Investigator's Signature Date

APPENDIX F

HP QUESTIONNAIRE

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

Hereditary Pancreatitis Data Collection Questionnaire

Instructions:
Thank you for participating in the Hereditary Pancreatitis Study at the University of Pittsburgh. Please complete this questionnaire as much as possible and return it with your blood sample to our research center. All participants (with and without pancreatitis) are to complete this questionnaire. It is very important to be as accurate as possible. Please note that all information will be kept confidential as part of the study. If you have any questions and/or need assistance completing this questionnaire please contact the study by calling our toll free number (1-888-PITT-DNA or 1-888-748-8362).

Part A: Demographic Information

Today's Date: ☐☐/☐☐/☐☐☐☐

Name: _____ _____
Last First Middle Maiden SS# (last 4 digits, only)

Address: _____
Number and Street Apt. #

_____ _____ _____ _____
City State Zip Code Country (e.g. USA)

Contact Numbers: (_____) _____ (____) _____
Area code Home Phone Area code Alternate Phone (e.g. work, cell)

_____
Personal E-mail

1. How did you first learn about our HP research study? (check one, only)

☐ My doctor referred me

Your doctor's name & hospital: _____

Doctor's phone: _____ fax: _____

☐ A family member ☐ The Internet ☐ Newspaper article

☐ Other source: _____

2. Have you ever participated in a study on pancreatitis? ☐ Yes ☐ No
If yes, please explain study, and when and where you participated (indicate specific institution).

_____

☐☐☐-☐☐☐☐ ☐☐/☐☐/☐☐☐☐

Initials HP Study # Date of Birth (Month/Date/Year)

3. Sex: ☐ Male ☐ Female

4. Birthdate: (month/day/year) ☐☐/☐☐/☐☐☐☐

5. Where were you born? city_____ state_____ country (e.g. USA) _____

6. Where have you lived most of your life? (city/state) _____

How many years? ☐☐☐

How would you describe this area? ☐ urban ☐ suburban ☐ rural area

7. Height: ☐ ft ☐☐ inches

8. Current Weight: ☐☐☐ lbs.

9. Greatest Weight: ☐☐☐ lbs. (not including pregnancy)

10. Race/Ethnicity:

☐ American Indian/Alaska Native ☐ Indian ☐ Chinese/Japanese ☐ Black/African American

☐ White ☐ Middle Eastern ☐ Native Hawaiian/ Other Pacific islander

☐ Hispanic/Latino (please specify Spanish subculture) _____

☐ Other (please specify) _____

11. From what countries did your ancestors originate?

Be as specific as possible, add region or city, if known. Example: Germany (Bavaria) or Italy (Rome).

Please indicate if you have Jewish heritage.

Mother's Father: _____ Father's Father: _____

Mother's Mother: _____ Father's Mother: _____

Part B: Pancreatitis

To be complete by those with ANY TYPE of Pancreatitis

12. Have you ever been diagnosed with ANY TYPE of pancreatitis?

☐ Yes ☐ No (SKIP TO PART C on page #7)

13. When did you first have pain that you believe came from your pancreas?

(month/year) ☐☐/☐☐☐☐

14. Has your doctor ever told you that you have hereditary or familial pancreatitis?

☐ Yes ☐ No

15. Pancreas divisum is a structural defect that causes the pancreas to have 2 ducts leading to the lower intestine instead of just one. Has you doctor ever told you that you have "pancreatic divisum?"

☐ Yes ☐ No ☐ I am not sure

Acute Pancreatitis

16. Have you ever been told that you have acute pancreatitis?

Note: Acute pancreatitis is defined as a sudden-onset of abdominal pain due to inflammation of the pancreas. It causes high amylase and/or lipase and may require hospitalization (overnight stay in a hospital), pain medication and withholding food +/- liquids.

☐ Yes ☐ No (go to question #23)

If yes, when were you first told by a doctor that you have acute pancreatitis?

