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Title of the Project:

**Pancreatic Cancer Registry in Atlantic Canada:
Framework for Genetic, Epidemiological and Clinical Outcomes Studies of
Sporadic and Familiar Tumors**

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List of all abbreviations in alphabetical order

Atlantic Canada	Provinces of Nova Scotia, New Brunswick, Princess Edward Island, Newfoundland and Labrador
BRCA1	Breast cancer gene 1
BRCA2	Breast cancer gene 2
Ca19.9	Carcinogen antigen 19.9 (tumor marker)
CT	Computerized tomography
DNA	Deossinucleic acid
ERCP	Endoscopic retrograde cholangio pancreatography
EUS	Endoscopic ultrasound
FPC	Familial Pancreatic Cancer
5-FU	5 Fluoro Uracil (chemotherapy agent)
HNPCC	Hereditary non polyposis colonic cancer
MRI	Magnetic resonance imaging
PACGENE	Pancreatic Cancer Genetic Epidemiology Consortium
PET	Positron emission tomography
PC	Pancreatic Cancer
RNA	Ribosinucleic acid
SEER	Surveillance Epidemiology and End Results
US	Ultrasonography

Overview of the Study

Background: Pancreatic cancer (PC) is a highly lethal malignancy representing 10% of all gastrointestinal tumors with the majority of patients dying shortly after diagnosis. The only potential cure for PC is surgical resection that is carried out only in 10-20% of all patients because the tumor has already spread or medical co-morbidities make the risk of perioperative mortality prohibitive. Even when surgery is performed, the median survival is 14-16 months as recurrent disease is common and PC is poorly responsive to chemotherapy or radiation.

Rationale of the study: Recent studies have shown that up to 10% of PCs are diagnosed in families where more than one member has suffered from the same tumor. Several inherited genetic mutations might explain this phenomenon and are currently the focus of gene profiling. The clinical application of these findings may change the management of high-risk individuals as it occurred for other genetically transmitted tumors (e.g. colorectal, breast, thyroid cancers).

Epidemiology of PC in Atlantic Canada: Incidence of PC in Atlantic Canada has been stable in the last decades. In 2006 the total number of patients diagnosed with PC was 145 (5 in Newfoundland, 15 in Princess Edward Island, 65 in Nova Scotia and 55 in New Brunswick). It is expected that about 12-14 cases of PC diagnosed each year in Atlantic Canada may be familial.

Current Limitations: The incidence and prevalence of familial PC in Atlantic Canada is currently unknown and advances in epidemiological research in this field are needed. The current lack of knowledge might significantly impact the chances of early diagnosis and survival in high risk individuals for PC in this part of the Country.

Hypothesis: That the incidence of familial PC in Atlantic Canada is comparable to the rates reported in the literature and that a genetic defect is responsible for the transmission of this condition. Screening for PC in high-risk individuals might improve the outcomes of this tumor by early diagnosis and therapy.

Primary aim of this study: A) to study the incidence of familial PC and variables influencing survival for patients affected by sporadic PC in Atlantic Canada. B) To assess the impact of screening program for PC in high risk individuals.

Secondary aims of this study: To obtain tumor tissue samples (when available), and peripheral blood bank from all patients diagnosed with PC in Atlantic Canada. To obtain peripheral blood samples from healthy individuals of identified high risk families to study the genetic profile of familial PC and patterns of transmission.

Methods: A central prospective registry for all the Atlantic Canada Provinces will be established to capture all the newly diagnosed PC patients for the next 5 years. All the collected variables will be matching the format already used for the registry established in Ontario. The two registries will be able to merge data for statistical analysis. Peripheral blood and or tumor samples (when possible) will be collected from patients with new onset of PC and screening questionnaires will be administered to family members of patients affected by PC. If familial PC is suspected, blood samples will be obtained from family members participating to this study and pedigrees generated for

future screenings. Genetic analysis of all samples will be carried out at laboratories at Mount Sinai Hospital (Toronto) under the supervision of Dr. Steve Gallinger to investigate gene mutations and their penetrance. For screening purposes, serum tumor markers and imaging modalities for high risk individuals will be performed at 6 months intervals.

Feasibility: The management of patients affected by PC is complex and needs advanced expertise in many disciplines and the majority of PC patients are referred to tertiary medical centers. Contrary to other areas in North America and Europe, in Atlantic Canada there are only three University Medical Centers where the majority of these patients are referred to: Victoria General Hospital in Halifax (NS), Moncton General Hospital (NB) and Memorial University Hospital in St. Johns' (NFL). The advantage of centralized patient referral and the fact that the mobility of the population in Atlantic Canada is significantly less than in other parts of the Country, make our Institution an ideal center for epidemiological studies on familial conditions.

Importance of this study: PC has poor prognosis. Familiar transmission of PC may occur in up to 10% of cases and early diagnosis by screening modalities may have a significant impact on year-life saved. Therefore, the creation of a familiar PC registry in Atlantic Canada would contribute to the advancement of genetic research and direct education and screening to high risk families where tumor related deaths may be prevented.

Time frame: Establishment of a PC registry in Atlantic Canada will require 6 months after being funded. Recruitment of patients with PC and screening of their family members will start before the end of the 7th month and continue for 5 years. The support of external funding will be sought to maintain the academic goals of this study after the 5th year.

Academic objectives of this study: In addition to the potential health gains for families at high risk for PC, the establishment of this study would have several academic benefits for Dalhousie University and the primary investigators. First of all, it will allow the development of methodological framework and scientific productivity to obtain national and international recognition for the investigators to access external grants for future research. Secondly, it will allow Dalhousie University to be part of a prestigious consortium for the study of genetic defects that will promote cooperation among academic Institutions with invaluable scientific benefits. Thirdly, the Atlantic Canada registry for familiar PC might be an important legacy for future researchers as its inclusion in the Nova Scotia Cancer Society would allow future continuation of the project and epidemiological studies of PC in Atlantic Canada.

1a. Introduction

Pancreatic ductal adenocarcinoma (PC) is the 5th leading cause of cancer death worldwide¹. Despite recent advances in surgery, chemo and radiation therapy, the prognosis of PC remains poor with overall 5-year survival rate of less than 5%. When PC is diagnosed and treated by surgical resection in early stage, 5-year survival rates improve up to 40%².

The identification of individuals at high risk for developing PC and the development of appropriate screening tests for these individuals would offer the best chance of reducing the high mortality rates of this disease.

It has been suggested that various environmental and lifestyle risk factors³, occupational exposures⁴ and medical conditions⁵ predispose to PC. However, cigarette smoking is the only environmental risk factor that has been consistently associated with the development of PC^{6,7}. In addition, several case-control studies demonstrated that a family history of PC is an important risk factor for developing PC, with risks ranging from 2.7-16%, even after adjusting for environmental risk factors and diabetes mellitus^{8,9,10,11,12,13,14}.

This risk increases with the number of affected individuals within kindred¹⁵. Until the late 1980's, only case reports have suggested that PC aggregates in some families^{16,17,18}.

The first systematic study of a larger cohort of families with PC was published only in 1989¹⁹. Afterwards, several registries for familial pancreatic cancer (FPC) were established in the United States^{20,21,22} and Europe^{23,24}, to collect and analyze these rare families. FPC is a very heterogeneous and yet not well-defined hereditary tumor entity. At present there is no standardized definition for FPC, but most authors apply the term to families with at least 2 first-degree relatives with confirmed PC in the absence of an accumulation of other cancers that are known to be familial^{15,25}.

