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Screening for Pancreatic Cancer: A Systematic Evidence Review for the U.S. Preventive Services Task Force

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Structured Abstract

Objective: We conducted a systematic evidence review to support the U.S. Preventive Services Task Force (USPSTF) in updating their recommendation on screening for pancreatic cancer. Our review addresses the following Key Questions (KQs):

1. Does screening for pancreatic adenocarcinoma improve cancer morbidity or mortality or all-cause mortality; and 1a) Does screening effectiveness vary by clinically relevant subpopulations (e.g., by age group, family history of pancreatic cancer, personal history of new-onset diabetes, or other risk factors)?
2. What is the diagnostic accuracy of screening tests for pancreatic adenocarcinoma?
3. What are the harms of screening for pancreatic adenocarcinoma?
4. Does treatment of screen-detected or asymptomatic pancreatic adenocarcinoma improve cancer mortality, all-cause mortality, or quality of life?
5. What are the harms of treatment of screen-detected pancreatic adenocarcinoma?

Data Sources: We searched Cochrane Central Register of Controlled Trials, Medline, and PubMed, and reference lists of relevant systematic reviews. We searched for articles published from 2002 to October 3, 2017, and updated our search on April 27, 2018. We also searched ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP), for relevant ongoing studies.

Study Selection: We reviewed 19,596 abstracts and 824 articles against specified inclusion criteria. Eligible studies included those written in English and conducted in adults age 18 years or older with or without risk factors for pancreatic cancer. For key questions on screening, we included imaging-based screening protocols. For key questions on treatment, we included studies of adults with screen-detected or asymptomatic pancreatic adenocarcinoma.

Data Analysis: We conducted dual, independent critical appraisal of all provisionally included studies and abstracted study details and results from fair- and good-quality studies. Because of the limited number of studies and the population heterogeneity, we provided a narrative synthesis of results and used summary tables to allow for comparisons across studies. After confirming that the yield of different imaging modalities was similar across studies, we calculated a pooled diagnostic yield across studies and produced forest plots to illustrate the range of effects seen across studies. For harms of screening (KQ3) and harms of treatment (KQ5), we stratified results by procedural and psychosocial harms.

Results: We included 13 unique prospective cohort screening studies (24 articles) reporting results for 1,317 people. Studies were conducted in the U.S., Canada, and Europe, and all screening populations except one small comparison group were exclusively in persons at elevated familial or genetic risk for pancreatic cancer. No studies reported on the effect of screening for pancreatic adenocarcinoma on cancer morbidity, mortality, or all-cause mortality (KQ1); and no studies reported on the effectiveness of treatment for screen-detected pancreatic adenocarcinoma (KQ4).

Thirteen fair quality studies reported on the diagnostic accuracy of screening tests for pancreatic adenocarcinoma (KQ2). Across these studies, 18 cases of pancreatic adenocarcinoma were detected. Twelve of 18 cases (66.7%) were detected at stage I or II or classified as “resectable.” Pooled yield for all screening tests to detect pancreatic adenocarcinoma on initial screening in high-risk populations was 7.8 per 1000 (95% confidence interval, 3.6 to 14.7); and for total yield including both initial and repeat screening, it was 15.6 per 1000 (95% CI, 9.3 to 24.5).

Harms of screening for pancreatic adenocarcinoma

Procedural harms of screening were evaluated in eight screening studies (n=675); psychological harms were assessed in two studies (n=277). Details on the assessment of harms were variably reported. In two studies (n=277) in which 150 individuals received ERCP as a diagnostic followup test, 15 people (10%) reported acute pancreatitis, nine of which required hospitalization. No evidence of increased worry, distress, depression, or anxiety after screening was reported, compared to before screening.

Harms of treatment of screen-detected pancreatic adenocarcinoma

Of the 57 people who underwent surgery across all studies, six studies (n=32 people receiving surgery) assessed harms of treatment of screen-detected pancreatic adenocarcinoma (KQ5), with 7 harms detected in two studies. Methods of assessing harms were variably reported. Harms included one person experiencing stricture to the hepaticojejunal anastomosis at 11 months after surgery, one with unspecified post-operative complications, 2 with post-operative fistula and 3 cases of diabetes. In the two studies that systematically assessed harms in all surgical patients (n=12 people receiving surgery), no harms were reported.

Limitations: No randomized trials of screening were identified. The body of evidence includes observational screening studies with limited sample sizes and focused on populations with known familial risk, many with a substantial proportion of people with known genetic mutations. No studies included a clinical followup or unscreened comparison group, limiting assessment of diagnostic accuracy. Of those studies that reported harms of screening or treatment, limitations included inadequate description of the methods of assessing harms, including whether all participants were systematically assessed.

Conclusions: Imaging-based screening in groups at high familial risk can detect pancreatic adenocarcinoma with limited evidence of minimal harms. However, the clinical impact of screening is not well documented. There is insufficient evidence to assess benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma.

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Chapter 1. Introduction

Purpose

The United States Preventive Services Task Force (USPSTF) will use this report to update their 2004 recommendation against routine screening for pancreatic cancer.¹

Condition Background

Condition Definition

There are two types of pancreatic tumors: exocrine tumors, which develop from exocrine cells that form glands and ducts that make pancreatic enzymes to digest foods; and endocrine tumors, which develop from endocrine cells that produce hormones such as insulin.²

This report focuses on pancreatic ductal adenocarcinoma. Most pancreatic tumors (95%) are exocrine tumors with malignant histologies; 90 percent of these are ductal adenocarcinoma. Typically, pancreatic cancer is synonymous with pancreatic adenocarcinoma. Less than 5 percent of pancreatic tumors are endocrine tumors, also known as neuroendocrine tumors (NETs or PNETs) or islet cell tumors, which are not addressed in this review. Other exocrine tumors include solid-pseudopapillary neoplasm (<1%), acinar cell carcinoma (<1%), pancreatoblastoma (<1%), and serous cystadenocarcinoma, a benign lesion (<1%).

Prevalence and Burden

Pancreatic adenocarcinoma is the third most common cause of cancer death among men and women in the United States, and the 11th most common case of incident cancer.³ In 2018, an estimated 55,440 people will be diagnosed with pancreatic adenocarcinoma, with 44,330 deaths.⁴ Data from the Surveillance Epidemiology and End Results (SEER) registry show the incidence rates of pancreatic adenocarcinoma decreased by 19 percent among men and by 5 percent among women from 1977–2005, possibly due to decreased exposure to risk factors such as smoking.⁵ Between 2005 and 2014, incidence rates of pancreatic adenocarcinoma rose 0.5 percent each year, while death rates (10.9 per 100,000 people per year) over the same time period were stable.^{6,7} As treatment and screening advances improve for other cancers, pancreatic adenocarcinoma may be the leading cause of cancer mortality by 2030.⁸

SEER data show that men are more likely to be diagnosed with pancreatic adenocarcinoma than women (14.2 new cases in men per 100,000 people versus 11.1 new cases in women per 100,000 people).⁶ The highest incidence rates occur in African-American males (17.0 per 100,000 people) and the lowest incidence rates occur in American Indian/Alaskan Native females (8.3 per 100,000 people).^{6,9} Incidence increases sharply with increasing age (70.4 cases per 100,000 in people ages 65 and older) with a median age at diagnosis of 71 years.^{6,9}

According to the American Cancer Society, the overall 5-year survival rate for pancreatic adenocarcinoma is 8 percent;¹⁰ however, survival rates vary by subtype and stage at diagnosis. More than 80 percent of incident cases are detected at advanced stage when surgical intervention is not recommended and 5-year survival is 2 percent to 5 percent. Only 9 percent of cases are detected at stage I or II, when surgery is most likely to improve survival (**Table 1**). Eligibility for surgical resection improves prognosis but is typically an option only for early stage tumors. Additional factors such as positive resection margins, poor tumor differentiation, larger tumor size, lymph node involvement, and high levels of carbohydrate antigen 19-9 (CA 19-9) adversely impact prognosis.⁹

Natural History and Prognosis

Early- and Late-Stage Pancreatic Adenocarcinoma

The prognosis of pancreatic adenocarcinoma depends largely on stage at diagnosis and whether the tumor can be surgically resected. Typically, resectable tumors include those where the tumor has not grown large enough to invade any major blood vessels. People with resectable cancers are recommended for primary curative surgery if they have a performance status and comorbidity profile capable of withstanding major abdominal surgery.¹¹

According to the American Cancer Society, the average 5-year survival rate for patients with early stage disease is 32 percent,⁴ but this varies by whether people underwent surgery. Data from SEER and the National Cancer Database (NCDB) have shown that the median survival among people who underwent surgery ranged from 15 to 27 months.¹²⁻¹⁷ Among people who did not undergo surgery, median survival ranged from 3 to 8 months.¹²⁻¹⁷ All of these observational database studies may be limited by selection bias, where people who did not have surgery may have been sicker to begin with than people who did have surgery. Therefore, survival may not be directly comparable between people who do or do not undergo surgery for pancreatic cancer. One long-term SEER study estimated 10-year overall survival of 14,868 cases of invasive pancreatic adenocarcinoma (any stage) diagnosed between 1973-2009 and *not* treated with surgery at 1 percent.¹⁸

Survival among people with early stage disease also varies by patient age, tumor grade, extent of excision, and additional treatment received. A SEER study evaluated pancreatic adenocarcinoma survival stratified by AJCC stage and tumor grade.¹⁹ Among 8,082 people, all of whom had cancer-directed surgery, higher grade was an independent predictor of survival across all stages; low-grade stage I patients survived a median of 25 months compared with 17 months for high-grade stage I patients.¹⁹ A study of 19,031 people with stage I or II pancreatic adenocarcinoma from the NCDB, all of whom survived at least 90 days after surgical resection, showed that median survival was 17.6 months in the surgery-only group compared with 22.1 months in the group who underwent surgery plus adjuvant chemotherapy ($p < 0.001$).²⁰

Borderline resectable tumors may be treatable by surgery, but often are larger and close to major arteries, raising concerns that resection may be incomplete, thus leaving the patient with positive surgical margins or undetected microscopic metastases. These tumors may be recommended for

preoperative therapy, such as chemotherapy, and then restaged before surgical planning.¹¹ One study from the NCDB including 44,852 stage IIA-III patients diagnosed from 2004 to 2013 showed that 58 percent did not undergo surgical treatment.²¹ Median survival was 10.3 months for this group compared with 13.1 months for patients who did have surgery with negative surgical margins. Less than 7 percent of the total population received neoadjuvant therapy and median survival for this group was 23.2 months for those that had negative surgical margins, but these results may reflect selection bias.

People with locally advanced disease or metastatic disease generally are not recommended for curative surgery. A small proportion may still undergo palliative surgery; however, survival for these stages is poor overall regardless of treatment received. According to the American Cancer Society, the average 5-year survival rate for patients with regional disease is 12 percent.⁴ Half of all cases of pancreatic adenocarcinoma are diagnosed at a distant stage and the 5-year survival rate is 3 percent.⁴ A SEER study of 28,918 people with stage IV metastatic pancreatic adenocarcinoma showed that 1.6 percent underwent surgery, primarily people younger than 70 years, with smaller tumor sizes located in the head of the pancreas.²² The median survival times were 7 months for the group who underwent surgery and 2 months for the group who did not.

Potential Precursors to Pancreatic Adenocarcinoma

Diagnosing potential precursor lesions via screening is an active area of research because it has potential to reduce pancreatic cancer incidence; however, surgical treatment of these lesions also has the potential to increase harms. Precursor lesions to invasive pancreatic adenocarcinoma include pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasm (IPMN), and mucinous cystic neoplasm (MCN); these lesions are classified as low- or high-grade (high-grade also may be called carcinoma in situ).²³ Typically, high-grade precursor lesions are considered for surgical intervention while low-grade lesions are observed.²⁴ IPMN and MCN may co-occur with invasive carcinoma (2%–3% and 1% of all exocrine tumors, respectively).

Pancreatic intraepithelial neoplasia (PanIN) is a microscopic (<5mm) precursor lesion for pancreatic adenocarcinoma located in the pancreatic duct.^{23, 25, 26} PanIN lesions can exhibit papillary or flat growth with mucinous secretion.²³ They are classified into one of four groups (PanIN-1A, PanIN-1B, PanIN-2, and PanIN-3) reflecting progression of histologic grade toward invasive cancer. A recently proposed classification system suggested reclassifying as 2 groups: low-grade (all except PanIN-3) and high-grade (PanIN-3 only, also referred to as carcinoma in situ).²³ Two autopsy studies have shown carcinoma in situ may be found in a quarter of cases with pancreatic cancer (whether clinically known or detected on autopsy), but not in controls.^{27, 28}

PanIN lesions are difficult to detect on imaging due to their small size;^{26, 29} lesions are often detected post-operatively, so preoperative screening, treatment, and surveillance strategies are unclear.²⁶ One study of 152 people who had pancreatic surgery or biopsy for an indication other than pancreatic adenocarcinoma showed 82 (54%) had a PanIN lesion.³⁰ A study of 584 people who underwent pancreatic resection for diagnoses other than adenocarcinoma or IPMN at a U.S. cancer center showed that 153 (26%) resected lesions had PanIN histology.³¹ After a median

followup of 3 years in 134 of these individuals, only one person (with an initial PanIN-1B diagnosis) developed pancreatic adenocarcinoma. Long-term survival of people with PanIN lesions that do not progress to pancreatic adenocarcinoma is unknown.^{31, 32}

Intraductal papillary mucinous neoplasm (IPMN) is a larger (>10mm) precursor lesion for pancreatic adenocarcinoma characterized by papillary growth and mucinous secretion either in the side-branch pancreatic ducts or main pancreatic duct.^{23, 25, 26} A population-based study conducted in Olmsted County, Minnesota estimated the prevalence of IPMN as 26.0 cases per 100,000 persons (95% confidence interval, 14.5 to 37.4).³³ Side-branch IPMNs have a lower subsequent malignancy rate (estimated between 1 and 25%) compared with main duct IPMNs (estimated between 40 and 50%).³⁴⁻³⁸ IPMNs can be classified as having low-grade, intermediate-grade, or high-grade dysplasia (also referred to as carcinoma in situ); they may also be associated with an invasive carcinoma.²³ IPMN can be detected on imaging and may be preceded by symptoms similar to pancreatitis, including pain, diabetes, and weight loss; patients also may be asymptomatic.^{39, 40}

People with IPMN may be recommended for surgical treatment if they have additional high-risk features such as main duct involvement, cyst size ≥ 4 cm, rapid changes in size over time, or an invasive component.^{41, 42} People with IPMN without invasion may be recommended for regular imaging surveillance. One review suggested that 6 percent to 12 percent of asymptomatic, small, branch duct lesions enlarged or progressed to malignancy over an unspecified amount of time.³⁴ A surveillance study of 577 people with branch duct IPMN found that 4.3 percent developed pancreatic adenocarcinoma within 5 years of IPMN diagnosis.⁴³ An analysis of 136 people who underwent surgery for IPMN at a U.S. hospital between 1987–2003 found that 38 percent had IPMN associated with invasive carcinoma.⁴⁴ Five-year survival rates were 77 percent for noninvasive IPMNs and 43 percent for IPMNs with invasive carcinoma. Four out of nine deaths in the noninvasive group were due to adenocarcinoma whereas all 21 deaths in the invasive group were from adenocarcinoma.

Unresected IPMN lesions may regress over time, but the evidence on regression is limited.⁴⁵ One study showed that among 664 people with pancreatic cystic lesions (including IPMN), 15 (2.3%) decreased in size over a median follow-up of 33 months.³⁸ A systematic review and meta-analysis of studies in people with IPMN who were not surgically treated showed malignant progression to invasive disease occurred in 11.4% of patients over follow-up durations ranging from 25 to 70 months.⁴⁶ The IPMN-specific mortality rate (regardless of progression) was 23 per 1,000 person-years.

Mucinous cystic neoplasm (MCN) typically presents as a large (average 50mm or larger) solitary pancreatic cyst characterized by mucin-producing cells and a thick ovarian-like stroma with estrogen and progesterone receptors.^{35, 47-49} MCN lesions are rarer than IPMN, with one study showing that among 851 resected pancreatic cystic neoplasms from a single U.S. hospital over 33 years, 23 percent were diagnosed as MCN compared with 38 percent as IPMN.⁵⁰ Similar to IPMNs, MCNs are classified as low, intermediate-, or high-grade dysplasia (also referred to as carcinoma in situ) and up to one-third are associated with invasive carcinoma.^{23, 47, 48} MCN can be detected on imaging and can present with symptoms of abdominal pain, abdominal fullness, jaundice, and/or nausea; they also may be detected incidentally without symptoms.^{35, 47, 51}

Approximately 95 percent of MCN diagnoses occur in women.^{35, 47-49}

Surgical treatment is recommended for all MCN lesions. People with MCN often have better prognosis than people with IPMN due to less aggressive tumor biology.^{52, 53} In addition, 98 percent of MCN lesions occur in the tail of the pancreas (as opposed to the head) where distal pancreatectomy is less complex.⁴⁷⁻⁴⁹ The 5-year survival of MCN without associated invasive carcinoma is 100 percent, and additional surveillance following successful surgery is not recommended.^{35, 47} For people with MCN with an invasive component, the 5-year survival is lower, at around 60 percent.^{35, 47, 48} The proportion of MCN lesions that progress to pancreatic adenocarcinoma and timeframe for progression are unclear.³⁵

Risk Factors

Based on data from 2013-2015, approximately 1.6% of people in the general population will be diagnosed with pancreatic cancer during their lifetime.⁷ Germline mutations, older age, family history, diabetes, and tobacco use are well-established risk factors; comorbid conditions such as chronic pancreatitis and obesity also increase risk for pancreatic adenocarcinoma.⁵⁴⁻⁵⁷

Genetic and Hereditary Factors

Family History

Approximately 5-10 percent of cases of pancreatic adenocarcinoma are familial with no known genetic mutations.⁵⁵⁻⁵⁸ According to one meta-analysis and one pooled analysis, having a positive family history for pancreatic adenocarcinoma (defined as having at least one first-degree relative with pancreatic adenocarcinoma in most studies) is associated with a relative risk (RR) of 1.8.^{59, 60}

Known Genetic Mutations

An estimated 3-5 percent of cases of pancreatic adenocarcinoma have inherited genetic mutations.⁵⁸ Mutations in several genes are associated with the development of pancreatic adenocarcinoma, with risk ratios ranging from 3.5 for *BRCA2* to 132 for Peutz-Jeghers syndrome.^{55, 61}

- Peutz-Jeghers Syndrome, caused by a mutation in the *STK11/LKB1* gene
- *CDKN2A/p16* mutations
- *BRCA1* or *BRCA2* mutations
- Hereditary pancreatitis caused by *PRSS1* and/or *SPINK1* mutations; *CTFR* mutations
- Lynch syndrome, caused by *MLH1*, *MSH2*, *MSH6*, or *PMS2* germline mutations
- *ATM* mutations^{55, 56, 61, 62}

Ashkenazi Jewish Heritage

Ashkenazi Jewish individuals have an increased risk of pancreatic adenocarcinoma of with RRs

of approximately 1.4⁶³ to 1.8⁶⁴ compared with non-Jewish people. These risk estimates may be even higher for Jewish people with one of several genetic mutations (*BRCA1*, *BRCA2*, *MSH2*, or *MSH6*).⁶⁵⁻⁶⁷ Eldridge et al., noted that the increased risk for pancreatic adenocarcinoma in Jewish individuals was not explained by other non-genetic risk factors such as smoking, obesity, and diabetes, and may be predominantly due to genetics.⁶³ Individuals with *BRCA1*, *BRCA2*, or other high-risk genetic mutations may be recommended for pancreatic adenocarcinoma screening regardless of whether they are of Ashkenazi Jewish ancestry.

Hereditary Pancreatitis

Chronic pancreatitis may be hereditary if associated with one of several genetic mutations (*PRSS1*, *SPINK1*, and *CTFR*) and/or an incidence of disease within a family that is higher than one would expect by chance alone. Hereditary pancreatitis has been associated with RRs for pancreatic adenocarcinoma ranging from 50 to 80.⁵⁵ Despite the high increased risk of pancreatic adenocarcinoma associated with pancreatitis, patients with hereditary pancreatitis account for a very small fraction of all cases of pancreatic adenocarcinoma.

Other Risk Factors

Age

Most cases of pancreatic adenocarcinoma occur in people over age 55.⁷

Chronic Pancreatitis

A history of chronic pancreatitis (inflammation of the pancreas that impairs one's ability to digest food and produce hormones) has been associated with RRs for pancreatic adenocarcinoma ranging from 2.71 to 13.3.^{68,69} As opposed to acute pancreatitis, which often develops in response to pancreatic injury, chronic pancreatitis involves progressive inflammatory pancreas changes that can lead to permanent structural damage and impairment of exocrine and endocrine function.

Existing or New-Onset Diabetes

Diabetes has been studied the most and has been consistently associated with an increased risk of pancreatic adenocarcinoma across seven meta-analyses and seven pooled analyses.⁵⁶ A 2011 meta-analysis with 20,410 cases of pancreatic adenocarcinoma from 35 cohort studies found a summary RR of 1.94 (95% CI, 1.66 to 2.27) associated with diabetes mellitus.⁷⁰ Diabetes also appears to be associated with increased pancreatic adenocarcinoma mortality relative to people with pancreatic adenocarcinoma and no diabetes diagnosis.^{71,72}

New onset diabetes in adulthood may be an early manifestation of pancreatic adenocarcinoma.⁷³ ⁷⁴ In a U.S.-based case control study (510 cases, 463 controls), 15 percent of cases of pancreatic adenocarcinoma had developed new-onset diabetes less than 3 years before diagnosis compared to 3 percent of controls (Adjusted Odds Ratio 6.40; 95% CI, 3.37 to 12.2); a loss of more than 3 percent of body weight also was more common in cases versus controls (71% vs 7%, AOR 27.0;

95% CI, 17.1 to 42.6).⁷⁵ A larger, United Kingdom-based case-control study found similar results in primary care patients: new-onset diabetes less than 2 years before pancreatic adenocarcinoma diagnosis appeared in 13.6 percent of cases and 6 percent of controls (AOR 2.46, 95% CI, 2.16 to 2.80).⁷⁶

Tobacco Use

Smoking is the most well-established modifiable risk factor for pancreatic adenocarcinoma. A 2014 review and meta-analysis showed that the relative risk for pancreatic adenocarcinoma associated with any current cigarette use ranged from 1.5 to 2.2.⁵⁶ Relative risk estimates varied by dose in several studies,⁷⁷⁻⁷⁹ with one study showing an RR of 1.2 (95% CI, 1.2 to 1.3) among people who smoked 5 cigarettes per day to 2.0 (95% CI, 1.7 to 2.2) among people who smoked 40 cigarettes per day.⁷⁸ The association with history of tobacco use or smokeless tobacco use is less certain. Former cigarette use was associated with an increased risk of pancreatic adenocarcinoma in some studies but not all. Smokeless tobacco was associated with an RR for pancreatic adenocarcinoma of 1.6 (95% CI, 1.1 to 2.2) in one study,⁸⁰ but not in others.^{81, 82}

Obesity

According to several meta- and pooled-analyses, obesity, as measured by BMI ≥ 30 kg/m², has been associated with an increased RR for pancreatic adenocarcinoma ranging from 1.19 to 1.47.⁸³⁻⁸⁶ Several studies have shown a dose-response relationship between BMI and pancreatic adenocarcinoma risk, with the highest risk estimates for people in BMI categories above 35 kg/m².^{84, 85} A large cohort study demonstrated that obese patients undergoing bariatric surgery had a reduced risk of pancreatic cancer (hazard ratio 0.46, 95% CI, 0.22 to 0.97) compared to BMI- and comorbidity-matched people who did not undergo surgery.⁸⁷ Obesity also may be associated with increased risk of pancreatic adenocarcinoma mortality,⁸⁸ with a dose-response relationship associated with obesity in adulthood in one meta-analysis⁸⁹ and one pooled analysis of case-control studies.⁹⁰

Other Modifiable Risk Factors

Diet, alcohol, additional medical conditions, and certain types of medication may be associated with pancreatic adenocarcinoma risk.^{54, 56} Red meat, processed meat, and elevated sugar intake may be associated with a moderately increased risk (RR 1.1 to 1.4) of pancreatic adenocarcinoma.⁵⁶ Drinking more than 3 glasses of any alcoholic beverages per day may increase pancreatic adenocarcinoma risk by 20 percent.⁵⁶ A meta-analysis of 19 prospective cohort studies including data on more than 4 million people found that high (≥ 24 g per day)—but not low or moderate—alcohol consumption was associated with increased risk for pancreatic adenocarcinoma (RR 1.15; 95% CI, 1.06 to 1.25).⁹¹ Several meta-analyses showed *Helicobacter pylori* infection was associated with increased risk of pancreatic cancer with RRs ranging from 1.28 to 1.65.⁵⁶ The use of antidiabetic drugs other than metformin (e.g. insulin and sulfonylurea) may be associated with a moderate increased risk of pancreatic adenocarcinoma (RR 1.5 to 1.9), whereas metformin has been associated with a reduced risk (RR 0.5 to 0.9).⁵⁶ Statin use may reduce risk for pancreatic adenocarcinoma and reduce mortality.^{92, 93} Aspirin use was associated with reduced risk for pancreatic adenocarcinoma in one study.⁹⁴

Screening for Pancreatic Cancer

Currently, only a fraction of incident cases of pancreatic adenocarcinoma are detected at resectable (9%) or borderline resectable (10%) stages.⁷ Screening for pancreatic adenocarcinoma could detect more cancer at a stage where resection is possible, and improve survival through surgical resection. By this same reasoning, screening also could improve quality of life and limit harms associated with chemotherapy.

Imaging-Based Screening

Several imaging tests are used to detect pancreatic adenocarcinoma, including endoscopic ultrasonography (EUS), endoscopic retrograde cholangiopancreatography (ERCP), magnetic resonance imaging (MRI), magnetic resonance cholangiopancreatography (MRCP), abdominal ultrasonography, and computed topography (CT). EUS and MRI are considered the most accurate of these imaging tools, which are used primarily for diagnostic testing. However, they may also have a role in screening for people at high risk of pancreatic adenocarcinoma, such as those with known genetic mutations or a family history of pancreatic adenocarcinoma.^{95, 96}

- Endoscopic ultrasonography (EUS) examines the upper and lower gastrointestinal tract, including the pancreas, via insertion of a small tube with an ultrasound probe through the mouth and down into the stomach. Tissue can be sampled during EUS via fine needle aspiration (FNA) to evaluate lesions for malignancies and subsequent staging.⁹⁷ Endoscopic retrograde cholangiopancreatography (ERCP), a procedure that combines endoscopy with X-rays, can be used as a diagnostic tool.⁹⁵ The International CAPS Consortium discourages the use of ERCP as a screening tool because of risk for post-ERCP acute pancreatitis.⁹⁵
- Magnetic resonance imaging (MRI) allows for imaging of the entire abdomen and pelvis. It does not involve exposure to ionizing radiation and is less invasive than EUS, but cannot sample tissue so may require a separate biopsy procedure, which is invasive and carries risks.⁹⁸ Magnetic resonance cholangiopancreatography (MRCP) also does not involve radiation exposure and is a non-invasive alternative to ERCP for imaging pancreatic ductal anatomy for suspicious lesions.⁹⁸
- Computed topography (CT) for pancreatic adenocarcinoma often involves the use of a contrast dye, given by mouth or injection. CT scans are associated with potential harm from radiation exposure. They are used for diagnosis, tumor staging, and determining resectability.^{9, 98}

Biomarker-Based Screening

Despite an expanding literature on biomarkers and their potential diagnostic accuracy, there are currently no validated biomarkers for early detection of pancreatic adenocarcinoma.⁹⁹⁻¹⁰⁴

CA 19-9 has long been considered the best single candidate for a screening biomarker for early detection. CA 19-9 is elevated in the serum of people with pancreatic adenocarcinoma and may be used clinically as a prognostic tool in pancreatic cancer management for some patients.¹⁰⁵

However, its limited sensitivity and specificity have limited its usefulness as a screening method. A meta-analysis found the median sensitivity and specificity of CA 19-9 for the detection of pancreatic adenocarcinoma to be 75.5 percent and 77.6 percent, respectively, with positive predictive value of 0.5 percent to 0.9 percent.¹⁰⁶

Other potential single biomarker tests include carcinoembryonic antigen (CEA), which is used in the management of several gastrointestinal cancers, but lacks accuracy to support its use as a screening test.¹⁰⁵ Cell-surface proteins, 283 proteins according to one estimate,⁹⁶ are also overexpressed in pancreatic adenocarcinoma, but discriminatory abilities of these proteins in detecting pancreatic adenocarcinoma are largely unknown.

Micro-RNA patterns from circulating exosomes; hypermethylation of specific genes in circulating DNA (e.g., *BNC1*, *ADAMST1*, *NPTX2*, *ppENK*, *p16*, or *CDKN2a*);¹⁰⁷ and detection of circulating tumor cells are potential emerging biomarkers.^{96, 108} Mutated DNA and biomarkers may be detected in pancreatic juice,¹⁰⁹⁻¹¹¹ a liquid secreted by the pancreas which contains various enzymes.¹¹²

Multiple-biomarker panels may have the highest potential as a noninvasive screening test for pancreatic adenocarcinoma, given the heterogeneity of tumor types and the limited accuracy of any single biomarker.^{96, 113, 114} For example, a CA 19-9-based multiple biomarker panel was found to discriminate early-stage pancreatic adenocarcinoma from healthy controls with an area under the curve (AUC) of 0.89 (95% CI, 0.82 to 0.95) for all early-stage cancer (p=0.03) compared to CA 19-9 alone.¹¹⁵ Other studies have also found promising results, finding AUCs above 0.9 for multiple biomarker panels.^{116, 117} Most biomarker-based screening would require serum-based testing; however, stool- or saliva-based testing also have been explored.^{99, 118, 119}

Treatment Approaches

There are no known interventions to prevent pancreatic adenocarcinoma. Tobacco cessation or avoidance, healthy diet, and regular exercise may reduce modifiable risk for pancreatic adenocarcinoma along with several other cancers and chronic diseases.

Current treatment recommendations include surgery for early stage cancers (currently about 20% of all new cases), chemotherapy, and radiation (**Table 2**).

Surgical resection is the only treatment for pancreatic adenocarcinoma that offers a potential cure, but only people with non-metastatic disease are eligible for surgery.¹²⁰ Pancreatic cancers eligible for surgical treatment are generally classified as “resectable” or “borderline resectable” based on the likelihood of complete surgical resection.⁵⁷ Surgical options include a pancreaticoduodenectomy (a Whipple procedure), which removes the head of the pancreas, gallbladder, bile duct, and parts of the stomach and small intestine; a total pancreatectomy, which removes the whole pancreas, bile duct, gallbladder, spleen, nearby lymph nodes, and parts of the stomach and small intestine; and a distal pancreatectomy, which removes the body and tail of the pancreas as well as the spleen.

Any type of surgical resection for pancreatic adenocarcinoma carries significant morbidity (complication rates 20%–50%) and peri-operative mortality risks (1%–8%).¹²¹ Patients typically require a 1–3 week post-operative hospital stay and 3–6 months for full recovery.¹²² Complications can include fistula or leakage, delayed gastric emptying, acute pancreatitis, sepsis, and infection.^{123, 124} Since complication rates are lower at high-volume centers, the National Comprehensive Cancer Network (NCCN) recommends pancreatic resections be done at institutions that perform at least 15–20 resections annually.¹²⁰

Despite the favorable impact of surgical intervention on survival for people with early stage pancreatic adenocarcinoma, many patients still do not undergo surgery. In one National Cancer Data Base (NCDB) study (n=9559), 38 percent of people with resectable tumors (stage I only) diagnosed between 1995–2004 were never offered surgery.¹⁶ A more recent analysis of SEER data (n=6742) found that only 25 percent of people with localized pancreatic adenocarcinoma (excluding anyone with blood vessel or lymph node invasion) underwent surgery between 1988 and 2010, with no change in this proportion over time.¹² People treated at community hospitals are much less likely to undergo surgery or chemotherapy treatment.^{14, 15}

Current Clinical Practice and Recommendations of Others

No organizations currently recommend population-based screening for pancreatic adenocarcinoma. Screening for pancreatic adenocarcinoma detection in people with known genetic mutations or strong family history is recommended by several organizations (**Table 3**). Several countries maintain screening programs for people at high risk for pancreatic adenocarcinoma. For example, Denmark has a national screening program for residents with hereditary pancreatitis or a family history of pancreatic adenocarcinoma;¹²⁵ the Netherlands has screening program for people with a family history of pancreatic adenocarcinoma, carriers of known genetic mutations associated with hereditary syndromes, and people with Peutz-Jeghers syndrome;¹²⁶ and the Canadian province of Ontario has a screening program for people with a family history of pancreatic adenocarcinoma, carriers of known genetic mutations, people with Peutz-Jeghers syndrome, and people with hereditary pancreatitis.¹²⁷ Germany, Sweden, and Spain all have national familial pancreatic adenocarcinoma registries with screening recommendations for people aged 18 and older.¹²⁸⁻¹³⁰

Cancer programs in the U.S. also may refer family members of pancreatic adenocarcinoma patients for further evaluation, typically by multidisciplinary teams. U.S. registries for individuals at high risk of pancreatic adenocarcinoma include programs based at Johns Hopkins University,¹³¹ Memorial Sloan-Kettering Cancer Center,¹³² Columbia University Medical Center/New York Presbyterian Hospital,¹³³ University of Washington,¹³⁴ Oregon Health and Science University,¹³⁵ the Mayo Clinic,¹³⁶ University of Nebraska Medical Center¹³⁷ Thomas Jefferson University Hospital/Sidney Kimmel Cancer Center.¹³⁸

Previous USPSTF Recommendation

In 1996 and again in 2004, the USPSTF recommended against routine screening for pancreatic

cancer in asymptomatic adults using abdominal palpation, ultrasonography or serologic markers (D recommendation).^{1, 139}

In its 2004 recommendation, the USPSTF concluded there was no evidence that screening for pancreatic cancer is effective in reducing mortality, and that the harms of screening exceeded any potential benefit.¹ They concluded that there is a potential for significant harm because of the very low prevalence of pancreatic adenocarcinoma, limited accuracy of available screening tests, the invasive nature of diagnostic tests, and the poor outcomes of treatment.

The USPSTF noted in clinical considerations an interest in primary prevention of pancreatic cancer, including tobacco cessation and dietary measures, but that the evidence for diet-based prevention of pancreatic cancer is limited and conflicting.

The brief evidence review supporting the 2004 recommendation did not publish an analytic framework or inclusion and exclusion criteria. The search included systematic reviews, meta-analyses, randomized clinical trials, cost-effectiveness analyses, editorials, and commentaries, but did not include observational studies. This review noted gaps in evidence for the benefit or harm of identifying and screening high-risk groups, including the potential use of tumor markers in screening, and ongoing randomized clinical trials exploring treatment for pancreatic adenocarcinoma.¹⁴⁰

Chapter 2. Methods

Scope and Purpose

The USPSTF will use this evidence review to update their 2004 D recommendation on screening for pancreatic cancer.¹ This review addresses the benefits and harms associated with screening and treatment of screen-detected pancreatic adenocarcinoma.

Key Questions and Analytic Framework

We developed an analytic framework with five key questions (KQs) based on the previous review and a scan of the research conducted since the previous review (**Figure 1**).

KQs

1. Does screening for pancreatic adenocarcinoma improve cancer morbidity or mortality or all-cause mortality?
 - a. Does screening effectiveness vary by clinically relevant subpopulations (e.g., by age group, family history of pancreatic cancer, personal history of new-onset diabetes, or other risk factors)?
2. What is the diagnostic accuracy of screening tests for pancreatic adenocarcinoma?
3. What are the harms of screening for pancreatic adenocarcinoma?
4. Does treatment of screen-detected or asymptomatic pancreatic adenocarcinoma improve cancer mortality, all-cause mortality, or quality of life?
5. What are the harms of treatment of screen-detected pancreatic adenocarcinoma?

Data Sources and Searches

We worked with a research librarian to develop our literature search (**Appendix B**). All search strategies were peer-reviewed by a second research librarian.

We re-evaluated all articles included in the previous USPSTF Evidence Report on Pancreatic Cancer Screening.¹⁴⁰ Bridging from this previous review, we searched for articles published from 2002 to October 3, 2017. We searched Cochrane Central Register of Controlled Trials, MEDLINE, and PubMed, publisher-supplied to locate relevant studies for all KQs (**Appendix B**). Results of the literature search were imported into EndNote. We supplemented our database searches by reviewing reference lists from recent and relevant systematic reviews.^{95, 141-151} We also searched ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP) for relevant ongoing studies (**Appendix C**). We ran the searches again on April 27, 2018, to capture new literature from the intervening months.

Study Selection

A total of 19,596 abstracts were reviewed. Initial identification of low-relevance abstracts was conducted using key words relating to exclusion criteria. This identified 2,168 citations that were reviewed by a single investigator. The remaining 17,428 abstracts were dual-reviewed by two independent reviewers using Abstrackr, an online abstract reviewing platform. From the two processes, the team reviewed 824 full-text articles (**Appendix B Figure 1**) against specified inclusion criteria (**Appendix B Table 1**). We resolved discrepancies through consensus and consultation with a third investigator. We excluded articles that did not meet inclusion criteria or those we rated as poor quality.

For screening key questions (KQs 1, 2, 3), the population of interest was adults 18 years or older with or without risk factors for pancreatic adenocarcinoma (e.g. family history of pancreatic adenocarcinoma, personal history of new-onset diabetes or other risk factors). We excluded studies that focused solely on persons with confirmed genetic syndromes (e.g., Peutz-Jeghers syndrome, Lynch syndrome, hereditary pancreatitis, known mutations in *CDKN2A*, *BRCA1*, *BRCA2*, *CTFR*, or *ATM* genes). Studies with persons with high-risk genetic mutations or syndromes in addition to persons with other risk factors were included. We included any imaging-based screening protocol, and excluded studies using biomarker-based initial screening protocols as no validated biomarkers currently exist.⁹⁹ For diagnostic accuracy (KQ2), we included trials or cohort studies. For harms of screening (KQ3), we included randomized, controlled trials; controlled clinical trials; cohort studies; or case-control studies. Outcomes of interest were pancreatic adenocarcinoma-specific morbidity or mortality, all-cause mortality, or quality of life (KQ1); measures of diagnostic accuracy, including sensitivity, predictive value, and diagnostic yield (KQ2); or procedural or psychosocial harms of screening (KQ3).

For key questions on treatment (KQ4, KQ5) the population of interest was adults with screen-detected, asymptomatic, or incidentally detected pancreatic adenocarcinoma. We excluded studies of surgical intervention for early-stage pancreatic adenocarcinoma that was detected clinically or as a result of symptoms, as these study populations may not be an adequate proxy for screen-detected, asymptomatic, or incidentally detected populations. We excluded studies of people with pancreatic endocrine or exocrine tumors other than adenocarcinoma. We included studies reporting on surgical resection with or without chemotherapy or radiation. We excluded studies on chemotherapy or palliative care alone. Studies eligible for KQ4 needed to have a comparison group of either no treatment or delayed treatment; thus, we excluded comparative effectiveness screening or treatment studies. Outcomes of interest were morbidity or mortality, quality of life (KQ4) or any surgical harms (KQ5).