(month/year) ☐☐/☐☐☐☐

Did your doctor give you a specific reason for your acute pancreatitis? ☐ Yes ☐ No

If yes, below please check all that apply to the cause of your pancreatitis:

☐ Trauma, please specify: _____
☐ Systemic disease (e.g. HUS), please specify: _____
☐ Medications, please specify: _____
☐ Infection (e.g. virus), please specify: _____
☐ Obstruction/structural (e.g. divisum, biliary), please specify: _____
☐ Gallstones
☐ Alcohol
☐ Calcium abnormalities
☐ Hyperlipidemia/Triglyceride abnormalities
☐ Familial/Hereditary
☐ Other, please specify: _____

17. Have you ever been hospitalized (at least overnight) for acute pancreatitis? ☐ Yes ☐ No

If yes, what was the date of your first hospitalization for pancreatitis?

(month/year) ☐☐/☐☐☐☐

How long was your first hospitalization for pancreatitis? (days) ☐☐☐

18. Have you ever been admitted to the intensive care unit (ICU) of the hospital for pancreatitis?

☐ Yes ☐ No

If yes, what was the date of your first ICU hospitalization? (month/year) ☐☐/☐☐☐☐

How long was your first ICU hospitalization for pancreatitis? (days) ☐☐☐

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

19. Have you had more than one attack of acute pancreatitis? ☐ Yes ☐ No

If yes, how many attacks have you had? ☐☐☐

How many hospitalizations have you had? ☐☐☐

20. How long does an attack of acute pancreatitis usually last? ☐☐ hours or ☐☐ days

21. Have you ever been told that you have necrotizing pancreatitis? ☐ Yes ☐ No ☐ I am not sure

22. Have you ever had a pseudocyst? ☐ Yes ☐ No ☐ I am not sure

Chronic Pancreatitis

23. Have you ever been told that you have chronic pancreatitis?

Note: Chronic pancreatitis is defined as irreversible scarring of the pancreas that can be seen on a CT scan, ultrasound, or by special testing. Symptoms, such as pain, must last 6 months or longer. This is not the same as severe acute pancreatitis.

☐ Yes ☐ No (go to question #29)

If yes, when were you first told by a doctor that you have chronic pancreatitis?

(month/year) ☐☐/☐☐☐☐

24. How was the diagnosis of chronic pancreatitis made? (check all that apply)

☐ CT Scan ☐ Biopsy ☐ Transabdominal Ultrasound ☐ EUS (endoscopic ultrasound) ☐ Abdominal X-ray
☐ Tube (secretin) test ☐ ERCP ☐ MRCP ☐ Fecal Elastase ☐ Abdominal pain ☐ Blood tests
☐ Other _____ ☐ I am not sure

If applicable, what did your CT, ultrasound, or ERCP show? (check all that apply)

☐ Calcifications ☐ Pseudocyst ☐ Fluid collections ☐ Dilated duct

☐ I don't know (but was abnormal)

25. Please describe your pancreatitis by marking the relevant boxes below.

☐ I do not have pain from my pancreas

☐ I have episodes of pain (pain free between episodes): (please check the box that describes your pain, typically)

☐ Mild ☐ Moderate ☐ Severe

☐ I have constant abdominal pain: (please check the box that describes your pain, typically)

☐ Mild ☐ Moderate ☐ Severe

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

26. If you have episodes of pain, how long does the pain last?

☐☐ hours or ☐☐ days

27. If you have episodes of pain, how many episodes do you have in a month and in a year?

☐☐☐ episodes in a month, and

☐☐☐ episodes in a year

28. How many times have you been hospitalized (overnight or longer) for chronic pancreatitis?

☐☐☐ times in the last 12 months, and

☐☐☐ times in my whole life

Symptoms of Pancreatitis

29. How many work days or school days have you lost in the last month and in the last year due to pain? ☐ Not applicable

☐☐ Days in the last month AND ☐☐☐ Days in the last year

30. Are you on disability or unemployed because of your pain? ☐ Yes ☐ No

31. What do you believe caused your pancreatitis? _____

32. What triggers a painful episode of pancreatitis or abdominal (or back) pain? (check all that apply)

☐ Alcohol ☐ Emotional stress ☐ Spicy meals ☐ Fatty meals ☐ Large meals

☐ Menstrual period ☐ Pregnancy/delivery

☐ Others (e.g. medications, infection), please specify: _____

☐ There seems to be no specific trigger ☐ N/A I do not get pain from my pancreas

33. Check one for each:

Food makes the pain:	☐ Better	☐ Worse	☐ No difference	
Antacids make the pain:	☐ Better	☐ Worse	☐ No difference	☐ Not tried
Bowel movements make the pain:	☐ Better	☐ Worse	☐ No difference	

