Communication from the ASGE Standards of Practice Committee

GUIDELINE

ASGE American Society for Gastrointestinal Endoscopy

American Society for Gastrointestinal Endoscopy guideline on screening for pancreatic cancer in individuals with genetic susceptibility: methodology and review of evidence

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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 the 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.

The American Society for Gastrointestinal Endoscopy (ASGE) Standards of Practice Committee has developed guidelines for pancreatic cancer screening in individuals at increased risk of pancreatic cancer because of genetic susceptibility. These guidelines follow the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology.[1-3] In formulating these guidelines, we conducted extensive literature reviews, including 2 formal systematic reviews of the literature, and meta-analyses. To make all the information we collected and analyzed readily assessable, this guideline is presented in 2 documents. This document details guideline methodology including formulation of clinical questions, literature searches, data analyses, panel composition, evidence profiles, and other considerations like cost-effectiveness, patient preferences, and health equity. For each clinical question, this document includes outcomes of interest, pooled effect estimates, and evidence that was considered by the panel in making final recommendations. The "Summary and Recommendations" is published separately and provides a summary of our findings and final recommendations (this issue).

METHODS

Formulation of clinical questions

Our guideline addressed 3 questions using GRADE methodology (Table 1). For these questions we followed the PICO format: P, population in question; I, intervention; C, comparator; and O, outcomes of interest. For all clinical questions, potentially relevant patient-important outcomes were identified a priori and rated from "critical" to "important" through a consensus process. This guideline also addressed additional questions regarding frequency and timing of screening (Table 2).

Literature search and study selection criteria

To inform the guideline panel, 2 comprehensive literature searches were performed by a medical librarian using

TABLE 1. Summary of population, intervention, comparator, and outcomes questions

Question	Population	Intervention	Comparator	Outcomes	Rating
1	Individuals at increased risk of pancreatic cancer because of genetic susceptibility	Screening	No screening	All-cause mortality	Critical
2	Individuals at increased risk of pancreatic cancer because of genetic susceptibility undergoing screening	Magnetic resonance imaging	EUS	Pancreatic cancer mortality	Critical
3a	Individuals with *BRCA2* pathogenic variant*	Screening	No screening	Cumulative yield of screening	Critical
3b	Individuals with *BRCA1* pathogenic variant*	Screening	No screening	Detection of resectable and borderline-resectable lesions	Important
				Psychological benefits	Important
				Harms	Critical

*For questions 3a and 3b, we also evaluated cumulative lifetime risk of pancreatic cancer.

Ovid MEDLINE, EMBASE, and Wiley Cochrane. The searches were limited to English-language articles with animal studies excluded. The searches were divided into 2 broad categories:

1. *Screening for pancreatic cancer in populations at high risk because of genetic mutations.* We identified an existing meta-analysis on this topic[4] and performed an updated literature search. We used Ovid MEDLINE and EMBASE from January 2017 through March 2020. We used major search terms and subheadings including "pancreas cancer," pancreas neoplasm," "screening," "population surveillance," "early detection," "endoscopic ultrasound," and "magnetic resonance imaging" (Appendix 1, available online at www.giejournal.org).
2. *Risk of pancreatic adenocarcinoma among individuals with* BRCA1, BRCA2, *and* PALB2 *pathogenic variants.* We used Ovid MEDLINE from 1946 and EMBASE from 1988 to December 2019. We used major search terms and subheadings including "*BRCA1*," "*BRCA2*," "*PALB2*," "hereditary breast and ovarian cancer syndrome," "fanconi anemia," "pancreas cancer," pancreas neoplasm," and "pancreas tumor" (Appendix 1).

For each PICO question, a literature search for existing systematic reviews and meta-analyses was also performed. If none was identified, a full systematic review and meta-analysis (when possible) was conducted using the recommendations of the Preferred Reporting Items for Systematic Reviews and Meta-analyses criteria.[5] Citations were imported into EndNote (Thompson Reuters, Philadelphia, Pa, USA), and duplicates were removed. The EndNote library was then uploaded into Covidence (www.covidence.org). Studies were first screened by title and abstract and then by full text by 2 independent reviewers (D.S.F. and R.S.K.), and all conflicts were resolved by consensus. Exclusion criteria for reviewed studies included wrong disease, wrong study population, wrong outcome, or wrong study design. When applicable, available systematic reviews and meta-analyses were updated based on literature review as described above. A total of 36 studies were included as evidence for the guideline.

Data extraction and statistical analysis

Data were extracted by 2 independent reviewers (A.H.C. and M.S.S.) using Excel (Microsoft Corporation, Redmond, Wash, USA). The primary estimate of effect was based on a priori identified outcomes of interest. For PICO questions 1 and 2, we used a meta-analysis to generate summary estimates of diagnostic yield, pooled relative risk (RR), odds ratio (OR), or proportions. Heterogeneity was assessed using the I^2 and Q statistic. Significant heterogeneity was defined at $I^2 > 50\%$ and significant $P < .05$) on the Q statistic. Random-effects models were used for most analyses (if significant heterogeneity was detected); otherwise, fixed-effects models were used. Studies were weighted based on size. Publication bias was assessed using funnel plots. Statistical analyses were performed using Comprehensive Meta Analysis V_3 (Biostat Inc, Englewood, NJ, USA).

For PICO questions 3a and 3b, we used a meta-analysis to generate summary estimates of the RR, OR, or standardized incidence ratio (SIR) of pancreatic cancer overall, by *BRCA1* versus *BRCA2*, male versus female, and by age at cancer diagnosis. We specified a random-effects model using the method of DerSimonian and Laird,[6] with the estimate of heterogeneity taken from the Mantel-Haenszel model. Our analysis pooled standardized mean differences by the method of Cohen.[7] We pooled the RR and OR together, relying on the rare disease assumption that the RR and OR are measuring the same quantity for *BRCA1/2*-associated pancreatic cancer. We used the pooled estimates of RR and SIR to estimate the cumulative lifetime risk of pancreatic cancer to age 80.

Panel composition and conflict of interest management

We assembled an international panel of stakeholders to review evidence and make recommendations. The panel consisted of lead authors (A.H.C., M.S.S.), committee members with expertise in methodology, systematic reviews and meta-analyses (N.C.T. and S.W.), pancreatic cancer screening content experts (M.I.C., R.S.K., E.M.S.),

TABLE 2. Summary of additional management questions addressed in the guideline using non–Grading of Recommendations Assessment, Development and Evaluation methodology

Question	Population	Management question
4	Individuals at increased risk of pancreatic cancer because of genetic susceptibility	How often should screening for pancreatic cancer be performed?
5	Individuals at increased risk of pancreatic cancer because of genetic susceptibility undergoing screening a) *BRCA2* pathogenic variant b) *BRCA1* pathogenic variant c) PALB2 pathogenic variant d) Familial pancreatic cancer e) Familial atypical multiple mole melanoma syndrome f) Peutz-Jeghers syndrome g) Ataxia-telangiectasia mutated heterozygotes with first- or second-degree relative with pancreatic cancer h) Lynch syndrome with first- or second-degree relative with pancreatic cancer i) hereditary pancreatitis	At what age should screening for pancreatic cancer start?

cancer epidemiologist (T.R.), pancreatic cancer surgeon (C.M.V.), radiologist (D.V.S.), oncologists (T.G. and M.H.), cancer geneticist (D.L.R), pediatric gastroenterologist (D.S.F), and committee chair (B.J.Q.). Two patient representatives from the Facing Hereditary Cancer Empowered, an advocacy organization for families facing hereditary cancers, were also included.

Two virtual meetings were convened on October 3 and October 24, 2020. All panel members were required to disclose potential financial and intellectual conflicts of interest, which were addressed according to ASGE policies set forth in the ASGE Conflict of Interest and Resolution Policy https://www.asge.org/docs/default-source/default-document-library/coi-full-policy-for-asge-and-publications_edd_2-10-20.pdf.

Certainty in evidence, outcomes, and definitions

The certainty in the body of evidence (also known as quality of the evidence or confidence in the estimated effects) was assessed using the GRADE framework as previously described (Table 3).[1,3,8] 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. High-risk lesions were defined as pancreatic cancer, high-grade dysplasia, and grade III pancreatic intraepithelial neoplasia (PanIN).[9-12] Resectable and borderline-resectable pancreatic cancers were defined any T1-3 and N0-2 pancreatic cancer, whereas cancers that were staged T4 or M1 were deemed unresectable. High-risk resectable lesions were defined as resectable and borderline-resectable pancreatic cancers, high-grade dysplasia, and grade III PanIN. Harms were defined as harms from the screening tests (EUS and/or magnetic resonance imaging [MRI]), rates of low-yield pancreatic surgery in the screened population, and rate of adverse events from pancreatic cancer surgery resulting from positive screening tests. Low-yield surgery was defined as surgery that did not yield cancer, high-grade dysplasia, or grade III PanIN. For individuals with *BRCA1* and *BRCA2* pathogenic variants, we also sought to determine the cumulative lifetime risk of pancreatic cancer and the impact of age, gender, and family history of pancreatic cancer on risk. For the purposes of this document, pancreatic cancer refers to pancreatic ductal adenocarcinoma.