For all key questions we limited studies to settings conducted in countries categorized as “Very High” in the Human Development Index.¹⁵²

Quality Assessment and Data Abstraction

At least two reviewers independently critically appraised all articles that met the inclusion criteria based on the USPSTF’s design-specific quality criteria for trials (**Appendix B Table 2**).

We rated articles as good, fair, or poor quality. A good-quality study met all criteria. A fair-quality study did not meet, or it was unclear if it met, at least one criterion but had no known important limitations that could invalidate its results. A poor-quality study had a single fatal flaw or multiple important limitations; we excluded poor-quality studies from this review. Disagreements about critical appraisal were resolved by consensus and, if needed, in consultation with a third independent reviewer.

One reviewer extracted key elements of included studies into a Microsoft Access® database (Microsoft Corporation, Redmond, Washington). A second reviewer checked the data for accuracy. Evidence tables were tailored for each KQ. Tables generally included details on study design and quality, setting and population (e.g., country, inclusion criteria, age, sex, race/ethnicity), screening or treatment details, length of followup, and outcomes.

Data Synthesis and Analysis

We synthesized results by KQ. We used a standardized summary of evidence table to summarize the overall strength of evidence for each KQ. This table included the number and design of included studies, summary of results, consistency or precision of results, reporting bias, summary of study quality, limitations of the body of evidence, and applicability of the findings.

Because of the limited number of studies and the population heterogeneity, we provided a narrative synthesis of results and used summary tables to allow for comparisons across studies. For screening test performance (KQ2), we could only report on the yield of cancers as the (diagnostic) outcome, as we could not calculate sensitivity and specificity from the included studies. For harms of screening (KQ3), we stratified results by type of harm (i.e., procedural, psychosocial).

For quantitative analyses, we calculated diagnostic yield of pancreatic adenocarcinoma and 95 percent CIs assuming binomial distribution. After confirming that the yield of different imaging modalities was similar across studies, we also calculated a pooled diagnostic yield across studies and produced forest plots to illustrate the range of effects seen across studies. We calculated diagnostic yield from initial screen (baseline) and from initial screening and repeated screening combined where possible. We could not calculate the screening rate for repeat screenings alone because the number of participants undergoing repeated screenings was not clearly or consistently reported across studies.

Grading the Strength of the Body of Evidence

We graded the strength of evidence by each KQ according to guidance from the Agency for Healthcare Research and Quality (AHRQ) for Evidence-based Practice Centers,¹⁵³ which was informed by the Grading of Recommendations Assessment, Development and Evaluation (GRADE) Working Group.¹⁵⁴ For each KQ we grade the evidence according to consistency (similarity of effect direction and size), precision (degree of certainty around an estimate), reporting bias (potential for bias related to publication, selective outcome reporting, or selective

analysis reporting), and study quality (i.e., study limitations). These are four of the five suggested domains; we did not address the fifth required domain—directness—in the summary of evidence as directness is addressed in the design and structure of the key questions (i.e., whether the evidence links the interventions directly to a health outcome).

Consistency was rated as reasonably consistent, inconsistent, or not applicable (e.g., single study). Precision was rated as reasonably precise, imprecise, or not applicable (e.g., no evidence). Reporting bias was rated as suspected, undetected, or not applicable (e.g., when there is insufficient evidence for a particular outcome). Study quality reflects the quality ratings of the individual trials and indicates the degree to which the included studies for a given outcome have a high likelihood of adequate protection against bias. The body of evidence limitations field highlights important restrictions in answering the overall KQ (e.g., lack of replication of interventions, non-reporting of outcomes important to patients).

We provide an overall assessment of the strength of evidence for each KQ. “High” indicates high confidence that the evidence reflects the true effect and that further research is very unlikely to change our confidence in the estimate of effects. “Moderate” suggests moderate confidence that the evidence reflects the true effect and that further research may change our confidence in the estimate of effects. “Low” indicates low confidence that the evidence reflects the true effect and that further research is likely to change our confidence in the estimate of effects. A grade of “insufficient” indicates that evidence is either unavailable or does not permit estimate of an effect. Applicability assesses how the overall body of evidence would apply to the U.S. population based on settings, populations and intervention characteristics. Two independent reviewers rated each KQ according to consistency, precision, reporting bias, and overall strength of evidence grade. We resolved discrepancies through consensus.

Expert Review and Public Comment

A draft research plan that included the analytic framework, KQs, and inclusion criteria was available for public comment from April 27, 2017 through May 24, 2017. We made no substantive changes to our review methods based on the comments received.

A draft version of this report was reviewed by invited content experts and federal partners, who are listed in the acknowledgements. Comments received during this process were presented to the USPSTF during its deliberation of the evidence and, subsequently, addressed in this version of the report.

USPSTF Involvement

We worked with four USPSTF liaisons at key points throughout the review process to develop and refine the analytic framework and KQs and to resolve issues regarding the scope of the final evidence review. This research was funded by the Agency for Healthcare Research and Quality under a contract to support the work of the USPSTF. Agency staff provided oversight for the project, assisted in external review of the draft report, and reviewed the draft report.

Chapter 3. Results

We included 13 unique prospective cohort screening studies, reported in 24 articles (**Table 4**), none of which were included in the previous evidence review.¹⁴⁰ No studies reported on the effect of screening for pancreatic adenocarcinoma on cancer morbidity, mortality, or all-cause mortality (KQ1); 13 studies (24 articles)^{125-127, 129, 133, 155-173} reported on the diagnostic accuracy of screening tests for pancreatic adenocarcinoma (KQ2); nine studies (18 articles)^{125-127, 129, 133, 155-162, 166-170} reported on the harms of screening for pancreatic adenocarcinoma (KQ3); no studies reported on the effectiveness of treatment for screen-detected pancreatic adenocarcinoma (KQ4); and six studies (12 articles)^{125, 129, 133, 156, 157, 160-163, 165, 169, 173} reported on the harms of treatment of screen-detected pancreatic adenocarcinoma (KQ5).

Articles most commonly were excluded due to lack of relevance to pancreatic adenocarcinoma screening or treatment, ineligible population (populations with personal history of pancreatic adenocarcinoma, symptomatic populations, studies focusing only on populations with known genetic mutations associated with increased risk of pancreatic adenocarcinoma), ineligible study design (comparative effectiveness studies, case reports, case series, narrative reviews), and ineligible outcomes (not reporting morbidity, mortality, quality of life, diagnostic accuracy, screening harms, or treatment harms). The most common reasons for poor quality exclusion were insufficient information on patient recruitment or screening process (**Appendix B Table 1**). **Appendix C** provides a list of all excluded studies, with the main reason for their exclusion.

Description of Included Studies

In total, 13 included screening studies reported screening results for 1,317 people. All studies used a prospective cohort design. These cohorts were relatively small; the study samples ranged from 38 to 239 people. No included studies included an un-screened comparison arm, and none were designed to evaluate test accuracy. One study included comparison group of individuals undergoing EUS or ERCP for non-pancreatic indications.¹⁶⁰

Seven studies (n=776) were conducted in the U.S.^{133, 155, 159, 160, 165, 171, 172}; one in Canada¹²⁷; and five in Northern European countries (two in the Netherlands;^{126, 157} one in Sweden;¹⁶⁴ one in Denmark;¹²⁵ and one in Germany¹²⁹). All studies were conducted in or in conjunction with academic medical center settings, typically specialty care settings connected to high-risk surveillance clinics.^{127, 129, 159, 160, 164, 165, 171, 172} All U.S.-based studies were conducted in the context of cancer centers or large tertiary care academic centers.^{133, 155, 159, 160, 165, 171, 172} Non U.S.-based studies were conducted in the context of screening or surveillance programs in countries with national health care systems^{125, 126, 129, 164} or at academic medical centers.^{127, 157} Seven studies used existing familial pancreatic cancer registries to recruit participants.^{125, 127, 133, 155, 159, 160} Other recruitment methods included physician or genetic counselor referral. Three studies were conducted at multiple sites.^{126, 129, 165}

Included Populations

All screening populations except one small comparison group were exclusively in persons at elevated risk for pancreatic adenocarcinoma, and included predominantly people with family history of pancreatic adenocarcinoma, with or without confirmed genetic mutations or syndromes (**Table 5**). In 10 studies, more than 50 percent of the study population had a family history of cancer; in eight studies, 90 percent to 100 percent of the study population had a family history of cancer.^{129, 133, 159, 160, 164, 165, 172} Only three studies (n=232) exclusively included relatives of people with pancreatic adenocarcinoma.^{129, 133, 155} One study included an asymptomatic control group of people receiving imaging for other clinical indications unrelated to the pancreas (n=138).¹⁶⁰

Definitions of family history varied widely across studies, but all studies had inclusion criteria aimed at identifying those at greatest risk for pancreatic adenocarcinoma. Inclusion criteria generally required at least two affected relatives and at least one affected first-degree relative for study entry. For example, two U.S.-based studies limited study entry to people with three or more relatives with pancreatic adenocarcinoma, one or two of which were first-degree relatives.^{159, 160} Another U.S.-based study required two or more relatives with pancreatic adenocarcinoma or one with pancreatic adenocarcinoma at age less than 55 years to be considered moderate risk; 43 percent of the study population had two affected relatives, while an additional 26 percent had three or more affected relatives.¹³³

Twelve studies included people with confirmed genetic mutations or syndromes; typically these populations made up less than 25 percent of the study population with the exception of three studies whose populations exceeded 50 percent people with confirmed genetic conditions; one was conducted in the U.S.¹⁷¹ and the other two were conducted in the Netherlands: the Dutch Familial Pancreatic Cancer (FPC) study (n=139)^{126, 158, 167, 170} and the study by Poley and colleagues (n=44).¹⁵⁷ No studies reported on flow through the screening program separately for individuals with confirmed genetic mutations or syndromes.

Personal history of other types of cancer or diabetes also were reported. Diabetes status was reported in six studies, and ranged from 4 percent to 24 percent of the study population.^{125, 127, 133, 159, 160, 165} Two studies specified that patients with diabetes (3.9%¹³³ and 4.2%¹⁶⁵ of study population) had type 2 diabetes; the other 4 studies did not specify type of diabetes. One study specified that patients with diabetes (5.0% of study population) were diagnosed prior to 1 year ago;¹²⁷ the other five studies did not report time since diagnosis. Personal history of non-pancreatic cancer was reported in six studies which ranged from 6 percent to 43 percent of the study populations.^{126, 127, 133, 159, 160, 171}

Study populations contained a slightly higher proportion of female participants compared to male (range of female participants 53.6% to 71.6%; the population in the single study with an asymptomatic comparison group was 43% female). Mean age of participants ranged from 50 to 60 years. Race and ethnicity were inconsistently reported across studies. Eight studies reported Ashkenazi Jewish ancestry, which accounted for from less than 10 percent of the study population¹²⁹ to more than 49 percent in one study.¹³³ Eight studies also reported race/ethnicity, and in these eight studies the proportion of white participants was 88 percent to 100 percent.

Three of the six studies that did not report on white race/ethnicity were conducted in Northern European countries (Sweden, Denmark, and the Netherlands).^{125, 126, 164} The other three studies that did not report on white race/ethnicity were based in the U.S.: One was based at Johns Hopkins University¹⁵⁹ and reported that 13.2 percent of participants were of Ashkenazi Jewish ancestry, one was at the Greater Midwest Pancreatic Screening Clinic in Wisconsin,¹⁷¹ and one was at the Moffitt Cancer Center in Florida.¹⁷²

Various behavioral risk factors were included in eleven studies. All eleven reported on smoking status, in which the proportion of current smokers ranged from 0 percent to 25 percent. Alcohol use was reported in six studies; measures of alcohol use varied across studies but ranged from 40 percent to 56 percent in studies reporting “regular” use. One study reported social or occasional alcohol use at 77 percent,¹³³ and one reported history of heavy alcohol use at 10 percent.¹⁷²

Protocols for Initial and Repeated Screening

Initial Screening Protocols

A total of nine small, prospective, fair quality studies (n=885) evaluated EUS (with or without additional imaging) as the initial screening test for pancreatic abnormalities. Four studies evaluated EUS as the sole screening test: one at Johns Hopkins University in the U.S. (n=38);¹⁵⁹ one at the Moffitt Cancer Center in the U.S. (n=58);¹⁷² one from the Danish National Screening Program (n=71);¹²⁵ and one from the Netherlands (n=44, a study that pre-dated the Dutch Familial Pancreatic Cancer Study).¹⁵⁷ Two additional studies from the U.S. evaluated multiple screening modalities in which the screeners were blinded to the results from either test: EUS and CT screening (n=78 high-risk people and 138 asymptomatic controls who underwent EUS only) at Johns Hopkins Hospital,¹⁶⁰ and EUS, CT, and MRI screening (n=216) within the Cancer of the Pancreas Screening Study 3 (CAPS3) consortium including 5 U.S. hospitals.¹⁶⁵ The last three studies evaluated EUS plus MRI (or MRCP) in: the Dutch FPC Study (n=139),¹²⁶ the U.S. (n=31),¹³³ and the Familial Pancreatic Cancer (FaPaCa) study in Germany (n=72).¹²⁹

Two small, prospective, fair quality studies (n=294) evaluated CT imaging to screen for pancreatic abnormalities.^{160, 165} Both took place in the U.S. and were led by the same author, but do not overlap in populations. One evaluated CT and EUS screening in 78 people (screeners were blinded to the results of either screening test)¹⁶⁰ and the other evaluated CT with EUS and MRI in 216 people (again screeners were blinded to the results of any other test).¹⁶⁵

A total of eight small, prospective, fair quality studies (n=849) evaluated MRI or MRCP as the initial screening test for pancreatic abnormalities. Three studies evaluated MRI as the sole screening test, one from the Greater Midwest Pancreatic Cancer Screening Clinic in the U.S. (n=65),¹⁷¹ one from the Toronto Screening Program in Canada (n=175)¹²⁷ and the other from Sweden (n=40);¹⁶⁴ one additional study from the U.S. evaluated MRCP alone (n=109).¹⁵⁵ Three studies evaluated MRI and/or MRCP as initial screening tests along with EUS: the Dutch FPC Study in the Netherlands (n=139),¹²⁶ a study based at Columbia University Medical Center (n=51),¹³³ and the FaPaCa study in Germany (n=72).¹²⁹ One study, the CAPS3 study from the U.S., evaluated MRI plus EUS and CT (n=216).¹⁶⁵

All studies had final pathology determined using samples obtained by FNA and/or surgery.

Surveillance and Clinical Followup

After initial screening, followup time ranged from 12 to 60 months. All studies included at least 12 months of followup after screening. Eleven studies conducted annual followup repeat screening for screen-negatives; while one study used a 1- to 3-year range for followup testing.¹⁶⁵ For people with abnormal results, screening protocols typically had branches for immediate biopsy (typically with EUS-guided FNA) or surgery for solid lesions or those otherwise likely malignancies, or surveillance at 3–6 months for less concerning abnormalities. Detailed descriptions of all included screening programs are in **Table 6**. All studies reported final pathology of detected cases of pancreatic adenocarcinoma.

Outcome Assessment

Diagnostic Accuracy Outcomes

All included studies conducted followup diagnostic testing only on individuals with abnormal screening results, and did not provide followup data on screen-negative populations. Further, test-positive rates were not consistently reported, and many cases of precursor lesions were detected and removed surgically. Therefore, only diagnostic yield of each screening test is possible, whereas sensitivity, specificity, predictive value, and other measures of diagnostic accuracy are not available. Most studies with multiple imaging tests did not report whether pancreatic adenocarcinoma or other pathology findings were detected on one or more screening exams, so we cannot evaluate yield based on individual imaging tests. No included studies reported results separately for risk-based subgroups of family history, known genetic mutations, or other risk factors.

Screening Harms (Procedural)

Eight studies (n=763) reported screening procedure harms.^{125, 126, 129, 133, 155, 157, 159, 160} However, five of these studies do not report how harms were assessed or if they were assessed routinely for all participants for which procedures.^{125, 126, 129, 133, 157} Three studies (n=386) assessed procedure-related harms by calling patients within a week after the procedure.^{155, 159, 160} Of these, all three studies reported harms of EUS or ERCP (one with or without FNA¹⁵⁹); one reported harms of CT,¹⁶⁰ and one reported harms of MRI.¹⁵⁵

Further, overdiagnosis as a potential harm of screening was difficult to assess, since pathology data is often not available before surgical intervention, and the detection and surgical removal of precursor lesions may represent clinical benefit.

Screening Harms (Psychosocial)

Two screening programs (n=271), the Dutch FPC^{126, 158, 167, 170} and Toronto programs,^{127, 166, 168} assessed potential psychosocial harms longitudinally between pre- and post-screening. The Dutch FPC program (n=140) assessed outcomes via survey before the initial screening, shortly

after initial screening, as well as four other time points during subsequent screenings (up to 2 years and 2 subsequent screenings). Outcomes assessed included perceived risk, cancer worry, and anxiety and depression, as well as a battery of individual items that assessed concern about a variety of potential issues that could arise from screening from informing children or family.^{126, 158, 167, 170} The Toronto study (n=131) assessed, also via survey, perceived pancreatic cancer risk and worry, as well as a measure of general distress derived from the Brief Symptom Inventory (BSI) before initial screening and 3 months after screening in people with familial pancreatic cancer.^{127, 166, 168} Neither study's assessment of harms included a comparison group or reference population.

Clinical Followup of Detected Cases (Treatment Effectiveness)

Possibly due to sparse detection of pancreatic adenocarcinoma, studies typically reported details of detected cases in a case report format. Details were variably provided across studies and included risk factors, family history, stage at detection, whether detected on initial or repeated screening, treatment received, and possibly clinical status at followup.

Treatment Harms

Surgical harms were reported in six studies (n=32 people receiving surgery).^{125, 129, 133, 157, 160, 165} Methods of harm assessment were inconsistently reported across studies. Two studies assessed surgical procedure-related harms through clinical followup of all patients for at least 12 months;^{160, 165} no other studies reported how surgical harms were assessed or if they were assessed routinely for all participants or all procedures.

Quality

All studies were fair quality. In all studies, only participants with positive screening results underwent the reference test. More than half of studies had small sample sizes (<75 participants). Five studies reported blinding during the screening process.^{126, 129, 159, 160, 165} In four studies, screeners were blinded to each patient's other test results. In one study, the radiologist was blinded to patient risk factors. Less common were issues with incomplete reporting of the participant selection process, the threshold for a positive screening result, participant flow through the screening program, intervals between the screening test and the reference standard, and how harms were assessed. Follow-up rates were reported in six studies and ranged from 67.0 percent to 97.1 percent.

KQ1. Does Screening for Pancreatic Adenocarcinoma Improve Cancer Morbidity or Mortality or All-Cause Mortality?

KQ1a. Does Screening Effectiveness Vary by Clinically Relevant Subpopulations?

No studies met inclusion criteria for KQ1 or KQ1a.

KQ2. What Is the Diagnostic Accuracy of Screening Tests for Pancreatic Adenocarcinoma?

Summary of Results

Of 1317 people screened, 57 people underwent surgery; 14 ended up having confirmed pancreatic cancer and 38 having precursor lesions. Four additional people had advanced pancreatic cancer diagnosed without surgical intervention.

Across all studies (n=1317), 18 cases of pancreatic adenocarcinoma were detected: nine on initial screening, eight on repeat screening, and one case in which the timing of detection was not reported. Six studies (n=824) found no cases of pancreatic adenocarcinoma on initial screening;^{125, 127, 160, 165, 171, 172} three of these found 6 cases of pancreatic adenocarcinoma on repeat screening. The remaining seven studies (n=493) found a total of nine cases on initial screening and an additional two cases on repeat screening.^{126, 133, 155, 157, 159, 164} The single study reporting screening results in an average risk comparison population (n=138) found no cases of pancreatic adenocarcinoma or precursor lesions.¹⁶⁰ Pooled yield for all screening tests to detect pancreatic adenocarcinoma on initial screening in high-risk populations was 7.8 per 1000 (95% CI, 3.6 to 14.7); and for total yield including both initial and repeat screening, it was 15.6 per 1000 (95% CI 9.3 to 24.5) (**Figure 2**)

EUS was the most commonly reported initial screening modality. Across studies using EUS or MRI screening, diagnostic yield for pancreatic adenocarcinoma ranged from 0 to 75.0 per 1000 (7.5%), with three of the smallest studies finding the largest yields and wide confidence intervals around the estimates. For studies with larger sample sizes, yields ranged from 0 to 28.2 per 1000 (2.8%). The yield of CT for pancreatic adenocarcinoma ranged from zero to 12.8 per 1000 across two studies.

All screening modalities detected precursor lesions of IPMN, PanIN, or IPMN/PanIn combined. For detection of these precursor lesions, diagnostic yield ranged from 17.2 to 105.3 per 1000 (1.72% to 10.53%) for EUS alone, to 0 to 50.0 per 1000 for MRI/MRCP alone. For detection of precursor lesions across studies using multiple screening modalities, yields ranged from 7.2 to 129.0 per 1000.

Detailed Results

Of 1317 people screened across all studies, screen positive results were inconsistently reported across studies, prohibiting assessment of false positive rates. Biopsy rates were also inconsistently reported. In total, 57 surgeries were reported across all studies; of these, 14 resulted in a diagnosis of pancreatic adenocarcinoma. Of the remaining 43 surgeries, 38 removed precursor lesions with IPMN or PanIN, and 5 contained either neuroendocrine tumors, liver hyperplasia, or benign serous cystadenoma. Four additional people had advanced pancreatic adenocarcinoma diagnosed without surgical intervention (**Table 7**).

In total, 18 cases of pancreatic adenocarcinoma were detected: nine on initial screening, eight on

repeated screening or during surveillance of abnormal screening results, and one at an unspecified point during the screening program (**Tables 8 and 9**). All cases of pancreatic adenocarcinoma were detected in high-risk study populations.

Detected cases were in persons with a mean age of 59.9 years at detection (range 44 to 81); 12 of 18 cases were in women (66.7%). The mean number of affected relatives was three (range 1 to 7 relatives) in 15 persons with a diagnosis of cancer. Nine of 18 cases (52.9%) were detected on initial screening, and eight were detected on repeated screening (one NR). Seven of 11 cases (63.6%) had a known genetic mutation (2 FAMMM, 4 *BRCA2*, 1 *CDKN2A*).

Twelve of 18 cases (66.6%) were detected at stage I or II or classified as “resectable.” Of these, eight were detected through initial screening, three were detected on repeat screening, and one was detected during surveillance following previous abnormal findings (a person with IPMN on initial screening and stage IIA cancer detected at 24 months; Case #5 in **Table 10**). Of the six cases detected at stage III or IV, one was detected at initial screening, three were detected on repeat screening, one was detected at an unspecified point in the screening program, and one was detected during surveillance following previous abnormal findings (a person with cysts identified on initial screening, duct abnormalities detected at 12 months, and an unresectable mass at 14 months that was later confirmed as stage IV disease; Case #9 in **Table 10**).

Yield of Screening EUS to Detect Pancreatic Adenocarcinoma

The yield of EUS-based screening in nine studies (n=885) ranged from 0 to 68.2 cases per 1,000 high-risk persons. Among 11 total pancreatic adenocarcinoma cases detected with EUS across all nine studies, seven were detected on initial screening, three were detected on repeat screening, and one was detected at an unspecified point in the screening program. Of these pancreatic adenocarcinoma cases, three were detected at stage I, one was stage IIA, three were stage IIB, three were metastatic, and one was reported as resectable with no stage given.

Two small studies found diagnostic yields of 68.2 per 1000 (6.8%)¹⁵⁷ and 64.5 per 1000 (6.45%),¹³³ but confidence intervals were wide in both studies. In the Dutch study by Poley and colleagues (n=44), the population was 52.3 percent people with known genetic mutations or syndromes;¹⁵⁷ in a study based at Columbia University Medical Center (n=51), 100 percent of the study population had a family history of pancreatic adenocarcinoma.¹³³ In the Dutch study by Poley and colleagues, all three detected pancreatic adenocarcinoma cases were people with known mutations (2 with FAMMM and one with *BRCA2*).¹⁵⁷

Yield of Screening CT to Detect Pancreatic Adenocarcinoma

In two studies reporting CT (n=294),^{160, 165} the yield of CT for pancreatic adenocarcinoma ranged from zero to 12.8 per 1000.

Yield of Screening MRI to Detect Pancreatic Adenocarcinoma

Across eight studies reporting MRI screening results (n=849), the yield of pancreatic ductal adenocarcinoma following MRI screening ranged from 0 to 75.0 cases per 1,000 persons.

Among a total of 11 pancreatic adenocarcinoma cases detected across all eight studies, five were detected on initial screening, three were detected on repeat screening, one was detected at an unspecified point in the screening program, and two were detected during surveillance of IPMN or other cysts. Of these pancreatic adenocarcinoma cases, two were detected at stage IA, two were stage IIA, one was stage IIB, one was stage III, four had metastatic disease, and the remaining case was reported as resectable with no stage given.

Detection of IPMN or PanIn Precursor Lesions

In total, the screening programs identified a total of 38 individuals with IPMN (n=5), PanIN (n=13) or both IPMN and PanIN (n=20) (**Table 8**). It is unclear if the clinical significance of these findings suggests potential clinical benefit or potential harm from overdiagnosis.

KQ3. What Are the Harms of Screening for Pancreatic Adenocarcinoma?

Summary of Results

Procedural harms of screening were evaluated in eight screening studies (n=675);^{125, 126, 129, 133, 155, 157, 159, 160} psychological harms were assessed in two studies (n=271).^{126, 127} Details on the assessment of harms were variably reported. In two studies (n=277)^{159, 160} in which 150 individuals underwent ERCP as a diagnostic followup test, 15 people (10%) reported acute pancreatitis, nine of which required hospitalization. No evidence of increased worry, distress, depression, or anxiety after screening was reported, compared to before screening.^{168, 170}

Detailed Results

Procedural Harms

Eight screening studies (n=675) reported screening procedure-related harms (**Table 11**).^{125, 126, 129, 133, 155, 157, 159, 160} Five studies (n=485) reported harms of EUS alone,^{125, 126, 133, 155, 157, 160} two studies (n=150) reported harms of diagnostic followup ERCP,^{159, 160} and two studies (n=45) reported harms of diagnostic followup FNA.^{129, 159} Two studies (n=160) reported harms of MRI and one (n=98) reported harms of MRCP.¹⁵⁵ One study reported harms of CT.¹⁶⁰

Six of eight studies (n=421) identified no harms related to screening procedures.^{125, 126, 129, 133, 155, 157} Two studies identified harms from EUS, CT, and followup ERCP for abnormal EUS.^{159, 160}

Harms of EUS Plus or Minus Followup ERCP and/or FNA

Five studies (n=340) reported no complications related to EUS.^{125, 126, 133, 157} One study (n=38) reported no fever, bleeding, pain, or pancreatitis¹⁵⁹ for EUS with or without FNA. One study found that in 216 people receiving EUS, mild post-EUS pain was reported in 55 (25.5%), and adverse events related to anesthesia were reported in 13 people (6.0%).¹⁵⁹

Of 150 individuals who underwent ERCP as an intermediate test across two studies,^{159, 160} 15 people (10%) reported acute pancreatitis, nine of which required hospitalization. One study (n=24 receiving ERCP) found two cases of acute pancreatitis, one requiring hospitalization¹⁵⁹ and the other (n=126 receiving ERCP) found eight cases (6.3%) of pancreatitis requiring hospitalization (mean hospital stay 8.25 days) and five cases not requiring hospitalization. Cases of acute pancreatitis were similar between high risk and control groups.

Across two studies^{129, 159} and 45 people receiving EUS-guided FNA for diagnostic followup from initial EUS screening, no adverse events were reported.

Harms of MRI or MRCP

No complications were reported in two studies describing 240 people receiving screening MRI or MRCP.

Harms of CT

In 78 high-risk individuals and an unreported number of asymptomatic participants receiving CT in a single study,¹⁶⁰ there was one case (0.005%) of mild reaction to contrast that resolved.

Psychosocial Harms

Two screening studies (n=271)^{126, 127} assessed psychosocial harms (**Table 12**). In the Dutch FPC study,^{126, 158, 167, 170} the majority of respondents reported normal levels of distress at all time points.¹⁷⁰ Cancer Worry Scale scores decreased steadily and significantly over time (14.4 at baseline, 12.1 at 2 years, p<0.01), indicating reduced levels of worry from pre-screening to post-screening. Though there is no hard threshold for scoring the CWS, a score of 12 or higher (on a scale of 8, lower worry to 32, higher worry) may indicate severe worry levels,¹⁷⁰ so this change may indicate some clinical relevance.

In the Toronto program,^{127, 166, 168} scores of perceived pancreatic cancer risk, pancreatic cancer worry, and general distress were all similar between baseline and 3 months post-screening (**Table 13**).¹⁶⁸ On a self-rated worry scale from 1 (not at all) to 4 (a lot) point Likert scale, mean scores were between 1 and 2 and were similar at baseline and 3 months followup. Levels of distress were in the normal range at both time points; perceived risk as a self-reported percentage chance was 42.07 percent at baseline and 37.68 percent at 3 months followup (change not significant).

KQ4. Does Treatment of Screen-Detected or Asymptomatic Pancreatic Adenocarcinoma Improve Cancer Mortality, All-Cause Mortality, or Quality of Life?

No studies met inclusion criteria for KQ4.

No studies met our criteria, typically because of the lack of comparison groups in the studies

designs. This lack of comparison prohibits direct comparison of treatment outcomes in screen-detected compared to clinically-detected cancers. However, some studies reported treatment outcomes for select individual cases; and several studies have published longer-term followup at the cohort level. This information is provided in **Appendix D**. Briefly, six individuals—out of 10 for which data were available—were alive at 12 to 63 months followup,^{125, 129, 157, 159} two with distant metastases reported at 12 and 16 months.^{129, 157}

KQ5. What Are the Harms of Treatment of Screen-Detected Pancreatic Adenocarcinoma?

Of the 57 people who underwent surgery across all studies, harms of surgery were assessed in six studies including 32 people receiving surgery (56.1%, n=28; **Table 14**).^{125, 129, 133, 157, 160, 165} Methods of assessing harms were only reported in two U.S.-based studies, and were defined as clinical followup at 1 year in one study (n=5 receiving surgery)¹⁶⁵ and clinical followup at 1 month and 12 months after surgery (n=7 receiving surgery).¹⁶⁰ In the remaining studies, methods of assessing harms, and whether they were assessed in all study patients, were not reported. No studies reported assessing or identifying psychosocial harms following surgical intervention.

Harms following surgery were reported in seven people in two studies.^{125, 129} In the Danish screening program, stricture to the hepaticojejunal anastomosis was reported in one person 11 months after surgery, and unspecified post-operative complications in the other.¹²⁵ In the FaPaCa study of 10 people receiving surgery, two cases of post-operative fistula were reported, as well as three cases of diabetes, though it is not clear whether these were caused by surgery or existing co-morbidities.¹²⁹ In the two studies that systematically assessed harms in all surgical patients (n=12 people receiving surgery), no harms were reported.^{160, 165} The remaining two studies, neither of which reported methods of assessing harms (n=8 people receiving surgery), reported absence of surgical harms.^{133, 157}

Chapter 4. Discussion

Summary of Evidence

Thirteen fair quality prospective cohort screening studies of asymptomatic individuals at high familial risk for pancreatic adenocarcinoma (n=1317) met inclusion criteria for this review. Other than one study that included a small average risk comparison group (n=138), no screening studies in people without genetic syndromes or a strong family history met our inclusion criteria. All included studies represent new evidence since the previous evidence review, which did not identify any studies of screening for pancreatic adenocarcinoma.¹⁴⁰ While these populations are at particularly high risk and would normally be outside of the scope of the USPSTF, these represent the most clinically relevant populations for screening.

A summary of the evidence is provided in **Tables 15** and **16**. We found no studies evaluating whether screening for pancreatic adenocarcinoma impacts morbidity or mortality. We found low strength of evidence that imaging-based screening can detect pancreatic adenocarcinoma and its precursor lesions in individuals at high familial risk, and low strength of evidence that screening is associated with minimal to no psychosocial or procedural harms. We found insufficient evidence to assess measures of diagnostic accuracy, including sensitivity, specificity, predictive value, or false positives. Additionally, we found insufficient evidence to assess the benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma.

Detection of Pancreatic Adenocarcinoma

The yield of screening to detect pancreatic adenocarcinoma was low even in populations at elevated risk (7.8 per 1000 for initial screening; 15.6 per 1000 for the entire screening program). It appears that imaging-based screening with EUS or MRI can detect pancreatic adenocarcinoma, but there is insufficient evidence to evaluate the impact of screening on morbidity and mortality compared to clinical detection.

Observational data clearly suggest a survival benefit associated with earlier stage at detection, and surgical resection of early stage adenocarcinoma further enhances survival (**Chapter 1**). In this review, 12 of 18 (66.7%) cases detected through either initial screening or repeat screening were detected at stage I or II, when surgical intervention has the greatest potential to improve survival. This appears to be a more favorable proportion than the 9 percent to 19 percent of individuals who present clinically at early stage (**Table 1**),⁷ though sample sizes were limited and there was insufficient evidence to directly compare screen-detected and clinically detected pancreatic adenocarcinoma within the present review. Taken together, the included studies suggest that imaging-based screening in high-risk populations may result in stage shift. However, it is unclear if this represents a different spectrum of disease, is a result of lead-time bias, or provides evidence supporting screening. Two individuals reported in the included studies presented with advanced stage cancer during surveillance of abnormal screening findings, suggesting rapid progression of disease. Further, it is unknown if people with screen-detected adenocarcinoma will respond to treatment similarly to those with clinically-detected early stage adenocarcinoma, or if morbidity and mortality outcomes differ for screen-detected pancreatic

adenocarcinoma.

Detection of Precursor Lesions

Detection of precursor lesions of IPMN or PanIN ranged from 0 to 129 per 1000. However, studies did not systematically follow up these lesions for progression to adenocarcinoma, so this level of detection may or may not represent a clinical benefit, since it is yet unclear if detection and management of precursor lesions results in a decrease in cancer incidence, morbidity or mortality. Although the detection and removal of precursor lesions may be a preferable endpoint to pancreatic adenocarcinoma, in the absence of clear evidence about progression and assessment of lead time bias, potential overdiagnosis and subsequent harms associated with treatment of precursor lesions remain a possibility.

Harms of Screening and Treatment

In addition to the potential for overdiagnosis of precursor lesions, screening, followup testing, and surgical treatment may result in harms. Potential harms of endoscopic screening can include perforation (which can lead to death in a minority of cases), infection, iatrogenic pancreatitis, hemorrhage, bile peritonitis, and malignant seeding.¹⁷⁴ Screening for pancreatic adenocarcinoma also may be associated with psychosocial harms such as anxiety, depression, or cancer worry.^{167, 175} We found sparse evidence on the harms of screening, but the available evidence suggests few harms beyond a risk of acute pancreatitis following ERCP in two studies. In two studies (n=271) no evidence of psychosocial harm was detected.

Pancreatic surgery is associated with complication rates of 20%–50% in the post-operative period (**Chapter 1**). However, evidence on the harms of surgical intervention in screen-detected pancreatic adenocarcinoma was very limited, and could indicate an underestimate of harms in this body of evidence.

Applicability to Other Risk Groups

Although the high-risk populations included here are typically outside of the purview of the USPSTF, they represent the best data available on screening for pancreatic adenocarcinoma. Included populations were at known elevated pancreatic adenocarcinoma risk based on family history, and are enriched with people with known genetic mutations or syndromes. Only about 10 percent of pancreatic adenocarcinoma cases have a familial basis; of those, only about 20 percent are currently attributed to inherited genetic mutations.^{55, 61} Genetic mutations associated with seemingly sporadic pancreatic adenocarcinoma risk may lead to an expanded role for genetic risk stratification for screening,¹⁷⁶ but would still apply to a minority of people. The implications of these results to other at-risk populations are unknown, including those with new-onset diabetes, smoking history, or chronic pancreatitis.

Considerations for Risk Assessment in Primary Care

Given the low prevalence of pancreatic adenocarcinoma even in high-risk groups, risk assessment and identifying subgroups at the highest risk for pancreatic adenocarcinoma is critical for improving screening.⁹⁶ Increasingly, screening protocols expanding to include multiple behavioral and genetic risk factors that may be useful for primary care clinicians, including people with new-onset diabetes, smokers, and people over age 50.^{62, 66, 99, 177-179} Clinical identification of people who may be eligible for cancer detection based on presence of a series of otherwise nonspecific symptoms has been suggested, such as abdominal pain, back pain, pain while eating, unintentional weight loss, or diarrhea.^{64, 75, 76, 99, 180, 181} A U.S.-based modeling study demonstrated that incorporating demographic and behavioral risk factors, symptoms, comorbidities, and liver, pancreas, and gallbladder function could inform combined risk assessment, suggesting potential applications for electronic health record alerts.¹⁸²

Several validated risk assessment tools that combine symptoms and genetic and behavioral risk factors may help assess risk for pancreatic adenocarcinoma, and some are available as software packages or online tools with potential relevance to primary care (**Table 17**). These include QCancer,¹⁸³⁻¹⁸⁶ which was developed and validated in the United Kingdom and provides risk estimates across a range of tumor sites; PancPRO,¹⁸⁷⁻¹⁸⁹ which uses family history to estimate the probability an individual will develop familial pancreatic adenocarcinoma; and Your Disease Risk,^{190, 191} which offers risk assessments for 12 cancers and other health conditions. These tools ask users to input information, such as age, sex, height, weight, family history of pancreatic adenocarcinoma and other conditions, personal history of cancer, chronic and hereditary conditions, symptoms, smoking status, alcohol use, and diet. Validation studies have shown these tools to have relatively high concordance, with areas under the receiver operating characteristic curve of 0.71¹⁹⁰ to 0.92.¹⁸⁶

Limitations of Included Studies

The included body of evidence is subject to small sample sizes, not unexpected considering the low prevalence of high-risk populations and pancreatic adenocarcinoma. All studies except one¹⁶⁰ included only high-risk populations without controls, and many studies included a substantial proportion of people with known genetic mutations. Even among the three studies that included 100 percent of their study populations based on family history,^{129, 133, 155} pancreatic adenocarcinoma detection rates varied because of small samples and subsequent detection of previously unknown genetic mutations within populations during study followup.

No randomized trials of screening were included. No studies included a clinical followup or unscreened comparison group, so complete assessment of diagnostic accuracy is not possible. Some studies that evaluated multiple screening tests did not report whether imagers were blinded to results from other imaging and therefore, able to interpret test results independently. In addition, most studies with multiple imaging tests did not report whether pancreatic adenocarcinoma or other pathology findings were detected on one or more screening exams, so we cannot evaluate yield of individual imaging tests.

No included studies reported results stratified by family history, genetic mutation status, or other risk factors. Diagnostic yields were often reported for a multiple-test protocol, so yields within subgroups or attributable to specific screening tests were rarely reported. Harms of screening or treatment were not reported in all studies; of those studies that did, limitations included inadequate description of the methods of assessing harms, including whether all participants were systematically assessed.

Limitations of Our Approach

We included populations with family history of pancreatic adenocarcinoma, but excluded those whose study populations were solely people with known genetic mutations or syndromes. We did this to focus on evidence for primary care-relevant risk factors; however, this criterion was somewhat arbitrary since familial aggregation represents at least some level of genetic risk, in addition to aggregation of behavioral or environmental risk factors. As such this report should not be interpreted as an estimate of the yield of screening in people with known genetic mutations or syndromes, as studies exclusively focused on those populations were excluded.

