Review

Screening for Pancreatic Cancer in High-Risk Individuals: A Call for Endoscopic Ultrasound

Alberto Larghi,[1] Elizabeth C. Verna,[2] Piera Giuseppina Lecca,[1] and Guido Costamagna[1]

Abstract   Pancreatic cancer has a dismal prognosis, and early detection through screening is likely to be our best hope to improve survival. The relatively low incidence of pancreatic cancer and the insensitive screening techniques available currently render this approach prohibitively expensive and inefficient in the general population. Screening has begun, however, in the subset of patients at the highest risk of disease, such as those with inherited risk due to familial multiorgan cancer syndromes or in familial groupings of pancreatic cancer with yet unidentified genetic abnormalities, termed familial pancreatic cancer. Screening is currently done at several large centers in the world, each with a unique multidisciplinary approach and series of screening tests. Endoscopic ultrasound has emerged as the most promising imaging test given its high sensitivity and potential for tissue sampling. However, this potential to detect and cure early lesions should be carefully balanced with the risk of overtreatment, especially in view of the morbidity and mortality of pancreatic surgery. Additional experience to help determine the best screening strategy is greatly needed. Screening should therefore be done at experienced centers with multidisciplinary teams of specialists and in the context of research protocols.

Pancreatic adenocarcinoma is the fourth leading cause of cancer death in men and women in most western countries (1). In 2000, there were ~216,400 new cases diagnosed worldwide and 213,500 cancer-related deaths (2). The dismal prognosis of this disease is clearly depicted by its virtually uniform fatality. Although our understanding of pancreatic cancer precursors remains incomplete, advances in our comprehension of genetic susceptibility as well as the recent description of the possibly premalignant stages of the disease have greatly advanced our knowledge in the past decade.

Due to the rapid progression of most pancreatic cancers, early detection through screening will be required to improve long-term outcomes. Pancreatic neoplasia does meet some of the WHO criteria for principles of screening. It is a prevalent disease with high morbidity and mortality, with the possibility for cure if diagnosed at an early stage. Some proof of this principle has come from a series in Japan where 100% of patients were cured with resection of pancreatic lesions <1 cm (3). In addition, there is mounting evidence of identifiable latent or premalignant stages of disease, such as intraductal papillary mucinous neoplasms (IPMN; refs. 4–6) and the more recently described pancreatic intraepithelial neoplasia (PanIN;

refs. 7, 8). To date, however, due to the relatively low incidence of the disease, no screening strategy is thought to be adequately safe, sensitive, and economically feasible to be implemented in the general population. More realistic is to target individuals at the highest risk for pancreatic neoplasia, in whom screening and surveillance may be maximally effective. As it is now known that ~3% to 16% of pancreatic cancers are either syndromic or familial (9–16), patients with known genetic syndromes that predispose them to the disease or with a strong family history may be offered screening and surveillance in an attempt to detect pancreatic neoplasia at a curable stage.

Several growing cohorts of high-risk patients are now enrolled in screening protocols throughout the world (17–22). Each center has its own algorithm, but all involve a multidisciplinary team of specialists and a combination of imaging techniques. Endoscopic ultrasound (EUS) may currently be the most promising imaging modality for screening and surveillance of these high-risk individuals (17–23). Data are preliminary, however, and the timing of screening initiation, the appropriate surveillance intervals, and the best therapeutic algorithm when abnormalities are found remain to be determined.

Who Is at Risk?

Risk factors for pancreatic cancer include an inherited predisposition, tobacco exposure, chronic pancreatitis, diabetes mellitus, and, most significantly, advanced age (23–27). However, the prevalence of the disease in the elderly is too low to justify screening even in smokers, and the only clinical scenario in which screening programs are currently implemented is in the setting of known inherited predisposition. An inherited risk for pancreatic malignancy is believed to occur in three distinct clinical settings: familial multiorgan cancer syndromes, genetically driven chronic diseases not directly associated with cancer syndromes, and familial groupings of

Translational Relevance

Pancreatic cancer remains a lethal malignancy, and widespread screening for early detection and cure is prohibitively expensive. Screening and surveillance may be cost-effective, however, in certain individuals at the highest risk, such as those patients with familial and genetic syndromes predisposing to the disease. Although the optimal approach has not yet been determined, endoscopic ultrasound has emerged as the most promising imaging modality for pancreatic cancer screening. Screening protocols are now established at several specialized centers throughout the world, with the goals of both improving survival and quality of life in these high-risk subjects but also to gather information that will have implications for prevention and treatment of sporadic pancreatic cancer. Additional long-term data will be required before recommendations can be applied broadly in clinical practice, but as the screening algorithms improve over time those at high risk for pancreatic cancer are likely to benefit from screening and surveillance.

pancreatic cancer with yet unidentified genetic abnormalities, termed familial pancreatic cancer (FPC; Table 1). The familial multiorgan cancer syndromes that predispose to pancreatic cancer include Peutz-Jeghers syndrome, familial atypical multiple mole melanoma, familial breast-ovarian cancer, hereditary nonpolyposis colorectal cancer, and familial adenomatous polyposis.

Peutz-Jeghers syndrome is caused by an autosomal dominant mutation of the *STK11/LKB1* gene (28) and carries the highest lifetime risk of pancreatic cancer among these syndromes. Peutz-Jeghers syndrome is characterized by multiple hamartomatous polyps of the gastrointestinal tract and perioral pigmented lesions as well as an increased risk of several cancers including those of the esophagus, stomach, small intestine, lung, breast, uterus, ovary, and pancreas (29). The relative risk

of pancreatic carcinoma in patients with Peutz-Jeghers syndrome has been estimated to be $\sim$132-fold above that of the general population, with a cumulative risk of 36% by age 65 years (29).

Familial atypical multiple mole melanoma, a rare autosomal dominant syndrome characterized by a germ-line mutation of the *CDKN2a* gene, is associated with the development of multiple nevi, melanomas, and 9- to 22-fold increase in the risk of pancreatic cancer (30–32). No pancreatic cancer has been described in melanoma-prone families without *CDKN2a* germline mutations. This has led some to reclassify this as a new hereditary cancer syndrome called pancreatic carcinoma melanoma syndrome (32, 33) or familial atypical multiple mole melanoma-pancreatic carcinoma (34). However, the two *CDKN2a* founder mutations (Val^{126}Asp and Gly^{101}Trp) have been observed in families with and without pancreatic cancer, thus suggesting a more complex scenario with other factors (genetic and/or environmental) possibly involved in pancreatic cancer development (35). The cumulative risk of pancreatic cancer in *CDKN2a* mutation carriers is $\sim$17% by age 75 years (30, 36).