External review

The guideline was reviewed by the GIE Editorial Board, Governing Board, and made available for public comment on the ASGE website.

RESULTS

For each clinical question, we summarized the results for a priori identified outcomes of interested. Other considerations including cost-effectiveness, patient preferences and acceptability, and equity that are common to more than 1 questions have also been summarized.

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*).

TABLE 3. Interpretation of the definitions of the strength of recommendation using Grading of Recommendations Assessment, Development and Evaluation framework

Implications for	Strong recommendation	Conditional recommendation
Patients	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals in this situation would want the suggested course of action, but many would not.
Clinicians	Most individuals should receive the test. Formal decision aids are not likely to be needed to help individual patients make decisions consistent with their values and preferences.	Recognize that different choices will be appropriate for individual patients and that you must help each patient arrive at a management decision consistent with his or her values and preferences. Decision aids may be useful in helping individuals to make decisions consistent with their values and preferences.
Policymakers	The recommendation can be adopted as policy in most situations. Compliance with this recommendation according to the guideline could be used as a quality criterion or performance indicator.	Policymaking will require substantial debate and involvement of various stakeholders.

Adapted from Andrews et al, 2013.[143]

We performed a systematic review and meta-analysis (Fig. 1) that identified 25 studies for inclusion.[13-37] All studies were conducted in Europe or North America, except 1 conducted in Asia. In aggregate, 3253 patients were enrolled, in whom 70 screen-detected pancreatic cancers were diagnosed. The most common indication for screening was familial pancreatic cancer (FPC), and the most common pathogenic variant noted was *BRCA1/2*. Considering all outcomes together, the overall quality of evidence was found to be low. A summary of outcomes and their assessment can be seen in Table 4.

All-cause mortality

For the outcome of all-cause mortality, we identified 2 studies from our systematic review that reported this outcome. In 1 study, 14 pancreatic cancers were found among a cohort of 354 high-risk individuals screened and followed for a median of 5.6 years.[15] Of the 10 screen-detected cancers, 9 were surgically resectable stage 1 or 2 cancers and 1 was metastatic cancer. Four patients were diagnosed with pancreatic cancer because of symptoms after stopping screening, of which 3 were metastatic. The 3-year survival was significantly higher in the screen-detected cancers when compared with symptomatic cancers (85% vs 25%).[15] Overall, for screen-detected pancreatic cancers, the 1- and 5-year survival rates were 90% and 60%, the latter of which is substantially better than reported for the general population within the Surveillance, Epidemiology, and End Results Program (SEER) database (8.9%).[38] In a second study by Vasen et al,[32] among 411 high-risk individuals who underwent screening at 3 European centers, 75% of the screen-detected cancers were eligible for surgical resection and patients had a 5-year survival rate of 24%, outcomes that were substantially better than in historic control subjects.[32] While assessing the certainty of evidence, we rated down the evidence for imprecision because of small number of studies and patients and overall judged the quality of evidence to be very low. Our literature search resulted in no studies to inform the outcome of pancreatic cancer–related mortality in screen-detected pancreatic cancer.

Yield of screening for high-risk lesions

Our literature search identified 25 studies that assessed the yield of screening for patients with genetic susceptibility to pancreatic cancer. Screening results were stratified by yield of first-time screening and cumulative yield of screening, which included yield of all reported rounds of screening. In aggregate, studies included 3253 patients who underwent pancreatic cancer screening. Of these, 88 patients were found to have high-risk lesions on screening, including 10 with high-grade dysplasia, 11 with grade III PanIN, and 70 with pancreatic cancer. The cumulative yield of screening for high-risk lesions was 3.1% (95% confidence interval [CI], 2.2%-4.3%; $P = .02$ and $I^2 = 40.5$) (Fig. 2). Detection of specific lesions was as follows: pancreatic cancer, 2.7% (95% CI, 2.0%-3.6%; $P = .10$ and $I^2 = 27.6\%$) (Fig. 3); high-grade dysplasia, .9% (95% CI, .6%-1.4%; $P = .95$ and $I^2 = .0$); grade III PanIN lesions, .8% (95% CI, .5%-1.3%; $P = .99$ and $I^2 = .0$). The yield of first-time screening for high-risk lesions was 1.9% (95% CI, 1.3%-2.6%; $P = .10$ and $I^2 = 28.7$). The quality of evidence was judged to be low.

Yield of screening for resectable and borderline-resectable lesions

The yield of screening for high-risk resectable lesions (defined as resectable or borderline-resectable pancreatic cancer, high-grade dysplasia, or grade III PanIN) was 2.1% (95% CI, 1.4%-3.1%; $P = .007$ and $I^2 = 45.6$ (Fig. 4). The yield of screening for resectable or borderline-resectable pancreatic cancer was 1.9% (95% CI, 1.3%-2.7%; $P = .11$ and $I^2 = 26.7$). The proportion of screen-detected cancers that were resectable or borderline-resectable was 60% (95% CI, 43.7%-74.4%; $P = .51$ and $I^2 = .0$) (Fig. 5). Among cancers diagnosed within the SEER database, 9% were categorized as resectable, 10% borderline-resectable,

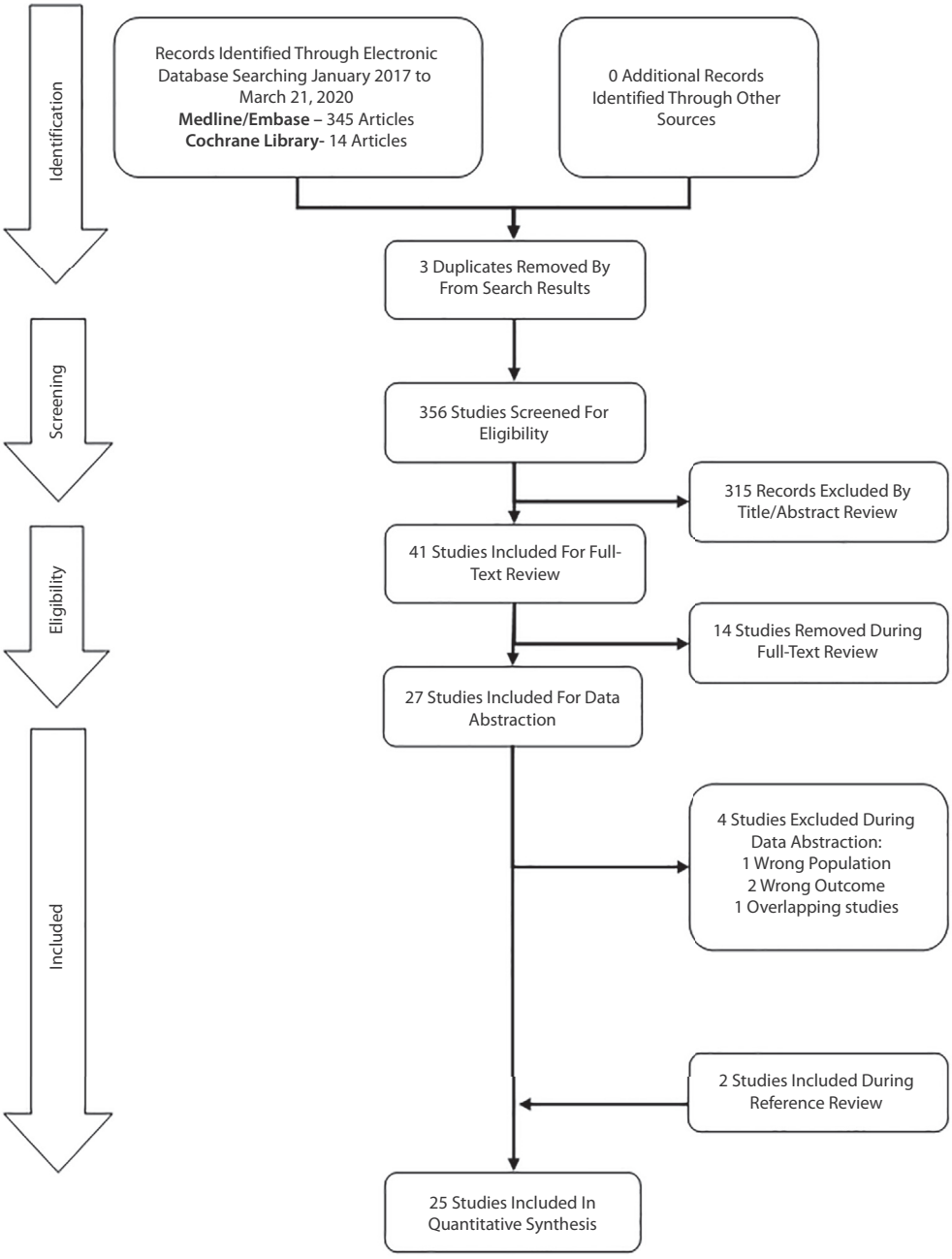

Figure 1. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the studies included in the systematic review regarding screening for pancreatic cancer in individuals at increased risk of pancreatic cancer because of genetic susceptibility.

and 80% unresectable at diagnosis.[39] We rated the evidence down for indirectness, and therefore the quality of evidence was judged to be very low.