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

34. Do you have one or more of the following pancreatitis-associated <u>diseases</u>?

☐ Diabetes (high blood sugar)	starting in: (month/year)	☐☐/☐☐☐☐
☐ Diarrhea (controlled with pancreatic enzymes)	starting in: (month/year)	☐☐/☐☐☐☐
☐ Pancreatic stones	starting in: (month/year)	☐☐/☐☐☐☐
☐ Other (_____)	starting in: (month/year)	☐☐/☐☐☐☐

35. Do you use <u>pain medication</u> on a <u>regular basis</u> for your pancreatitis? ☐ Yes ☐ No

If no, have you ever used pain medication in the past? ☐ Yes ☐ No

36. Have you ever taken any of the following medications/supplements (recommended by your doctor)? (<u>check all that apply and specify your medications and doses in Part D, page#</u>)

☐ Pancreatic enzymes ☐ Insulin ☐ Oral hypoglycemics ☐ PPI (e.g. Prilosec, Nexium)

☐ H2 blockers (e.g. Zantac) ☐ Vitamins/minerals ☐ None of these

37. Which therapies have been attempted, and what was the outcome on your disease?
(please check all that apply)

<u>Medical therapies*</u>:	**Helpful**	**Unchanged**	**Worse**	**Not sure**	**Not tried**
Pancreatic enzymes	☐	☐	☐	☐	☐
Octreotide	☐	☐	☐	☐	☐
Pain Medications	☐	☐	☐	☐	☐
Bentyl	☐	☐	☐	☐	☐
ADEK vitamins	☐	☐	☐	☐	☐
Medium chain triglycerides (MCT)	☐	☐	☐	☐	☐
Antioxidants (e.g. vitamin E, selenium)	☐	☐	☐	☐	☐
Dietary Modifications Please explain: _____	☐	☐	☐	☐	☐
Other: _____	☐	☐	☐	☐	☐

*Please specify medications/supplements in the Medications (Part F, pages #11-13) section of this questionnaire.

<u>ERCP therapies</u>:	**Helpful**	**Unchanged**	**Worse**	**Not sure**	**Not tried**	**Year**
Sphincterotomy	☐	☐	☐	☐	☐	☐☐☐☐
Stenting	☐	☐	☐	☐	☐	☐☐☐☐
Stone Extraction	☐	☐	☐	☐	☐	☐☐☐☐
Other: _____	☐	☐	☐	☐	☐	☐☐☐☐

☐☐☐-☐☐☐☐ Initials HP Study # ☐☐/☐☐/☐☐☐☐ Date of Birth (Month/Date/Year)

Surgical therapies:	**Helpful**	**Unchanged**	**Worse**	**Not sure**	**Not tried**	**Year**
Partial/full pancreatic resection	☐	☐	☐	☐	☐	☐☐☐☐
Whipple	☐	☐	☐	☐	☐	☐☐☐☐
Frey's procedure	☐	☐	☐	☐	☐	☐☐☐☐
Puestow	☐	☐	☐	☐	☐	☐☐☐☐
Pseudocyst operation	☐	☐	☐	☐	☐	☐☐☐☐
Cholecystectomy (Gallbladder removed)	☐	☐	☐	☐	☐	☐☐☐☐
Celiac nerve block	☐	☐	☐	☐	☐	☐☐☐☐
Other: _____	☐	☐	☐	☐	☐	☐☐☐☐

Part C: Medical History

38. Have you ever been diagnosed with pancreatic cancer? ☐ Yes ☐ No

If yes, when were you diagnosed? (month/year) ☐☐/☐☐☐☐

39. What are YOUR usual medical problems? (check all that you consider to be a significant problem)

☐ I do not have any major medical problems and consider myself in good health.
☐ Diabetes (treated with insulin)
☐ Diabetes (treated with diet or pills)
☐ Gall stones
☐ Ulcers
☐ Inflammatory bowel disease (e.g. Crohn's disease, Ulcerative colitis)
☐ Primary biliary cirrhosis
☐ Gastritis (upset stomach or pain)
☐ Heartburn/reflux
☐ Back injury/Back pain
☐ Diarrhea (Does it improve with pancreatic enzymes?): ☐ Yes ☐ No ☐ I haven't tried enzymes
☐ Thyroid disorder, please specify: _____
☐ Autoimmune disorder (e.g. lupus/SLE, Sjögrens), please specify: _____
☐ Other problems, please explain type and give age at diagnosis: _____