Besides the isolated aggregation of PC in a majority of families, several hereditary disorders predispose to PC. These include hereditary pancreatitis, Peutz-Jeghers syndrome, familial atypical multiple mole melanoma (FAMMM), familial breast and ovarian cancer and possibly HNPCC²⁶. However, a recent segregation analysis found evidence for involvement of a major gene in the etiology of PC²⁷.

Several authors estimated that there may be an inherited component to PC in patients with pancreatic cancer, ranging from 3-16%, although conclusive epidemiologic data are still lacking^{11,20,22,28}.

1b. Biology of cancer cell transformation

Cancer development is characterized by a complex series of phenomena occurring at the DNA level. Genomic instability, epigenetic factors and a relaxation in cell cycle control might confer growth advantages on transformed cells, thus favoring hyperplasia and the onset of cancer. Genetic instability increases the probability of the activation of oncogenes and the inactivation of tumor suppressor genes, ultimately leading to cancer growth. Since it is inherently unstable, DNA in mammalian cells is commonly damaged, giving rise to some 20,000 lesions per day per cell²⁹, the main sources of which are spontaneous depurination, damage from reactive oxygen species and deamidation of bases³⁰. The outcome of DNA damage varies, but it is generally adverse. Acute effects arise from a disturbed DNA metabolism, triggering cell cycle arrest or cell death. The long-term effects are due to irreversible mutations that contribute to the formation of cancer cells³¹.

1c. Mechanisms that prevent cancer cell transformation

A complex system of enzymes and cofactors is deployed to repair DNA damage. So far, some 130 human DNA repair genes have been identified, but there are probably many more, since the functions of < 50% of known and putative genes are understood³². At least 5, partly overlapping, main repair pathways are known: base excision repair (BER), nucleotide excision repair (NER),

homologous recombination (HR), non-homologous end-joining (NHEJR) and mismatch and recombination repair (MMR)^{30,33,34}. Life requires a fine balance between the avoidance and the generation and persistence of mutations. Genetic diversity in the germline is essential for the selection of genetic fitness, but germline mutations might cause hereditary diseases. Mutations in somatic cells can have numerous consequences, cancer probably being the most serious. An inadequate DNA repair system is now considered one of the cellular alterations that may cause a predisposition to cancer. In humans some syndromes with an enhanced risk of cancer are characterized by germline mutations of genes involved in DNA repair^{31,35,36,37,38} (Table 1).

Table 1. Humans syndromes cancer prone with germline mutations of genes involved in DNA repair, causing defective genome maintenance

Syndrome	Mutated gene/s	Pathway	Cancer predisposition
Xeroderma pigmentosum (AR)	Seven genetic complementation groups (<i>XP-A XP-G</i>)	NER	UV-induced skin cancers
Hereditary non-polyposis colon cancer (HNPCC)	<i>MLH1</i> (50%), <i>MSH2</i> (40%), <i>MSH6</i> (10%), <i>PMS2</i> , <i>PMS1</i>	MMR	Colon cancer (70–85%), endometrial carcinoma (50%), other cancers (15%)
Multiple colorectal adenomas and carcinomas with no germline APC defect	<i>MUTYH</i>	BER	So far first evidence indicating that mutations in BER genes are involved in cancer
Ataxia teleangiectasia (AT) and Nijmegen breakage syndrome		DSBs response/repair	Lymphomas
BRCA 1/BRCA 2	<i>BRCA1</i> , <i>BRCA2</i>	HR	Breast and ovarian cancers

2a. Epidemiology of pancreatic cancer

PC is a highly lethal and common malignancy, accounting for an annual incidence of 1-10/100,000¹⁴ and a mortality rate of more than 95% at 5 years³⁹. During the last decades no significant improvement in patients' survival has been observed as illustrated in **figure 1**⁴⁰.

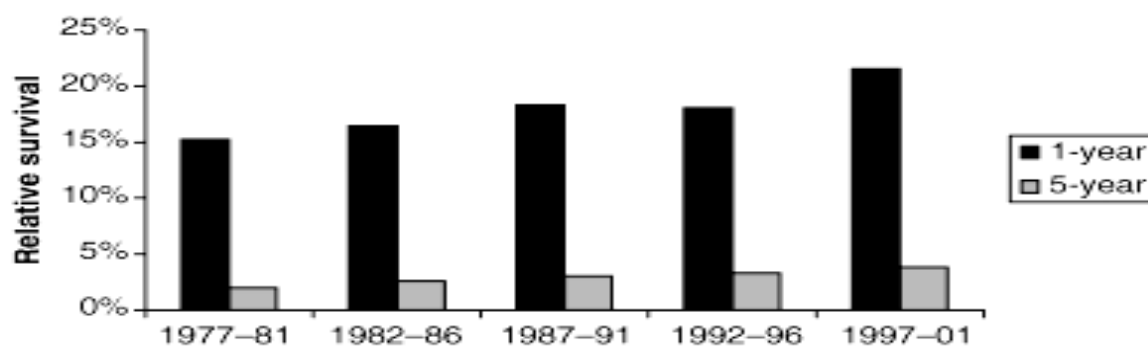


Figure 1. The age-specific incidence rates of pancreatic cancer in five consecutive time periods between 1977 and 2001

Of the approximately 30,000 cases diagnoses each year in the Unites States, approximately 5-10% of patients have a family history of PC ⁴¹.

In Canada, PC is the 9th most common malignancy while it is 4th for mortality rate⁴². The lifetime probability of developing PC in Canada is 1.2% for males and 1.4% for females and the total number of patients who developed PC in 2006 was 3,449 ⁴². Statistics on the incidence of FPC in Canada are currently not available.

In Atlantic Canada, the number of patients diagnosed with PC has been relatively stable during the last decade. In 2006 the total number of patients diagnosed with PC was 145 (5 in Newfoundland, 15 in Princess Edward Island, 65 in Nova Scotia and 55 in New Brunswick) . It is expected that about 12-14 cases of PC diagnosed each year in Atlantic Canada may be familiar ⁴² (Table 2).

Table 2. Canadian data on the most common cancers diagnosed in 2006

Actual Data for New Cases for the Most Common Cancers by Sex and Geographic Region, Most Recent Year¹, Canada

	New Cases													
	Canada	NL*	PE	NS	NB	QC	ON	MB	SK	AB	BC	YT	NT	NU
Males														
All Cancers	74,800	1,150	410	2,800	2,000	18,800	28,000	2,700	2,700	6,400	9,400	50	40	25
Prostate	19,500	260	120	730	550	3,900*	7,700	680	950	1,950	2,500	10	5	–
Lung	11,600	180	60	450	350	3,700	3,800	410	340	780	1,350	10	5	10
Colorectal	10,000	240	55	390	240	2,600	3,600	390	360	810	1,300	10	10	5
Bladder**	4,600	70	25	180	130	1,450	1,400	170	180	420	610	–	–	–
Non-Hodgkin Lymphoma	3,200	30	20	120	100	720	1,200	110	120	290	440	–	–	–
Kidney	2,600	40	15	100	95	700	1,000	130	90	220	240	–	–	–
Leukemia	2,400	20	20	70	45	560	1,000	80	110	180	280	–	–	–
Oral	2,200	45	5	85	50	560	780	90	65	160	270	–	5	–
Melanoma	2,100	35	10	95	55	290	1,000	70	45	230	360	–	–	–
Stomach	1,900	40	10	65	45	480	710	80	50	140	230	–	–	–
Pancreas	1,650	15	15	60	65	470	530	80	50	120	220	–	–	–

– Fewer than 3 cases

* Likely an underestimate of the number of cases, see *Appendix II: Methods*.