Psychological benefits of screening

To assess the psychological impacts of pancreatic cancer screening, we used an existing systematic review by Cazacu et al[40] that included cross-sectional and prospective studies. Among high-risk individuals, screening was associated with positive psychological benefits. Screening participants had low-to-moderate levels of pancreatic cancer–related distress at the start that improved significantly over time. Participants rated their risk of developing pancreatic cancer significantly lower when they underwent annual screening than when they did not. One study showed a slight increase in cancer worry at a 1-year assessment that was associated with an elevated perceived risk of developing cancer and having a family member affected by pancreatic cancer before age 50 years.[41] In 1 study measuring general quality of life, there was a significant reduction in the negative emotional scores at the 1-year postscreening.[42] A study by O'Neill et al,[43] published

TABLE 4. Evidence profile for question 1: Should individuals at increased risk of pancreatic cancer because of genetic susceptibility undergo screening for pancreatic cancer?

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
3-year survival						
1	Observational studies	Not serious	Not serious	Not serious	Serious*	None
5-year survival						
2	Observational studies	Not serious	Not serious	Not serious	Serious*	None
Cumulative yield of screening for high-risk lesions (pancreatic ductal adenocarcinoma, HGD, PanIN III)						
25	Observational studies	Not serious	Not serious	Not serious	Not serious	None
Cumulative yield of high risk lesions that are resectable/borderline-resectable						
25	Observational studies	Not serious	Not serious	Serious	Not serious	None
Psychological benefits						
6	Observational studies	Not serious	Not serious	Not serious	Not serious	None
Harms: Adverse outcomes from EUS or MRI						
22	Observational studies	Not serious	Not serious	Not serious	Not serious	None
Harms: Surgery for low-yield lesions						
22	Observational studies	Not serious	Not serious	Not serious	Not serious	None
Harms: Adverse outcomes from surgery						
8	Observational studies	Not serious	Not serious	Not serious	Serious*	None

SEER, Surveillance, Epidemiology, and End Results Program; *HGD*, high-grade dysplasia; *MRI*, magnetic resonance imaging; *PanIN III*, grade III pancreatic intraepithelial neoplasia.
*Very small number of patients.

after the Cazacu et al systematic review, assessed participants of the national Australian pancreatic screening program and found positive psychological benefits at the 1-year postintervention, irrespective of screening result. No negative impact of screening was noted. The study reported improvements in the impact of events scale, psychological consequences questionnaire, and the cancer worry scale. While assessing the certainty of evidence of this outcome using the GRADE approach, we judged the quality of evidence to be low.

Harms from screening

We categorized harms from pancreatic cancer screening into adverse outcomes from screening tests (EUS and MRI), low-yield surgery as a result of positive screening results, and adverse events from pancreatic surgery performed for positive screening results.

Adverse events from screening tests EUS and MRI. For this outcome, we identified 6 studies from our systematic review that specifically reported on adverse events from EUS and MRI.[19,21,23,24,28,33] No adverse events from EUS or MRI were noted among the 350 participants included in these 6 studies. Generally, harms from MRI are very uncommon and mostly limited to allergic reactions from intravenous contrast.[44] Approximately 2% of patients experience claustrophobia in the scanner, necessitating intervention.[45] Implanted devices, metallic foreign bodies, pregnancy, and hemodynamic instability are all relative contraindications to MRI. Adverse events from diagnostic EUS are uncommon and occur in less than 1% of patients.[46] In a study of 355 patients who underwent EUS with FNA for a solid pancreatic mass, adverse events were reported in 2.5% of patients, with 2% needing hospitalization.[47] Adverse events included acute pancreatitis (n = 3), abdominal pain (n = 3), fever (n = 2), and sedation-related hypoxia (n = 1).

Low-yield surgeries. We defined low-yield surgeries as those where surgical pathology did not show pancreatic cancer, high-grade dysplasia, or grade III PanIN. In most such cases, pathology showed low-grade intraductal papillary mucinous neoplasms (IPMNs) or PanIN lesions. Low-grade pancreatic lesions can be safely managed with

TABLE 4. Continued

Screening	Effect: No screening	Effect: Relative [95% confidence interval]	Certainty	Importance
3-year survival				
Survival 85% in screening group vs 25% in patients who stopped screening			⨁◯◯◯ Very low	Critical
5-year survival				
24% (Vasen et al[32]) and 60% (Canto et al[38]) vs 8% from historical cohort (SEER)			⨁◯◯◯ Very low	Critical
Cumulative yield of screening for high-risk lesions (pancreatic ductal adenocarcinoma, HGD, PanIN III)				
Overall 3.1% [2.5-4.3]; pancreatic ductal adenocarcinoma 2.7% [1.9-3.6]; HGD .89% [.58-1.4]; PanIN III .82% [.54-1.3]			⨁◯◯ Low	Critical
Cumulative yield of high risk lesions that are resectable/borderline-resectable				
Proportion of screen-detected cancers resectable or borderline-resectable = 68.2% [48.7%-82.9%] vs symptomatic cancers from SEER database resectable or borderline-resectable = 9%.			⨁◯◯◯ Very low	Critical
Psychological benefits				
Overall positive psychological impact. Cancer worry decreased significantly. Lower perceived risk of cancer even when lesions detected. Reduction in negative emotional consequences of psychological consequences questionnaire at 1 year			⨁⨁◯◯ Low	Important
Harms: Adverse outcomes from EUS or MRI				
No adverse outcomes from screening EUS or MRI reported by 6/25 screening studies. External literature: diagnostic EUS <1%, EUS with FNA 2% adverse outcome rate MRI: claustrophobia 2%, very rare allergic reaction or nephrogenic systemic fibrosis			⨁⨁◯◯ Low	Important
Harms: Surgery for low-yield lesions				
Proportion of patient screened who underwent low-yield surgery = 2.8% [1.9-4.1] Proportion of all pancreatic surgeries that were low yield = 46.6% [34.1-59.4]			⨁⨁◯◯ Low	Important
Harms: Adverse outcomes from surgery				
Adverse outcomes from surgery among all screened 1.5% [.6-3.6] Adverse outcomes from surgery among those undergoing surgery 19.9% [7.4-43.4]			⨁◯◯◯ Very low	Important

surveillance.[9] Therefore, we surmised that such surgeries constituted a potential harm. Patients in whom surgical pathology showed neuroendocrine tumors were excluded from this analysis because optimal management of these lesions remains controversial.[48,49] For this outcome, we identified 22 studies from our meta-analysis that reported the rate of low-yield surgery. On meta-analysis using random-effects modeling, the pooled rate of low-yield surgery was 2.8% (95% CI, 1.9%-4.1%; $P = .003$ and $I^2 = 51.4$) of the total screened population. Among all patients who had pancreatic surgery as a result of screening (n = 181), the pooled proportion of low-yield surgery was 46.6% (95% CI, 34.2%-59.4%; $P = .15$ and $I^2 = 26.2$) (Fig. 6). Our findings are similar to those reported in a meta-analysis by Paiella et al[50] where 6% of a pancreatic cancer screening population underwent surgery, of which 68.1% (95% CI, 59.5%-76.7%) were considered low yield.

Adverse events from pancreatic surgery. We identified 6 studies that reported adverse events from pancreatic surgery in patients undergoing screening. Three studies that included 13 pancreatic surgeries reported no adverse events.[21,27,33] Langer et al[22] reported on 7 pancreatic surgeries resulting in 4 adverse events (fistulae, postoperative diabetes, and hernia), Joergensen et al[19] reported on 2 pancreatic surgeries resulting in 2 adverse events (hepaticojejunostomy stricture with cholangitis and a "nonfatal complication"), and Canto et al[15] reported on surgeries in 48 patients with 17 patients developing adverse events (fistulae, surgical site infections, cholangitis, diabetes, delayed gastric emptying, and malabsorption). When a meta-analysis was performed, adverse events were noted in 19.9% of surgeries (95% CI, 7.4%-43.4%; $P = .05$ and $I^2 = 49.7$). Among all patients undergoing screening, surgical adverse events were noted in 1.5% (95% CI, .6%-3.6%; $P = .01$ and $I^2 = 61.4$) of the screening population. While assessing the certainty of evidence of these 3 outcomes using a GRADE approach, we judged the quality of evidence to be low.

