

Familial pancreatic cancer: genetic advances

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Beset by poor prognosis, pancreatic ductal adenocarcinoma is classified as familial or sporadic. This review elaborates on the known genetic syndromes that underlie familial pancreatic cancer, where there are opportunities for genetic counseling and testing as well as clinical monitoring of at-risk patients. Such subsets of familial pancreatic cancer involve germline cationic trypsinogen or *PRSS1* mutations (hereditary pancreatitis), *BRCA2* mutations (usually in association with hereditary breast–ovarian cancer syndrome), *CDKN2* mutations (familial atypical mole and multiple melanoma), or DNA repair gene mutations (e.g., *ATM* and *PALB2*, apart from those in *BRCA2*). However, the vast majority of familial pancreatic cancer cases have yet to have their genetic underpinnings elucidated, waiting in part for the results of deep sequencing efforts.

The most common type of pancreatic cancer is pancreatic ductal adenocarcinoma (abbreviated as PDA or PDAC), accounting for >90% of pancreatic cancers. Forty-four-thousand new PDAC cases occur in the United States every year. Nearly 40,000 deaths related to complications of PDAC occur annually in the United States. By 2020, PDAC will be the second leading cause of cancer-related mortality (Ma and Jemal 2013). Unfortunately, median survival is measured in months, and 5-yr survival is <5%–10%, attributable largely to presentation of disease at late stages. Recent genetic evidence suggests that preneoplastic cells may undergo epithelial–mesenchymal transition (EMT) and circulate in the blood to participate potentially in the formation of metastasis, which also may be a contributing factor to decreased survival (Rhim et al. 2012). The remaining subtypes include neuroendocrine tumors, which originate in islet cells, and mucinous cystadenocarcinomas arising from intraductal papillary mucinous neoplasms (IPMNs) and mucinous cystic neoplasms (MCNs). Rare pancreatic tumors include lymphomas, sarcomas, acinar cell carcinomas, adenosquamous carcinomas, colloid carcinomas, giant cell tumors, pancreatoblastomas, serous cystadenomas, signet ring cell

carcinomas, solid and pseudopapillary tumors, and undifferentiated carcinomas.

As with some other cancers, PDAC may be classified further into either sporadic or hereditary. Sporadic PDAC reflects a combination of somatic genomic, genetic, and epigenetic alterations with a complex interplay with environmental factors (cigarette smoking, alcohol, and/or obesity). It is estimated that 5%–10% of PDAC has a hereditary basis with ~80% penetrance (Permut-Wey and Egan 2009). Some of these inherited conditions are well characterized for their incriminating germline gene mutations and recognizable clinical or phenotypic features, while others await identification of germline gene mutations through genomic or exomic sequencing efforts, building on other past approaches such as copy number variations (CNVs).

There is no uniform definition of nonsyndromic familial pancreatic cancer. It is likely that as more discoveries elucidate the genetics underlying familial pancreatic cancer, classification schemes will emerge, as has been evident for hereditary breast–ovarian cancer syndrome and Lynch syndrome, an inherited colorectal cancer predisposition syndrome. At the same time, clinical registries have led to “working” definitions. One such illustration is that familial pancreatic cancer is defined as a kindred with a pair of first-degree relatives with pancreatic cancer (Klein et al. 2004); in this context, the risk of developing pancreatic cancer in an at-risk family member is sixfold. This rises significantly more so if there are three or more first-degree relatives with pancreatic cancer (Hruban et al. 2010; Klein 2013). Other operational definitions take into account the age of onset of pancreatic cancer in a family with pancreatic cancer cases. Whereas risk assessment scores are used widely for hereditary breast cancer (National Comprehensive Cancer Network guidelines version 4.2013) and are emerging in Lynch syndrome (referred to as PREMM1,2,6) (Kastrinos et al. 2011), this approach (referred to as PancPRO) is in its nascency for potential widespread use (Wang et al. 2007).

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The following sections delineate the subtypes of syndromic hereditary pancreatic cancer in which germline genetic mutations have been identified and nonsyndromic familial pancreatic cancer in which genetic information is emerging. Whenever possible, links to the pathogenesis of sporadic PDAC are emphasized.

