Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE American Society for Gastrointestinal Endoscopy

ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations

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Prepared by: ASGE STANDARDS OF PRACTICE COMMITTEE

This document was reviewed and approved by the Governing Board of the American Society for Gastrointestinal Endoscopy.

This guideline document was prepared by the Standards of Practice Committee of the American Society for Gastrointestinal Endoscopy using the best available scientific evidence and considering a multitude of variables including, but not limited to, adverse events, patients' values, and cost implications. The purpose of these guidelines is to provide best practice recommendations that may help standardize patient care, improve patient outcomes, and reduce variability in practice. We recognize that clinical decision-making is complex. Guidelines, therefore, are not a substitute for a clinician's judgment. Such judgments may, at times, seem contradictory to our guidance because of many factors that are impossible to fully consider by guideline developers. Any clinical decisions should be based on the clinician's experience, local expertise, resource availability, and patient values and preferences. This document is not a rule and should not be construed as establishing a legal standard of care or as encouraging, advocating for, mandating, or discouraging any particular treatment. Our guidelines should not be used in support of medical complaints, legal proceedings, and/or litigation because they were not designed for this purpose.

Pancreatic cancer is a rare but lethal cancer with a lifetime incidence of approximately 1.6%[1,2] and 5-year survival of 10%.[3] Pancreatic cancer accounts for 3% of all newly diagnosed cancers and 8% of all cancer-related deaths in the United States in 2020,[3] and the incidence is anticipated to rise over the next decade.[4] Biologically aggressive behavior, advanced stage at the time of diagnosis, and poor response to oncologic therapies have been proposed as reasons for dismal outcomes in pancreatic cancer.[5]

Diagnosis at earlier stages of disease is associated with improved survival, with 93% 10-year survival among stage 0 cancers and 34% to 39% 5-year survival among stage I cancers.[6,7] However, by the time patients develop symptoms, almost 80% have advanced disease that is inoperable.[8] In 2019, the U.S. Preventive Services Task Force reaffirmed their earlier guidelines by continuing to recommend against screening for pancreatic cancer in average-risk adults.[9] This decision was based in part on the low incidence of pancreatic cancer in the general population. Importantly, the U.S. Preventive Services Task Force specifically stated that those recommendations did not apply to high-risk populations because of inherited genetic susceptibility. Although other guidelines have provided recommendations for individuals with genetic susceptibility, those guidelines have relied primarily on consensus of expert opinion.[10-14]

The aim of this American Society for Gastrointestinal Endoscopy (ASGE) guideline is to provide evidence-based recommendations on screening for pancreatic cancer in individuals with genetic susceptibility. Although pathogenic germline variants in several genes have been associated with increased risk for pancreatic cancer, these guidelines focus on *BRCA1* and *BRCA2* because of their higher prevalence in the population.[15-23] Familial pancreatic cancer (FPC) kindreds were defined as kindreds containing at least a pair of first-degree relatives with pancreatic cancer without an association with a known hereditary cancer syndrome.[24-27] Modeling studies strongly suggest autosomal-dominant inheritance of a rare allele as the likely etiology.[28] Furthermore, most pancreatic cancer screening studies included those with FPC syndrome, and therefore we made screening recommendations for these individuals. Recommendations made in these guidelines should be used in the context of the individual patient and clinical setting, such that the ultimate decision regarding pancreatic cancer screening should be made with consideration of patient values, preferences, and availability of local expertise.

METHODS

This document was prepared by the Standards of Practice Committee of the ASGE and was conceptualized and conducted according to the Grading of Recommendations Assessment, Development and Evaluation (GRADE).[29-31] Evidence was presented to a panel of experts representing various stakeholders including oncology, radiology, genetics, epidemiology, and gastroenterology. Two patient advocates were also included. All panel members were required to disclose potential financial and intellectual conflicts of interest, which were addressed according to ASGE policies. In developing these recommendations, we took into consideration the certainty in the evidence, benefits and harms of different management options, feasibility, patient values and preferences, resources utilization, cost-effectiveness, and health equity. The final wording of the recommendations including direction and strength were approved by all members of the panel and the ASGE governing board. Stronger recommendations are typically stated as "we recommend…," whereas weaker recommendations are indicated by phrases such as "we suggest…."

These guidelines addressed the following clinical questions using the GRADE format:

1. Should individuals at increased risk of pancreatic cancer because of genetic susceptibility undergo screening for pancreatic cancer?
2. Should individuals at increased risk of pancreatic cancer because of genetic susceptibility undergo screening with endoscopic ultrasound EUS or magnetic resonance imaging (MRI)?
3. (a) Should individuals with the *BRCA2* pathogenic variant undergo screening for pancreatic cancer?
   (b) Should individuals with the *BRCA1* pathogenic variant undergo screening for pancreatic cancer?

Relevant clinical outcomes included all-cause mortality, pancreatic cancer mortality, overall yield of screening, detection of surgically resectable and borderline-resectable pancreatic cancer, psychological benefits, and harms. Yield of screening was defined as detection of any high-risk lesions, pancreatic cancer, high-grade dysplasia, and grade III pancreatic intraepithelial neoplasia. Surgically resectable and borderline-resectable pancreatic lesions were defined as any T1-3 and N0-2 pancreatic cancer, high-grade dysplasia, or grade III pancreatic intraepithelial neoplasia. Harms were defined as harms from screening tests, rates of low-yield pancreatic surgery in the screened population, and rates of adverse events from pancreatic cancer surgery resulting from positive screening tests. For the purposes of this document, pancreatic cancer refers to pancreatic ductal adenocarcinoma.

This guideline also addressed the frequency of and starting age at screening using a non-GRADE format for individuals with the following genetic susceptibility conditions: FPC, familial atypical multiple mole melanoma (FAMMM) syndrome, Peutz-Jeghers syndrome, ataxia telangiectasia due to mutation in the ataxia telangiectasia mutated (*ATM*) gene, Lynch syndrome, and hereditary pancreatitis. In making these recommendations, the panel considered available literature and existing guidelines.