Other considerations

Patient values. We did not find any studies that compared patients undergoing screening with those who refused or were not offered participation in a screening program. Several studies found that diagnosing cancer at an early stage and contributing to scientific research were the most common motivations among patients to consider screening.[51-53] One study found that 88% of participants concluded that the advantages of screening outweighed

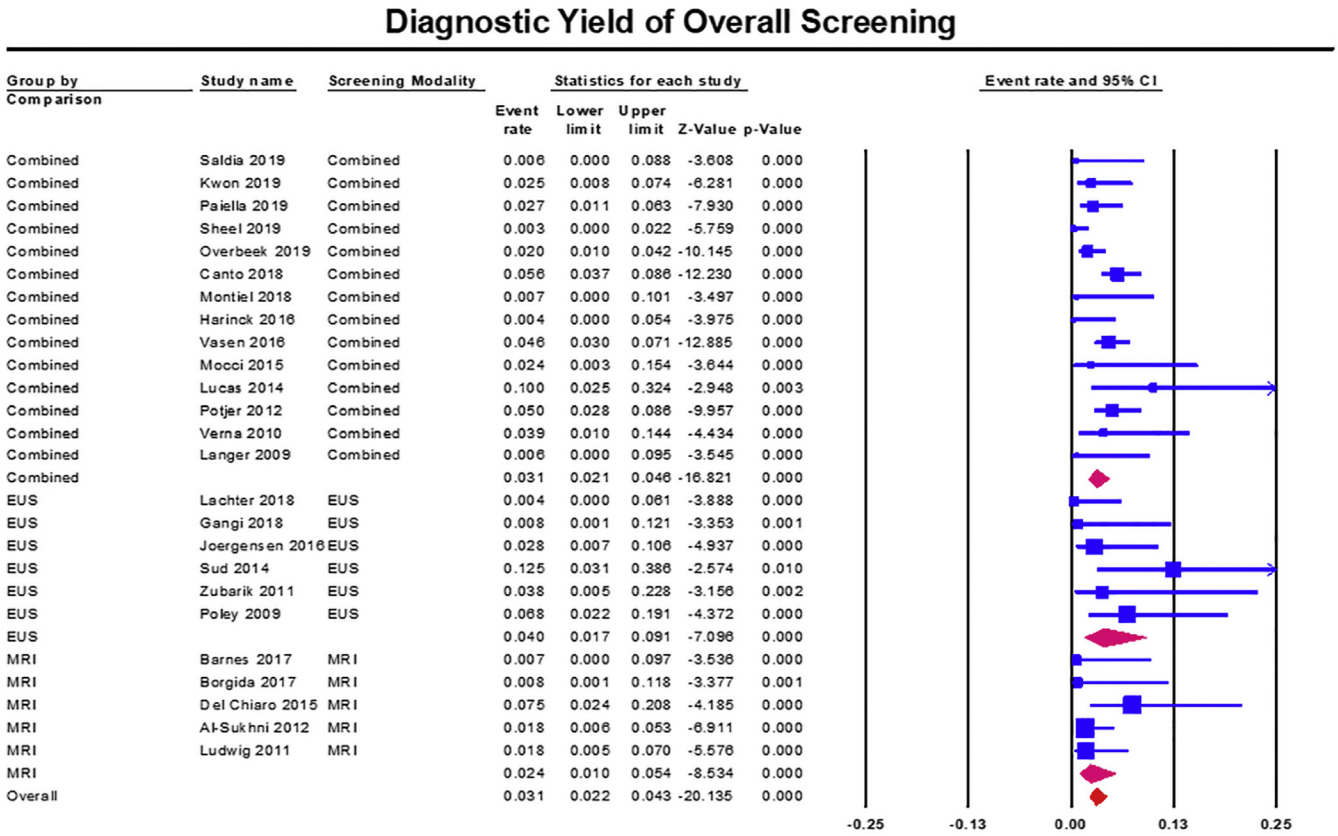

Figure 2. Forest plot of the 25 studies showing the cumulative yield (ie, pancreatic cancer, high-grade dysplasia, grade III pancreatic intraepithelial neoplasia) of screening in individuals at increased risk of pancreatic cancer because of genetic susceptibility. *CI*, Confidence interval; *MRI*, magnetic resonance imaging.

disadvantages and 54% reported a lower personal risk of developing pancreatic cancer by participating in a screening program.[53] Another study found that despite a desire for knowledge, most patients only had a limited understanding of pancreatic cancer screening.[51] This study also found that having a family history of cancer increased motivation to participate in screening. During panel discussions, patient representatives stated that providers rarely discussed pancreatic cancer risks with high-risk individuals, and most were unaware of any screening options.

Cost-effectiveness of screening. We performed a literature review to assess cost-effectiveness of pancreatic cancer screening. Corral et al[39] used a Markov model to compare screening with no screening in high-risk individuals, defined as those with lifetime risk >5% or relative risk >5-fold for pancreatic cancer. Screening was found to be cost-effective for high-risk individuals between the ages of 40 and 76 years. Kowada[54] reported on a cost-effectiveness study using a Markov model and found that no screening was the most expensive strategy with minimal benefits. Joergensen et al[19] used data from a Danish pancreatic cancer surveillance program on patients with FPC and hereditary pancreatitis and found yearly EUS to be a cost-effective strategy. In a cost-analysis, Bruenderman et al[55] found biannual screening using MRI for patients with Peutz-Jehgers syndrome, hereditary pancreatitis, FPC, p16-Leiden mutations, and new-onset diabetes over age 50 years to be "affordable." Using a Markov model, Pandharipande et al[56] found that a 1-time MRI screening performed at age 50 years resulted in life expectancy gains for men with >2.4 times and women with >2.7 increased risk for pancreatic cancer. Of note, this model found that benefit was derived predominantly from the detection of cystic precursors and, to a lesser extent, early pancreatic ductal adenocarcinoma. In another disease simulation model, Pandharipande et al[57] focused on *BRCA2* patients and found that a 1-time screening resulted in only a small increase in life expectancy, whereas annual screening resulted in a decrease in life expectancy because of false-positive tests results. This model did not report on EUS or combined EUS and MRI screening strategy and assigned a lower RR for pancreatic cancer to *BRCA2* patients than noted in our meta-analysis (3.5 vs 5.1). We did not review the analysis by Rulyak and Brentnall[58] or Rubenstein et al[59] because these were performed using data from >10 years ago. During discussion, our panel noted significant variability in cost of screening based on

