Screening of Patients at Risk for Familial Pancreatic Cancer: What Is Beneficial?

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KEYWORDS

• Pancreatic cancer • Familial pancreatic cancer • High-risk individuals • Screening • Surveillance

KEY POINTS

- Familial cancer predisposition syndromes, hereditary pancreatitis, and familial pancreatic cancer are significant risk factors for developing pancreatic cancer.
- Certain high-risk individuals should undergo screening for pancreatic cancer with EUS or MRI/magnetic resonance retrograde cholangiopancreatography.
- The goal of screening is to identify early cancer or precancerous lesions (branch-duct IPMNs, mucinous cystic neoplasms, and PanINs) that can be curatively resected.

INTRODUCTION

Pancreatic cancer is projected to be the third most deadly cancer in the United States in 2017. Despite advances in treatment, the 5-year survival remains dismal, estimated to be 8%.[1] At the time of diagnosis, only 15% to 20% of patients are candidates for surgical resection, the only potentially curable treatment, because of locoregional spread or metastatic disease. Routine screening for pancreatic cancer is not recommended because it remains a rare disease with an incidence of only 9 per 100,000 persons per year and a cumulative lifetime risk of 1.5%.[2] Identifying patients at increased risk for the development of pancreatic cancer is paramount to early diagnosis and successful treatment.

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Family history is essential in identifying individuals at increased risk for developing pancreatic cancer. It is estimated that 1% to 10% of those diagnosed with pancreatic cancer have a family history of the disease.[3,4] Although environmental exposures, such as cigarette smoking, can confer some increased familial risk of developing pancreatic cancer, it is now widely accepted that this increased familial risk is largely caused by genetic inheritance.

Several different etiologies can lead to this increased inherited risk for pancreatic cancer including hereditary tumor predisposition syndromes, hereditary pancreatitis, and a growing list of newly identified mutations leading to familial pancreatic cancer (**Table 1**).[5] This growing understanding led the International Cancer of the Pancreas Screening (CAPS) Consortium to release guidelines in 2012 regarding which of these high-risk patients should undergo screening for pancreatic cancer.[6] However, there is still much uncertainty regarding the optimal screening approach and management of pancreatic lesions identified in this unique patient population.

HEREDITARY RISK FOR PANCREATIC CANCER

Hereditary Cancer Predisposition Syndromes

Known cancer predisposition syndromes account for an estimated 20% of the observed familial aggregation of pancreatic cancer.[2] Hereditary predisposition syndromes associated with pancreatic cancer include familial atypical multiple mole melanoma (FAMMM) syndrome, Peutz-Jeghers syndrome, hereditary breast-ovarian

Table 1
Hereditary risk for pancreatic cancer

	Involved Genes	Risk of Pancreatic Cancer	CAPS Screening Recommendations[6]
Hereditary Cancer Predisposition Syndromes			
Familial atypical multiple mole melanoma	CDKN2A/ p16-Leiden	17% by 75 y[8]	Yes, if one affected FDR
Peutz-Jeghers	STK11/LKB1	36% life-time risk[12]	Yes, regardless of family history
Hereditary breast-ovarian cancer	BRCA1 BRCA2	1.5%–2.1% by 70 y[14] 3.6% lifetime risk[15]	No recommendation Yes, if one affected FDR or two affected family members
Hereditary nonpolyposis colorectal carcinoma	MLH1, MSH2, MSH6	3.7% by 70 y[16]	Yes, if one affected FDR
Familial adenomatous polyposis	APC	~2% lifetime risk[17]	No recommendation
Hereditary pancreatitis	PRSS1, SPINK1, CFTR	40% by 70 y[19]	No recommendation
Familial pancreatic cancer	BRCA2, PALB2, ATM	2 affected FDRs, 8%–12% lifetime risk 3 affected FDR, 16%–30% lifetime risk[22]	Yes, if two or more affected blood relatives, with at least one affected FDR

Abbreviations: CAPS, International Cancer of the Pancreas Screening, FDR, first degree relative.

cancer (HBOC), hereditary nonpolyposis colorectal carcinoma, and familial adenomatous polyposis.