SUMMARY OF RECOMMENDATIONS

Details of our literature searches, data analyses, pooled effect estimates, evidence profiles, forest plots, and panel deliberation for each outcome can be found in the methodology and technical review document (this issue). A summary of our final recommendations for screening patients at high risk of pancreatic cancer are listed in Table 1.

Question 1: Should individuals at increased risk of pancreatic cancer because of genetic susceptibility undergo screening for pancreatic cancer?

> ***Recommendation 1.*** **In individuals at increased risk of pancreatic cancer because of genetic susceptibility, we suggest screening for pancreatic cancer compared with no screening** (*conditional recommendation, low quality of evidence*).

Summary of evidence. For this question, we performed a systematic review and meta-analysis. Our search identified 25 studies for inclusion. These studies included individuals with FPC, Peutz-Jeghers syndrome, FAMMM, and Lynch syndrome as well as those with *BRCA1*, *BRCA2*, *ATM,* and *PALB*2 pathogenic variants. Outcomes of interest were all-cause mortality, yield of screening for high-risk lesions, yield of screening for resectable and borderline-resectable lesions, and harms from screening.

We did not find any clinical trials that compared outcomes of screen-detected pancreatic cancers with a control group of patients who did not undergo screening. Two studies compared outcomes of screen-detected pancreatic cancers with historic control subjects and found improved survival in screen-detected pancreatic cancer.[32,33] One study found that 3-year survival was significantly higher in screen-detected cancers when compared with individuals with symptomatic cancers who were noncompliant with screening (85% vs 25%).[32]

For the outcome of cumulative yield of screening for high-risk lesions, our analysis showed a pooled yield of 3.1% (95% confidence interval [CI], 2.2%-4.3%; $P = .02$, $I^2 = 40.5$). For resectable and borderline-resectable lesions, the pooled yield was 2.1% (95% CI, 1.4%-3.1%; $P = .007$ and $I^2 = 45.6$). The proportion of screen-detected cancers that were resectable or borderline-resectable was 60.0% (95% CI, 43.7%-74.4%; $P = .51$ and

TABLE 1. Summary of recommendations

Question	Recommendation and quality of evidence
1	In individuals at increased risk of pancreatic cancer because of genetic susceptibility, we suggest screening for pancreatic cancer compared with no screening (*conditional, low quality*)
2	In individuals at increased risk of pancreatic cancer because of genetic susceptibility, we suggest screening with EUS, EUS alternating with MRI, or MRI based on patient preference and available expertise (*conditional, very low quality*) • EUS may be preferred: as the initial screening test; for patients at very high risk for pancreatic cancer like Peutz-Jeghers syndrome and FAMMM; when EUS can be combined with screening upper endoscopy or colonoscopy (eg, Lynch and Peutz-Jeghers syndrome); when there is a contraindication to MRI (eg, claustrophobia, contrast allergy, implanted metal, and renal failure) • MRI may be preferred: for patients at increased risk of adverse events from anesthesia or invasive procedures; for patients who place a high value on avoiding invasive testing; when MRI may be combined with other imaging (eg, enterography for Peutz-Jeghers syndrome).
3a	In individuals with *BRCA2* pathogenic variant, we suggest screening for pancreatic cancer compared with no screening (*conditional, very low quality*)
3b	In individuals with *BRCA1* pathogenic variant, we suggest screening for pancreatic cancer compared with no screening (*conditional, very low quality*)
4	In individuals at increased risk of pancreatic cancer because of genetic susceptibility, we suggest that annual screening be performed *(conditional, very low quality)*
5	In individuals at increased risk for pancreatic cancer, we suggest the age at which to begin screening should vary by individual genetic condition *(conditional, very low quality)*
6	For each of the following conditions, we recommend the following starting ages:
	(a) *BRCA2* pathogenic variant: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
	(b) *BRCA1* pathogenic variant: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
	(c) *PALB2* pathogenic variant: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
	(d) FPC syndrome: age 50 or 10 years earlier than the youngest relative with pancreatic cancer (screening is recommended for all first-degree relatives of affected family members).
	(e) FAMMM syndrome: age 40 or 10 years earlier than the youngest relative with pancreatic cancer.
	(f) Peutz-Jeghers syndrome: age 35 or 10 years earlier than the youngest relative with pancreatic cancer.
	(g) Heterozygotes for *ATM* pathogenic variant with first- or second-degree relative with pancreatic cancer: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
	(h) Lynch syndrome with first- or second-degree relative with pancreatic cancer: age 50 or 10 years earlier than the youngest relative with pancreatic cancer.
	(i) Autosomal-dominant hereditary pancreatitis: age 40.

ATM, Ataxia-telangiectasia mutated; *EUS*, endoscopic ultrasound; *FAMMM*, familial atypical multiple mole melanoma; *FPC*, familial pancreatic cancer; *MRI*, magnetic resonance imaging.

I^2 = .0). Population-based data show that only 20% of symptomatic cancers were diagnosed when they were resectable or borderline-resectable, whereas 30% were locally advanced and 50% were metastatic.[8] This suggests that screening was associated with a substantial stage shift because almost 2 of 3 screen-detected pancreatic cancers were resectable or borderline-resectable.

Among included studies, no adverse events were reported because of screening EUS or MRI. Although EUS and MRI were safe, these tests can be costly and may result in overdiagnosis.

Considering all patients who underwent screening for pancreatic cancer, in 22 studies, the pooled rate of low-yield pancreatic surgery was low at 2.8% (95% CI, 1.9%-4.1%; P = .003 and I^2 = 51.4). Low-yield surgery was defined as surgery that did not yield cancer, high-grade dysplasia, or grade III pancreatic intraepithelial neoplasia. However, among 181 patients who had pancreatic surgery as a result of screening, the pooled proportion of low-yield surgery was high at 46.6% (95% CI, 34.2-59.4%; P = .15 and I^2 = 26.2), and the pooled rate of adverse events was also high at 19.9% (95% CI, 7.4%-43.4%; P = .05 and I^2 = 49.7). Therefore, the potential harms from screening must be carefully considered when enrolling individuals into a screening program.