Familial breast-ovarian cancer is associated with germ-line mutations in the *BRCA1* or *BRCA2* genes. The risk of pancreatic cancer is 2.26 times that of the normal population in carriers of BRCA1 mutations in a large study from Thompson et al. (37), whereas carriers of germ-line *BRCA2* mutations have a lifetime risk of pancreatic cancer of $\sim$5% (38). Interestingly, 6% to 19% of FPC kindreds have been found to harbor germ-line *BRCA2* mutations, some arising in families without cancers of the breast or ovary (39–41). These data make BRCA2 germ-line mutations the most commonly identified genetic alteration in patients with FPC.

Hereditary nonpolyposis colorectal cancer, caused by mutations in DNA mismatch repair genes, is characterized by cancers of the colon, endometrium, stomach, small intestine, ovary, and urinary tract and was first described to have an association with pancreatic adenocarcinoma in 1985 (42). Subsequent investigation has been somewhat conflicting as to the magnitude of this risk, but pancreatic cancer is nevertheless

Table 1. Clinical settings associated with an increased risk of inherited pancreatic cancer

Clinical setting	Gene	Risk
Familial multiorgan cancer syndromes		
Peutz-Jeghers syndrome	*STK11/LKB1*	RR = 132
		CLR = 36%
Familial atypical multiple mole melanoma	*CDKN2a*	CLR = 17%
Familial breast-ovarian cancer	*BRCA2*	RR = ~5%
	BRCA1	?
Hereditary nonpolyposis colorectal cancer	*MLH1, MSH2, MSH6, PMS1, PMS2*	?
Familial adenomatous polyposis	*APC*	?
Genetically driven chronic diseases		
Hereditary pancreatitis	*PRSS1*	CLR = 40%
Cystic fibrosis	*CFTR*	RR = 3.5
Fanconi anemia	*FA*	?
Ataxia telangiectasia	*ATM*	?
FPC		
Pancreatic cancer in ≥3 first-degree relatives		RR = 32
Pancreatic cancer in 2 first-degree relatives		RR = 6.4
Pancreatic cancer in 1 first-degree relatives		RR = 4.5

Abbreviations: RR, relative risk; CLR, cumulative lifetime risk.

included as a hereditary nonpolyposis colorectal cancer-associated tumor in the revised Bethesda guidelines (43). Finally, familial adenomatous polyposis, which is due to a mutation in the tumor suppressor gene APC, appears to confer a 4-fold increase in risk of pancreatic cancer (44). These data may be an overestimation as invasive duodenal cancer, a tumor strongly associated with familial adenomatous polyposis, may be mistakenly classified as pancreatic cancer.

The second clinical setting with an inherited predisposition to pancreatic cancer is in genetically driven chronic disease states not directly associated with multiorgan malignancy. Hereditary pancreatitis, which is caused by an autosomal dominant mutation of the cationic trypsinogen protein PRSS1, has the highest penetrance of any genetic pancreatic cancer syndrome (45). Patients with this syndrome have a cumulative risk of pancreatic cancer that approaches 40% by age 70 years, with an estimated 50-fold increase in risk of pancreatic cancer overall (46). Tobacco exposure compounds this risk as well as hastens the onset of the disease (47). Pancreatic cancer has also been reported at an increased rate in patients and families with cystic fibrosis (48, 49), ataxia telangiectasia (50, 51), Fanconi anemia (52), and insulin-dependent diabetes mellitus with exocrine insufficiency (53).

The third clinical setting is FPC, which is generally defined as families in which two or more first-degree relatives are affected by pancreatic cancer, without fulfilling the criteria for one of the above-described cancer syndromes. This exact definition, however, remains a matter of debate (54). Studies of familial aggregation in this population have shown a 2.8- to 18-fold increase in the risk of pancreatic cancer in patients with a positive family history when compared with controls (11, 55–59), with a risk that tends to increase with the number of affected kindreds. Data from the National Familial Pancreas Tumor Registry in the United States have shown that patients with one, two, and three or more affected first-degree relatives, had a 4.5-, 6.4-, and 32-fold higher risk of developing pancreatic cancer, respectively (60). Hopefully in the near future, the addition of computerized risk assessment tools, such as the PancPRO prediction model developed at Johns Hopkins (61), will help to more accurately assess individual's risk of developing pancreatic cancer in FPC.

Detailed investigation into families with a high penetrance of pancreatic cancer has lead to several pathogenic discoveries. The familial distribution of the disease in FPC varies but usually suggests an autosomal dominant transmission with reduced or variable penetrance. Although the precise genetic abnormality underlying FPC is still unknown, it is likely that many yet unidentified genes are involved. One such gene was recently described when a family of western European descent (Family X) was investigated, leading to the identification of a susceptibility locus through linkage analysis in the q32-34 region of chromosome 4 (62). Microarray gene expression analysis of the pancreatic tissue from a member of the Family X then revealed overexpression of the cytoskeletal protein *palladin* due to a germ-line missense mutation (P239S), which segregated with the affected family members (63). Pogue-Geile et al. (64) subsequently provided evidence that this P239S *palladin* variant may function as an oncogene and postulated that it may play a role in sporadic pancreatic cancer. The locus 4q32-34 and the P239S mutation, however, have not been found in a significant proportion of other families

with hereditary or early-onset pancreatic tumors (65, 66). Additional studies are needed before conclusions can be drawn, but the *palladin* gene is unlikely to have an important role in FPC.

Who Should Be Screened and When Should Screening Begin?