40. For YOU, which medical condition has the biggest affect on your life?

_____

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

41. Are you allergic to anything? (please select all that apply)

- ☐ Seasonal allergies (e.g. hayfever, molds, dust, pollen, spores)
- ☐ Food items
- ☐ Cosmetics
- ☐ Medications, please specify: _____
- ☐ Other, please specify: _____

If you have allergies, what are your symptoms when your allergies occur? (please select all that apply)

- ☐ Runny nose, watery eyes
- ☐ Itchy/ raised rash/hives
- ☐ Respiratory difficulties
- ☐ Anaphylaxis
- ☐ Asthma
- ☐ Eczema
- ☐ Other, please specify: _____

Part D: General Health Survey

This survey asks for your views about your general health. This information will help you keep track of how you feel and how well 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.

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

Excellent	Very good	Good	Fair	Poor
☐	☐	☐	☐	☐

43. 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	Yes limited a little	No not limited at all
Moderate activities, such as moving a table, pushing a vacuum cleaner, bowling, or playing golf	☐	☐	☐
Climbing several flights of stairs	☐	☐	☐

44. 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	No
Accomplished less than you would like	☐	☐
Were limited in the kind of work or other activities	☐	☐

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

45. 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	No
Accomplished less than you would like	☐	☐
Didn't do work or other activities as carefully as usual	☐	☐

---

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

Not at all	A little bit	Moderately	Quite a bit	Extremely
☐	☐	☐	☐	☐

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.

47. How much of the time during the *past 4 weeks*...

	All of the time	Most of the time	A good bit of the time	Some of the time	A little the time	None of the time
Have you felt calm and peaceful?	☐	☐	☐	☐	☐	☐
Did you have a lot of energy?	☐	☐	☐	☐	☐	☐
Have you felt downhearted and blue?	☐	☐	☐	☐	☐	☐

---

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

All of the time	Most of the time	Some of the time	A little of the time	None of the time
☐	☐	☐	☐	☐

Part E: Environmental Exposures

49. What has been your usual occupation or job -- the one you have worked at the longest?

Job / Occupation: _____

Number of years employed in this position: ☐☐

☐☐☐-☐☐☐☐ Initials HP Study # ☐☐/☐☐/☐☐☐☐ Date of Birth (Month/Date/Year)

Please note that smoking & the use of alcohol strongly influence the risk of pancreatic diseases. Please answer the following questions as accurately as possible.

Tobacco Use

50. Have you ever smoke cigarettes?

- ☐ never (less than 100 cigarettes in your life)
- ☐ started (month/year) ☐☐/☐☐☐☐
- ☐ quit (month/year) ☐☐/☐☐☐☐

51. On the average, how many cigarettes do / did you smoke per day? ☐☐

Alcohol Use

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

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

☐ Yes. ☐ No (less than 20 drinks in a lifetime) (go to Part F, question #62)

53. In the months *before* getting pancreatitis, OR if no history of pancreatitis, in general,

How many drinks were you generally able to consume in a day?	☐☐
Did close friends or relatives worry or complain about your drinking?	☐ Yes ☐ No
Did you sometimes take a drink in the morning when you first got up?	☐ Yes ☐ No
Did a friend or family member ever tell you about things you said or did while you were drinking that you could not remember?	☐ Yes ☐ No
Did you feel the need to cut down on your drinking other than to prevent attacks of pancreatitis?	☐ Yes ☐ No

54. How old were you when you <u>began drinking</u> at least once per month? ☐☐

<u>Questions 55 – 60 refer to when you drank the most alcohol, or the heaviest drinking for you</u>