On the other hand, pancreatic cancer screening was associated with several psychological benefits based on a systematic review of 7 studies.[34] Screening participants had low-to-moderate levels of pancreatic cancer-related distress at the start, which improved significantly over time. Lastly, several studies reported screening to be cost-effective in high-risk populations.[35-37]

Based on our analysis and panel discussions, we concluded that the benefits of screening for pancreatic cancer in those with genetic susceptibility to pancreatic cancer outweigh the potential risks and made a conditional recommendation for screening. The overall quality of evidence was low. Patients should be counseled about the risks and benefits of screening before screening is initiated.

Question 2: Should individuals at increased risk of pancreatic cancer because of genetic susceptibility undergo screening with EUS or MRI?

Recommendation 2. **In patients at increased risk of pancreatic cancer because of genetic susceptibility, we suggest screening with EUS, EUS alternating with MRI, or MRI based on patient preference and available expertise** (*conditional recommendation, very low quality of evidence*).

- EUS:
  - o May be preferred: as the initial screening test; for patients at very high risk for pancreatic cancer like Peutz-Jeghers syndrome and FAMMM; when EUS can be combined with screening upper endoscopy or colonoscopy (eg, Lynch and Peutz-Jeghers syndrome); when there is a contraindication to MRI (eg, claustrophobia, contrast allergy, implanted metal, and renal failure).
  - o A linear array echoendoscope may be preferable over a radial echoendoscope.
- MRI:
  - o May be preferred: for patients at increased risk of adverse events from anesthesia or endoscopic procedures; for patients who place a high value on avoiding invasive testing; when MRI may be combined with other imaging (eg, enterography for Peutz-Jeghers syndrome).
  - o A contrast-enhanced exam using intravenous agents is preferred, a minimum of 1.5-T magnet should be applied using phased-array coils, and a 3-T magnet may have an additional advantage in detection of small pancreatic lesions because of superior soft tissue resolution.

Summary of evidence. We conducted a meta-analysis based on the systematic review performed for Question 1. Of the 25 included studies, 6 studies (n = 338) used only EUS, 5 studies (n = 455) used only MRI, and 14 studies (n = 2460) used a combination of EUS and MRI. Outcomes of interest for this question were yield of screening for high-risk lesions, high-risk resectable lesions, and harms from screening EUS and MRI. The pooled cumulative yield of screening for high-risk lesions did not differ between EUS and MRI (4.0% [95% CI, 1.7%-9.1%], P = .18, I^2 = 34.4 for EUS; 2.4% [95% CI, 1.0%-5.4%], P = .21, I^2 = 31.0 for MRI; and 3.1% [95% CI, 2.1%-4.6%], P = .022, I^2 = 48.4 for a combination of EUS and MRI). The pooled yield of screening for high-risk *resectable* lesions also did not differ among the 2 modalities (3.9% [95% CI, 1.7%-8.5%], P = .18, I^2 = 34.4 for EUS; 1.8% [95% CI, .8%-4.0%], P = .38, I^2 = 5.4 for MRI; and 1.7% [95% CI, 1.0%-3.0%], P = .006, I^2 = 55.9 for a combination of EUS and MRI). Although there was a trend toward EUS demonstrating a higher diagnostic yield when compared with MRI, this did not reach statistical significance. There may be 2 possible explanations for this trend. First, referral bias may be present because patients at higher risk for pancreatic cancer may be more likely to undergo EUS. Second, EUS may be more sensitive than MRI at detecting small solid pancreatic lesions as demonstrated in 2 studies where almost all solid pancreatic cancers were only found by EUS.[38,39]

Six studies (n = 350) reporting on adverse outcomes from screening EUS or MRI found none.[20,36,40-43] We rated down the evidence for imprecision. Thus, the overall quality of evidence was very low.

When EUS is performed for screening, a linear-array echoendoscope may be preferable because a randomized controlled study showed that it detected more pancreas lesions than a radial echoendoscope (82% vs 67%, P < .001).[44] The choice of echoendoscope should also take into consideration the endoscopist's training and experience. When MRI is performed for screening, we suggest the study should be performed with and without intravenous contrast, using at minimum a 1.5-T magnet.[45,46] A 3-T magnet may provide additional advantage in detection of small pancreatic lesions because of superior soft tissue resolution.[47]

Question 3a: Should individuals with *BRCA2* pathogenic variant undergo screening for pancreatic cancer?

Recommendation 3a. **In individuals with *BRCA2* pathogenic variant, we suggest screening for pancreatic cancer compared with no screening** (*conditional recommendation, very low quality of evidence*).

Summary of evidence. For this question, we conducted a systematic review and meta-analysis, with the help of an independent, expert biostatistician and cancer epidemiologist (T.R.R.). We aimed to determine the risk of pancreatic cancer in individuals with *BRCA1/2* pathogenic variants. A lifetime risk of pancreatic cancer >5% or a relative risk >5 has been proposed as the threshold to identify individuals who are high risk for pancreatic cancer[48] and was adopted as a threshold for our panel.

Our search resulted in 11 studies (n = 62,269). We assessed the risk of pancreatic cancer in these patients using 2 methods: relative risk (RR) and standardized incidence rate (SIR). The RR of pancreatic cancer in *BRCA2* was reported in 5 studies, and the pooled estimate of RR for pancreatic cancer was 5.1 (95% CI, 3.9-6.3; P = .41, I^2 = .0). Using this estimate, we computed the absolute lifetime risk of pancreatic cancer to age 80 to be 5.2%.[49-53] Three studies reported on SIR for pancreatic cancer in *BRCA2*, with a pooled estimate of SIR for pancreatic cancer of 7.2 (95% CI, 1.5-13.0; P = .001, I^2 = 85.0). Using this

estimate, we computed the cumulative lifetime risk of pancreatic cancer to age 80 to be 7.4%.[54-56]

There was no significant difference between men and women for the risk of pancreatic cancer. Furthermore, reporting on family history of pancreatic cancer in *BRCA2* was limited.