** Inter-provincial variation. Ontario does not report in situ bladder cases. It is estimated including in situ cases for Ontario would result in 2100 bladder cancer cases among men and 820 among women. See text.

¹ 2003 for Canada, Newfoundland and Labrador, Quebec, Ontario; 2004 for Prince Edward Island, Nova Scotia, New Brunswick, Manitoba, Saskatchewan, Alberta, British Columbia; 2000-2004 average for Yukon, Northwest Territories, Nunavut.

Note: Total of rounded numbers may not equal rounded total number and an average is used for the territories. Counts exclude cases of non-melanoma (basal cell and squamous cell) skin cancer.

Source: Surveillance Division, CCDPC, Public Health Agency of Canada

Ninety-five percent of pancreatic neoplasms are ductal adenocarcinomas, and 80% of patients with ductal adenocarcinomas present with metastatic disease, leading to an extremely poor 5-year survival rate of 4-6% ^{42,43}.

The Surveillance Epidemiology and End Results (SEER) Program reports an overall age-adjusted incidence rate of 11 per 100,000 individuals⁴⁴. Individuals of African descent have a higher incidence rate (14.9 per 100,000) than Caucasian (10.9 per 100,000), and the incidence of pancreatic cancer is higher among men (12.5 per 100,000) compared to women (9.8 per 100,000) ⁴⁴.

2b. Risk factors for pancreatic cancer

To date, the three most consistent risk factors reported for pancreatic cancer are older age, cigarette smoking, and family history of the disease ^{43,45}.

These findings underscore the role of both genes and environment in the development of PC and have spurred further research. Several lines of investigation (family clustering, case-control studies, and cohort studies) have provided impetus for conducting more extensive genetic epidemiologic investigations.

Although about 90% of PC patients report a negative family history of pancreatic cancer, familial clustering in the remaining 5% to 10% of the disease (presumably attributed to inheritance of moderate or high penetrance genes) has been reported^{18,46,47,48,49}.

Formal case-control investigations provide persuasive evidence that a family history of PC is a risk factor, and some have further elaborated the role of cigarette smoking or age at diagnosis of pancreatic cancer in the family setting. In a Canadian sample, 7.8% of 179 pancreatic cancer cases and only 0.6% of 179 controls had a family history of pancreatic cancer, a 13-fold difference, with no differences in environmental risk factors between the two groups⁹.

An increased risk of PC was reported among relatives of 363 Italian cases compared with relatives of 1,234 controls [odds ratio, 2.8; 95% confidence interval (95% CI), 1.3-6.3], after adjusting for tobacco, dietary factors, and history of diabetes or pancreatitis¹⁰. PC risk was higher among close relatives of 362 pancreatic cancer patients in Louisiana compared with 1,408 controls (odds ratio, 5.25; CI, 2.08-13.21) and a multicenter US study of 484 cases and 2,099 controls found that relatives of individuals with pancreatic cancer have 3.2-fold (95% CI, 1.8-5.6) increased odds of developing pancreatic cancer compared with relatives of controls, even after adjusting for age at diagnosis/interview, geographic area, and gender⁵⁰. Relatives of individuals with pancreatic cancer who were long-term smokers (defined as being smokers for more than 20 years) had an odds of developing PC of 5.3 (95% CI, 2.1-13.4) compared with 2.2 (95% CI, 1.0-7.9) among relatives of pancreatic cancer cases who were not long-term smokers⁵¹.

A southeast Michigan study of 247 cases and 420 controls reported a relative risk of 8.23 for PC among smokers who had first-degree relative diagnosed before 60 years of age (95% CI, 2.18-31.07) and a relative risk of 2.15 among nonsmokers with a comparable family history (95% CI, 0.63-7.27). Having a family history of PC diagnosed at any age increased the risk of PC 2.49-fold (95% CI, 1.32-4.69)¹³.

A recent study of 426 unselected sequential Mayo Clinic patients with PC and 3,355 of their first-degree relatives obtained standardized incidence ratios using SEER data. Overall, the standardized incidence ratio for PC to first-degree relatives was 1.88 (95% CI, 1.27-2.68), and this risk increased to 2.86 (95% CI, 1.15-5.89) if the proband was younger than 60 years of age at diagnosis⁵². Similar findings were observed in a study of the Iceland genealogy database, which evaluated 930 cases among 32,534 at-risk individuals, and yielded a standardized incidence ratio of 2.33 (90% CI, 1.83-2.96) for first-degree relatives⁵³.

In the American Cancer Society's Cancer Prevention Study II cohort of 1,102,308 individuals, 3,751 prospectively developed PC during 14 years of follow-up. After adjusting for age, the relative risk of developing PC in individuals who reported a positive family history of PC at baseline was 1.5 (95% CI, 1.1-2.1). This risk estimate was unchanged after adjusting for history of gallstones, body mass index, smoking history, alcohol consumption, history of diabetes, and several dietary factors⁵⁴.

A prospective study of first-degree relatives of FPC cases in the National Familial Pancreatic Tumor Registry found that the standardized incidence ratio was 9.0 (95% CI, 4.5-16.1) for PC compared with the SEER population, whereas for relatives of non-FPC cases the standardized incidence ratio was not significantly increased⁵⁵.

This risk in FPC kindreds was evaluated in individuals with three or more (32.0; 95% CI, 10.2-74.7), two (6.4; 95% CI, 1.8-16.4), or one (4.6; 95% CI, 0.5-16.4) first-degree relative(s) with PC.

2c. Genetic syndromes associate with pancreatic cancer

Studies of PC in the context of genetic syndromes have yielded further evidence for the role of inherited risk for PC. **Table 3** illustrates all the genetic syndromes that have been found to be associated with PC. It is now accepted that FPC is an identifiable entity (kindreds containing at least two affected first-degree relatives), and that genetic predisposition is a plausible explanatory

etiology⁵⁶. The proportion of FPC explained by mutations in tumor suppressor genes that give rise to familial cancer syndromes is still unclear. Lal et al. reported that 13% of families classified as at high or intermediate risk of PC were found to carry BRCA1, BRCA2 or p16 germ line mutations⁵⁷. Murphy et al. found that 17.2% of pancreatic cancer probands with at least two additional blood relatives with PC carry deleterious BRCA2 mutations⁵⁸. A mutation in palladin gene has just been described in a unique pancreatic cancer-prone family followed by the University of Washington⁵⁹. This single family demonstrates an autosomal dominant inheritance of adenocarcinoma of the pancreas in concert with insulin-dependent diabetes mellitus and exocrine insufficiency. The importance of this gene in pancreatic cancer carcinogenesis is suggested by the overexpression of Palladin RNA in tissues from both familial and sporadic pancreatic adenocarcinomas and in precancerous dysplasia. Additional studies are needed to define the role/frequency of this mutation in hereditary and sporadic cases.

Because it is well-known that hereditary forms of breast cancer and colorectal cancer present at a younger age than their sporadic counterparts, it is also plausible that PC patients from FPC pedigrees develop PC at a younger age compared with sporadic pancreatic cancer.