Who should be screened among patients with each of the above risks remains widely debated, and the lack of evidence for a clearly effective screening algorithm limits the patient population likely to benefit at this time. Due to the lack of evidence, consensus practice recommendations as to who to screen, based largely on expert opinion, were developed during the Fourth International Symposium of Inherited Diseases of the Pancreas in 2003 (17). A threshold of a >10-fold increased risk for developing pancreatic cancer was chosen to select individuals who may benefit from screening. This threshold includes family members with ≥3 first-degree relatives with pancreatic cancer, patients with familial atypical multiple mole melanoma, Peutz-Jeghers syndrome, and hereditary pancreatitis, all individuals carrying an estimated risk way above of this threshold and for whom the available data clearly support screening. Moreover, individuals with three pancreatic cancer cases among first-, second-, and third-degree relatives, with at least one of these being a first-degree relative, and subjects with BRCA2 mutations and at least one case of pancreatic cancer within second-degree relatives were considered to be at high risk by expert opinion and were also felt to be candidates for screening (17). It is not clear what to do with the more numerous subjects with a 5- to 10-fold risk of developing pancreatic cancer. Patients in this risk category, for example, include those with two affected first-degree relatives, in whom most centers would perform screening and surveillance. Future studies are needed to establish the risk threshold at which screening is cost-effective and beneficial to the individuals screened.

If screening is to be initiated, when to start is also unknown. Current practices are individualized based on the individual's risk as well as clinical experience and recommendations from large volume centers. In patients with FPC, the greatest increased risk of pancreatic cancer over normal occurs among relatives who are ages ~45 to 65 years (60). In addition, genetic anticipation is likely to occur (67). Based on these data and on current recommendations for other inherited cancers, it seems reasonable in these individuals to begin screening at age 40 years or 10 years before the age of the youngest affected kindred (18, 68). These recommendations do not take into account the presence of coexisting risk factors, particularly smoking, which has been reported to decrease the age of pancreatic cancer development in FPC and hereditary pancreatitis by one and two decades, respectively (47, 69). In addition, patients with Peutz-Jeghers syndrome are more likely to develop cancer at a younger age (40 ± 16.2 years; ref. 29), and screening is generally recommended to begin as early as age 25 to 30 years (18).

There is also no consensus as to how frequently surveillance should be done, but several large centers have published their screening protocols. Researchers from the Johns Hopkins Medical Institution, for example, perform annual surveillance based on screening for other inherited cancers (20). Researchers

from the University of Washington, differently, surveil patients every 2 to 3 years until the patient approaches the age of the youngest affected kindred and then annually thereafter (68). In the EUROPAC, surveillance intervals are based on whether *K-ras* mutations are present in the pancreatic juice collected at the time of baseline endoscopic retrograde cholangiopancreatography (ERCP; ref. 70). In positive cases, annual ERCP with mutational analysis and EUS/computed tomography (CT) are recommended, whereas the same tests can be done every 3 years in *K-ras*-negative patients (70).

Although these screening recommendations are published and being implemented by many centers around the world, it remains unclear whether screening any specific population will be cost-effective. Although Peutz-Jeghers syndrome carries the greatest known lifetime risk of any of the known genetic cancer syndromes, in cost-effectiveness analysis, whether to screen this population remains debatable (71). There is also still no evidence supporting the cost-effectiveness of screening for pancreatic cancer in patients with hereditary nonpolyposis colorectal cancer, familial adenomatous polyposis, or familial breast-ovarian cancer. This cost-effectiveness is likely to improve, however, with improved screening techniques and clarification of the clinical management following screening examinations. In fact, such cost-effectiveness modeling will depend heavily on the specific population and the algorithm applied to the EUS findings encountered. For example, the guidelines for screening patients with hereditary pancreatitis remain very unclear despite the very high lifetime risk of cancer in this population. The pancreatic parenchymal changes make this population very difficult to screen with any imaging modality. In addition, a recent Markov modeling analysis did not support screening when selecting first-degree relatives of FPC kindreds with EUS findings of chronic pancreatitis (72). When the highest risk patients are selected, however, one-time screening with EUS has been modeled to be relatively cost-effective with a ratio of $16,885/life years saved, but with many assumptions and without accounting for the repeated surveillance examinations currently being used in practice (73).

What Lesions Are We Looking for?

There are three well-defined lesions that clinicians are looking to detect and treat through screening: small masses, IPMN, and histologically defined preneoplastic PanIN lesions.

Small asymptomatic masses (<1 cm) may be detected with EUS, which has been reported to have a higher sensitivity than CT for solid lesions <2 cm (74). Small masses once resected are associated with an extremely high rate of survival (3), and patients with small masses are among those most likely to benefit from screening.

Recent data also strongly support the importance of IPMN as a precursor of pancreatic cancer in high-risk individuals (19). IPMN and pancreatic cysts in general are being discovered with increased frequency because of the widespread use of abdominal imaging (75) and only a minority of these cysts carry the risk of malignancy (76). IPMN are pancreatic lesions that develop from the malignant transformation of the cells lining the pancreatic ducts and are characterized by mucin production, cystic dilation of the pancreatic ducts, and intraductal papillary growth (77). IPMN may involve the main duct (IPMN-M), the branch ducts (IPMN-B), or both (mixed type;

ref. 5), and their prognosis varies depending on the location. IPMN-M have a 70% risk of containing a malignancy at the time of diagnosis, making surgical resection the recommended management (6). Conversely, IPMN-B have a 25% risk of containing a malignancy and a 15% risk of malignant transformation during follow-up, which makes observation an acceptable initial strategy with resection only in those patients with progressive disease (6, 78–80). Current guidelines recommend resection of IPMN-B with a diameter ≥3 cm, with mural nodule, with main pancreatic duct dilation ≥6mm, and in symptomatic patients (6). This more conservative approach to IPMN-B, however, may not be appropriate in high-risk individuals in whom cases of rapid growth and malignant transformation have been documented (19).

PanIN lesions are generally composed of columnar and cuboidal cells with varying degrees of atypia, which involve small ducts and are therefore not visible with conventional imaging (7, 8). The consensus pathologic classification of preneoplastic ductal lesions (7) has provided a framework for a more accurate estimation of the incidence of PanIN lesions and developed a classification system to estimate the degree of atypia seen on pathology. According to the consensus, PanIN 1 lesions are hyperplastic with a minimal degree of atypia and can be further subclassified into PanIN 1A and 1B based on the presence of micropapillary infoldings. PanIN 2 lesions are low-grade dysplasia and may include loss of polarity and pseudostratification, nuclear crowding, enlarged nuclei, and hyperchromatism. PanIN 3 lesions are high-grade dysplasia or carcinoma *in situ* with the addition of atypical mitoses and luminal necrosis, but all contained within the basement membrane (7).