We included only treatment studies conducted with screen-detected or asymptomatic populations. While consistent with the goals and key questions of the review, this limited our ability to comment systematically on the extensive literature showing the survival benefits of surgery for early-stage pancreatic adenocarcinoma and the significant morbidities that can occur during the post-operative period. The sparsity of harms reported in the included evidence should be interpreted not that surgical treatment is without risks, but rather that the magnitude of these potential harms is not well understood among people with screen-detected disease.

We excluded study populations with pancreatic endocrine tumors or exocrine tumors other than adenocarcinoma because of the distinct etiologies of these tumors. We limited our literature search to imaging-based screening studies, excluding biomarker-based screening studies, based on consensus in the field that these markers are not yet of sufficient precision to warrant screening studies.

Future Research Needs

The body of evidence in pancreatic adenocarcinoma would be strengthened with the addition of controlled trials that include screening and usual care groups of people at increased risk for pancreatic adenocarcinoma and the demonstration of improved morbidity or mortality. However, randomized trials would require large sample sizes and adequate followup time, and may not be practical to conduct. In the absence of such evidence, research is needed on how to best evaluate the health outcomes of screening using rigorous observational studies and statistical methods. Further, given the low incidence and severity of pancreatic adenocarcinoma and the potential survival benefits of early intervention, approaches to identifying individuals at the highest risk who should receive screening or followup are needed, such as through multiple risk factor assessments that may include otherwise nonspecific symptoms. As less invasive screening tests emerge, such as serum testing for multiple-biomarker panels, screening studies that include these

will be warranted. More research is also needed on the progression rates of various precursor lesions to pancreatic adenocarcinoma, and health outcomes and harms in people with these detected lesions, as well as incidentally-detected cancers. Continued understanding of the harms of screening and treatment, including those associated with the detection of precursor lesions, are also needed.

Conclusions

Imaging-based screening in groups at high familial risk can detect pancreatic adenocarcinoma and its precursor lesions with limited evidence of minimal harms. However, the impact of screening on morbidity and mortality in groups at high familial risk is not well documented, nor is the impact of screening in other groups at risk for pancreatic adenocarcinoma due to other behavioral or clinical risk factors. There is insufficient evidence to assess benefits or harms of surgical intervention for screen-detected pancreatic adenocarcinoma.

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Figure 1. Analytic Framework

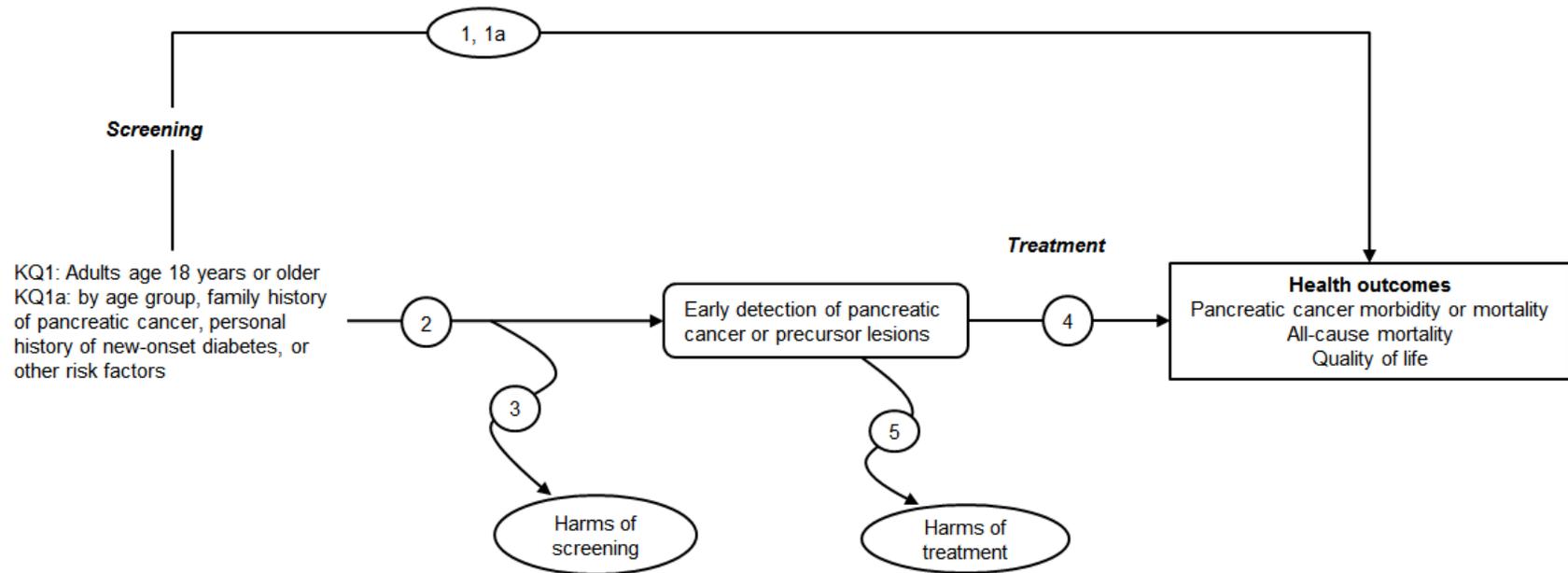
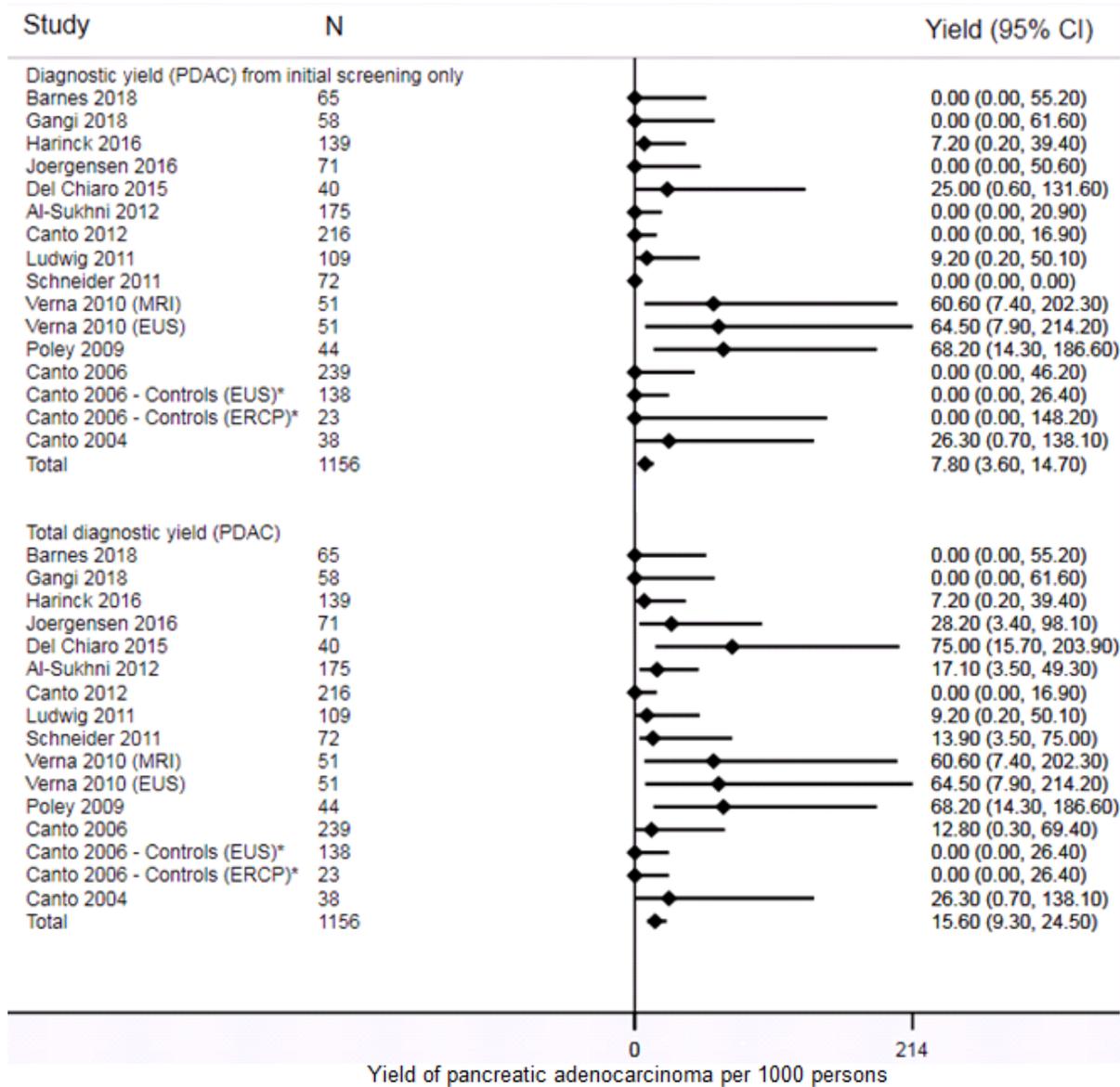


Figure 2. Diagnostic yield of prospective cohort screening studies in individuals at high risk of pancreatic adenocarcinoma



* Control group for Canto 2006 (n=161) not included in total N or total diagnostic yield

Table 1. Proportion of pancreatic cancers by clinical and AJCC stage and corresponding survival rates

Clinical stage ^{57*}	AJCC stage	Proportion of incident cases	5-year overall survival rate
Resectable	I/II	9%	10%-35% ^{4, 192‡}
Borderline resectable	II/III	10%	10%-35% ^{192‡}
Locally advanced [†]	III	30%	<5% ¹⁵⁰
Metastatic [†]	IV	50%	~2% ¹⁹³

Abbreviations: AJCC=American Joint Committee on Cancer

*Clinical stage defined by likelihood of successful surgery. Surgical staging criteria generally overlap with TNM staging criteria, but take into account tumor involvement of major vessels in the upper abdomen, which affect the likelihood of completely resecting the tumor. The TNM Staging System is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).

†Surgery not recommended

‡Depending on whether the tumor is completely resected

Table 2. Treatment recommendations for pancreatic cancer by clinical and AJCC stage

Clinical stage ^{57*}	AJCC stage	Chemotherapy recommendations	Radiation recommendations
Resectable	I/II	Neoadjuvant chemotherapy with high risk profile [†] with or without adjuvant chemotherapy for 6 months. 6 months' adjuvant chemotherapy for all others.	Concurrent with chemotherapy in patients with no neoadjuvant therapy and who have positive margins or node-positive disease
Borderline resectable	II/III	Neoadjuvant chemotherapy or adjuvant chemotherapy for total of 6 months.	
Locally advanced - not recommended for surgery	III	Adjuvant chemotherapy for patients with favorable comorbidity profile	Concurrent with chemotherapy in patients who do not develop metastatic disease during initial treatment
Metastatic - not recommended for surgery	IV	Palliative chemotherapy	Palliative radiation therapy

Abbreviations: AJCC=American Joint Committee on Cancer

*Clinical stage defined by likelihood of successful surgery. Surgical staging criteria generally overlap with TNM staging criteria, but take into account tumor involvement of major vessels in the upper abdomen, which affect the likelihood of completely resecting the tumor. The TNM Staging System is based on the extent of the tumor (T), the extent of spread to the lymph nodes (N), and the presence of metastasis (M).

[†] High risk profile can include people with poor performance status or comorbid conditions that may put them at high risk for abdominal surgery complications; people with high CA 19-9 levels

Table 3. Recent recommendations of other groups on screening for pancreatic cancer

Organization Country Year	Recommendation
American Academy of Family Physicians ¹⁹⁴ U.S. 2016	Adopted USPSTF recommendation against routine screening for pancreatic cancer in asymptomatic adults using abdominal palpation, ultrasonography, or serologic markers.
American Cancer Society ² U.S. 2016	Does not include screening for pancreatic cancer among its cancer screening guidelines. ACS states, “At this time, no major professional groups recommend routine screening for pancreatic cancer in people who are at average risk. This is because no screening test has been shown to lower the risk of dying from this cancer.” ¹⁹⁵
American College of Gastroenterology ¹⁹⁶ U.S. 2015	<p>Recommends individuals be considered at risk for hereditary pancreatic cancer if they:</p> <ul style="list-style-type: none"> • Have a known genetic syndrome associated with pancreatic cancer; • Have two relatives (including one first-degree relative) with pancreatic cancer; • Have three or more relatives with pancreatic cancer; or • Have a history of hereditary pancreatitis. <p>ACG also provides recommendations on the genes that should be considered during genetic testing of patients with suspected hereditary pancreatic cancer. According to ACG, due to the low incidence and prevalence of pancreatic cancer, it is not cost-effective to screen an asymptomatic general population.</p>
Royal Australian College of General Practitioners ¹⁹⁷ Australia 2016	Does not include screening for pancreatic cancer among its published guidelines on early detection of cancers
National Institute for Health and Care Excellence (NICE) ¹⁸¹ U.K. 2015	<p>Recommends using a suspected cancer pathway referral (for an appointment within 2 weeks) to refer people for pancreatic cancer if they are aged 40 and over and have jaundice.</p> <p>Recommends consideration of an urgent direct access CT scan (within 2 weeks) or an urgent ultrasound scan to assess for pancreatic cancer in people aged 60 and over with weight loss and one of the following: diarrhea, back pain, abdominal pain, nausea, vomiting, constipation, or new onset diabetes.</p> <p>NICE also has issued recommendations calling for further research on the diagnostic accuracy of tests available in primary care for suspected pancreatic cancer,¹⁹⁸ as well as the predictive value of symptoms for pancreatic cancer.¹⁹⁹</p>
European Society for Medical Oncology ²⁰⁰ Europe 2015	<p>Describes risk factors for pancreatic cancer, including:</p> <ul style="list-style-type: none"> • Genetic mutations in <i>BRCA2</i>, <i>p16</i>, <i>ATM</i>, <i>STK11</i>, <i>PRSS1/PRSS2</i>, <i>SPINK1</i>, <i>PALB2</i>, and DNA mismatch repair genes; • Family history of pancreatic cancer; and • Tobacco smoking, obesity, alcohol consumption, chronic pancreatitis. <p>Emphasizes the importance of screening high-risk individuals before symptoms arise, but does not provide an explicit recommendation or guideline for or against screening.</p>
Cancer Research UK ²⁰¹ U.K. 2014	No recommendation to screen for pancreatic cancer. States, “At the moment, there is no screening test reliable enough to use for pancreatic cancer in people at average risk.”

Table 3. Recent recommendations of other groups on screening for pancreatic cancer

Organization Country Year	Recommendation
Japan Pancreas Society ²⁰² Japan 2013	<p>States there is scientific evidence to support the following recommendations (“Grade B” recommendations):</p> <ul style="list-style-type: none"> • Patients should undergo further examination to detect pancreatic cancer if they have more than one of the following risk factors: <ul style="list-style-type: none"> • Family history of pancreatic cancer or hereditary pancreatic cancer syndrome; • Accompanying diseases such as diabetes mellitus, chronic pancreatitis, hereditary pancreatitis, intraductal papillary mucinous neoplasm, pancreatic cysts, or obesity; and • Lifestyle habits such as tobacco use or heavy drinking. • Patients should undergo further examination to detect pancreatic cancer if they have unexplainable abdominal pain, back pain, jaundice, body weight loss, early-onset diabetes mellitus, or deterioration of diabetes mellitus. • Ultrasound should be used as the first screening exam for pancreatic cancer.
International Cancer of the Pancreas Screening (CAPS) Consortium ⁹⁵ International 2012	<p>Recommends against screening in the general population. However, members recommend screening in the following high-risk groups:</p> <ul style="list-style-type: none"> • Individuals with 2 or more blood relatives (including at least one first-degree relative) with pancreatic cancer; • Carriers of <i>p16</i>, <i>BRCA2</i>, and hereditary non-polyposis colorectal cancer (HNPCC) mutations with a first-degree relative with pancreatic cancer; and • All individuals with Peutz-Jeghers syndrome.
Italian Registry for Familial Pancreatic Cancer ¹²⁸ Italy 2010	<p>Recommends annual screening with EUS +/- MRI in the following high-risk groups starting at age 45 or 15 years earlier than the earliest occurrence of PDAC in the family:</p> <ul style="list-style-type: none"> • Those with ≥3 FDRs, SDRs, or TDRs with PDAC in the same lineage; • Those with <i>BRCA2</i>, <i>BRCA1</i>, or <i>p16</i> variants with ≥1 FDR or SDR with PDAC; • A verified germline carrier of a Peutz-Jeghers syndrome kindred; • Those with ≥2 relatives in the same lineage affected with PDAC, at least one of whom is an FDR; • Those with hereditary pancreatitis; • Those with a ≥10-fold elevated risk of developing pancreatic cancer based on the PancPRO software.¹⁸⁷
International Symposium of Inherited Diseases of the Pancreas ²⁰³ International 2007	<p>Recommends screening in individuals with ≥10-fold elevated risk of developing pancreatic cancer, including:</p> <ul style="list-style-type: none"> • FAMMM kindreds with <i>p16</i> variant and ≥1 case of PDAC in a FDR or SDR; • Those with Peutz-Jeghers syndrome; • Those with hereditary pancreatitis; • Those with ≥3 FDRs, SDRs, or TDRs with PDAC; and • Possibly those with <i>BRCA2</i> or <i>BRCA1</i> variants with ≥1 case of PDAC in a FDR or SDR. <p>There was no consensus on a screening test, initiation age, or screening interval.</p>

Abbreviations: USPSTF = U.S. Preventive Services Task Force; PDAC = pancreatic ductal adenocarcinoma; FAMMM = familial atypical multiple mole melanoma; FDR = first-degree relative; SDR = second-degree relative; TDR = third-degree relative

Table 4. Included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	Screening population	N	Setting	Recruitment method	Recruitment period	Participant selection	Key inclusion / exclusion criteria	Include d for KQs
Barnes, 2018 ¹⁷¹ U.S. Fair	Adults with confirmed genetic mutation or family history of PDAC	75 enrolled; 65 screened	Pancreatic cancer screening clinic, academic medical center	Referrals from genetic counselors, treating physicians, or patient self-referrals	2012-2017	All eligible from referrals	Age 50 or within 10 years of youngest affected relative. Individuals with (a) ≥ 3 relatives with PDAC, including ≥ 1 FDR; or (b) 2 FDRs with PDAC; or (c) 1 FDR and 1 SDR with PDAC and PancPRO risk $\geq 5\%$; or (d) PJS; or (3) <i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i> , <i>ATM</i> , <i>CDKN2A</i> , or Lynch syndrome with 1 FDR or SDR with PDAC	2
Gangi, 2018 ¹⁷² U.S. Fair	Adults with confirmed genetic mutation or family history of PDAC	58	Comprehensive cancer center, academic medical center (Moffitt Cancer Center)	Referrals from physicians at Moffitt Cancer Center, other physicians, or by patient self-referral	2007-2017	All eligible from referrals	No personal history of PDAC, no prior pancreatic resection, no prior abdominal CT, MRI/MRCP, or EUS in past 3 years, no coexisting cancer, no HIV/AIDS, no pregnancy. Age ≥ 40 or within 10 years of youngest affected relative, life expectancy ≥ 5 years. Individuals with (a) ≥ 2 relatives with PDAC, including ≥ 1 FDR; or (b) PJS and age >30 ; or (c) HP; or (d) FAMMM; or (e) <i>BRCA2</i> and ≥ 1 FDR or SDR with PDAC	2
Harinck, 2016 ^{126, 158, 167, 170} Dutch Familial Pancreatic Cancer Study Netherlands Fair	Asymptomatic adults with confirmed genetic mutation or family history of PDAC	139 (from 81 families)	Academic medical center; multi-site	Recruited and evaluated by clinical geneticists at 5 medical centers in the Netherlands	2006-2013	Unknown	No personal history of PDAC, no upper GI tract obstruction, ASA score <3 . Asymptomatic, age ≥ 45 (age ≥ 30 for PJS patients) or within 10 years of youngest relative with PDAC, and (a) with <i>CDKN2A</i> variant; or (b) with confirmed PJS; or (c) with <i>BRCA1</i> , <i>BRCA2</i> , p53 or mismatch repair gene and family history of PDAC in ≥ 2 affected relatives; or (d) FDRs of patients with FPC ^c	2, 3

Table 4. Included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	Screening population	N	Setting	Recruitment method	Recruitment period	Participant selection	Key inclusion / exclusion criteria	Include d for KQs
Joergensen, 2016 ¹²⁵ Danish National Screening Program Denmark Fair	Adults with HP or family history of PDAC	71 (from 30 families)	Hereditary pancreatitis registry, academic medical center	HP group: identified from previous population-based study that recruited from HP registry and clinician referral. FPC group: Referrals from clinical genetics departments from across Denmark	2006-2014	Unknown	Age ≥30, able to endure a pancreatic resection. Individuals had (a) HP ^d ; or (b) FPC ^e	2, 3, 5
Del Chiaro, 2015 ¹⁶⁴ Sweden Fair	Adults with confirmed genetic mutation or family history of PDAC	40	Academic medical center (Karolinska University Hospital)	Relatives of patients treated for PDAC at Karolinska University Hospital, referrals from other Swedish centers, referrals from general practitioners	2010-2013	Unknown	Age ≥45 or within 10 years of youngest relative with PDAC. Individuals who (a) had 2 relatives (≥1 FDR) in the same lineage with PDAC; or (b) had ≥3 relatives (FDRs, SDRs or TDRs) in the same lineage with PDAC; or (c) had <i>BRCA1</i> , <i>BRCA2</i> , or <i>p16</i> variant and 1 FDR or SDR with PDAC; or (d) were verified germline carriers of PJS kindreds.	2

Table 4. Included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	Screening population	N	Setting	Recruitment method	Recruitment period	Participant selection	Key inclusion / exclusion criteria	Include d for KQs
Al-Sukhni, 2012 ^{127, 166, 168} Toronto Screening Program Canada Fair	Adults with confirmed genetic mutation or PJS or HP or family history of PDAC	262 (from 158 families)	Academic medical center (Mt Sinai Hospital & University Health Network, Toronto)	Cancer-related registries, studies, and research centers in Toronto, polyposis database, physician referral, self- referral, or local genetics center	2003-2011	Unknown	Asymptomatic individuals who: (a) were FDRs or SDRs of a PDAC patient in a family with ≥ 2 PDAC patients in the same lineage; or (b) had <i>p16</i> or <i>STK11</i> variants; or (c) had <i>BRCA1</i> or <i>BRCA2</i> variants and ≥ 1 blood relative with PDAC; or (d) had a clinical diagnosis of HP or PJS	2, 3
Canto, 2012 ^{163, 165} CAPS3 U.S. Fair	Adults with PJS or family history of PDAC or HBOC + family history of PDAC	216	Academic medical center; multi-site	Identified by participating sites (Johns Hopkins Hospital, Mayo Clinic, UCLA, Dana Farber Cancer Institute, MD Anderson Cancer Center) or through websites (for the CAPS 3 study, Lustgarten Foundation, and clinicaltrials.gov)	2006-2009	Consecutive	Karnofsky performance status ≥ 60 , no prior pancreas screening, no suspicion of pancreatic disease, no prior pancreas surgery, no medical conditions that could affect screening. ^b Age 40-80 or within 10 years of youngest relative with PDAC (or age ≥ 30 for PJS patients) and (a) had PJS; or (b) had HBOC with ≥ 1 affected FDR or SDR with PC; or (c) were relatives of patients with FPC with ≥ 1 affected FDR.	2, 5

Table 4. Included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	Screening population	N	Setting	Recruitment method	Recruitment period	Participant selection	Key inclusion / exclusion criteria	Include d for KQs
Ludwig, 2011 ¹⁵⁵ U.S. Fair	Adults with family history of PDAC	109	Familial pancreatic cancer registry, academic cancer center (MSKCC)	At-risk relatives who met eligibility criteria for the Familial Pancreatic Tumor Registry at Memorial- Sloan Kettering Cancer Center were invited to participate	2002-2009	All eligible from registry	Age ≥ 35 , no prior PDAC. Individuals had (a) ≥ 1 FDR diagnosed with PDAC before age 50; or (b) ≥ 1 FDR with PDAC and ≥ 1 other relative with PDAC, including; or (c) ≥ 3 SDRs with PDAC; or (d) known BRCA mutation and ≥ 1 relative with PDAC.	2, 3
Schneider, 2011 ^{129, 156, 161, 162, 169} FaPaCa Germany Fair	Adults with family history of PDAC	72	Familial pancreatic cancer registry, academic medical center; multi-site	FaPaCa registry participants who met eligibility criteria for screening program were invited to participate	2002-2009 ^h	All eligible from registry	FaPaCa registry enrollees who had no personal history of PDAC, were age ≥ 40 or within 10 years of youngest relative with PDAC and were (a) FDRs of an affected patient of an FPC ^f family; or (b) members of an FPC ^f family with a known genetic mutation such as <i>BRCA2</i> , <i>PALB2</i> , or <i>CDKN2A</i> .	2, 3, 5

Table 4. Included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	Screening population	N	Setting	Recruitment method	Recruitment period	Participant selection	Key inclusion / exclusion criteria	Include d for KQs
Verna, 2010 ¹³³ U.S. Fair	Adults with family history of PDAC	51 (from 43 families)	Familial pancreatic cancer registry, academic medical center (Columbia/NY Presbyterian)	Those referred to Pancreas Cancer Prevention and Genetics Program at Columbia University Medical Center/New York Presbyterian Hospital with a family history of pancreatic cancer and interest in their risk of disease were invited to participate	2005-2008	Unknown	Moderate risk: ≥ 2 relatives (FDRs, SDRs, or TDRs) with PDAC; or 1 FDR with PDAC <55 years old but not meeting high risk criteria. High risk: (a); had FPC ⁹ ; or (b) had known genetic syndrome (PJS, Lynch syndrome, <i>BRCA1</i> , <i>BRCA2</i> , FAMMM, or HP). Patients at average risk (≥ 1 relative with PDAC age >55) were generally not recommended for screening unless significant psychological distress led them to prefer to be screened.	2, 3, 5
Poley, 2009 ¹⁵⁷ Netherlands Fair	Asymptomatic adults with confirmed genetic mutation or family history of PDAC	44	Academic medical center	Recruited and evaluated by clinical geneticist	2005-2007	Unknown	Asymptomatic, age ≥ 40 or within 5 years of youngest relative with PDAC, no abdominal imaging in prior 3 years. Individuals had (a) ≥ 2 FDRs with PDAC; or (b) a known pathogenic mutation; or (c) family history of HBOC, Lynch syndrome, or Li-Fraumeni syndrome and had familial clustering of PDAC in ≥ 2 relatives.	2, 3, 5

Table 4. Included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	Screening population	N	Setting	Recruitment method	Recruitment period	Participant selection	Key inclusion / exclusion criteria	Include d for KQs
Canto, 2006 ¹⁶⁰ U.S. Fair	High-risk group: Adults with PJS or family history of PDAC Controls Adults with no suspicion of pancreatic disease	High-risk: 78 Controls: 161	Academic medical center (Johns Hopkins)	NFPTR, Johns Hopkins Colorectal Tumor Registry, referral from physician or genetic counselor. Control patients referred by gastroenterolo gist or endoscopist scheduled to perform EUS and/or ERCP	2001-2004	Unknown	Karnofsky performance status ≥60, able to undergo endoscopy, no suspected pancreatic disease, no previous gastrectomy or pancreatic resection. PJS group: Age ≥30 and with ≥2 criteria for PJS ^a . Family history group: age ≥40 or within 10 years of youngest relative with PDAC and from a family with ≥3 affected members, including ≥1 affected FDR. Control group: age ≥30 undergoing EUS and/or ERCP for non-pancreatic indications and with no personal or family history or PDAC and no suspicion of pancreatic disease.	2, 3, 5
Canto, 2004 ¹⁵⁹ U.S. Fair	Adults with PJS or family history of PDAC	38	Familial pancreatic cancer registry, academic medical center (Johns Hopkins)	NFPTR registry, self- referral, physician referral, Johns Hopkins Colorectal Tumor Registry	1998-2001	Consecutive	NFPTR group: NFPTR enrollees who: (a) had ≥3 relatives with PDAC, including ≥2 affected FDRs; and (b) were an FDR of ≥1 affected family member; and (c) were age ≥40 or within 10 years of the youngest affected relative. PJS group: Enrollees in the Johns Hopkins Hereditary Colorectal Tumor Registry who had PJS, pathologically confirmed hamartomatous polyps, family history of PJS, and/or characteristic mucocutaneous pigmentation	2, 3

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; PJS = Peutz-Jeghers syndrome; HP = hereditary pancreatitis; HBOC = hereditary breast and ovarian cancer; FDR = first-degree relative; SDR = second-degree relative; TDR = third-degree relative; FPC = familial pancreatic cancer; NFPTR = National Familial Pancreas Tumor Registry; CAPS = Cancer of the Pancreas Screening Study; NR = not reported; ASA = American Society of Anaesthesiologists; FaPaCa = German National Case Collection of Familial Pancreatic Cancer; FAMMM = Familial atypical multiple mole melanoma syndrome

^a Criteria for PJS include characteristic intestinal hamartomatous polyps, mucocutaneous melanin deposition, and family history of PJS

^b Medical conditions that could affect screening include: severe medical illness, bleeding diathesis or thrombocytopenia, renal insufficiency, allergic reaction to radiographic contrast material, morbid obesity, severe claustrophobia, and upper gastrointestinal tract obstruction.

Table 4. Included prospective cohort studies of screening for pancreatic adenocarcinoma

^c For Harinck 2016, familial pancreatic cancer was defined as a family with (a) ≥ 2 affected FDRs; **or** (b) ≥ 3 relatives in which the affected cases are FDR or SDRs of each other; **or** (c) ≥ 2 SDRs of whom at least one was aged <50 at time of diagnosis.

^d For Joergensen 2016, hereditary pancreatitis was defined as having a PRSS1 mutation OR having ≥ 2 FDRs or ≥ 3 SDRs in two or more generations with recurrent acute pancreatitis, and/or chronic pancreatitis

^e For Joergensen 2016, familial pancreatic cancer was defined as FDRs of patients with PDAC in families with 2 cases of PDAC where one relative was <50 years of age at diagnosis, or where ≥ 3 FDRs had PDAC

^f For Schneider 2011, familial pancreatic cancer was defined as a family with ≥ 2 FDRs with confirmed diagnosis of PDAC without evidence of another inherited tumor syndrome

^g For Verna 2010, familial pancreatic cancer was defined as having (a) ≥ 3 relatives (FDRs, SDRs, or TDRs) with PDAC; **or** (b) ≥ 2 FDRs with PDAC; **or** (c) 1 FDR and 1 SDR with PDAC, with ≥ 1 diagnosed age <55 .

^h FaPaCa registry started recruitment in July 1999, but screening program started in 2002

Table 5. Population characteristics for included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	N	Mean age (SD), range, years	Female, n (%)	White race and Jewish ancestry, n (%)	Family history of PDAC, n (%)	Known genetic mutation or syndrome, n (%)	Clinical risk factors, n (%)	Behavioral risk factors, n (%)
Barnes, 2018 ¹⁷¹ U.S. Fair	75 enrolled ^a ; 65 screened	56 (14) ^b , NR	46 (61.3)	White: NR Jewish: NR	Overall^c: 33 (44.0) Affected relatives: ≥2 FDRs: 12 (16.0) ≥3 any-degree relative: 16 (21.3) ≥1 FDR and ≥1 SDR: 5 (6.7)	Overall: 42 (56.0) <i>ATM</i> : 8 (10.7) <i>BRCA1</i> : 6 (8.0) <i>BRCA2</i> : 18 (24.0) <i>PALB2</i> : 3 (4.0) <i>CDKN2A</i> : 4 (5.3) Lynch syndrome: 2 (2.7) PJS: 1 (1.3)	Personal history of non-pancreatic cancer: 32 (42.7) Median BMI (IQR): 29 (8)	Current smokers: 0 (0) Former smokers: 18 (24.0) Never smokers: 56 (74.7) Unknown tobacco history: 1 (1.3)
Gangi, 2018 ¹⁷² U.S. Fair	58	60 (NR), NR	35 (60.3)	White: NR Jewish: NR	Overall: 57 (98.3) Affected relatives: ≥3 FDRs: 10 (17.2) 2 FDRs: 29 (50.0) ≥3 any-degree relative, including 1 FDR: 9 (15.5) 1 FDR or 1 SDR: 9 (15.5)	Overall: 10 (17.2) <i>BRCA2</i> : 9 (15.5) PJS: 1 (1.7)	NR	History of smoking: 8 (13.8) History of heavy alcohol use: 6 (10.3)
Harinck, 2016 ^{126, 158, 167, 170} Dutch FPC Study Netherlands Fair	139 (from 81 families)	51.1 (9.7), 20-73	76 (54.7)	White: NR Jewish: NR	Overall: 68 (48.9) FPC ^d : 68 (48.9)	Overall: 71 (51.1) PJS (<i>LKB1</i>): 7 (5.0) Li-Fraumeni syndrome (<i>p53</i>): 3 (2.2) <i>BRCA1</i> : 3 (2.2) <i>BRCA2</i> : 20 (14.4) FAMMM syndrome (<i>CDKN2A</i>): 38 (27.3)	Personal history of: Diabetes: NR Non-pancreatic cancer: 40 (28.8) Melanoma: 24 (17.3)	Current smokers: 16 (11.5)

Table 5. Population characteristics for included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	N	Mean age (SD), range, years	Female, n (%)	White race and Jewish ancestry, n (%)	Family history of PDAC, n (%)	Known genetic mutation or syndrome, n (%)	Clinical risk factors, n (%)	Behavioral risk factors, n (%)
Joergensen, 2016 ¹²⁵ Danish National Screening Program Denmark Fair	71 (from 30 families)	51.1 (NR), 26-72	35 (49.3)	White: NR Jewish: NR	Overall: 40 (56.3) ^e N (%) of 30 enrolled families with PDAC: Any cases: 23 (76.6) 1 case: 2 (6.7) 2 cases: 10 (33.3) 3 cases: 10 (33.3) ≥4 cases: 1 (3.3)	Overall: NR ^f HP: 31 (43.7) N (%) of 30 enrolled families with <i>PRSS-1</i> : 8 (26.7)	Personal history of: Diabetes (Type NR): 13 (18.3) Pancreatitis: 26 (36.6) N (%) of 30 enrolled families with cases of: Breast cancer: 5 (16.7%) Lung cancer: 3 (10%) Colon cancer: 2 (6.7%)	Current smoker: 18 (25.4) Former smoker: 17 (23.9) Never smoker: 36 (50.7)
Del Chiaro, 2015 ¹⁶⁴ Sweden Fair	40	49.9 (NR), 23-76	24 (60.0)	White: NR Jewish: NR	Overall: 38 (95.0) Affected relatives: 2 relatives: 14 (35.0) 3 relatives: 17 (42.5) 4 relatives: 5 (12.5) 5 relatives: 2 (5.0)	Overall: 8 (20.0) ^g <i>p16</i> : 4 (10.0) <i>BRCA1</i> : 1 (2.5) <i>BRCA2</i> : 3 (7.5)	Personal history of diabetes: NR	Current smokers: 4 (10.0)
Al-Sukhni, 2012 ^{127, 166, 168} Toronto Screening Program Canada Fair	262 ^m (from 158 families)	54 (NR), 22-89	173 (66.0)	White: 222 (84.7) Ashkenazi Jewish: 54 (20.6)	Overall: 159 (60.7) ≥2 affected relatives: 159 (60.7)	Overall: 93 (35.5) <i>PJS</i> : 7 (2.7) <i>HP</i> : 2 (0.8) <i>BRCA1</i> : 5 (1.9) <i>BRCA2</i> : 68 (26.0) <i>p16</i> : 11 (4.2)	Personal history of: Diabetes (Type NR): 13 (5.0) ⁿ Pancreatitis: 3 (1.2) ⁱ Non-pancreatic cancers: 62 (23.6) Family history of multiple primary cancers: 10 (3.8) BMI ≥30: 41 (17.0) ^j BMI 25-29.9: 87 (36.1) ^j BMI <25: 113 (46.9) ^j	Current smoker: 29 (11.8) ⁱ Former smoker: 89 (36.2) ⁱ Never smoker: 128 (52.0) ⁱ Alcohol intake: ≥1 drink/day: 44 (18.1) ⁱ 1-6 drink/week: 76 (31.3) ⁱ <1 drink/week: 59 (24.3) ⁱ <1 drink/month or never: 64 (26.3) ⁱ

Table 5. Population characteristics for included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	N	Mean age (SD), range, years	Female, n (%)	White race and Jewish ancestry, n (%)	Family history of PDAC, n (%)	Known genetic mutation or syndrome, n (%)	Clinical risk factors, n (%)	Behavioral risk factors, n (%)
Canto, 2012 ^{163, 165} CAPS3 U.S. Fair	216	56.1 (NR), 28-79	116 (53.6)	White: 212 (98.1) Ashkenazi Jewish: 28 (13.0)	Overall: 195 (90.3) Affected FDRs: 2 FDRs: 75 (34.7) ≥3 FDRs: 120 (55.6)	Overall: 21 (9.9) PJS: 2 (0.9) BRCA 2+ relative with PDAC: 19 (8.9)	Personal history of Type II diabetes: 9 (4.2)	Ever smoker: 18 (8.3) Regular or heavy alcohol use: 120 (55.6)
Ludwig, 2011 ¹⁵⁵ U.S. Fair	109	54 (11.4), 33-86	78 (71.6)	White: 100 (91.7) Jewish: 36 (33.0)	Overall: 109 (100) Affected FDRs: 1 FDR: 16 (14.7) 2 FDRs: 56 (51.4) 3 FDRs: 21 (19.8) 4 FDRs: 11 (10.3) 5 FDRs: 3 (2.8)	Overall: 7 (6.4) BRCA1/2: 7 (6.4)	Personal history of diabetes: NR Obese BMI: 15 (13.8) Overweight BMI: 24 (22.0) Normal BMI: 70 (64.2)	Current Smokers: 9 (8.3) Past Smokers 37 (33.9) Never Smokers: 63 (57.8)
Schneider, 2011 ^{129, 156, 161, 162, 169} FaPaCa Germany Fair	76	60 (NR), 35-85	NR (NR)	White: 76 (100) Ashkenazi Jewish: 0	Overall: 76 (100) Affected relatives: 2 FDRs or from MPCs family without genetic mutation: 44 (57.9) 3 relatives: 15 (19.7) 4 relatives: 13 (17.1) 5 relatives: 3 (3.9)	Overall: 2 (2.7) BRCA2: 2 (2.7)	Personal history of diabetes: NR Family history of: Diabetes: 1 (1.3) Pancreatitis: 2 (2.6) Breast cancer: 11 (14.5) Colon cancer: 8 (10.5) Lung cancer: 5 (6.6)	Smoking status: NR
Verna, 2010 ¹³³ U.S. Fair	51 (from 43 families)	52 (12.3), 29-77	33 (64.7)	White: 49 (96.1) Ashkenazi Jewish: 25 (49.0)	Overall: 51 (100) Affected FDRs: 0 FDRs: 7 (13.7) 1 FDRs: 29 (56.9) 2 FDRs: 12 (23.5) ≥3 FDRs: 3 (5.9) Affected relatives: 1 relative: 16 (31.4) 2 relatives: 22 (43.1) ≥3 relatives: 13 (25.5)	Overall: 7 (13.7) ^h BRCA1/2: 7 (13.7) ^h Family history suggestive of: BRCA1/2: 17 (33.3) HNPCC: 3 (5.9) FAMMM syndrome: 3 (5.9)	Personal history of: Type II diabetes: 2 (3.9) Non-pancreatic cancer: 15 (29.4)	Ever smoker: 17 (33.3) Previous heavy alcohol use: 3 (5.9) Social or occasional alcohol use: 39 (76.5) No alcohol use: 9 (17.6)

Table 5. Population characteristics for included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	N	Mean age (SD), range, years	Female, n (%)	White race and Jewish ancestry, n (%)	Family history of PDAC, n (%)	Known genetic mutation or syndrome, n (%)	Clinical risk factors, n (%)	Behavioral risk factors, n (%)
Poley, 2009 ¹⁵⁷ Netherlands Fair	44	NR (NR), 32-75	26 (59.1)	White: 44 (100) Jewish: NR	Overall: 21 (47.7) ≥2 affected FDRs: 21 (47.7)	Overall: 23 (52.3) PJS: 2 (4.5) HP ^k : 2 (4.5) FAMMM syndrome (<i>CDKN2A</i>): 13 (29.5) <i>BRCA1</i> : 3 (6.8) <i>BRCA2</i> : 2 (4.5) Li-Fraumeni syndrome (<i>p53</i>): 1 (2.3)	Personal history of diabetes: NR	Smoking status: NR
Canto, 2006 ¹⁶⁰ U.S. Fair	High risk group: 78	52 (NR), 32-77	44 (56.4)	White: 73 (94.0) Ashkenazi Jewish: 31 (40.0)	Overall: 72 (92.3) Affected FDRs: 1 FDR: 49 (62.8) 2 FDRs: 16 (20.5) 3 FDRs: 6 (7.7) 4 FDRs: 1 (1.3) Affected^l relatives: 3 relatives: 39 (50.0) 4 relatives: 19 (24.4) 5 relatives: 12 (15.4) 6 relatives: 2 (2.6) From kindred with young-onset PDAC (age <60): 48 (61.5)	Overall: 8 (10.3) PJS: 6 (7.7) <i>BRCA2</i> : 2 (2.6)	Personal history of: Diabetes (Type NR): 19 (24.4) Pancreatitis: 3 (3.8) Breast or ovarian cancer: 5 (6.4) Family history of: Diabetes: 33 (42.3) Breast or ovarian cancer: 27 (34.6)	Current smoker: 15 (19.2) Ever smoker: 35 (44.9) Regular alcohol intake: ^l 31 (39.7)
	Control group: 161	54 (NR), 30-80	69 (42.9)	White: 143 (88.8) Ashkenazi Jewish: 10 (6.2)	Overall: 0 (0)	NR	Personal history of diabetes (Type NR): 37 (23.0)	Current smoker: 32 (19.9) Ever smoker: 82 (50.9) Regular alcohol intake: ^l 69 (42.9)

Table 5. Population characteristics for included prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country Quality	N	Mean age (SD), range, years	Female, n (%)	White race and Jewish ancestry, n (%)	Family history of PDAC, n (%)	Known genetic mutation or syndrome, n (%)	Clinical risk factors, n (%)	Behavioral risk factors, n (%)
Canto, 2004 ¹⁵⁹ U.S. Fair	38	56.5 (NR), NR	23 (60.5)	White: NR Ashkenazi Jewish: 5 (13.2)	Overall: 37 (97.4) Affected FDRs: 1 FDR: 21 (55.3) 2 FDRs: 5 (13.2) 3 FDRs: 9 (23.7) 4 FDRs: 2 (5.3) Affected relatives: 0 relatives: 1 (2.6) 2 relatives: 6 (15.8) 3 relatives: 13 (34.2) 4 relatives: 11 (28.9) 6 relatives: 4 (10.5) 7 relatives: 3 (7.9)	Overall: 1 (2.6) PJS: 1 (2.6)	Personal history of: Diabetes (Type NR): 7 (18.4) Pancreatitis: 0 (0) Non-pancreatic cancer: 12 (31.6) Family history of: Diabetes: 26 (68.4) Pancreatitis: 11 (28.9) Breast cancer: 21 (55.3)	Current smoker: 5 (13.2) Ever smoker: 18 (47.4) Regular alcohol intake: ^j 16 (42.1)

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; PJS = Peutz-Jeghers syndrome; HP = hereditary pancreatitis; HBOC = hereditary breast and ovarian cancer; FDR = first-degree relative; SDR = second-degree relative; TDR = third-degree relative; FPC = familial pancreatic cancer; CAPS = Cancer of the Pancreas Screening Study; NR = not reported; FaPaCa = German National Case Collection of Familial Pancreatic Cancer; FAMMM = Familial atypical multiple mole melanoma syndrome; HNPCC: hereditary nonpolyposis colorectal cancer

^a For Barnes 2018, population characteristics are provided for the 75 individuals enrolled in the study. Population characteristics are not reported separately for the 65 individuals who underwent screening.

