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AGA Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals: Expert Review

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DESCRIPTION: The purpose of this American Gastroenterological Association Institute Clinical Practice Update is to describe the indications for screening for pancreas cancer in high-risk individuals. **METHODS:** The evidence reviewed in this work is based on reports of pancreas cancer screening studies in high-risk individuals and expert opinion. **BEST PRACTICE ADVICE 1:** Pancreas cancer screening should be considered in patients determined to be at high risk, including first-degree relatives of patients with pancreas cancer with at least 2 affected genetically related relatives. **BEST PRACTICE ADVICE 2:** Pancreas cancer screening should be considered in patients with genetic syndromes associated with an increased risk of pancreas cancer, including all patients with Peutz–Jeghers syndrome, hereditary pancreatitis, patients with CDKN2A gene mutation, and patients with 1 or more first-degree relatives with pancreas cancer with Lynch syndrome, and mutations in BRCA1, BRCA2, PALB2, and ATM genes. **BEST PRACTICE ADVICE 3:** Genetic testing and counseling should be considered for familial pancreas cancer relatives who are eligible for surveillance. A positive germline mutation is associated with an increased risk of neoplastic progression and may also lead to screening for other relevant associated cancers. **BEST PRACTICE ADVICE 4:** Participation in a registry or referral to a pancreas Center of Excellence should be pursued when possible for high-risk patients undergoing pancreas cancer screening. **BEST PRACTICE ADVICE 5:** Clinicians should not screen average-risk individuals for pancreas cancer. **BEST PRACTICE ADVICE 6:** Pancreas cancer screening in high-risk individuals should begin at age 50 years, or 10 years younger than the initial age of familial onset. Screening should be initiated at age 40 years in CKDN2A and PRSS1 mutation carriers with hereditary pancreatitis and at age 35 years in the setting of Peutz–Jeghers syndrome. **BEST PRACTICE ADVICE 7:** Magnetic resonance imaging and endoscopic ultrasonography (EUS) should be used in combination as the preferred screening modalities in individuals undergoing pancreas cancer screening. **BEST PRACTICE ADVICE 8:** The target detectable pancreatic neoplasms are resectable stage I pancreatic ductal adenocarcinoma and high-risk precursor neoplasms, such as intraductal papillary mucinous neoplasms with high-grade dysplasia and some enlarged pancreatic intraepithelial neoplasias. **BEST PRACTICE ADVICE 9:** Screening intervals of 12 months should be considered when there are no concerning pancreas lesions, with shortened intervals and/or the performance of EUS in 6–12 months directed towards lesions determined to be low risk (by a multidisciplinary team). EUS evaluation should be performed within 3–6 months for indeterminate lesions and within 3 months for high-risk lesions, if surgical resection is not planned. New-onset diabetes in a high-risk individual should lead to additional diagnostic studies or change in surveillance interval. **BEST PRACTICE ADVICE 10:** Decisions regarding therapy directed towards abnormal findings detected during screening should be made by a dedicated multidisciplinary team together with the high-risk individual and their family. **BEST PRACTICE ADVICE 11:** Surgical resection should be performed at high-volume centers. **BEST PRACTICE ADVICE 12:** Clinicians should consider discontinuing pancreas cancer screening in high-risk individuals when they are more likely to die of non-pancreas cancer–related causes due to comorbidity and/or are not candidates for pancreas resection. **BEST PRACTICE ADVICE 13:** The limitations and potential risks of pancreas cancer screening should be discussed with patients before initiating a screening program.

Keywords: Pancreas Cancer; Cancer Screening.

Pancreas cancer has a poor prognosis. In 2019, approximately 56,770 people were diagnosed with pancreas cancer and 45,750 died of the disease.[1] Pancreas cancer is the third most common cause of cancer death in the United States and is on a rapid trajectory to becoming the second-leading cause by the year 2030.[2] The age-adjusted annual incidence of 12.9 cases per 100,000 person years closely mirrors the death rate of 11.0 deaths per 100,000 person-years.[1] Five-year survival rates are influenced by disease stage at presentation. The 5-year survival rate for metastatic disease is 2.9%, increasing to 12.4% for regional disease and 37.4% for localized disease.[2] Most cases, however, are detected at an advanced stage and pancreas cancer metastasizes rapidly.