We did not find any studies that reported on all-cause or pancreatic cancer–related mortality in screen-detected pancreatic cancer in *BRCA2*. We estimated the yield of screening for high-risk lesions in *BRCA1/2* using a meta-analysis on pancreatic cancer screening studies (see Questions 1 and 2). Of the 25 studies, 8 (n = 375 patients) reported on *BRCA1/2*. The yield of screening was not reported separately for *BRCA1* and *BRCA2*. The pooled yield of screening for these individuals was 8.6% (95% CI, 4.5%-16.0%; $P = .21$, $I^2 = 27.4$). No information on harms of screening specific to *BRCA1/2* was available. We rated down the evidence for imprecision. Thus, the overall quality of evidence was very low. In balancing the desirable and undesirable effects of screening and considering all possible outcomes, the panel made a conditional recommendation for pancreatic cancer screening in patients with *BRAC2* pathogenic variant.

Question 3b: Should individuals with a *BRCA1* pathogenic variant undergo screening for pancreatic cancer?

> ***Recommendation 3b.*** **In individuals with *BRCA1* pathogenic variant, we suggest screening for pancreatic cancer compared with no screening** (*conditional recommendation, very low quality of evidence*).

Summary of evidence. We used the aforementioned systematic review for this question. We did not find any studies that reported on all-cause or pancreatic cancer–related mortality in screen-detected pancreatic cancer in *BRCA1*. The RR of pancreatic cancer in *BRCA1* was reported in 4 studies, and the pooled estimate of RR for pancreatic cancer was 1.9 (95% CI, 1.0-2.8; $P = .28$, $I^2 = 21.0$). When this estimate was used, the cumulative lifetime risk of pancreatic cancer to age 80 was 3.5%.[51-53,57] Three studies reported on the SIR of pancreatic cancer in *BRCA1*, and the pooled estimate of SIR for pancreatic cancer was 3.7 (95% CI, 2.5-4.8; $P = .45$, $I^2 = .0$).[54-56] Using this estimate, we computed the cumulative lifetime risk of pancreatic cancer to age 80 to be 3.8%. We rated down the evidence for imprecision. Thus, the overall quality of evidence was very low. As with *BRCA2*, there was no significant difference between men and women for the risk of pancreatic cancer, and there was limited reporting on family history of pancreatic cancer.

As noted, the magnitude of association between pancreatic cancer and *BRCA1* was lower when compared with *BRCA2* and did not appear to cross our threshold of 5% lifetime risk. Several potential explanations for this effect were considered by the panel in depth:

- Fewer individuals with *BRCA1* pathogenic variants were included in studies, and very few *BRCA1*-related pancreatic cancers were noted in these studies. Therefore, this low rate maybe because of selection bias and not a true biologic effect.
- Before 2012, the association between pancreatic cancer and *BRCA1* was largely ignored, thus further limiting long-term data on the subject.
- Based on our meta-analysis, we can place high confidence in our finding that carriers of *BRCA1/2* were at increased risk of pancreatic cancer. However, there is less confidence in the precision regarding the magnitude of risk. Therefore, even though the SIR was 3.7%, the true risk could be higher if more patients were included.
- The CI was up to 4.8%, which overlapped with the CI for *BRCA2* estimates. Therefore, separating the recommendations for *BRCA1* and *BRCA2* would not be supported by the current evidence.
- There are no differences in response to chemotherapy between *BRCA1*- and *BRCA2*-related pancreatic cancers.

After considering these factors, the panel made a conditional recommendation for screening in *BRCA1*, despite the lifetime risk of pancreatic cancer not reaching the 5% threshold. Given the potentially lower rate of pancreatic cancer in this patient population, clinicians should initiate screening with caution. Patients should be made aware of their risk of developing pancreatic cancer and the potential harms from screening. Screening may not be warranted in patients who place a high value on avoiding harms from medical interventions.

BRCA1/2 germline pathogenic variants affect up to 7% of all patients diagnosed with pancreatic cancer.[58] Our analysis did not reveal any subgroups of the *BRCA1/2* population who were at increased risk for pancreatic cancer. We did not find any large studies that included data on family history of pancreatic cancer, and therefore the influence of this variable on pancreatic cancer risk could not be determined. Additionally, risk estimates for pancreatic cancer reported above were based on populations that included those with and without a family history of pancreatic cancer, and most patients with *BRCA1/2*-related pancreatic cancer did not have a family history of pancreatic cancer. Several studies found no association between family history of cancer and increased risk of pancreatic cancer in *BRCA1/2*.[59,60] In a study of 71 patients with pancreatic cancer and *BRCA1* (n = 21), *BRCA2* (n = 49), or both (n = 1), a family history of pancreatic cancer (first- or second-degree relative) was noted in only 33% of pancreatic cancer patients, suggesting that almost 2 in 3 pancreatic cancers would have been missed had screening been

limited to only those with a family history of pancreatic cancer.[61] We also acknowledged other limitations of relying on family history including incompleteness and inaccuracies of family history records, small families, and situations in which many family members died prematurely in wars or natural disasters.[62-64] Therefore, the panel did not recommend that individuals with *BRCA1/2* pathogenic variants be required to have a family history of pancreatic cancer to be considered for pancreatic cancer screening.

Of note, tumors with deficient homologous recombination because of abnormalities such as *BRCA1/2* are responsive to both platinum-based chemotherapeutic regimens and poly (ADP-ribose) polymerase inhibitors.[17,65-67] With these regimens, increased rates of pathologic response in patients with borderline-resectable pancreatic cancers and prolonged survival in those with advanced disease have been reported,[16,17,67] which further supports our conditional recommendation for screening in this patient population.

TIMING AND FREQUENCY OF SCREENING

Question 4: How often should screening for pancreatic cancer be performed in individuals who are at increased risk of pancreatic cancer because of genetic susceptibility?

Recommendation 4. **In individuals at increased risk of pancreatic cancer because of genetic susceptibility, we suggest that annual screening be performed** (*conditional recommendation, very low quality of evidence*).