^b Barnes 2018 reports age as median (interquartile range) rather than mean (standard deviation)

^c For Barnes 2018, 33 participants were classified as having “familial pancreatic cancer” [defined as having (a) ≥ 3 relatives with PDAC, including ≥ 1 FDR; or (b) 2 FDRs with PDAC; or (c) 1 FDR and 1 SDR with PDAC and PancPRO risk $\geq 5\%$]. The remaining 42 individuals were classified as having a known genetic mutation; however, the inclusion criteria specify that those with BRCA1, BRCA2, PALB2, ATM, CDKN2A, or Lynch syndrome also had to have ≥ 1 FDR or SDR with PDAC. Only patients with PJS (n=1) could be enrolled in the study regardless of family history of PDAC.

^d For Harinck 2016, 68 participants were classified as having “familial pancreatic cancer” [defined as a member of a family with (a) ≥ 2 affected FDRs; **or** (b) ≥ 3 relatives in which the affected cases are FDR or SDRs of each other; **or** (c) ≥ 2 SDRs of whom at least one was aged <50 at time of diagnosis]. The remaining 71 participants (classified as having a known genetic mutation) have a range of 0-7 relatives with PDAC; the authors do not report the total number of study participants who have relatives with PDAC.

^e For Joergensen 2016, the population was classified as the familial pancreatic cancer group (n=40; 56.3%) and the hereditary pancreatitis group (n=31; 43.7%). However, some patients in the hereditary pancreatitis group also had a family history of PDAC. The authors report that 76.6% of the 30 enrolled families had a family history of PDAC, but they do not report the number of enrolled individuals with a family history of PDAC.

^f For Joergensen 2016, 26.7% of the 30 enrolled families had a *PRSS-1* variant. The authors do not report the number of enrolled individuals with this variant.

^g For Del Chiaro 2015, genetic testing during the study identified 4 patients (10.0%) with a p16 variant, 3 patients (7.5%) with *BRCA2* variant, and 1 patient (2.5%) with *BRCA1* variant. The authors do not report whether there is overlap in these populations (i.e., whether any patients had multiple variants)

^h For Verna 2010, 19 patients were tested for *BRCA1* and *BRCA2*, and 7 of the 19 (36.8%) tested positive for *BRCA1* or *BRCA2*.

ⁱ For Al-Sukhni 2012, the denominators differ for various baseline characteristics based on which participants enrolled, dropped out, and returned the baseline questionnaire. The denominator is n=262 except for the following: personal history of diabetes or pancreatitis (n=250), smoking status (n=246), frequency of alcohol use (n=243), and BMI (n=241)

^j For Canto 2004 and Canto 2006, regular alcohol intake was defined as ≥ 2 drinks/week for women; ≥ 3 drinks/week for men

^k For Poley 2009, one of the patients with hereditary pancreatitis had a known *PRSS-1* mutation

Table 5. Population characteristics for included prospective cohort studies of screening for pancreatic adenocarcinoma

¹ For Verna 2010, “affected relatives” refers to first-, second-, or third-degree relatives

^m For Al-Sukhni 2012, baseline characteristics are reported for 262 patients enrolled in program; however, only 175 patients underwent screening. The study does not report baseline characteristics separately for the 175 patients who underwent screening.

ⁿ For Al-Sukhni 2012, N (%) for diabetes represents individuals diagnosed with diabetes mellitus prior to 1 year ago. No other studies report time since diagnosis of diabetes.

Table 6. Description of screening programs for pancreatic adenocarcinoma from included prospective cohort studies

Author, year Screening program Country Quality	Screening population	Initial screening protocol	Diagnostic workup ^b	Blinding procedures	Repeated screening and surveillance protocol	Follow-up, in months	Outcomes assessed
Barnes, 2018 ¹⁷¹ U.S. Fair	Adults with confirmed genetic mutation or family history of PDAC	MRI	Patients with suspicious lesions on MRI underwent EUS +/- FNA. Those with abnormalities on EUS/FNA were discussed at a multidisciplinary conference and managed according to the consensus of the clinical team, including referral to surgery if needed.	EUS was assessed with knowledge of MRI test results	Patients with no pancreatic abnormalities were rescreened annually using the same screening protocol. Surveillance for patients with abnormalities were individualized according to the consensus of the multidisciplinary conference.	NR	Diagnostic yield
Gangi, 2018 ¹⁷² U.S. Fair	Adults with confirmed genetic mutation or family history of PDAC	EUS	Patients with lesions ≥ 1 cm on EUS underwent FNA. If FNA results were consistent with cancer, patients underwent standard workup and staging with radiology studies and surgical and/or oncologic evaluation.	NR	Patients with no pancreatic abnormalities were rescreened annually using the same screening protocol for 5 years. Patients with lesions < 1 cm underwent repeat EUS at 3 months followed by MRI/MRCP at 6 months followed by annual MRI/MRCP if lesions were unchanged in size. Patients with benign or indeterminate results on FNA underwent CT. Those with indeterminate CT results underwent repeat EUS in 3 months.	Planned 60.0	Diagnostic yield
Harinck, 2016 ^{126, 158, 167, 170} Dutch FPC Study Netherlands Fair	Asymptomatic adults with confirmed genetic mutation or family history of PDAC	EUS and MRI	Patients with lesions detected on EUS had a case description and video recording reviewed by endosonographers. Patients with suspected malignancy or premalignant lesions were referred for surgery.	MRI and EUS were assessed without knowledge of other test results	Patients with lesions of unknown significance were rescreened in 3 months. Those with cysts or side-branch IPMN with diameter 10-30mm without malignant features were rescreened in 6 months. Those with negative findings on initial screen were rescreened annually.	Planned 12.0	Diagnostic yield Screening harms Treatment outcomes
Joergensen, 2016 ¹²⁵ Danish National Screening Program Denmark Fair	Adults with HP or family history of PDAC	EUS ^a	Patients with suspicious masses on EUS underwent FNA. If FNA identified potential malignancy or dysplasia, diagnostic laparoscopic US +/- biopsy was performed. Those with suspected or confirmed malignancy or dysplasia were referred to surgery.	NR	Patients with suspected lesions but negative biopsy results underwent control EUS. All patients who screened negative remained in the screening program and continued receiving annual EUS and CA 19-9 testing.	Mean 60.0 (range 2.0-92.0)	Diagnostic yield Screening harms Treatment outcomes Treatment harms

Table 6. Description of screening programs for pancreatic adenocarcinoma from included prospective cohort studies

Author, year Screening program Country Quality	Screening population	Initial screening protocol	Diagnostic workup ^b	Blinding procedures	Repeated screening and surveillance protocol	Follow-up, in months	Outcomes assessed
Del Chiaro, 2015 ^{164b} Sweden Fair	Adults with confirmed genetic mutation or family history of PDAC	MRI	Patients with abnormalities on MRI underwent EUS +/- FNA and/or CT. Those with suspected cancer or premalignant lesions were referred for surgery.	NR	Patients with unspecified findings or IPMN without indication for surgery were recommended for a 6-month followup MRI. Those who screened negative on initial MRI were rescreened after 1 year using the same screening protocol.	Mean 12.9 (range 0-36.0)	Diagnostic yield
Al-Sukhni, 2012 ^{127, 166, 168} Toronto Screening Program Canada Fair	Adults with confirmed genetic mutation or PJS or HP or family history of PDAC	MRI	Patients with abnormal findings on MRI underwent followup MRI plus CT, EUS, and/or ECRP within 3-6 months. If followup testing identified suspected malignancy or dysplasia, surgery was recommended.	NR	All patients, including those who screened negative on initial testing and resected patients who did not have invasive cancer, underwent annual testing under the same screening protocol.	Mean 50.4 (range 0-98.4)	Diagnostic yield Screening harms Treatment outcomes
Canto, 2012 ^{163, 165} CAPS3 U.S. Fair	Adults with PJS or family history of PDAC or HBOC + family history of PDAC	EUS and CT and MRI/MRCP	Patients with abnormalities on any of the 3 initial screening tests underwent FNA as part of the EUS procedure. ERCP was performed at the discretion of the clinical team. Those with suspected pancreatic neoplasms were referred for surgery.	MRI, CT, and EUS were assessed without knowledge of other test results	Patients with worrisome lesions but no resection scheduled were rescreened at 3 months. Those with small cysts or non-worrisome lesions were rescreened at 6-12 months. Those with normal pancreas or pancreatitis-like abnormalities were rescreened at 1-3 years.	Mean 28.8 (range 14.0-47.2)	Diagnostic yield Treatment harms
Ludwig, 2011 ¹⁵⁵ U.S. Fair	Adults with family history of PDAC	MRCP or CT for those unwilling to undergo MRCP	Patients with lesions on MRCP underwent EUS. Those with suspected pre-malignant or malignant lesions on EUS underwent immediate FNA. Those with suspected pre-malignant or malignant lesions on followup testing were referred for surgery.	NR	Patients with normal results on initial screening continued to undergo annual testing under same screening protocol.	Planned 24.0	Diagnostic yield Screening harms

Table 6. Description of screening programs for pancreatic adenocarcinoma from included prospective cohort studies

Author, year Screening program Country Quality	Screening population	Initial screening protocol	Diagnostic workup ^b	Blinding procedures	Repeated screening and surveillance protocol	Follow-up, in months	Outcomes assessed
Schneider, 2011 ^{129, 156, 161, 162, 169} FaPaCa Germany Fair	Adults with family history of PDAC	EUS and MRI/MRCP	Patients with suspicious lesions underwent repeat EUS in 6 weeks or EUS-FNA if lesions were potentially suggestive of malignancy. Those with suspected malignancy or pre-malignancy on followup tests were referred to surgery.	MRI assessed without knowledge of other test results	Patients who screened negative continued to undergo annual screening. Interdisciplinary board could recommend close followup (repeated EUS and MRI/MRCP after 12 weeks, re-evaluation after 6 months and 12 months).	Median 44.0	Diagnostic yield Screening harms Treatment outcomes Treatment harms
Verna, 2010 ^{133b} U.S. Fair	Adults with family history of PDAC	EUS or MRI	Patients with abnormalities underwent EUS-FNA. ERCP was performed at the discretion of the interventional endoscopist.	Radiologist was blinded to patient's pancreatic risk factors	High-risk patients and those who underwent partial pancreatectomies were re-screened every 6 months. Those at moderate risk underwent annual imaging. Those at average risk returned for annual visits and further testing if they developed symptoms or new onset diabetes.	NR	Diagnostic yield Screening harms Treatment outcomes Treatment harms
Poley, 2009 ¹⁵⁷ Netherlands Fair	Asymptomatic adults with confirmed genetic mutation or family history of PDAC	EUS	Patients with abnormalities on EUS underwent CT and/or MRI. Criteria for referral to surgery NR.	NR	Patients with small cystic lesions were followed up bi-annually with EUS and MRI.	NR	Diagnostic yield Screening harms Treatment outcomes Treatment harms
Canto, 2006 ^{160b} U.S. Fair	High-risk: Adults with PJS or family history of PDAC Controls: Adults with no suspicion of pancreatic disease	High-risk: EUS and CT Controls: EUS and/or ERCP	Both groups: Patients with abnormalities on EUS underwent EUS-FNA during the same procedure and were offered ERCP. Those with suspected malignancy or dysplasia on followup testing were referred for surgery.	EUS, FNA and CT were assessed without knowledge of other test results.	Both groups: Patients who had abnormalities on EUS but did not have surgery were offered followup EUS, FNA, and CT within 3-6 months. All patients were offered repeat EUS within 1 year of the initial screening.	Planned 12.0	Diagnostic yield Screening harms Treatment outcomes Treatment harms

Table 6. Description of screening programs for pancreatic adenocarcinoma from included prospective cohort studies

Author, year Screening program Country Quality	Screening population	Initial screening protocol	Diagnostic workup ^b	Blinding procedures	Repeated screening and surveillance protocol	Follow-up, in months	Outcomes assessed
Canto, 2004 ¹⁵⁹ U.S. Fair	Adults with PJS or family history of PDAC	EUS	Patients with abnormalities on EUS underwent EUS-FNA at the same procedure, underwent CT, and were offered ERCP. Those with suspected malignancy or dysplasia on followup testing were referred for surgery.	FNA and CT were assessed without knowledge of other test results.	Patients who had abnormalities on EUS but did not undergo surgery were offered followup EUS, FNA, and CT within 3-6 months. All patients were offered repeat EUS within 1 year of initial screening and were followed until the end of the study.	Mean 22.4 (range 11.3-50.5)	Diagnostic yield Screening harms Treatment outcomes

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; PJS = Peutz-Jeghers syndrome; HP = hereditary pancreatitis; FPC = familial pancreatic cancer; NFPTR = National Familial Pancreas Tumor Registry; CAPS = Cancer of the Pancreas Screening Study; NR = not reported; FaPaCa = German National Case Collection of Familial Pancreatic Cancer; EUS = endoscopic ultrasound; CT = computed tomography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; OGTT = oral glucose tolerance test; HBOC = hereditary breast and ovarian cancer; FNA = fine-needle aspiration

^a Two patients underwent US due to severe claustrophobia

^b Final pathology was determined by surgery except as noted. For Del Chiaro 2015 and Verna 2010, final pathology was determined by surgery or FNA. For the control group for Canto 2006, final pathology was determined by ERCP.

Table 7. Findings from screening programs for pancreatic adenocarcinoma across included prospective cohort studies

Finding	N
People screened	1317
Abnormal findings (test positive)	Inconsistently reported (~323)
Received FNA/biopsy	Inconsistently reported (~93)
Confirmed pancreatic adenocarcinoma on biopsy/FNA/CT (advanced disease, no surgical intervention)	4
Surgeries performed	57
Confirmed pancreatic adenocarcinoma on surgery	14
Other confirmed findings on surgery	43
IPMN	5
PanIN	9
IPMN + PanIN	20
SCA + PanIN	4
Other (NET; SCA; liver hyperplasia)	5

Abbreviations: FNA = fine-needle aspiration; CT = computed tomography; IPMN = Intraductal papillary mucinous neoplasm; PanIN = Pancreatic Intraepithelial Neoplasia; SCA = serous cystadenoma

Table 8. Results from prospective cohort studies of screening for pancreatic adenocarcinoma^a

Author, year Screening program Country Quality	Initial screening test	Screened with initial test, N	Definition of abnormal results on initial screening test	Abnormal results on initial test, N ^g	PDAC detected, N	PDAC yield per 1000 persons (95% CI) ⁱ	PDAC stage at detection: N	IPMN, PanIN and other pathology	Other pathology , N ^b	Other pathology, yield per 1000 persons
Gangi, 2018 ¹⁷² U.S. Fair	EUS	58	Presence of a mass or cyst	19	0	0 (0-61.6) ⁱ	N/A	IPMN + PanIN	1	17.2
Joergensen, 2016 ¹²⁵ Danish National Screening Program Denmark Fair	EUS	71	Suspicious mass suggestive of PDAC or high-grade dysplasia	NR	2	28.2 (3.4-98.1)	T3N0M0 (Stage IIA): 1 ^k T1N0M0 (Stage IA): 1 ^k	NR	NR	N/A
Poley, 2009 ¹⁵⁷ Netherlands Fair	EUS	44	Mass lesions, cystic lesions, duct aberrations and signs of chronic pancreatitis	11 ^e	3	68.2 (14.3-186.6)	T3N1M0 (Stage IIB): 2 T1N0M0 (Stage IA): 1	NR	NR	N/A
Canto, 2004 ¹⁵⁹ U.S. Fair	EUS	38	(a) Presence of focal lesion such as a mass, nodule, or cyst; or (b) ≥3 of 9 EUS features of chronic pancreatitis	29	1	26.3 (0.7-138.1)	T2N1M0 (Stage IIB): 1	IPMN + PanIN	1	26.3
								PanIN	2	52.6
								PanIN + SCA	2	52.6
								SCA	1	26.3
Canto, 2006 ^{160a} U.S. Fair	EUS and CT	78	(a) Presence of focal lesion such as a mass, nodule, or cyst; or (b) ≥3 of 9 EUS features of chronic pancreatitis	EUS: 17 CT: NR	1	12.8 (0.3-69.4)	Metastatic to the liver (Stage NR) ^k	IPMN	1	12.8
								PanIN	1	12.8
								IPMN + PanIN	5	64.1
	EUS and/or ERCP	EUS: 138 ^h ERCP: 23 ^h	(a) Presence of focal lesion such as a mass, nodule, or cyst; or (b) ≥3 of 9 EUS features of chronic pancreatitis	EUS: 1 ERCP: 0	0	0 (0-26.4) ⁱ ERCP: 0 (0-148.2) ⁱ	N/A	Any precursor lesions	0	0

Table 8. Results from prospective cohort studies of screening for pancreatic adenocarcinoma^a

Author, year Screening program Country Quality	Initial screening test	Screened with initial test, N	Definition of abnormal results on initial screening test	Abnormal results on initial test, N ^g	PDAC detected, N	PDAC yield per 1000 persons (95% CI) ⁱ	PDAC stage at detection: N	IPMN, PanIN and other pathology	Other pathology , N ^b	Other pathology, yield per 1000 persons
Canto, 2012 ^{163, 165} CAPS3 U.S. Fair	EUS and CT and MRI/MRCP	216	Main pancreatic duct dilation (duct diameter, >3mm in the head, 2mm in the body, and 1mm in the tail). Reporting of imaging findings was standardized across MRI, CT, and EUS using nomenclature developed at a prior 2004 CAPS consensus.	CT: 24 EUS: 92 MRI: 72	0	0 (0- 16.9) ⁱ	N/A	IPMN + PanIN (multifocal)	5	23.1
Harinck, 2016 ^{126, 158, 167, 170} Dutch FPC Study Netherlands Fair	EUS and MRI	139	Solid lesions of any size and cystic lesions larger than 10mm. These include all solid lesions suspicious for malignancy and any lesion that fulfils the revised Sendai criteria for surgery or close followup ^d	EUS: 8 MRI: 9	1	7.2 (0.2- 39.4)	T1N0M0 (Stage IA):1	PanIN (multifocal)	1	7.2
Al-Sukhni, 2012 ^{127, 166, 168} Toronto Screening Program Canada Fair	MRI	175	Pancreatic mass, main duct dilation suggesting MD- IPMN or mass causing duct obstruction, branch duct dilation with communication to the main duct suggesting BD-IPMN, or extra- pancreatic mass or lesions.	19	3	17.1 (3.5- 49.3)	T1N1M0 (Stage IIB):1 ^k Unresected mass >3cm (Stage NR): 2 ^k	IPMN	1	5.7
								IPMN + PanIN	1	5.7
								Neuroendocrine tumor	1	5.7
Schneider, 2011 ^{129, 156, 161, 162, 169m} FaPaCa Germany Fair	EUS and MRI/MRCP	72	Detectable solid or cystic lesions that could not be classified as a benign or malignant lesion by imaging, cases of diffuse parenchymal irregularities. MRI/MRCP images evaluated for filling defects, stenoses, duct interruption, focal lesions, focal hypoenhancement	26	1	13.9 (3.5- 75.0)	Stage NR: 1 ^l (patient had lung metastases on 12 month followup)	IPMN + PanIN	2	27.8
								PanIN	3	41.7
								PanIN + SCA	1	13.9
								SCA	2	27.8
								Liver hyperplasia	1	13.9

Table 8. Results from prospective cohort studies of screening for pancreatic adenocarcinoma^a

Author, year Screening program Country Quality	Initial screening test	Screened with initial test, N	Definition of abnormal results on initial screening test	Abnormal results on initial test, N ^g	PDAC detected, N	PDAC yield per 1000 persons (95% CI) ⁱ	PDAC stage at detection: N	IPMN, PanIN and other pathology	Other pathology , N ^b	Other pathology, yield per 1000 persons
Verna, 2010 ^{133a} U.S. Fair	EUS or MRI	EUS: 31 MRI: 33	EUS: mass lesions, IPMNs, cysts, and chronic pancreatitis-like parenchymal changes MRI: NR	EUS: 27 MRI: 11	2	EUS: 64.5 (7.9- 214.2) MRI: 60.6 (7.4- 202.3)	Stage IV metastatic:1 Resectable PDAC with multifocal IPMN + PanIN2: 1	IPMN + PanIN (multifocal)	4	EUS: 129.0 MRI: 121.2
Barnes, 2018 ¹⁷¹ U.S. Fair	MRI	65	Any lesion with (a) serial growth; (b) size >20mm; (c) solid component; or (d) mural nodule.	28	0	0 (0- 55.2) ⁱ	N/A	Any precursor lesions ^j	0	0
Del Chiaro, 2015 ^{164a} Sweden Fair	MRI	40	Solid nodules and suspected IPMN lesions.	16	3 ^c	75.0 (15.7- 203.9)	T1N0M0 (Stage IA): 1 T3N0M0 (Stage IIA) with IPMN: 1 ^k T4N1M0 (Stage III): 1 ^{ck}	IPMN with progression	2	50.0
Ludwig, 2011 ¹⁵⁵ U.S. Fair	MRCP	109	Cystic lesions with a solid or nodular component, pancreatic duct dilation, pancreatitis or other lesions deemed concerning by a multidisciplinary group	18	1	9.2 (0.2- 50.1)	T3N0M0 (Stage IIA): 1	IPMN	1	9.2
								IPMN + PanIN	1	9.2
								PanIN	2	18.3
								PanIN + SCA	1	9.2

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; EUS = endoscopic ultrasound; CT = computed tomography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; IPMN = Intraductal papillary mucinous neoplasm; PanIN = Pancreatic Intraepithelial Neoplasia; SCA = serous cystadenoma; CAPS = Cancer of the Pancreas Screening Study; N/A = not applicable; FPC = familial pancreatic cancer

Note: Yield calculated as (number of patients with final pathology ÷ number receiving screening test) * 1000 persons

^a Final pathology was determined by surgery except as noted. For Del Chiaro 2015 and Verna 2010, final pathology was determined by surgery or FNA. For the control group for Canto 2006, final pathology was determined by ERCP.

^b Represents final pathologies as determined by surgery or FNA. Does not include suspected IPMNs and PanINs followed in surveillance.

^c For Del Chiaro 2015, one detected PDAC cases was found at initial screening (T1N0M0; Stage IA), one case was under surveillance for a branch-duct IPMN and after 2 years of surveillance PDAC was found (T3N0M0; Stage IIA), and one case (T4N1M0; Stage III) was detected at 36 months having missed an annual screening.

^d Criteria were: cysts ≥3cm, cysts with thickened/enhancing cyst walls and/or mural nodules and/or solid component, main branch IPMN with main pancreatic duct ≥10mm and side branch IPMN with side duct dilations/cysts >10mm.

^e Screening detected 12 abnormal findings in 11 individuals

Table 8. Results from prospective cohort studies of screening for pancreatic adenocarcinoma^a

^f For Joergensen 2016, the population was classified as the familial pancreatic cancer group (n=40; 56.3%) and the hereditary pancreatitis group (n=31; 43.7%). However, some patients in the hereditary pancreatitis group also had a family history of PDAC. The authors report that 76.6% of the 30 enrolled families had a family history of PDAC, but they do not report the number of enrolled individuals with a family history of PDAC.

^g Represents number of patients with abnormal results as defined by each individual study, according to the criteria in the “definition of abnormal results” column. These criteria often were designed to detect not only PDAC and precursor lesions, but also findings such as pancreatitis or neuroendocrine tumors

^h Canto 2006 reports that 161 patients were enrolled in the control group, and reports results separately for abnormalities on EUS among 138 controls and abnormalities on ERCP for 23 patients.

ⁱ Confidence intervals were calculated based on the data provided in each study. For most studies, confidence intervals are 95% CIs and are two sided. For studies that detected 0 relevant findings (Canto 2006 control group, Canto 2012, Gangi 2018, Barnes 2018), confidence intervals are 97.5% CIs and are one-sided.

^j Barnes 2018 reports that two patients had suspected branch-duct IPMN on EUS, one of which was negative for malignancy on cytology. However, neither IPMN was confirmed by surgical pathology.

^k Detected during repeat screening, not on initial screen

^l Schneider 2011 does not report whether case was detected on initial screening or repeat screening

^m Three articles report longer term followup of the FaPaCa cohort combined with other cohorts. One article¹⁶¹ reports results from a cohort in Leiden (Germany) and separately reports results from the FaPaCa cohort extending 2 years beyond the Schneider 2011 article; this article reports on the detection of 1 PDAC case in the FaPaCa cohort, which is the same number of PDAC cases reported in Schneider 2011. Two other articles^{156, 162} report combined results from the Leiden cohort, a cohort in Madrid (Spain), and the FaPaCa cohort extending 6 years beyond the Schneider 2011 article; these articles report on the detection of 1 PDAC case¹⁶² or 2 PDAC cases¹⁵⁶ but do not report results separately by site.

Table 9. Yield on initial and repeated screening for pancreatic adenocarcinoma from prospective cohort studies

Author, year	Initial screening test	Screened with initial test, N	Abnormal results on initial test, N	PDAC detected following initial screen, N	PDAC yield following initial screen, per 1000 persons, (95% CI) ^c	PDAC detected on repeated screen, N	Total PDAC detected, N	Total PDAC yield per 1000 persons, (95% CI) ^c
Gangi, 2018 ¹⁷²	EUS	58	19	0	0 (0-61.6) ^d	0	0	0 (0-61.6) ^d
Joergensen, 2016 ¹²⁵	EUS	71	NR	0	0 (0-50.6) ^d	2	2	28.2 (3.4-98.1)
Poley, 2009 ¹⁵⁷	EUS	44	11	3	68.2 (14.3-186.6)	0	3	68.2 (14.3-186.6)
Canto, 2004 ¹⁵⁹	EUS	38	29	1	26.3 (0.7-138.1)	0	1	26.3 (0.7-138.1)
Canto, 2006 ¹⁶⁰	High risk: EUS and CT	78	EUS: 17 CT: NR	0	0 (0-46.2) ^d	1	1	12.8 (0.3-69.4)
	Controls: EUS and/or ERCP	EUS: 138 ERCP: 23	1	0	EUS: 0 (0-26.4) ^d ERCP: 0 (0-148.2) ^d	0	0	0 (0-26.4) ^d
Canto, 2012 ^{163, 165}	EUS and CT and MRI/MRCP	216	CT: 24 EUS: 92 MRI: 72	0	0 (0-16.9) ^d	0	0	0 (0-16.9) ^d
Harinck, 2016 ^{126, 158, 167, 170}	EUS and MRI	139	EUS: 8 MRI: 9	1	7.2 (0.2-39.4)	0	1	7.2 (0.2-39.4)
Al-Sukhni, 2012 ^{127, 166, 168}	MRI	175	19	0	0 (0-20.9) ^d	3	3 ^e	17.1 (3.5-49.3)
Schneider, 2011 ^{129, 156, 161, 162, 169}	EUS and MRI/MRCP	72	26	NR	NR	NR	1	13.9 (3.5-75.0)
Verna, 2010 ^{133a}	EUS or MRI	EUS: 31 MRI: 33	EUS: 27 MRI: 11	2	EUS: 64.5 (7.9-214.2) MRI: 60.6 (7.4-202.3)	0	2	EUS: 64.5 (7.9-214.2) MRI: 60.6 (7.4-202.3)
Barnes, 2018 ¹⁷¹	MRI	65	28	0	0 (0-55.2) ^d	0	0	0 (0-55.2) ^d
Del Chiaro, 2015 ¹⁶⁴	MRI	40	16	1	25.0 (0.6-131.6)	2	3 ^a	75.0 (15.7-203.9)
Ludwig, 2011 ¹⁵⁵	MRCP	109	18	1	9.2 (0.2-50.1)	0	1	9.2 (0.2-50.1)
TOTAL		1156^b		9	7.8 (3.6-14.7)	8	18^f	15.6 (9.3-24.5)

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; EUS = endoscopic ultrasound; CT = computed tomography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; CAPS = Cancer of the Pancreas Screening Study; N/A = not applicable; FPC = familial pancreatic cancer

Note: Yield calculated as (number of patients with final pathology ÷ number receiving screening test) * 1000 persons

^a For Del Chiaro 2015, one detected PDAC case (T1N0M0; Stage IA) was found at initial screening, one case (T3N0M0; Stage IIA) was found after 2 years of being in surveillance for a branch-duct IPMN, and one case (T4N1M0; Stage III) was detected at 36 months having missed an annual screening

^b Total excludes controls from Canto 2006 and includes 51 total high risk cases from Verna 2010

^c Confidence intervals were calculated based on the data provided in each study. Confidence intervals are 95% CIs and are two sided, except as noted.

^d Confidence interval is 97.5% CI and is one-sided.

^e For Al Sukhni 2012, two PDAC cases (one Stage IV, and one T1N1M0; Stage IIB) were detected on repeat screening. Another case (Stage IV) was detected after 16 months of being in surveillance for cysts identified on initial screen.

^f Total includes one PDAC case detected in Schneider 2011 study, but study did not report whether this case was detected on initial or repeated screen.

Table 10. Treatment and followup of pancreatic adenocarcinoma cases identified in prospective cohort screening studies

Case number	Author, year Study name or Country	Age at diagnosis	Sex	Number of affected relatives (total)	Genetic variant, ancestry	Detected at initial vs. repeat screening	PDAC stage at detection	Treatment	Follow- up time (months)	Status at time of followup
1	Harinck, 2016 ^{126, 158, 167, 170} Dutch FPC Study	52	Female	7	<i>CDKN2A</i>	Initial	T1N0M0, Stage IA	Surgery	36 ^c	Local recurrence with metastases, PDAC death (36 mos)
2	Joergensen, 2016 ¹²⁵ Danish Natl Prgm	63	Male	3	NR	Repeat ^e	T1N0M0, Stage IA	Surgery	63 ^d	Alive
3	Joergensen, 2016 ¹²⁵ Danish Natl Prgm	60	Female	3	NR	Repeat ^f	T3N0M0, Stage IIA	Surgery	7 ^d	Died from complications of unrelated cardiac surgery, not further specified
4	Del Chiaro, 2015 ¹⁶⁴ Sweden	49	Female	2	None	Initial	T1N0M0, Stage IA	Surgery	NR	NR
5	Del Chiaro, 2015 ¹⁶⁴ Sweden	62	Female	3	None	Surveillance of IPMN ^g	T3N0M0, Stage IIA	Surgery	24 ^c	NR
6	Del Chiaro, 2015 ¹⁶⁴ Sweden	44	Male	2	None	Repeat	T4N1M0, Stage III	Surgery	NR	NR
7	Al-Sukhni, 2012 ^{127, 166, 168} Canada	57	Female	2	NR ^a	Repeat	T1N1M0, Stage IIB	Surgery and chemotherapy	36 ^c	Local recurrence (30 mos), PDAC death (36 mos)
8	Al-Sukhni, 2012 ^{127, 166, 168} Canada	65	Female	1	<i>BRCA2</i> ^a	Repeat	Stage IV ^{bh}	Chemotherapy	NR	Alive, tumor reduction from treatment
9	Al-Sukhni, 2012 ^{127, 166, 168} Canada	81	Male	1	NR	Surveillance of cysts ⁱ	Stage IV ^b	None	< 6 ^c	PDAC death (<6 mos from detection)
10	Ludwig, 2011 ¹⁵⁵ USA	58	Female	2	NR	Initial	T3N0M0, Stage IIA	Surgery	NR	NR

Table 10. Treatment and followup of pancreatic adenocarcinoma cases identified in prospective cohort screening studies

Case number	Author, year Study name or Country	Age at diagnosis	Sex	Number of affected relatives (total)	Genetic variant, ancestry	Detected at initial vs. repeat screening	PDAC stage at detection	Treatment	Follow-up time (months)	Status at time of followup
11	Schneider, 2011 ^{129, 156, 161, 162, 169} FaPaCa	52	Female	NR	NR	NR	Stage IV ⁱ	Surgery	12	Alive, lung metastases
12	Verna, 2010 ¹³³ USA	61	Male	2	<i>BRCA2</i>	Initial	Resectable PC, stage NR	Surgery	NR	Alive
13	Verna, 2010 ¹³³ USA	58	NR	2	NR	Initial	Stage IV ^b	Chemotherapy	NR	Alive
14	Poley, 2009 ¹⁵⁷ Netherlands	69	Male	2	<i>BRCA2</i>	Initial	T3N1M0, Stage IIB	Surgery	16 ^d	Local recurrence, died (16 mos after surgery) ^k
15	Poley, 2009 ¹⁵⁷ Netherlands	51	Female	NR	FAMMM	Initial	T1N0M0, Stage IA	Surgery	16 ^d	Alive, local recurrence and liver metastases
16	Poley, 2009 ¹⁵⁷ Netherlands	76	Female	NR	FAMMM	Initial	T3N1M0, Stage IIB	Surgery	18 ^d	Alive
17	Canto, 2006 ¹⁶⁰ USA	76	Female	6	<i>BRCA2</i> ^a	Repeat	Liver and pancreatic mass; adenocarcinoma by percutaneous biopsy	No surgery, unspecified treatment	NR	Alive, undergoing treatment for metastatic pancreatic cancer
18	Canto, 2004 ¹⁵⁹ USA	45	Female	7	None	Initial	T2N1M0, Stage IIB	Surgery, postoperative radiation and chemotherapy	60	Alive

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; FAMMM = familial atypical multiple mole melanoma; FPC = familial pancreatic cancer; NR = not reported; FaPaCa = German National Case Collection of Familial Pancreatic Cancer;

Note: Staging information is based on data provided in the studies and the American Joint Committee on Cancer's staging criteria²⁰⁴

^a Indicates individual has Ashkenazi Jewish ancestry

^b Patient had liver metastases

^c Followup time since diagnosis of PDAC

^d Followup time since surgery

^e Diagnosed on fourth EUS screening examination

^f Diagnosed on second EUS screening examination

^g IPMN detected on initial screen, progression identified at 24 months. Patient underwent surgery at 24 months

Table 10. Treatment and followup of pancreatic adenocarcinoma cases identified in prospective cohort screening studies

^h Patient had normal pancreas on 3 consecutive MRIs, then missed her fourth annual appointment. Nine months later, patient presented with pancreas tumor and metastases

ⁱ Cysts were identified at initial screen, and followed at 6 month intervals. At 1 year in surveillance, MRI showed cut-off peripheral duct branches in the pancreatic head. CT showed no evidence of a mass and before EUS could be performed patient developed jaundice, weight loss and diabetes. Two months later CT showed unresectable mass at the head of the pancreas. Liver metastases was detected on another CT 2 months later, and confirmed by percutaneous biopsy

^j Assumed stage IV, authors report that patient has lung metastases

^k Authors report that patient had an uneventful recovery from surgery. However, 10 months later, a local recurrence of the tumor was shown and the patient died 16 months after surgery. The authors do not report whether the death was attributable to PDAC.