Table 3. Hereditary syndromes and genes associated with pancreatic cancer

Syndrome	Gene(s)	Chromosome Location	References
Hereditary breast cancer, early onset 2	BRCA2	13q12	56,57,58
Familial atypical multiple mole melanoma syndrome	CDKN2A / p16	9p21	60,61
Peutz-Jeghers syndrome	STK11/LKB1	19p13	62
Fanconi Anemia Syndrome	FANCC, FANCG	9q22, 9p13	63,64,65
Hereditary pancreatitis	PRSS1	7q35	66,67
Hereditary nonpolyposis colorectal cancer	hMLH2,hPMS2,hMSH6	2p15,3p25,7p1,2p16	67
Cystic fibrosis (heterozygotes)	CFTR	7q31	68

3a. Diagnosis of pancreatic cancer

Advances in technology have meant that the sensitivity for detecting smaller lesions is improving, as is the identification of extra-pancreatic spread⁶⁹.

3a1. Tumor markers: The most commonly used marker in everyday practice CA19-9 has a sensitivity of 70–90% and specificity of 90%, and is better than other markers, including CA-50 and DU-PAN-2 and CEA⁷⁰. False positive results are often obtained in benign obstructive jaundice, chronic pancreatitis even in the absence of bile duct obstruction and ascites. CA19-9 is particularly useful in assessing response to prognosis and treatment in advanced cases, identifying early recurrence in resected cases and as an aid in preoperative staging^{71,72}.

3a2. Non-invasive imaging techniques: Transabdominal ultrasound can be the initial investigation and may detect tumors >2 cm in size, dilatation of the biliary and main pancreatic ducts and possible extra-pancreatic spread— notably, liver metastases, with a diagnostic accuracy of 75%⁷³, but it is not useful in early disease, if the bile duct is not dilated and in obese patients. Therefore contrast-enhanced multidetector CT scan is the single most useful imaging procedure (using a pancreas protocol CT with 1 mm images) and can achieve diagnostic rates of 97% for PC⁷⁴. The accuracy for predicting an unresectable lesion is 90%, but the accuracy of predicting a resectable lesion is much less at 80–85%^{75,76,77}. False negative results before laparotomy are mainly due to small hepatic metastases <1 cm and small peritoneal deposits. Lymph node staging is inaccurate in the absence of systematic biopsy⁷⁸. Magnetic resonance imaging produces similar results to contrast-enhanced multislice CT and is useful for patients who cannot receive intravenous contrast^{79,80}. Positron emission tomography (PET) cannot differentiate inflammatory conditions from tumors accurately and the sensitivity is 71–87% with

specificity of around 64–80%⁸¹. The use of fusion CT-PET scanning adds little if anything to the use of CT alone⁸². Measurement of tumor metabolism by nuclear magnetic spectroscopy holds considerable promise as a diagnostic technique but is very much in development⁸³.

3a3. Invasive imaging techniques: Endoluminal ultrasonography (EUS) has similar accuracy to CT in the staging of pancreatic cancer but is undoubtedly better for the detection of early pancreatic tumors as small as 2–3 mm⁷⁵. The addition of fine needle aspiration (FNA) cytology to EUS is highly accurate for identifying malignancy in lesions identified on EUS and not seen on CT scan⁸⁴. The drawbacks of EUS are that distant metastases and nodal involvement cannot be accurately assessed. The sensitivity and specificity of endoscopic retrograde cholangiopancreatography (ERCP) alone are 70–82% and 88–94%, respectively, in symptomatic patients or those with suspected pancreatic cancer but should no longer be used as a pure imaging tool given the developments in magnetic resonance cholangiopancreatography and EUS^{75,82}. ERCP is used to insert biliary stents for relief of obstructive jaundice⁸⁵ and to gain cytological diagnosis by sampling or brushings. These can also be obtained at percutaneous transhepatic cholangiography (PTHC)¹¹⁷.

3a4. Diagnostic biopsy: Percutaneous FNA cytology has a sensitivity and specificity of 69% and 100%, respectively, for tissue diagnosis¹¹⁷, but concerns have remained about intraperitoneal seeding, with an incidence of up to 16%⁸⁶. The diagnostic accuracy of EUS with FNA carries a sensitivity and specificity of >90% and ~100%, respectively, but requires an expert team with the presence of a cytologist examining the tissue specimens in the EUS suite, repeating the procedure until the diagnosis is conclusive⁸⁷. The incidence of carcinomatosis is much less after EUS-guided biopsy than percutaneous biopsy⁸⁸. A further development is the use of EUS with an endoscopic trucut biopsy needle⁸⁹. EUS-guided biopsy is thus the preferred procedure if histological confirmation is needed in cases of advanced pancreatic cancer before chemotherapy or to diagnose small uncharacterized lesions.

3a5. Laparoscopy and laparoscopic ultrasound: Laparoscopy with laparoscopic ultrasound enables intraoperative scanning of the liver and pancreas to be performed and is highly predictive of resectability, altering the management of 15% of patients already assessed as resectable by dual-phase helical CT⁹⁰. Selective laparoscopy based on the serum level of CA19-9 is a more efficient strategy, reducing the proportion of patients undergoing laparoscopic ultrasound from 100% to around 45% while increasing the yield from 15% to 25%⁹¹.

4a. Palliative treatment options for pancreatic cancer (inoperable disease)

The only potential cure for PC is surgical resection with negative margins. This option is possible only for the minority of patients affected by PC. The majority of them are diagnosed when the tumor is already too advanced to be resected. For these patients, palliative therapy is the only option for quality of life improvement. Currently, palliative chemotherapy is administered only for patients with good performance status. Survival benefit for palliative chemotherapy has been shown only in a few randomized trials.

4a.1 Palliative therapy for symptoms caused by pancreatic cancer

The treatment of patients who have localized advanced disease, metastases or deteriorated performance status is directed at symptom control.

1. **Pain:** Intractable pain is a major problem and often necessitates the use of high-dose opiate analgesia. Complementary approaches include intraoperative, percutaneous radiological guided neurolytic celiac plexus block and bilateral or unilateral thoracoscopic splanchnicectomy. In general, the results are disappointing and are particularly poor for patients with tumors in the body and tail of the pancreas.
2. **Weight loss:** weight loss initially is due to pancreatic exocrine insufficiency owing to obstruction of the main pancreatic duct as well as exclusion of bile acids from obstruction of the main bile duct. Fat maldigestion may also contribute to abdominal pain and bloating. Relief of biliary obstruction and pancreatic enzyme supplementation will alleviate these symptoms. Cachexia can be a marked feature of the later stages of pancreatic cancer, with no good treatment.
3. **Biliary and duodenal obstruction:** Biliary stenting using endoscopic retrograde cholangiography (ERCP) is the preferred option with the combined percutaneous approach employed only if the former is technically not possible. The life of a plastic stent is about 3 months, causing recurrent jaundice. Self-expanding metal (and covered) stents have greatly reduced the risk of obstruction and acute cholangitis. Metal stents should be used for patients with a good performance status and favorable prognosis (locally advanced primary tumor <3 cm) and plastic ones for those patients with metastases and tumors ≥ 3 cm in diameter. Expandable metal stents are being increasingly deployed endoscopically for duodenal obstruction (occurs in $\sim 15\%$), with a technical success rate of around 85%, but may be associated with serious complications, including perforation, fistula and bleeding and recurrent obstruction due to stent migration or fracture. Surgical bypass (open and laparoscopic) can be used to relieve jaundice using a Roux-en-Y loop hepatojejunostomy, and duodenal obstruction by gastrojejunostomy, especially in younger patients and both can be achieved laparoscopically.

