Familial risk factors for pancreatic cancer and screening of high-risk patients

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INTRODUCTION

Pancreatic ductal adenocarcinoma (pancreatic cancer [PC]) is one of the leading causes of cancer-related mortality worldwide [1]. Most symptomatic patients with PC have advanced, incurable disease at diagnosis. Even in those with apparently resectable tumors, prognosis is poor. Given that outcomes may be better following resection of small invasive cancers, it is hoped that screening and detection of asymptomatic, early, potentially curable PC and its precursors will improve outcomes. Individuals at increased risk for PC based on family history or an identifiable genetic predisposition are potential targets for selective screening and curative or preventive treatment.

This topic reviews the epidemiology and genetic basis of familial pancreatic cancer (FPC) and FPC-associated genetic syndromes, the diagnostic tests used for screening, and the risks and benefits of screening for PC. A more detailed discussion of epidemiology and risk factors for PC, and the clinical evaluation and staging workup of newly diagnosed PC, are addressed separately. (See "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer" and "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer".)

EPIDEMIOLOGY AND RISK FACTORS

An estimated 10 to 15 percent of PCs are attributable to genetic causes [2-7]. PC aggregates in some families, and approximately 5 to 10 percent of individuals with PC have a family history of the disease [3,5].

There are two broad categories of hereditary risk for PC:

- Inherited genetic predisposition syndromes associated with PC (table 1) [7,8].
- Familial pancreatic cancer (FPC), which is defined as a family with a pair of affected first-degree relatives (FDRs; parent-child or sibling pair) who do not meet criteria for a known PC-associated genetic predisposition syndrome.

The major gene causing most cases of hereditary PC is not yet known. Pathogenic germline variants (PGVs) in the breast cancer associated (*BRCA*) 1 and 2 genes are the most commonly associated mutations, occurring in 13 to 19 percent of FPC families [9,10]. Next generation sequencing has led to discovery of other genes causing hereditary pancreatic ductal adenocarcinoma: the partner and localizer of *BRCA2* (*PALB2*) gene and the ataxia-telangiectasia mutated (*ATM*) gene [11,12]. PGVs are especially common in individuals with early onset pancreatic cancer (EOPC; ie, developing before age 50). In a cohort study of 138 patients with EOPC identified at a single institution over a 10-year period and who had germline testing, 44 (32 percent) had a PGV [13]. (See "Molecular pathogenesis of exocrine pancreatic cancer".)

In kindreds with FPC, the cumulative risk of developing PC ranges from 1.5 to 13 percent depending on the number of affected blood relatives [1,10-12,14-18]. Cigarette smoking contributes to the risk of PC in patients with hereditary pancreatitis and FPC, and is associated with an earlier PC diagnosis by approximately 20 years [19,20]. (See 'Familial pancreatic cancer' below and "Epidemiology and nonfamilial risk factors for exocrine pancreatic cancer", section on 'Cigarette smoking'.)

Although some studies suggest that patients from affected families present at an earlier age as compared with noninherited disease (especially for individuals with genetic predisposition syndromes, including hereditary pancreatitis), the median age for development of FPC is about the same as that for sporadic PC (approximately 65 years), and the majority of incident FPC cases arise in individuals age 60 years or older [21].

GENETIC PREDISPOSITION SYNDROMES

Hereditary pancreatitis — Hereditary pancreatitis is an autosomal dominant disorder that accounts for a small fraction of cases of chronic pancreatitis. Autosomal dominant hereditary

pancreatitis is most often associated with mutations in serine protease 1 gene (*PRSS1*) on chromosome 7q35, which encodes cationic trypsinogen. Rarely, autosomal dominant-appearing hereditary pancreatitis is identified in a kindred that does not have an identifiable *PRSS1* mutation. (See "Pancreatitis associated with genetic risk factors", section on 'Genetics'.)

The majority of affected individuals develop chronic pancreatitis before the age of 20 years and often before the age of five. Chronic inflammation in hereditary pancreatitis leads to accelerated mutation accumulation and clonal expansion required for development of PC [17]. Hereditary pancreatitis is associated with a markedly increased risk of PC, although it accounts for a very small fraction of PC cases [1,14,22]. The magnitude of lifetime risk is estimated to be 25 to 44 percent [14,15]. In one study that included 200 patients with hereditary pancreatitis, the cumulative risk of PC in affected family members at 50, 60, and 75 years was 10, 19, and 54 percent, respectively [15]. The standardized incidence ratio (SIR) compared with the general population was 87 [15]. The risk of PC appears to be highest in smokers, diabetics, and in those with a paternal inheritance pattern [14,15,19].

Inherited cancer susceptibility syndromes — Between 4 and 20 percent of patients with PC have germline mutations in known cancer predisposition genes [6,23-29]. The most common inherited cancer susceptibility syndromes and their approximate lifetime risk for PC are summarized in the table (table 1).

Hereditary breast cancer: BRCA and PALB2 — Hereditary breast and ovarian cancer is characterized by the presence of germline mutations in one of two cancer susceptibility genes: breast cancer associated (*BRCA*) 1 and 2. The risk of PC may be elevated two- to threefold in *BRCA1* mutation carriers, but the risk has not been well established, as it is with *BRCA2* gene mutations [7,18,30-32]. In one familial pancreatic cancer (FPC) registry study, *BRCA1* mutations (by full sequencing) were not highly prevalent [33]. By contrast, *BRCA2* mutations have been found in as many as 5 to 17 percent of patients with FPC [10,34,35]. PC risk in *BRCA2* gene mutation carriers is elevated with a relative risk (RR) that ranges from 3.3 to 10 [7,32,36,37]. (See "Cancer risks and management of BRCA1/2 carriers without cancer".)

BRCA mutations are particularly prevalent among patients of Ashkenazi Jewish origin. An estimated 1.7 to 21 percent of patients of Ashkenazi Jewish origin who have PC carry a *BRCA* mutation, many of whom lack a family history of typical *BRCA*-associated cancers [25,35,38,39]. Because of this, some have suggested that the diagnosis of PC in an Ashkenazi individual should prompt referral for *BRCA* testing [39], including the founder *BRCA2* gene mutation, 6174delT, that is present in 1 percent of Ashkenazi Jewish individuals [40] and 4 percent of PC patients [41].

Germline mutations in the partner and localizer of *BRCA2* (*PALB2*) gene also confer an increased risk of PC [11,42]. The PALB2 protein binds with the BRCA2 protein and stabilizes it in the nucleus; the BRCA2/PALB2 complex is part of the Fanconi Anemia DNA repair pathway that acts in double-stranded DNA repair. *PALB2* mutations have been identified in 2.1 to 4.9 percent of FPC kindreds [5,43,44]. The magnitude of risk for PC is markedly lower than that for breast cancer. In a cohort of 524 families with germline *PALB2* mutations, the cumulative risk of PC was estimated to be 1 to 4 percent by age 80, as compared with an estimated 53 percent risk of breast cancer in women [42]. The risk of developing PC in patients with a *PALB2* mutation and an affected first-degree relative (FDR) is unclear, as family history of PC was not considered in this cohort analysis. (See "Overview of hereditary breast and ovarian cancer syndromes", section on 'PALB2'.)

Peutz-Jeghers syndrome — Germline mutations in the *STK11* gene are associated with Peutz-Jeghers syndrome (PJS), an autosomal dominant disorder in which affected individuals develop hamartomatous polyps of the gastrointestinal tract, pigmented macules on the lips and buccal mucosa, and a variety of gastrointestinal malignancies [45]. Patients with PJS have a dramatically increased risk of developing PC, with an 11 to 36 percent lifetime risk to age 70 (relative risk 132) [7,45-47]. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management".)

Furthermore, both somatic and germline mutations of the *STK11* gene have been identified in PC, suggesting that genetic alterations of the *STK11* gene may play a causal role in carcinogenesis and that the same gene contributes to the development of both sporadic and familial forms of cancer [48]. (See "Molecular pathogenesis of exocrine pancreatic cancer", section on 'STK11'.)