Familial atypical multiple mole melanoma

FAMMM is associated with multiple nevi, atypical nevi, and cutaneous or ocular malignant melanomas.[2] FAMMM is inherited in an autosomal-dominant manner but has a highly variable disease penetrance. At least one-quarter of patients with this syndrome have mutations in the *CDKN2A* (cyclin-dependent kinase inhibitor 2A) gene, also known as the *p16* gene.[7] Patients with a particular *CDKN2A* mutation, *p16-Leiden*, have been shown to be at increased risk for not only malignant melanoma but also pancreatic cancer. Patients with this *p16-Leiden* mutation have a significant risk of developing pancreatic cancer with an estimated cumulative risk by the age of 75 of 17% and a mean age at diagnosis of 58 years (range, 38–77 years).[8] FAMMM should be considered in patients with invasive melanoma and two or more relatives with invasive melanoma or pancreatic cancer on one side of their family, or if they have three or more primary invasive lesions.[9]

Peutz-Jeghers syndrome

Peutz-Jeghers syndrome is characterized by hamartomatous gastrointestinal polyps and mucocutaneous pigmentation with autosomal-dominant inheritance.[10] This syndrome occurs secondary to mutations in the serine/threonine kinase gene (*STK11/LKB1*), which is thought to act as a tumor suppressor gene. Patients with Peutz-Jeghers syndrome are at increased risk for gastrointestinal malignancies (gastroesophageal, small intestine, colorectal, pancreas) and breast and gynecologic malignancies with a risk of malignancy at any site by the age of 70 years of 85%. These patients have a cumulative lifetime risk of developing pancreatic cancer of 11% to 36%.[11,12]

Hereditary breast-ovarian cancer

HBOC syndrome is associated with germline mutations in *BRCA1* and *BRCA2* genes and is characterized by an increased risk for male and female breast cancer; ovarian cancer; and less commonly pancreatic cancer, prostate cancer, and melanoma.[13] *BRCA1* gene mutation carriers have been shown to have an estimated cumulative risk of developing pancreatic cancer by the age of 70 of 2.1% (male) and 1.5% (female).[14] *BRCA2* gene mutations carries are considered to be at a higher risk for developing pancreatic cancer with a cumulative age-adjusted lifetime risk of 3.6%.[15]

Hereditary nonpolyposis colorectal carcinoma

Hereditary nonpolyposis colorectal carcinoma, or Lynch syndrome, is an autosomal-dominant condition secondary to mutations in DNA mismatch repair genes: *MLH1*, *MSH2*, *MSH6*, or *PMS2*. Patients with Lynch syndrome are most susceptible to colorectal and endometrial cancers. Patients harboring these mutations have also been shown to have an increased risk for the development of pancreatic cancer with a cumulative risk by the age of 70 years of 3.68%. The median age of pancreatic cancer diagnosis in this group of patients was 51.5 years (range, 19–85).[16]

Familial adenomatous polyposis

Familial adenomatous polyposis is characterized by the formation of numerous adenomatous polyps forming in the large intestine and increased risk for developing early onset colorectal cancer caused by mutations in the *APC* gene. Although not widely studied, it is reported that these patients also have an increased risk of developing pancreatic cancer, with a relative risk of 4.5 compared with the general population.[17]

Hereditary Pancreatitis

Hereditary pancreatitis causes chronic inflammation of pancreas resulting in a predisposition to developing pancreatic adenocarcinoma. Hereditary pancreatitis is characterized by recurrent acute pancreatitis episodes and typically presents at an early age, within the first two decades of life. These patients are at risk to go on to develop chronic pancreatitis–associated risk of pancreatic fibrosis, pseudocysts, pancreatic duct strictures, exocrine insufficiency, and diabetes mellitus.[15,18] Hereditary pancreatitis is inherited in autosomal-dominant or autosomal-recessive forms and mutations to the following genes have been implicated in this disease process: *PRSS1*, *SPINK1*, and *CFTR*.

PRSS1

Mutation to the *PRSS1* gene is the most common genetic disruption leading to hereditary pancreatitis, present in 80% of cases, and is inherited in an autosomal-dominant fashion. The *PRSS1* gene encodes for the most abundant isoform of trypsin secreted by the pancreas. Many mutations in the *PRSS1* gene have been identified in patients with hereditary pancreatitis, the most common being to regions of the gene that encode regulatory domains that defend against premature activation of trypsin in the pancreas.[18]

SPINK1

SPINK1 encodes a protein that is a trypsin inhibitor found in pancreatic acinar cells and acts to inhibit prematurely activated trypsin from activating other pancreatic zymogens.[18] *SPINK1* mutations that result in hereditary pancreatitis are typically inherited in an autosomal-recessive fashion.