Table 11. Screening procedure-related harms in prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country, Quality	Test type	N receiving test	Definition of harms	N with harm	% with harm
Joergensen, 2016 ¹²⁵ Danish National Screening Program Denmark, Fair	EUS	71	Any complications	0	0
Harinck, 2016 ^{126, 158, 167, 170} Dutch FPC Study Netherlands, Fair	EUS	139	Any procedure related adverse events	0	0
Poley, 2009 ¹⁵⁷ Netherlands, Fair	EUS	44	Any complications	0	0
Verna, 2010 ¹³³ U.S., Fair	EUS or MRI	51	Any complications	0	0
Ludwig, 2011 ^{155e} U.S., Fair	MRI	109	Complications related to screening	0	0
	EUS	15	Any complications (including poor tolerance of the procedure)	0	0
	MRCP	98	Requiring intravenous sedation for MRCP	0	0
Schneider, 2011 ^{129, 156, 161, 162, 169} FaPaCa Germany, Fair	FNA	7	Adverse events of FNA	0	0
Canto, 2006 ^{160e} U.S., Fair	CT	HR: 78 CG: NR ^d	Mild contrast allergic reaction (in controls), resolved	HR: 0 CG: 1	HR: 0 CG: NR
	EUS	HR: 78 CG: 138	Mild post-procedure abdominal pain ^b	HR: 22 CG: 33	HR: 28% ^a CG: 24%
	EUS	HR: 78 CG: 138	Prolonged sedation, muscle aches, nausea, vomiting related to sedation or general anesthesia	HR: 6 CG: 7	HR: 7.5% ^a CG: 5%
	ERCP	HR: 67 CG: 59	Acute pancreatitis not requiring hospitalization	HR: 1 CG: 4	HR: 1.5% ^a CG: 6.8%
			Acute pancreatitis requiring hospitalization ^c	HR: 4 CG: 4	HR: 6.0% ^a CG: 6.8%
Canto, 2004 ^{159e} U.S., Fair	EUS +/- FNA	38	Fever, bleeding, abdominal pain or pancreatitis	0	0
	ERCP	24	Post-ERCP mild pancreatitis	2 (1 requiring hospitalization)	8.3%

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; EUS = endoscopic ultrasound; CT = computed tomography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; ERCP = endoscopic retrograde cholangiopancreatography; FNA = fine needle aspiration; HR = high-risk group; CG = control group; FaPaCa = German National Case Collection of Familial Pancreatic Cancer; FPC = familial pancreatic cancer

Note: Italics indicate N was calculated from author-reported percentage

^a p-value not significant when comparing HR to controls for mild procedure-related abdominal pain (p = 0.51), symptoms related to sedation or general anesthesia (p = 0.48), or for acute pancreatitis (p = 0.38)

^b None required treatment

^c Mean hospitalization stay was 8.25 days, range 2-12 days

^d Canto 2006 does not report the number of patients from the control group who underwent CT

^e Three studies (Ludwig 2011, Canto 2006, Canto 2004) assessed procedure-related harms by calling all patients within a week after the procedure. The other 5 studies do not report how harms were assessed or if they were assessed routinely for all participants or all procedures.

Table 12. Perceived risk, cancer worries, anxiety and depression from Dutch FPC prospective cohort study of screening for pancreatic adenocarcinoma, n=140

	T0	T1	T2	T3	T4	T5	Average
Perceived risk of developing PDAC without surveillance, mean (scale 0-100)	34	46	46	42	46	47	44.3
Perceived risk of developing PDAC with surveillance, mean (scale 0-100)	24	28	32	26	32	33	29.4
Cancer Worry Scale score, mean (scale 8-32) ^b	14.4	14.0	13.3	12.4	12.5	12.1	13.0 ^a
HADS-A score, mean (scale 0-21)	5.3	4.6	4.3	4.3	4.4	4.5	4.5
HADS-A score categories:							
- Normal level of anxiety (score <8, %)	69	81	84	75	80	78	79%
- Elevated distress (score 8-10, %)	14	13	9	19	14	12	14%
- Significant distress (score >10, %)	17	6	7	6	6	10	7%
HADS-D score, mean (scale 0-21)	2.5	2.4	2.6	2.9	3.2	2.8	2.8
HADS-D score categories:							
- Normal level of anxiety (score <8, %)	91	90	93	92	87	90	91%
- Elevated distress (score 8-10, %)	3	6	4	4	6	6	5%
- Significant distress (score >10, %)	6	4	3	4	7	4	5%

Abbreviations: PC, pancreatic cancer; HADS-A, Hospital Anxiety and Depression Scale, 7-item subscale for anxiety; HADS-D, Hospital Anxiety and Depression Scale, 7-item subscale for depression

Note: Data are from Konings 2016¹⁷⁰ article as part of Dutch Familial Pancreatic Cancer (FPC) study. Time periods are represented as T0: after genetic counseling (pre-screening); T1: after intake by gastroenterologist; T2: after initial MRI/EUS screening; T3: after second MRI/EUS screening; T4: after third MRI/EUS; T5: after fourth MRI/EUS

^a significant intra-individual decrease over time (in comparison with first assessment at T0), non-proportional analysis, p<0.01

^b Eight item scale, scored 8-32. Cut-off is not clearly described, but a score C14 could indicate moderate to high levels of cancer worries²⁰⁵

Table 13. Perceived risk, cancer worries, and distress among FPC group (n=131) from Canadian prospective cohort study of screening for pancreatic adenocarcinoma

	N	Pre-screening, mean (SD)	3-month post-screening, mean (SD)
Perceived pancreatic cancer risk ^a	83	42.07 (23.8)	37.68 (23.0)
Pancreatic cancer worry ^{b, c}	89	1.59 (0.14)	1.55 (0.12)
General distress ^d	63	33 (45)	29 (42)

Abbreviations: FPC = familial pancreatic cancer; SD = standard deviation

Note: Data are from Maheu 2010¹⁶⁸ article as part of Toronto Screening Study.

^a Self-rated perceived lifetime risk of developing pancreatic cancer on a scale from 0 to 100%.

^b Self-rated frequency of worry about developing pancreatic cancer in the previous month on a 4-point Likert scale (values were: 1 = not at all/rarely, 2 = sometimes, 3 = often, 4 = a lot).

^c The authors reported that cancer worry decreased significantly among subgroups of people with 2 relatives with pancreatic cancer ($p < 0.001$) or ≥ 3 relatives with pancreatic cancer ($p < 0.007$; data not shown in paper).

^d BSI-18 comprises (a) three subscales measuring the psychological symptoms of somatization, depression, and anxiety and (b) one global index of distress, the Global Severity Index (GSI). The GSI represents the sum of the three subscales, providing an overall score of individuals' psychological distress. Raw GSI scores are converted to standardized T scores based on gender-keyed norms; for example, a converted T score of 60 represents a raw male score of 46 or a raw female score of 68. A converted T score ≥ 60 identifies levels consistent with clinical distress.

Table 14. Surgery-related harms in prospective cohort studies of screening for pancreatic adenocarcinoma

Author, year Screening program Country, Quality	N receiving surgery	Assessment of harms	Definition of harms	N with harm	% with harm
Joergensen, 2016 ¹²⁵ Danish National Screening Program Denmark, Fair	2	NR	Stricture to hepaticojejunal anastomosis with cholangitis ^d	1 ^b	50%
			Postoperative complications, not further specified	1 ^c	50%
Canto, 2012 ^{163, 165} U.S., Fair	5	Clinical followup for a minimum of 1 year	Major adverse events, not further specified	0	0
Schneider, 2011 ^{129, 156, 161, 162, 169} FaPaCa Germany, Fair	10	NR	Pancreatic fistula, not further specified ^f	2	20%
			Diabetes, not further specified ^e	3	30%
Verna, 2010 ¹³³ U.S., Fair	5	NR	Significant complications, not further specified	0	0
Poley, 2009 ¹⁵⁷ Netherlands, Fair	3	NR	Harms from surgery, not further specified ^a	0	0
Canto, 2006 ¹⁶⁰ U.S., Fair	7	Clinical followup at 1 month and 12 months post-surgery for all surgical patients	Significant post-operative complications, not further specified	0	0
TOTAL	32	Mixed	Any harm	7	25%

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; NR = not reported

Note: Of the 6 studies that report ANY harms or assessment of harms, 32 persons had surgery. Of those 32 who had surgery that were eligible for reporting harms, 7 harms were reported (25%). It should be noted that only 3 of the 6 studies assessed harms in a systematic way. Types of surgeries varied across studies, and there was no consistency between surgery type and harms

^a Poley 2009 stated that one patient had “an uneventful recovery” from surgery. The paper did not report information on recovery from surgery for the other two patients who underwent surgery.

^b Hospital stay of 9 days.

^c Hospital stay of 8 days.

^d Occurred 11 months post-surgery

^e It is not clear from the paper whether these cases were pre-existing or resulting from surgery. The study text provides no information on the resolution of these cases.

^f The authors report that fistulas were “treated conservatively.”

Table 15. Summary of Evidence by Key Question

Key Question	Studies (k), observations (n), study designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ1: Effect of screening on health outcomes	No studies	NA	NA	NA	Insufficient for benefit	NA
KQ2: Diagnostic accuracy of screening	k=13 prospective cohort studies n=1317 EUS: k=9; n=885 MRI/MRCP: k=8; n=849 CT: k=2; n=294	Across all studies (n=1317), 18 cases of PDAC were detected; 9 on initial screening. No evidence available for diagnostic accuracy. Pooled yield for all screening tests to detect PDAC on initial screening was 7.8 per 1000 (95% CI 3.6-14.7); and for total yield including both initial screening and repeated screening, was 15.6 per 1000 (95% CI 9.3-24.5). Diagnostic yield similar for EUS/ERCP and MRI/MRCP. Initial screening with CT (n=294) yielded 1 PDAC case (yield 12.8 per 1000).	Inconsistent, imprecise	Small sample sizes; no un-screened comparison groups; little to no subgroup analyses of screening yield in different risk groups. Reporting bias not detected. All studies were of fair quality.	Low for accuracy	Most applicable to populations who are white or with Northern European ancestry with established family history or genetic risk for pancreatic cancer seen in tertiary care centers.

Table 15. Summary of Evidence by Key Question

Key Question	Studies (k), observations (n), study designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ3: Harms of screening	<p>Total: k=9 prospective cohort studies n=938</p> <p>Procedural harms (k=8; n=675)</p> <p>EUS/ERCP: k=7; n=574</p> <p>MRI/MRCP: k=2; n=240</p> <p>CT: k=1; n=78</p> <p>FNA: k=2; n=45</p> <p>Psychosocial harms: k=2 prospective cohort studies; n=271</p>	<p>Procedural harms: EUS: 55/216 (25%) mild post-EUS pain; 13/216 (6%) adverse events related to anesthesia.</p> <p>ERCP: 15/150 (10%) acute pancreatitis, 9 requiring hospitalization</p> <p>MRI/MRCP: None reported</p> <p>CT: 1/78 mild reaction to contrast (k=1)</p> <p>FNA: None reported</p> <p>Psychosocial harms: Cancer worry: 1 study reported (benefit) decrease in worry between pre-and post-screening</p> <p>Cancer distress, depression, or anxiety: no evidence of harm</p>	Inconsistent, imprecise	Not all studies reported methods of assessment of harms; few studies assessed psychosocial harms. Reporting bias not detected. All studies were of fair quality.	Low for harms	Most applicable to populations who are white or with Northern European ancestry with established increased family history or genetic risk for pancreatic cancer seen in tertiary care centers.
KQ4: Effect of treatment on health outcomes	No studies	NA	NA	NA	Insufficient for benefit	NA

Table 15. Summary of Evidence by Key Question

Key Question	Studies (k), observations (n), study designs	Summary of Findings	Consistency and Precision	Other Limitations	Strength of Evidence	Applicability
KQ5: Harms of treatment	k=6 prospective cohort studies n=32 people receiving surgery	Seven instances of surgical harms were reported in 32 cases of surgery. One (stricture to hepaticojejunal anastomosis) occurred 11 months post-operatively; and the others (diabetes, fistula) in the immediate post-operative period. No information was reported about assessment or instances of psychosocial harms.	Inconsistent, imprecise	Harms were inconsistently reported, as were the methods of assessing harms. For studies reporting harms, whether they were assessed consistently in all study participants was not well reported. Reporting bias not detected. All studies were of fair quality.	Insufficient for harms	NA

Abbreviations: KQ = key question; PDAC = pancreatic ductal adenocarcinoma; NA = not applicable; EUS = endoscopic ultrasound; ERCP = endoscopic retrograde cholangiopancreatography; CT = computed tomography; MRI = magnetic resonance imaging; MRCP = magnetic resonance cholangiopancreatography; FNA = fine-needle aspiration

Table 16. Summary of existing and new evidence on screening for pancreatic adenocarcinoma

	Rationale and foundational evidence for previous D recommendation (2004) ^{140 1}	New evidence findings	Limitations of new evidence	Consistency of new evidence with foundational evidence and current understanding
Benefits	<p>Screening: The 2004 evidence update found no direct evidence on the benefits of screening for pancreatic cancer, and no high-quality evidence on the accuracy of screening tests.</p> <p>Treatment: There was no established evidence of the effectiveness of surgery, adjuvant chemotherapy, or radiation therapy for pancreatic cancer.</p>	<p>Screening: Based on 13 prospective screening studies, imaging-based screening in groups at high familial risk can detect pancreatic adenocarcinoma and its precursor lesions. Across all studies (n=1317), 18 cases of pancreatic adenocarcinoma were detected, 12 at early stage disease. There was no direct evidence of the impact of screening on morbidity or mortality.</p> <p>Treatment: No included studies.</p>	<p>Screening: Inconsistent reporting of test positives and no follow-up of screen-negative people prohibit assessment of sensitivity or specificity screening tests. The current evidence applies primarily to populations at high risk due to family history.</p> <p>Treatment: No included studies.</p>	<p>Screening: Included studies provide new evidence on the diagnostic yield of screening high-risk populations at increased familial risk.</p> <p>Treatment: A survival advantage associated with surgical intervention for early stage cancer is established, but there continues to be very limited evidence on the outcomes of treatment in screen-detected pancreatic adenocarcinoma.</p>
Harms	<p>Screening: The USPSTF concluded that there is potential for significant harm because of the low prevalence of pancreatic cancer, limited accuracy of screening tests, and the invasive nature of diagnostic tests.</p> <p>Treatment: The USPSTF concluded that there are poor outcomes from treatment for pancreatic cancer.</p>	<p>Screening: EUS was associated with mild post-EUS pain and adverse events related to anesthesia (7 studies). ERCP was associated with acute pancreatitis. Harms of MRI (2 studies) or CT (1 study) were minimal. There was no evidence of psychosocial harm from screening (2 studies).</p> <p>Treatment: In 32 cases of surgery, 7 instances of surgical harms were reported, including stricture to hepaticojejunal anastomosis, diabetes, fistula, or unspecified complications. There was no included evidence on the psychosocial harms of surgical intervention.</p>	<p>Screening: Harms were inconsistently reported, as were methods of assessment.</p> <p>Treatment: Harms were inconsistently reported, as were methods of assessment.</p>	<p>Screening: All studies on screening harms represent new evidence.</p> <p>Treatment: All studies on treatment harms represent new evidence. While the morbidities of surgical intervention are established, there is little evidence to estimate these events following treatment of screen-detected pancreatic adenocarcinoma.</p>

Abbreviations: USPSTF = U.S. Preventive Services Task Force; EUS = endoscopic ultrasound; ERCP = endoscopic retrograde cholangiopancreatography; CT = computed tomography; MRI = magnetic resonance imaging

Table 17. Online tools and software packages for assessing risk of PDAC

Tool name	Last update	Sponsoring organization(s)	Location	Description	Data used to assess risk	Populations in which tool has been validated (year)	C statistic ^a from validation study
Qcancer ¹⁸³⁻¹⁸⁶	2017	ClinRisk, University of Nottingham	U.K.	Intended for use in the U.K population. Provides risk of undiagnosed cancer for an individual across a range of tumor sites. Algorithms are based on routinely collected data from thousands of general practitioners across the U.K., and are updated and recalibrated annually.	<ul style="list-style-type: none"> - Age & sex - Postal code - Height & weight - Smoking and alcohol - Family history (various) - Chronic conditions (various) - Symptoms (various) - Reasons for recent GP visits 	2.15 million U.K. general surgery patients aged 30-84 (2013) ¹⁸⁶ 1.24 million U.K. general surgery patients aged 30-84(2012) ¹⁸⁴	2013 study: 0.89 (females); 0.92 (males) (2013) ¹⁸⁶ 2012 study: 0.84 (females); 0.87 (males) ¹⁸⁴
PancPRO ¹⁸⁷⁻¹⁸⁹	2015	Johns Hopkins University, Sidney Kimmel Comprehensive Cancer Research Center	Baltimore, MD (USA)	Statistical model that uses family history to estimate the probability an individual carries a gene effect for PDAC and the probability the individual will develop PDAC. Available for free for research and counseling through the BayesMendel R software package.	Family history (including for the individual and each relative): <ul style="list-style-type: none"> - Exact relation to the individual - PDAC diagnosis (yes or no) - Age at diagnosis - Current age or age at last followup if unaffected 	6,134 individuals (age NR) with family history of PDAC enrolled in the NFPTR (2007) ¹⁸⁷	0.75 (95% CI 0.68 to 0.81)
Your Disease Risk ^{190, 191}	2013	Siteman Cancer Center at Barnes-Jewish Hospital, Washington University School of Medicine	St. Louis, Mo (USA)	Offers assessments for 12 cancers and other health conditions. The site includes prevalence and relative risk estimates used in the disease risk calculations. Assessments are updated every 3 years after a review of scientific literature, and smaller updates are made as needed, such as after major new research findings.	<ul style="list-style-type: none"> - Age & sex - Height & weight - Personal history of cancer - Family history of PDAC - Smoking status - Presence of diabetes, high blood sugar, chronic pancreatitis - Diet (vegetable intake) 	71,788 women age 40-70 in the NHS cohort and 38,953 men age 40-70 in the HPFS cohort (2004) ¹⁹⁰	0.71 (95% CI 0.66 to 0.76)

Abbreviations: PDAC = pancreatic adenocarcinoma; U.K. = United Kingdom; EHR = electronic health record; NFPTR = National Familial Pancreatic Tumor Registry; NHS = Nurses Health Study; HPFS = Health Professionals Followup Study; N/A = not applicable

^a C-statistic is equal to the area under the Receiver Operating Characteristic (ROC) curve and ranges from 0.5 to 1. It gives the probability that a randomly selected patient with a certain condition (such as PDAC) had a higher risk score than a patient who did not have the condition

Literature Search Strategies for Primary Literature

Sources Searched
Ovid MEDLINE(R) without Revisions <1996 to September Week 3 2017>, Ovid MEDLINE(R) Epub Ahead of Print <October 03, 2017>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <October 03, 2017>, Ovid MEDLINE(R) Daily Update <October 03, 2017>
Cochrane Central Register of Controlled Trials (CENTRAL)
PubMed, Publisher Supplied Segment

Key:

- / = subject heading
- \$ = truncation
- * = truncation
- ab = word in abstract
- adj# = adjacent within x number of words
- fs = floating subheading
- kw = keyword
- pt = publication type
- ti = word in title

OID MEDLINE

Pancreatic Adenocarcinoma Screening Trials (KQ1)

- 1 Pancreatic Neoplasms/
- 2 Carcinoma, Pancreatic Ductal/
- 3 Pancreatic Cyst/
- 4 Pancreatic Pseudocyst/
- 5 exp Pancreas/
- 6 Carcinoma in Situ/
- 7 exp Adenocarcinoma/
- 8 6 or 7
- 9 5 and 8
- 10 pancreatic intraepithelial neoplas*.ti,ab.
- 11 panin.ti,ab.
- 12 intraductal papillary mucinous neoplas*.ti,ab.
- 13 ipmn.ti,ab.
- 14 mucinous cystic neoplas*.ti,ab.
- 15 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti.
- 16 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti,ab.
- 17 limit 16 to ("in data review" or in process or "pubmed not medline")
- 18 1 or 2 or 3 or 4 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 17
- 19 Mass Screening/

Appendix A. Detailed Methods

20 "Early Detection of Cancer"/
21 exp Ultrasonography/
22 Endoscopic Ultrasound-Guided Fine Needle Aspiration/
23 exp Magnetic Resonance Imaging/
24 Cholangiography/
25 Cholangiopancreatography, Endoscopic Retrograde/
26 Positron-Emission Tomography/
27 exp Tomography, Emission-Computed/
28 Tomography, X-Ray Computed/
29 Angiography/
30 Computed Tomography Angiography/
31 Four-Dimensional Computed Tomography/
32 Positron Emission Tomography Computed Tomography/
33 Single Photon Emission Computed Tomography Computed Tomography/
34 Tomography, Spiral Computed/
35 Multidetector Computed Tomography/
36 screen*.ti,ab.
37 ultrasonogra*.ti,ab.
38 ultrasound*.ti,ab.
39 magnetic resonance imag*.ti,ab.
40 (cholangiography or cholangiopancreato*).ti,ab.
41 positron emission tomograph*.ti,ab.
42 computed tomograph*.ti,ab.
43 (ct scan* or pet scan* or mri or octreoscan* or octreotide scan*).ti,ab.
44 angiograph*.ti,ab.
45 ercp.ti,ab.
46 or/19-45
47 18 and 46
48 *Pancreatic Neoplasms/di [Diagnosis]
49 *Carcinoma, Pancreatic Ductal/di [Diagnosis]
50 *Pancreatic Cyst/di [Diagnosis]
51 *Pancreatic Pseudocyst/di [Diagnosis]
52 48 or 49 or 50 or 51
53 47 or 52
54 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials
as topic/ or meta-analysis as topic/ or pragmatic clinical trials as topic/
55 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or
pragmatic clinical trial).pt.
56 Random*.ti,ab.
57 control groups/ or double-blind method/ or single-blind method/
58 clinical trial*.ti,ab.
59 controlled trial*.ti,ab.
60 (meta analy* or metaanaly*).ti,ab.
61 54 or 55 or 56 or 57 or 58 or 59 or 60
62 53 and 61
63 limit 62 to yr="2002 -Current"

Appendix A. Detailed Methods

- 64 limit 63 to english language
- 65 animals/ not (humans/ and animals/)
- 66 64 not 65
- 67 remove duplicates from 66

Pancreatic Adenocarcinoma Screening Dx Accuracy (KQ2)

- 1 Pancreatic Neoplasms/
- 2 Carcinoma, Pancreatic Ductal/
- 3 Pancreatic Cyst/
- 4 Pancreatic Pseudocyst/
- 5 exp Pancreas/
- 6 Carcinoma in Situ/
- 7 exp Adenocarcinoma/
- 8 6 or 7
- 9 5 and 8
- 10 pancreatic intraepithelial neoplas*.ti,ab.
- 11 panin.ti,ab.
- 12 intraductal papillary mucinous neoplas*.ti,ab.
- 13 ipmn.ti,ab.
- 14 mucinous cystic neoplas*.ti,ab.
- 15 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti.
- 16 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti,ab.
- 17 limit 16 to ("in data review" or in process or "pubmed not medline")
- 18 1 or 2 or 3 or 4 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 17
- 19 Mass Screening/
- 20 "Early Detection of Cancer"/
- 21 exp Ultrasonography/
- 22 Endoscopic Ultrasound-Guided Fine Needle Aspiration/
- 23 exp Magnetic Resonance Imaging/
- 24 Cholangiography/
- 25 Cholangiopancreatography, Endoscopic Retrograde/
- 26 Positron-Emission Tomography/
- 27 exp Tomography, Emission-Computed/
- 28 Tomography, X-Ray Computed/
- 29 Angiography/
- 30 Computed Tomography Angiography/
- 31 Four-Dimensional Computed Tomography/
- 32 Positron Emission Tomography Computed Tomography/
- 33 Single Photon Emission Computed Tomography Computed Tomography/
- 34 Tomography, Spiral Computed/
- 35 Multidetector Computed Tomography/
- 36 screen*.ti,ab.

Appendix A. Detailed Methods

37 ultrasonogra*.ti,ab.
38 ultrasound*.ti,ab.
39 magnetic resonance imag*.ti,ab.
40 (cholangiography or cholangiopancreato*).ti,ab.
41 positron emission tomograph*.ti,ab.
42 computed tomograph*.ti,ab.
43 (ct scan* or pet scan* or mri or octreoscan* or octreotide scan*).ti,ab.
44 angiograph*.ti,ab.
45 ercp.ti,ab.
46 or/19-45
47 18 and 46
48 *Pancreatic Neoplasms/di [Diagnosis]
49 *Carcinoma, Pancreatic Ductal/di [Diagnosis]
50 *Pancreatic Cyst/di [Diagnosis]
51 *Pancreatic Pseudocyst/di [Diagnosis]
52 48 or 49 or 50 or 51
53 47 or 52
54 "Sensitivity and Specificity"/
55 "Predictive Value of Tests"/
56 ROC Curve/
57 Receiver operat*.ti,ab.
58 ROC curve*.ti,ab.
59 sensitivit*.ti,ab.
60 specificit*.ti,ab.
61 predictive value.ti,ab.
62 accuracy.ti,ab.
63 false positive*.ti,ab.
64 false negative*.ti,ab.
65 miss rate*.ti,ab.
66 error rate*.ti,ab.
67 False Negative Reactions/
68 False Positive Reactions/
69 Diagnostic Errors/
70 "Reproducibility of Results"/
71 Reference Values/
72 Reference Standards/
73 Observer Variation/
74 or/54-73
75 53 and 74
76 limit 75 to yr="2002 -Current"
77 limit 76 to english language
78 animals/ not (humans/ and animals/)
79 77 not 78
80 remove duplicates from 79

Appendix A. Detailed Methods

Pancreatic Adenocarcinoma Screening Harms (KQ3)

- 1 Pancreatic Neoplasms/
- 2 Carcinoma, Pancreatic Ductal/
- 3 Pancreatic Cyst/
- 4 Pancreatic Pseudocyst/
- 5 exp Pancreas/
- 6 Carcinoma in Situ/
- 7 exp Adenocarcinoma/
- 8 6 or 7
- 9 5 and 8
- 10 pancreatic intraepithelial neoplas*.ti,ab.
- 11 panin.ti,ab.
- 12 intraductal papillary mucinous neoplas*.ti,ab.
- 13 ipmn.ti,ab.
- 14 mucinous cystic neoplas*.ti,ab.
- 15 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti.
- 16 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti,ab.
- 17 limit 16 to ("in data review" or in process or "pubmed not medline")
- 18 1 or 2 or 3 or 4 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 17
- 19 Mass Screening/
- 20 "Early Detection of Cancer"/
- 21 exp Ultrasonography/
- 22 Endoscopic Ultrasound-Guided Fine Needle Aspiration/
- 23 exp Magnetic Resonance Imaging/
- 24 Cholangiography/
- 25 Cholangiopancreatography, Endoscopic Retrograde/
- 26 Positron-Emission Tomography/
- 27 exp Tomography, Emission-Computed/
- 28 Tomography, X-Ray Computed/
- 29 Angiography/
- 30 Computed Tomography Angiography/
- 31 Four-Dimensional Computed Tomography/
- 32 Positron Emission Tomography Computed Tomography/
- 33 Single Photon Emission Computed Tomography Computed Tomography/
- 34 Tomography, Spiral Computed/
- 35 Multidetector Computed Tomography/
- 36 screen*.ti,ab.
- 37 ultrasonogra*.ti,ab.
- 38 ultrasound*.ti,ab.
- 39 magnetic resonance imag*.ti,ab.
- 40 (cholangiography or cholangiopancreato*).ti,ab.
- 41 positron emission tomograph*.ti,ab.

Appendix A. Detailed Methods

- 42 computed tomograph*.ti,ab.
43 (ct scan* or pet scan* or mri or octreoscan* or octreotide scan*).ti,ab.
44 angiograph*.ti,ab.
45 ercp.ti,ab.
46 or/19-45
47 18 and 46
48 *Pancreatic Neoplasms/di [Diagnosis]
49 *Carcinoma, Pancreatic Ductal/di [Diagnosis]
50 *Pancreatic Cyst/di [Diagnosis]
51 *Pancreatic Pseudocyst/di [Diagnosis]
52 48 or 49 or 50 or 51
53 47 or 52
54 (harm or harms or harmful or harmed).ti,ab.
55 (adverse effects or mortality).fs.
56 Mortality/
57 Morbidity/
58 death/
59 (death or deaths).ti,ab.
60 (adverse adj (effect* or event* or outcome* or reaction*)).ti,ab.
61 complication*.ti,ab.
62 side effect*.ti,ab.
63 safety.ti,ab.
64 perforat*.ti,ab.
65 exp Infection/
66 Iatrogenic Disease/
67 Cross Infection/
68 iatrogen*.ti,ab.
69 Hemorrhage/
70 Postoperative Hemorrhage/
71 (hemorrhag* or haemorrhag*).ti,ab.
72 Peritonitis/
73 Bile/
74 72 and 73
75 Neoplasm Seeding/
76 ((neoplas* or malignan*) adj2 seed*).ti,ab.
77 Anxiety/
78 (anxiet* or anxious*).ti,ab.
79 Depression/
80 (cancer adj2 worr*).ti,ab.
81 54 or 55 or 56 or 57 or 58 or 59 or 60 or 61 or 62 or 63 or 64 or 65 or 66 or 67 or 68 or 69
or 70 or 71 or 74 or 75 or 76 or 77 or 78 or 79 or 79 or 80
82 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials
as topic/ or meta-analysis as topic/ or pragmatic clinical trials as topic/
83 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or
pragmatic clinical trial).pt.
84 Random*.ti,ab.

Appendix A. Detailed Methods

85 control groups/ or double-blind method/ or single-blind method/
86 clinical trial*.ti,ab.
87 controlled trial*.ti,ab.
88 (meta analy* or metaanaly*).ti,ab.
89 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or
retrospective studies/
90 cohort.ti,ab.
91 longitudinal.ti,ab.
92 retrospectiv*.ti,ab.
93 prospectiv*.ti,ab.
94 case-control studies/
95 case control*.ti,ab.
96 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95
97 53 and 81 and 96
98 limit 97 to yr="2002 -Current"
99 limit 98 to english language
100 animals/ not (humans/ and animals/)
101 99 not 100
102 remove duplicates from 101

Pancreatic Adenocarcinoma Treatment Trials and Cohort Studies (KQ4)

1 Pancreatic Neoplasms/
2 Carcinoma, Pancreatic Ductal/
3 Pancreatic Cyst/
4 Pancreatic Pseudocyst/
5 exp Pancreas/
6 Carcinoma in Situ/
7 exp Adenocarcinoma/
8 6 or 7
9 5 and 8
10 pancreatic intraepithelial neoplas*.ti,ab.
11 panin.ti,ab.
12 intraductal papillary mucinous neoplas*.ti,ab.
13 ipmn.ti,ab.
14 mucinous cystic neoplas*.ti,ab.
15 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or
carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or
malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti.
16 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or
carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or
malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti,ab.
17 limit 16 to ("in data review" or in process or "pubmed not medline")
18 1 or 2 or 3 or 4 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 17
19 Treatment Outcome/
20 Treatment Failure/
21 Pancreatectomy/

Appendix A. Detailed Methods

- 22 Pancreaticoduodenectomy/
- 23 pancreatetectom*.ti,ab.
- 24 Pancreaticoduodenectom*.ti,ab.
- 25 (surger* or surgical).ti.
- 26 (surger* or surgical).ti,ab.
- 27 limit 26 to ("in data review" or in process or "pubmed not medline")
- 28 resect*.ti,ab.
- 29 exp Radiotherapy/
- 30 (radiotherap* or radiation therap* or radio therap*).ti.
- 31 (radiotherap* or radiation therap* or radio therap*).ti,ab.
- 32 limit 31 to ("in data review" or in process or "pubmed not medline")
- 33 whipple.ti,ab.
- 34 Chemoradiotherapy/
- 35 Chemoradiotherapy, Adjuvant/
- 36 Antineoplastic Combined Chemotherapy Protocols/
- 37 Chemotherapy, Adjuvant/
- 38 Consolidation Chemotherapy/
- 39 Chemotherapy, Cancer, Regional Perfusion/
- 40 Induction Chemotherapy/
- 41 Maintenance Chemotherapy/
- 42 Photochemotherapy/
- 43 chemotherap*.ti.
- 44 chemotherap*.ti,ab.
- 45 limit 44 to ("in data review" or in process or "pubmed not medline")
- 46 folfirinox.ti,ab.
- 47 Leucovorin/
- 48 Fluorouracil/
- 49 Capecitabine/
- 50 gemcitabine.ti,ab.
- 51 gemzar.ti,ab.
- 52 5-fu.ti,ab
- 53 Paclitaxel/
- 54 Albumin-Bound Paclitaxel/
- 55 Camptothecin/
- 56 Antineoplastic Agents/
- 57 19 or 20 or 21 or 22 or 23 or 24 or 25 or 27 or 28 or 29 or 30 or 32 or 33 or 34 or 35 or 36
or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or
54 or 55 or 56
- 58 18 and 57
- 59 *Pancreatic Neoplasms/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy,
Surgery, Therapy]
- 60 *Carcinoma, Pancreatic Ductal/dh, dt, rt, su, th [Diet Therapy, Drug Therapy,
Radiotherapy, Surgery, Therapy]
- 61 *Pancreatic Cyst/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
- 62 *Pancreatic Pseudocyst/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy,
Surgery, Therapy]

Appendix A. Detailed Methods

- 63 59 or 60 or 61 or 62
- 64 58 or 63
- 65 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ or pragmatic clinical trials as topic/
- 66 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt.
- 67 Random*.ti,ab.
- 68 control groups/ or double-blind method/ or single-blind method/
- 69 clinical trial*.ti,ab.
- 70 controlled trial*.ti,ab.
- 71 (meta analy* or metaanaly*).ti,ab.
- 72 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/
- 73 cohort.ti,ab.
- 74 longitudinal.ti,ab.
- 75 retrospectiv*.ti,ab.
- 76 prospectiv*.ti,ab.
- 77 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76
- 78 64 and 77
- 79 limit 78 to yr="2002 -Current"
- 80 limit 79 to english language
- 81 animals/ not (humans/ and animals/)
- 82 80 not 81

Pancreatic Adenocarcinoma Treatment Harms (KQ5)

- 1 Pancreatic Neoplasms/
- 2 Carcinoma, Pancreatic Ductal/
- 3 Pancreatic Cyst/
- 4 Pancreatic Pseudocyst/
- 5 exp Pancreas/
- 6 Carcinoma in Situ/
- 7 exp Adenocarcinoma/
- 8 6 or 7
- 9 5 and 8
- 10 pancreatic intraepithelial neoplas*.ti,ab.
- 11 panin.ti,ab.
- 12 intraductal papillary mucinous neoplas*.ti,ab.
- 13 ipmn.ti,ab.
- 14 mucinous cystic neoplas*.ti,ab.
- 15 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti.
- 16 ((pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*) adj3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts)).ti,ab.
- 17 limit 16 to ("in data review" or in process or "pubmed not medline")

Appendix A. Detailed Methods

- 18 1 or 2 or 3 or 4 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 17
- 19 Treatment Outcome/
- 20 Treatment Failure/
- 21 Pancreatectomy/
- 22 Pancreaticoduodenectomy/
- 23 pancreatectom*.ti,ab.
- 24 Pancreaticoduodenectom*.ti,ab.
- 25 (surger* or surgical).ti.
- 26 (surger* or surgical).ti,ab.
- 27 limit 26 to ("in data review" or in process or "pubmed not medline")
- 28 resect*.ti,ab.
- 29 exp Radiotherapy/
- 30 (radiotherap* or radiation therap* or radio therap*).ti.
- 31 (radiotherap* or radiation therap* or radio therap*).ti,ab.
- 32 limit 31 to ("in data review" or in process or "pubmed not medline")
- 33 whipple.ti,ab.
- 34 Chemoradiotherapy/
- 35 Chemoradiotherapy, Adjuvant/
- 36 Antineoplastic Combined Chemotherapy Protocols/
- 37 Chemotherapy, Adjuvant/
- 38 Consolidation Chemotherapy/
- 39 Chemotherapy, Cancer, Regional Perfusion/
- 40 Induction Chemotherapy/
- 41 Maintenance Chemotherapy/
- 42 Photochemotherapy/
- 43 chemotherap*.ti.
- 44 chemotherap*.ti,ab.
- 45 limit 44 to ("in data review" or in process or "pubmed not medline")
- 46 folfirinox.ti,ab.
- 47 Leucovorin/
- 48 Fluorouracil/
- 49 Capecitabine/
- 50 gemcitabine.ti,ab.
- 51 gemzar.ti,ab.
- 52 5-fu.ti,ab.
- 53 Paclitaxel/
- 54 Albumin-Bound Paclitaxel/
- 55 Camptothecin/
- 56 Antineoplastic Agents/
- 57 19 or 20 or 21 or 22 or 23 or 24 or 25 or 27 or 28 or 29 or 30 or 32 or 33 or 34 or 35 or 36
or 37 or 38 or 39 or 40 or 41 or 42 or 43 or 45 or 46 or 47 or 48 or 49 or 50 or 51 or 52 or 53 or
54 or 55 or 56
- 58 18 and 57
- 59 *Pancreatic Neoplasms/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy,
Surgery, Therapy]
- 60 *Carcinoma, Pancreatic Ductal/dh, dt, rt, su, th [Diet Therapy, Drug Therapy,

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Radiotherapy, Surgery, Therapy]

- 61 *Pancreatic Cyst/dt, rt, su, th [Drug Therapy, Radiotherapy, Surgery, Therapy]
- 62 *Pancreatic Pseudocyst/dh, dt, rt, su, th [Diet Therapy, Drug Therapy, Radiotherapy, Surgery, Therapy]
- 63 59 or 60 or 61 or 62
- 64 58 or 63
- 65 (harm or harms or harmful or harmed).ti,ab.
- 66 (adverse effects or mortality).fs.
- 67 Mortality/
- 68 Morbidity/
- 69 death/
- 70 (death or deaths).ti,ab.
- 71 (adverse adj (effect* or event* or outcome* or reaction*)).ti,ab.
- 72 complication*.ti,ab.
- 73 side effect*.ti,ab.
- 74 safety.ti,ab.
- 75 "Drug-Related Side Effects and Adverse Reactions"/
- 76 Long Term Adverse Effects/
- 77 Radiation Exposure/
- 78 Radiation Injuries/
- 79 Abnormalities, Radiation-Induced/
- 80 Cardiotoxicity/
- 81 Leukemia, Radiation-Induced/
- 82 Neoplasms, Radiation-Induced/
- 83 Osteoradionecrosis/
- 84 Radiation Pneumonitis/
- 85 Radiodermatitis/
- 86 (radiation adj2 (expos* or damag* or induce* or injur*)).ti,ab.
- 87 osteoradionecrosis.ti,ab.
- 88 radiodermatitis.ti,ab.
- 89 cardiotoxic*.ti,ab.
- 90 Nausea/
- 91 (nausea or nauseous*).ti,ab.
- 92 Vomiting/
- 93 vomit*.ti,ab.
- 94 Diarrhea/
- 95 diarrhea.ti,ab.
- 96 diarrhoea.ti,ab.
- 97 Alopecia/
- 98 alopeci*.ti,ab.
- 99 (hair* adj3 loss*).ti,ab.
- 100 (appetite adj3 loss*).ti,ab.
- 101 Fatigue/
- 102 (fatigu* or letharg*).ti,ab.
- 103 Fever/
- 104 fever*.ti,ab.