Surgical resection of localized disease represents the greatest chance for a curative therapy. The US Preventive Services Task Force (USPSTF) Evidence Report notes that "Screening to detect pancreas cancers and their precursor lesions could improve survival if it facilitated surgical resection for early-stage disease. Since incident pancreas cancer is rare … identifying populations at the highest risk for pancreatic cancer is critical to developing meaningful

Abbreviations used in this paper: **AGA, American Gastroenterological Association; CI, confidence interval; EUS, endoscopic ultrasonography; MRI, magnetic resonance imaging; PanIN, pancreatic intraepithelial neoplasia; USPSTF, US Preventive Services Task Force.**

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Table 1. Risk for Pancreatic Cancer Related to Genetic Mutation

Genes	Common name	Risk of pancreatic cancer
STK11/LKB1	Peutz–Jeghers syndrome	RR, 132 (95% CI, 44–261)
PRSS1	Hereditary pancreatitis	SIR, 53 (95% CI, 23–105)
CDKN2A	Familial atypical multiple mole/melanoma syndrome	RR, 13–39
MLH1, MSH2, MSH6	Lynch syndrome	RR, 8.6–11
TP53	Li-Fraumeni syndrome	RR, 7.3 (95% CI, 2–19)
ATM	NA	RR, 3.92 (95% CI, 0.44–14.2)
BRCA1	Hereditary breast and ovarian cancer	RR, 2.26 (95% CI, 1.26–4.06)
BRCA2, PALB2		RR, 3.5–6.2 (95% CI 1.87–6.58)
Familial pancreas cancer in 1 or 2 first-degree relatives	Familial pancreas cancer	RR, 4–9.3

From Davee et al,[9] adapted with permission.
NA, not applicable; RR, relative risk; SIR, standardized incidence ratio.

screening or early detection programs."[3] The lifetime risk of pancreas cancer is approximately 1.3% in the general population. A lifetime risk >5% has been utilized to define high-risk individuals.[4] Eighty-five percent to 90% of pancreas cancer cases are sporadic, while 5%–10% have familial risk and 3%–5% are due to inherited genetic syndromes.[5,6] Pancreas cancer screening has been performed in individuals identified as high risk due to inherited genetic syndromes, germline mutations (including BRCA 2 and PALB2), and a history of familial pancreas cancer, as part of screening studies based at academic centers.

This expert review was commissioned and approved by the American Gastroenterological Association (AGA) Institute Clinical Practice Updates Committee and the AGA Governing Board to provide timely guidance on a topic of high clinical importance to the AGA membership, and underwent internal peer review by the Clinical Practice Updates Committee and external peer review through the standard procedures of *Gastroenterology*.

Methods

This article is not based on a formal systematic review but instead seeks to provide practical clinically applicable advice based on the best available evidence and expert opinion. The focus is on primary screening rather than management of abnormal screening test results. The advice applies to high-risk individuals.

What High-Risk Groups Should Be Considered for Pancreas Cancer Screening?

Studies to date have demonstrated variability regarding definitions of high-risk groups and the age at which screening should be initiated. The genetic basis of much of the inherited susceptibility to pancreas cancer remains unexplained (in approximately 90% of cases) and family history is important in risk stratification. Familial pancreas cancer is defined as a kindred with pancreas cancer occurring in 2 or more first-degree relatives that does not meet the criteria for other hereditary cancer syndromes. Pancreas cancer risk is influenced by the number of relatives affected and their relationship. There is an 8%–12% lifetime risk (6.4×) with 2 first-degree relatives with pancreas cancer and a 40% lifetime risk with 3 or more first-degree relatives (32×).[7] In addition, earlier age of onset confers an increased risk (kindreds with onset younger than 50 years have a relative risk of 9.3).[8]

Genetic risk factors that confer the greatest degree of risk for pancreas cancer (summarized in Table 1) include Peutz–Jeghers syndrome (associated with STK11 germline gene mutations; 132× increased risk, mean age of development of 40.8 years), hereditary pancreatitis (predominantly PRSS1 mutations; 40% lifetime risk related to chronic pancreatitis, mean age of development of 54 years), familial atypical multiple mole melanoma syndrome (CDKN2A mutations; 13–39×, mean age of development of 59 years), and Lynch syndrome (mismatch repair genes: MLH1, MSH2, MSH6; 8.6–11×, 3.7% lifetime risk). Incomplete or low penetrance is a common feature of familial pancreas cancer genes and a family history of pancreas cancer is an important consideration for identified mutations other than Peutz–Jeghers syndrome or hereditary pancreatitis with longstanding chronic calcific pancreatitis.[4] Surveillance and management of individuals with hereditary pancreatitis is challenging and should be performed at expert centers.