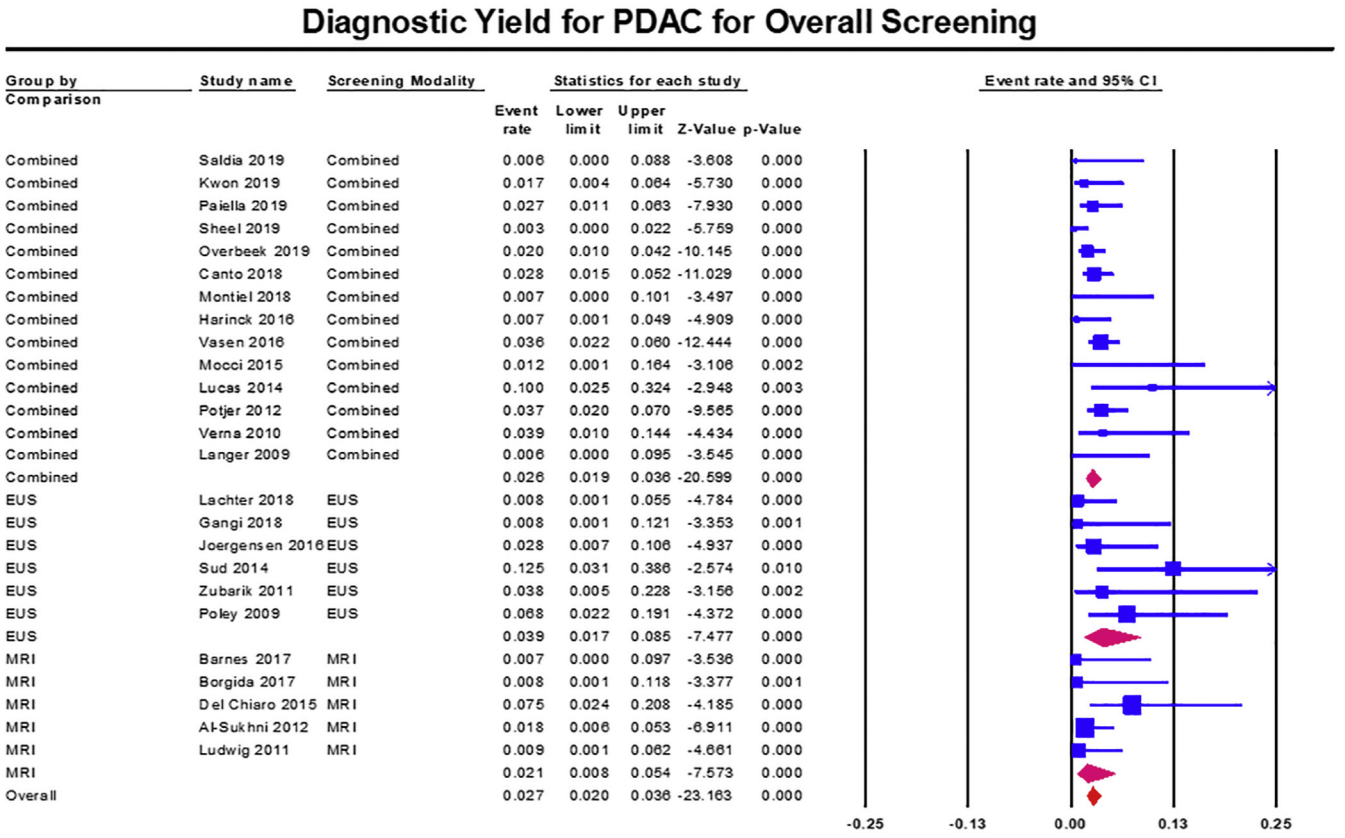

Figure 3. Forest plot of the 25 studies showing the cumulative yield of pancreatic cancer screening in individuals at increased risk of pancreatic cancer because of genetic susceptibility. *PDAC*, Pancreatic ductal adenocarcinoma; *CI*, confidence interval; *MRI*, magnetic resonance imaging.

geographic location, practice setting, and type of insurance.

Discussion

The panel discussed the 25 studies from the systematic review and highlighted limitations regarding heterogeneity in patient population, screening protocols, outcomes ascertained, and result reporting. Panel members agreed that resectable or borderline-resectable pancreatic cancers were potentially curable and therefore appropriate targets for screening. Of note, previous guidelines had considered only stage 1 pancreatic cancer to be the primary target for screening.[60,61] Our present definition of resectable or borderline-resectable pancreatic cancer (T1-3 and/or N0-2) may underestimate the positive impact of screening because some patients with even locally unresectable cancer like T4 cancers may be downstaged with chemoradiation therapy to allow for surgical resection. Surgical treatment may also be beneficial for selected patients with oligometastatic cancers.

The panel questioned whether surgical resections for precursors lesions like low-grade IPMN should be categorized as a harm of screening. Some panelists stated that in selected young patients, given their long life expectancy, resection of even low-grade IPMNs may be appropriate to prevent malignant transformation in the future. The panel suggested an alternative approach to categorizing surgery based on surgical pathology findings: high-yield surgery: cancer, high-grade IPMN, or high-grade PanIN; intermediate-yield surgery: precancerous precursors like IPMN or PanIN lesions other than high-grade lesions; and low-yield surgery: non-neoplastic lesions like serous cystadenoma or pseudocysts. The panel also recommended that harms of screening should include failure of screening, recognizing that this was not reported in most studies.

The panel noted that a significant number of low-yield surgeries were performed for pancreatic cysts and suggested that the low accuracy of preoperative tests in distinguishing between malignant and benign pancreatic cysts may explain several low-yield surgeries.[62,63] Furthermore, in previous years even small branch-duct IPMNs were believed to have significant malignant potential in high-risk individuals, and surgery for such patients was recommended.[60] Although the natural history of small IPMNs in high-risk individuals is still not fully understood, there is now growing consensus that individuals with genetic susceptibility to pancreatic cancer with IPMN should undergo pancreatic resection for broadly the same

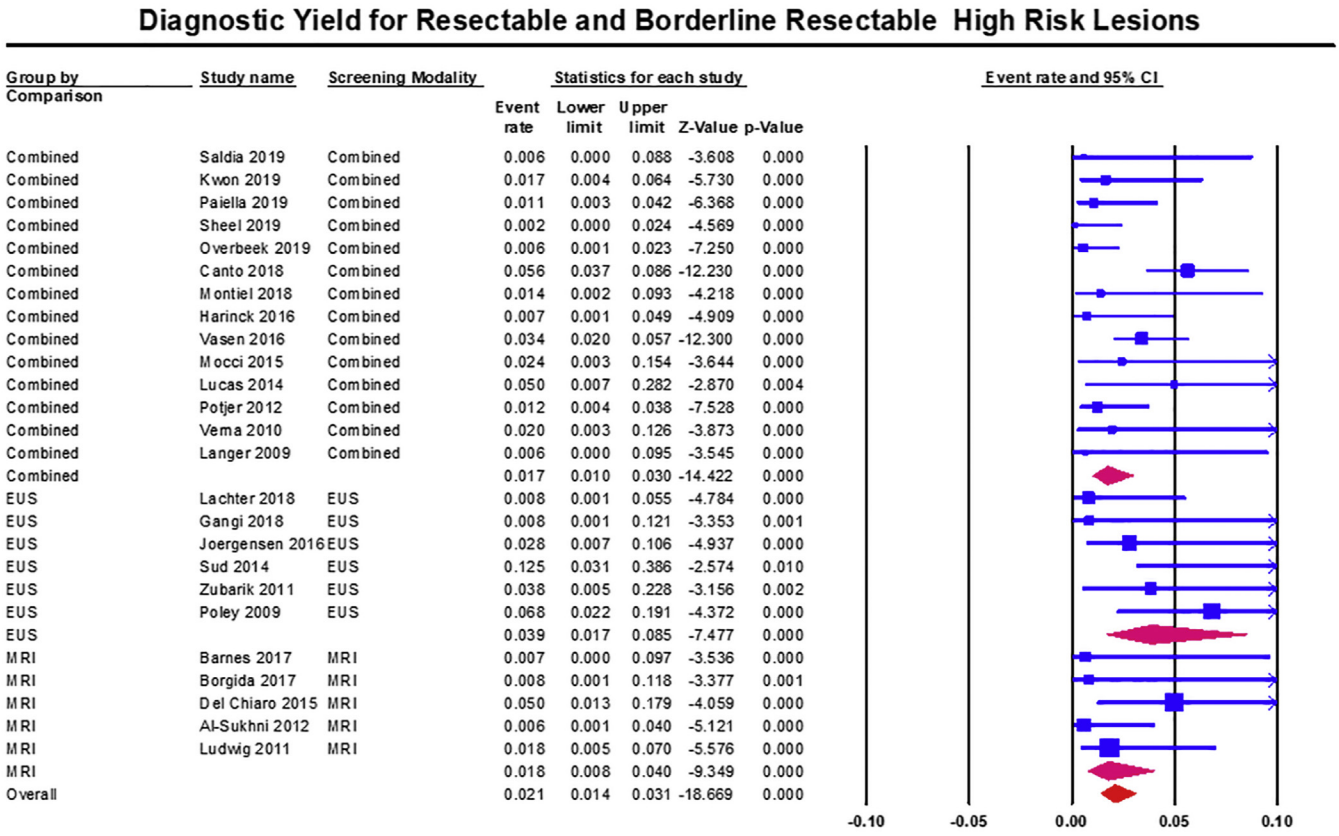

Figure 4. Forest plot of the 24 studies showing the cumulative yield of resectable or borderline-resectable high-risk lesions (defined as resectable or borderline-resectable pancreatic cancer, high-grade dysplasia, or grade III pancreatic intraepithelial neoplasia) in screening in individuals at increased risk of pancreatic cancer because of genetic susceptibility. *CI*, Confidence interval; *MRI*, magnetic resonance imaging.