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105 (mouth adj2 (sore or sores)).ti,ab.
106 Pain/
107 pain*.ti.
108 Constipation/
109 constipat*.ti,ab.
110 Contusions/
111 bruise*.ti,ab.
112 ((lung* or pulmonary or heart or cardiac or cardio* or kidney* or renal or nephro* or nerve* or neural*) adj2 (damag* or injur*)).ti,ab.
113 exp Postoperative Complications/
114 65 or 66 or 67 or 68 or 69 or 70 or 71 or 72 or 73 or 74 or 75 or 76 or 77 or 78 or 79 or 80 or 81 or 82 or 83 or 84 or 85 or 86 or 87 or 88 or 89 or 90 or 91 or 92 or 93 or 94 or 95 or 96 or 97 or 98 or 99 or 100 or 101 or 102 or 103 or 104 or 105 or 106 or 107 or 108 or 109 or 110 or 111 or 112 or 113
115 clinical trials as topic/ or controlled clinical trials as topic/ or randomized controlled trials as topic/ or meta-analysis as topic/ or pragmatic clinical trials as topic/
116 (clinical trial or controlled clinical trial or meta analysis or randomized controlled trial or pragmatic clinical trial).pt.
117 Random*.ti,ab.
118 control groups/ or double-blind method/ or single-blind method/
119 clinical trial*.ti,ab.
120 controlled trial*.ti,ab.
121 (meta analy* or metaanaly*).ti,ab.
122 cohort studies/ or longitudinal studies/ or follow-up studies/ or prospective studies/ or retrospective studies/
123 cohort.ti,ab.
124 longitudinal.ti,ab.
125 retrospectiv*.ti,ab.
126 prospectiv*.ti,ab.
127 case-control studies/
128 case control*.ti,ab.
129 115 or 116 or 117 or 118 or 119 or 120 or 121 or 122 or 123 or 124 or 125 or 126 or 127 or 128
130 64 and 114 and 129
131 limit 130 to yr="2002 -Current"
132 limit 131 to english language
133 animals/ not (humans/ and animals/)
134 132 not 133
135 remove duplicates from 134

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CENTRAL

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- #1 (pancrea* or Acinar* or Acinus or hepatopancreat* or ampull*):ti,ab,kw near/3 (cancer* or carcinoma* or adenocarcinoma* or apudoma* or adenoma* or carcinoid* or sarcoma* or malignan* or tumor* or tumour* or neoplas* or lesion* or cyst or cysts):ti,ab,kw
- #2 panin:ti,ab,kw
- #3 ("intraductal papillary mucinous" next neoplas*):ti,ab,kw
- #4 ipmn:ti,ab,kw
- #5 (mucinous cystic next neoplas*):ti,ab,kw
- #6 {or #1-#5}
- #7 screen*:ti,ab,kw
- #8 ultrasonogra*:ti,ab,kw
- #9 ultrasound*:ti,ab,kw
- #10 ("magnetic resonance" next imag*):ti,ab,kw
- #11 mri:ti,ab,kw
- #12 (cholangiography or cholangiopancreato*):ti,ab,kw
- #13 tomograph*:ti,ab,kw
- #14 (ct or pet or octreotide):ti,ab,kw near/2 scan:ti,ab,kw
- #15 octreoscan:ti,ab,kw
- #16 angiograph*:ti,ab,kw
- #17 ercp:ti,ab,kw
- #18 {or #7-#17}
- #19 pancreatectom*:ti,ab,kw
- #20 Pancreaticoduodenectom*:ti,ab,kw
- #21 (surger* or surgical):ti,ab,kw
- #22 resect*:ti,ab,kw
- #23 radiotherapy:ti,ab,kw
- #24 (radiation next therap*):ti,ab,kw
- #25 (therap* next radiation):ti,ab,kw
- #26 whipple:ti,ab,kw
- #27 chemoradiotherap*:ti,ab,kw
- #28 chemotherap*:ti,ab,kw
- #29 photochemotherap*:ti,ab,kw
- #30 folfirinox:ti,ab,kw
- #31 Leucovorin:ti,ab,kw
- #32 Fluorouracil:ti,ab,kw
- #33 Capecitabine:ti,ab,kw
- #34 gemcitabine:ti,ab,kw
- #35 gemzar:ti,ab,kw
- #36 5-fu:ti,ab,kw
- #37 Paclitaxel:ti,ab,kw
- #38 Camptothecin:ti,ab,kw
- #39 {or #19-#38}
- #40 #18 or #39

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#41 #6 and #40 Publication Year from 2002 to 2017

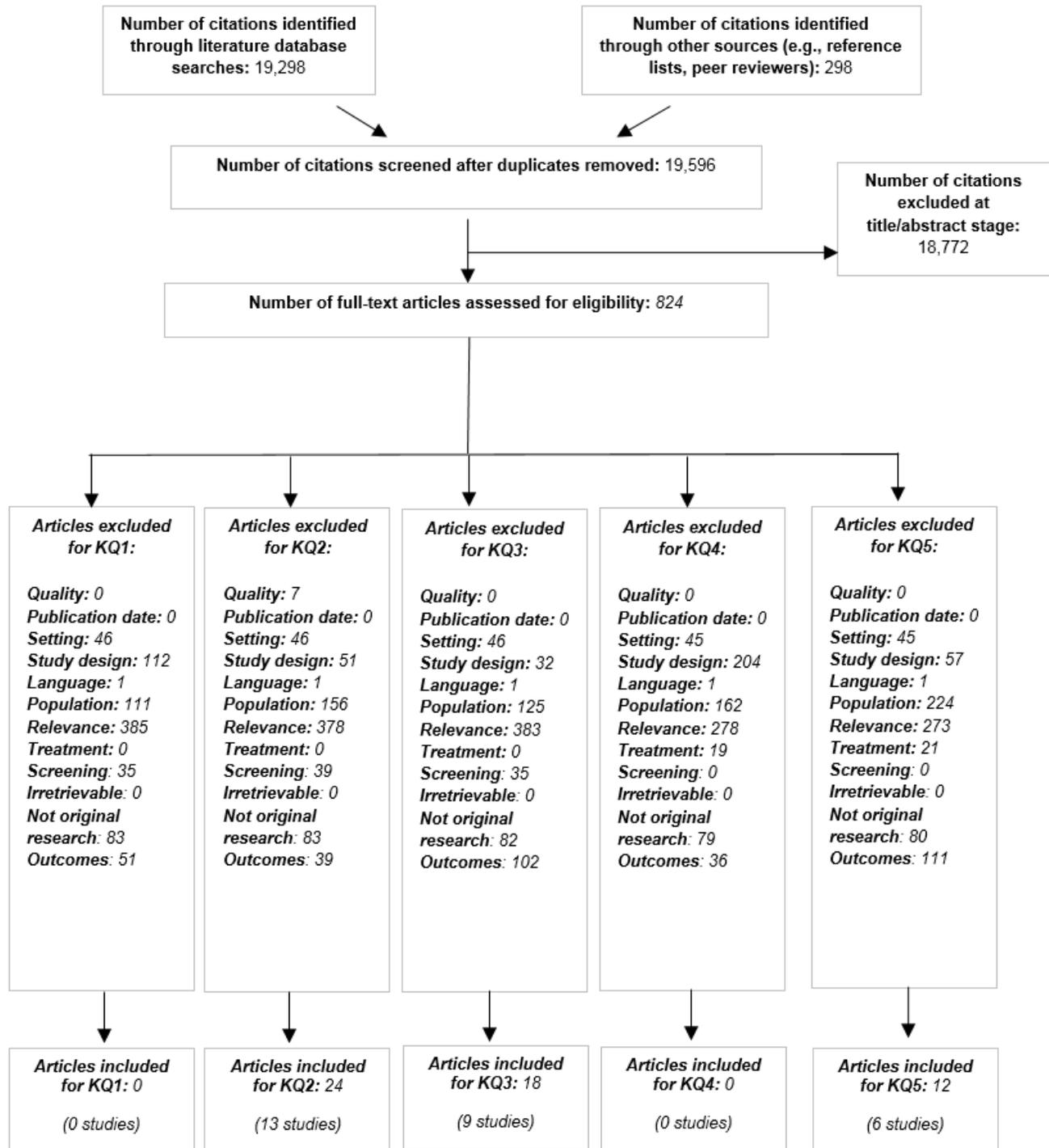
PubMed, Publisher Supplied Segment

Search	Query
#33	Search #32 AND publisher[sb] AND English[language] AND ("2002"[Date - Publication] : "3000"[Date - Publication])
#32	Search #9 OR #11 OR #20 OR #26 OR #31
#31	Search #3 AND #23 AND #30
#30	Search #27 OR #28 OR #29
#29	Search (lung* [tiab] OR pulmonary [tiab] OR heart [tiab] OR cardiac [tiab] OR cardio* [tiab] OR kidney* [tiab] OR renal [tiab] OR nephro* [tiab] OR nerve* [tiab] OR neural* [tiab]) AND (damage* [tiab] OR injur* [tiab])
#28	Search cardiotoxic* [tiab] Or osteoradionecrosis [tiab] OR radiodermatitis [tiab] OR nausea [tiab] OR nauseous* [tiab] OR vomit* [tiab] OR diarrhea [tiab] OR diarrhoea [tiab] OR alopeci* [tiab] OR "hair loss"[tiab] OR "loss of appetite"[tiab] OR "appetite loss"[tiab] OR fatigu* [tiab] OR letharg* [tiab] OR fever* [tiab] OR mouth sore* [tiab] OR pain* [tiab] OR constipat* [tiab] OR contusion* [tiab] OR bruis* [tiab]
#27	Search (radiation [tiab] AND (expos* [tiab] OR damag* [tiab] OR induce* [tiab] OR injur* [tiab]))
#26	Search #3 AND #23 AND #25
#25	Search #8 OR #24
#24	Search cohort* [tiab] OR longitudinal [tiab] OR "follow up"[tiab] OR followup [tiab] OR prospectiv* [tiab] OR retrospectiv* [tiab]
#23	Search #21 OR #22
#22	Search radiation [tiab] AND therap* [tiab]
#21	Search pancreatectom* [tiab] OR pancreaticoduodenectom* [tiab] OR surger* [tiab] OR surgical [tiab] OR resect* [tiab] OR radiotherapy [tiab] OR whipple [tiab] OR chemoradiotherap* [tiab] OR chemotherap* [tiab] OR photochemotherap* [tiab] OR folfirinox [tiab] OR Leucovorin [tiab] OR Fluorouracil [tiab] OR Capecitabine [tiab] OR gemcitabine [tiab] OR gemzar [tiab] OR 5-fu [tiab] OR Paclitaxel [tiab] OR Camptothecin [tiab]
#20	Search #3 AND #4 AND #19
#19	Search #12 OR #13 Or #14 OR #15 OR #16 OR #17 OR #18
#18	Search anxiet* [tiab] OR anxious* [tiab] OR depress* [tiab] OR "cancer worry"[tiab] OR "cancer worries"[tiab]
#17	Search malignan* [tiab] AND seed* [tiab]
#16	Search neoplas* [tiab] AND seed* [tiab]
#15	Search bile [tiab] AND peritonitis [tiab]
#14	Search perforat* [tiab] OR infect* [tiab] OR iatrogen* [tiab] OR hemorrhag* [tiab] OR haemorrhag* [tiab]
#13	Search (adverse [tiab] AND (effect* [tiab] OR event [tiab] OR outcome [tiab] OR reaction [tiab]))

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Search	Query
#12	Search harm[tiab] OR harms[tiab] OR harmful[tiab] OR harmed[tiab] OR mortal*[tiab] OR death*[tiab] OR complication*[tiab] OR "side effect"[tiab] OR "side effects"[tiab] OR safety[tiab]
#11	Search #3 AND #4 AND #10
#10	Search sensitiv*[tiab] OR specificit*[tiab] OR predictive value[tiab] OR predictive values[tiab] OR accuracy[tiab] OR false positive[tiab] OR false positives[tiab] OR false positivity[tiab] OR false positivities[tiab] OR false negative[tiab] OR false negatives[tiab] OR false negativity[tiab] OR false negativities[tiab] OR miss rate[tiab] OR miss rates[tiab] OR error rate[tiab] OR error rates[tiab] OR roc curve[tiab] OR roc curves[tiab] OR receiver operat*[tiab] OR reference value[tiab] OR reference values[tiab] OR reference standard[tiab] OR reference standards[tiab]
#9	Search #3 AND #4 AND #8
#8	Search #5 OR #6 OR #7
#7	Search metaanaly*[tiab] or "meta analysis"[tiab]
#6	Search (control[tiab] OR controls[tiab] OR controlled[tiab]) AND (trial[tiab] OR trials[tiab])
#5	Search "clincial trials"[tiab] OR "clinical trial"[tiab] OR random*[tiab]
#4	Search screen*[tiab] OR ultrasonogra*[tiab] OR ultrasound*[tiab] OR tomograph*[tiab] OR magnetic resonance imag*[tiab] OR cholangiography[tiab] OR cholangiopancreato*[tiab] OR ct scan*[tiab] OR pet scan*[tiab] OR mri[tiab] OR octreoscan*[tiab] OR octreotide scan*[tiab] OR angiograph*[tiab] OR ercp[tiab]
#3	Search #1 OR #2
#2	Search pancreatic intraepithelial neoplas*[tiab] OR panin[tiab] OR intraductal papillary mucinous neoplas*[tiab] OR ipmn[tiab] OR mucinous cystic neoplas*[tiab]
#1	Search (pancreas[tiab] OR pancreati*[tiab] OR pancreato*[tiab] OR Acinar*[tiab] OR Acinus[tiab] OR hepatopancreat*[tiab] OR ampull*[tiab]) AND (cancer*[tiab] OR carcinoma*[tiab] OR adenocarcinoma*[tiab] OR apudoma*[tiab] OR adenoma*[tiab] OR carcinoid*[tiab] OR sarcoma*[tiab] OR malignan*[tiab] OR tumor*[tiab] OR tumour*[tiab] OR neoplas*[tiab] OR lesion*[tiab] OR cyst[tiab] OR cysts[tiab])

Appendix A Figure 1. Literature Flow Diagram



Abbreviations: KQ = Key question

Appendix A Table 1. Inclusion and Exclusion Criteria

	Included	Excluded
Population	<p>KQs 1–3: Adults age ≥18 years, with or without risk factors for pancreatic adenocarcinoma (e.g., family history of pancreatic cancer, personal history of new-onset diabetes, or other risk factors)*</p> <p>KQs 4, 5: Adults with screen-detected or asymptomatic pancreatic adenocarcinoma</p>	<p>KQs 1–3:</p> <ul style="list-style-type: none"> • Children and adolescents • Persons with history of pancreatic cancer • Studies focusing only on persons with a known genetic syndrome associated with increased risk for pancreatic cancer (e.g., Peutz-Jeghers syndrome, Lynch syndrome, hereditary pancreatitis, known mutations in <i>CDKN2A</i>, <i>BRCA1</i>, <i>BRCA2</i>, <i>CTFR</i>, or <i>ATM</i> genes)[†] <p>KQs 4, 5: Symptomatic populations with pancreatic adenocarcinoma; populations with pancreatic endocrine or exocrine tumors other than adenocarcinoma</p>
Setting	Studies conducted in countries categorized as “Very High” on the 2016 Human Development Index (as defined by the United Nations Development Programme) ¹	
Screening test	Any imaging-based screening protocol, including but not limited to computed tomography scan, endoscopic ultrasonography, magnetic resonance imaging, and abdominal ultrasonography	Serum, stool, or saliva-based testing for biomarkers, such as cancer antigen 19-9, carcinoembryonic antigen, cell-surface proteins, micro-RNA, hypermethylation of specific genes in circulating DNA, circulating tumor cells, or multiple-biomarker panels
Treatment	KQs 4, 5: Surgical resection, with or without chemotherapy or radiation therapy	Chemotherapy or palliative care alone
Comparisons	<p>KQ 1: No screening</p> <p>KQ 2: Reference standard (e.g., clinical followup)</p> <p>KQ 4: No treatment or delayed treatment</p>	Comparative effectiveness screening or treatment studies
Outcomes	<p>KQs 1, 4: Reduced pancreatic adenocarcinoma morbidity or mortality, reduced all-cause mortality, and improved quality of life</p> <p>KQ 2: Sensitivity, specificity, positive predictive value, and lesion detection rate</p> <p>KQs 3, 5: Any harm from screening or treatment, including false-positive or false-negative results, serious psychological harms, or screening- or treatment-related adverse events</p>	KQ 3: Incidentally identified lesions
Study design	<p>All KQs: Fair- or good-quality studies (according to design-specific USPSTF criteria) published from 2002 to the present[‡]</p> <p>KQ 1: Randomized, controlled trials; controlled clinical trials</p> <p>KQ 2: Diagnostic accuracy studies with a reference standard; systematic evidence reviews</p> <p>KQs 3, 5: Randomized, controlled trials; controlled clinical trials; cohort studies; case-control studies</p> <p>KQ 4: Randomized, controlled trials; controlled clinical trials; cohort studies</p>	Poor-quality studies with a fatal flaw; studies occurring outside of the specified publication dates; case reports and case series; narrative reviews, commentaries, editorials, theses, qualitative studies, ecologic studies, comparative effectiveness studies, and decision analyses; studies not available in the English language

Abbreviations: DNA=deoxyribonucleic acid; RNA=ribonucleic acid.

* Results were stratified by risk factors, such as age, sex, or clinical characteristics, where possible.

[†] Studies consisting entirely of populations with high-risk genetic syndromes were excluded, but studies that include persons with high-risk genetic syndromes in addition to persons with other risk factors were not excluded.

[‡] Studies included in the previous USPSTF review (search dates through December 2001) that meet current inclusion criteria were evaluated, but none of them met our inclusion criteria.

Appendix A Table 2. Quality Assessment Criteria

Study Design	Quality criteria
Randomized controlled trials USPSTF methods ²	<ul style="list-style-type: none"> • Valid random assignment? • Was allocation concealed? • Was eligibility criteria specified? • Were groups similar at baseline? • Were measurements equal, valid, and reliable? • Was there intervention fidelity? • Was there adequate adherence to the intervention? • Were outcome assessors blinded? • Was there acceptable followup? • Were the statistical methods acceptable? • Was the handling of missing data appropriate? • Was there evidence of selective reporting of outcomes? • Was the device calibration and/or maintenance reported?
Observational studies (e.g., prospective cohort studies), adapted from the Newcastle-Ottawa Scale (NOS) ³	<ul style="list-style-type: none"> • Was the cohort systematically selected to avoid bias? • Was eligibility criteria specified? • Were groups similar at baseline? • Was the outcome of interest not present at baseline? • Were measurements equal, valid, and reliable? • Were outcome assessors blinded? • Was there acceptable followup? • Were the statistical methods acceptable? • Was the handling of missing data appropriate?
Diagnostic accuracy studies adapted from QUADAS I and II ^{4, 5}	<ul style="list-style-type: none"> • Screening test relevant, available for primary care, and adequately described • Study uses a credible reference standard performed regardless of test results • Reference standard interpreted independently of screening test • Handles indeterminate results in a reasonable manner • Spectrum of patients included in study • Sample size reported • Administration of reliable screening test

Abbreviations: USPSTF = U.S. Preventive Services Task Force

References

1. United Nations Development Programme. Human Development Index: 2016 Rankings. United Nations Development Programme [2017 December 1]. <http://hdr.undp.org/en/2016-report>.
2. U.S. Preventive Services Task Force. U.S. Preventive Services Task Force Procedure Manual. Rockville, MD: U.S. Preventive Services Task Force; 2015.
3. Wells GA, Shea B, O'Connell D, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Ottawa: University of Ottawa [2018 August 23]. http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp.
4. Whiting P, Rutjes AW, Reitsma JB, et al. The development of QUADAS: a tool for the quality assessment of studies of diagnostic accuracy included in systematic reviews. BMC Med Res Methodol. 2003;3:25. PMID: 14606960.
5. Whiting PF, Rutjes AW, Westwood ME, et al. QUADAS-2: a revised tool for the quality assessment of diagnostic accuracy studies. Ann Intern Med. 2011;155(8):529-36. PMID: 22007046.

Appendix B. Included Studies

Ludwig E, Olson SH, Bayuga S, Simon J, Schattner MA, Gerdes H, et al. Feasibility and yield of screening in relatives from familial pancreatic cancer families. *Am J Gastroenterol*. 2011;106(5):946-54.

Joergensen MT, Gerdes AM, Sorensen J, Schaffalitzky de Muckadell O, Mortensen MB. Is screening for pancreatic cancer in high-risk groups cost-effective? - Experience from a Danish national screening program. *Pancreatology*. 2016;16(4):584-92.

Poley JW, Kluijt I, Gouma DJ, Harinck F, Wagner A, Aalfs C, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. *Am J Gastroenterol*. 2009;104(9):2175-81.

Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. *Clin Gastroenterol Hepatol*. 2004;2(7):606-21.

Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, et al. Screening for early pancreatic neoplasia in high-risk individuals: a prospective controlled study. *Clin Gastroenterol Hepatol*. 2006;4(6):766-81; quiz 665.

Del Chiaro M, Verbeke CS, Kartalis N, Pozzi Mucelli R, Gustafsson P, Hansson J, et al. Short-term Results of a Magnetic Resonance Imaging-Based Swedish Screening Program for Individuals at Risk for Pancreatic Cancer. *JAMA Surgery*. 2015;150(6):512-8.

Verna EC, Hwang C, Stevens PD, Rotterdam H, Stavropoulos SN, Sy CD, et al. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. *Clinical Cancer Research*. 2010;16(20):5028-37.

Canto MI. Value of EUS screening in patients with high risk factors for pancreatic cancer (focus on familial pancreatic cancer). *Pancreatology Conference: 20th meeting of the international association of pancreatology, IAP 2016 Japan* [Internet]. 2016; 16(4 Supplement 1):[S19-s20 pp.]. Available from: <http://onlinelibrary.wiley.com/doi/10.1111/pan.12700>.

Barnes CA, Krzywda E, Lahiff S, et al. Development of a high risk pancreatic screening clinic using 3.0 T MRI. *Fam Cancer*. 2018;17(1):101-11. PMID: 29101607.

Gangi A, Malafa M, Klapman J. Endoscopic Ultrasound-Based Pancreatic Cancer Screening of High-Risk Individuals: A Prospective Observational Trial. *Pancreas*. 2018;19:19. PMID: 29683970.

FaPaCa Study – Marburg, Germany

Schneider R, Slater EP, Sina M, Habbe N, Fendrich V, Matthai E, et al. German national case collection for familial pancreatic cancer (FaPaCa): ten years experience. *Fam Cancer*. 2011;10(2):323-30.

Langer P, Kann PH, Fendrich V, Habbe N, Schneider M, Sina M, et al. Five years of prospective screening of high-risk individuals from families with familial pancreatic cancer. *Gut*. 2009;58(10):1410-8.

Potjer TP, Schot I, Langer P, Heverhagen JT, Wasser MN, Slater EP, et al. Variation in precursor lesions of pancreatic cancer among high-risk groups. *Clin Cancer Res*. 2013;19(2):442-9.

Bartsch DK, Slater EP, Carrato A, Ibrahim IS, Guillen-Ponce C, Vasen HF, et al. Refinement of screening for familial pancreatic cancer. *Gut*. 2016;65(8):1314-21.

Appendix B. Included Studies

Vasen H, Ibrahim I, Ponce CG, Slater EP, Matthai E, Carrato A, et al. Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers. *J Clin Oncol*. 2016;34(17):2010-9.

Toronto Screening Study

Al-Sukhni W, Borgida A, Rothenmund H, Holter S, Semotiuk K, Grant R, et al. Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. *J Gastrointest Surg*. 2012;16(4):771-83.

Maheu C, Vodermaier A, Rothenmund H, Gallinger S, Ardiles P, Semotiuk K, et al. Pancreatic cancer risk counselling and screening: impact on perceived risk and psychological functioning. *Familial Cancer*. 2010;9(4):617-24.

Hart SL, Torbit LA, Crangle CJ, Esplen MJ, Holter S, Semotiuk K, et al. Moderators of cancer-related distress and worry after a pancreatic cancer genetic counseling and screening intervention. *Psychooncology*. 2012;21(12):1324-30.

Dutch PC Screening Study

Harinck F, Konings I, Kluijt I, Poley JW, Hooft JE, Dullemeijer HM, et al. A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. *Gut* [Internet]. 2016; 65(9):[1505-13 pp.]. Available from: <http://onlinelibrary.wiley.com/doi/10.1136/gut.2016.131505>

Konings IC, Sidharta GN, Harinck F, Aalfs CM, Poley JW, Kieffer JM, et al. Repeated participation in pancreatic cancer surveillance by high-risk individuals imposes low psychological burden. *Psychooncology*. 2016;25(8):971-8.

Konings IC, Harinck F, Kuenen MA, Sidharta GN, Kieffer JM, Aalfs CM, et al. Factors associated with cancer worries in individuals participating in annual pancreatic cancer surveillance. *Fam Cancer*. 2016.

Harinck F, Nagtegaal T, Kluijt I, Aalfs C, Smets E, Poley JW, et al. Feasibility of a pancreatic cancer surveillance program from a psychological point of view. *Genetics in Medicine*. 2011;13(12):1015-24.

CAPS 3 (5 sites in USA) - MRI, CT, EUS

Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, et al. Frequent detection of pancreatic lesions in asymptomatic high-risk individuals. *Gastroenterology*. 2012;142(4):796-804; quiz e14-5.

Shin EJ, Topazian M, Goggins MG, Syngal S, Saltzman JR, Lee JH, et al. Linear-array EUS improves detection of pancreatic lesions in high-risk individuals: a randomized tandem study. *Gastrointest Endosc*. 2015;82(5):812-8.

Canto MI, Almario JA, Schulick RD, et al. Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance. *Gastroenterology*. 2018;155(3):740-51 e2. PMID: 29803839.

Appendix C. Excluded Studies

E Codes
E1. Not relevant
E2. Not English
E3. Not original research
E4. Publication date (exclude articles published 2001 and earlier)
E5. Ineligible SETTING (see “very high HDI” list below)
E6. Ineligible POPULATION E6a. (For KQs 1-3) Persons with history of PC E6b. (For KQs 1-3) Persons with known genetic syndrome comprise the entire study population E6c. (For KQs 1-3) Children, adolescents, any other ineligible population E6d. (For KQs 4, 5) Symptomatic or non-screen-detected populations E6e. (For KQs 4, 5) Persons with pancreatic endocrine, exocrine or other non-adenocarcinoma tumors
E7. Ineligible SCREENING (e.g. biomarker testing)
E8. Ineligible TREATMENT (e.g. chemotherapy or palliative care alone)
E9. Ineligible OUTCOMES E9a. (for KQ 3): Incidentally identified lesions E9b. Incomplete study / protocol only E9c. Other ineligible outcomes (see table below)
E10. Ineligible STUDY DESIGN E10a. (for KQ 1, 2, 4): No comparison group E10b. Comparative effectiveness study E10c. Other ineligible design (see table below)
E11. Irretrievable
E12. Poor QUALITY

- | | |
|--|---|
| <p>1. Grade B pancreatic fistulas do not affect survival after pancreatectomy for pancreatic cancer: A multicenter observational study. <i>Surgery (United States)</i>. 160 (2) (pp 293-305), 2016. Date of Publication: 01 Aug 2016.. 2016; PMID: CN-01197238. KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6.</p> | <p>4. Addeo P, Delpero JR, Paye F, et al. Pancreatic fistula after a pancreaticoduodenectomy for ductal adenocarcinoma and its association with morbidity: a multicentre study of the French Surgical Association. <i>HPB</i>. 2014;161:46-55. PMID: 23461663. KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6.</p> |
| <p>2. Aahlin EK, Olsen F, Uleberg B, et al. Major postoperative complications are associated with impaired long-term survival after gastro-esophageal and pancreatic cancer surgery: a complete national cohort study. <i>BMC Surgery</i>. 2016;161:32. PMID: 27193578. KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E9c.</p> | <p>5. Alemanno G, Bergamini C, Martellucci J, et al. Surgical outcome of pancreaticoduodenectomy: high volume center or multidisciplinary management?. <i>Minerva Chirurgica</i>. 2016;711:8-14. PMID: 25922054. KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.</p> |
| <p>3. Abu Hilal M, Richardson JR, de Rooij T, et al. Laparoscopic radical 'no-touch' left pancreateosplenectomy for pancreatic ductal adenocarcinoma: technique and results. <i>Surgical Endoscopy</i>. 2016;309:3830-8. PMID: 26675941. KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E8.</p> | <p>6. Alexander BM, Fernandez-Del Castillo C, Ryan DP, et al. Intraductal papillary mucinous adenocarcinoma of the pancreas: clinical outcomes, prognostic factors, and the role of adjuvant therapy. <i>Gastrointestinal Cancer Research</i>. 2011;44:116-21. PMID: 22368734. KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.</p> |

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141. D'Angelo F, Antolino L, Farcomeni A, et al. Neoadjuvant treatment in pancreatic cancer: Evidence-based medicine? A systematic review and meta-analysis. *Medical Oncology*. 2017;345:85. PMID: 28391577. **KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E8.**
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143. Date K, Ohtsuka T, Nakamura S, et al. Surveillance of patients with intraductal papillary mucinous neoplasm with and without pancreatectomy with special reference to the incidence of concomitant pancreatic ductal adenocarcinoma. *Surgery*. 2018;1632:291-299. PMID: 29221879. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E62.**
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149. de Rooij T, Lu MZ, Steen MW, et al. Minimally Invasive Versus Open Pancreatoduodenectomy: Systematic Review and Meta-analysis of Comparative Cohort and Registry Studies. *Annals of Surgery*. 2016;2642:257-67. PMID: 26863398. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**
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163. Du C, Chai NL, Linghu EQ, et al. Incidents and adverse events of endoscopic ultrasound-guided fine-needle aspiration for pancreatic cystic lesions. *World Journal of Gastroenterology*. 2017;2330:5610-5618. PMID: 28852320. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
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167. Dumitrascu T, Barbu ST, Purnichescu-Purtan R, et al. Risk factors for surgical complications after central pancreatectomy. *Hepato-Gastroenterology*. 2012;59114:592-8. PMID: 22353528. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.**
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170. Ecker BL, Simmons KD, Zaheer S, et al. Blood Transfusion in Major Abdominal Surgery for Malignant Tumors: A Trend Analysis Using the National Surgical Quality Improvement Program. *JAMA Surgery*. 2016;1516:518-25. PMID: 26763765. **KQ1E1, KQ2E1, KQ3E1, KQ4E6e, KQ5E6e.**
171. El Nakeeb A, El Shobary M, El Dosoky M, et al. Prognostic factors affecting survival after pancreaticoduodenectomy for pancreatic adenocarcinoma (single center experience). *Hepato-Gastroenterology*. 2014;61133:1426-38. PMID: 25436321. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
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208. Gangl O, Sahara K, Kornprat P, et al. Preparing for prospective clinical trials: a national initiative of an excellence registry for consecutive pancreatic cancer resections. *World Journal of Surgery*. 2014;382:456-62. PMID: 24121365. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6.**
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Appendix C. Excluded Studies

211. Ge Ps Gaddam S Keach Jw Mullady D Fukami N Edmundowicz Sa Azar Rr Shah Rj Murad Fm Kushnir Vm Ghassemi Kf Sedarat A Watson Rr Amateau Sk Brauer Bc Yen Rd Hosford L Hollander T Donahue Tr Schulick Rd Edil Bh McCarter Md Gajdos C Attwell Ar Muthusamy Vr Ear Predictors for Surgical Referral in Patients with Pancreatic Cystic Lesions Undergoing Endoscopic Ultrasound: results from a Large Multicenter Cohort Study. *Pancreas*. 2016;451:51-57. PMID: CN-01209243. **KQ1E6, KQ2E6, KQ3E6, KQ4E1, KQ5E12.**
212. Gemmel C, Eickhoff A, Helmstadter LRiemann JF. Pancreatic cancer screening: state of the art. *Expert review of gastroenterology & hepatology*. 2009;31:89-96. PMID: 19210116. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
213. Gianotti L, Tamini N, Gavazzi F, et al. Consequences of Increases in Antibiotic Resistance Pattern on Outcome of Pancreatic Resection for Cancer. *Journal of Gastrointestinal Surgery*. 2017;5:5. PMID: 28681215. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.**
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215. Giovinazzo F, Turri G, Katz MH, et al. Meta-analysis of benefits of portal-superior mesenteric vein resection in pancreatic resection for ductal adenocarcinoma. *British Journal of Surgery*. 2016;1033:179-91. PMID: 26663252. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**
216. Girometti R, Pravisan R, Intini SG, et al. Evolution of incidental branch-duct intraductal papillary mucinous neoplasms of the pancreas: A study with magnetic resonance imaging cholangiopancreatography. *World Journal of Gastroenterology*. 2016;2243:9562-9570. PMID: 27920477. **KQ1E9, KQ2E6, KQ3E9, KQ4E1, KQ5E1.**
217. Glasgow RE, Jackson HH, Neumayer L, et al. Pancreatic resection in Veterans Affairs and selected university medical centers: results of the patient safety in surgery study. *Journal of the American College of Surgeons*. 2007;2046:1252-60. PMID: 17544083. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E12.**
218. Glasgow RE, Jackson HH, Neumayer L, et al. Pancreatic resection in Veterans Affairs and selected university medical centers: results of the patient safety in surgery study. *Journal of the American College of Surgeons*. 2007;2046:1252-60. PMID: 17544083. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E6.**
219. Glebova NO, Hicks CW, Tosoian JJ, et al. Outcomes of arterial resection during pancreatectomy for tumor presented at the vascular and endovascular surgery society paper session 2 at the 2015 Vascular Annual Meeting of the Society for Vascular Surgery, Chicago, Ill, June 17-20, 2015. *Journal of vascular surgery*. 2016;633:722-729.e1. PMID: CN-01171725. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E10.**
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221. Goh BK, Tan YM, Cheow PC, et al. Cystic lesions of the pancreas: an appraisal of an aggressive resectional policy adopted at a single institution during 15 years. *American Journal of Surgery*. 2006;1922:148-54. PMID: 16860621. **KQ1E1, KQ2E1, KQ3E1, KQ4E6e, KQ5E6e.**
222. Gomatos IP, Halloran C, Ghaneh P, et al. Management and Outcome of 64 Patients with Pancreatic Serous Cystic Neoplasms. *Digestive Surgery*. 2016;333:203-12. PMID: 26918360. **KQ1E6e, KQ2E6e, KQ3E6e, KQ4E6e, KQ5E6e.**
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224. Gong Z, Holly EA, Bracci PM. Obesity and survival in population-based patients with pancreatic cancer in the San Francisco Bay Area. *Cancer Causes & Control*. 2012;23(12):1929-37. PMID: 23015286. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E9.**
225. Gonzalo-Marin J, Vila JJ, Perez-Miranda M. Role of endoscopic ultrasound in the diagnosis of pancreatic cancer. *World Journal of Gastrointestinal Oncology*. 2014;69:360-8. PMID: 25232461. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
226. Goshima S, Kanematsu M, Nishibori H, et al. CT of the pancreas: comparison of anatomic structure depiction, image quality, and radiation exposure between 320-detector volumetric images and 64-detector helical images. *Radiology*. 2011;260(1):139-147. PMID: CN-00801245. **KQ1E9, KQ2E10, KQ3E9, KQ4E1, KQ5E1.**
227. Goto T, Matsumoto I, Toyama H, et al. Complications after laparoscopic distal pancreatectomy. *Surgical Endoscopy and Other Interventional Techniques*. Conference: 23rd International Congress of the European Association for Endoscopic Surgery, EAES 2015 Bucharest Romania. Conference Start: 20150603 Conference End: 20150606. Conference Publication: (. 2016;30:S136. PMID: CN-01174184. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.**
228. Govindarajan A, Tan JC, Baxter NN, et al. Variations in surgical treatment and outcomes of patients with pancreatic cancer: a population-based study. *Annals of Surgical Oncology*. 2008;15(1):175-85. PMID: 17909913. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E6.**
229. Grant FM, Protic M, Gonen M, et al. Intraoperative fluid management and complications following pancreatectomy. *Journal of Surgical Oncology*. 2013;107(5):529-35. PMID: 23136127. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6e.**
230. Greer J, Brand RE. Screening for pancreatic cancer: current evidence and future directions. *Gastroenterology & Hepatology*. 2007;3(12):929-38. PMID: 21960811. **KQ1E3, KQ2E3, KQ3E3, KQ4E1, KQ5E1.**
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232. Grieser C, Heine G, Stelter L, et al. Morphological analysis and differentiation of benign cystic neoplasms of the pancreas using computed tomography and magnetic resonance imaging. *Rofo: Fortschritte auf dem Gebiete der Rontgenstrahlen und der Nuklearmedizin*. 2013;185(3):219-27. PMID: 23196834. **KQ1E6, KQ2E6, KQ3E6, KQ4E1, KQ5E1.**
233. Groot VP, Rezaee N, Wu W, et al. Patterns, Timing, and Predictors of Recurrence Following Pancreatectomy for Pancreatic Ductal Adenocarcinoma. *Annals of Surgery*. 2018;267(5):936-945. PMID: 28338509. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
234. Grose D, McIntosh D, Jamieson N, et al. The role of induction chemotherapy + chemoradiotherapy in localised pancreatic cancer: initial experience in Scotland. *Journal of Gastrointestinal Oncology*. 2017;8(4):683-695. PMID: 28890819. **KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E8.**
235. Grover SJ, Joo K. Screening for Pancreatic Cancer in High-risk Populations. *Gastroenterol Clin North Am*. 2016;45(1):117-27. PMID: 26895684. **KQ1E3, KQ2E3, KQ3E3, KQ4E1, KQ5E12.**
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237. Gudjonsson B. Pancreatic Cancer: 80 Years of Surgery-Percentage and Repetitions. *HPB Surg*. 2016;2016:6839687. PMID: 27847403. **KQ1E10, KQ2E10, KQ3E10, KQ4E10, KQ5E102.**