Familial atypical multiple mole and melanoma syndrome — Pathogenic variants in the cyclin-dependent kinase inhibitor 2A (*CDKN2A*) gene (*p16* or multiple tumor suppressor-1 gene) characterize the familial atypical multiple mole and melanoma (FAMMM) syndrome, a disorder associated with multiple nevi, cutaneous and ocular malignant melanomas, as well as a high risk for PCs. The variant FAMMM-pancreatic carcinoma syndrome has been identified in families with a specific 19-base-pair deletion in the *p16* gene (the p16 Leiden mutation), which is associated with a cumulative risk of pancreatic carcinoma of up to 21 percent by age 75 [49-55]. In two reports, the odds ratio of developing pancreatic cancer in carriers of a *CDKN2A* mutation were 12.3 and 36, respectively [56,57]. (See "Inherited susceptibility to melanoma".)

Lynch syndrome — Individuals with inherited germline mutations in mismatch repair (MMR) genes, in particular mutL homolog 1 (*MLH1*), mutS homolog 2 (*MSH2*), and mutS homolog 6 (*MSH6*), have Lynch syndrome and are at increased risk of PC [58,59]. In a study of 147 families

with MMR gene mutation, of whom 21 percent had at least one PC within the family, the cumulative risk of PC was 3.7 percent by age 70 [60]. The risk may differ according to genotype, with the highest risk in *MLH1* mutation carriers [7,61]. The PCs that develop in individuals with Lynch syndrome have a characteristic medullary histology. Individuals who have a medullary PC should have their pedigree evaluated to determine if they are a Lynch syndrome kindred [62]. (See "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Extracolonic manifestations'.)

Ataxia-telangiectasia — Monoallelic pathogenic variants in the ataxia-telangiectasia mutated (*ATM*) gene, are associated with an increased risk of PC [7,12,63,64]. In a cohort study of 130 pancreatic cancer kindreds with a pathogenic germline *ATM* variant derived from pancreatic cancer family registries in the United States and Canada, the relative risk of pancreatic cancer in carriers versus noncarriers was 6.5 (95% CI 4.5-9.5), and the cumulative estimated risk of pancreatic cancer in carriers was 1.1 percent by age 50, 6.3 percent by age 70, and 9.5 percent by age 80 [64]. Rare biallelic variants in *ATM* give risk to ataxia-telangiectasia. (See "Ataxia-telangiectasia".)

FAMILIAL PANCREATIC CANCER

Familial pancreatic cancer (FPC) is defined as an inherited predisposition to PC that is based on family clustering in families in which there is at least a pair of first-degree relatives (FDRs) with pancreatic ductal adenocarcinoma in the absence of a known genetic susceptibility syndrome. A specific gene defect responsible for FPC has not been identified. Segregation models support a rare but dominant susceptibility gene that is carried by approximately 7 in every 1000 individuals [65].

Prospective analysis of data from a large FPC registry led to quantitative estimates of PC risk in at-risk relatives [3,21,66]. In this cohort, the risk of PC for a member of a FPC family was ninefold higher than for the sporadic PC kindreds [3]. Individuals with an affected FDR had an 18-fold higher risk, and the risk increased with the total number of affected blood relatives. The number of affected relatives with a first-degree relationship to the at-risk individual also increases PC risk [3,66] as does a young age of onset of pancreatic cancer in relatives [66].

REFERRAL FOR GENETIC EVALUATION

All patients diagnosed with PC should undergo assessment to develop a preliminary determination of the risk of a familial predisposition to cancer [67]. This assessment includes a

detailed personal and family cancer history (in first-degree relatives [FDRs] and second-degree relatives), including the type of cancer and age at diagnosis, and ancestry.

Individuals (affected or unaffected by PC) should be considered to be at high risk for hereditary PC if they have any of the following:

- A known genetic syndrome associated with PC, including hereditary breast-ovarian cancer syndrome, familial atypical multiple melanoma and mole syndrome, Peutz-Jeghers syndrome (PJS), Lynch syndrome, and Li-Fraumeni syndrome, or other gene mutations associated with an increased risk of pancreatic adenocarcinoma (eg, the ataxia-telangiectasia mutated [*ATM*] gene)
- Two relatives with pancreatic adenocarcinoma, where one is an FDR
- Three or more relatives with PC on the same side of the family
- Hereditary pancreatitis

In 2018, the American Society of Clinical Oncology (ASCO) published a provisional clinical opinion on identification and management of patients and family members with a possible inherited predisposition to PC [67]. This included the recommendation that "all patients diagnosed with pancreatic adenocarcinoma should undergo assessment of risk for hereditary syndromes known to be associated with an increased risk for pancreatic adenocarcinoma." This stance was adopted in early 2020 by the National Comprehensive Cancer Network (NCCN) [68].

High-risk individuals should be referred for genetic counseling and germline genetic testing as appropriate. Access to clinical genetic testing has improved, and the cost is significantly lower and more affordable for multigene panel testing.

Consistent with ASCO and NCCN guidelines, we recommend germline genetic testing for patients with PC and an unremarkable family history if an informative result could directly benefit the patient or his or her family members [67,68]. Pathogenic germline variants in cancer predisposition genes are detected in approximately 4 to 20 percent of patients with PC, including those with apparently sporadic tumors [6,23-29]. However, approximately one-half of patients with PC who are found to carry a pathogenic genetic variant have no family history of PC and/or do not meet clinical criteria for the hereditary syndrome corresponding to their diagnosis.

In addition to identifying hereditary cancer syndromes that may impact cancer screening guidelines and influence genetic testing for relatives, the results of testing may impact clinical management of the PC, as some of the deleterious PC susceptibility gene mutations are

therapeutically targetable. These include genes such as breast cancer associated (*BRCA*) 1, *BRCA2*, and partner and localizer of *BRCA2* (*PALB2*) tumor suppressor genes involved with the repair of DNA. As an example, in the setting of *BRCA* mutations, the poly(ADP-ribose) polymerases (PARPs) of the base excision repair pathway are an excellent therapeutic target by PARP inhibitors. (See "Genetic testing" and "Genetic counseling: Family history interpretation and risk assessment" and "Atypical (dysplastic) nevi", section on 'FAMM syndrome' and "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management", section on 'Diagnosis' and "Pancreatitis associated with genetic risk factors", section on 'Genetic testing' and "Initial systemic chemotherapy for metastatic exocrine pancreatic cancer", section on 'Patients with homologous recombination repair deficiency' and "Lynch syndrome (hereditary nonpolyposis colorectal cancer): Clinical manifestations and diagnosis", section on 'Indications for germline testing'.)

The importance of genetic testing is highlighted in a comparative study of the progression rates of high-risk individuals according to germline mutation status, in which 15 (of 464, 4.3 percent) familial pancreatic cancer (FPC) relatives had a previously unrecognized gene mutation (nine *ATM*, two *BRCA2*, one *BRCA1*, one *PALB2*, one tumor protein p53 [*TP53*], and one carboxypeptidase A1 [*CPA1*]) [69]. The cumulative incidence of PC, high-grade dysplasia, or worrisome features in the pancreas was significantly higher in germline mutation carriers (hazard ratio [HR] 2.85, 95% CI 1-8.18). The cumulative 10-year incidence of pancreatic ductal adenocarcinoma or high-grade dysplasia was significantly higher in individuals with a deleterious germline mutation (n = 134) as compared with those without (n = 330 [22 versus 7 percent, p = 0.02]).

One contemporary study suggests that cohorts that include only mutation-negative FPC kindreds may not exceed the current threshold of 5 percent lifetime risk for which pancreatic cancer surveillance is suggested [70]. This was illustrated in a prospective study of 201 mutation-negative FPC kindreds with a mean baseline age of 54 years. During a mean follow-up of over five years during which both endoscopic ultrasound and magnetic resonance imaging (MRI)/magnetic resonance cholangiopancreatography were performed at every visit, none developed pancreatic ductal adenocarcinoma. By contrast, in individuals with a genetic mutation (mostly high-risk CKDN2A-positive individuals) the cumulative PC incidence was 9.3 percent.