4a.2 Palliative chemo and radiation therapy

1. **Chemotherapy:** PC is highly resistant to conventional methods of cytotoxic treatment and radiotherapy. Few chemotherapeutic agents have been shown to have reproducible response rates of more than 10%. 5-Fluorouracil (5FU) is an inhibitor of thymidylate synthetase (essential for synthesis of DNA nucleotides) and has been the most widely used in advanced pancreatic cancer, with a median survival of around 5–6 months and is better than the best supportive care⁹². A pivotal trial in 1997 meant that the nucleoside analogue, gemcitabine, replaced 5FU as the preferred drug⁹³. Although the median survival improvement in favor of gemcitabine compared with 5FU was slight (5.7 vs. 4.4 months), the 1-year survival rate was more encouraging (18% vs. 2%), and most importantly, the toxicity was relatively mild and achieved a better clinical response (24% vs. 5%, respectively)⁹³.
2. **Chemo-radiotherapy and follow-on chemotherapy:** Radiotherapy has been widely used for the treatment of PC^{94,95}. The main drawback is the limit on the dosage owing to the close proximity of adjacent radiosensitive organs. External beam radiotherapy is

routinely used with 5FU as a radiosensitising agent (chemo-radiotherapy), although gemcitabine is now being evaluated as an alternative radiosensitiser. Newer techniques such as conformal radiotherapy are now being used, but these studies almost invariably employ follow-on chemotherapy once the chemo-radiotherapy has been completed. A recent meta-analysis demonstrated that chemo-radiotherapy is better than radiotherapy alone and that there is no survival difference between chemoradiotherapy plus follow-on chemotherapy and chemotherapy alone⁹⁵. A recent phase III study compared chemo-radiotherapy and follow-on gemcitabine with gemcitabine alone in patients with locally advanced disease⁹⁶. The trial was closed prematurely because of significant toxicity in the combination arm and significantly reduced median survival in the combination arm (8.4 vs. 14.3 months; $p = 0.014$).

4b. Curative treatment options for pancreatic cancer (resectable disease)

4b1. Selection and staging: Once the pancreatic cancer has been identified, the patient needs to be assessed for fitness for major surgery and the tumor staged preoperatively for respectability. Venous resection is necessary during the course of a pancreatectomy in 5–10% of patients. Vascular reconstruction in this context results in a median and long-term survival that is similar to that of patients not needing a venous reconstruction⁹⁷. It should be emphasized, however, that routine venous resection in patients with significant venous involvement is not feasible and the results of arterial reconstruction are unacceptably poor⁹⁸. The resection rates and short- and long-term results are significantly better in high-volume centers, and major pancreas cancer surgery should only be undertaken in regional and supraregional centers^{99,100}.

4b2. Surgical techniques: The aim of surgery is to achieve complete clearance of macroscopic tumor with clear microscopic resection margins, even if there are lymph node metastases. In practical terms a large proportion of patients (at least 35%) are histologically staged complete clearance of macroscopic tumor with positive resection margins⁷⁴. The standard operation for tumors of the head of the pancreas is the Kausch–Whipple partial pancreateoduodenectomy (KW-PPD)¹⁰¹. Patients with tumors of the pancreatic body or tail undergo left pancreatectomy usually with en bloc resection of the spleen and hilar lymph nodes⁹⁸. There is no role for total pancreatectomy unless this is the only means by which a radical resection can be achieved⁹⁸. Postoperative morbidity remains high at around 40% even in supraregional units¹⁰². Independent risk factors are age >70 years, extended resections and small main pancreatic duct diameter measuring less than 3 mm¹⁰³.

4c. Adjuvant treatment after surgical resection

4c1. Chemotherapy: Radical resection alone will result in a 5-year survival of only 10% owing to recurrence after surgery⁹⁸. Nearly all patients develop metastatic disease, most commonly of the liver and peritoneum but also the lungs, and this may occur with or without local recurrence^{98,104,105}. Although chemo-radiation to the area of the resection may reduce the local failure rate, survival length is the same as with systemic chemotherapy¹⁰⁶. After pancreatic resection, the most important independent prognostic markers are lymph node status, tumor size and tumor grade^{107,108}. The results from two large randomized trials show that adjuvant systemic chemotherapy will increase the 5-year survival from 9% to 12% with resection alone to 21–29% and 23% with either 5FU and folinic acid or gemcitabine, respectively¹⁰⁹. The survival benefit of adjuvant chemotherapy is maintained irrespective of the type of operation used and whether or not patients develop postoperative complications¹¹⁰. Adjuvant chemo-radiotherapy has been used in the USA on the basis of a small randomized trial^{111,112} as well as apparently improving survival as reported in a non-randomized series of patients^{113,114}, but these results have not been confirmed

in large randomized trials^{115,116}, so the focus has moved to whether chemo-radiotherapy and follow-on chemotherapy represents a better alternative than chemotherapy alone. The results of meta-analysis using individual patient data reject the use of chemo-radiation and provide powerful evidence for systemic chemotherapy¹¹⁶.

5a. Prognostic factors of pancreatic cancer

The key factors relating to the overall prognosis of PC are¹¹⁷:

- tumor grade (cellular differentiation)
- maximal diameter of the tumor mass (tumor size)
- lymph-node metastasis (lymphovascular invasion) at the moment of diagnosis.

The microscopic resection margin status is also an important survival factor after surgical treatment, although less so if the patient is treated with postoperative adjuvant chemotherapy¹¹⁸. A positive microscopic resection margin (R1) is operationally defined as at least one cancer cell within 1 mm of any surface of the resected specimen. A positive R1 margin is unrelated to tumor diameter but rather to histological grade and lymph node status, indicating that this has more to do with the biology of the tumor than with physical factors¹⁰⁸.

6. Current limitations and rationale of the study

At the population level, no studies have evaluated the survival trends and the potential effects of advances in diagnoses and treatment for early PC in high risk families. Because survival of individuals with PC is dismal with most patients dying within 5 years¹¹⁹, early diagnosis is very important as surgical resection may be curative for these patients. Nowadays, early diagnosis of PC is possible because of the recent advances in diagnostic modalities such as computerized tomography, magnetic resonance (MRI), conventional ultrasonography (US) and endoscopic ultrasonography^{120,121,122}. Therefore, population based studies are necessary to test the hypothesis that screening programs for individuals with high risk of PC may have a significant impact in their treatment strategy. Population based studies are fundamental in prognostication, as they are more reflective of general population trends rather than the selected estimates derived from referral centers. Family history screening of many hundreds of PC patients is required to identify the most informative kindreds suitable for linkage analysis of FPC and to obtain adequate numbers of biospecimens (DNA) for genotyping. The effort required to conduct an informative linkage analysis of this magnitude was recently illustrated by 12-center experience of the Genetic Epidemiology of Lung Cancer Consortium, which screened 26,108 lung cancer patients to identify 771 family pedigrees that were developed or genetic linkage, and with a final sample of 52 families that were ultimately genotyped¹²³.