55. How old were you when you began drinking <u>the most alcohol</u> in your life? ☐☐

56. On the <u>AVERAGE</u> about how many drinks would you have on a drinking day? ☐☐

57. How many <u>days per month</u> did you drink at this level? ☐☐

58. What is the <u>MOST</u> number of drinks you would have in any one day? ☐☐

59. How many of the following would you consume in an average month of heaviest drinking?

Beer ☐☐☐ Wine ☐☐☐ Mixed Drinks ☐☐☐

60. How long did you drink alcohol at the heaviest level? in months ☐☐ or years ☐☐

Initials	HP Study #	Date of Birth (Month/Date/Year)
☐☐☐-	☐☐☐☐	☐☐/☐☐/☐☐☐☐

61. What was your heaviest use of alcohol over any 6-month period of time? (mark one, only)

☐ Less than once a week ☐ 1-2 drinks/week ☐ 3-4 drinks/week

☐ 5-6 drinks/week ☐ 1-2 drinks/day ☐ More than 3 drinks/day

If more than 3 drinks/day, please specify number ☐☐☐

Did this 6-month period of alcohol use occur BEFORE or AFTER your onset of pancreatitis? (mark one, only)

☐ Not applicable. I have never had pancreatitis

☐ Before. How many years before your first attack? ☐☐ Years

☐ AFTER. How many years after your first attack? ☐☐ Years

Part F: Medications

Please list all your current and routine medication(s)/supplement(s). Include over-the-counter (OTC) medicine/supplements you take on a regular basis (vitamins, antioxidants, etc), when you started taking them, and if you are taking them for your pancreas. If you need more space, please use the back of this sheet.

62. Pancreatic Enzymes: ☐ N/A

Name: Dose per meal:	No. of meals/day:		Started (month/year):
_____	_____	_____	☐☐/☐☐☐☐
	Dose per snack:	No. of snacks/day:	
	_____	_____	

63. Insulin: ☐ N/A

Name:	Units per day:	Started (month/year):
_____	_____	☐☐/☐☐☐☐
_____	_____	☐☐/☐☐☐☐

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

64. Do you use pain medication on a regular basis? ☐ Yes ☐ No

If no, have you ever used pain medication in the past? ☐ Yes ☐ No

Please circle the type of pain medicine you regularly use/used from the list below.

ASPIRIN-TYPE MEDICATIONS			IBUPROFEN-TYPE MEDICATIONS			
Acuprin	Excederin		Advil	Feldene	Meclomen	Ponstel
Anacin	Fiorinal		Aleve	Fenoprofen	Mefanamic Acid	Piroxicam
Ascriptin	Halfprin		Anaprox	Flurbiprofen	Midol 200	Relafen
Axotol	Lortab		Ansaid	Haltran	Motrin	Sulindac
Azdone	Norgesic		Cataflam	Ibuprofen	Nalfon	Tolectin
Bufferin	Percodan		Clinoril	Indocin	Nambumeton	Tolmetin
Damason	Roxiprin		Daypro	Indomethacin	Naprosyn	Toradol
Easprin	Soma Cmpd.		Diclofenac	Ketoprofen	Naproxen Sodium	Trendar
Ecotrin	Synalgos		Diflunisal	Lodine	Nuprin	Voltaren
Empirin	Talwin		Dolobid	Medipren	Orudis	
Equagesic			Etodolac	Meclofenamate	Oruvail	

How many of these pills from the above table do you take per day? ☐☐

65. Other Prescription Medication and Supplements: (check the first box if this is for the pancreas)

*Please include any prescription **pain medications**, such as morphine (e.g. MS Contin, Kadian), fentanyl (e.g. Duragesic), methadone (e.g. Dolophine), etc.

Name:	Dose Size:	Doses per day:	Started (month/year):
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐

☐ **Check if continued on back**

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

66. Over-the-counter (OTC) Medications and Supplements: (check the first box if this is for the pancreas) *Please include over the counter **pain medications**

Name:	Dose Size:	Doses per day:	Started (month/year):
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐
☐ _____	_____	_____	☐☐/☐☐☐☐

☐ **Check if continued on back**

Part G: Family History

Please list any other relatives who are participating in this research study. ☐ No other relatives

_____	_____	_____	_____
First Name	Last Name	First Name	Last Name

☐ **Check if continued on back of page**

Please complete the tables below for relatives who have the following health problems. Include your grandparents, parents, sisters/brothers, children, aunts/uncles, and first cousins. Add additional information to the back of the pages, if necessary.

Note that in order to respect the privacy of your family members please use relationships, only, (e.g. mother, brother, etc.) when giving information.

67. Pancreatitits: ☐ None of my family members have pancreatitis

Family Member (relationship, only)	Maternal or Paternal?	Age at Diagnosis	Age at Death, if applicable	Type of Pancreatitis, if known
1.				
2.				
3.				