PANCPRO is a statistical model for assessing the probability that an individual carries a germline deleterious mutation of a susceptibility gene for PC and the risk of developing a future PC based on the individual's family history [71,72]. A modified risk prediction tool for individuals with a family history of breast, ovarian, or pancreatic cancer (BRCAPANCPRO) derived from analysis of

the Johns Hopkins National Familial Pancreas Tumor Registry pedigrees can predict future risk of PC development [73] and may potentially aid risk stratification.

Although models such as these may represent an accurate predictor of the likelihood of developing a PC in high-risk families, external validation in other populations and consideration of other risk factors is needed to allow improved risk stratification and selection for targeted screening [74].

PANCREATIC CANCER SCREENING

Our approach — The decision to perform screening for PC requires a discussion of the risks, benefits, and lack of definitive data on long-term screening outcomes. The decision should be guided by individual patient values and preferences. Screening should only be performed in patients who are candidates for pancreas surgery. Screening for PC should preferably be performed in the setting of a research protocol at an experienced center with a multidisciplinary team.

The optimal screening strategy for patients at risk for hereditary PC is not clear. Guidelines for screening for PC have been published by several groups [6,75-80]. Our approach to screening for individuals with an increased risk for pancreatic adenocarcinoma, such as those with hereditary pancreatitis and other high-risk conditions, are largely consistent with guidelines from the American Gastroenterological Association (AGA), the International Cancer of the Pancreas Screening (CAPS) Consortium (table 2), and the American College of Gastroenterology (ACG) [6,76,79].

The American Society for Gastrointestinal Endoscopy (ASGE) has also published a guideline on screening for pancreatic cancer in individuals with a genetic susceptibility [80]. Of note, the ASGE guidelines are recommending PC screening in breast cancer associated (*BRCA*)1 and *BRCA2* mutation carriers even without a family history of PC in a blood relative [80]. In our view, there is insufficient evidence to support this recommendation, and we follow the recommendations of the CAPS consortium (table 2).

General population-based screening for average-risk patients is not recommended [79,81] because the average lifetime risk for developing PC is too low (approximately 1 in 60 in the United States) [82].

Candidates for screening — We screen for PC in the following individuals [6,75,79] (see 'Inherited cancer susceptibility syndromes' above):

Patients with a known high-risk genetic syndrome:

- Breast cancer associated (*BRCA*) 2 pathogenic variant with at least one affected first-degree relative (FDR) or at least two affected relatives of any degree
- *BRCA1*, partner and localizer of *BRCA2* (*PALB2*), ataxia-telangiectasia mutated (*ATM*), and Lynch syndrome pathogenic variant carriers with one or more affected FDRs
- Patients with Peutz-Jeghers syndrome (PJS), regardless of family history
- Patients with *CDKN2A* (*p16*) pathogenic variants, regardless of family history
- Hereditary pancreatitis with a *PRSS1* pathogenic variant regardless of family history (see 'Hereditary pancreatitis' above)

Patients without a known high-risk inherited pathogenic variant but with at least one pair of affected FDR in the kindred:

- At least three affected relatives on the same side of the family, of whom at least one is an FDR of the individual being considered for surveillance
- At least two affected relatives who are FDRs of each other, of whom at least one is an FDR of the individual being considered for surveillance
- At least two affected relatives on the same side of the family, of whom at least one is an FDR of the individual being considered for surveillance

Screening modality and timing — For most patients, we perform endoscopic ultrasound (EUS) and/or MRI/magnetic resonance cholangiopancreatography (MRCP). This recommendation is based on a cross-sectional blinded comparison of EUS, MRI, and computed tomography (CT) demonstrating comparable frequent detection of pancreatic lesions by EUS and MRI, compared with CT (table 3) [83]. EUS and MRI have been shown to be complementary, and both are recommended [70,84]. EUS may be better for detection of solid lesions, while MRI/MRCP is superior to EUS for visualization of cystic lesions [84].

We base our approach to beginning screening on the mean expected age of development of PC and the youngest age of onset of PC in the family [6,75]. In familial pancreatic cancer (FPC) relatives, we begin screening at age 50, or 10 years younger than the youngest relative with PC [6,85]. For mutation carriers with modestly increased risk (*ATM*, *PALB2*), we also recommend beginning at age 45 or 50. We begin screening for PC at a younger age in patients with a higher risk of developing PC, although the actual age remains controversial among experts from established PC surveillance programs. We recommend initiating screening in *CDKN2A* mutation-

positive patients and hereditary pancreatitis with a *PRSS1* mutation at age 40 years [6,79]. For patients with PJS, we begin screening at age 35. (See "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management" and 'Epidemiology and risk factors' above.)

For most patients with a normal pancreas on imaging, repeat pancreatic imaging (EUS and/or MRI/MRCP) can be performed every year, typically alternating EUS and MRCP until a lesion is detected. A shorter screening interval (eg, every six months) is appropriate for very high-risk individuals such as *CDKN2A* germline mutation carriers and individuals with Peutz-Jeghers syndrome. (See 'Diagnostic yield, benefits, and harms' below and "Peutz-Jeghers syndrome: Clinical manifestations, diagnosis, and management", section on 'Pancreatic cancer'.)

The age for stopping screening should be individualized based on each patient's medical status (eligibility for surgical treatment of detected lesions), life expectancy, and preferences.

Pancreatic surveillance intervals for detected lesions that are thought not to require imminent surgical management are influenced by the size, number, and type of lesion (solid versus cystic), growth rate, and concerning features.

The management of pancreatic lesions and intervals for surveillance as recommended by the CAPS Consortium are outlined in the table (table 2) [6] and discussed in detail below. (See 'Management and follow-up of identified lesions' below.)

Screening targets — Screening for PC aims to detect early invasive tumors and preinvasive lesions (intraductal papillary mucinous neoplasms [IPMNs] and pancreatic intraepithelial neoplasia [PanINs]) with high-grade neoplastic changes [86-89].

- **Intraductal papillary mucinous neoplasms (IPMNs)** – IPMNs are potentially malignant intraductal epithelial neoplasms that are grossly visible (>1 cm) and are composed of mucin-producing columnar cells. IPMNs are highly prevalent in individuals with hereditary FPC [87,90]. Over time, IPMNs can develop increasingly dysplastic features (graded as low, intermediate, or high) and eventually transform into invasive adenocarcinoma. (See 'Diagnostic yield, benefits, and harms' below and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Pathophysiology and clinical manifestations", section on 'Progression to pancreatic cancer'.)

  Evidence on the frequency and rate at which IPMNs progress to invasive PC in high-risk individuals as compared with sporadic IPMNs is lacking. In patients with apparently sporadic noninvasive IPMNs, it may take three to five years for a clinically detectable noninvasive lesion to progress to an invasive PC [91]. The risk for progression to high-grade dysplasia (in situ carcinoma) or invasive disease is much higher for main-duct IPMNs

(MD-IPMNs) than it is for branch-duct IPMNs (BD-IPMNs). On the other hand, among patients with small BD-IPMN(s) followed for over five years, only 2.4 to 6.9 percent of these lesions progress to invasive PC [92,93]. (See 'Cystic pancreatic lesions' below and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management".)

The natural history of low-risk IPMNs in high-risk individuals is also not well understood. In fact, some tiny cystic lesions visualized by EUS will be found to be visible PanINs in resected patients [83,94,95]. In the setting of FPC, the presence of multiple small "imaging" BD-IPMNs may indicate the presence of high-grade PanIN (PanIN-3) lesions elsewhere in the pancreas [96].