Hereditary pancreatitis

The most appreciated and recognized risk factor for sporadic PDAC is chronic pancreatitis, which is triggered by acinar cell damage followed by autodigestion, a proinflammatory milieu, and fibrosis (Lowenfels et al. 1993; Yadav and Lowenfels 2013). Chronic pancreatitis results in manifestations of exocrine insufficiency and endocrine insufficiency, the latter typically following the former. An uncommon form of chronic pancreatitis is hereditary pancreatitis, which is an autosomal dominant inherited disorder and highly penetrant (>80%) and typically manifests prior to the age of 30 (Whitcomb 2013), although this may be dependent on ancestral origin in the family. Clinical suspicion is triggered by a family history of two or more first-degree relatives (or three or more second-degree relatives) with recurrent acute pancreatitis or chronic pancreatitis spanning two or more generations.

Germline mutations in *PRSS1* (protease, Ser1 [chromosome 7q35]), which encodes the cationic trypsinogen protein, are associated with hereditary pancreatitis (Whitcomb et al. 1996). Trypsinogen is abundant in acinar cells. It hydrolyzes dietary proteins at lysine and arginine residues, thereby activating proenzymes. Premature activation of trypsinogen results in acute pancreatitis (Fig. 1). The original description of a germline mutation in *PRSS1* was an arginine-to-histidine substitution at amino acid 117, referred to as R117H. Arg117 is sensitive to trypsin, and cleavage at this site allows for inactivation of trypsin. However, this mutation eliminates the trypsin hydrolysis site. Other mutations have also been described in cationic

trypsinogen, some of which are listed here: N29I, A16V, D22G, K23R, A121T, and R122C. R116C is a rare mutation that may result in misfolding of the protein and present an alternative cause of activation (Kereszturi et al. 2009). Patients with hereditary pancreatitis have recurrent acute pancreatitis, which can often evolve into chronic pancreatitis. Their lifetime risk for PDAC is 35-fold (or more) by ages 70–75. Patients with hereditary pancreatitis may benefit from a low-fat (low-triglyceride) diet and abstinence from cigarette smoking and alcohol as a means to ameliorate progression to chronic pancreatitis.

Modeling of hereditary pancreatitis has revealed that pancreata from *Elastase-R122H* (*mPRSS1*) transgenic mice display early-onset acinar cell injury and inflammatory cell infiltration (Archer et al. 2006). With age, the transgenic mice develop pancreatic fibrosis and display acinar cell dedifferentiation and an augmented response to cerulein-induced pancreatitis. Finally, activation of c-jun N-terminal kinase and extracellular signal-regulated kinase was observed, which may be linked to activation of inflammation in these mice.

Chymotrypsin C (CTRC) gene (chromosome 1p36.21) mutations can be found in chronic pancreatitis (Rosendahl et al. 2008). CTRC mutations appear to boost the effects of the mutant forms of cationic trypsinogen (Fig. 1; Szabo and Sahin-Toth 2012). Two alterations in the CTRC gene, R254W and K247_R254del, were significantly overrepresented in a study of cohorts of patients with idiopathic chronic pancreatitis and hereditary pancreatitis (Rosendahl et al. 2008). Functional analysis of the CTRC variants showed impaired activity and/or reduced secretion, which resulted in “removal” of the normal negative degradative influence of CTRC on trypsin levels.

The aforementioned mutations in hereditary pancreatitis, especially in *PRSS1*, need to be distinguished from other mutations found in sporadic idiopathic chronic pancreatitis. The serine protease inhibitors of the Kazal type (SPINK) are a family of genes in which *SPINK1*