☐ **Check if continued on back of page**

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

68. Have any of your relatives had genetic testing for hereditary pancreatitis? ☐ Yes ☐ No
If yes, please explain.

_____

_____

69. <u>Pancreatic Cancer</u>: ☐ None of my family members have pancreatic cancer

Family Member (relationship, only)	Maternal or Paternal?	Age at Diagnosis	Age at Death, if applicable	Please indicate risk factors/ cause, if known
1.				
2.				
3.				

☐ Check if continued on back of page

70. Have any of your relatives had genetic testing for pancreatic cancer? ☐ Yes ☐ No
If yes, please explain.

_____

_____

71. <u>Other Cancers</u>: ☐ None of my family members have other cancers

Family Member (relationship, only)	Maternal or Paternal?	Type of cancer (primary site/where cancer started)	Age at Diagnosis	Age at Death, if applicable
1.				
2.				
3.				

☐ Check if continued on back of page

72. Have any of your relatives had genetic testing for hereditary cancer? ☐ Yes ☐ No
If yes, please explain.

_____

_____

☐☐☐-☐☐☐☐ Initials HP Study # ☐☐/☐☐/☐☐☐☐ Date of Birth (Month/Date/Year)

73. Cystic Fibrosis (CF): ☐ None of my family members have CF or have been diagnosed as a CF carrier*

Family Member (relationship, only)	Maternal or Paternal?	Age at Diagnosis	Age at Death, if applicable	Please indicate if they have CF or if they are a CF carrier*, only
1.				
2.				
3.				

*CF carrier means that this person does not have CF but their children can have CF (if both parents are CF carriers)

☐ **Check if continued on back of page**

74. Have any of your relatives had genetic testing for cystic fibrosis? ☐ Yes ☐ No
If yes, please explain.

_____

_____

This section below will be used to build your family tree. Please fill in information for each family member.

75. Are your parents or grandparents related to each other (share the same blood relatives)?

☐ Yes ☐ No

If yes, please explain: _____

76. Are you a twin? ☐ Yes ☐ No

If yes: ☐ Identical ☐ Not Identical (fraternal twins)

Father's Side (Paternal Side)

Your Father: Birthdate ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

His parents (your paternal grandparents):

His Father: Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

His Mother: Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐☐☐-☐☐☐☐	☐☐/☐☐/☐☐☐☐
Initials HP Study #	Date of Birth (Month/Date/Year)

His brothers and sisters (your paternal aunts and uncles): List in order from oldest to youngest

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ **Check if continued on back of page**

***If you have the above information on paternal cousins, great-grandparents, great aunts and uncles, and distant cousins, please list this information on the back side of the page.**

Mother's Side (Maternal Side)

Your Mother: Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

Her parents (your maternal grandparents):

Her Father: Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

Her Mother: Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

Her brothers and sisters (your maternal aunts and uncles): List in order from oldest to youngest.

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ **Check if continued on back of page**

***If you have the above information on maternal cousins, great-grandparents, great aunts and uncles, and distant cousins, please list this information on the back side of the page.**

Your siblings (sisters/brothers): List in order from oldest to youngest, and do not include yourself in the list.

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐☐☐-☐☐☐☐ Initials HP Study #

☐☐/☐☐/☐☐☐☐ Date of Birth (Month/Date/Year)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ **Check if continued on back of page**

***If you have the above information on your nieces and nephews, please list this information on the back side of the page.**

Your children: List in order from oldest to youngest

☐ I do not have any children.

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ Male ☐ Female Birthdate: ☐☐/☐☐/☐☐☐☐ ☐ Living ☐ Deceased (age at death ☐☐)

☐ **Check if continued on back of page**

***If you have the above information on your grandchildren, please list this information on the back side of the page.**

-Additional Information-

Please add any additional comments or information regarding you or your family's medical history.

_____

_____

_____

_____

You are finished. Thank you for completing the questionnaire. If necessary, we may contact you by phone for additional information or clarification of the information you have provided. This call should only take a few minutes. Are you willing to provide us with a contact person (s) in the event that we are unable to reach you for this information? ☐ Yes ☐ No

If yes, enter contact information below (please include name, relationship to you, and contact information).