- **Pancreatic intraepithelial neoplasia (PanIN)** – PanIN lesions are noninvasive microscopic pancreatic duct neoplasms. These lesions are typically <5 mm in size and too small to be visualized by imaging. Most ductal adenocarcinomas are considered to arise from PanIN, presumably developing as a result of a series of genetic events. However, although PanIN is considered to represent a precursor lesion to invasive ductal adenocarcinoma, it appears that only a small fraction of low-grade PanIN progress to PanIN-3 and then to invasive cancer. PanIN are more common, more often multifocal, and of a higher grade in patients with hereditary PC [18,86,87]. (See "Pathology of exocrine pancreatic neoplasms", section on 'Pancreatic intraepithelial neoplasia'.)

Diagnostic yield, benefits, and harms — Several studies have evaluated the diagnostic yield of screening [83,94,95,97-105]. These studies have reported the detection of asymptomatic precursor lesions and PCs at baseline and follow-up in 3.9 to 50 percent of individuals, depending on whether only resected neoplasms or all pancreatic lesions (resected or not) were used as an end point (table 3) [5,70,94,95,97,98,100-102,104,106-108]. Small cysts (typically BD-IPMNs) are the most common abnormality detected on screening for PC [83]. Some tiny cystic lesions that do not communicate with the pancreatic duct are PanIN lesions [83,95].

The benefits of screening include early detection of invasive pancreatic ductal adenocarcinomas, at a time when they are asymptomatic and more likely to be amenable to potentially curative resection, and identification of high-risk preinvasive neoplasms, such as MD-IPMNs and PanIN-3 [104]. Screening for PC in high-risk individuals may also be cost effective [109-111]. In one cohort study of 79 high-risk Leiden *p16* (*CDKN2A*) mutation carriers who were screened using MRI/MRCP, the number needed to be screen to detect and treat one PC was 11 [97].

There are no randomized trials of screening versus no screening in high-risk populations. The possible benefits of screening have been demonstrated in retrospective and prospective cohort studies:

- At least two of the reports are derived from the prospective multicenter CAPS study program:

  - In a single institution cohort study of 354 individuals at high risk for PC who underwent baseline EUS to rule out incident pancreatic cancer followed by periodic surveillance with EUS, MRI, and/or CT, pancreatic lesions with worrisome features or rapid cyst growth were detected in 68 patients (19 percent) [112]. The majority were benign. Overall, 24 (7 percent) had neoplastic progression over a 16-year period (14 ductal adenocarcinomas and 10 high-grade dysplasia BD-IPMN or PanIN-3 lesions), and the rate of neoplastic progression was 1.6 percent per year. Risk factors for neoplastic progression included age >60 years, presence of ≥3 cysts, and/or a mildly dilated main duct at baseline. (See 'Outcomes of surgery' below.)

  - The multicenter CAPS-5 study enrolled 1461 high-risk individuals, of whom 49 percent had a pathogenic variant in a pancreatic cancer susceptibility gene (the remainder were high-risk because of familial pancreatic cancer without a known pathogenic variant) [113]. The surveillance protocol consisted of annual EUS or MRI/MRCP, often alternating between methods. Over the course of seven years of surveillance, ten pancreatic ductal adenocarcinomas were identified (one in every 160 person-years) and there were three additional cases of high-grade dysplasia (PanIN-3). Of the ten pancreatic cancers, one was metastatic at diagnosis (and diagnosed four years after the individual dropped out of surveillance), seven were stage I at diagnosis, and two were stage II or III.

    In a further analysis of the entire CAPS cohort (CAPS1-5, enrolling from 1998 to 2021, and totaling 1731 patients), there were 26 cases of invasive pancreatic cancer diagnosed over a 20+-year period, corresponding to a detection rate of 5/15 pancreatic cancers diagnosed per 1000 person-years of surveillance [one individual diagnosed with pancreatic cancer per year for every 194 screened). Of the 19 cases diagnosed during surveillance, 58 percent were stage I and 5 percent stage IV. Five-year survival for those with cancer detected by surveillance was 73 percent, and the median overall survival was 9.8 years. By contrast, six of the seven pancreatic cancers diagnosed outside surveillance were stage IV at diagnosis, and median survival was 1.5 years (HR for death 0.13, 95% CI 0.03-0.5).

- Additional information is available from a systematic review of 16 published PC screening studies, which showed that PC screening (as compared with no screening) resulted in a higher curative resection rate (60 versus 25 percent, p = 0.011), and longer median survival time (14.5 versus 4 months, p <0.001) [108]. Furthermore, in patients who underwent regular physical examinations, more stage I pancreatic cancers were observed (19 versus 2.6 percent, p = 0.001) suggesting a stage shift towards earlier disease.

- The fraction of screened patients who have potentially resectable early-stage tumors has been lower in other series. As an example, in a report from the Dutch Familial Pancreatic Cancer Surveillance Study Group, only 60 percent of the identified pancreatic cancers were potentially resectable, and surveillance did not translate into improved long-term outcomes [70]. This has been potentially attributed to a predominance of *CDKN2A* carriers (70 percent in this series), as they tend to have more aggressive disease that might benefit from more frequent surveillance.

  This issue was addressed in a larger cohort study of 347 carriers of a pathogenic variant in *CDKN2A* who participated in a longitudinal surveillance protocol, and were followed for a median of 5.8 years [55]. The surveillance protocol consisted of MRI/MRCP every 12 months, but since 2012, participants were also able to receive an optional EUS every 12 months, alternating with MRI/MRCP (thus, screening every six months). A total of 36 cases of pancreatic cancer were diagnosed in 31 individuals, and the cumulative incidence to age 70 in this cohort was 20.7 percent. Thirty of the 36 cancers (83 percent) were considered resectable at diagnosis, 12 of which were stage I tumors. The stage shift towards earlier stage disease with decreasing the screening interval from every 12 to every 6 months is remarkable. Median survival after diagnosis of primary pancreatic cancer was 26.8 months

Potential harms of screening include procedure-associated complications, particularly for invasive procedures like EUS. Screening can also cause harm by overdiagnosis, resulting in treatment of nonneoplastic or low-grade neoplastic lesions (serous cystadenomas, low-grade PanIN associated with lobulocentric parenchymal atrophy) [5,94,95,100,101]. In patients with hereditary pancreatitis, the "background noise" from severe chronic pancreatitis makes PC screening particularly challenging [105]. False-positive cytology from subcentimeter solid indeterminate lesions may also lead to unnecessary surgery and anxiety [95,97]. (See 'Management and follow-up of identified lesions' below.)

Outcomes of surgery for screen-detected lesions are discussed below. (See 'Outcomes of surgery' below.)

Is there a role for prophylactic surgery? — Prophylactic surgery is not recommended for asymptomatic individuals without an identifiable lesion, given the short term risks of pancreatectomy and the metabolic consequences, including permanent exocrine insufficiency and diabetes, which have a detrimental impact on long-term survival.

Evaluation of new-onset diabetes in patients undergoing screening — Routinely screening for new-onset diabetes in high-risk patients is controversial, but routine monitoring of blood glucose (fasting blood glucose and/or hemoglobin A1C) can be considered at baseline and with continued surveillance [6]. (See 'Blood tests' below.)

As new onset of diabetes may be indicative of an underlying pancreatic neoplasm in a high-risk individual, we perform urgent imaging (within two weeks) with EUS/MRCP/pancreatic protocol CT scan in such patients to evaluate the pancreas [6,79]. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Specific tests used in the initial evaluation'.)

SCREENING MODALITIES

There is no consensus as to the best imaging method for screening high-risk individuals, and there are few prospective data comparing outcomes from different screening strategies. However, endoscopic ultrasound (EUS) and/or magnetic resonance-based imaging appear to have the highest yield and do not involve ionizing radiation [6,79]. There is insufficient evidence to support the use of biomarkers for screening for PC.

Imaging — Several imaging modalities have been evaluated for screening for PC in high-risk individuals.

Endoscopic ultrasound — EUS is one of the most sensitive and specific imaging tests for the pancreas. It allows detection, staging, and tissue sampling of pancreatic neoplasms, including minute lesions. (See "Endoscopic ultrasound in the staging of exocrine pancreatic cancer", section on 'Accuracy of EUS' and "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Sonographic findings'.)