7. Study Design

The Atlantic Canada familiar PC registry will be created with funding from the Junior Clinical Scholar Award through Dalhousie University. Data will be prospectively collected for all patients diagnosed with PC in Atlantic Canada (Nova Scotia, New Brunswick, Princess Edward Island, Newfoundland and Labrador). The registry and its database will be constructed to match the same format as the one already ongoing in Ontario. Our data collection site will cooperate with Mount Sinai Hospital in Toronto (Ontario) where Dr. S Gallinger is leading the Canadian registry for research on familiar PC. Their registry has already screened 980 patients with identification of 63 probands and 290 of high risk relatives during the time interval between 1998 and 2006 (year of publication)¹²⁴. Other data collection sites participating to the Pancreatic Cancer Genetic Epidemiology Consortium (PACGENE) are: Dana-Farber Cancer Institute (Boston, MA), The Sol

Goldman Pancreatic Cancer Research Center at Johns Hopkins University (Baltimore, MD), Karmanos Cancer Institute-Wayne State University (Detroit, MI), Mayo Clinic (Rochester, MN), M.D. Anderson Cancer Center (Houston, TX), Creighton University (Omaha, NE) and University of Toronto (Mount Sinai Hospital, Toronto, Canada). Directors of these units form the Steering Committee, which governs the consortium’s activities and use of the resource. The Statistical Genetics and Data Management Core, located at Mayo Clinic, provides all programming, statistical analysis, and data management for the PACGENE Consortium. The Pathology and Archival Genotyping Core, located at Johns Hopkins University, performs all pathology review, DNA preparation from archival tissue, and tissue genotyping as needed. Genotyping services are largely outsourced to high-through-put facilities, including the Center for Inherited Disease Research, funded by the National Institute of Health (NIH)¹²⁵. An external advisory committee composed of individuals with expertise in statistical genetics, epidemiology, surgery and pathology provides advice. Figure 2 represents the overall organization of the PACGENE Consortium.

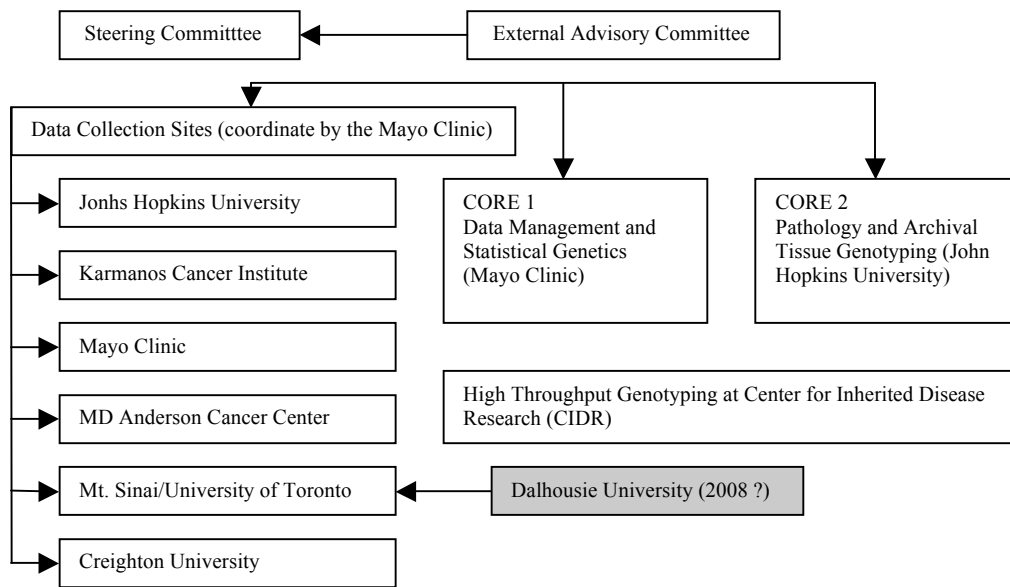


Figure 2. Organization of the PACGENE Consortium with Dalhousie University as a potential collaborative Institution of Mt. Sinai Hospital (University of Toronto) Data Collection Site

8a. Primary Aim of the study

To identify the incidence of FPC in Atlantic Canada by detecting probands through the combination of three mechanisms: screening family histories of incidental PC patients, physician referrals, and /or through Internet recruitment. Histology confirmation will be sought for primary adenocarcinoma of the pancreas whenever possible (International Classification of Diseases-Oncology site codes C25.0-25.3, C25.7, C25.9 and morphology codes 8140/3 and 8140/6)¹²⁶. Proband eligibility will include having at least one blood relative with pancreatic cancer.

8b. Secondary aims of the study

To evaluate the current status of medical and surgical care that patients newly diagnosed with PC receive in Atlantic Canada. This study will allow the investigators to assess the overall survival and disease free survival of participating patients, the time interval between clinical presentation and radiological diagnosis, the time interval between diagnosis and referral to specialists, the time interval between specialists' assessment and surgical or palliative therapy is provided, the percentage of patients who receive adjuvant chemotherapy after surgical resection, the percentage of patients who are referred to palliative specialists, outcomes of surgical interventions.

9. Hypothesis

That the incidence of familial PC in Atlantic Canada is comparable to the rates reported in the literature and that a genetic defect is responsible for the transmission of this condition and that screening for PC in high-risk individuals might improve the outcomes of this tumor by early diagnosis and therapy. These hypotheses will be tested by comparing the incidence of suspected cases of familial PC in our region with the ones reported in other geographical areas such as Ontario, USA and Germany for example where registries for FPC have been already enrolling patients for several years.

To assess that a genetic defect with variable penetrance is responsible for FPC, data collected in Atlantic Canada will be submitted to the PACGENE Consortium to enlarge the pool of patients enrolled in this multicentric study.

To assess the impact of screening for PC, the percentage of patients diagnosed with early stage of the tumor in high risk families undergoing screening program with serial imaging tests will be compared to the percentage of patients diagnosed with the same condition but affected by sporadic PC.

To assess possible disparities of patients' care in different areas of Atlantic Canada (e.g. waiting time for specialist assessment, waiting time for radiological tests, surgical procedures etc.) and possible differences in outcomes by Medical Centers where these patients are referred to for treatment options.

10a. Definition for familial pancreatic cancer

Currently, there is no consensus on the definition for familial pancreatic cancer. Some centers define familial pancreatic cancer as:

A) Any PC presenting in families where two or more members have been affected regardless of their degree of relationship.

More stringent diagnostic criteria are used by other authors and they are the following:

B) Two or more first-degree relatives with PC or

C) Two or more second-degree relatives with PC, one of whom has early-onset pancreatic cancer (age <50 years at diagnosis).

In familial pancreatic cancer the observed to expected rate of PC is significantly raised in comparison to sporadic PC¹²⁷:

- 4-fold in families with one first-degree relative
- 6.4-fold where there are two affected relatives
- 32-fold with three relatives with pancreatic cancer

11. Methods

Prospective data collection of all cases of PC in Atlantic Canada (Nova Scotia, New Brunswick, Prince Edward Island, Newfoundland and Labrador) will be performed and identification of probands for FPC will be obtained by any combination of three mechanisms: screening family histories of incidental PC patients, physician referrals and / or through Internet recruitment.

All potential probands will complete a family history screening questionnaire (see appendix of the protocol for details on the standardized questionnaire), which seeks cancer family history on first-degree, second-degree, and third-degree relatives to establish eligibility for further study as a high risk family.

If a patient's family history does not contain at least two blood relatives with PC, no further recruitment for the PACGENE Consortium will be pursued.