These lesions are thought to be precursors to pancreatic adenocarcinoma for several reasons. There is evidence that PanIN is almost universally found in the tissue surrounding invasive cancers (81), as well as anecdotal evidence that high-grade PanIN lesions left *in situ* in patients undergoing partial pancreatic resection often progress to invasive lesions (82). More convincing proof has been provided by the genetic and molecular alterations that they share with invasive carcinomas (4). *K-ras*, *p16*, and telomere length have all been shown to be abnormal in a significant proportion of PanIN lesions (83–85).

Thus far, no imaging modality is able to visualize PanIN lesions in any clinical setting. There are some reports that PanIN may be associated with EUS changes consistent with chronic pancreatitis, but the sensitivity and specificity of this relationship are unknown (86). EUS also provides the ability to perform tissue sampling with fine-needle aspiration (EUS-FNA) and offers an additionally potential way to diagnose this important high-risk lesion. The value of random tissue sampling at EUS remains unknown.

Is EUS the Best Test for Screening and Surveillance of High-Risk Individuals?

The use of EUS in screening patients at high risk for pancreatic cancer was first reported by physicians at the University of Washington caring for a large pedigree of patients with pancreatic cancer, the Family X (53). In an attempt to discover imaging findings that would identify other family members destined to develop pancreatic cancer, they found

that EUS was able to detect abnormalities not seen on CT, magnetic resonance imaging, and positron emission tomography examinations (21). In most cases, the EUS findings were confirmed at ERCP, which led to an empiric approach using EUS followed by ERCP when needed in this family and others with FPC (21, 68). Chronic pancreatitis-like abnormalities, such as multifocal clusters of 2 to 8 mm hypoechoic lobules, echogenic foci and strands, and hyperchoic pancreatic duct walls, were the most frequent findings (21, 68). The ERCP abnormalities included irregularly dilated main pancreatic duct with saccular changes in the branch ducts, the latter corresponding to large cystic spaces and fibrosis observed on pathology (87). A total of 46 subjects have been evaluated with this approach thus far (68). Twenty-four of them were found to have chronic pancreatitis-like EUS abnormalities. A total of 28 subjects also underwent ERCP without complications and 13 were found to have an abnormal pancreatogram. Twelve of these 13 patients underwent pancreatectomy (10 total and 2 distal) and all of them were found to have widespread dysplasia, involving primarily small and medium size ducts, with no cases of invasive carcinoma (68).

The same screening protocol using EUS with ERCP only in those patients with abnormal EUS findings has subsequently been adopted by investigators at Johns Hopkins (CAPS 1 study; ref. 20), with the addition of dual-phase, multidetector, thin-section CT scan after 2001 (CAPS 2 study; ref. 19). A total of 116 subjects have been evaluated in these two series. One hundred nine patients had FPC (103 with three or more affected relatives) and 7 had Peutz-Jeghers syndrome. Overall, "neoplastic-type lesions" were identified in 29 (25%) patients, 7 with a mass, 11 with nodules, and 11 with cystic lesions and/ or a focally dilated pancreatic duct. The most common findings at ERCP were pancreatic duct dilation, saccular deformities of the pancreatic branch ducts, and findings consistent with chronic pancreatitis, as described by Brentnall et al. (21).

Fifteen of these 29 patients had definitive diagnoses made, 14 on surgical resection and 1 based on clinical follow-up. Detailed characteristics and findings in each of these 15 patients are shown in Table 2. Overall, 8 (53%) patients had an IPMN, one a T_2N_1 adenocarcinoma, and one with dysplasia on EUS-FNA had diffuse PanIN 1A and 1B lesions on resection. Five patients with a cystic or a solid lesion on EUS as their indication for surgery had benign lesions at resection: two serous multiloculated cystadenomas, one accessory spleen, one pancreatic abscess, and one focal fibrosis. However, in all but three subjects who underwent surgery, areas of PanIN 1 to 3 were incidentally discovered in the resected specimens, mostly with a diffuse distribution throughout the pancreas.

These data from the Johns Hopkins investigators provide evidence that, in a highly selective population of high-risk individuals, screening and surveillance by EUS may detect early pancreatic lesions, allowing for curative resection. EUS performed better than CT, which missed one pancreatic head mass, two cystic lesions, and a pancreatic abscess (Table 2), and even better than ERCP, which missed most of the lesions.

EUS, however, also led to resection of likely benign lesions in several patients who went to surgery, emphasizing the difficulty of pancreatic cancer screening in subjects who frequently have witnessed the ravages of terminal pancreatic cancer in their relatives. Abnormal imaging and/or cytologic findings in this setting will inevitably lead to resection and overtreatment in

some cases, and additional experience is needed to improve the specificity of EUS findings (88). Pancreatic nodules at several centers (20, 68) have been found to be due to focal fibrosis and inflammation in the surgical specimens, indicating that these lesions may have been managed with close follow-up. The enthusiasm for surgery in these patients must be carefully balanced with the relatively high risks of morbidity and mortality associated with pancreatic surgery. In fact, one individual from family X who was already diabetic underwent total pancreatectomy because of the fear of developing cancer and she died postoperatively.[3] Targeted real-time FNA may help establish which lesions need to be resected and can really only be done by EUS. The value of random EUS-FNA, on the other hand, remains completely unknown and should only be done in approved protocols because it may result in overtreatment.

The specificity of EUS may also be enhanced by using it in combination with new-generation, such as contrast-enhanced multidetector row helical CT as well as magnetic resonance imaging/magnetic resonance cholangiopancreatography (89, 90). CT and magnetic resonance imaging/magnetic resonance cholangiopancreatography may also detect extrapancreatic neoplasms located beyond the imaging range of EUS, which appear to occur more frequently in these patients (20). Due to the poor interobserver agreement for EUS findings in this patient population, even between experienced endosonographers (91), longitudinal follow-up of patients by the same operator may be of great importance (92). Lastly, EUS may not be the best test for all patients, especially those with hereditary pancreatitis in whom the severity of the chronic changes of the pancreatic parenchyma can render the search for small abnormalities prohibitively difficult.