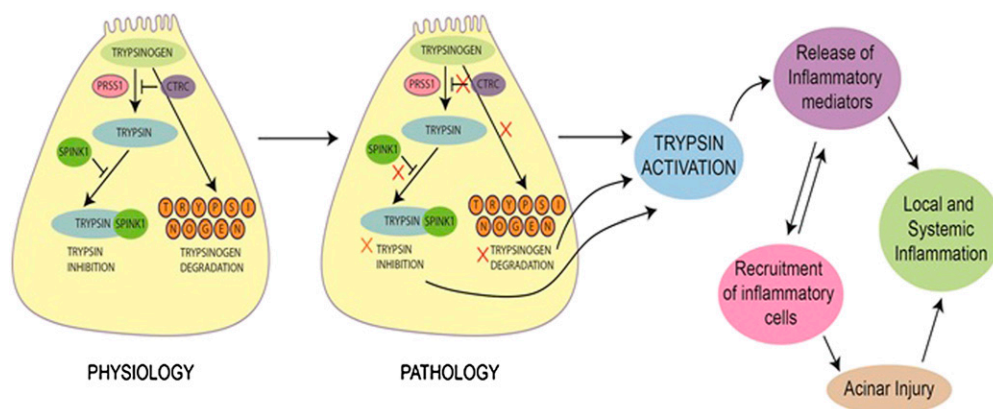


Figure 1. Trypsinogen–trypsin cascade. Under normal physiological conditions in the pancreatic acinar cell, trypsinogen activates trypsin, a serine protease, resulting in hydrolysis of proteins. This is held in balance by trypsinogen degradation and inhibition of trypsin. However, trypsinogen mutations can result in constitutive trypsin activation, establishing a cascade of events involving acinar cell injury, recurrent acute pancreatitis, and, as observed in hereditary pancreatitis, a progression to chronic pancreatitis and an increased risk for PDAC. This is augmented by mutations in CTRC in both hereditary pancreatitis and idiopathic chronic pancreatitis. Thus, SPINK1 mutations may be important in a modifier capacity in idiopathic chronic pancreatitis.

mutations (e.g., N34S) are found to be associated in some patients who have idiopathic chronic pancreatitis (Fig. 1). Similarly, heterozygous mutations in the cystic fibrosis transmembrane receptor (*CFTR*) gene may be found in a subset of these patients (Cohn et al. 1998, 2000; Sharer et al. 1998). *CFTR* is an ion channel involved in the transport of chloride and thiocyanate. While *CFTR* gene mutations are traditionally associated with cystic fibrosis, they may also contribute to chronic pancreatitis. *CFTR* mutations lead to impaired chloride secretion and/or loss of bicarbonate secretion across ductal epithelial cells, which causes the accumulation of protein-rich materials, damage to acini, and subsequent fibrosis (Ooi et al. 2011).

Familial atypical mole and multiple melanoma (FAMMM) syndrome

An autosomal dominant disorder, FAMMM is characterized by the following in a family: melanomas in more than one first- or second-degree relative, high total body nevi count (often >50), and nevi with certain histopathological features. The melanomas can arise from the atypical moles or de novo (superficially spreading melanoma and/or nodular melanoma). Three original descriptions in different kindreds implicated germline mutations or microdeletions in *CDNK2* (chromosome 9p21.3), in particular restricted to the p16INK4a isoform (chromosome 9p21.3), as causative for FAMMM (Gruis et al. 1995; Ranade et al. 1995). These mutant p16 proteins cannot inhibit the cyclin D1/CDK4 or cyclin D1/CDK6 complex. *CDNK2* mutations are associated with 60%–90% melanoma risk by age 80 as well as an increased pancreatic cancer risk of up to 20% by age 75. Other studies have led to equally worrisome correlations. In one study, there was a 25% increased risk of pancreatic cancer in FAMMM kindreds, and in another study, a cohort showed a 13-fold to 22-fold increase in pancreatic cancer (Lynch et al. 2008). The age of onset of pancreatic cancer in FAMMM is quite variable, perhaps reflecting incomplete penetrance. Importantly, nearly 90% of sporadic PDACs harbor alterations (promoter hypermethylation, mutations, and microdeletions) in *CDKN2*, providing insights between the pathogenesis of FAMMM and the pathogenesis of sporadic PDAC. It should be noted that while melanoma and pancreatic cancer constitute the two most frequent cancers, respectively, in FAMMM, anecdotal reports note a variety of other cancers in association with FAMMM, but a clear pattern is lacking. Interestingly, *CDK4* mutations that occur in the *CDKN2*-binding domain have been reported in FAMMM kindreds (Zuo et al. 1996). Abnormal cell cycle progression and proliferation in FAMMM is evident also in sporadic PDAC. The reasons underlying the tissue-specific functional consequences of mutant p16 protein in FAMMM are not clear. It is likely that mutant p16 protein promotes genomic instability in sporadic PDAC by virtue of its contribution to uncontrolled cell division (Campbell et al. 2010).