Summary of evidence. Based on our systematic review of the literature, we found no studies that assessed patient outcomes based on screening frequency. To determine the frequency of screening, we relied on existing practices on screening frequency and models of pancreatic cancer progression times. We reviewed screening intervals in studies included in our meta-analysis (Question 1). Of the 25 included studies, 9 reported screening intervals, of which 8 performed screening annually or sooner.[32,36,41,68-73] We therefore concluded that most centers perform annual screening. We then reviewed models of pancreatic cancer progression times. We found 1 tumor growth model based on mean differences in age between patients with early and advanced tumors and a second model based on analysis of imaging studies done before the diagnosis of pancreatic cancer.[74,75] Both models predicted that the progression from localized to advance stage could occur within 1 year.[74,75] Based on the above evidence, we recommend annual screening for pancreatic cancer.

Question 5: At what age should screening for pancreatic cancer start in individuals who are at increased risk of pancreatic cancer because of genetic susceptibility?

Recommendation 5. **In individuals at increased risk for pancreatic cancer because of genetic susceptibility, we suggest that the starting age for screening should vary based on the underlining genetic condition** (*conditional recommendation, very low quality of evidence*).

Summary of evidence. For this question, we again used the RR > 5 or lifetime risk of pancreatic cancer > 5% threshold, which has been adopted by other guidelines[10-13] and found to be cost-effective,35 to define populations at increased risk of pancreas cancer. [35] We reviewed the literature, and based on genetic susceptibility to pancreatic cancer, we identified all patient groups who met this threshold. We also reviewed the patient populations enrolled in the 25 studies that were included our meta-analysis (Question 1) to identify high-risk conditions. We did not find any studies that reported on mortality or yield of screening based on age of screened participants. Based on best available evidence, we determined that screening should` start at an age of 1 standard deviation below the reported mean age of cancer diagnosis for that population. For genetic susceptibility conditions like Peutz-Jeghers syndrome and FAMMM that conferred a ≥10 RR of pancreatic cancer, we determined that screening should start at age 2 standard deviation below the reported mean age of pancreatic cancer diagnosis for that population. Our recommendations on age to begin screening are summarized in Table 1.

Diabetes, older age, cigarette smoking, obesity, or a history of chronic pancreatitis increase the risk of developing pancreatic cancer but to a lesser degree than genetic susceptibility conditions mentioned above.[76-80] These conditions were outside the purview of this guideline but were addressed by the 2019 U.S. Preventive Services Task Force guidelines.[9] The U.S. Preventive Services Task Force did not recommended pancreatic cancer screening for asymptomatic persons who have these risk factors. Patients with a family history of pancreatic cancer who do not meet criteria for FPC are at an approximately 2-fold increased risk of developing pancreatic cancer.[81,82] The degree of relatedness and age at onset of pancreatic cancer in the index patient does not appear to affect pancreatic cancer risk. Pancreatic cancer screening for these patients is also generally not recommended.

FUTURE DIRECTIONS

Our systematic literature review highlighted several areas in need of more data to inform pancreatic cancer

screening in high-risk populations. Future studies should address the following:

1. *Role of other risk factors.* Age, male gender, obesity, smoking, and alcohol are known risk factors for pancreatic cancer. The interaction between these risk factors in individuals with genetic susceptibility to pancreatic cancer are unknown. Cancer models that take these and other risk factors into account are needed to identify those who are most likely to benefit from screening.
2. *Biomarkers.* Although EUS and MRI are effective tools to diagnose early-stage pancreatic cancer, neither modality can reliably diagnose pancreatic cancer precursors like high-grade pancreatic intraepithelial neoplasia. Furthermore, these tests are expensive, require significant equipment and expertise, and are not widely available. For population-level screening to be possible, noninvasive biomarkers that can accurately identify precursor lesions and early-stage pancreatic cancer will be essential.
3. *Circulating tumor cells.* Circulating tumor cells and DNA may allow for diagnosis of early-stage pancreatic cancer; however, these techniques need to be validated in large studies on diverse patient populations.
4. *Management after normal screening examination.* More outcomes data are needed to determine whether those with a normal baseline screening examination or multiple normal screening examinations can safely prolong the screening interval.

What Is New

These guidelines suggest that all patients with *BRCA1/2* pathogenic variant, regardless of family history of pancreatic cancer, should undergo screening for pancreatic cancer. Previous guidelines limited screening to those with a family history of pancreatic cancer.

SUMMARY

These ASGE guidelines use the best available evidence to make recommendations for pancreatic cancer screening for individuals at increased risk of pancreatic cancer because of genetic susceptibility. When compared with symptom-detected pancreatic cancers, screen-detected pancreatic cancers are more likely to be diagnosed at an earlier stage and may have superior outcomes. Our guidelines suggest annual screening with EUS, MRI, or a combination of these modalities. The age to start screening should depend on the genetic condition. These guidelines focus on *BRCA1/2*, acknowledging the recent development of effective chemotherapy regimens for *BRCA1/2*-related cancer. Low-yield pancreatic surgery and adverse events from pancreatic surgery that is performed based on results of screening tests constitute the harms of pancreatic cancer screening and should be taken into account before initiating a screening program. Patients should be carefully counseled regarding the benefits and harms of screening in the context of their values and preferences before they are enrolled in a screening program.

GUIDELINE UPDATE

ASGE guidelines are reviewed for updates approximately every 5 years, or in the event that new data may influence a recommendation. Updates follow the same ASGE guideline development process.