FPC kindreds are evaluated for suitability for linkage analysis by inspection of their pedigree and also by using linkage simulation programs (i.e., SLINK)¹²⁸. In the development of PACGENE kindreds, probands (or next of kin if the proband is deceased) will be contacted and asked to consent to provide names and addresses of additional family members, or alternatively to seek consent from family members. Expanded families will include available first-degree, second-degree, and third-degree adult relatives of all PC cases. Invited relatives will be asked to complete their own consent form, family history and risk factors questionnaires, and medical release forms when pertinent to confirm the diagnosis of cancers and to obtain pathology records and archival specimens when needed.

Thirty milliliters of blood samples from the proband and other participating family members will be obtained and sent to Mount Sinai's laboratory to be processed. Samples will be shipped by overnight express.

All the medical records, diagnosis, dates of the procedures, and pathology will be reviewed and confirmed. If available, formalin-fixed, paraffin-embedded block with tissue for DNA samples from all the probands and affected relatives will be obtained. Archival tissue will be requested and sent to Toronto for storage until ready for processing by the Pathology and Archival Tissue Genotyping Core. There, DNA will be extracted from unstained 10- μ m slides after deparaffinizing as previously described¹²⁹.

Members of identified high-risk families for PC will be informed of their status and asked to participate to screening program that will entail the use of interval imaging modality every 6 months. Imaging modality will include at least one of the following abdominal test: dedicated pancreatic US, intravenous and oral contrast CT scan or gadolinium contrast MRI.

12. Relevance of the Study

PC has poor prognosis with the majority of patients dying during the first 24 months after diagnosis. The only curative therapy for PC is surgical resection with negative margins. Surgical treatment is possible only for the minority of patients because the tumor has tendency for early metastasis or the risk of perioperative mortality is too high for pre-existing patients' comorbidities. Familiar transmission of PC may occur in up to 10% of cases and early diagnosis by screening

modalities may have a significant impact on year-life saved. Therefore, the creation of a familiar PC registry in Atlantic Canada would contribute to the advancement of genetic research and direct education and screening to high risk families where tumor related deaths may be prevented. In addition to the potential health gains for families at high risk for PC, the establishment of this study would have several academic benefits for Dalhousie University and the primary investigators. First of all, it will allow the development of methodological framework and scientific productivity to obtain national and international recognition for the investigators to access external grants for future research. Secondly, it will allow Dalhousie University to be part of a prestigious consortium for the study of genetic defects that will promote cooperation among academic Institutions with invaluable scientific benefits. Thirdly, the Atlantic Canada registry for familiar PC might be an important legacy for future researchers as its inclusion in the Nova Scotia Cancer Society would allow future continuation of the project and epidemiological studies of PC in Atlantic Canada.

13a. Eligibility

- All individuals newly diagnosed with PC in the Atlantic Canada Provinces and
- Their relatives
- Participating individuals have to be able to give their informed consent before enrollment in this study. If unable to consent, their legal guardians will be approached and asked for their written permission.
- Patients affected by PC will have to be diagnosed by at least one of the following criteria:
 - Clinical findings supported by at least one radiological imaging modality
 - Clinical findings supported by elevation of serum tumor marker for PC (CA19-9)
 - Tissue diagnosis obtained by biopsy, surgical resection, autopsy
 - Post mortem exam

13b. Exclusion Criteria

- Inability to obtain written consent to enroll in this study
- Diagnosis of endocrine tumors of the pancreas
- Suspected diagnosis of PC but that does not satisfy eligibility criteria

14. Recruitment

Each individual affected by PC diagnosed in Atlantic Canada is recorded at the specific Provincial Cancer Registry where the diagnosis is made. Currently, in Atlantic Canada there are four operating Cancer Registries (Nova Scotia, New Brunswick, Princess Edward Island and Newfoundland-Labrador). All four Cancer Registries are accessible for epidemiological studies by researchers after formal application is submitted. Patients with PC are recorded in these registries by the Revised 10th International Classification of Diseases (ICD-10) code number C25. Diagnosis of PC is recorded as ICD-10 number 25 when radiological findings are consistent with PC or when tissue diagnosis is available from biopsy or surgical resections or when post-mortem autopsy findings are provided to the Cancer Registries.

Recruitment of all the subjects in this study will occur by prospectively collecting data available from the Provincial Cancer Registries in Atlantic Canada. The next of kin of individuals with PC will be contacted by the study coordinator(s) using telephone numbers and address information provided in the Provincial Cancer Registries. Family members related to each patient affected by PC will be offered participation to this study if their contact information are provided by the next of kin or by the patients affected by PC themselves.

As reported in Table 2, 140-150 patients with PC are diagnosed each year in Atlantic Canada. From databases already active in Ontario and in the USA, an average of 4 family members related to each PC patient will be contacted. Therefore we estimate that each year, 550-650 individuals will be screened and offered participation to this prospective study. The expected participation rate for screening programs is 50-60%. Therefore the anticipated number of

individuals recruited in this study is 300-350 per year for a total of 1,500-1,750 at the end of the 5th year.

15. Measurements

In addition to clinical and family history questionnaires (see appendix), all consenting probands and family members will complete a risk factor questionnaire seeking information on demographics (age, sex, ethnicity and religious heritage), medical history and medications, lifestyle, and possible PC risk factors (alcohol intake, smoking, occupational exposures). Specific information about cigarette smoking will include ever smoked 100 cigarettes in lifetime (yes/no), age started, age stopped, number of cigarettes per day currently and average of number over lifetime, and overall number of year smoked.

Date of diagnosis (clinical, radiological, or by tissue sampling), imaging modality used for diagnosis (US, CT, MRI, ERCP etc.) as well as the time of referral to specialists such as surgeons, gastroenterologists, medical oncologists or interventional radiologists will be captured. All interventions provided to PC patients for potential cure or palliation will be evaluated and recorded. For all the individuals undergoing surgery, date of the operation, medical center where the operation occurred and surgeons performing the operation, date of admission and discharge, possible adverse events, number of blood transfusions required during their hospital stay, surgical pathology for pTNM staging and cell differentiation, status of surgical margins, referral to medical oncologists and radiation therapists for palliative care (yes/no), adjuvant therapy and duration, number of hospital readmissions and date of death (when appropriate) will be recorded. For all the individuals identified as members of high-risk families and consenting to undergo interval imaging modalities of the pancreas (US, CT or MRI), results of the tests will be collected. In addition, if abnormalities are detected during any of the radiological tests, all the interventions and surgical procedures performed to any of the participants will be recorded as for patients diagnosed with PC enrolled in this study.

16. Feasibility

The management of patients affected by PC is complex and needs advanced expertise in many disciplines and the majority of PC patients are referred to tertiary medical centers. Contrary to other areas in North America and Europe, in Atlantic Canada there are only three University Medical Centers where the majority of these patients are referred to: Victoria General Hospital in Halifax (NS), Moncton General Hospital (NB) and Memorial University Hospital in St. Johns' (NFL). The advantage of centralized patient referral and the fact that the mobility of the population in Atlantic Canada is significantly less than in other parts of the Country, make our Institution an ideal center for epidemiological studies on familial conditions.

Preliminary contacts with all the Cancer Centers in Atlantic Canada and key specialists practicing at Dalhousie University, in Moncton and St. Johns were positive for collaboration with the investigators of this study. Access to Cancer Registries already existing in all four provinces will allow the capturing of the majority of newly diagnosed PC in Atlantic Canada.