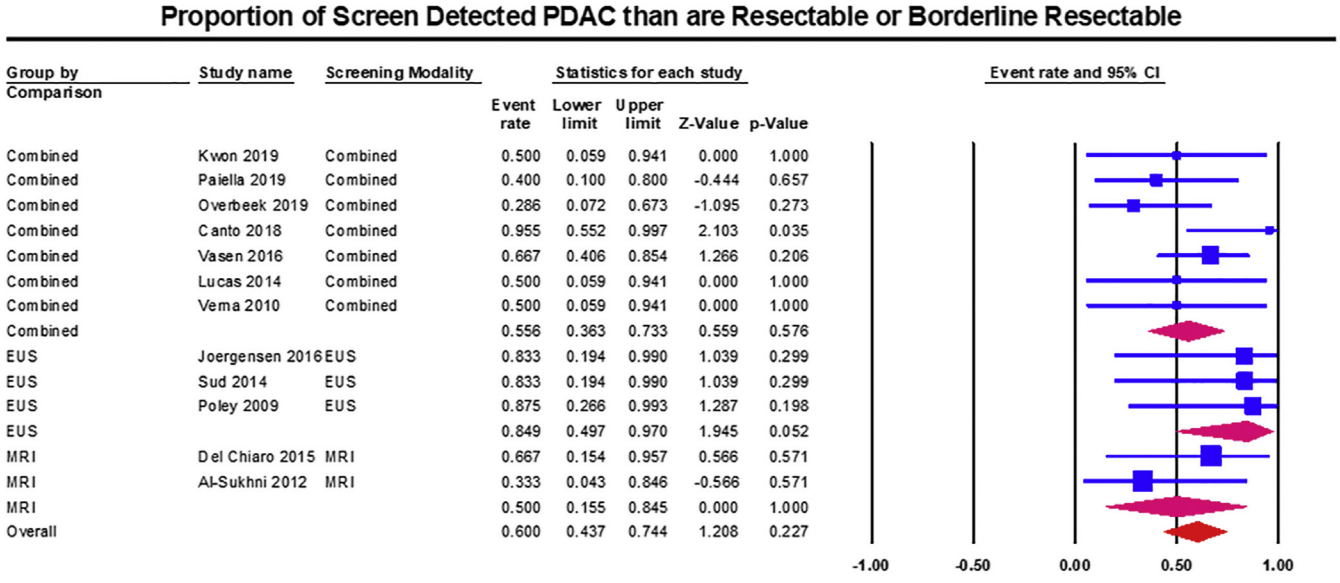

Figure 5. Forest plot of the 12 studies showing the proportion of screen-detected pancreatic cancers that are resectable or borderline-resectable. *PDAC*, Pancreatic ductal adenocarcinoma; *CI*, confidence interval; *MRI*, magnetic resonance imaging.

indications as average-risk individuals, and surgery for branch-duct IPMNs based on size alone is no longer recommended.[61]

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

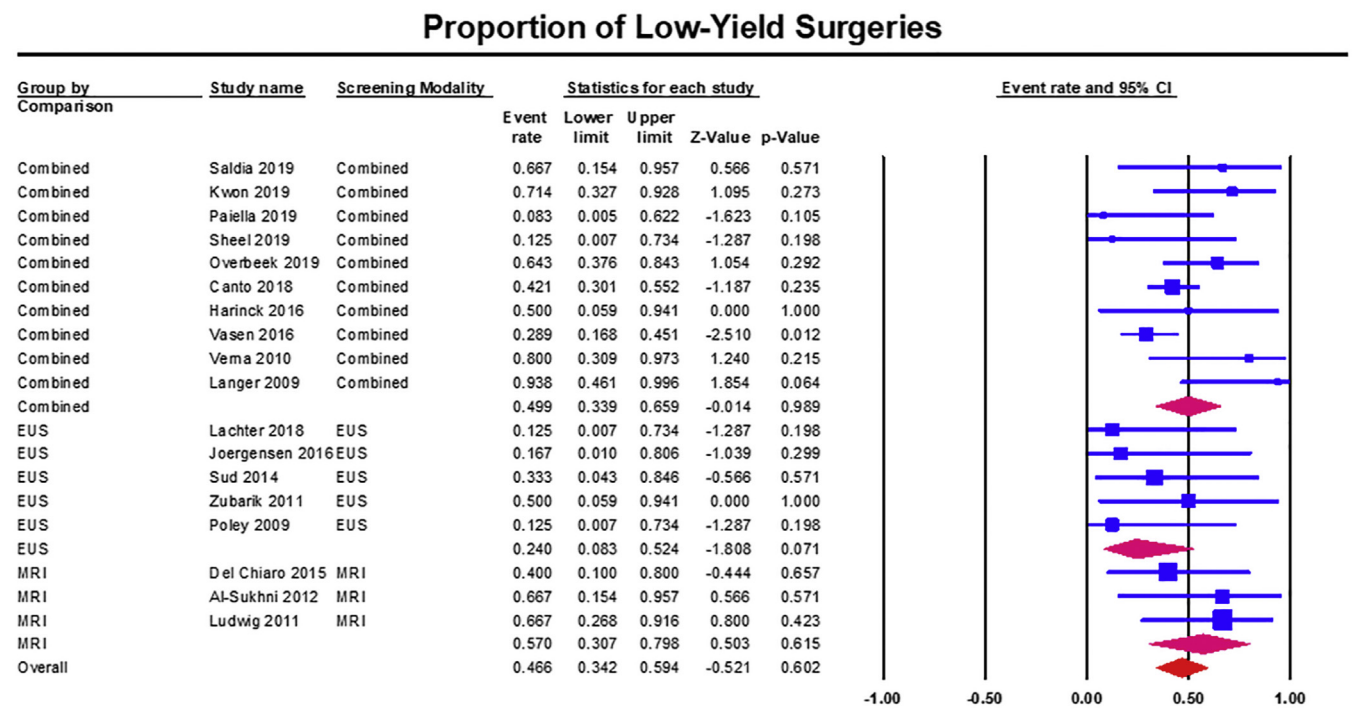

Figure 6. Forest plot of the 22 studies showing the proportion of patients screened who undergo low-yield surgery. *CI*, Confidence interval; *MRI*, magnetic resonance imaging.

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*).

We used the same systematic review from question 1 to inform this question. Of the 25 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. Considering all outcomes together, the overall quality of evidence was judged to be low. A summary of outcomes and their assessment can be seen in Table 5.

Yield of screening for high-risk lesions

The overall yield of screening for high-risk lesions did not differ between EUS and MRI: 4.0% (95% CI, 1.7%-9.1%; $P = .18, I^2 = 34.4$) in studies using only EUS, 2.4% (95% CI, 1.0%-5.4; $P = .21$, $I^2 = 31.0$) in studies using only MRI, and 3.1% (95% CI, 2.1%-4.6%; $P = .022, I^2 = 48.4$) in studies that using a combination of EUS and MRI (Fig. 2). The yield of screening for pancreatic cancer was 3.9% (95% CI, 1.7%-8.5%; $P = .18$, $I^2 = 34.4$) for studies using only EUS, 2.1% (95% CI, .8%-5.4%; $P = .16$, $I^2 = 39.7$) for studies using only MRI, and 2.6% (95% CI, 1.9%-3.6%; $P = .19$, $I^2 = 24.3$) for studies using a combination of EUS and MRI (Fig. 3). While assessing the certainty of evidence of this outcome using the GRADE approach, we judged the quality of evidence to be low.

Yield of screening for high-risk resectable lesions

Yield of screening for high-risk resectable lesions was 3.9% (95% CI, 1.7%-8.5%; $P = .18$, $I^2 = 34.4$) for studies using only EUS, 1.8% (95% CI, .8%-4.0%; $P = .38$, $I^2 = 5.4$) for studies using only MRI, and 1.7% (95% CI, 1.0%-3.0%; $P = .006$, $I^2 = 55.9$) for studies using a combination of EUS and MRI (Fig. 4). While assessing the certainty of evidence, we rated down evidence for imprecision and overall judged the quality of evidence to be very low.

Harms

See Harms from screening under question 1, above.

Other considerations

Patient preferences. We performed a literature review to assess the role of patient preferences in pancreatic cancer screening of high-risk populations. Harinck et al[53] surveyed participants of the Dutch pancreatic cancer surveillance study of whom nearly 96% had undergone both EUS and MRI. Four percent did not undergone MRI because of claustrophobia or metallic foreign body. There was no significant difference between patient preference for EUS or MRI, with 10% reporting EUS to extremely uncomfortable, mostly because the sedation-related experience, and 11% reporting MRI to be extremely uncomfortable, predominantly because of claustrophobia. In a follow-up study, Konings et al[52] reported that 10% of

TABLE 5. Evidence profile for question 2: Should individuals at increased risk of pancreatic cancer because of genetic susceptibility undergo screening with EUS or MRI?