Upon determination that FAMMM exists in a kindred, genetic testing and counseling should be explored, complemented by careful dermatological examinations and

consideration of noninvasive or invasive screening of the pancreas (see below).

Peutz-Jeghers (PJ) syndrome and other colon cancer syndromes: associations with pancreatic cancer

As an autosomal dominant disorder characterized by germline *STK11* (*LKB1*) gene mutations, patients have early onset of large, multiple small intestinal and colonic polyps with increased risk of cancers at these sites (Rustgi 2007). As patients age, they have an increased risk of breast, lung, pancreatic, cervical, and other cancers. The types of pancreatic cancers include PDAC, IPMN, and serous cystadenocarcinomas (Sato et al. 2001). One comprehensive Dutch study of PJ syndrome patients revealed a 26% increased risk of pancreatic cancer by age 70 yr and relative risk of 76 (Korsse et al. 2013). Patients may also present with ampullary cancer or distal bile duct cancer. Conditional deletion of *Lkb1* in the mouse pancreas results in postnatal acinar cell degeneration, acinar-to-ductal metaplasia, and serous cystadenomas (Hezel et al. 2008), suggesting some discordance between the pancreatic phenotype observed in PJ syndrome patients and this particular mouse model. In that vein, patients with familial adenomatous polyposis (FAP), characterized by germline *APC* gene mutations resulting in derangement of Wnt signaling, do not typically have pancreatic cancer but may have ampullary cancer or duodenal cancer. This suggests that *APC* mutations are not critical in sporadic PDAC. Lynch syndrome is an inherited form of colon cancer that is associated with germline mismatch repair (MMR) gene mutations (e.g., *hMLH1*, *hMSH2*, *hMSH6*, and *hPMS2*), resulting in microsatellite instability (MSI) in the colon cancers (and extracolonic cancers that are associated with Lynch syndrome). In a study of 147 families with germline MMR gene mutations, the cumulative risk of pancreatic cancer was 1.31% up to age 50 yr and 3.68% up to age 70 yr, an 8.6-fold increase compared with the general population (Kastrinos et al. 2009). However, MSI is not common in sporadic PDAC.

DNA repair defects: a potential unifying theme in a subset of familial pancreatic cancer

DNA repair processes respond to DNA damage, which can occur through abnormal endogenous cellular processes (e.g., mismatch of nucleotide bases, depurination, β elimination, and hydroxyl radical damage) or exposure to exogenous agents (ultraviolet light, ionizing radiation, and chemical carcinogens). One particularly cancer-causing type of DNA damage, based on the ability to promote loss of heterozygosity and translocations, is double-stranded breaks (DSBs). Repair of DSBs can involve non-homologous end-joining (NHEJ), microhomology-mediated end-joining (MMEJ), and homologous recombination (HR). FANCC and FANCI, as part of the Fanconi anemia complement of repair proteins, help preserve the integrity of replication forks during S phase. When replication forks collapse into DSBs, repair is then completed with assistance from ATM, BRCA2, and PALB2 (Fig. 2).