BRCA2 mutations are the most common identifiable genetic factor, recognized in 5%–17% of familial pancreas cancer kindreds and confer a relative risk of 3.5–6.2 (95% confidence interval [CI], 1.87–6.58).[10] PALB2 mutations are estimated to confer similar risk. Additional mutations associated with hereditary pancreas cancer with estimates of increased risk in the range of 4–13×, include CDKN2A, ATM, and TP53 (Li-Fraumeni syndrome).[11] Recent studies of multigene germline testing in pancreas cancer patients have identified variability in the strength of association between certain genes and pancreas cancer risk (including weak link to APC mutations). Deleterious gene mutations are a risk factor for neoplastic progression among familial pancreatic cancer relatives, with a significantly increased cumulative incidence of pancreatic cancer, high-grade dysplasia, or imaging worrisome features (hazard ratio, 2.85; 95% CI, 1.0–8.18).[12]

At What Age Should Screening Begin?

The mean age at diagnosis of pancreas cancer in individuals with familial pancreas cancer is 68 years. Studies in high-risk individuals have identified increasing numbers of lesions in

individuals older than 50 years and an increase in lesions with high-grade dysplasia in those older than 65 years.[13] Initiation of screening at age 50 years or 10 years younger than the initial age of onset has been suggested in the guidelines of the American College of Gastroenterology[11] and pursued in screening programs at Centers of Excellence. Screening has been initiated at age 40 years in PRSS1 mutation carriers with hereditary pancreatitis, age 40 years in CKDN2A mutation carriers, and at age 35 years in the setting of Peutz–Jeghers syndrome, due to the younger age of onset of pancreas cancer observed in these populations.

Additional nongenetic risk factors for the development of pancreas cancer include tobacco use, chronic pancreatitis, obesity, and diabetes. New-onset diabetes has been recognized to be associated with the development of pancreas cancer in a small proportion of patients, typically preceding cancer diagnosis by 36 months.[14] New-onset diabetes mellitus in an individual older than 50 years with a history of smoking or weight loss is estimated to have an 8-fold increased in relative risk of developing pancreas cancer at a mean age of 71 years.[15] New-onset diabetes in a high-risk individual should lead to additional diagnostic studies or shortening of the surveillance interval. Additional data regarding the degree to which additional risk factors influence the onset of pancreas cancer in high-risk individuals is required.

What Are the Benefits of Pancreas Cancer Screening in High-Risk Individuals?

Pancreas cancer is frequently metastatic within a short time after it is detectable by current testing modalities. The mortality from pancreas cancer remains very high. Complete resection of localized pancreas cancer at present remains the only reliable potentially curative therapy. Precursor lesions to pancreas cancer include pancreatic intraepithelial neoplasia-3 (PanIN3) lesions and cystic lesions with high-grade dysplasia. Identification of these lesions along with small, localized solid tumors is therefore the goal of dedicated screening and surveillance in high-risk populations.

A recent meta-analysis identified 1551 familial high-risk individuals undergoing pancreas cancer screening reported in 16 studies. Pancreas cancer, PanIN3, or intraductal papillary mucinous neoplasms with high-grade dysplasia were detected in 1.82% (30 subjects), which was much higher than the expected yield of undiagnosed pancreas cancer in an average-risk population. Six percent (93 patients) of patients underwent surgery. Surgical pathology of pancreas resections identified low-grade lesions in 68.1% of cases.[13] The authors concluded that their findings appeared to support the utility of pancreas cancer screening protocols, however, patients should be aware of the likelihood that surgery may be recommended. In 2019, the systemic review of the USPSTF evaluated 13 studies, including 1317 patients at high familial risk undergoing screening with computed tomography, magnetic resonance imaging (MRI), or endoscopic ultrasonography (EUS). Studies consisting entirely of populations with known genetic syndromes associated with pancreas cancer were excluded. A total of 18 cases of pancreas cancer were identified (15.6 cases per 1000 persons). Fifty-seven patients underwent surgery. Fourteen had pancreas cancer, 38 had precursor lesions, and 5 had neuroendocrine tumors, liver hyperplasia, or serous cystadenoma.[3] A prospective screening study utilizing MRI in 79 individuals with CDKN2A mutations identified 9 invasive pancreas cancers over a median of 4 years. Eleven patients needed to be screened to detect and treat 1 pancreas cancer.[14]

A recent analysis of a screening cohort of 354 high-risk individuals suggested a survival benefit in those with pancreas cancer or high-grade precursor neoplasms detected during surveillance. Twenty individuals diagnosed with pancreas malignancy or high-grade precursor neoplasm during surveillance had a median survival time of 5.3 years (interquartile range, 1.2–11.1 years) vs 1.4 years (interquartile range, 0.4–3.5 years) in the 4 individuals who did not undergo recommended surveillance (lesions detected after symptomatic presentation).[15] In a small cohort of screen-detected pancreatic cancers, the 1-year and 5-year survival rates were 90% and 60%, respectively.[16] Furthermore, detected pancreatic adenocarcinomas are more likely to be resectable when detected during surveillance (90%)[15] and surgical resection of detected pancreatic neoplasms was associated with zero perioperative mortality and acceptable morbidity in individuals prospectively followed in 3 expert European centers.[17] Additional data regarding the impact of screening programs on pancreas cancer–related morbidity and mortality is required. Further advancement in nonsurgical treatments, such as ablation or chemotherapy, may additionally enhance the benefits of screening.