What Is the Best Management of the Lesions Found?

There is no established management algorithm for patients in whom abnormalities are found by screening or surveillance. The two areas of greatest controversy are (*a*) Should all the lesions found at screening or surveillance be resected? and (*b*) Should the entire pancreas be removed once surgical management is chosen?

When a lesion with clear-cut features of malignancy (mass) or potential for progression (IPMN) is discovered, surgical resection should be recommended without hesitation. An aggressive approach should also be used for IPMN-B in the highest-risk individuals as they may become malignant within a short period (19). In patients with lesions of less clear significance, however, pancreatic cancer screening cannot be equated to colorectal cancer screening where precursor lesions (polyps) can be *in vivo* characterized and removed at the time of colonoscopy without significant complications. Pancreatic surgery carries significant morbidity and mortality, and the risk of overtreatment must be weighed against the risk of allowing a lethal cancer to progress. A better understanding of the histopathologic and clinical correlates to specific and standardized EUS findings will require additional investigation.

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[3] T.A. Brentnall, personal communication.

Table 2. Characteristics of the 15 high-risk individuals from the CAPS 1 (20) and CAPS 2 (19) studies for whom a definitive diagnosis was obtained after the discovery of abnormal findings at screening or during surveillance

Patient	Underlying condition	No. relatives with pancreatic cancer	Pancreatic neoplastic-type lesion and FNA results	Surgery	Pathology
1	FPC	7	Head: 2.1 cm mass by EUS; EUS-FNA: not done	Pancreaticoduodenectomy	T_2N_1 adenocarcinoma, PanIN 1 and 2 at margin
2	PJS	0	Uncinate: 2.0 cm mass by EUS and CT; EUS-FNA: not done	Pancreaticoduodenectomy	Borderline IPMN; diffuse PanIN 1 and 2
3	FPC	2	Head: 1.5 cm cystic mass by EUS and CT; EUS-FNA: benign pancreatic cells in a mucinous background	Pancreaticoduodenectomy	Benign serous multiloculated cystadenoma
4	FPC	3	Head: 1.3 cm cystic mass by EUS and CT; EUS-FNA: nondiagnostic	Pancreaticoduodenectomy	Benign serous multiloculated cystadenoma; focal PanIN 1
5	FPC	4	Tail: 1.0 cm mass by EUS and CT EUS-FNA: ectopic spleen by positive specific immunocytochemical staining	Distal pancreatectomy	Diffuse PanIN 1 and 2; ectopic spleen; 0.5 cm microcystic serous cystadenoma
6	FPC	6	Body: 1.6 cm mass by EUS EUS-FNA: nondiagnostic	Distal pancreatectomy	Diffuse, multiple, PanIN 1-3; pancreatic abscess; mild focal acute and chronic pancreatitis
7	FPC	3	Dysplasia in random EUS-FNA	Distal pancreatectomy	Diffuse PanIN 1A and 1B; mild focal acute and chronic pancreatitis
8	PJS	0	Uncinate: 1.5 cm cyst by EUS and CT; EUS-FNA: not done	Pylorus-sparing pancreaticoduodenectomy	Branch-type IPMN with carcinoma *in situ*
9	FPC	3	Tail: 1.4 and 1.1 cm cysts by EUS and CT: EUS-FNA: mucinous ductal epithelium suspicious for IPMN	Distal pancreatectomy	Two branch-type IPMN-adenomas; multifocal PanIN 1-3 with possible focus of microinvasive adenocarcinoma
10	FPC	3	Head and body: 9 and 10 mm focal cystic dilation of main pancreatic duct by EUS* EUS-FNA: mucinous ductal epithelium suspicious for IPMN	Extended pylorus-sparing pancreaticoduodenectomy	Incipient IPMN [†]
11	FPC	4	Tail: 1 cm hypoechoic nodule by EUS; EUS-FNA: atypical, neoplastic-type pancreatic ductal epithelium (repeated twice)	Distal pancreatectomy	Focal fibrosis, atrophy; diffuse multiple foci of PanIN 1 and 2
12 [‡]	FPC	3	Head: 1.5 cm cyst by EUS and CT; EUS-FNA: mucinous ductal epithelium suspicious for IPMN	Pylorus-sparing pancreaticoduodenectomy	Two branch-type IPMN adenomas; diffuse PanIN 1 and 2; multifocal chronic pancreatitis
13 [‡]	FPC	3	Head: 1.4 cm cyst by EUS; EUS-FNA: not done	Pylorus-sparing pancreaticoduodenectomy	Branch-type IPMN adenoma; multifocal PanIN 1A and 2 associated with focal fibrosis and atrophy
14 [‡]	FPC	5	Uncinate: 6 mm cyst, which enlarged to 9 mm after 3 mo by EUS and CT; EUS-FNA: not done	No surgery	Adenocarcinoma at percutaneous biopsy of liver and pancreatic masses
15 [‡]	FPC	5	Head: 6 mm cyst with mural nodule by EUS; EUS-FNA: mucinous ductal epithelium with cellular atypia	Pylorus-sparing pancreaticoduodenectomy	Branch-type IPMN adenoma; diffuse PanIN 1 and 2; multifocal diffuse chronic pancreatitis

*A 6 mm cyst in the body was seen at CT.
[†]The two cystic lesions identified preoperatively could not be identified in the resected specimen because of processing problems.
[‡]Lesions were detected during surveillance.

Once the decision is made that a patient needs surgery, the final decision is how much of the pancreas to remove. The frequent incidental discovery in the resected specimens of PanIN lesions (73% in the series form The John Hopkins; see Table 2), usually with a diffuse multifocal distribution, makes total pancreatectomy the only intervention able to completely eradicate the disease. The observation of distinct *K-ras* gene mutations in separately microdissected PanIN lesions supports the multifocal nature of FPC (86). This strategy is not uniformly employed, however, due to the morbidity of total pancreatectomy. In the initial experience at the University of Washington, all the patients from Family X underwent total pancreatectomy, whereas partial pancreatectomy was done in all the other high-risk cases (68). Their current protocol, however, employs laparoscopic distal pancreatectomy followed by complete pancreatectomy when multifocal disease and high-grade PanIN are found (22). At John Hopkins, partial pancreatectomy is usually offered with subsequent strict follow-up with EUS and CT (18). No data, however, are available on the performance of imaging in the evaluation of the residual pancreas, particularly of the area adjacent to the resection margin where the ability to recognize recurrent or metachronous lesions could be altered. In addition, it is also not known how many of these patients will eventually develop other lesions. Follow-up data on all of these issues will help to guide and individualize these difficult decisions.