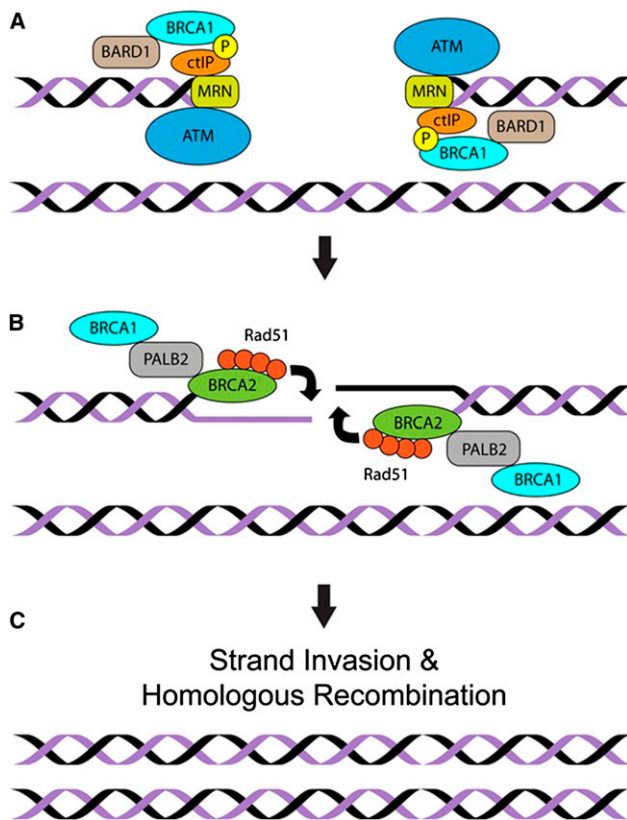


Figure 2. DNA repair and HR. Mutations in the DNA repair cascades provide clues in the pathogenesis of familial pancreatic cancer. dsDNA breaks are recognized first by several protein complexes: BRCA1–BARD1; CTIP (C-terminal-binding protein, interacting protein), which associates with MRN (consisting of MRE11, RAD50, and NBS1, also known as Nibrin); and the ATM protein kinase. (A) These enzyme complexes are needed to perform the exonucleolytic resection of one of strand of DNA at the DSB, generating a 3' overhang. BRCA1 fosters the accumulation of PALB2, a functional partner of BRCA2. (B) BRCA2 serves as a reservoir of RAD51, which is loaded onto the newly created ssDNA. RAD51 promotes invasion of this ssDNA into the intact sister chromatid to complete the repair of the DSB through replication of the sister (not shown). (C) The copied DNA is then resolved into two intact sister chromatids, completing the repair process.

The ATM kinase is activated by DSBs to delay cell cycle progression and promote DSB resection. This resection of one strand of DNA creates a single-stranded element onto which RAD51 is loaded by BRCA2 and PALB2 (Zhang et al. 2009). RAD51 then helps pair this strand with the template on the double-strand sister chromatid to replace damaged segments through replication and recombination (Fig. 2). Germline mutations in some of the DNA repair genes have been discovered in familial pancreatic cancer. The relevance of this is that accumulation of damaged DNA can trigger different states—senescence, apoptosis, or unregulated cell division—that may lead to formation of cancer.

Approximately 5%–10% of breast cancers are believed to be hereditary in nature, many of which are associated

with germline BRCA1 or BRCA2 mutations. Of note, up to 10% of sporadic PDACs are believed to harbor BRCA2 mutations. Compared with BRCA1 mutation carriers, BRCA2 mutation carriers are at increased risk for pancreatic cancer. In a study of 173 families with germline BRCA2 mutations and breast/ovarian cancers, representing a cohort of 3728 individuals, the relative risk of pancreatic cancer was 3.51 (Goldgar 1995). This risk is particularly evident in families of Ashkenazi Jewish descent, where a germline 6174delT BRCA2 mutation has been reported (Ozçelik et al. 1997). Some estimates indicate that up to 10% of familial pancreatic cancer may be attributable to germline BRCA2 mutations, although the age of onset may not be particularly early in life. In a separate study, the relative risk of pancreatic cancer was nearly 2.3 in BRCA1 mutation carriers (Thompson et al. 2002). Analysis of conditional knockouts of *Brca2* in the mouse pancreas has produced conflicting results on KRASG12D-driven pancreatic carcinogenesis. In one setting, *Brca2* accelerates lesions in KRASG12D-expressing mice irrespective of *Trp53* status, with evidence of only loss of one allele of *Brca2* being necessary (Skoulidis et al. 2010). In another mouse model, *Brca2* loss decelerates KRASG12D-driven pancreatic carcinogenesis but accelerates it when combined with *Trp53* mutation (Rowley et al. 2011), again underscoring the careful interpretation that is necessary of some mouse models to correlate with human pancreatic cancer.

In a genome-wide sequencing analysis of nearly 170 families with familial pancreatic cancer, two families were identified as having germline heterozygous ATM mutations, and four families had deleterious homozygous ATM mutations (Roberts et al. 2012). PALB2 performs its tumor suppressor role at least in part by supporting HR-type DSB repair (HR-DSBR) through physical interactions with BRCA1, BRCA2, and RAD51 (Zhang et al. 2009). In an analysis of nearly 100 families with familial pancreatic cancer, four families had evidence of protein-truncating mutations in PALB2 (Jones et al. 2009), confirmed in another study (Tischkowitz et al. 2009). The role of the *Palb2* mutation in the initiation of pancreatic cancer via loss of its chromosome integrity maintenance role has not been investigated to date in mouse pancreata. However, *Palb2* is known to play an important cancer-suppressive role in another tissue (namely, the breast), as it synergizes with *Trp53* to limit mammary tumors in mice (Bowman-Colin et al. 2013). It is likely that germline BRCA2, ATM, or PALB2 mutations in human familial pancreatic cancer contribute to defective DNA repair, accumulation of damaged DNA, genomic instability, and eventual cancer formation. Genomic instability is a hallmark feature of sporadic PDAC (Campbell et al. 2010), and understanding defective DNA repair mechanisms may shed light on the molecular pathogenesis of sporadic PDAC.