Furthermore, unlike CT, EUS involves high frequency ultrasound and not ionizing radiation. It typically does not require contrast injection. EUS imaging can also be coupled with collection of pancreatic secretions and/or pancreatic neoplastic tissue (during fine needle aspiration/biopsy) for biomarker analysis. The disadvantage of EUS as a screening modality is that is typically requires sedation and is associated with variability in interpretation of pancreatic abnormalities, even among experts [114].

Magnetic resonance imaging and magnetic resonance cholangiopancreatography — MRI provides complete abdominal imaging of the abdomen and pelvis, unlike EUS. In addition, MRI can detect extra-pancreatic neoplasms, which is a benefit for high-risk individuals. Magnetic resonance cholangiopancreatography (MRCP) images the fluid-filled pancreatic duct and branches, along with cystic pancreatic lesions and duct communication. Secretin has been injected during MRCP (off-label use in the United States) to improve pancreatic duct imaging and detection of ductal abnormalities [115,116].

The main disadvantages of MRI include the inability to image individuals with implanted metal (such as pacemakers, defibrillators, certain artificial joints and valves) and claustrophobia. (See "Principles of magnetic resonance imaging".)

Computed tomography — CT is a rapid, high-resolution imaging method for visualizing the pancreas, including all abdominal and pelvic organs. It typically requires only two breath-holds for complete imaging and has a more open scanner, unlike MRI, which takes approximately 45 minutes and has a more enclosed gantry. It is a widely available imaging test, relative to MRI and EUS. The disadvantage of CT is that it involves ionizing radiation (a particular concern in high-risk individuals) and side effect of intravenous contrast injection. Furthermore, CT has a relatively low detection rate for small lesions in the high-risk population [83,95,98,106]. (See 'Comparative efficacy' below and "Diagnosis and treatment of an acute reaction to a radiologic contrast agent".)

Endoscopic retrograde cholangiopancreatography — Endoscopic retrograde cholangiopancreatography (ERCP) is not recommended for routine screening and surveillance due to the risk of post-ERCP pancreatitis [6]. Studies examining the benefit of ERCP for screening high-risk individuals are conflicting. In one prospective study of 14 individuals from three familial pancreatic cancer (FPC) families, ERCP identified mild and focal side-branch-duct irregularities, and ectasia and main-duct strictures in all seven patients with an abnormal EUS [106]. All patients with an abnormal ERCP were found to have low-grade dysplasia at pancreatectomy. However, another prospective screening study of 78 individuals at high risk for PC showed that when ERCP was performed routinely for abnormal EUS, it provided no additional clinically relevant information and was associated with a 7 percent rate of pancreatitis [94]. (See "Post-endoscopic retrograde cholangiopancreatography (ERCP) pancreatitis".)

Transabdominal ultrasound — Transabdominal ultrasound is not a recommended for pancreas screening and surveillance in a high-risk population due to the relatively low sensitivity for small pancreatic lesions [6].

Comparative efficacy — Several studies have evaluated the yield of imaging in detecting early PC and preinvasive lesions. However, comparison of the diagnostic yield and accuracy of screening tests is limited by the variability in the study populations, type of screening modalities, and imaging protocols. However, these data suggest that EUS and MRI/MRCP both have limitations based on the underlying lesion but detect more lesions as compared with CT scan:

- In a comparative study of EUS, secretin-enhanced MRI/MRCP, and CT in 225 asymptomatic high-risk individuals (the CAPS3 study), in the 216 screened individuals, EUS and MRI detected significantly more (mostly small cystic) pancreatic lesions as compared with CT (43, 33, and 11 percent, respectively) [83]. For cystic lesions, MRCP provided the best visualization of cyst communication with the main pancreatic duct.

- In another prospective study, 139 high-risk individuals underwent EUS and MRI for initial screening for PC [84]. Clinically relevant lesions were defined as any solid lesion, cysts ≥3 cm, or cysts with thickened/enhancing cyst walls and/or mural nodules and/or a solid component, main-duct intraductal papillary mucinous neoplasms (IPMNs) with main pancreatic duct ≥10 mm, and side-branch IPMNs with side-duct dilations/cysts >10 mm. A total of 11 clinically relevant lesions were detected by either EUS or MRI in nine high-risk individuals (6 percent). Six of the 11 were detected by both modalities; two additional lesions were apparent on EUS only (the only two solid lesions that were found on initial screening), and three additional lesions (all three cysts ≥10 mm) were found by MRI only. EUS and MRI detected clinically relevant pancreatic lesions in 6 percent. These results suggest that both imaging techniques were complementary rather than interchangeable, but that MRI might have important limitations for timely detection of small solid lesions.

- In a Dutch study of 366 individuals with mutation-negative FPC or pancreatic cancer susceptibility gene mutation carriers who were screened annually with EUS and MRI/MRCP, EUS was more sensitive at detecting solid lesions (100 versus 22 percent), while MRI/MRCP was superior to EUS at detecting cystic lesions overall (83 versus 42 percent) but less so in the subgroups of cysts larger than 1 cm (92 versus 70 percent) [70]. EUS and MRI/MRCP were equally sensitive in detecting indeterminate lesions and dilated main pancreatic ducts. For most pancreatic abnormalities (except for solid lesions), combining EUS and MRI/MRCP at the same visit resulted in a higher sensitivity than either of the two tests alone. However, surveillance imaging did not lead to early recognition or treatment of resectable pancreatic lesions.

Biomarkers — Several biomarkers are being evaluated in order to improve early diagnosis of high-grade neoplasms not detectable by imaging and to aid the appropriate selection of high-

risk individuals for surveillance versus surgery [117].

Blood tests — The most useful serum tumor marker for PC is carbohydrate antigen 19-9 (CA 19-9). (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Role of tumor markers'.)

There are limited data on the performance characteristics of CA 19-9 in patients at high-risk of PC. In one study of targeted screening of individuals with at least one affected relative with PC, serum CA 19-9 was elevated in 27 of 546 (4.9 percent). Neoplastic or malignant findings were detected on subsequent EUS in only five patients (0.9 percent), and only one was a pancreatic adenocarcinoma (0.2 percent) [109]. Despite the limited data on the clinical utility of CA 19-9 in high-risk individuals, current international consensus guidelines recommend adding this test if there is concern for PC when there are worrisome features on abdominal imaging [6].

Aberrant expression of microRNAs (MiRNAs; short noncoding segments of RNA that regulate gene expression) are potential diagnostic markers for several solid tumors, including PC [118-121]. Assays for multiple microRNAs performed in combination with CA 19-9 may improve diagnostic accuracy [122]. However, additional studies are needed in high-risk cohorts.

Studies examining combinations of tumor-specific circulating proteins (including CA 19-9) plus metabolites, as well as circulating proteins plus mutations in cell-free DNA in the blood show promise for early detection of potentially resectable PC, but additional studies are needed in high-risk cohorts, especially those with underlying pancreatitis. (See "Clinical manifestations, diagnosis, and staging of exocrine pancreatic cancer", section on 'Other markers'.)

Routine monitoring of blood glucose (fasting blood glucose and/or hemoglobin A1C) can be considered at baseline and with continued surveillance because abnormal testing should prompt further evaluation [6]. (See 'Evaluation of new-onset diabetes in patients undergoing screening' above.)