DISCLOSURE

The following authors disclosed financial relationships: M. Sawhney: Stockholder with Allurion Technology, Inc; research support and food and beverage from Olympus Corporation of the Americas and Boston Scientific Corporation. N. Thosani: Consultant for and has received travel compensation and food and beverage from Boston Scientific Corporation; consultant for TaeWoong Medical; consultant for and has received research support and food and beverage from Pentax of America, Inc; receives royalties from UpToDate; has received research support and food and beverage from Endogastric Solutions; speaker for and has received food and beverage from AbbVie, Inc; advisory board for ColubrisMX, Inc. S. Wani: Consultant for and has received food and beverage from Boston Scientific Corporation; consultant for Medtronic, Exact Sciences, and Interpace; advisory board for Cernostics. M. Canto: Consultant for Exact Sciences; has received research support and food and beverage from Endogastric Solutions and Pentax of America, Inc; has received food and beverage from Pentax of America, Inc, Boston Scientific Corporation, and AbbVie, Inc; receives royalties from UpToDate. D. Fishman: Food and beverage compensation from AbbVie, Inc, and Boston Scientific Corporation. T. Golan: Consultant/advisor for AbbVie, Inc, Teva Pharmaceutical Industries Ltd, and Bayer AG; speaker for AbbVie, Inc, Bioline, and Roche; consultant for and research support from AstraZeneca and Merck Sharp & Dohme Corp. M. Hidalgo: Stock and other ownership interests in Nelum Corp and Champions Oncology; stock and honoraria from Agenus and InxMed; research support from BiolineRx, Erytech Pharma, BioExcell, and TOP Alliance Biosciences; travel compensation from Bayer HealthCare Pharmaceuticals, Inc; food and beverage compensation from Boehringer Ingelheim Pharmaceuticals, Inc, Pfizer, Inc, and Sunovion Pharmaceuticals, Inc. D. Sahani: Travel compensation and food and beverage from GE Healthcare; food and beverage compensation from Abbott Laboratories. All other authors disclosed no financial relationships.

ACKNOWLEDGMENTS

We thank Emily Groesbeck and Wenora Johnson, 2 patient representatives from the Facing Hereditary Cancer Empowered (FORCE), an advocacy organization for families facing hereditary cancers, for participating in our panel as well as Dr Anne Marie Lennon, Dr Emad Qayed, Dr Ajay Pal Singh, and Dr Jenifer Lightdale for their review of this document.

This guideline was funded exclusively by the American Society for Gastrointestinal Endoscopy; no outside funding was received to support the development of this guideline.

REFERENCES

1. SEER cancer stat facts: pancreatic cancer. Available at https://seer.cancer.gov/statfacts/html/pancreas.html. Accessed July 15, 2021.
2. American Cancer Society. Key statistics for pancreatic cancer. Available at https://www.cancer.org/cancer/pancreatic-cancer/about/key-statistics.html. Accessed July 15, 2021.
3. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2020. CA Cancer J Clin 2020;70:7-30.
4. Rahib L, Smith BD, Aizenberg R, et al. Projecting cancer incidence and deaths to 2030: the unexpected burden of thyroid, liver, and pancreas cancers in the United States. Cancer Res 2014;74:2913-21.
5. Kamisawa T, Wood LD, Itoi T, et al. Pancreatic cancer. Lancet 2016;388:73-85.
6. van Roessel S, Kasumova GG, Verheij J, et al. International validation of the eighth edition of the American Joint Committee on Cancer (AJCC) TNM staging system in patients with resected pancreatic cancer. JAMA Surg 2018;153:e183617.
7. Kanno A, Masamune A, Hanada K, et al. Multicenter study of early pancreatic cancer in Japan. Pancreatology 2018;18:61-7.
8. Henrikson NB, Bowles EJA, Blasi PR, et al. U.S. Preventive Services Task Force evidence syntheses, formerly systematic evidence reviews. Screening for pancreatic cancer: a systematic evidence review for the U.S. Preventive Services Task Force. Rockville, MD: Agency for Healthcare Research and Quality; 2019.
9. Owens DK, Davidson KW, Krist AH, et al. Screening for pancreatic cancer: US Preventive Services Task Force reaffirmation recommendation statement. JAMA 2019;322:438-44.
10. Goggins M, Overbeek KA, Brand R, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut 2020;69:7-17.