What Modalities Should Be Utilized for Pancreas Cancer Screening?

MRI and EUS (linear array) are currently the preferred modalities for pancreas cancer screening due to their high sensitivity for the detection of pancreas lesions and low risk profile.[3] EUS and MRI have been shown to have good concordance for pancreas lesion size, number, and location[13] and have been found to be complementary,[18] with MRI being particularly sensitive for the detection of cystic lesions and EUS for solid lesions. Precise lesion sampling can be achieved with EUS-guided fine-needle aspiration. In a review of 9 studies involving 885 familial-risk patients, EUS-based screening was found to have diagnostic yield for pancreas adenocarcinoma ranging from 0 (97.5% CI, 0.0–16.9) to 68.2 (95% CI, 14.3–186.6) cases per 1000 persons. Among 8 studies involving 842 familial-risk patients, MRI-based screening had diagnostic yield for pancreas adenocarcinoma ranging from 0 (97.5% CI, 0.0–16.9) to 75 (95% CI, 15.7–203.9) cases per 1000 individuals.[3] The yield of 13 cohort screening studies (n = 1317) in high-risk individuals using computed tomography, EUS, or MRI was 15.6 cases of pancreas cancer per 1000 individuals.[1] EUS and MRI technologies are consistently improving, with increased ability to detect pancreatic lesions. The inability to reliably detect and distinguish PanINs remains a limitation of current imaging.

What Are the Harms of Pancreas Cancer Screening?

Harms can occur at any point in the screening and treatment process. The most apparent harm is the morbidity and mortality associated with segmental pancreas resection. Reported rates of perioperative mortality after pancreatectomy for neoplastic disease outside of screening studies range from 3.7% to 4.6%,[19] with more recent estimates closer to 2%. Surgery for screen-detected pancreatic lesions in 48 high-risk

individuals was associated with no mortality and morbidity comparable to other indications. The type of surgery for detected pancreatic neoplasms remains controversial, given the morbidity and mortality risk for total pancreatectomy, which should be weighed against the risk for a metachronous pancreas cancer originating in the remnant pancreas (20%).[16]

Screening introduces the possibility of exposure to surgical resections of uncertain benefit, which may include the resection of commonly identified benign or low-risk lesions and those that are already metastatic. Current imaging technologies lack specificity to distinguish low- and high-grade precursor pancreas lesions. Possible complications of the screening process include injury related to the performance of screening procedures, such as the administration of intravenous contrast, EUS-guided pancreas biopsy, anesthesia-related complications, and diagnosis and therapy directed towards incidental non-pancreatic findings. MRI and EUS have been recognized as the screening modalities with the most favorable risk–benefit characteristics, supplanting endoscopic retrograde cholangiopancreatography due to the risk of pancreatitis (and the inability to provide information regarding the pancreas parenchyma) and computed tomography due to radiation exposure.

Participation in a screening program has the potential to increase patient anxiety related to the development of cancer, however, studies have demonstrated the absence of an increase in risk perception and cancer worry,[20] and participation may reduce anxiety in some patients.[21] The USPSTF concluded that "imaging based screening in groups at high familial risk can detect pancreatic adenocarcinoma with limited evidence of minimal harms,"[3] as no serious harms from initial screening were reported in 8 studies, involving 675 patients. Patients may incur financial burdens related to the expense of screening participation.

How Frequently Should Surveillance Imaging/Testing Be Performed?

There is currently a high likelihood of mortality once pancreas cancer is metastatic. The benefits of screening are complicated by a relatively short "therapeutic window" of time for potential curative therapy from when pancreas cancer is detectable to when it is metastatic. The frequency of surveillance imaging after a normal baseline examination requires additional study. Pancreas cystic lesions, including side-branch intraductal papillary mucinous neoplasms are frequently detected (approximately 40% of patients) in individuals undergoing high-risk screening.[13] Guidelines for surveillance imaging in average-risk individuals with pancreas cysts are based on the presence of high-risk features and the size of the cyst, and typically range from 6 to 24 months. A 2015 AGA study estimated the risk of pancreas cyst (intraductal papillary mucinous neoplasms) progression to be approximately 0.25% per year in average-risk individuals.[22] Surveillance intervals in high-risk individuals with pancreas cysts without high-risk features should be the same as or more intensive than average-risk individuals.