Pancreatic juice and pancreatic cyst fluid — Pancreatic juice collected at the time of ERCP and cyst fluid obtained via an EUS-guided fine needle aspiration can be analyzed for molecular markers. Next generation sequencing can be performed at low cost to detect low frequency mutations in pancreatic juice and pancreatic cyst fluid [123]. Although data are scarce, the genetic alterations (aberrant methylation, mutant oncogene Kras2, inactivated tumor suppressor genes SMAD4 and p53) in FPC appear to be similar to those detected in sporadic PC [124]. Potential markers include mutant *GNAS* (specific for IPMNs), mutant *KRAS*, and mutant TP53 [88,124,125]. In one prospective study of FPC relatives and controls, mutant *TP53* DNA was present in pancreatic juice in 29 of 43 patients with pancreatic ductal adenocarcinoma and four of eight patients with high-grade dysplasia lesions (high-grade

pancreatic intraepithelial neoplasia [PanIN-3] and high-grade IPMN), but not in any samples from normal or benign disease controls and screened individuals without advanced lesions [125]. Further studies are needed to validate these results. (See "Molecular pathogenesis of exocrine pancreatic cancer", section on 'Molecular screening and early detection'.)

MANAGEMENT AND FOLLOW-UP OF IDENTIFIED LESIONS

Pancreatic lesions will be detected in up to 42 percent of high-risk individuals (predominantly relatives of kindreds with familial pancreatic cancer [FPC]) [83]. Most of these are managed conservatively and do not need surgery. However, the consensus regarding surgical indications for lesions detected by screening is evolving [6]. The few published reports are based on limited numbers of patients [126,127]. For management of pancreatic lesions that are detected on imaging, individualized decision making for surveillance and treatment within multidisciplinary programs is recommended. However, when pancreatic surgery is necessary, it is best performed at a high-volume specialty center [128,129]. (See 'Referral for genetic evaluation' above.)

Type of lesion

Solid pancreatic lesions — Fewer than 2 percent of pancreatic lesions detected at baseline screening are solid [83]. In individuals with a solid pancreatic lesion on endoscopic ultrasound (EUS) and/or MRI, we perform triple-phase, helical multidetector row (pancreatic protocol) CT [6].

Some indeterminate solid lesions identified only by EUS are cancers, but they can be benign lesions, such as non-metastatic pancreatic neuroendocrine tumors or low-grade pancreatic intraepithelial neoplasia (PanIN) with focal associated lobulocentric parenchymal atrophy [83,94,95,98]. The decision to perform EUS fine-needle aspiration (FNA) on solid lesions should be individualized. If the pancreatic lesion can be safely aspirated, and the cytological results might impact patient management, we would perform EUS-FNA. The impact is potentially greater for right sided pancreatic lesions requiring Whipple surgery, versus left sided tail lesions that could be readily excised, including minimally invasive approaches. It should be noted that false positive cytological results can lead to unnecessary surgery [95].

Surgical resection has been recommended for a solid pancreatic lesion ≥5 mm of indeterminate pathology or if additional evaluation does not yield a definitive preoperative diagnosis [6]. However, in patients with a new indeterminate solid lesion of this size that is detected on only one imaging modality, in whom initial EUS-FNA is negative, and in whom surgery is not planned,

follow-up imaging (EUS and pancreatic protocol CT testing) at three months is a reasonable choice.

Unambiguous solid lesions (≥1 cm or seen on multiple imaging modalities) are more ominous, and the threshold for resection is much lower, as subcentimeter solid pancreatic lesions can be clinically significant [130].

Invasive pancreatic cancer — All suspected invasive PCs should be resected. However, the surgical approach to high-risk individuals undergoing resection for suspected cancer is controversial. Most experts do not recommend total pancreatectomy unless necessary to achieve a completely negative (R0) resection margin [6]. There is controversy as to what to do if there is PanIN at the surgical margin. Most experts would not pursue additional surgery in this setting [131], but if high-grade PanIN (PanIN-3) is identified at the margin, follow-up imaging is recommended within six months of surgery and indefinitely because of the risk for new or metachronous pancreatic neoplasms [6].

Cystic pancreatic lesions — Approximately one-third of individuals have one or more cysts at baseline screening [83]. The prevalence increases by age, with cystic lesions detected in 14 percent of subjects younger than 50 years old, 34 percent of subjects 50 to 59 years old, and 53 percent of subjects 60 to 69 years old [83]. The majority of cystic lesions detected by screening appear to be low-risk branch-duct intraductal papillary mucinous neoplasms (IPMNs). The majority of such branch-duct IPMNs (BD-IPMNs) remain stable during surveillance [5,97,98,100,101]. (See "Intraductal papillary mucinous neoplasm of the pancreas (IPMN): Evaluation and management", section on 'Branch-duct IPMN'.)

The optimal approach to evaluating pancreatic cysts is unclear. Our approach is more conservative as compared with guidelines for sporadic pancreatic cysts, and we do not routinely perform EUS-FNA [6,130,132-134]. This is because benign IPMNs may be a marker of a generalized field effect in genetically predisposed individuals as both PanIN-3 lesions and high-grade dysplasia and/or main-duct involvement have been found in patients who did not meet Sendai/American Gastroenterological Association (AGA) criteria for surgical resection [5,6,83,94,95,103,132,133]. EUS-FNA in the clinical management of most pancreatic cysts is limited, given the low accuracy of cytology in cystic lesions and the low volume of cyst fluid aspirated from small cysts (which comprise the majority of detected lesions in high-risk individuals) [135,136]. (See "Pancreatic cystic neoplasms: Clinical manifestations, diagnosis, and management", section on 'EUS-FNA findings associated with specific cysts'.)

However, when a suspected BD-IPMN develops worrisome features, when there is a solid lesion ≥5 mm, or when there is an asymptomatic main pancreatic duct stricture (with or without a

mass), EUS-FNA should be performed [6].

The risk of neoplastic progression was assessed in a large high-risk cohort after baseline screening (median follow-up time 5.6 years), and 19 percent of individuals developed pancreatic lesions with worrisome features (solid mass, multiple cysts, cyst size >3 cm, thickened/enhancing walls, mural nodule, dilated main pancreatic duct >5 mm, or abrupt change in duct caliber) or rapid cyst growth (>4 mm/year) [112]. The cumulative incidence of PC or high-grade dysplasia was 7 percent (14 pancreatic ductal adenocarcinomas and 10 high-grade IPMNs or PanINs).

Main pancreatic duct strictures/dilation without an associated lesion — If an indeterminate main pancreatic duct stricture without a mass is detected, repeat imaging should be performed within three months to potentially detect occult neoplasia not visible by EUS, CT, and MRI. Endoscopic retrograde cholangiopancreatography (ERCP) should be avoided as a diagnostic modality for main pancreatic duct strictures because of the associated risk for pancreatitis [6,94].

Recommendations for surgical resection — Surgical resection is indicated in patients with any of the following:

- Solid pancreatic lesion ≥5 mm of indeterminate pathology or if additional evaluation does not yield a definitive preoperative diagnosis.
- Any positive or highly suspicious FNA result, except for a pancreatic neuroendocrine tumor.
- Main-duct IPMNs with any one of the following:
  - Main pancreatic duct dilation of ≥10 mm [6]
  - Main pancreatic duct stricture [6]
  - Mural nodules
- BD-IPMNs with any one of the following:
  - Rapid growth (ie, >5 mm over six months)
  - Mural nodules or an enhancing solid component [6]
  - Abrupt main pancreatic duct caliber change with distal atrophy (even if no mass is visible) [6]
  - Main pancreatic duct dilation of ≥10 mm
  - Positive cytology [6]
  - Associated symptoms of pancreatitis, jaundice, or pancreatic-type pain [6]

- Asymptomatic main pancreatic duct stricture with an associated suspicious mass.

Surveillance for patients without a surgical indication — For patients who do not meet these criteria for surgery, repeat imaging in three months if worrisome features are present [79,133]. Worrisome features include the following:

- Solid lesion with main pancreatic duct size of 5 to 9 mm in diameter
- Main pancreatic duct stricture and/or dilation ≥6 mm of unknown etiology without an associated mass [6]
- Solid lesion <5 mm of uncertain significance [6]

Repeat imaging in six months is recommended for patients who have the following imaging abnormalities [6]:

- Cystic lesion (presumed BD-IPMN) ≥3 cm in size
- Cystic lesion with associated main pancreatic duct 5 to 9 mm
- Cystic lesion associated with lymphadenopathy
- Cyst growth rate of ≥5 mm in two years
- Increased serum carbohydrate antigen 19-9 (CA 19-9)

Individuals without worrisome features of malignancy should undergo repeat imaging in 12 months.