_____

_____

----------End of Questionnaire----------

BIBLIOGRAPHY

[1] The University of Cincinnati Pancreatic Disease Center. *Hereditary Pancreatitis.* 2005. www.ucpancreas.org/hereditarypancreatitis.html

[2] Kattwinkel J, et. al. *Hereditary pancreatitis: three new kindreds and a critical review of the literature.* Pediatrics, 1973; 51(1): 55-69.

[3] Raj K Rolston, MD and Jeffrey A Kant, MD, PhD. *Genetic Testing in Acute and Chronic Pancreatitis.* Current Gastroenterology Reports, 2001; 3: 115-120.

[4] Turk DC, Flor H. Chronic pain: A biobehavioral perspectives. In: Gatchel RJ, Turk DC (eds). *Psychosocial Factors in Pain. Critical Perspectives.* New York: The Guilford Press, 1999; 18-34.

[5] Ware JE et al. *SF-12v2™: How to Score Version 2 of the SF-12® Health Survey*. Lincoln, RI, USA: Quality Metric, .

[6] Dysvik E, Guttormsen Vinsnes A, Eikeland O. *The effectiveness of a multidisciplinary pain management programme managing chronic pain.* International Journal of Nursing Practice, 2004; 10: 224-234.

[7] Applebaum-Shapiro, SE and Whitcomb, DC et. al. Hereditary Pancreatitis in North America: The Pittsburgh-Midwest Multi-Center Pancreatic Study Group Study. Pancreatology, 2001: 1(5): 439-443.

[8] Whitcomb DC and Chimera, C et. al. Pearl, 2005; 1(1). www.pancreas.org

[9] UptoDate. *Acute Pancreatitis.* www.uptodate.com Accessed 4/2006.

[10] Etemad, B and Whitcomb, D. *Chronic Pancreatitis: Diagnosis, Classification, and New Genetic Developments.* Gastroenterology, 2001; 120: 682-707.

[11] Falk RT, et. al. *Life-style risk factors for pancreatic cancer in Louisiana: a case-control study*. Am J Epidemiol, 1988; 128: 324.

[12] Mack TM, et. al. *Pancreas cancer and smoking, beverage consumption, and past medical history*. J Natl Cancer Inst, 1986; 76: 49.

[13] Everhart J, et. al. *Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis.* JAMA, 1995; 273: 1605.

[14] Jemel A, et. al. *Cancer Statistics, 2005.* CA Cancer J Clin, 2005; 55: 10.

[15] Steer ML, et. al. *Chronic pancreatitis.* N Engl J Med, 1995; 332: 1482.

[16] Sossenheimer MJ, et. al. *Clinical characteristics of hereditary pancreatitis in a large family, based on high risk haplotype.* Am J Gastroenterol, 1997; 92: 1113.

[17] Choudari CP, et. al. *Hereditary pancreatitis: Clinical presentation, ERCP findings, and outcome of endoscopic therapy.* Gastrointestinal Endoscopy, 2002; 56(1): 66-71.

[18] Ammann RW, et. al. *The natural history of pain in alcoholic chronic pancreatitis.* Gastroenterology, 1999; 116: 1132.

[19] DiMagno EP. *Relations between pancreatic enzyme outputs and malabsorption in severe pancreatic insufficiency.* N Engl J Med, 1973; 288: 813.

[20] Whitcomb, David. Pancreas.org: a site for information and help. http://www.pancreas.org/index.html Accessed last February 2006.

[21] Whitcomb, David and Lehel Somogyi. *Lessons from Hereditary Pancreatitis.* Croatan Medical Journal, 2001; 42(4): 484-487.

[22] Howes N, et. al. *Clinical and genetic characteristics of hereditary pancreatitis in Europe.* Clinical Gastroenterology and Hepatology, 2004; 2(3): 252-261.

[23] Niels T and Joachim Mossner. *Genetic aspects of chronic pancreatitis.* Med Sci Monit, 2004; 10(12): RA325-328.

[24] Online Mendelian Inheritance in Man, Johns Hopkins University. *Pancreatitis, Hereditary.* http://www.ncbi.nlm.nih.gov/entrez/query.fcgi?db=OMIM Last accessed February 2006.

[25] Ravnik-Glavac M, et. al. *Evidence that hereditary pancreatitis is genetically heterogeneous disorder.* Pflugers Arch, 2000; 439 (3 Suppl): R50-52.