11. Aslanian HR, Lee JH, Canto MI. AGA clinical practice update on pancreas cancer screening in high-risk individuals: expert review. Gastroenterology 2020;159:358-62.
12. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110:223-62;quiz 263.
13. Săftoiu A, Hassan C, Areia M, et al. Role of gastrointestinal endoscopy in the screening of digestive tract cancers in Europe: European Society of Gastrointestinal Endoscopy (ESGE) position statement. Endoscopy 2020;52:293-304.
14. Daly MB, Pal T, Berry MP, et al. Genetic/familial high-risk assessment: breast, ovarian, and pancreatic, Version 2.2021, NCCN Clinical Practice Guidelines in Oncology. J Natl Compr Canc Netw 2021;19:77-102.
15. Dudley B, Karloski E, Monzon FA, et al. Germline mutation prevalence in individuals with pancreatic cancer and a history of previous malignancy. Cancer 2018;124:1691-700.
16. Golan T, Barenboim A, Lahat G, et al. Increased rate of complete pathologic response after neoadjuvant FOLFIRINOX for *BRCA* mutation carriers with borderline resectable pancreatic cancer. Ann Surg Oncol 2020;27:3963-70.
17. Golan T, Hammel P, Reni M, et al. Maintenance olaparib for germline *BRCA*-mutated metastatic pancreatic cancer. N Engl J Med 2019;381:317-27.
18. Grant RC, Selander I, Connor AA, et al. Prevalence of germline mutations in cancer predisposition genes in patients with pancreatic cancer. Gastroenterology 2015;148:556-64.
19. Hu C, LaDuca H, Shimelis H, et al. Multigene hereditary cancer panels reveal high-risk pancreatic cancer susceptibility genes. JCO Precis Oncol. Epub 2018 Jul 25.
20. Lucas AL, Frado LE, Hwang C, et al. *BRCA1* and *BRCA2* germline mutations are frequently demonstrated in both high-risk pancreatic cancer screening and pancreatic cancer cohorts. Cancer 2014;120:1960-7.
21. Salo-Mullen EE, O'Reilly EM, Kelsen DP, et al. Identification of germline genetic mutations in patients with pancreatic cancer. Cancer 2015;121:4382-8.
22. Yurgelun MB, Chittenden AB, Morales-Oyarvide V, et al. Germline cancer susceptibility gene variants, somatic second hits, and survival outcomes in patients with resected pancreatic cancer. Genet Med 2019;21:213-23.
23. Golan T, Kindler HL, Park JO, et al. Geographic and ethnic heterogeneity of germline *BRCA1* or *BRCA2* mutation prevalence among patients with metastatic pancreatic cancer screened for entry into the POLO trial. J Clin Oncol 2020;38:1442-54.
24. Klein AP, Brune KA, Petersen GM, et al. Prospective risk of pancreatic cancer in familial pancreatic cancer kindreds. Cancer Res 2004;64:2634-8.
25. Tersmette AC, Petersen GM, Offerhaus GJ, et al. Increased risk of incident pancreatic cancer among first-degree relatives of patients with familial pancreatic cancer. Clin Cancer Res 2001;7:738-44.
26. Copur MS, Talmon GA, Wedel W, et al. Hereditary vs familial pancreatic cancer: associated genetic syndromes and clinical perspective. Oncology 2020;34:196-201.
27. Petersen GM. Familial pancreatic cancer. Semin Oncol 2016;43:548-53.
28. Klein AP, Beaty TH, Bailey-Wilson JE, et al. Evidence for a major gene influencing risk of pancreatic cancer. Genet Epidemiol 2002;23:133-49.
29. ASGE Standards of Practice Committee; Qumseya B, Sultan S, et al. ASGE guideline on screening and surveillance of Barrett's esophagus. Gastrointest Endosc 2019;90:335-59.
30. Standards of Practice Committee; Wani S, Qumseya B, et al. Endoscopic eradication therapy for patients with Barrett's esophagus-associated dysplasia and intramucosal cancer. Gastrointest Endosc 2018;87:907-31.
31. Guyatt GH, Oxman AD, Vist GE, et al. GRADE: an emerging consensus on rating quality of evidence and strength of recommendations. BMJ 2008;336:924-6.
32. 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;155:740-51.
33. Vasen H, Ibrahim I, Robbers K, 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;34:2010-9.
34. Cazacu IM, Luzuriaga Chavez AA, Saftoiu A, et al. Psychological impact of pancreatic cancer screening by EUS or magnetic resonance imaging in high-risk individuals: a systematic review. Endosc Ultrasound 2019;8:17-24.
35. Corral JE, Das A, Bruno MJ, et al. Cost-effectiveness of pancreatic cancer surveillance in high-risk individuals: an economic analysis. Pancreas 2019;48:526-36.
36. Joergensen MT, Gerdes AM, Sorensen J, et al. Is screening for pancreatic cancer in high-risk groups cost-effective? Experience from a Danish national screening program. Pancreatology 2016;16:584-92.