CFTR

Cystic fibrosis is a multiorgan disease that results secondary to a mutation in the cystic fibrosis transmembrane conductance regulatory gene (*CFTR*) causing a disruption in sodium, chloride, and bicarbonate transport. The typical presentation of cystic fibrosis with thick secretions and severe lung disease secondary to autosomal-recessive inheritance of the F508D mutation rarely causes pancreatitis. Hereditary pancreatitis secondary to *CFTR* mutations is instead more commonly associated with milder defects in *CFTR* gene and mild presentations of cystic fibrosis.[18]

Hereditary pancreatitis and risk of pancreatic cancer

Patients with hereditary pancreatitis are at increased risk for subsequently developing pancreatic adenocarcinoma. In one cohort study comparing those with hereditary pancreatitis (based on age of first episode of pancreatitis <30 years, positive family history, and no other likely cause) with population-based control subjects, patients with hereditary pancreatitis had an estimated cumulative risk of developing pancreatic cancer by the age of 70 of 40%; this cumulative risk was 75% in patients with paternal inheritance. Of the patients that went on to develop pancreatic cancer, the mean age of diagnosis was 56.9 years.[19] From analysis of data from the European Registry of Hereditary Pancreatitis and Pancreatic Cancer including 112 families from 14 countries, the cumulative risk of developing pancreatic cancer at 70 years after symptom onset was 44% with a standardized incidence ratio of 67%.[20] Furthermore, almost half of all deaths in a French cohort study of patients with hereditary pancreatitis were secondary to pancreatic cancer.[21]

Familial Pancreatic Cancer

One accepted operational definition of familial pancreatic cancer is “families with two or more first degree relatives (FDR) with pancreatic cancer that do not fulfill the criteria

of any other inherited tumor syndrome," thus excluding those with cancer predisposition syndromes or hereditary pancreatitis.[5] Despite the numerous syndromes discussed previously that result in an increased risk for pancreatic cancer, familial pancreatic cancer accounts for most cases where there is an increased inherited risk of developing pancreatic cancer.

A detailed family history remains the most important clinical tool for stratifying high-risk individuals. For example, those with one, two, or three affected FDRs have a 4.6-fold, 6.4-fold, and 32-fold increased risk of developing pancreatic cancer, respectively.[22] There is also strong evidence for anticipation in familial pancreatic cancer, meaning individuals in successive generations are at risk at an earlier age than their predecessors.[23]

Recent advances in whole-genome sequencing has led to the discovery of several genes that can harbor mutations causing familial pancreatic cancer, including *BRCA2*, *PALB2*, and *ATM*. Likely more familial mutations will be identified as research into this area continues to grow.

BRCA2

BRCA2 is the most well described familial pancreatic cancer gene. Breast cancer occurs commonly in patients with *BRCA2* mutations in association with HBOC. Pancreatic cancer can develop in families with HBOC syndrome; however, pancreatic cancer has also been shown to run in families with *BRCA2* mutations in the absence of breast cancer.[24] In one study analyzing DNA from familial pancreatic cancer kindreds, who did not have another inherited tumor syndrome, 17.2% of patients had deleterious *BRCA2* mutations.[25]

PALB2

PALB2 has been shown to be a binding partner of BRCA1 and BRCA2 and that this interaction is important for DNA repair.[26] Through exome sequencing, *PALB2* mutations were shown to occur in 3.1% (4 out of 96) of patients with familial pancreatic cancer.[27] In a subsequent European study, *PALB2* mutations were identified in 3.7% of patients with familial pancreatic cancer.[28]

ATM

The *ATM* gene encodes a serine/threonine kinase involved in DNA double-strand break repair. Ataxia-telangiectasia is an autosomal-recessive syndrome that occurs in patients with homozygous mutations in *ATM* and is characterized by cerebellar ataxia; oculomotor apraxia; telangiectasias of the conjunctiva and skin; immunodeficiency; sensitivity to ionizing radiation; and an increased risk of malignancies, such as lymphoma and leukemia.[29] Genome-wide sequencing revealed that in familial pancreatic cancer kindreds with three affected family members, 4.6% carried heterozygous deleterious mutations in *ATM*.[30]

SCREENING HIGH-RISK INDIVIDUALS

Which Patients Should Be Screened?