Conclusions

Very little is known about the natural history of early pancreatic cancer, but given the uniform fatality of the disease the development of a screening protocol for those patients with the highest risk is a priority. The learning curve in pancreatic cancer screening and surveillance has just begun, and at this time, there are more questions than answers. However, the published data suggest that EUS-based screening and surveillance of high-risk individuals has the potential to detect pancreatic neoplasms at a curable stage. This process may be enhanced by the addition of CT and magnetic resonance imaging. The potential to cure or prevent pancreatic neoplasia, however, must be weighed against the risk of overtreatment of healthy individuals with surgical procedures that carry significant morbidity and mortality. Better characterization of the lesions for which surgical resection is required is greatly needed and will eventually minimize this risk. Long-term follow-up data from large multicenter studies will be necessary before recommendations can be applied broadly into clinical practice, but as the screening diagnostic and treatment algorithms improve over time, those at high risk for pancreatic cancer are likely to benefit from screening and surveillance.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

References

1. Jemal A, Siegel R, Ward E, Murray T, Xu J, Thun MJ. Cancer statistics, 2007. CA Cancer J Clin 2007;57: 43–66.
2. Parkin DM, Bray F, Ferlay J, Pisani P. Estimating the world cancer burden: Globocan 2000. Int J Cancer 2001;94:153–6.
3. Ariyama J, Suyama M, Satoh K, Sai J. Imaging of small pancreatic ductal adenocarcinoma. Pancreas 1998;16:396–401.
4. Feldmann G, Beaty R, Hruban RH, Maitra A. Molecular genetics of pancreatic intraepithelial neoplasia. J Hepatobiliary Pancreat Surg 2007;14:224–32.
5. McGrath K, Slivka A. Diagnosis and management of intraductal papillary mucinous neoplasia. Nat Clin Pract Gastroenterol Hepatol 2005;2:316–22.
6. Tanaka M, Chari S, Adsay V, et al. International consensus guidelines for management of intraductal papillary mucinous neoplasms and mucinous cystic neoplasms of the pancreas. Pancreatology 2006;6: 17–32.
7. Hruban RH, Adsay NV, Albores-Saavedra J, et al. Pancreatic intraepithelial neoplasia: a new nomenclature and classification system for pancreatic duct lesions. Am J Surg Pathol 2001;25:579–86.
8. Real FX. A "catastrophic hypothesis" for pancreas cancer progression. Gastroenterology 2003;124: 1958–64.
9. Klein AP, Hruban RH, Brune KA, Petersen GM, Goggins M. Familial pancreatic cancer. Cancer J 2001;7:266–73.
10. Goggins M, Kern SE, Offerhaus JA, Hruban RH. Progress in cancer genetics: lessons from pancreatic cancer. Ann Oncol 1999;10 Suppl 4:4–8.
11. Ghadirian P, Boyle P, Simard A, Baillargeon J, Maisonneuve P, Perret C. Reported family aggregation of pancreatic cancer within a population-based case-control study in the Francophone community in Montreal, Canada. Int J Pancreatol 1991;10:183–96.
12. Lynch HT. Genetics and pancreatic cancer. Arch Surg 1994;129:266–8.

13. Lynch HT, Smyrk T, Kern SE, et al. Familial pancreatic cancer: a review. Semin Oncol 1996;23:251–75.
14. Lynch HT, Fitzsimmons ML, Smyrk TC, et al. Familial pancreatic cancer: clinicopathologic study of 18 nuclear families. Am J Gastroenterol 1990;85:54–60.
15. Bartsch DK, Kress R, Sina-Frey M, et al. Prevalence of familial pancreatic cancer in Germany. Int J Cancer 2004;110:902–6.
16. Hemminki K, Li X. Familial and second primary pancreatic cancers: a nationwide epidemiologic study from Sweden. Int J Cancer 2003;103:525–30.
17. Brand RE, Lerch MM, Rubinstein WS, et al. Advances in counselling and surveillance of patients at risk for pancreatic cancer. Gut 2007;56:1460–9.
18. Canto MI. Screening for pancreatic neoplasia in high-risk individuals: who, what, when, how? Clin Gastroenterol Hepatol 2005;3:S46–8.
19. Canto MI, Goggins M, Hruban RH, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. Clin Gastroenterol Hepatol 2006;4:766–81; quiz 665.
20. Canto MI, Goggins M, Yeo CJ, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clin Gastroenterol Hepatol 2004;2: 606–21.
21. Brentnall TA, Bronner MP, Byrd DR, Haggitt RC, Kimmey MB. Early diagnosis and treatment of pancreatic dysplasia in patients with a family history of pancreatic cancer. Ann Intern Med 1999;131:247–55.
22. Brentnall TA. Management strategies for patients with hereditary pancreatic cancer. Curr Treat Options Oncol 2005;6:437–45.
23. Canto MI. Strategies for screening for pancreatic adenocarcinoma in high-risk patients. Semin Oncol 2007;34:295–302.
24. Fuchs CS, Colditz GA, Stampfer MJ, et al. A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch Intern Med 1996;156:2255–60.
25. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. Interna-