Screening/surveillance should be continued until the patient is no longer a surgical candidate.

The extent of surgery (partial versus total pancreatectomy) is driven by the extent of disease (multifocality of lesions, location of dominant lesion) and the patient's life expectancy and overall health, considered with the risks and benefits of the type of surgery [79]. Multidisciplinary, individualized decision making is highly recommended [46].

Pancreatic neuroendocrine tumors — Well-differentiated pancreatic neuroendocrine tumors have been detected within FPC screening programs [70,83,94,98]. Pancreatic neuroendocrine tumors <0.5 cm (microadenomas) are essentially benign lesions. Most surgically resected pancreatic neuroendocrine tumors between 0.5 and 1 cm are cured with resection [137]. Further surveillance is not indicated. (See "Surgical resection of sporadic pancreatic neuroendocrine tumors".)

Outcomes of surgery — The clinical outcomes of 48 of 354 high-risk individuals after pancreatic resection of screen-detected neoplasms (22 solid masses, 25 cysts, 1 pancreatic duct stricture) have been reported [138]. The majority had partial pancreatectomy, and metachronous PCs developed in the remnant pancreas of two patients with prior surgery for

benign precursor lesions. The median length of stay was seven days, and the postoperative complication rate was 35 percent, comparable to that for standard indications. There was no perioperative mortality. Importantly, 9 of the 10 screen-detected PCs were resectable, with a three-year survival of 85 percent, compared with 25 percent in cancers detected outside surveillance. With continued follow-up of the patients with resectable pancreatic ductal adenocarcinoma, the five-year overall survival rate was 60 percent.

SOCIETY GUIDELINE LINKS

Links to society and government-sponsored guidelines from selected countries and regions around the world are provided separately. (See "Society guideline links: Pancreatic cancer".)

SUMMARY AND RECOMMENDATIONS

- **Epidemiology and risk factors** – An estimated 10 to 15 percent of pancreatic cancers (PCs) are attributable to genetic causes, of which there are two broad categories:
  - A small but clinically important proportion of PCs are associated with mutations in known predisposition genes, even in patients who have apparently sporadic tumors. (See 'Genetic predisposition syndromes' above.)
  - Familial pancreatic cancer (FPC) is defined as a family with a pair of affected first-degree relatives (FDRs; parent-child or sibling pair) who do not meet criteria for a known PC-associated genetic predisposition syndrome. (See 'Epidemiology and risk factors' above.)
- **Screening high-risk populations**
  - **Rationale** – Screening for PC aims to identify early invasive PCs and preinvasive lesions (intraductal papillary mucinous neoplasms [IPMNs] and pancreatic intraepithelial neoplasia) with high-grade neoplastic changes. (See 'Screening targets' above and 'Diagnostic yield, benefits, and harms' above.)
  - **Targets for screening** – We screen the following individuals for PC (see 'Candidates for screening' above):
    - Patients with Peutz-Jeghers syndrome (PJS), regardless of family history

- Patients with cyclin-dependent kinase inhibitor 2A pathogenic variants (*CDKN2A*; *p16*), regardless of family history
- Hereditary pancreatitis with a *PRSS1* pathogenic variant, regardless of family history
- Breast cancer associated (*BRCA*) 2 pathogenic variants with at least one affected FDR or at least two affected relatives of any degree
- *BRCA1*, partner and localizer of *BRCA2* (*PALB2*) pathogenic variants, ataxia-telangiectasia (*ATM*), and Lynch syndrome mutation carriers with one or more affected FDRs
- Regardless of gene mutation status, any individual belonging to a kindred with at least two affected FDRs.

- **Age to start screening**:
  - For individuals from a familial PC kindred without a known germline pathogenic variant, we begin screening at age 50 to 55, or 10 years younger than the youngest PC in the family.
  - For pathogenic variant carriers with modestly increased ris*k (BRCA2*, *ATM*, *PALB2*), we also recommend beginning at age 45 or 50.
  - For patients with a higher risk of developing PC (eg, in those with *CDKN21A* pathogenic variants, PJS, and hereditary pancreatitis), we begin screening at age 40.

- **What tests are appropriate?**
  - We suggest checking serum carbohydrate antigen 19-9 (CA 19-9) if there are worrisome findings on pancreatic imaging. Assay of fasting blood glucose and/or hemoglobin A1C may be warranted in new-onset diabetes. (See 'Blood tests' above.)
  - As new onset of diabetes may be indicative of an underlying pancreatic neoplasm in a high-risk individual, we perform urgent imaging (within two weeks) with endoscopic ultrasound (EUS)/magnetic resonance cholangiopancreatography (MRCP) or pancreatic protocol CT scan. (See 'Evaluation of new-onset diabetes in patients undergoing screening' above.)

- For most patients with a normal pancreas on initial imaging, we repeat pancreatic imaging yearly, alternating between EUS and MRI/MRCP. A shorter screening interval is appropriate for very high-risk individuals such as *CDKN2A* germline mutation carriers and individuals with Peutz-Jeghers syndrome. (See 'Screening modality and timing' above.)

- We do not perform prophylactic surgery in asymptomatic individuals without an identifiable lesion, given the short-term risks of pancreatectomy and the metabolic consequences. (See 'Is there a role for prophylactic surgery?' above.)

- **Management of identified lesions**

  - Individualized decision making for surveillance and treatment of detected lesions within multidisciplinary programs is recommended. (See 'Management and follow-up of identified lesions' above.)

  - The choice of surgery or continued pancreatic surveillance at specific intervals is influenced by the size and type of lesion (solid versus cystic), the growth rate, and concerning features (table 2). EUS fine-needle aspiration (FNA) should be performed only for solid lesions ≥5 mm, cystic lesions with worrisome features, and asymptomatic main pancreatic duct strictures (with or without a mass).

    The optimal approach to evaluating pancreatic cysts is not established. We do not routinely perform EUS-FNA unless a suspected branch-duct IPMN (BD-IPMN) develops worrisome features, when there is a solid lesion ≥5 mm, or when there is an asymptomatic main pancreatic duct stricture (with or without a mass). (See 'Type of lesion' above.)

    Surgical resection is indicated in patients with any of the following:

    - Any positive FNA result, except for a pancreatic neuroendocrine tumor.

    - Main-duct IPMNs with main pancreatic duct dilation ≥10 mm; a main pancreatic duct stricture; or mural nodules. (See 'Cystic pancreatic lesions' above.)

    - BD-IPMNs with rapid growth (ie, >5 mm over six months), mural nodules or an enhancing solid component, abrupt main pancreatic duct caliber change with distal atrophy (even if no mass is visible), main pancreatic duct dilation of ≥10 mm, positive cytology, or associated symptoms of pancreatitis, jaundice, or pancreatic-type pain.

- Asymptomatic main pancreatic duct stricture or dilation with an associated suspicious mass. (See 'Main pancreatic duct strictures/dilation without an associated lesion' above.)

- Resection has been recommended for a solid pancreatic lesion ≥5 mm of indeterminate pathology or if additional evaluation does not yield a definitive preoperative diagnosis. However, in patients with a new indeterminate solid lesion of this size that is detected on only one imaging modality, with negative initial EUS-FNA, follow-up imaging at three months is reasonable.

  Unambiguous solid lesions (≥1 cm or seen on multiple imaging modalities) are more ominous, and the threshold for resection is much lower, as subcentimeter solid pancreatic lesions can be clinically significant. (See 'Solid pancreatic lesions' above.)