CAPS released guidelines in 2012 regarding patient screening for pancreatic cancer.[6] They recommended against screening in the general population given the low lifetime risk of developing pancreatic cancer. The CAPS guidelines recommend screening should be considered for the following at-risk individuals:

- Those with two or more affected blood relatives, with at least one affected FDR.
- Those with Peutz-Jeghers syndrome, regardless of family history of pancreatic cancer.

- *p16* mutations carriers with one affected FDR.
- BRCA2 mutation carriers with one affected FDR, or two affected family members.
- *PALB2* mutation carriers with one affected FDR.
- Those with Lynch syndrome (mismatch repair gene mutation carriers) with one affected FDR.

At What Age Should Screening Be Initiated?

No consensus guideline has been reached on when screening should begin for high-risk individuals. The average age of diagnosis of familial pancreatic cancer is 68 years.[22] In a prospective trial screening high-risk individuals, Canto and colleagues[31] initiated screening at age 40 or 10 years younger than the youngest relative with pancreatic cancer. However, pancreatic lesions identified on screening imaging were much more common in patients greater than 50 years of age, and high-grade neoplasms were resected only in individuals older than 60 years. These results argue that screening for high-risk individuals should begin in the fifth or sixth decade of life because this produces the highest diagnostic yield. Given anticipation has been described in familial pancreatic cancer, it is reasonable to consider screening individuals 10 years before the earliest diagnosis of pancreatic cancer in their family. Patients with Peutz-Jeghers syndrome are another notable exception with a mean age of diagnosis of pancreatic cancer of 41 years, suggesting screening should begin at an earlier age in this high-risk group.[12]

How Should High-Risk Individuals Be Screened?

Endoscopic ultrasound (EUS) and MRI are the best screening modalities for high-risk individuals. Computed tomography, MRI, and EUS were compared in a multicenter prospective study screening a cohort of 216 high-risk individuals with familial pancreatic cancer, the largest study to date comparing screening modalities in high-risk individuals. Computed tomography scan only visualized 13.8% of all detectable lesions, compared with MRI/magnetic resonance retrograde cholangiopancreatography and EUS, which visualized 77% and 79% of all detectable lesions, respectively. This study also reported a diagnostic yield of first-time screening of 42.6% (pancreatic mass, cyst, or isolated dilated main pancreatic duct identified in 92 of 216 high-risk individuals).[31]

MANAGEMENT OF LESIONS IDENTIFIED IN HIGH-RISK INDIVIDUALS

The management of lesions identified when screening high-risk individuals is a challenging issue. The goal of screening this patient population is to identify early stage pancreatic cancer that can be resected with negative margins, or alternatively, to identifying precursor lesions that can be curatively resected. Known precursor lesions include pancreatic intraepithelial neoplasms (PanINs), intraductal papillary mucinous neoplasms (IPMNs), and mucinous cystic neoplasms (MCNs). It has been shown that pancreatic tissue from patients with a family history of pancreatic cancer that developed disease requiring resection have a greater number of precursor lesions, the precursor lesions were more often multifocal, and there was a higher rate of high-grade lesions when compared with nonfamilial cases.[32] Despite the known higher prevalence of microscopic precursor lesions in patients with a family history, there currently are no screening methods to accurately identify these microscopic high-risk lesions. Instead, current screening modalities, such as EUS and MRI, are sensitive at identifying small, radiographically suspicious lesions, most commonly cysts.

Branch Duct Intraductal Papillary Mucinous Neoplasms

Most cystic lesions identified on screening are branch duct IPMNs (BD-IPMNs). The updated Fukuoka International Consensus Guidelines help guide the management of sporadic BD-IPMNs. Surgical resection is considered in individuals with symptoms attributable to the suspect lesion, cysts greater than 3 cm, and cysts with mural nodules.[33] These recommendations are based on the risk of the lesions harboring or progressing to invasive disease. There is less knowledge about the risk of malignancy or progression to malignancy of BD-IPMNs identified in individuals with a family history of pancreatic cancer. A retrospective study reviewed the progression to pancreatic cancer in 300 individuals with BD-IPMNs, and evaluated a subgroup of 16 patients from this cohort with a family history of at least one first-degree relative with a history of pancreatic cancer. After controlling for age by comparing patients greater than 70 year old, they found no difference in the frequency of developing pancreatic cancer in follow-up for BD-IPMNs in patients with a family history of pancreatic cancer compared with those without.[34] A separate retrospective study also demonstrated that in resected IPMNs (including main duct, branch duct, and mixed) there was no difference in pathologic grade or invasive components of the resected IPMN when comparing those with a family history of pancreatic cancer with those without.[35]