tional Pancreatitis Study Group. N Engl J Med 1993; 328:1433–7.
26. Everhart J, Wright D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA 1995;273:1605–9.
27. Lowenfels AB, Maisonneuve P. Risk factors for pancreatic cancer. J Cell Biochem 2005;95:649–56.
28. Hemminki A, Markie D, Tomlinson I, et al. A serine/threonine kinase gene defective in Peutz-Jeghers syndrome. Nature 1998;391:184–7.
29. Giardiello FM, Brensinger JD, Tersmette AC, et al. Very high risk of cancer in familial Peutz-Jeghers syndrome. Gastroenterology 2000;119:1447–53.
30. Goldstein AM, Fraser MC, Struewing JP, et al. Increased risk of pancreatic cancer in melanoma-prone kindreds with p16INK4 mutations. N Engl J Med 1995;333:970–4.
31. Parker JF, Florell SR, Alexander A, DiSario JA, Shami PJ, Leachman SA. Pancreatic carcinoma surveillance in patients with familial melanoma. Arch Dermatol 2003;139:1019–25.
32. Lynch HT, Fusaro RM, Lynch JF, Brand R. Pancreatic cancer and the FAMMM syndrome. Fam Cancer 2008;7:103–12.
33. Bartsch DK, Sina-Frey M, Lang S, et al. CDKN2A germline mutations in familial pancreatic cancer. Ann Surg 2002;236:730–7.
34. Lynch HT, Brand RE, Hogg D, et al. Phenotypic variation in eight extended CDKN2A germline mutation familial atypical multiple mole melanoma-pancreatic carcinoma-prone families: the familial atypical mole melanoma-pancreatic carcinoma syndrome. Cancer 2002;94:84–96.
35. Goldstein AM, Struewing JP, Chidambaram A, Fraser MC, Tucker MA. Genotype-phenotype relationships in U.S. melanoma-prone families with CDKN2A and CDK4 mutations. J Natl Cancer Inst 2000;92: 1006–10.
36. Vasen HF, Gruis NA, Frants RR, van Der Velden PA, Hille ET, Bergman W. Risk of developing

pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion of p16 (p16-Leiden). Int J Cancer 2000;87: 809–11.

37. Thompson D, Easton DF. Cancer Incidence in BRCA1 mutation carriers. J Natl Cancer Inst 2002;94: 1358–65.

38. Goggins M, Schutte M, Lu J, et al. Germline BRCA2 gene mutations in patients with apparently sporadic pancreatic carcinomas. Cancer Res 1996;56:5360–4.

39. Hahn SA, Greenhalf B, Ellis I, et al. BRCA2 germline mutations in familial pancreatic carcinoma. J Natl Cancer Inst 2003;95:214–21.

40. Murphy KM, Brune KA, Griffin C, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer Res 2002;62:3789–93.

41. Couch FJ, Johnson MR, Rabe KG, et al. The prevalence of BRCA2 mutations in familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2007;16:342–6.

42. Lynch HT, Voorhees GJ, Lanspa SJ, McGreevy PS, Lynch JF. Pancreatic carcinoma and hereditary nonpolyposis colorectal cancer: a family study. Br J Cancer 1985;52:271–3.

43. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261–8.

44. Giardiello FM, Offerhaus GJ, Lee DH, et al. Increased risk of thyroid and pancreatic cancer in familial adenomatous polyposis. Gut 1993;34: 1394–6.

45. Lowenfels AB, Maisonneuve P, Whitcomb DC. Risk factors for cancer in hereditary pancreatitis. International Hereditary Pancreatitis Study Group. Med Clin North Am 2000;84:565–73.

46. Lowenfels AB, Maisonneuve P, DiMagno EP, et al. Hereditary pancreatitis and the risk of pancreatic cancer. International Hereditary Pancreatitis Study Group. J Natl Cancer Inst 1997;89:442–6.

47. Lowenfels AB, Maisonneuve P, Whitcomb DC, Lerch MM, DiMagno EP. Cigarette smoking as a risk factor for pancreatic cancer in patients with hereditary pancreatitis. JAMA 2001;286:169–70.

48. Neglia JP, FitzSimmons SC, Maisonneuve P, et al. The risk of cancer among patients with cystic fibrosis. Cystic Fibrosis and Cancer Study Group. N Engl J Med 1995;332:494–9.

49. Maisonneuve P, Marshall BC, Lowenfels AB. Risk of pancreatic cancer in patients with cystic fibrosis. Gut 2007;56:1327–8.

50. Swift M, Sholman L, Perry M, Chase C. Malignant neoplasms in the families of patients with ataxia-telangiectasia. Cancer Res 1976;36:209–15.

51. Narita T, Takagi K. Ataxia-telangiectasia with dysgerminoma of right ovary, papillary carcinoma of thyroid, and adenocarcinoma of pancreas. Cancer 1984;54: 1113–6.

52. Couch FJ, Johnson MR, Rabe K, et al. Germ line Fanconi anemia complementation group C mutations and pancreatic cancer. Cancer Res 2005;65:383–6.

53. Evans JP, Burke W, Chen R, et al. Familial pancreatic adenocarcinoma: association with diabetes and early molecular diagnosis. J Med Genet 1995;32:330–5.

54. Lynch HT, Brand RE, Deters CA, Shaw TG, Lynch JF. Hereditary pancreatic cancer. Pancreatology 2001;1:466–71.

55. Tersmette AC, Petersen GM, Offerhaus GJ, et al. Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. Clin Cancer Res 2001;7:738–44.

56. Falk RT, Pickle LW, Fontham ET, Correa P, Fraumeni JF, Jr. Life-style risk factors for pancreatic cancer in Louisiana: a case-control study. Am J Epidemiol 1988;128:324–36.

57. Fernandez E, La Vecchia C, D'Avanzo B, Negri E, Franceschi S. Family history and the risk of liver, gallbladder, and pancreatic cancer. Cancer Epidemiol Biomarkers Prev 1994;3:209–12.

58. Silverman DT, Schiffman M, Everhart J, et al. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br J Cancer 1999;80:1830–7.

59. Amundadottir LT, Thorvaldsson S, Gudbjartsson DF, et al. Cancer as a complex phenotype: pattern of cancer distribution within and beyond the nuclear family. PLoS Med 2004;1:e65.

60. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004;64:2634–8.

61. Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: risk assessment for individuals with a family history of pancreatic cancer. J Clin Oncol 2007;25:1417–22.

62. Eberle MA, Pfutzer R, Pogue-Geile KL, et al. A new susceptibility locus for autosomal dominant pancreatic cancer maps to chromosome 4q32-34. Am J Hum Genet 2002;70:1044–8.

63. Ronty M, Taivainen A, Moza M, Otey CA, Carpen O. Molecular analysis of the interaction between palladin and α-actinin. FEBS Lett 2004;566:30–4.