Approaches to discovery of new gene mutations

Although advances have been made in associating germline gene mutations with some forms of familial pancreatic cancer, our full realization of the degree to which

Table 1. Summary of recent GWAS in sporadic PDAC

Reference	Chromosome	SNP	Potential gene of interest
Amundadottir et al. 2009	9q34	rs505922	First intron of blood group ABO (group O decreases risk of PDAC)
Petersen et al. 2010	1q32.1	rs3790844 ^a	NR5A2
	5p15.33	rs401681	CLPTM1L-TERT
	13q22.1	rs9543325	Nongenic region
		rs9564966	
Wu et al. 2011	5p13.1		
	10q26.11		
	13q22.1		
	21q21.3		
	21q22.3		
	22q13.32		

^aStrongest of five SNPs.

pancreatic cancer is driven by underlying genetic predisposition requires further elucidation. Initial clues were provided by an analysis of CNVs. CNVs correspond to large regions of the genome that have been duplicated, deleted, or inverted or undergone translocation and can provide clues as to potential genes that contribute to pathogenesis of inherited and/or sporadic cancer. In an initial study of 57 familial pancreatic cancer kindreds, a total of 56 unique genomic regions with CNVs were identified that were not present in controls, including 31 amplifications and 25 deletions (Lucito et al. 2007). In a subsequent study of 120 familial pancreatic cancer cases (and 1194 controls), a total of 93 nonredundant familial pancreatic cancer-specific CNVs (53 losses and 40 gains) were identified in 50 cases, with each CNV present in a single individual (Al-Sukhni et al. 2012).

Genome-wide associations studies (GWASs) in patients with sporadic PDAC may highlight gene loci that could be tested for linkage in familial pancreatic cancer (Petersen et al. 2010; Wu et al. 2011). To that end, susceptibility loci have been identified, although differences in results may be attributable to the evaluation of different populations (Table 1). Deep DNA sequencing efforts, which are ongoing, in familial pancreatic cancer should shed new insights into new genes, genotypic–phenotypic correlations, pathways in familial and sporadic PDAC pathogenesis, and, hopefully, opportunities for diagnosis and therapy. An example of the latter is the potential application of poly-ADP-ribose polymerase (PARP) inhibitors or mitomycin C in BRCA2⁺ mutation carriers with pancreatic cancer.

Translational applications

Certainly, in familial pancreatic cancer where the gene mutation is known, genetic counseling and testing should be offered. This has important clinical implications in the affected individual as well as for at-risk individuals in the family. There is no consensus as to how to screen clinically individuals with known genetic mutations or those who have a strong family history absent a known genetic mutation for the possibility of incipient early pancreatic cancer. Clinical screening approaches segregate into non-invasive imaging of the pancreas (magnetic resonance imaging [MRI] or computerized tomography [CT]) or

invasive methodologies, such as endoscopic ultrasound (Canto et al. 2012). One study found that in asymptomatic patients with familial pancreatic cancer, 7% had pancreatic cancer, and 16% had IPMN (Poley et al. 2009), suggesting that screening may be effective to detect preneoplastic or early stage neoplastic lesions. However, the age at which to start (and stop) screening, the subsequent frequency of screening, and how to manage ambiguous lesions are not clear (Canto et al. 2013).

New approaches under investigation (not yet established for implementation) would involve strategies for the detection of circulating pancreatic cells in the blood of at-risk familial pancreatic cancer patients, especially those with small lesions (e.g., IPMN). Furthermore, developments in imaging with molecular probes might improve on the threshold of detection provided by either MRI or CT. As more genomic and genetic information emerges to unravel the mechanistic underpinnings of familial pancreatic cancer, undoubtedly new translational applications will evolve.

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