Given these findings, the criteria for surgical resection of BD-IPMNs identified in patients with a family history of pancreatic cancer should be no different from sporadically identified BD-IPMNs. Further studies into the biologic progression of IPMNs to pancreatic cancer in the setting of known hereditary precursor mutations are needed to help better guide management of BD-IPMNs in high-risk individuals with known germline mutations. The CAPS consensus guidelines recommend repeat surveillance for BD-IPMNs without high-risk stigmata at intervals consistent with those recommended by the Fukuoka guidelines depending on lesion size.[6]

Pancreatic Intraepithelial Neoplasms

PanIN lesions arise in small pancreatic ducts, typically measure less than 0.5 cm, and are classified based on degree of dysplasia as PanIN-1, PanIN-2, or PanIN-3 (carcinoma *in situ*) lesions.[36] From genetic analysis, it is thought that PanIN lesions progressively become more dysplastic through a stepwise accumulation of mutations (*KRAS2* in PanIN-1, inactivation of *p16/CDKN2A* in PanIN-2, and inactivation of *TP53* and *MAD4/DPC4* in PanIN-3), ultimately progressing to invasive carcinoma.[37] Given this stepwise progression to invasive pancreatic cancer, identifying PanIN lesions in high-risk individuals would be an optimal opportunity for cure before progression to invasive disease in screening programs for familial pancreatic cancer. However, two complicating factors include lack of understanding of the rate of progression of early PanIN lesions to invasive disease and the limited ability to detect PanINs with current imaging techniques.

PanIN lesions have been shown to be more common in pancreatic tissue of high-risk individuals who underwent resection for suspicious lesions. Brune and colleagues[38] analyzed the histology of resected pancreas specimens from individuals screened in the CAPS 1 and CAPS 2 and identified PanIN lesions in 100% of resected specimens (eight of eight specimens). Notably, there were a mean of 34 PanIN lesions per resected specimen, as compared with a mean of 1.9 lesions in control cases. In only one specimen was PanIN-3 present. It currently is not known if PanIN lesions progress to malignancy faster in high-risk individuals than the general population, but it seems early PanIN lesions are more prevalent and multifocal. Although resection of PanIN lesions is considered a success of screening programs because of their

potential for malignancy, surveillance must continue after resection because the remaining pancreatic tissue remains at risk.

Because PanIN lesions are a histologic finding without a known clinical correlate it is difficult to accurately identify these lesions with current imaging modalities, such as EUS and MRI. However, it has been demonstrated that PanIN lesions in resected specimens correlate with lobular atrophy of pancreatic parenchyma, which is detected with standard EUS, resembling chronic pancreatitis-like changes.[38] This finding on screening EUS should raise suspicion for precursor PanIN lesions and close clinical follow-up.

Mucinous Cystic Neoplasms

MCNs are a less commonly identified precursor lesion than BD-IPMNs or PanINs in high-risk individuals. MCNs are detected with traditional radiographic screening and are characterized by a well-circumscribed cystic lesion with thick septae and do not seem to communicate with the duct system.[39] In patients who underwent resection for sporadic MCNs, invasive disease was found in approximately 11% of resected specimens. Furthermore, those with no pathologic findings of invasive disease had a 5-year survival approaching 100%.[40] The underlying risk of invasive disease and the rate of progression to invasive disease in high-risk individuals with MCNs are yet to be studied. Despite this, given the potential for cure in noninvasive MCNs, current guidelines recommend considering resection for all MCNs in surgically fit patients.[33] This recommendation should hold true in high-risk individuals. Fine-needle aspiration of these lesions for cytology and tumor marker analysis is helpful in determining cyst type, because serous cystadenomas do not warrant resection.

Nonsuspicious Cysts, Duct Strictures, and Solid Lesions

The CAPS consensus guidelines recommend repeat surveillance after 6 to 12 months for nonsuspicious cysts and repeat surveillance in 3 months for pancreatic duct strictures.[6] Solid lesions are rarely encountered when screening high-risk individuals, present in only 1.4% of patients in one study.[31] Although rare, solid lesions found on screening should be considered very high risk. The decision to proceed to surgical resection for these lesions should be discussed in a multidisciplinary setting at high-volume centers. If surgical resection is not pursued, solid lesions should be surveilled within 3 months. Lesion characteristics, such as larger than 1 cm and growth on interval follow-up, should raise suspicion for progression and prompt further discussion regarding resection.