Many pancreas screening studies in high-risk individuals have utilized surveillance intervals of 6–12 months, with follow-up of abnormal findings (such as main pancreas duct stricture or a <1 cm solid lesion) within 3–6 months. The presence of 3 or more pancreas cysts or dilation of the main pancreas duct at baseline examination was found to be a risk factor for progression in a cohort of 354 high-risk individuals followed for up to 16 years (mean, 5.6 years).[18] Nine of 10 pancreas adenocarcinomas detected during surveillance were resectable with an 85% 3-year survival rate vs 1 of 4 adenocarcinomas presenting symptomatically with a 25% 3-year survival rate.[18] Among 13 studies (1317 patients) with 18 pancreas adenocarcinomas detected, 9 were detected on initial imaging and 9 were detected on surveillance imaging. Twelve patients were early stage and 6 were advanced stage.[3]

The target treatment threshold for surgical resection of most studies has been set at PanIN3, cystic lesions with high-grade dysplasia, or localized small solid tumors (T1N0M0). PanIN1 and PanIN2, along with benign cystic lesions, have been recognized frequently in high-risk groups and there is a significant potential for overdiagnosis and overtreatment. The limitation of screening with clinical imaging is that microscopic PanINs with high-grade dysplasia cannot be diagnosed accurately, underscoring the need for alternative or complementary approaches, including biomarkers. Thus, therapeutic decisions should be made as part of a dedicated multidisciplinary team. Abnormal screening test results that do not lead to surgical resection (such as early PanIN lesions and benign cysts) may require more intensive surveillance. The majority of clinically significant lesions were detected in surveillance after an abnormal baseline examination. Advanced pancreas malignancy after a normal baseline examination was typically detected after 12 or more months.[14,23] EUS-guided fine-needle aspiration may play an important role in further defining detected lesions of high or indeterminate risk. Additional information on the natural history of low-risk lesions in high-risk groups is required.

Are There Evidence-Based Guidelines for Pancreas Cancer Screening in High-Risk Individuals?

In 2015, the American College of Gastroenterology published clinical guidelines on hereditary gastrointestinal cancer syndromes, including those that confer a risk of pancreas cancer.[11] Conditional recommendations (based on very low quality of evidence) included annual surveillance for pancreas cancer utilizing MRI and EUS at an experienced center in individuals who are known mutation carriers of hereditary syndromes, including Peutz–Jeghers, hereditary pancreatitis, familial atypical multiple melanoma and mole syndrome, and members of familial pancreatic cancer kindreds with a pancreatic cancer–affected first-degree relative. Surveillance was also recommended for mutation carriers in *BRCA1, BRCA2, PALB2, ATM*, and Lynch syndrome with a first- or second-degree relative affected with pancreatic cancer. Annual surveillance was recommended to start at age 50 years (35 years of age for Peutz–Jeghers syndrome) or 10 years younger than the earliest age of pancreatic cancer in the family.

The International Cancer of the Pancreas Consortium reported on expert opinion regarding pancreas cancer screening in high-risk individuals in 2013[4] and updated these in 2019.[24] In 2019, the USPSTF made a recommendation against screening asymptomatic individuals not known to be at high risk of pancreatic cancer.[3]

Limitations and Future Directions

Data regarding screening effectiveness, cost-effectiveness, and the impact of screening programs on pancreas adenocarcinoma–specific morbidity and mortality, including settings outside of high-volume academic centers and clinical trials, are required.[3] Randomized, prospective study of the impact of screening (vs no screening) on survival is needed, although this might be challenging to conduct, given implementation of clinical screening as standard of care in some practices.

Further data are required to define groups at the highest risk for development of pancreas cancer. There is a need to further refine screening tests with high sensitivity and specificity and ability to detect high-grade precursors, including non-imaging–based biomarkers. The role of a blood test for pancreatic cancer screening in a high-risk group needs further study. Emerging data suggest the potential for circulating tumor DNA and other markers (CancerSEEK) to be highly specific and reasonably sensitive for detection of pancreatic cancer, even in a general non–high-risk population. More data are required regarding the natural history of precursor lesions stratified across high-risk groups

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Conflicts of interest
The authors disclose the following: H. Aslanian is a consultant for Olympus and Boston Scientific and a speaker for GI Supply. The remaining authors disclose no conflicts.