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239. Guo Q, Kang M, Zhang B, et al. Elevated levels of CA 19-9 and CEA in pancreatic cancer-associated diabetes. *Journal of Cancer Research & Clinical Oncology*. 2010;13611:1627-31. PMID: 20174821. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
240. Gupta PK, Turaga KK, Miller WJ, et al. Determinants of outcomes in pancreatic surgery and use of hospital resources. *Journal of Surgical Oncology*. 2011;1046:634-40. PMID: 21520092. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6d.**
241. Halloran CM, Cox TF, Chauhan S, et al. Partial pancreatic resection for pancreatic malignancy is associated with sustained pancreatic exocrine failure and reduced quality of life: a prospective study. *Pancreatology*. 2011;116:535-45. PMID: 22094930. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E9.**
242. Halloran CM, Ghaneh P, Bosonnet L, et al. Complications of pancreatic cancer resection. *Digestive Surgery*. 2002;192:138-46. PMID: 11979003. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E3.**
243. Halloran CM, Ghaneh P, Costello E, Neoptolemos JP. Trials of gene therapy for pancreatic carcinoma. *Current Gastroenterology Reports*. 2005;73:165-9. PMID: 15913472. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
244. Hanada K, Okazaki A, Hirano N, et al. Effective screening for early diagnosis of pancreatic cancer. *Best Pract Res Clin Gastroenterol*. 2015;296:929-39. PMID: 26651254. **KQ1E3, KQ2E3, KQ3E3, KQ4E1, KQ5E12.**
245. Harada T, Baril P, Gangeswaran R, et al. Identification of genetic alterations in pancreatic cancer by the combined use of tissue microdissection and array-based comparative genomic hybridisation. *British Journal of Cancer*. 2007;962:373-82. PMID: 17242705. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
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254. Hasselgren K, Halldestam I, Fraser MP, et al. Does the Introduction of Laparoscopic Distal Pancreatectomy Jeopardize Patient Safety and Well-Being?. *Scand J Surg*. 2016; PMID: 26929282. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E10.**
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269. Herrmann K, Erkan M, Dobritz M, et al. Comparison of 3'-deoxy-3'-[18F]fluorothymidine positron emission tomography (FLT PET) and FDG PET/CT for the detection and characterization of pancreatic tumours. *European Journal of Nuclear Medicine & Molecular Imaging*. 2012;395:846-51. PMID: 22278320. **KQ1E6, KQ2E6, KQ3E6, KQ4E1, KQ5E1.**
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281. Ikemoto J, Hanada K, Minami T, et al. Prospective Follow-up Study of the Recurrence of Pancreatic Cancer Diagnosed at an Early Stage: The Value of Endoscopic Ultrasonography for Early Diagnosis of Recurrence in the Remnant Pancreas. *Pancreas*. 2018;474:482-488. PMID: 29517631. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E62.**
282. Ikeuchi N, Itoi T, Sofuni A, et al. Prognosis of cancer with branch duct type IPMN of the pancreas. *World Journal of Gastroenterology*. 2010;1615:1890-5. PMID: 20397268. **KQ1E10, KQ2E9, KQ3E9, KQ4E1, KQ5E1.**

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283. Ikezawa K, Uehara H, Sakai A, et al. Risk of peritoneal carcinomatosis by endoscopic ultrasound-guided fine needle aspiration for pancreatic cancer. *Journal of Gastroenterology*. 2013;488:966-72. PMID: 23065024. **KQ1E6, KQ2E6, KQ3E6, KQ4E1, KQ5E1.**
284. Illes D, Terzin V, Holzinger G, et al. New-onset type 2 diabetes mellitus--A high-risk group suitable for the screening of pancreatic cancer?. *Pancreatology*. 2016;162:266-71. PMID: 26777407. **KQ1E10, KQ2E12, KQ3E9, KQ4E1, KQ5E1.**
285. Imamura M, Doi R, Imaizumi T, et al. A randomized multicenter trial comparing resection and radiochemotherapy for resectable locally invasive pancreatic cancer. *Surgery*. 2004;1365:1003-11. PMID: 15523393. **KQ1E1, KQ2E1, KQ3E1, KQ4E10c, KQ5E9.**
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287. Imbe K, Nagata N, Hisada Y, et al. Validation of the American Gastroenterological Association guidelines on management of intraductal papillary mucinous neoplasms: more than 5 years of follow-up. *Eur Radiol*. 2017; PMID: 28770404. **KQ1E10, KQ2E6, KQ3E9, KQ4E1, KQ5E1.**
288. Ingkakul T, Sadakari Y, Ienaga J, et al. Predictors of the presence of concomitant invasive ductal carcinoma in intraductal papillary mucinous neoplasm of the pancreas. *Annals of Surgery*. 2010;251:70-5. PMID: 20009749. **KQ1E6, KQ2E6, KQ3E6, KQ4E1, KQ5E1.**
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290. Iott M, Neben-Wittich M, Quevedo JF, Miller RC. Adjuvant chemoradiotherapy for resected pancreas cancer. *World Journal of Gastrointestinal Surgery*. 2010;211:373-80. PMID: 21160900. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
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292. Iqbal J, Ragone A, Lubinski J, et al. The incidence of pancreatic cancer in BRCA1 and BRCA2 mutation carriers. *Br J Cancer*. 2012;10712:2005-9. PMID: 23099806. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E62.**
293. Iqbal N, Lovegrove RE, Tilney HS, et al. A comparison of pancreaticoduodenectomy with extended pancreaticoduodenectomy: a meta-analysis of 1909 patients. *European Journal of Surgical Oncology*. 2009;351:79-86. PMID: 18356005. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E6d.**
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295. Jaap K, Fluck M, Hunsinger M, et al. Analyzing the Impact of Compliance with National Guidelines for Pancreatic Cancer Care Using the National Cancer Database. *J Gastrointest Surg*. 2018;2810:018-3742. PMID: 0. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E62.**
296. Jabbar Ks Verbeke C, Hyltander Ag Sjoval H, Hansson Gc, Sadik R. Proteomic mucin profiling for the identification of cystic precursors of pancreatic cancer. *Journal of the national cancer institute*. 2014;1062 (no pagination:). PMID: CN-01209493. **KQ1E7, KQ2E7, KQ3E7, KQ4E1, KQ5E12.**
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299. Jang DK, Lee SH, Lee JK, et al. Comparison of cytological and histological preparations in the diagnosis of pancreatic malignancies using endoscopic ultrasound-guided fine needle aspiration. *Hepatobiliary & Pancreatic Diseases International*. 2017;164:418-423. PMID: 28823373. **KQ1E10b, KQ2E10b, KQ3E10b, KQ4E1, KQ5E1.**
300. Jang JY, Kang JS, Han Y, et al. Long-term outcomes and recurrence patterns of standard versus extended pancreatectomy for pancreatic head cancer: a multicenter prospective randomized controlled study. *Journal of Hepato-biliary-pancreatic Sciences*. 2017;247:426-433. PMID: 28514000. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**
301. Jang JY, Kang MJ, Heo JS, et al. A prospective randomized controlled study comparing outcomes of standard resection and extended resection, including dissection of the nerve plexus and various lymph nodes, in patients with pancreatic head cancer. *Annals of Surgery*. 2014;2594:656-64. PMID: 24368638. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E6.**
302. Jang KM, Kim SH, Kim YK, et al. Missed pancreatic ductal adenocarcinoma: Assessment of early imaging findings on prediagnostic magnetic resonance imaging. *European Journal of Radiology*. 2015;848:1473-9. PMID: 26032128. **KQ1E6a, KQ2E6a, KQ3E6a, KQ4E1, KQ5E1.**
303. Jenssen CKahl S. Management of Incidental Pancreatic Cystic Lesions. *Viszeralmedizin*. 2015;311:14-24. PMID: 26288611. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
304. Jiang HY, Kohtakang EL, Asai KShum JB. Predictive Power of the NSQIP Risk Calculator for Early Post-Operative Outcomes After Whipple: Experience from a Regional Center in Northern Ontario. *J Gastrointest Cancer*. 2017; PMID: 28462447. **KQ1E1, KQ2E1, KQ3E1, KQ4E6e, KQ5E6e.**
305. Jones MJ, Buchanan AS, Neal CP, et al. Imaging of indeterminate pancreatic cystic lesions: a systematic review. *Pancreatology*. 2013;134:436-42. PMID: 23890144. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
306. Jooste V, Dejardin O, Bouvier V, et al. Pancreatic cancer: Wait times from presentation to treatment and survival in a population-based study. *Int J Cancer*. 2016;1395:1073-80. PMID: 27130333. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E62.**
307. Kalogeraki A, Papadakis GZ, Tamiolakis D, et al. EUS - Fine- Needle Aspiration Biopsy (FNAB) in the Diagnosis of Pancreatic Adenocarcinoma: A Review. *Romanian Journal of Internal Medicine*. 2016;541:24-30. PMID: 27141567. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
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309. Kamata K, Kitano M, Kudo M, et al. Value of EUS in early detection of pancreatic ductal adenocarcinomas in patients with intraductal papillary mucinous neoplasms.[Erratum appears in *Endoscopy*. 2014 Apr;46(4):358]. *Endoscopy*. 2014;461:22-9. PMID: 24218310. **KQ1E10a, KQ2E6, KQ3E9, KQ4E1, KQ5E1.**
310. Kamisawa T, Wood LD, Itoi TTakaori K. Pancreatic cancer. *Lancet*. 2016;38810039:73-85. PMID: 26830752. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E32.**
311. Kamphues C, Bova R, Schricke D, et al. Postoperative complications deteriorate long-term outcome in pancreatic cancer patients. *Annals of Surgical Oncology*. 2012;193:856-63. PMID: 21879265. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6d.**

Appendix C. Excluded Studies

312. Kang HJ, Lee JM, Joo I, et al. Assessment of Malignant Potential in Intraductal Papillary Mucinous Neoplasms of the Pancreas: Comparison between Multidetector CT and MR Imaging with MR Cholangiopancreatography. *Radiology*. 2016;279(1):128-39. PMID: 26517448. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
313. Kang JS, Jang JY, Heo JS, et al. Long-term outcomes and recurrence patterns of standard versus extended pancreatotomy in terms with pancreatic head cancer-a multicenter prospective randomized controlled study. *Journal of hepato-biliary-pancreatic sciences*. Conference: joint congress of the 6th biennial congress of the asian-pacific hepato-pancreato-biliary association and the 29th meeting of japanese society of hepato-biliary-pancreatic surgery. Japan. 2017;24:A162. PMID: CN-01408660. **KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E8.**
314. Kang KM, Lee JM, Shin CI, et al. Added value of diffusion-weighted imaging to MR cholangiopancreatography with unenhanced mr imaging for predicting malignancy or invasiveness of intraductal papillary mucinous neoplasm of the pancreas. *Journal of Magnetic Resonance Imaging*. 2013;38(3):555-63. PMID: 23390008. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
315. Kang MJ, Jang JY, Lee KB, et al. Long-term prospective cohort study of patients undergoing pancreatotomy for intraductal papillary mucinous neoplasm of the pancreas: implications for postoperative surveillance. *Annals of Surgery*. 2014;260(2):356-63. PMID: 24378847. **KQ1E1, KQ2E1, KQ3E1, KQ4E9, KQ5E9.**
316. Kantor O, Talamonti MS, Sharpe S, et al. Laparoscopic pancreaticoduodenectomy for adenocarcinoma provides short-term oncologic outcomes and long-term overall survival rates similar to those for open pancreaticoduodenectomy. *American Journal of Surgery*. 2017;213(3):512-515. PMID: 28049562. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**
317. Kargozaran H, Vu V, Ray P, et al. Invasive IPMN and MCN: same organ, different outcomes?. *Annals of Surgical Oncology*. 2011;18(2):345-51. PMID: 20809175. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
318. Kasi PM, Pedersen KSMcWilliams RR. BRCA2-associated pancreatic cancer and current screening guidelines. *Cancer*. 2015;121(17):3046. PMID: 26018189. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E32.**
319. Kassauei K, Habbe N, Mullendore ME, et al. Mitochondrial DNA mutations in pancreatic cancer. *International Journal of Gastrointestinal Cancer*. 2006;37(2-3):57-64. PMID: 17827523. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
320. Kasumova GG, Eskander MF, de Geus SWL, et al. Regional variation in the treatment of pancreatic adenocarcinoma: Decreasing disparities with multimodality therapy. *Surgery*. 2017;162(2):275-284. PMID: 28487044. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6.**
321. Katuchova J, Bober JRadonak J. Postoperative complications and survival rates for pancreatic cancer patients. *Wiener Klinische Wochenschrift*. 2011;123(3-4):94-9. PMID: 21253778. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6.**
322. Katz MH, Savides TJ, Moossa ARBouvet M. An evidence-based approach to the diagnosis and staging of pancreatic cancer. *Pancreatology*. 2005;5(6):576-90. PMID: 16110256. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
323. Kauhanen S, Rinta-Kiikka I, Kempainen J, et al. Accuracy of 18F-FDG PET/CT, Multidetector CT, and MR Imaging in the Diagnosis of Pancreatic Cysts: A Prospective Single-Center Study. *Journal of Nuclear Medicine*. 2015;56(8):1163-8. PMID: 26045314. **KQ1E10, KQ2E6, KQ3E9, KQ4E1, KQ5E1.**
324. Kauhanen SP, Komar G, Seppanen MP, et al. A prospective diagnostic accuracy study of 18F-fluorodeoxyglucose positron emission tomography/computed tomography, multidetector row computed tomography, and magnetic resonance imaging in primary diagnosis and staging of pancreatic cancer. *Annals of Surgery*. 2009;250(6):957-63. PMID: 19687736. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**

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476. Moriya T, Traverso W. Fate of the pancreatic remnant after resection for an intraductal papillary mucinous neoplasm: a longitudinal level II cohort study. *Archives of Surgery*. 2012;147:528-34. PMID: 22351878. **KQ1E10a, KQ2E6d, KQ3E9, KQ4E1, KQ5E1.**
477. Mornex Françoise, Girard Nicolas, Scoazec Jean-Yves, Bossard Nadine, Ychou Marc, Smith Denis, Seitz Jean-François, Valette Pierre-Jean, Roy Pascal, Rouanet Philippe. Feasibility of preoperative combined radiation therapy and chemotherapy with 5-fluorouracil and cisplatin in potentially resectable pancreatic adenocarcinoma: The French SFRO-FFCD 97-04 Phase II trial. *International Journal of Radiation Oncology• Biology• Physics*. 2006;655:1471-1478. PMID: . **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E62.**
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533. Pandharipande PV, Heberle C, Dowling EC, et al. Targeted screening of individuals at high risk for pancreatic cancer: Results of a simulation model. *Radiology*. 2015;2751:177-87. PMID: CN-01079887. **KQ1E10, KQ2E10, KQ3E10, KQ4E1, KQ5E1.**
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541. Park HJ, Jang KM, Song KD, et al. Value of unenhanced MRI with diffusion-weighted imaging for detection of primary small (\leq 20 mm) solid pancreatic tumours and prediction of pancreatic ductal adenocarcinoma. *Clin Radiol*. 2017; PMID: 28784320. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**

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544. Parra-Membrives P, Martinez-Baena DSanchez-Sanchez F. Late Biliary Complications after Pancreaticoduodenectomy. *American Surgeon*. 2016;825:456-61. PMID: 27215728. **KQ1E1, KQ2E1, KQ3E1, KQ4E6e, KQ5E6e.**
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546. Paye F, Micelli Lupinacci R, Bachellier P, et al. Distal pancreatectomy for pancreatic carcinoma in the era of multimodal treatment. *British Journal of Surgery*. 2015;1023:229-36. PMID: 25533421. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E6.**
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548. Pei Q, Zou X, Zhang X, et al. Diagnostic value of EUS elastography in differentiation of benign and malignant solid pancreatic masses: a meta-analysis. *Pancreatology*. 2012;125:402-8. PMID: 23127527. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
549. Pelaez-Luna M, Takahashi N, Fletcher JGChari ST. Resectability of presymptomatic pancreatic cancer and its relationship to onset of diabetes: a retrospective review of CT scans and fasting glucose values prior to diagnosis. *American Journal of Gastroenterology*. 2007;10210:2157-63. PMID: 17897335. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E10.**
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551. Pendola F, Gadde R, Ripat C, et al. Pancreatic neck/body benign and low grade malignant tumors: Is central pancreatectomy better than distal pancreatectomy? An update meta-analysis. *Annals of Surgical Oncology*. Conference: 69th Annual Cancer Symposium of the Society of Surgical Oncology Boston, MA United States. Conference Start: 20160302 Conference End: 20160305. Conference Publication: (var.pagings). 2016;231 suppl. 1:S167-s168. PMID: CN-01173671. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E10.**
552. Pendola F, Gadde R, Ripat C, et al. Distal pancreatectomy for benign and low grade malignant tumors: Short-term postoperative outcomes of spleen preservation-A systematic review and update meta-analysis. *Journal of Surgical Oncology*. 2017;1152:137-143. PMID: 28133818. **KQ1E9b, KQ2E9b, KQ3E9b, KQ4E9b, KQ5E9b.**
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554. Pergolini I, Sahora K, Ferrone CR, et al. Long-term Risk of Pancreatic Malignancy in Patients With Branch Duct Intraductal Papillary Mucinous Neoplasm in a Referral Center. *Gastroenterology*. 2017;21:21. PMID: 28739282. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
555. Petermann D, Demartines NSchafer M. Severe postoperative complications adversely affect long-term survival after R1 resection for pancreatic head adenocarcinoma. *World Journal of Surgery*. 2013;378:1901-8. PMID: 23564215. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6.**
556. Pezzilli R, Falconi M, Zerbi A, et al. Clinical and patient-reported outcomes after pancreatoduodenectomy for different diseases: a follow-up study. *Pancreas*. 2011;406:938-45. PMID: 21562441. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.**
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558. Pezzilli R, Calculli L. Branch-type intraductal papillary mucinous neoplasm of the pancreas: clinically and patient-reported outcomes. *Pancreas*. 2015;442:221-6. PMID: 25423561. **KQ1E10, KQ2E10, KQ3E9, KQ4E1, KQ5E1.**
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561. Pindak D, Tomas M, Dolnik J, et al. Morbidity, mortality and long term survival in patients with vascular resection in pancreatic cancer - single center experience. *Neoplasma*. 2017;643:460-463. PMID: 28253726. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**
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564. Plotkin A, Ceppa EP, Zarzaur BL, et al. Reduced morbidity with minimally invasive distal pancreatectomy for pancreatic adenocarcinoma. *HPB*. 2017;193:279-285. PMID: 28161217. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**
565. Poruk KE, Firpo M, Mulvihill SJ. Screening for pancreatic cancer. *Adv Surg*. 2014;48:115-36. PMID: 25293611. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E32.**
566. Postlewait Lm, Ethun Cg, McInnis Mr, Merchant N, Parikh A, Idrees K, Isom Ca, Hawkins W, Fields Rc, Strand M, Weber S, Cho Cs, Salem Ai, Martin Rc, Scoggins C, Bentrem D, Kim Hj, Carr J, Ahmad S, Abbott D, Wilson G, Kooby Da, Maithele Sk. A multicenter study of 349 pancreatic mucinous cystic neoplasms: preoperative risk factors for adenocarcinoma. *Annals of surgical oncology*. 2016;231 suppl. 1:S160. PMID: CN-01173679. **KQ1E6, KQ2E6, KQ3E6, KQ4E9, KQ5E92.**

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567. Postlewait LM, Ethun CG, McInnis MR, et al. A multicenter study of 349 pancreatic mucinous cystic neoplasms: Preoperative risk factors for adenocarcinoma. *Annals of Surgical Oncology*. Conference: 69th Annual Cancer Symposium of the Society of Surgical Oncology Boston, MA United States. Conference Start: 20160302 Conference End: 20160305. Conference Publication: (var.pagings). 2016;231 suppl. 1:S160. PMID: CN-01173679. **KQ1E7, KQ2E7, KQ3E7, KQ4E1, KQ5E1.**
568. Pugalenti A, Protic M, Gonen M, et al. Postoperative complications and overall survival after pancreaticoduodenectomy for pancreatic ductal adenocarcinoma. *Journal of Surgical Oncology*. 2016;1132:188-93. PMID: 26678349. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E6.**
569. Qin JZhang B. Best combination of multiple diagnostic tests for screening purposes. *Statistics in Medicine*. 2010;2928:2905-19. PMID: 20862668. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
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571. Raigani S, Ammori J, Kim JHardacre JM. Trends in the treatment of resectable pancreatic adenocarcinoma. *Journal of Gastrointestinal Surgery*. 2014;181:113-23. PMID: 24002769. **KQ1E1, KQ2E1, KQ3E1, KQ4E9, KQ5E9.**
572. Ramirez PJVickers SM. Adenoviral gene therapy for pancreatic adenocarcinoma. *Current Surgery*. 2004;614:351-8. PMID: 15276339. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
573. Raptis DA, Fessas C, Belasyse-Smith PKurzawinski TR. Clinical presentation and waiting time targets do not affect prognosis in patients with pancreatic cancer. *Surgeon Journal of the Royal Colleges of Surgeons of Edinburgh & Ireland*. 2010;85:239-46. PMID: 20709279. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E9.**
574. Rautou PE, Levy P, Vullierme MP, et al. Morphologic changes in branch duct intraductal papillary mucinous neoplasms of the pancreas: a midterm follow-up study. *Clinical Gastroenterology & Hepatology*. 2008;67:807-14. PMID: 18304885. **KQ1E9, KQ2E9, KQ3E9, KQ4E1, KQ5E1.**
575. Ravikumar R, Sabin C, Abu Hilal M, et al. Portal vein resection in borderline resectable pancreatic cancer: a United Kingdom multicenter study. *Journal of the American College of Surgeons*. 2014;2183:401-11. PMID: 24484730. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**
576. Rebours Vinciane Boutron-Ruault Marie-Christine Schnee Matthieu Férec Claude Maire Frédérique Hammel Pascal Ruzniewski Philippe Lévy Philippe Risk of pancreatic adenocarcinoma in patients with hereditary pancreatitis: a national exhaustive series. *The American journal of gastroenterology*. 2008;1031:111. PMID: . **KQ1E7, KQ2E7, KQ3E7, KQ4E1, KQ5E12.**
577. Reddymasu SC, Gupta N, Singh S, et al. Pancreato-biliary malignancy diagnosed by endoscopic ultrasonography in absence of a mass lesion on transabdominal imaging: prevalence and predictors. *Digestive Diseases & Sciences*. 2011;566:1912-6. PMID: 21188524. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
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580. Renz BW, Khalil PN, Mikhailov M, et al. Pancreaticoduodenectomy for adenocarcinoma of the pancreatic head is justified in elderly patients: A Retrospective Cohort Study. *International Journal Of Surgery*. 2016;28:118-25. PMID: 26906329. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E6.**

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582. Riall TSLillemo KD. Underutilization of surgical resection in patients with localized pancreatic cancer. *Annals of Surgery*. 2007;2462:181-2. PMID: 17667494. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
583. Richter S, Uslar V, Tabriz N Weyhe D. Progressive postresection program (pPRP) after pancreatic resection for malignancy and precancerous lesions. European surgical research. Conference: 133rd congress of the german society of surgery, DGCH 2016. Germany. 2016;571-2:76. PMID: CN-01375530. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
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585. Risch HA, Yu H, Lu LKidd MS. Detectable Symptomatology Preceding the Diagnosis of Pancreatic Cancer and Absolute Risk of Pancreatic Cancer Diagnosis. *American Journal of Epidemiology*. 2015;1821:26-34. PMID: 26049860. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
586. Roch AM, Ceppa EP, Al-Haddad MA, et al. The natural history of main duct-involved, mixed-type intraductal papillary mucinous neoplasm: parameters predictive of progression. *Annals of Surgery*. 2014;2604:680-8; discussion 688-90. PMID: 25203885. **KQ1E10a, KQ2E10a, KQ3E9, KQ4E1, KQ5E1.**
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590. Rodriguez-D'Jesus A, Fernandez-Esparrach G, Boadas J, et al. Impact of endoscopic ultrasonography (EUS) and EUS-guided fine-needle aspiration on the management of pancreatic cystic lesions. *European Journal of Gastroenterology & Hepatology*. 2016;289:1094-9. PMID: 27286570. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
591. Rodriguez-D'Jesus A, Fernandez-Esparrach G, Marra-Lopez C, et al. Adverse events of EUS-guided FNA of pancreatic cystic and solid lesions by using the lexicon proposed in an ASGE workshop: a prospective and comparative study. *Gastrointestinal Endoscopy*. 2016;834:780-4. PMID: 26301408. **KQ1E10, KQ2E10, KQ3E6, KQ4E1, KQ5E1.**
592. Rosales-Velderrain A, Bowers SP, Goldberg RF, et al. National trends in resection of the distal pancreas. *World Journal of Gastroenterology*. 2012;1832:4342-9. PMID: 22969197. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.**
593. Rosok BI, Marangos IP, Kazaryan AM, et al. Single-centre experience of laparoscopic pancreatic surgery. *British Journal of Surgery*. 2010;976:902-9. PMID: 20474000. **KQ1E1, KQ2E1, KQ3E1, KQ4E6e, KQ5E6e.**
594. Rudloff U, Maker AV, Brennan MFallen PJ. Randomized clinical trials in pancreatic adenocarcinoma. *Surgical Oncology Clinics of North America*. 2010;191:115-50. PMID: 19914563. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**

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595. Ruf J, Lopez Hanninen E, Bohmig M, et al. Impact of FDG-PET/MRI image fusion on the detection of pancreatic cancer. *Pancreatology*. 2006;66:512-9. PMID: 17106215. **KQ1E6, KQ2E6, KQ3E6, KQ4E1, KQ5E1.**
596. Ruiz-Tovar J, Martin-Perez E, Fernandez-Contreras ME, et al. Identification of prognostic factors in pancreatic cancer. *Cirugia y Cirujanos*. 2011;794:313-22. PMID: 21951885. **KQ1E2, KQ2E2, KQ3E2, KQ4E2, KQ5E2.**
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598. Rulyak SJ, Brentnall TA. Inherited pancreatic cancer: surveillance and treatment strategies for affected families. *Pancreatology*. 2001;15:477-85. PMID: 12120228. **KQ1E10a, KQ2E12, KQ3E9, KQ4E1, KQ5E12.**
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600. Rustemovic N, Kalauz M, Grubelic Ravic K, et al. Differentiation of Pancreatic Masses via Endoscopic Ultrasound Strain Ratio Elastography Using Adjacent Pancreatic Tissue as the Reference. *Pancreas*. 2017;463:347-351. PMID: 28099260. **KQ1E1, KQ2E6, KQ3E1, KQ4E1, KQ5E1.**
601. Rustemovic N, Opacic D, Ostojic Z, et al. Comparison of elastography methods in patients with pancreatic masses. *Endoscopic Ultrasound*. 2014;3Suppl 1:S4. PMID: 26425528. **KQ1E9b, KQ2E9b, KQ3E9b, KQ4E9b, KQ5E9b.**
602. Ryozaawa S, Iwano H, Taba K, et al. Genetic diagnosis of pancreatic cancer using specimens obtained by EUS-FNA. *Digestive Endoscopy*. 2011;23 Suppl 1:43-5. PMID: 21535200. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
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604. Sadakari Y, Ohuchida K, Nakata K, et al. Invasive carcinoma derived from the nonintestinal type intraductal papillary mucinous neoplasm of the pancreas has a poorer prognosis than that derived from the intestinal type. *Surgery*. 2010;1476:812-7. PMID: 20060146. **KQ1E9, KQ2E9, KQ3E9, KQ4E1, KQ5E1.**
605. Sadeghi A, Mohamadnejad M, Islami F, et al. Diagnostic yield of EUS-guided FNA for malignant biliary stricture: a systematic review and meta-analysis. *Gastrointestinal Endoscopy*. 2016;832:290-8.e1. PMID: 26422979. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E1.**
606. Sadr-Azodi O, Gudbjornsdottir SL, Jung R. Pattern of increasing HbA1c levels in patients with diabetes mellitus before clinical detection of pancreatic cancer - a population-based nationwide case-control study. *Acta Oncologica*. 2015;547:986-92. PMID: 25734801. **KQ1E7, KQ2E7, KQ3E7, KQ4E1, KQ5E1.**
607. Saftoiu A, Vilmann P, Gorunescu F, et al. Accuracy of endoscopic ultrasound elastography used for differential diagnosis of focal pancreatic masses: a multicenter study. *Endoscopy*. 2011;437:596-603. PMID: 21437851. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
608. Sagami R, Nishikiori H, Anami K, et al. Utility of Endoscopic Ultrasonography Screening for Small Pancreatic Cancer and Proposal for a New Scoring System for Screening. *Pancreas*. 2018;472:257-264. PMID: 29329161. **KQ1E9, KQ2E12, KQ3E9, KQ4E1, KQ5E12.**
609. Sahakyan MA, Edwin B, Kazaryan AM, et al. Perioperative outcomes and survival in elderly patients undergoing laparoscopic distal pancreatectomy. *Journal of Hepato-biliary-pancreatic Sciences*. 2017;241:42-48. PMID: 27794204. **KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E8.**

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610. Sahakyan MA, Kazaryan AM, Rawashdeh M, et al. Laparoscopic distal pancreatectomy for pancreatic ductal adenocarcinoma: results of a multicenter cohort study on 196 patients. *Surgical Endoscopy*. 2016;308:3409-18. PMID: 26514135. **KQ1E1, KQ2E1, KQ3E1, KQ4E10b, KQ5E10b.**
611. Sahakyan MA, Rosok BI, Kazaryan AM, et al. Impact of obesity on surgical outcomes of laparoscopic distal pancreatectomy: A Norwegian single-center study. *Surgery*. 2016;1605:1271-1278. PMID: 27498300. **KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E8.**
612. Saito M, Ishihara T, Tada M, et al. Use of F-18 fluorodeoxyglucose positron emission tomography with dual-phase imaging to identify intraductal papillary mucinous neoplasm. *Clinical Gastroenterology & Hepatology*. 2013;112:181-6. PMID: 23142206. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
613. Sakamoto H, Harada S, Nishioka N, et al. A Social Program for the Early Detection of Pancreatic Cancer: The Kishiwada Katsuragi Project. *Oncology*. 2017;93 Suppl 1:89-97. PMID: 29258101. **KQ1E10a, KQ2E6, KQ3E6, KQ4E1, KQ5E12.**
614. Salem AI, Alfi M, Winslow E, et al. Has survival following pancreaticoduodenectomy for pancreas adenocarcinoma improved over time?. *Journal of Surgical Oncology*. 2015;1126:643-9. PMID: 26388048. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E6d.**
615. Sallinen V, Haglund C, Seppanen H. Outcomes of resected nonfunctional pancreatic neuroendocrine tumors: Do size and symptoms matter?. *Surgery*. 2015;1586:1556-63. PMID: 26070847. **KQ1E6e, KQ2E6e, KQ3E6e, KQ4E6e, KQ5E6e.**
616. Salmiheimo A, Mustonen H, Stenman UH, et al. Systemic Inflammatory Response and Elevated Tumour Markers Predict Worse Survival in Resectable Pancreatic Ductal Adenocarcinoma. *PLoS ONE [Electronic Resource]*. 2016;119:e0163064. PMID: 27632196. **KQ1E1, KQ2E1, KQ3E1, KQ4E10a, KQ5E9.**
617. Salvia R, Crippa S, Falconi M, et al. Branch-duct intraductal papillary mucinous neoplasms of the pancreas: to operate or not to operate?. *Gut*. 2007;568:1086-90. PMID: 17127707. **KQ1E9, KQ2E9, KQ3E9, KQ4E1, KQ5E1.**
618. Samawi H, Yin Y, Lim H, Renouf D, Cheung W. Primary care vs. oncology-driven surveillance following adjuvant chemotherapy in resected pancreas cancer. *Journal of clinical oncology. Conference: 217 annual meeting of the american society of clinical oncology, ASCO. United states*. 2017;3515 Supplement 1) (no pagination:). PMID: CN-01398187. **KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E82.**
619. Samra JS, Bachmann RA, Choi J, et al. One hundred and seventy-eight consecutive pancreatoduodenectomies without mortality: role of the multidisciplinary approach. *Hepatobiliary & Pancreatic Diseases International*. 2011;104:415-21. PMID: 21813392. **KQ1E1, KQ2E1, KQ3E1, KQ4E6e, KQ5E6e.**
620. Sanchez-Cabus S, Adam JP, Pittau G, et al. Laparoscopic left pancreatectomy: early results after 115 consecutive patients. *Surgical Endoscopy*. 2016;3010:4480-8. PMID: 26895905. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.**
621. Sandanayake Ns, Andreola F, Camuzeaux S, Sinclair J, Chapman Mh, Webster G, Gentry-Maharaj A, Menon U, Jacobs I, Smith R, Pereira Sp, Timms J, Serum ceacam1 in the preclinical diagnosis of pancreatic adenocarcinoma. *Gut. Conference: british society of gastroenterology annual general meeting 21. United kingdom. Conference start: 21322. Conference end: 21325*. 2010;59:A82. PMID: CN-01267864. **KQ1E7, KQ2E7, KQ3E7, KQ4E1, KQ5E12.**
622. Sandanayake NS, Andreola F, Camuzeaux S, et al. Serum ceacam1 in the preclinical diagnosis of pancreatic adenocarcinoma. *Gut. Conference: british society of gastroenterology annual general meeting 2010. United kingdom. Conference start: 20100322. Conference end: 20100325*. 2010;59:A82. PMID: CN-01267864. **KQ1E10, KQ2E10, KQ3E10, KQ4E1, KQ5E1.**

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624. Santema TB, Visser A, Busch OR, et al. Hospital costs of complications after a pancreatoduodenectomy. *HPB*. 2015;178:723-31. PMID: 26082095. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.**
625. Santhosh S, Mittal BR, Bhasin D, et al. Role of (18)F-fluorodeoxyglucose positron emission tomography/computed tomography in the characterization of pancreatic masses: experience from tropics. *Journal of Gastroenterology & Hepatology*. 2013;282:255-61. PMID: 23278193. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
626. Santhosh S, Mittal BR, Bhasin D, et al. Dual-phase 18F-FDG PET/CT imaging in the characterization of pancreatic lesions: does it offer prognostic information?. *Nuclear Medicine Communications*. 2014;35(10):1018-25. PMID: 25023999. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
627. Sato N, Fukushima N, Matsubayashi HG, Goggins M. Identification of maspin and S100P as novel hypomethylation targets in pancreatic cancer using global gene expression profiling. *Oncogene*. 2004;238:1531-8. PMID: 14716296. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
628. Sauer BG, Shami VM. Survival in pancreatic cancer: the best is yet to come. *Gastrointestinal Endoscopy*. 2010;72(1):84-5. PMID: 20620275. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E3.**
629. Sawai Y, Yamao K, Bhatia V, et al. Development of pancreatic cancers during long-term follow-up of side-branch intraductal papillary mucinous neoplasms. [Erratum appears in *Endoscopy*. 2011 Jan;43(1):79]. *Endoscopy*. 2010;42(12):1077-84. PMID: 21120776. **KQ1E10a, KQ2E9, KQ3E9, KQ4E1, KQ5E1.**
630. Scheiman JM. Pancreatic Cysts - Part 1: Using the American Gastroenterological Association Guidelines for the Management of Pancreatic Cysts-A Practical Approach. *Pancreas*. 2017;466:742-744. PMID: 28609360. **KQ1E3, KQ2E3, KQ3E3, KQ4E3, KQ5E32.**
631. Schellhaas B, Vitali F, Wildner D, et al. Dynamics of Fukuoka Criteria and Patient Management in Pancreatic Intraductal Papillary Mucinous Neoplasms (IPMNs) During Follow-Up. *Medical Science Monitor*. 2017;23:1483-1492. PMID: 28348359. **KQ1E6d, KQ2E6d, KQ3E6d, KQ4E1, KQ5E1.**
632. Schietroma M, Pessia B, Carlei F, Amicucci G. Intestinal permeability changes, systemic endotoxemia, inflammatory serum markers and sepsis after Whipple's operation for carcinoma of the pancreas head. *Pancreatology*. 2017;175:839-846. PMID: 28803860. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E6.**
633. Schmidt RL, Witt BL, Matynia AP, et al. Rapid on-site evaluation increases endoscopic ultrasound-guided fine-needle aspiration adequacy for pancreatic lesions. *Digestive Diseases & Sciences*. 2013;58(3):872-82. PMID: 23053888. **KQ1E10, KQ2E10, KQ3E10, KQ4E1, KQ5E1.**
634. Schnelldorfer T, Sarr MG, Nagorney DM, et al. Experience with 208 resections for intraductal papillary mucinous neoplasm of the pancreas. *Archives of Surgery*. 2008;143(7):639-46; discussion 646. PMID: 18645105. **KQ1E6, KQ2E6, KQ3E6, KQ4E6, KQ5E6.**
635. Seppanen H, Juuti A, Mustonen H, et al. The Results of Pancreatic Resections and Long-Term Survival for Pancreatic Ductal Adenocarcinoma: A Single-Institution Experience. *Scandinavian Journal of Surgery: SJS*. 2017;106(1):54-61. PMID: 27130378. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E6.**
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638. Serrano PE, Herman JM, Griffith KA, et al. Quality of life in a prospective, multicenter phase 2 trial of neoadjuvant full-dose gemcitabine, oxaliplatin, and radiation in patients with resectable or borderline resectable pancreatic adenocarcinoma. *International Journal of Radiation Oncology, Biology, Physics*. 2014;902:270-7. PMID: 25104069. **KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E8.**
639. Shah A, Chao KS, Ostbye T, et al. Trends in racial disparities in pancreatic cancer surgery. *Journal of Gastrointestinal Surgery*. 2013;1711:1897-906. PMID: 24002757. **KQ1E1, KQ2E1, KQ3E1, KQ4E9, KQ5E9.**
640. Shah OJ, Gagloo MA, Khan IJ, et al. Pancreaticoduodenectomy: a comparison of superior approach with classical Whipple's technique. *Hepatobiliary & Pancreatic Diseases International*. 2013;122:196-203. PMID: 23558075. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
641. Shaib Y, Davila J, Naumann CEI-Serag H. The impact of curative intent surgery on the survival of pancreatic cancer patients: a U.S. Population-based study. *American Journal of Gastroenterology*. 2007;1027:1377-82. PMID: 17403071. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E9.**
642. Shamali A, De'Ath HD, Jaber B, et al. Elderly patients have similar short term outcomes and five-year survival compared to younger patients after pancreaticoduodenectomy. *International Journal Of Surgery*. 2017;45:138-143. PMID: 28782662. **KQ1E1, KQ2E1, KQ3E1, KQ4E1, KQ5E9c.**
643. Shapiro M, Chen Q, Huang Q, et al. Associations of Socioeconomic Variables With Resection, Stage, and Survival in Patients With Early-Stage Pancreatic Cancer. *JAMA Surgery*. 2016;1514:338-45. PMID: 26581025. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E9.**
644. Shikano T, Nakao A, Kodera Y, et al. Middle pancreatectomy: safety and long-term results. *Surgery*. 2010;1471:21-9. PMID: 19682717. **KQ1E1, KQ2E1, KQ3E1, KQ4E6e, KQ5E6e.**
645. Shin SH, Kim SC, Song KB, et al. Appraisal of Laparoscopic Distal Pancreatectomy for Left-Sided Pancreatic Cancer: A Large Volume Cohort Study of 152 Consecutive Patients. *PLoS ONE [Electronic Resource]*. 2016;119:e0163266. PMID: 27636547. **KQ1E1, KQ2E1, KQ3E1, KQ4E8, KQ5E8.**
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Appendix C. Excluded Studies

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776. Yang S, Zhang H, Ren X. The application of high-field magnetic resonance perfusion imaging in the diagnosis of pancreatic cancer. *Medicine*. 2017;9636:e7571. PMID: 28885324. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
777. Yang Y, Li L, Qu C, et al. Endoscopic ultrasound-guided fine needle core biopsy for the diagnosis of pancreatic malignant lesions: a systematic review and Meta-Analysis. *Scientific Reports*. 2016;6:22978. PMID: 26960914. **KQ1E6, KQ2E6, KQ3E6, KQ4E1, KQ5E1.**
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Appendix C. Excluded Studies