SUMMARY

Family history is a significant risk factor for developing pancreatic cancer and this hereditary risk can be secondary to familial cancer predisposition syndromes, hereditary pancreatitis, or familial pancreatic cancer. Certain high-risk individuals are recommended to undergo screening for pancreatic cancer with EUS or MRI/magnetic resonance retrograde cholangiopancreatography because of the potential to identify and curatively resect precursor lesions. To date, observational prospective studies screening patients with familial pancreatic cancer have been carried out in multiple countries with highly variable diagnostic yields (ranging from 1% to 50%).[6] Drawing conclusions about the utility of screening high-risk individuals based on these studies is difficult given their highly variable results because of underlying variation in the risk of the screened population, screening protocols used, follow-up duration, and outcomes

measured. It is clear, however, that many high-risk patients have pancreatic lesions identified on screening EUS or MRI and a certain population of these individuals can undergo curative resection of premalignant lesions before they progress to pancreatic cancer. Future research should focus on developing improved screening methods and optimizing screening protocols and the management of high-risk lesions.

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Familial risk factors for pancreatic cancer and screening of high-risk patients. UpToDate website. https://www.uptodate.com/contents/familial-risk-factors-for-pancreatic-cancer-and-screening-of-high-risk-patients. Updated Nov 2, 2018. Accessed January 2, 2019.Â Some people with pancreatic cancer have gene mutations (such as BRCA mutations) in all the cells of their body, which put them at increased risk for pancreatic cancer (and possibly other cancers). Testing for these gene mutations can sometimes affect which treatments might be helpful. It might also affect whether other family members should consider genetic counseling and testing as well. Information on inherited, hereditary or familial cancer, or family cancer syndrome in pancreatic cancer and the screening available.Â If you or a relative have been diagnosed with pancreatic cancer, you may be worried that other people in your family might be at risk of developing it. Sometimes cancers are said to â€˜run in the familyâ€™. This means there is a faulty gene in the family that is linked to a type of cancer and can be passed down from a parent to a child. People in a family who carry the faulty gene have an increased risk of developing that type of cancer, but it doesnâ€™t mean they will always develop it. In most cases pancreatic cancer doesnâ€™t run in families. However, a small number of rare genetic conditions are l Individuals at risk of PC were enrolled prospectively in a screening program in Taiwan. All risk individuals received genetic testing of cationic trypsinogen (PRSS1) gene and the serine protease inhibitor Kazal type 1 (SPINK1) gene.Â Two studies enrolled patients with a very low risk of developing pancreatic cancer based on family history 19,21 and those individuals therefore were not included in the analysis. Only four 4,7,20,25 of the 16 studies were scored as of "high quality." ...Â Familial Pancreatic Cancer at Elderly Siblings in Japan.Â Worldwide, several programs have been initiated for individuals at high risk for pancreatic cancer. Their first results suggest that surveillance in high-risk individuals is feasible, but their effectiveness in decreasing mortality remains to be proven. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut, 56(10), 1460-1469. doi:10.1136/gut.2006.108456. Brune, K. A., Lau, B., Palmisano, E., Canto, M., Goggins, M. G., Hruban, R. H., & Klein, A. P. (2010).Â International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut, 62(3), 339-347. doi:10.1136/gutjnl-2012-303108. Hu, C., Hart, S. N., Polley, E. C., Gnanaolivu, R., Shimelis, H., Lee, K. Y., â€¦ Bamlet, W. R. (2018). Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. Jama, 319(23), 2401-2409. doi:10.1001/jama.2018.6228. Experimental Design: Patients at high risk of pancreatic cancer were prospectively enrolled into a screening program. Endoscopic ultrasound (EUS), magnetic resonance imaging (MRI), and genetic testing were offered by a multidisciplinary team according to each patient's risk. Results: Fifty-one patients in 43 families were enrolled, with mean age of 52 years, 35% of whom were male.Â Finally, familial pancreatic cancer includes groups of patients with a strong family history of pancreatic cancer but without an identified genetic syndrome. Although the definition of familial pancreatic cancer is debated, it is generally defined as at least two first-degree relatives with pancreatic cancer, without meeting criteria for one of the above syndromes.