Certainty assessment						
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**
Cumulative yield for high-risk lesions (pancreatic ductal adenocarcinoma, high-grade dysplasia, grade III pancreatic intraepithelial neoplasia)						
25	Observational studies	Not serious	Not serious	Not serious	Not serious	None
Cumulative yield of pancreatic ductal adenocarcinoma						
25	Observational studies	Not serious	Not serious	Not serious	Not serious	None
Cumulative yield of resectable/borderline-resectable high-risk lesions						
25	Observational studies	Not serious	Not serious	Not serious	Serious *	None

MRI, Magnetic resonance imaging.
*Few people with high-risk lesions.

respondents continued to report MRI and 11% report EUS as uncomfortable. Only 3% of respondents "dreaded" their first MRI compared with 34% their first EUS. However, after having undergone the procedure, the percentage of respondents dreading their next EUS dropped significantly and to the same level as that of MRI (6%-9% vs 0%-8%, respectively). Another study found that patient motivation to undergo a particular screening test was related to whether the test was recommended by a physician, cost, degree of invasiveness, and comfort level.[51] Interestingly, those participants who had a family history of pancreatic cancer or a personal history of other cancers often preferred the more invasive screening techniques, believing that such tests were able to provide more accurate results. During the panel discussion, 1 patient representative noted that some patients may prefer MRI because it is noninvasive and does not require sedation, whereas others may prefer EUS because it is a "1 and done" procedure.

Cost-effectiveness. Corral et al[39] used a Markov model to compare MRI with EUS for screening high-risk individuals (see Cost-effectiveness of screening under question 1, above). They found MRI was the dominant strategy for individuals who had a 5- to 20-fold increased risk of pancreatic cancer. EUS was the dominant strategy for those who had a >20-fold increased risk of pancreatic cancer or if the cost of MRI exceeded $1600. Of note, this study did not analyze combining MRI and EUS for screening. Kowada[54] reported on a Markov model comparing cost-effectiveness of abdominal US, MRI, EUS, CT, and positron emission tomography for pancreatic cancer screening in familial high-risk individuals in Japan. Unexpectedly, this model found abdominal US to be the most cost-effective imaging modality for pancreatic cancer screening. Furthermore, unlike the Corral et al model, when the incidence of pancreatic cancer increased, MRI and not EUS became the dominant strategy. EUS was most cost-effective when the incidence of pancreatic cancer was between .008 and .016. The reason for divergent results noted in these 2 studies is not known.

Discussion

Previous studies and guidelines have found that abdominal US, CT, and ERCP are suboptimal for screening and have recommended that EUS and/or MRI should be used for pancreatic cancer screening.[61,64-68] When EUS is used for screening, using a linear-array echoendoscope may be preferred over a radial echoendoscope. In a randomized controlled study of 278 high-risk individuals undergoing pancreatic cancer screening, EUS using a linear-array echoendoscope detected more pancreatic lesions than a radial echoendoscope (82% vs 67%, respectively; $P < .001$).[69] Interestingly, in this tandem study, expert endosonographers missed 17.5% of pancreatic lesions during the first examination of the pancreas. A structured approach to EUS examination of the pancreas, perhaps similar to examining the right-sided colon segment twice during screening colonoscopy, may improve lesion detection.[70]

When MRI is used for screening, a contrast-enhanced examination using intravenous agents such as gadolinium chelate is preferred. For MRI acquisition, a minimum 1.5-T magnet should be applied using phased-array coils to maximize the signal-to-noise ratio. A 3-T magnet may have an additional advantage in detection of small pancreatic lesions because of superior soft-tissue resolution. A typical protocol should include a (1) breath-hold 2-dimensional axial in- and out-of-phase T1-weighted gradient-recalled echo sequence, (2) axial and coronal single-shot fast spin-echo breath-hold T2-weighted acquisition, (3) T2-weighted 2-dimensional and/or 3-dimensional T2-weighted MRCP, and (4) breath-hold or respiratory navigated, dynamic 3-dimensional fat-suppressed T1-weighted spoiled gradient-recalled echo axial MR images through the pancreas before and after

TABLE 5. Continued

Combined EUS-MRI vs. MRI vs. EUS	Effect		Certainty	Importance
	Relative [95% confidence interval]	Absolute [95% confidence interval]		
Cumulative yield for high-risk lesions (pancreatic ductal adenocarcinoma, high-grade dysplasia, grade III pancreatic intraepithelial neoplasia)				
Combined 3.1% [2.3-4.3] vs MRI 2.4% [1.0-5.4] vs EUS 4.0% [1.7-9.1]			⨁⨁◯◯ Low	Critical
Cumulative yield of pancreatic ductal adenocarcinoma				
Combined 2.6% [1.9-3.6] vs MRI 2.1% [.77-5.4] vs EUS 3.9% [1.7-8.5]			⨁⨁◯◯ Low	Critical
Cumulative yield of resectable/borderline-resectable high-risk lesions				
Combined 1.7% [1.0-2.9] vs MRI 1.8% [.77-4.0] vs EUS 3.9% [1.7-8.5]			⨁◯◯◯ Very low	Critical

administration of intravenous gadolinium chelate contrast.[34,68] The findings of early pancreatic cancer may be subtle, especially on noncontrast imaging, and may be seen best on enhanced 3-dimensional, T1-weighted, gradient-recalled echo sequences.[34,71]

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

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

In conjunction with an expert biostatistician and cancer epidemiologist (T.R.), we conducted a systematic review of risk of pancreatic cancer in individuals with the *BRCA1* and *BRCA2* pathogenic variant that resulted in 11 studies (n = 62,269) for our meta-analysis (Fig. 7).[72-82] No articles were excluded because of poor data quality or inadequate analyses. Estimates were generally made using small numbers of pancreatic cancer cases with *BRCA1/2* pathogenic variants (often <10 per group), as reflected in the CIs of the estimates. A summary of outcomes and their assessment can be seen in Table 6.

Lifetime risk of pancreatic cancer

For the outcome of lifetime RR of pancreatic cancer in individuals with the *BRCA2* pathogenic variant, we included 5 studies in our meta-analysis.[72,75-78] The pooled estimate of RR was 5.1 (95% CI, 3.9-6.3; P = .28 and I^2 = 21.0) (Table 7 and Fig. 8). When we used this estimate, the absolute lifetime risk of pancreatic cancer to age 80 was estimated to be 5.2%. While assessing the certainty of evidence, we judged the quality of evidence to be low.

Lifetime SIR of pancreatic cancer

For the outcome of lifetime SIR of pancreatic cancer in individuals with the *BRCA2* pathogenic variant, we included 3 studies in our meta-analysis.[79-81] The pooled estimate of SIR was 7.2 (95% CI, 1.5-13.0; P = .45 and I^2 = .0) (Table 7 and Fig. 8). When we used this estimate, the cumulative lifetime risk of pancreatic cancer to age 80 was estimated to be 7.4%. While assessing the certainty of evidence, we rated down for imprecision and therefore judged the quality of evidence to be very low.

Mortality

No studies reported on all-cause or pancreatic cancer–related mortality in screen-detected pancreatic cancer in individuals with the *BRCA2* pathogenic variant compared with unscreened individuals.

Yield of screening for high-risk lesions

For the outcome of overall yield of screening, 8 studies from our pancreatic cancer screening studies meta-analysis (see questions 1 and 2, above) addressed screening for pancreatic cancer in those with *BRCA1/2* and *PALB2*; however, these studies did not uniformly stratify results by mutation type. Across the 8 studies (n = 375), 219 patients were diagnosed with *BRCA2*, 50 with *BRCA1*, 11 with *PALB2*, and the remaining 95 were unspecified. The overall yield of high-risk lesions in this patient population undergoing screening with EUS, MRI, or a combined approach was 8.6% (95% CI, 4.5-16.0; P = .21 and I^2 = 27.4) (Fig. 9). While assessing the certainty of evidence, we rated down the evidence for impreciseness and thus judged the quality of evidence to be very low.

Yield of screening of resectable and borderline-resectable lesions

No studies reported on the detection of resectable and borderline-resectable lesions during screening in individuals with *BRCA2* pathogenic variant.