[26] Hoogerwerf WA, et. al. Trypsin mediates nociception via the proteinase-activated receptor 2: a potentially novel role in pancreatic pain. Gastroenterology, 2004; 127(3): 883-891.

[27] Hoogerwerf WA, et. al. *The Proteinase-Activated Receptor 2 Is Involved in Nociception.* The Journal of Neuroscience, 2001; 21(22): 9036-9042.

[28] Ambry Genetics. *Genetic Testing can be a powerful tool aiding in the diagnosis of chronic pancreatitis.* 2004. www.ambrygen.com

[29] National Guideline Clearinghouse. *Genetic testing for hereditary pancreatitis: guidelines for indications, counseling, consent and privacy issues.* 2003. www.guideline.gov

[30] Freedman, Steven D. *Treatment of chronic pancreatitis.* UpToDate. www.uptodate.com April 2005.

[31] Warshaw, AL, Banks PA, and Fernandez-del Castillo C. *AGA Technical review on treatment of pain in chronic pancreatitis.* Gastroenterology, 1998; 115: 765.

[32] Pancreas Center. *Pancreatic Pain Management.* Columbia University Department of Surgery. Accessed February 2006.

[33] The National Pancreas Foundation. *Hereditary Pancreatitis.* www.pancreasfoundation.org Accessed September 2005.

[34] McHugh, G, et. al. *Patient satisfaction with chronic pain management.* Nursing Standard, 2001; 15(51): 33-38.

[35] Keefe FJ, et. al. *Coping with pain: conceptual concerns and future directions.* Pain, 1992; 51: 131-134.

[36] Ilse, V, et. al. *Acceptance of pain is an independent predictor of mental well-being in patients with chronic pain: empirical evidence and reappraisal.* Pain, 2003; 106: 65-72.

[37] Herrmann, Elizabeth. *Coping Skills in Hereditary Pancreatitis Patients.* Pearl, 2006; 2(1). www.pancreas.org

[38] Yacavone RF, et. al. *Quality of life measurement in gastroenterology: what is available?* The American Journal of Gastroenterology, 2001; 96(2): 285-297.

[39] Ware JE et. al. *A 12-Item Short-Form Health Survey: Construction of scales and preliminary tests of reliability and validity.* Medical Care, 1996; 34(3):220-233.

[40] Bouchet, C et. al. *Selection of Quality-of-Life Measures for a Prevention Trial (A Psychometric Analysis).* Controlled Clinical Trials, 2000; 21(1):30-43.

[41] Broome AH, et. al. *Quality of Life After Treatment for Pancreatitis.* Annals of Surgery, 1996; 223(6): 665-672.

[42] Kurtz LF, et. al. *Self-help and support groups: a handbook for practitioners.* SAGE Publications, Thousand Oaks. 1997.

[43] Weiss JO, et. al. *The Genetic Alliance: A History of Advocacy Organizations.* 2004. www.geneticalliance.org

[44] Kyrouz EM, et. al. *A Review of Research On The Effectiveness of Self-Help Mutual Aid Groups.* American Self-Help Clearinghouse Self-Help Group Sourcebook (7th Edition), 2002; Chapter 5: 1-16.

[45] The National Organization for Rare Disorders (NORD) website. 2005. www.rarediseases.org

[46] Ware JE, et. al. How to Score Version 2 of the SF-12 Health Survey (With a Supplement Documenting Version 1). Lincoln, RI: QualityMetric Incorporated, 2002.

[47] Haugli, Liv, et. al. Learning to have less pain- is it possible? A one-year follow-up study of the effects of a personal construct group learning programme on patients with chronic musculoskeletal pain. Patient Education and Counseling, 2001; 45: 111-118.

[48] Wehler, M, et. al. *Health-Related Quality of Life in Chronic Pancreatitis: a Psychometric Assessment.* Scand J Gastroenterol, 2003; 10: 1083-1089.

[49] Broome, Audrey H, et. al. *Quality of Life After Treatment for Pancreatitis.* JOP, 1996; 223(6): 665-672.

[50] Nettleton, B et. al. Counselling: filling a gap in general practice. Patient Education and Counseling, 2000; 41: 197-207.

[51] Kyrouz, E et. al. *A Review of Research on the Effectiveness of Self-Help Mutual Aid Groups.* American Self-Help Clearinghouse Self-Help Group Sourcebook 7th Edition, 1998; 5: 1-16.