64. Pogue-Geile KL, Chen R, Bronner MP, et al. Palladin mutation causes familial pancreatic cancer and suggests a new cancer mechanism. PLoS Med 2006; 3:e516.

65. Earl J, Yan L, Vitone LJ, et al. Evaluation of the 4q32-34 locus in European familial pancreatic cancer. Cancer Epidemiol Biomarkers Prev 2006;15: 1948–55.

66. Zogopoulos G, Rothenmund H, Eppel A, et al. The P239S palladin variant does not account for a significant fraction of hereditary or early onset pancreas cancer. Hum Genet 2007;121:635–7.

67. McFaul CD, Greenhalf W, Earl J, et al. Anticipation in familial pancreatic cancer. Gut 2006;55:252–8.

68. Kimmey MB, Bronner MP, Byrd DR, Brentnall TA. Screening and surveillance for hereditary pancreatic cancer. Gastrointest Endosc 2002;56:S82–6.

69. Rulyak SJ, Lowenfels AB, Maisonneuve P, Brentnall TA. Risk factors for the development of pancreatic cancer in familial pancreatic cancer kindreds. Gastroenterology 2003;124:1292–9.

70. Vitone LJ, Greenhalf W, McFaul CD, Ghaneh P, Neoptolemos JP. The inherited genetics of pancreatic cancer and prospects for secondary screening. Best Pract Res Clin Gastroenterol 2006;20:253–83.

71. Latchford A, Greenhalf W, Vitone LJ, Neoptolemos JP, Lancaster GA, Phillips RK. Peutz-Jeghers syndrome and screening for pancreatic cancer. Br J Surg 2006;93:1446–55.

72. Rubenstein JH, Scheiman JM, Anderson MA. A clinical and economic evaluation of endoscopic ultrasound for patients at risk for familial pancreatic adenocarcinoma. Pancreatology 2007;7:514–25.

73. Rulyak SJ, Kimmey MB, Veenstra DL, Brentnall TA. Cost-effectiveness of pancreatic cancer screening in familial pancreatic cancer kindreds. Gastrointest Endosc 2003;57:23–9.

74. DeWitt J, Devereaux B, Chriswell M, et al. Comparison of endoscopic ultrasonography and multidetector computed tomography for detecting and staging pancreatic cancer. Ann Intern Med 2004;141:753–63.

75. Fernandez-del Castillo C, Targarona J, Thayer SP, Rattner DW, Brugge WR, Warshaw AL. Incidental pancreatic cysts: clinicopathologic characteristics and comparison with symptomatic patients. Arch Surg 2003;138:427–3; discussion 33–4.

76. Spinelli KS, Fromwiller TE, Daniel RA, et al. Cystic pancreatic neoplasms: observe or operate. Ann Surg 2004;239:651–7; discussion 7–9.

77. Tanaka M. Intraductal papillary mucinous neoplasm of the pancreas: diagnosis and treatment. Pancreas 2004;28:282–8.

78. Matsumoto T, Aramaki M, Yada K, et al. Optimal management of the branch duct type intraductal papillary mucinous neoplasms of the pancreas. J Clin Gastroenterol 2003;36:261–5.

79. Levy P, Jouannaud V, O'Toole D, et al. Natural history of intraductal papillary mucinous tumors of the pancreas: actuarial risk of malignancy. Clin Gastroenterol Hepatol 2006;4:460–8.

80. Tanno S, Nakano Y, Nishikawa T, et al. Natural history of branch duct intraductal papillary-mucinous neoplasms of the pancreas without mural nodules: long-term follow-up results. Gut 2008;57:339–43.

81. Hruban RH, Wilentz RE, Goggins M, Offerhaus GJ, Yeo CJ, Kern SE. Pathology of incipient pancreatic cancer. Ann Oncol 1999;10 Suppl 4:9–11.

82. McCarthy DM, Brat DJ, Wilentz RE, et al. Pancreatic intraepithelial neoplasia and infiltrating adenocarcinoma: analysis of progression and recurrence by DPC4 immunohistochemical labeling. Hum Pathol 2001;32:638–42.

83. Biankin AV, Kench JG, Dijkman FP, Biankin SA, Henshall SM. Molecular pathogenesis of precursor lesions of pancreatic ductal adenocarcinoma. Pathology 2003;35:14–24.

84. Wilentz RE, Geradts J, Maynard R, et al. Inactivation of the p16 (INK4A) tumor-suppressor gene in pancreatic duct lesions: loss of intranuclear expression. Cancer Res 1998;58:4740–4.

85. Fukushima N, Sato N, Ueki T, et al. Aberrant methylation of preproenkephalin and p16 genes in pancreatic intraepithelial neoplasia and pancreatic ductal adenocarcinoma. Am J Pathol 2002;160: 1573–81.

86. Brune K, Abe T, Canto M, et al. Multifocal neoplastic precursor lesions associated with lobular atrophy of the pancreas in patients having a strong family history of pancreatic cancer. Am J Surg Pathol 2006;30: 1067–76.

87. Meckler KA, Brentnall TA, Haggitt RC, et al. Familial fibrocystic pancreatic atrophy with endocrine cell hyperplasia and pancreatic carcinoma. Am J Surg Pathol 2001;25:1047–53.

88. Levy MJ. Screening for pancreatic cancer: searching for the right needle in the haystack. Clin Gastroenterol Hepatol 2006;4:684–7.

89. Faria SC, Tamm EP, Loyer EM, Szklaruk J, Choi H, Charnsangavej C. Diagnosis and staging of pancreatic tumors. Semin Roentgenol 2004;39: 397–411.

90. Francis IR. Pancreatic adenocarcinoma: diagnosis and staging using multidetector-row computed tomography (MDCT) and magnetic resonance imaging (MRI). Cancer Imaging 2007;7 Spec A:S160–5.

91. Topazian M, Enders F, Kimmey M, et al. Interobserver agreement for EUS findings in familial pancreatic-cancer kindreds. Gastrointest Endosc 2007;66: 62–7.

92. Deutsch JC. EUS screening of subjects at risk for familial pancreatic cancer: what to do and what to expect. Gastrointest Endosc 2007;66:68–9.

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