17. Statistical analysis

Bivariate analysis of statistical significance of continuous variables will be performed using 2 tail Student's t test. Proportions will be compared by Pearson's Chi Square with Yate's correction factor or Fisher's exact test whenever appropriate. Multivariable linear regression and logistic regression analysis will be performed to determine statistical significance of continuous or dichotomous variables adjusted for covariates and interaction terms. Continuous variables will be tested for normal distribution using the Kolmogorov-Smirnov test and log transformation will be performed for statistical analysis when appropriate. Kaplan Meier technique will be used to evaluate survival analysis and the log rank to assess for statistical differences for time dependent variables. The null hypothesis will be rejected fixing the probability of type I error at 0.05 and a type II error at 0.20. Two-tail probability distribution will be used for all the statistical analysis unless specified. SPSS® or SAS® statistical software (SPSS software, Chicago, Illinois, SAS

software, North Carolina) will be used to assist all the statistical computations.

18. Data management (confidentiality and quality monitoring)

Because of the sensitive information on health status and genetic profile collected on a large number of healthy individuals related to patients affected by PC, data of this study will be stored in a database accessible only to the primary investigator(s) and assistants. Investigators will comply fully with health information privacy rules of the Health Insurance Portability and Accountability Act. In addition, the PACGENE Consortium has been granted a Certificate of Confidentiality from the National Cancer Institute¹³⁰. Certificates of Confidentiality allow researchers to avoid the involuntary release of any portion of research records containing information that could be used to identify confidential information on study participants. All the data will be available to other researcher(s) if requested only when confidentiality of the participating individuals would be guaranteed by signing a written contract of accountability. All the relative data will be collected on paper (Protocol Forms (PF) attached to the appendix) and computer input information will be transferred to the database by the study coordinator(s) and study assistant(s). Paper and computerized database will be locked in a safe location where electronic and physical access to the information collected would not be possible to any other individual except the researcher(s) and study coordinator(s). This will be possible by the use of safety cabinet(s) and password(s) for the access to the electronic database. Cross analysis of random variables of the databases will be performed to assess the existence of potential transcription errors. If data entry errors are detected in one category, the corresponding paper copy of the data collection form will be retrieved and corrections made. At the end of each correction process, a new random sample of data will be retrieved and cross-examined until no more errors are detected. Back up copy of the databases will be performed after each updating session. Strategy for protecting confidentiality will include limiting the access to the computers and cabinets containing the primary data only to personnel responsible to update and collect the patients' information and the primary investigators.

19. Ethics

After obtaining ethical approval from the Dalhousie University Institutional Review Board, permission to conduct screening of family members of individuals affected by PC by using standardized questionnaires (see appendix) will be obtained by written or witnessed phone consent from each participant. A signed written consent form will be mailed to each individual who provided verbal consent and filed for completion of records in the FPC registry. As suggested by the International Ethical Guidelines for Biomedical Research Involving Human Subjects, five fundamental principles were satisfied in the design of this protocol: equipoise of treatments, respect for the patient's autonomy, non-maleficence, beneficence and justice¹³¹.

20. Timeline

The recruitment of the patients will occur during the 5-year period of this study and continued if external or internal funding would support the FPC registry in Atlantic Canada. Data collection and database entry will be performed during the entire duration of the protocol. Data analysis will be performed at 6 months intervals and scientific reports will be provided at yearly intervals or more often if necessary. Publication(s) of the results of the research will be performed at any time at discretion of the investigator(s) and final publication(s) within 6 months from the time of the last patient's data collection.

21. Budget

Category	Description of costs	Expected expenses per year of research (\$)	Number of years	Total Cost (\$)
Study coordinator	A full-time study coordinator will be employed for the execution of this project. The person who will be appointed to assist the primary investigator has to be a nurse who had already experience in conducting prospective trials. The study coordinator will be responsible for participants' identification from several sources: physicians' referral, cancer registries and internet driven self referral. The cost for a study nurse coordinator (grade 2/3) is currently at \$30-35 (plus benefits) dollars/hours. The individual identified to coordinate this study will have to provide coverage for recruitment and shipping/receiving of questionnaires and data collection for 5 days / week for 8 hours / day	60,000	5	300,000
Technical support for internet web page for potential self-referral and out of province referral	The estimated cost for creation of an internet web page dedicated to our protocol (education material, interface for patients' self referral or physicians' referral) is in the range 1,500-2000. Maintenance costs of the web page for each year of the study is \$500-800	2,000 (creation) 800	5	6,000
Office expenses, shipping of biological material	The cost for office expenses, mailing, fax and copy machine supplies and overnight shipping of biomedical specimens necessary for the study from all the Atlantic Canada medical centers to our Center and then to Toronto where they will be stored is estimated to be \$100 per participant. The estimated number of participants calculated by current epidemiological data from Atlantic Canada to be recruited per year is 300-350.	35,000	5	175,000
Data entry	Data entry in the computerized database will be responsibility of the full time study coordinator	-	-	-
Data analysis	Statistical analysis will be supported by a part-time biostatistician. The estimated time required for statistical analysis of the data stored in the database is 5-8 hours / month. The cost for statistical analysis is currently \$30/hour	2,500	5	12,500
Technology Support	Purchasing of Computer and software necessary for creation and maintenance of the registry	1,500 (computer) 1,000 (software)	one time cost	2,500
Travel / promotion / education	Costs for travel expenses (coordinator) and / promotion of findings and education for referring physicians			4,000
			Total	500,000

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Appendix

APPENDIX I: ACTUAL DATA FOR NEW CASES AND DEATHS

Table A1

Actual Data for New Cases of Cancer by Type and Sex, Canada, 2003

Cancer	ICDO-3 Site/Type ¹	Total	Males	Females
All Cancers	All invasive sites	143,466	74,848	68,618
Oral (Buccal Cavity and Pharynx)	C00-C14	3,153	2,162	991
Lip	C00	344	268	76
Tongue	C01-C02	727	492	235
Salivary Gland	C07-C08	361	201	160
Mouth	C03-C06	623	357	266
Nasopharynx	C11	214	145	69
Oropharynx	C10	140	101	39
Other and Unspecified	C09,C12-C14	744	598	146
Digestive Organs	C15-C26,C48	29,960	16,482	13,478
Esophagus	C15	1,382	1,008	374
Stomach	C16	2,902	1,897	1,005
Small Intestine	C17	507	277	230
Large Intestine	C18,C26.0	12,352	6,232	6,120
Rectum and Anus	C19-C21	6,528	3,812	2,716
Liver	C22.0	1,129	824	305
Gallbladder	C23	400	143	257
Pancreas	C25	3,449	1,663	1,786
Other and Unspecified	C22.1,C24,C26.1-.9,C48	1,311	626	685

– Not applicable

¹ Histology types 9590-9989 (leukemia, lymphoma and multiple myeloma), and 9050-9055 (mesothelioma) are excluded from other specific organ sites.

Note: ICDO-3 refers to the Third Edition of the International Classification of Diseases for Oncology. Figures are for invasive sites including in situ bladder and exclude non-melanoma (basal cell and squamous cell) skin cancer. Further information is available at: <http://www.phac-aspc.gc.ca/dsol-smed/index.html>.

Source: Surveillance Division, CCDPC, Public Health Agency of Canada