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Topic 83943 Version 36.0

GRAPHICS

Inherited cancer syndromes associated with increased risk of pancreatic cancer

Syndrome	Gene(s)	Estimated cumulative lifetime risk of pancreatic cancer (%)	Gene locus
Hereditary breast/ovarian cancer	*BRCA2*, *BRCA1*	≤5 (*BRCA1*); 5 to 10 (*BRCA2*)	13q
	PALB2	2 to 10	16p
Familial atypical multiple mole melanoma syndrome	*CDKN2A*	10 to 21	9p
Peutz-Jeghers syndrome	*STK 11*	11 to 36	19p
Hereditary nonpolyposis colon cancer (Lynch syndrome)	DNA mismatch repair genes	<5 to 10 (highest [6.2%] for *MLH1*; lowest [0.5] for *MSH2*)	2p, 3p, 7p
Hereditary pancreatitis	*PRSS1*, *SPINK1*	25 to 44	7q, 5q
Ataxia telangiectasia	*ATM*	6 to 10	11q
Li-Fraumeni syndrome	*P53*	5 to 10	17p
Familial adenomatous polyposis	*APC*	Unknown	5q

Graphic 61283 Version 5.0

International Cancer of the Pancreas Screening (CAPS) Consortium consensus on screening for pancreatic cancer in patients with increased risk for familial pancreatic cancer

Who?
▪ All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1*/*STK11* gene mutation)
▪ All carriers of a germline *CDKN2A* mutation
▪ Carriers of a germline *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, or *MSH6* gene mutation with at least 1 affected first-degree blood relative
▪ Individuals who have at least 1 first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)
When (at what age)?
▪ Age to initiate surveillance depends on an individual's gene mutation status and family history
• Familial pancreatic cancer kindred (without a known germline mutation): ◦ Start at age 50 or 55*, or 10 years younger than the youngest affected blood relative
• Mutation carriers: ◦ For *CDKN2A*¶ and Peutz-Jeghers syndrome, start at age 40 ◦ For *BRCA2*, *ATM*, *PALB2*, *BRCA1*, and *MLH1*/*MSH2*, start at age 45 or 50, or 10 years younger than the youngest affected blood relative
▪ There is no consensus on the age to end surveillance
How?
At baseline
▪ MRI/MRCP + EUS + fasting blood glucose and/or HbA1c
During follow-up
▪ Alternate MRI/MRCP and EUS (no consensus on if and how to alternate) ▪ Routinely test fasting blood glucose and/or HbA1c
On indication
▪ Serum CA 19-9: • If concerning features on imaging
▪ EUS-FNA only for: • Solid lesions of ≥5 mm • Cystic lesions with worrisome features • Asymptomatic MPD strictures (with or without mass)

▪ CT only for: • Solid lesions, regardless of size • Asymptomatic MPD strictures of unknown etiology (without mass)
Intervals and surgery
▪ 12 months: • If no abnormalities or only nonconcerning abnormalities (eg, pancreatic cysts without worrisome features)
▪ 3 or 6 months: • If concerning abnormalities for which immediate surgery is not indicated (refer to UpToDate text)
▪ Surgery: • If positive FNA and/or a high suspicion of malignancy on imaging (refer to UpToDate text) *When surgery is indicated, perform an oncologic radical resection at a specialty center*
Goals
▪ The goal of surveillance is to detect and treat the following pathologic lesions: • Stage I pancreatic cancer, confined to the pancreas, resected with negative margins • Pancreatic cancer precursor lesions with high-grade dysplasia (PanIN or IPMN)

LKB1: liver kinase B1; *STK11*: serine/threonine kinase 11; *CDKN2A*: cyclin-dependent kinase inhibitor 2A; *BRCA*: breast cancer associated; *PALB2*: partner and localizer of *BRCA2*; *ATM*: ataxia telangiectasia mutated; *MLH1*: mutL homolog 1; *MSH*: mutS homolog; MRI/MRCP: magnetic resonance imaging/magnetic retrograde cholangiopancreatography; EUS: endoscopic ultrasound; HbA1c: hemoglobin A1c; CA 19-9: carbohydrate antigen 19-9; FNA: fine-needle aspiration; MPD: main pancreatic duct; CT: computed tomography; PanIN: pancreatic intraepithelial neoplasia; IPMN: intraductal papillary mucinous neoplasm.

* Consensus as to when to start surveillance was not reached.

¶ Literature-based recommendation.

Graphic 107902 Version 3.0

Diagnostic yield of familial pancreatic cancer screening and surveillance

Study	High-risk group	Imaging tests	Diagnostic yield*
Brentnall 1999; n = 14	FPC	EUS + ERCP + CT	7/14 (50%)[¶]
Kimmey 2002; n = 46[Δ]	FPC	EUS; ERCP[◇]	12/46 (26%)[¶]
Canto 2004; n = 38	FPC, PJS	EUS; ERCP[◇], EUS-FNA[◇], CT[◇]	2/38 (5.3%)[¶]
Canto 2006; n = 78	FPC, PJS	EUS; CT[◇], EUS-FNA[◇], ERCP[◇]	8/78 (10.2%)[¶ §]
Poley 2009; n = 44	FPC, BRCA, PJS, CDKN2A, p53, hereditary pancreatitis	EUS; CT[◇], MRI[◇]	10/44 (23%)
Langer 2009; n = 76	FPC, BRCA	EUS + MRCP; EUS-FNA[◇]	1/76 (1.3%)[¶ §]
Verna 2010; n = 51	FPC, BRCA, CDKN2A	EUS and/or MRCP	6/51 (12%)[¶]
Ludwig 2011; n = 109	FPC, BRCA	MRCP; EUS[◇], EUS-FNA[◇]	9/109 (8.3%)[§]
Vasen 2011; n = 79	CDKN2A	MRI/MRCP	14/79 (18%)[¶]
Al-Sukhni 2011; n = 262	FPC, BRCA, PJS, CDKN2A, hereditary pancreatitis	MRI; CT[◇], EUS[◇], ERCP[◇]	19/262 (7.3%)[§]
Schneider 2011[¥]; n = 72	FPC, BRCA, PALB2	EUS+MRCP	11/72 (15%)[§]
Canto 2012; n = 216	FPC, BRCA, PJS	CT, MRI/MRCP, EUS; ERCP[◇]	5/216 (2.3%)[¶] – 92/216 (42%)
Harinck 2015; n = 139	FPC, BRCA, PJS, CDKN2A	MRI, EUS	11/139 (8%)[§]
Vasen 2016; n = 411	FPC, BRCA, PALB2, CDKN2A	MRI, MRCP, EUS	32/411 (7.8%)[¶ §]
Overbeek 2021; n = 366	FPC, CDKN2A, BRCA, PALB2, STK11/LKB1, TP53, ATM	EUS and MRI/MRCP	10/165 (6%) in mutation carriers; 0/201 in FPC kindreds[‡]

FPC: familial pancreatic cancer; EUS: endoscopic ultrasound; ERCP: endoscopic retrograde cholangiopancreatography; CT: computed tomography; PJS: Peutz-Jeghers syndrome; EUS-FNA: endoscopic ultrasound-guided fine needle aspiration; BRCA: breast-related cancer; CDKN2A: cyclin-dependent kinase inhibitor 2A; MRI: magnetic resonance imaging; MRCP: magnetic resonance cholangiopancreatography; IPMN: intraductal papillary mucinous neoplasms.

* Yield is defined as the detection of any pathologically proven (pre)malignant lesion (≥PanIN2/IPMN and pancreatic adenocarcinoma) and lesions that are morphologically suspicious for branch-duct IPMNs.

¶ Includes only pathologically proven pancreatic neoplasms (histology or cytology).

Δ Continuation of Brentnall 1999, included 14 high-risk individuals from Brentnall 1999.

◇ Test performed only as an additional test for detected abnormalities.

§ Includes baseline and follow-up.

¥ Continuation of Langer 2009, includes high-risk individuals from this series.

‡ None of the cases were FPC kindreds. Estimated cumulative incidence of pancreatic ductal adenocarcinoma in mutation carriers was 6.5% at 5 years and 9.3% at 10 years.

Graphic 107901 Version 2.0

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