37. Bruenderman E, Martin RC 2nd. A cost analysis of a pancreatic cancer screening protocol in high-risk populations. Am J Surg 2015;210:409-16.
38. Harinck F, Konings IC, Kluijt I, et al. A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. Gut 2016;65:1505-13.
39. Paiella S, Capurso G, Cavestro GM, et al. Results of first-round of surveillance in individuals at high-risk of pancreatic cancer from the AISP (Italian Association for the Study of the Pancreas) Registry. Am J Gastroenterol 2019;114:665-70.
40. Verna EC, Hwang C, Stevens PD, et al. Pancreatic cancer screening in a prospective cohort of high-risk patients: a comprehensive strategy of imaging and genetics. Clin Cancer Res 2010;16:5028-37.
41. Mocci E, Guillen-Ponce C, Earl J, et al. PanGen-Fam: Spanish registry of hereditary pancreatic cancer. Eur J Cancer 2015;51:1911-7.
42. Poley JW, Kluijt I, Gouma DJ, et al. The yield of first-time endoscopic ultrasonography in screening individuals at a high risk of developing pancreatic cancer. Am J Gastroenterol 2009;104:2175-81.
43. Lachter J, Rosenberg C, Hananiya T, et al. Screening to detect precursor lesions of pancreatic adenocarcinoma in high-risk individuals: a single-center experience. Ramb Maim Med J 2018;9:4.
44. Shin EJ, Topazian M, Goggins MG, et al. Linear-array EUS improves detection of pancreatic lesions in high-risk individuals: a randomized tandem study. Gastrointest Endosc 2015;82:812-8.
45. Burk KS, Lo GC, Gee MS, et al. Imaging and screening of pancreatic cancer. Radiol Clin North Am 2017;55:1223-34.
46. Corrias G, Raeside MC, Agostini A, et al. Pilot study of rapid MR pancreas screening for patients with BRCA mutation. Eur Radiol 2019;29:3976-85.
47. Barnes CA, Krzywda E, Lahiff S, et al. Development of a high risk pancreatic screening clinic using 3.0 T MRI. Fam Cancer 2018;17:101-11.
48. Canto MI, Harinck F, Hruban RH, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut 2013;62:339-47.
49. Easton D. Cancer risks in *BRCA2* mutation carriers: the breast cancer linkage consortium. J Natl Cancer Inst 1999;91:1310-6.
50. Van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, et al. Cancer risks in *BRCA2* families: estimates for sites other than breast and ovary. J Med Genet 2005;42:711-9.
51. Risch HA, McLaughlin JR, Cole DEC, et al. Population *BRCA1* and *BRCA2* mutation frequencies and cancer penetrances: a kin-cohort study in Ontario, Canada. J Natl Cancer Inst 2006;98:1694-706.
52. Moran A, O'Hara C, Khan S, et al. Risk of cancer other than breast or ovarian in individuals with *BRCA1* and *BRCA2* mutations. Fam Cancer 2012;11:235-42.
53. Hu C, Hart SN, Polley EC, et al. Association between inherited germline mutations in cancer predisposition genes and risk of pancreatic cancer. JAMA 2018;319:2401-9.
54. Iqbal J, Ragone A, Lubinski J, et al. The incidence of pancreatic cancer in *BRCA1* and *BRCA2* mutation carriers. Br J Cancer 2012;107:2005-9.
55. Mocci E, Milne RL, Mendez-Villamil EY, et al. Risk of pancreatic cancer in breast cancer families from the breast cancer family registry. Cancer Epidemiol Biomark Prevent 2013;22:803-11.
56. Mersch J, Jackson MA, Park M, et al. Cancers associated with *BRCA1* and *BRCA2* mutations other than breast and ovarian. Cancer 2015;121:269-75.
57. Thompson D, Easton DF. Cancer incidence in *BRCA1* mutation carriers. J Natl Cancer Inst 2002;94:1358-65.
58. Stoffel EM, McKernin SE, Brand R, et al. Evaluating susceptibility to pancreatic cancer: ASCO provisional clinical opinion. J Clin Oncol 2019;37:153-64.
59. Chahla E, Cheesman A, Mahon SM, et al. Frequency and significance of abnormal pancreatic imaging in patients with *BRCA1* and *BRCA2* genetic mutations. Scientifica (Cairo) 2016;2016:5619358.
60. Roch AM, Schneider J, Carr RA, et al. Are BRCA1 and BRCA2 gene mutation patients underscreened for pancreatic adenocarcinoma? J Surg Oncol 2019;119:777-83.
61. Golan T, Sella T, O'Reilly EM, et al. Overall survival and clinical characteristics of *BRCA* mutation carriers with stage I/II pancreatic cancer. Br J Cancer 2017;116:697-702.
62. Sijmons RH, Boonstra AE, Reefhuis J, et al. Accuracy of family history of cancer: clinical genetic implications. Eur J Hum Genet 2000;8:181-6.
63. Murff HJ, Byrne D, Syngal S. Cancer risk assessment: quality and impact of the family history interview. Am J Prev Med 2004;27:239-45.
64. Church J, McGannon E. Family history of colorectal cancer: How often and how accurately is it recorded? Dis Colon Rectum 2000;43:1540-4.
65. Lord CJ, Ashworth A. PARP inhibitors: synthetic lethality in the clinic. Science 2017;355:1152-8.
66. Golan T, Kanji ZS, Epelbaum R, et al. Overall survival and clinical characteristics of pancreatic cancer in BRCA mutation carriers. Br J Cancer 2014;111:1132-8.
67. O'Reilly EM, Lee JW, Zalupski M, et al. Randomized, multicenter, phase II trial of gemcitabine and cisplatin with or without veliparib in patients with pancreas adenocarcinoma and a germline *BRCA/PALB2* mutation. J Clin Oncol 2020;38:1378-88.
68. Potjer TP, Schot I, Langer P, et al. Variation in precursor lesions of pancreatic cancer among high-risk groups. Clin Cancer Res 2013;19:442-9.
69. Al-Sukhni W, Borgida A, Rothenmund H, et al. Screening for pancreatic cancer in a high-risk cohort: an eight-year experience. J Gastrointest Surg 2012;16:771-83.
70. Del Chiaro M, Verbeke CS, Kartalis N, et al. Short-term results of a magnetic resonance imaging-based swedish screening program for individuals at risk for pancreatic cancer. JAMA Surg 2015;150:512-8.
71. Saldia A, Olson SH, Nunes P, et al. Outcome of pancreatic cancer surveillance among high-risk individuals tested for germline mutations in *BRCA1* and *BRCA2*. Cancer Prev Res (Phila) 2019;12:599-608.
72. Overbeek KA, Levink IJ, Konings IC, et al. 12 Years of prospective pancreatic cancer surveillance: results of the Dutch nationwide program in high-risk individuals. Gastroenterology 2019;156(6 Suppl 1):S-756.
73. Sheel ARG, Harrison S, Sarantitis I, et al. Identification of cystic lesions by secondary screening of familial pancreatic cancer (FPC) kindreds is not associated with the stratified risk of cancer. Am J Gastroenterol 2019;114:155-64.
74. Yu J, Blackford AL, Dal Molin M, et al. Time to progression of pancreatic ductal adenocarcinoma from low-to-high tumour stages. Gut 2015;64:1783-9.
75. Gangi S, Fletcher JG, Nathan MA, et al. Time interval between abnormalities seen on CT and the clinical diagnosis of pancreatic cancer: retrospective review of CT scans obtained before diagnosis. AJR Am J Roentgenol 2004;182:897-903.
76. Lynch SM, Vrieling A, Lubin JH, et al. Cigarette smoking and pancreatic cancer: a pooled analysis from the pancreatic cancer cohort consortium. Am J Epidemiol 2009;170:403-13.
77. Farrow DC, Davis S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. Int J Cancer 1990;45:816-20.
78. Huxley R, Ansary-Moghaddam A, Berrington de González A, et al. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. Br J Cancer 2005;92:2076-83.
79. Michaud DS, Giovannucci E, Willett WC, et al. Physical activity, obesity, height, and the risk of pancreatic cancer. JAMA 2001;286:921-9.
80. Lowenfels AB, Maisonneuve P, Cavallini G, et al. Pancreatitis and the risk of pancreatic cancer. International Pancreatitis Study Group. N Engl J Med 1993;328:1433-7.
81. Permuth-Wey J, Egan KM. Family history is a significant risk factor for pancreatic cancer: results from a systematic review and meta-analysis. Fam Cancer 2009;8:109-17.

82. Brune KA, Lau B, Palmisano E, et al. Importance of age of onset in pancreatic cancer kindreds. J Natl Cancer Inst 2010;102:119-26.

Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; ATM, ataxia-telangiectasia mutated; CI, confidence interval; EUS, endoscopic ultrasound; FAMMM, familial atypical multiple mole melanoma; FPC, familial pancreatic cancer; GRADE, Grading of Recommendations Assessment, Development and Evaluation; MRI, magnetic resonance imaging; RR, relative risk; SIR, standardized incidence rate.

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0016-5107/$36.00
https://doi.org/10.1016/j.gie.2021.12.001
Received November 24, 2021. Accepted December 2, 2021.

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