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786. Yopp AC, Katabi N, Janakos M, et al. Invasive carcinoma arising in intraductal papillary mucinous neoplasms of the pancreas: a matched control study with conventional pancreatic ductal adenocarcinoma. *Annals of Surgery*. 2011;2535:968-74. PMID: 21422912. **KQ1E1, KQ2E1, KQ3E1, KQ4E10, KQ5E9.**
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789. Zhan Q, Deng X, Weng Y, et al. Outcomes of robotic surgery for pancreatic ductal adenocarcinoma. *Chinese Journal of Cancer Research*. 2015;276:604-10. PMID: 26752935. **KQ1E5, KQ2E5, KQ3E5, KQ4E5, KQ5E5.**
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796. Zhou J, Li CLZhang GW. Surgical treatment of pancreatic carcinoma. *Hepatobiliary & Pancreatic Diseases International*. 2003;21:139-41. PMID: 14607667. **KQ1E1, KQ2E1, KQ3E1, KQ4E6, KQ5E6.**
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Appendix C. Excluded Studies

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Appendix D Table 1. Narrative description of screening programs and high-risk populations

Screening Program	Screening program procedures	Definition of increased risk for PDAC
Barnes, 2018 U.S. Fair	<p>Recruitment: Eligible patients were high-risk individuals referred by a genetic counselor, treating physician, or patient self-referral to the Greater Midwest Pancreatic Cancer Screening Clinic at Froedtert Hospital and the Medical College of Wisconsin. Patients provided a detailed three-generation family history, and genetic counseling and testing was offered to patients with a pedigree suggestive of a hereditary cancer syndrome. Patients with a history suggestive of familial pancreatic cancer received 5-year and lifetime risk estimates for pancreatic cancer using the CancerGene PancPRO software.</p> <p>Initial screen: Baseline evaluation involved MRI, a medical history and physical exam, and measurement of serum creatinine, glycohemoglobin, vitamin D 25-hydroxy, CEA, and CA 19-9.</p> <p>Diagnostic workup: Those with suspicious lesions on MRI were referred for EUS. During the EUS procedure, FNA was performed at the discretion of the endoscopist during the same sedation, with on-site cytopathologic review of the specimens. If abnormalities were observed, patients were presented at a multidisciplinary pancreatic cancer conference and managed according to the consensus of the clinical team, including referral to surgery if necessary.</p> <p>Blinding: Gastroenterologists who performed EUS had knowledge of MRI results.</p> <p>Surveillance: Repeat screening was recommended annually (for those with negative findings on initial screen), or by consensus of the multidisciplinary PC conference (for those with abnormalities on screening).</p> <p>Harms and outcomes: The study does not report any screening-related harms, clinical followup of PDAC cases, or surgical harms.</p>	<p>Adults age ≥ 50 or within 10 years of youngest affected relative who had (a) ≥ 3 relatives with PDAC, including ≥ 1 FDR; or (b) 2 FDRs with PDAC; or (c) 1 FDR and 1 SDR with PDAC and PancPRO risk $\geq 5\%$; or (d) PJS; or (3) <i>BRCA1</i>, <i>BRCA2</i>, <i>PALB2</i>, <i>ATM</i>, <i>CDKN2A</i>, or Lynch syndrome with 1 FDR or SDR with PDAC</p>
Gangi, 2018 U.S. Fair	<p>Recruitment: Eligible patients were high-risk individuals referred by physicians at Florida’s Moffitt Cancer Center or the Lifetime Cancer Screening and Prevention Center, physicians in the community, or by patient-self-referral. Referred patients completed a self-reported risk factor questionnaire.</p> <p>Initial screen: Baseline evaluation involved EUS.</p> <p>Diagnostic workup: Those with a mass or cyst ≥ 1 cm on EUS underwent FNA during the same procedure with the aid of a cytopathology technician in the endoscopy suite. If FNA results were consistent with cancer, patients underwent standard workup and cancer staging of with radiology studies and surgical and/or oncologic evaluation.</p> <p>Blinding: NR</p> <p>Surveillance: Those with negative findings on initial screen underwent repeat EUS screening annually for 5 years. Those with lesions < 1 cm on initial screen underwent repeat EUS at 3 months; if lesions were unchanged, patients underwent repeat MRI/MRCP at 6 months followed by annual MRI/MRCP. Those with benign or indeterminate FNA results underwent a CT scan; if CT scans were indeterminate, patients underwent repeat EUS at 3 months.</p> <p>Harms and outcomes: The study does not report any screening-related harms, clinical followup of PDAC cases, or surgical harms.</p>	<p>Adults age ≥ 40 or within 10 years of youngest affected relative who had (a) ≥ 2 relatives with PDAC, including ≥ 1 FDR; or (b) PJS and age > 30; or (c) HP; or (d) FAMMM; or (e) <i>BRCA2</i> and ≥ 1 FDR or SDR with PDAC</p>

Appendix D Table 1. Narrative description of screening programs and high-risk populations

Screening Program	Screening program procedures	Definition of increased risk for PDAC
<p>Harinck, 2016 Dutch FPC Study Netherlands Fair</p>	<p>Recruitment: Eligible patients were asymptomatic high-risk individuals who were evaluated and recruited by clinical geneticists at 5 participating centers in the Netherlands (Erasmus MC-University Medical Center Rotterdam, Academic Medical Center Amsterdam, University Medical Center Groningen and the Netherlands Cancer Institute-Antoni van Leeuwenhoek Hospital). Geneticists verified patient eligibility based on detailed personal and family history, reviewing medical and pathological records for patients and family members, and reviewing genetic test information.</p> <p>Initial screen: Baseline evaluation involved EUS and MRI.</p> <p>Diagnostic workup: If lesions (clinically relevant or of unknown significance) were detected on EUS, a case description and video recording was sent to endosonographers for independent review. Final decision-making and further management was made by a multidisciplinary team of gastroenterologists, surgeons and radiologists. Those with solid lesions suspicious for malignancy, cystic lesions with malignancy or >30mm, or main branch IMPN with main pancreatic duct ≥10mm were recommended for surgery.</p> <p>Blinding: Participating gastroenterologists and radiologists were blinded to the baseline results of EUS or MRI.</p> <p>Surveillance: Repeat screening was recommended annually (for those with negative findings on initial screen), in 3 months (for those with lesions of unknown significance), and in 6 months (for those with cysts or side-branch IPMN with diameter 10-30mm without malignant features).</p> <p>Harms and outcomes: Psychosocial screening-related harms were assessed by questionnaires for all patients at baseline, after explanation of study procedures, after initial screening, and after followup screening at 12 months. The study reports that no screening procedure-related harms occurred, but does not report whether such harms were assessed systematically for all patients. The study reports clinical follow-up information, including survival, for screen-detected PDAC cases. The study does not report surgical harms.</p>	<p>Asymptomatic adults age ≥45 (age ≥30 for PJS patients) or within 10 years of youngest relative with PDAC, and (a) with <i>CDKN2A</i> variant; or (b) with confirmed PJS; or (c) with <i>BRCA1</i>, <i>BRCA2</i>, <i>p53</i> or mismatch repair gene and family history of PDAC in ≥2 affected relatives; or (d) FDRs of patients with FPC^b</p>
<p>Joergensen, 2016 Danish National Screening Program Denmark Fair</p>	<p>Recruitment: Eligible patients were high-risk individuals who were (a) identified from previous population-based study that recruited from a hereditary pancreatitis registry and clinician referral (HP group); or (b) referred from clinical genetics departments across Denmark. The study does not specify how patients were invited to participate.</p> <p>Initial screen: Baseline evaluation involved EUS (two subjects underwent annual US due to severe claustrophobia) and measurement of CA19-9 and Hba1C.</p> <p>Diagnostic workup: Those with suspicious masses on EUS underwent FNA. If FNA identified potential malignancy or dysplasia, diagnostic laparoscopic US with or without biopsy was performed. Those with suspected or confirmed malignancy or dysplasia were referred to surgery.</p> <p>Blinding: NR</p> <p>Surveillance: Those with suspected lesions but negative biopsy results underwent control EUS. All patients who screened negative remained in surveillance and continued receiving annual EUS and CA 19-9 testing.</p> <p>Harms and outcomes: The study reports that no screening procedure-related harms occurred, but does not report whether such harms were assessed systematically for all patients. Psychosocial screening-related harms were not assessed or reported. The study reports clinical followup information, including survival and surgical harms, for screen-detected PDAC cases.</p>	<p>Adults age ≥30 who were able to endure a pancreatic resection and who met criteria for (a) HP^c; or (b) FPC^d</p>

Appendix D Table 1. Narrative description of screening programs and high-risk populations

Screening Program	Screening program procedures	Definition of increased risk for PDAC
<p>Del Chiaro, 2015 Sweden Fair</p>	<p>Recruitment: Eligible patients were high-risk individuals who were (a) relatives of patients treated for PDAC at Karolinska University Hospital; (b) referred from other Swedish centers; or (c) referred by general practitioners. The study does not specify how patients were invited to participate.</p> <p>Initial screen: Baseline evaluation involved personal and family medical history, clinical exam, genetic testing (for <i>BRCA1</i>, <i>BRCA2</i>, and <i>p16</i>), and MRI.</p> <p>Diagnostic workup: Those with abnormalities on MRI (solid nodules and suspected IPMN lesions) underwent EUS +/- FNA and/or CT scan. Every patient with a positive finding on screening was discussed at a multidisciplinary conference. Those with suspected cancer or premalignant lesions were referred for surgery.</p> <p>Blinding: NR</p> <p>Surveillance: Patients who screened negative on initial MRI were rescreened after 1 year using the same screening protocol. Those with unspecified findings or IPMN without indication for surgery were recommended for a 6-month followup MRI.</p> <p>Harms and outcomes: The study does not report any screening-related harms, clinical followup of PDAC cases, or surgical harms.</p>	<p>Adults age ≥ 45 or within 10 years of youngest relative with PDAC who (a) had 2 relatives (≥ 1 FDR) in the same lineage with PDAC; or (b) had ≥ 3 relatives (FDRs, SDRs or TDRs) in the same lineage with PDAC; or (c) had <i>BRCA1</i>, <i>BRCA2</i>, or <i>p16</i> variant and 1 FDR or SDR with PDAC; or (d) were verified germline carriers of PJS kindreds.</p>
<p>Al-Sukhni, 2012 Toronto Screening Program Canada Fair</p>	<p>Recruitment: Eligible participants were asymptomatic members of FPC kindreds identified through (a) the clinic-based Familial Gastrointestinal Cancer Registry; (b) the population-based Ontario Pancreas Cancer Study at Mount Sinai Hospital in Toronto; (c) the Familial Breast Cancer Research Unit at Princes Margaret Hospital; (d) the Familial Breast Cancer Clinics at Mount Sinai Hospital and Sunnybrook Regional Cancer Center; (e) a polyposis database with PSJ information; (f) self-referral; (g) physician referral; or (h) local genetics centers. All were contacted by mail with an invitation letter.</p> <p>Initial screen: Prior to the first appointment, participants underwent genetic counseling and completed a baseline personal history and psychosocial questionnaire. Initial screening and subsequent annual screening involved MRI, meeting with a genetic counselor, and providing a blood sample.</p> <p>Diagnostic workup: Those with abnormalities on MRI (pancreatic mass, duct dilation suggesting IPMN, or extra-pancreatic mass or lesions) underwent followup MRI plus CT, EUS, and/or ECRP within 3-6 months. Abnormal findings on followup testing were reviewed by a hepatobiliary surgeon and a radiologist specialized in abdominal imaging, and surgery was recommended if malignancy or dysplasia were suspected.</p> <p>Blinding: NR</p> <p>Surveillance: All patients, including those who screened negative on initial screening and those who had surgery but did not have invasive cancer, were followed as part of the annual screening protocol.</p> <p>Harms and outcomes: Psychosocial screening-related harms were assessed by questionnaires mailed to all patients 3 months and 12 months after baseline. Screening procedure-related harms were not assessed or reported. The study reports clinical follow-up information, including survival, for screen-detected PDAC cases. No surgical harms were assessed or reported.</p>	<p>Asymptomatic adults who: (a) were FDRs or SDRs of a PDAC patient in a family with ≥ 2 PDAC patients in the same lineage; or (b) had <i>p16</i> or <i>STK11</i> variants; or (c) had <i>BRCA1</i> or <i>BRCA2</i> variants and ≥ 1 blood relative with PDAC; or (d) had a clinical diagnosis of HP or PJS</p>

Appendix D Table 1. Narrative description of screening programs and high-risk populations

Screening Program	Screening program procedures	Definition of increased risk for PDAC
Canto, 2012 CAPS3 U.S. Fair	<p>Recruitment: Eligible patients were asymptomatic high-risk individuals identified by participating sites (Johns Hopkins Hospital, Mayo Clinic, UCLA, Dana Farber Cancer Institute, MD Anderson Cancer Center) or through websites (for the CAPS 3 study, Lustgarten Foundation, and clinicaltrials.gov). The study does not specify how patients were invited to participate.</p> <p>Initial screen: Baseline evaluation involved screening by MRI/MRCP, CT, and EUS. EUS was performed last to enable FNA for any lesions detected by any of the 3 tests.</p> <p>Diagnostic workup: Those with abnormalities (pancreatic duct dilation) on any of the 3 initial screening tests underwent FNA as part of the EUS procedure. ERCP also was performed at the discretion of the clinical team. Those with suspected pancreatic neoplasms were referred for surgery.</p> <p>Blinding: Participating gastroenterologists and radiologists were blinded to the results of the other imaging tests.</p> <p>Surveillance: All patients were followed for a minimum of 1 year from baseline. Surveillance screening occurred at 3 months for those with worrisome lesions but no resection scheduled; at 6-12 months for those with small cysts or non-worrisome lesions; and at 1-3 years for those with normal pancreas or pancreatitis-like abnormalities.</p> <p>Harms and outcomes: The study does not report any assessment of screening-related harms. The study assessed surgical harms for those who underwent surgery for precursor lesions. No PDAC cases were detected.</p>	<p>Adults age 40-80 or within 10 years of youngest relative with PDAC (or age ≥ 30 for PJS patients) and (a) had PJS; or (b) had HBOC with ≥ 1 affected FDR or SDR with PC; or (c) were relatives of patients with FPC with ≥ 1 affected FDR.</p>
Ludwig, 2011 U.S. Fair	<p>Recruitment: Eligible patients were at-risk relatives who met eligibility criteria for the Familial Pancreatic Tumor Registry (FPTR) at Memorial-Sloan Kettering Cancer Center. All at-risk relatives who met eligibility criteria were approached by a study assistant and invited to participate in the registry and screening program.</p> <p>Initial screen: Baseline evaluation involved MRCP along with an office visit and physical exam. Registry participants also complete a detailed family history and epidemiology questionnaire. Genetic counseling is offered at study entry but is not a requirement.</p> <p>Diagnostic workup: Those with lesions on MRCP underwent EUS. Those with suspected pre-malignant or malignant lesions on EUS underwent immediate FNA. Following multidisciplinary team review, those with suspected pre-malignant or malignant lesions on followup testing were referred for surgery.</p> <p>Blinding: NR</p> <p>Surveillance: Those with normal results on initial screening continued to undergo annual testing under same screening protocol for the 2 years of the study.</p> <p>Harms and outcomes: Screening procedure-related harms were assessed by a study nurse who called all patients the day after the procedure. Psychosocial screening-related harms were not assessed or reported. No clinical follow-up information of screen-detected PDAC cases was provided. No surgical harms were assessed or reported.</p>	<p>Age ≥ 35 who had (a) ≥ 1 FDR diagnosed with PDAC before age 50; or (b) ≥ 1 FDR with PDAC and ≥ 1 other relative with PDAC, including; or (c) ≥ 3 SDRs with PDAC; or (d) known BRCA mutation and ≥ 1 relative with PDAC.</p>

Appendix D Table 1. Narrative description of screening programs and high-risk populations

Screening Program	Screening program procedures	Definition of increased risk for PDAC
Schneider, 2011 FaPaCa Germany Fair	<p>Recruitment: Eligible patients were high-risk individuals enrolled in the German National Case Collection of Familial Pancreatic Cancer (FaPaCa) who met criteria for the screening program. The study does not specify how patients were invited to participate.</p> <p>Initial screen: Baseline evaluation involved a physical exam, lab tests (serum assessment of liver & pancreas, blood count, CEA, CA 19-9), EUS, and abdominal MRI/MRCP.</p> <p>Diagnostic workup: Those with suspicious lesions on initial screening underwent repeat EUS in 6 weeks. Those with abnormalities potentially suggestive of malignancy underwent EUS-FNA. An interdisciplinary board reviewed any pathological findings. Those with suspected malignancy or pre-malignancy were referred to surgery.</p> <p>Blinding: Two experienced radiologists without knowledge of any clinical or other imaging results independently reviewed all MRIs.</p> <p>Surveillance: Those who screened negative continued to undergo annual screening. Interdisciplinary board could recommend close followup (repeated EUS and MRI/MRCP after 12 weeks, re-evaluation after 6 months and 12 months).</p> <p>Harms and outcomes: The study reports that no FNA-related harms occurred, but does not report whether such harms were assessed systematically for all patients. Psychosocial screening-related harms were not assessed or reported. The study reports clinical followup, including metastases and surgical harms, for screen-detected PDAC cases.</p>	<p>FaPaCa registry enrollees who had no personal history of PDAC, were age ≥ 40 or within 10 years of youngest relative with PDAC and were (a) FDRs of an affected patient of an FPC^e family; or (b) members of an FPC^e family with a known genetic variant such as <i>BRCA2</i>, <i>PALB2</i>, or <i>CDKN2A</i>.</p>
Verna, 2010 U.S. Fair	<p>Recruitment: Eligible patients were those referred to Pancreas Cancer Prevention and Genetics Program at Columbia University Medical Center/New York Presbyterian Hospital who had a family history of pancreatic cancer and an interest in their risk of disease. The study does not specify how patients were invited to participate.</p> <p>Initial screen: Baseline evaluation included a detailed personal and family medical history, physical exam, genetic counseling, blood sample. Patients were offered MRI or EUS as well as an oral glucose tolerance test and serum CA 19-9. Genetic testing was recommended at discretion of clinician and genetic counselor.</p> <p>Diagnostic workup: Those with abnormalities (mass lesions, cysts, or suspicious lymph nodes) underwent EUS-FNA. ECRP was performed at the discretion of the interventional endoscopist generally when ductal irregularities or changes consistent with IPMN required additional assessment.</p> <p>Blinding: Radiologist was blinded to patient's pancreatic risk factors.</p> <p>Surveillance: High-risk patients and those who underwent partial pancreatectomies were re-screened every 6 months. Those at moderate risk underwent annual imaging, and those at average risk returned for annual visits and further testing if they developed symptoms or new onset diabetes.</p> <p>Harms and outcomes: The study reports that no screening procedure-related harms occurred, but does not report whether such harms were assessed systematically for all patients. Psychosocial screening-related harms were not assessed or reported. The study reports clinical followup information, including survival, for screen-detected PDAC cases. No surgical harms were assessed or reported.</p>	<p>Moderate risk: ≥ 2 relatives (FDRs, SDRs, or TDRs) with PDAC; or 1 FDR with PDAC <55 years old but not meeting high risk criteria.</p> <p>High risk: (a); had FPC^f; or (b) had known genetic syndrome (PJS, Lynch syndrome, <i>BRCA1</i>, <i>BRCA2</i>, FAMMM, or HP).</p> <p>Patients at average risk (≥ 1 relative with PDAC age >55) were generally not recommended for screening unless significant psychological distress led them to prefer to be screened.</p>

Appendix D Table 1. Narrative description of screening programs and high-risk populations

Screening Program	Screening program procedures	Definition of increased risk for PDAC
<p>Poley, 2009 Netherlands Fair</p>	<p>Recruitment: Eligible patients were asymptomatic at-risk individuals recruited and evaluated by clinical geneticists at an academic medical center in the Netherlands. The study does not specify how patients were invited to participate.</p> <p>Initial screen: Following extensive evaluation by clinical geneticists, initial screening involved EUS.</p> <p>Diagnostic workup: Those with abnormalities on EUS (mass lesions, cystic lesions, duct aberrations, and signs of chronic pancreatitis) underwent CT and/or MRI. A multidisciplinary team discussed all findings. Criteria for referral to surgery was not reported.</p> <p>Blinding: NR</p> <p>Surveillance: Those with small cystic lesions were followed up bi-annually with EUS and MRI. No other surveillance strategy is reported.</p> <p>Harms and outcomes: The study reports that no screening procedure-related harms occurred, but does not report whether such harms were assessed systematically for all patients. Psychosocial screening-related harms were not assessed or reported. The study reports clinical followup information, including survival, for screen-detected PDAC cases. No surgical harms were assessed or reported.</p>	<p>Asymptomatic adults age ≥ 40 or within 5 years of youngest relative with PDAC who had (a) ≥ 2 FDRs with PDAC; or (b) a known pathogenic mutation; or (c) family history of HBOC, Lynch syndrome, or Li-Fraumeni syndrome and had familial clustering of PDAC in ≥ 2 relatives.</p>
<p>Canto, 2006 U.S. Fair</p>	<p>Recruitment: Eligible patients were asymptomatic high-risk individuals identified through (a) referral by physician or genetic counselor; or (b) invited by letter to participate through the National Familial Pancreas Tumor Registry (NFPTR) or the Johns Hopkins Hereditary Colorectal Tumor Registry. Those not already enrolled in the NFPTR were referred for enrollment to confirm eligibility. Consecutive patients undergoing EUS and/or ERCP for non-pancreatic indications at Johns Hopkins Hospital were enrolled as control patients.</p> <p>Initial screen: Baseline evaluation involved a family history and personal medical history questionnaire, physical exam, blood sample, genetic counseling, and screening by EUS and CT. Control patients underwent EUS and/or ERCP with the same procedures as the high-risk patients.</p> <p>Diagnostic workup: Those with abnormalities on EUS (focal lesion such as a mass, nodule, or cyst; or ≥ 3 of 9 EUS features of chronic pancreatitis) underwent EUS-guided FNA at the same procedure and were offered ERCP, usually at a separate visit. Those with abnormal findings on followup testing (suspected pancreatic mass, cystic lesion, nodule, or severe dysplasia) were referred to a pancreatic surgeon. Control patients underwent the same followup testing procedures as the high-risk patients.</p> <p>Blinding: EUS, FNA and CT results were assessed without knowledge of other test results.</p> <p>Surveillance: Patients who had abnormalities on EUS but did not have surgery were offered followup EUS, FNA, and CT within 3-6 months. All patients were offered repeat EUS within 1 year of the initial screening.</p> <p>Harms and outcomes: Screening procedure-related harms were assessed by telephone calls to all patients within 7 days after EUS and ERCP procedures. Psychosocial screening-related harms were not assessed or reported. The study reports clinical follow-up information, including survival, for screen-detected PDAC cases. The study also reports surgical harms among those who underwent surgery for precursor lesions.</p>	<p>PJS group: Age ≥ 30 and with ≥ 2 criteria for PJS^a.</p> <p>Family history group: age ≥ 40 or within 10 years of youngest relative with PDAC and from a family with ≥ 3 affected members, including ≥ 1 affected FDR.</p> <p>Control group: age ≥ 30 undergoing EUS and/or ERCP for non-pancreatic indications and with no personal or family history or PDAC and no suspicion of pancreatic disease.</p>

Appendix D Table 1. Narrative description of screening programs and high-risk populations

Screening Program	Screening program procedures	Definition of increased risk for PDAC
Canto, 2004 U.S. Fair	<p>Recruitment: Eligible patients were asymptomatic high-risk individuals identified through (a) the National Familial Pancreas Tumor Registry (NFPTR); (b) self-referral or physician referral because of a family history of pancreatic cancer; or (c) the Johns Hopkins Hereditary Colorectal Tumor Registry, which tracks patients and their families with Peutz–Jeghers syndrome. Eligible NFPTR patients were contacted by mail with an invitation letter; the first 30 patients who agreed to participate were enrolled. Seven patients identified through self-referral or physician referral were invited to enroll in the NFPTR and the screening program, and one PJS patient identified through the Johns Hopkins Hereditary Colorectal Tumor Registry also enrolled in the screening program.</p> <p>Initial screen: Baseline evaluation involved a complete history, physical exam, genetic counseling, and screening with EUS.</p> <p>Diagnostic workup: Those with abnormalities on EUS (focal lesion such as a mass, nodule, or cyst; or ≥ 3 of 9 EUS features of chronic pancreatitis) underwent EUS-guided FNA at the same procedure. Those with abnormal EUS also underwent CT and were offered ERCP. Those with abnormal findings on followup testing (suspected pancreatic cancer because of a mass or severe dysplasia) were referred to a pancreatic surgeon.</p> <p>Blinding: FNA and CT results were assessed without knowledge of other test results.</p> <p>Surveillance: All patients were offered repeat EUS within 1 year of the initial screening and were followed until the end of the study (mean 22.4 months).</p> <p>Harms and outcomes: Screening procedure-related harms were assessed by telephone calls to all patients within 7 days after EUS and ERCP procedures. Psychosocial screening-related harms were not assessed or reported. The study reports clinical follow-up information, including survival, for screen-detected PDAC cases. No surgical harms were assessed or reported.</p>	<p>NFPTR group: NFPTR enrollees who: (a) had ≥ 3 relatives with PDAC, including ≥ 2 affected FDRs; and (b) were an FDR of ≥ 1 affected family member; and (c) were age ≥ 40 or within 10 years of the youngest affected relative.</p> <p>PJS group: Enrollees in the Johns Hopkins Hereditary Colorectal Tumor Registry who had PJS, pathologically confirmed hamartomatous polyps, family history of PJS, and/or mucocutaneous pigmentation</p>

Abbreviations: PDAC = pancreatic ductal adenocarcinoma; PJS = Peutz-Jeghers syndrome; HP = hereditary pancreatitis; HBOC = hereditary breast and ovarian cancer; FDR = first-degree relative; SDR = second-degree relative; TDR = third-degree relative; FPC = familial pancreatic cancer; NFPTR = National Familial Pancreas Tumor Registry; CAPS = Cancer of the Pancreas Screening Study; NR = not reported; ASA = American Society of Anaesthesiologists; FaPaCa = German National Case Collection of Familial Pancreatic Cancer; FAMMM = Familial atypical multiple mole melanoma syndrome; EUS = endoscopic ultrasound; CT = computed tomography; MRI = magnetic resonance imaging; FNA = fine-needle aspiration; MRCP = magnetic resonance cholangiopancreatography; CEA = carcinoembryonic antigen; CA 19-9 = carbohydrate antigen 19-9

^a Criteria for PJS include characteristic intestinal hamartomatous polyps, mucocutaneous melanin deposition, and family history of PJS

^b For Harinck 2016, familial pancreatic cancer was defined as a family with (a) ≥ 2 affected FDRs; **or** (b) ≥ 3 relatives in which the affected cases are FDR or SDRs of each other; **or** (c) ≥ 2 SDRs of whom at least one was aged < 50 at time of diagnosis.

^c For Joergensen 2016, hereditary pancreatitis was defined as having a PRSS1 mutation **OR** having ≥ 2 FDRs or ≥ 3 SDRs in two or more generations with recurrent acute pancreatitis, and/or chronic pancreatitis

^d For Joergensen 2016, familial pancreatic cancer was defined as FDRs of patients with PDAC in families with 2 cases of PDAC where one relative was < 50 years of age at diagnosis, or where ≥ 3 FDRs had PDAC

^e For Schneider 2011, familial pancreatic cancer was defined as a family with ≥ 2 FDRs with confirmed diagnosis of PDAC without evidence of another inherited tumor syndrome

^f For Verna 2010, familial pancreatic cancer was defined as having (a) ≥ 3 relatives (FDRs, SDRs, or TDRs) with PDAC; **or** (b) ≥ 2 FDRs with PDAC; **or** (c) 1 FDR and 1 SDR with PDAC, with ≥ 1 diagnosed age < 55 .

Treatment outcomes of 18 screen-detected cases in included studies

In total, 18 cases of pancreatic adenocarcinoma were reported in 10 studies (**Evidence Report, Table 10**).¹⁻¹⁰ Fourteen of the 18 individuals with pancreatic adenocarcinoma underwent surgical intervention. Status at followup at a defined time period was reported for 10 people across seven studies.^{2, 5-10} Six individuals were alive at 12–63 months followup,^{2, 7, 9, 10} two with distant metastases reported at 12 and 16 months.⁷ Four people were deceased, one from other causes at 7 months followup and three with local recurrence (one with distant metastasis) at 16–36 months.^{5-7, 9} The most common surgical treatment underwent was total pancreatectomy (n=9, removing the entire pancreas, gallbladder, part of the stomach and small intestine, and spleen) followed by distal pancreatectomy (n=3, removing only the tail of the pancreas and spleen) and pancreaticoduodenectomy (n=2, removing the head of the pancreas). Four individuals with metastatic pancreatic adenocarcinoma underwent no surgery, although two did undergo chemotherapy treatment.

Longer-term followup results

Longer-term followup data is available for two included screening programs: The FaPaCa screening program in Germany,¹⁰⁻¹⁴ and the U.S.-based CAPS3 screening program¹⁵⁻¹⁷ (**Appendix D, Table 3**). It is not possible to identify which of the 18 cases included in the evidence report are represented in these data, as cohorts were combined before reporting these longer followup data. Taken together, these studies suggest that longer-term survival has been observed in people with screen-detected pancreatic adenocarcinoma, but direct comparison to clinically detected populations is not possible.

FaPaCa

Three articles¹²⁻¹⁴ provide followup data on the FaPaCa screening program^{10, 11} combined with results from screening programs at Leiden University Medical Center in the Netherlands, and at Ramon y Cajal University Hospital in Spain.

As reported in the Schneider 2011¹⁰ and Langer 2009¹¹ articles, the FaPaCa program detected one case of pancreatic adenocarcinoma over 7 years of followup, and this individual was alive with lung metastases 12 months after surgery. The number of pancreatic cancer cases identified in the longer-term followup articles are: 1 case detected over 9 years followup, survival not reported;¹² 1 case detected over 13 years followup, died 38 months after surgery from metastatic disease;¹³ and 2 cases detected over 13 years followup, survival not reported.¹⁴ However, it is not possible to determine whether each of these cases were part of the FaPaCa cohort, since the articles combine FaPaCa with results from other screening programs.

CAPS3

One article accepted for publication after our last literature search provides longer-term followup data on patients from the CAPS3 cohort^{15, 16} and the CAPS4 cohort (results not published), as well as previously reported results from the Canto 2004² and Canto 2006¹ studies. The article does not report results separately by study cohort.

Appendix D. Treatment outcomes for screen-detected PDAC cases

Together, the CAPS3,^{15, 16} Canto 2004,² and Canto 2006¹ studies detected 2 cases of pancreatic adenocarcinoma over 1 to 2 years followup. The longer-term followup article¹⁷ combining data on these three studies and the unpublished CAPS4 study reports that 14 cases of pancreatic adenocarcinoma were detected over a median followup of 5.6 years. Ten of the 14 cases were detected as part of the screening programs, including 5 patients who underwent surgery and were alive at 2 to 11 years after diagnosis, 4 patients who underwent surgery and died at 1 to 12 years after diagnosis, and 1 patient who did not undergo surgery and died less than 3 months after diagnosis. Four of the 14 pancreatic cancer cases were detected outside the screening programs (after late or stopped surveillance), including 1 patient who underwent surgery and died 4 years after diagnosis and 3 patients who did not undergo surgery and died 4 to 26 months after diagnosis.

Appendix D Table 2. Summary of findings from longer-term followup papers

Article	Population	N	Screening Period	N PDAC detected	PDAC details
Schneider, 2011 ¹⁰ (main FaPaCa paper)	FaPaCa only	72	2002-2009	1	Stage NR (pt had lung metastases on 12-mo f/u), alive at time of writing
Potjer 2012 ¹²	FaPaCa only	125	2002-2011	1	Found in pancreatic head, survival NR
Vasen 2016 ¹³	FaPaCa (n=184) and Madrid (n=30)*	214	2002-2015	1	Metastatic disease, died 38 mos after surgery
Bartsch 2016 ¹⁴	FaPaCa (n=210), Madrid (n=30) and Leiden (n=13)*	253	2002-2015	2	Stage 1 (n=1), Stage IIB (n=1). Survival not reported.
Canto 2018 ¹⁷	Canto 2004 (n=38); Canto 2006 (n=78); CAPS3 (n=216); CAPS4 (n=249)	354†	1998-2016	14	<p>10 cases detected during surveillance</p> <ul style="list-style-type: none"> - 2 of 10 were Stage IV - 5 resected patients alive 2-11 years after diagnosis - 4 resected patients died 1-12 years after diagnosis - 1 unresected patient died <3 mos after diagnosis <p>4 cases detected outside surveillance (late or stopped screening)</p> <ul style="list-style-type: none"> - 3 of 4 were Stage IV - 1 resected patient died 4 years after diagnosis - 3 unresected patients died 4-26 mos after diagnosis

* Results not reported separately by site

† Excluded 227 patients who continued surveillance at an outside institution or who had less than six months of followup after baseline screening. The study does not report the number of patients excluded separately by cohort.

Appendix D Table 3. Surgery type by study

Author, year	Number of patients receiving surgery	Type of surgery
Gangi, 2018	1	Distal pancreatectomy (n = 1)
Harinck, 2016	2	Distal pancreatectomy with splenectomy (n = 1)* Pancreaticoduodenectomy (n = 1)
Joergensen, 2016	2	Total pancreatectomy (n = 2)**
Del Chiaro, 2015	5	Total pancreatectomy (n = 2)** Distal pancreatectomy (n = 1) Pancreatoduodenectomy (n = 1)* 3 enucleations (n = 1)
Al-Sukhni, 2012	4	Total pancreatectomy (n = 1)* Whipple (n = 1) Spleen preserving distal pancreatectomy (n = 1) Laparoscopic distal pancreatectomy (n = 1)
Canto, 2012	5	Pancreatectomy (n = 5)
Ludwig, 2011	6	Distal pancreatectomy (n = 4) * Pancreaticoduodenectomy (n = 2)
Schneider, 2011	10	Exploration liver-wedge (n = 1) Distal pancreatectomy plus splenectomy (n = 3) Spleen preserving distal pancreatectomy (n = 3) Total pancreatectomy (n = 3)*
Verna, 2010	5	Total pancreatectomy (n = 1)* Distal pancreatectomy (n = 3) Central pancreatectomy (n = 1)
Poley, 2009	3	Pancreatic tail and spleen resection (n = 1)* Surgical resection of the pancreatic body and tail with en bloc resection of the spleen (n = 1)* EN bloc resection of the pancreatic body, tail and spleen (n = 1)*
Canto, 2006	7	Pyloric-sparing pancreaticoduodenectomy (extended and non-extended) (n = 5) Distal pancreatectomy with en bloc splenectomy (n = 1) Distal pancreatectomy and splenectomy (n = 1)
Canto, 2004	7	Whipple (n = 4)* Distal pancreatectomy (n = 3)

* = number of PDAC cases with that procedure

Appendix D Table 3. Surgery type by study

References

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Appendix E. Ongoing Studies

According to ClinicalTrials.gov there are 823 trials on pancreatic cancer in adults that currently do not have results and are either: recruiting, not yet recruiting, active, and enrolling by invitation. Of those 823, 7 studies mention screening. They are described in the table below by expected completion date (most recent first). The table below also includes a planned cohort study that does not yet have an entry in ClinicalTrials.gov.

NCT #	Title	Recruitment	Conditions	Interventions	Primary Outcome Measures	Sponsor/ Collaborators	Enrollment	Funded By	Study Designs	Start Date	Completion Date	URL
N/A	The New-Onset Diabetes (NOD) Cohort Study	Not yet recruiting	Pancreatic cancer	Blood collection	Prevalence of pancreatic cancer in patients with new-onset diabetes	National Cancer Institute; National Institute of Diabetes and Digestive and Kidney Diseases	10,000	NCI	Observational Cohort Prospective	Not yet started	Not yet determined	N/A
NCT01662609	Protocol for High-Risk Assessment, Screening, and Early Detection of Pancreatic Cancer	Active, not recruiting	Pancreatic Cancer	Procedure: Endoscopic Ultrasound (EUS)	Number of Abnormalities Detected by EUS	H. Lee Moffitt Cancer Center and Research Institute	90	Other	Observational Case-Only Prospective	Jun 2007	Dec 2019	https://ClinicalTrials.gov/show/NCT01662609
NCT02703545	International CAPS Registry: Pancreas Cancer Cases in Surveillance Programs (CAPS Registry)	Enrolling by invitation	Pancreas Cancer	None	Proportion of patients and resected lesions with pancreatic cancer in situ (high grade dysplasia) or invasive malignancy ^a	Johns Hopkins University	100	Other	Observational Case-Control Prospective	Feb 2014	Jul 2020	https://ClinicalTrials.gov/show/NCT02703545
NCT02478892	Screening for PDAC in BRCA1/2 Patients	Recruiting	Pancreatic Cancer	Device: prophylactic endoscopic ultrasound	Identifying pancreatic neoplastic lesions in patients with BRCA1/2 mutations ^b	Abramson Cancer Center of the University of Pennsylvania	200	Other	Observational Cohort Prospective	May 2015	May 2020	https://ClinicalTrials.gov/show/NCT02478892

Appendix E. Ongoing Studies

NCT #	Title	Recruitment	Conditions	Interventions	Primary Outcome Measures	Sponsor/ Collaborators	Enrollment	Funded By	Study Designs	Start Date	Completion Date	URL
NCT02000089	The Cancer of the Pancreas Screening-5 (CAPS5) Study	Recruiting	Pancreas Cancer	Drug: Human synthetic secretin	Evaluate pancreatic juice for early cancer markers	Johns Hopkins University ChiRhoClin, Inc.	2500	Other Industry	Observational Cohort Prospective	Jan 2014	Dec 2023	https://ClinicalTrials.gov/show/NCT02000089
NCT03250078	A Pancreatic Cancer Screening Study in High Risk Individuals Including Those with New-Onset Diabetes Mellitus	Recruiting	Pancreatic Neoplasms	Diagnostic Test: MRI/MRCP	Early Stage Pancreatic Cancer or Precursor Lesions	Western Connecticut Health Network	800	Other	Observational Cohort Prospective	Nov 2016	Nov 2023	https://ClinicalTrials.gov/show/NCT03250078
NCT02078245	Quality Control Study of MR Based Screening of Individual with Increased Risk for Pancreas Cancer.	Recruiting	Hereditary Pancreatitis Hereditary Pancreatic Cancer	Other: MRI	MRI accuracy and outcome of surveillance program	Karolinska University Hospital	100	Other	Observational Other Prospective	Aug 2010	Jan 2025	https://ClinicalTrials.gov/show/NCT02078245
NCT02309632	Pancreatic Cancer Screening of High-Risk Individuals in Arkansas	Active, not recruiting	Pancreatic Neoplasms ^c	Pancreatic Cancer Screening Pathway	Detection rate of PC and precancerous lesion	University of Arkansas	100	Other	Non-Randomized Intervention Parallel Assignment	Nov 2015	Nov 2026	https://ClinicalTrials.gov/show/NCT02309632

^a Additional outcomes: Proportion of specific types of pancreatic neoplasms by lesion type; Incidence of pancreatic in-situ and invasive malignancy after baseline screening; All-cause and disease specific mortality; Survival time from point of diagnosis and treatment

^b Additional outcomes: Other less common, but related mutations (ATM, PALB2) as well as mutations identified in the future.

^c Additional conditions: Peutz-Jeghers Syndrome; BRCA1 Gene Mutation; BRCA2 Gene Mutation; Ataxia Telangiectasia; Familial Atypical Mole-Malignant Melanoma Syndrome; Colorectal Neoplasms, Hereditary Nonpolyposis; Hereditary Pancreatitis

^d Additional conditions: Peutz-Jeghers Syndrome (PJS); Gene Mutation; Germline Mutation Carrier; Lynch Syndrome