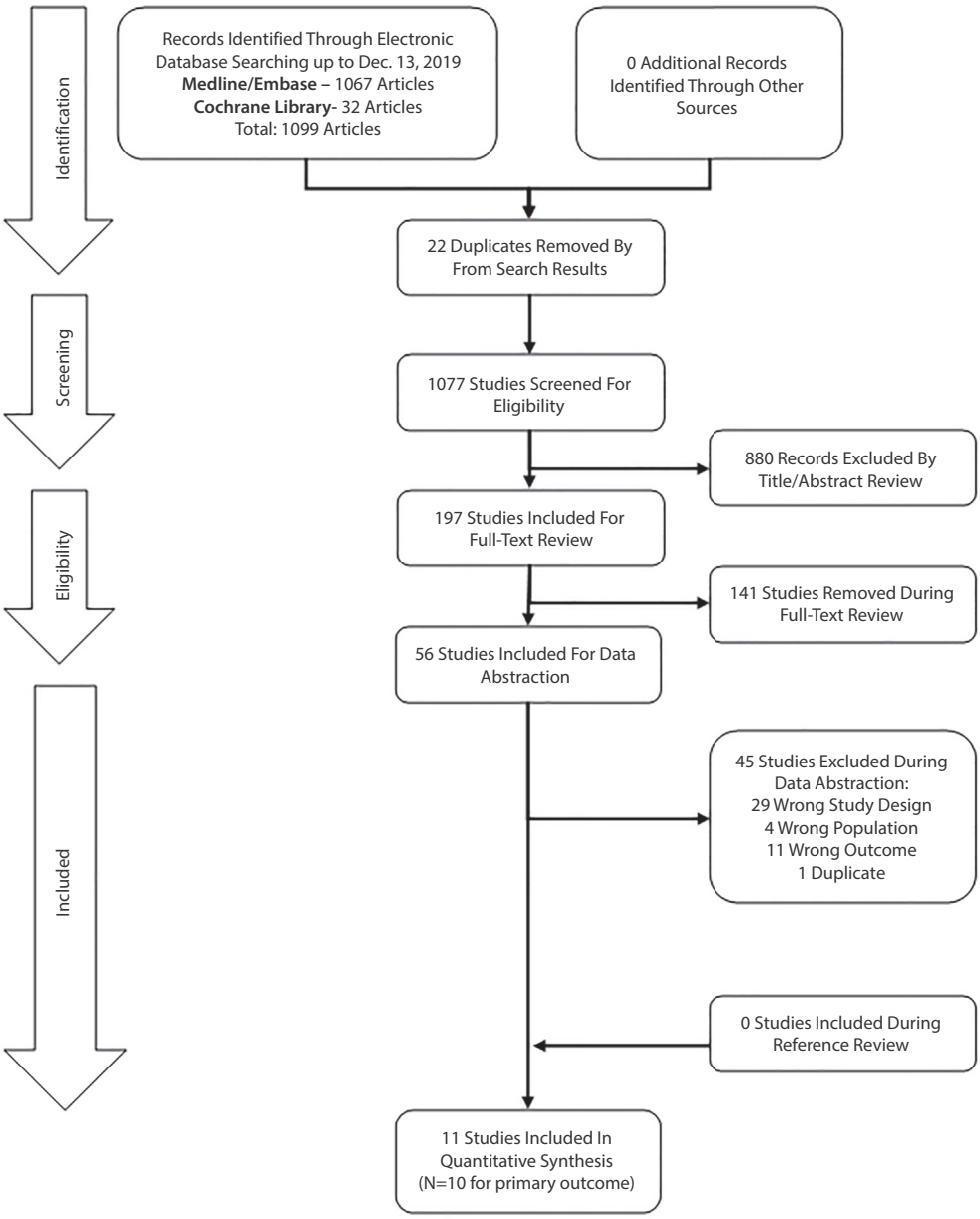

Figure 7. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram showing the studies included in the systematic review regarding risk of pancreatic cancer in individuals with *BRCA2* and *BRCA1* pathogenic variants.

Psychological benefits of screening

No studies reported on the psychological benefits of screening specific to individuals with the *BRCA2* pathogenic variant. See the same section under question 1, above.

Harms from screening

No studies reported on the harms from screening specific to individuals with the *BRCA2* pathogenic variant. See the same section under question 1, above.

Other considerations

Gender. Our analysis did not show any significant difference in the risk of pancreatic cancer between males and female with the *BRCA2* pathogenic variant. The pooled risk estimate was 5.05 (95% CI, 1.02-9.08) for *BRCA2* males compared with 3.56 (95% CI, 1.50-5.61) for *BRCA2* females, based on RR, and 5.81 (95% CI, 3.34-8.23) for *BRCA2* males compared with 5.7 (95% CI, 3.11-8.43) for *BRCA2* females, based on SIR.

Family history of pancreatic cancer. We were unable to determine whether family history of pancreatic cancer was a significant risk factor for pancreatic cancer in individuals with the *BRCA2* pathogenic variant because most studies did not report on family history of pancreatic cancer in the enrolled population. In a study of over 5000 women with the *BRCA1/2* pathogenic variant, Iqbal et al[79]

found that the OR of developing pancreatic cancer for women with a affected first-degree relative with pancreatic cancer was 46.5 (95% CI, 9.5-230) compared with women without an affected first-degree relative. However, this estimate was based on just 1 patient with *BRCA2* with a sister diagnosed with pancreatic cancer at age 79 years and 1 patient with *BRCA1* whose mother was diagnosed with pancreatic cancer at age 77 years. Contrary results were reported in a study of 47 patients with the *BRCA2* pathogenic variant and 36 patients with the *BRCA1* pathogenic variant, where a family history of pancreatic cancer was not associated with pancreatic abnormalities on imaging studies.[83] In another study of *BRCA1/2* patients, Chahla et al[84] also found no association between family history of pancreatic cancer and pancreatic cancer risk and further noted that none of the patients with pancreatic cancer in their study had a family history of pancreatic cancer.

In a provisional clinical opinion, the American Society of Clinical Oncology recommended universal genetic testing for all patients with pancreatic cancer regardless of family history because up to 50% of patients without a family history of pancreatic cancer have pancreatic cancer–predisposing mutations.[85] It is likely that a similar proportion of individuals with *BRCA1/2* pathogenic variants with pancreatic cancer may not have a family history of pancreatic cancer. 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.[86] The panel therefore does not recommend that individuals with the *BRCA1/2* pathogenic variant should be required to have a family history of pancreatic cancer to be considered for pancreatic cancer screening.

Other risk factors. Studies did not uniformly report on other risk factors, such as smoking, alcohol use, and history of pancreatitis or diabetes, and therefore we were unable to assess for their impact on risk of pancreatic cancer in individuals with the *BRCA2* pathogenic variant.

Discussion

Our analysis had several limitations. Sampling was not at random and varied substantially across studies. Some studies selected patients enrolled based on cancer, some on familial cancer patterns in the family, and some on known *BRCA1/2* pathogenic variant. Not all analyses used genetically tested individuals. Some studies inferred genetic mutation status (eg, in relatives) using statistical models. There could be overlap in the individuals reported in different studies because some centers may have contributed data to more than 1 study. Most, but not all, cancers were confirmed by review of medical records, resulting in the possibility of misclassification of cancer type. The extent of this misclassification appeared to be small but was difficult to estimate. Based on the above, we were confident of an increased risk of pancreatic cancer in individuals with the *BRCA2* pathogenic variant. However, the exact magnitude of this increased risk could not be precisely estimated because of these limitations.

The reliance on family history to identify patients at increased cancer risk was explored and included acknowledging that risk models that included family history may be flawed because of incomplete and inaccurate family history records, small families, and in situations where many family members died prematurely in wars or natural disasters.[87-89] One study reported that the accuracy of family history for cancers other than breast and colorectal was as low as 37%.[87] One panelist noted that some of their Ashkenazi Jewish patients with *BRCA* mutations were the only surviving members of their family from the Holocaust and would not qualify for pancreatic cancer screening if a family history threshold was applied. Some panelists noted that their institution already offered screening to all *BRCA* patients regardless of family history.

A patient representative on the panel stated that for patients with the *BRCA1/2* pathogenic variant, caregivers rarely discuss the risk of pancreatic cancer and that the discussion mostly centers around risks of breast and ovarian cancer. She believed most patients were unaware of their pancreatic cancer risk and screening options. She emphasized the need for patient and provider education on this topic.

In balancing the desirable and undesirable effects of screening, the patient advocate also voiced the importance of the value patients place on cancer preventive surgery. The patient advocate and oncologists noted that the *BRCA* patient population was especially proactive and was accepting of preventive surgeries such as mastectomy, hysterectomy, and oophorectomy and therefore may also be accepting of pancreatic cancer screening and the option to decide about potential surgery.

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

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

We used the same systematic review as in question 3a to determine the risk of pancreatic cancer in individuals with the *BRCA1* pathogenic variant (Fig. 7). A summary of outcomes and their assessment can be seen in Table 8.

TABLE 6. Evidence profile for question 3a: Should individuals with the *BRCA2* pathogenic variant undergo screening for pancreatic cancer?

		Certainty assessment			
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**	**Imprecision**
BRCA2: *Lifetime relative risk of PDAC*					
5	Observational studies	Not serious	Not serious	Not serious	Not serious
BRCA2: *Lifetime SIR of PDAC*					
3	Observational studies	Not serious	Not serious	Not serious	Serious *
Cumulative yield of screening for high-risk lesions (BRCA1/2)					
8	Observational studies	Not serious	Not serious	Not serious	Serious *

PDAC, Pancreatic ductal adenocarcinoma; *SIR*, standardized incidence ratio.
*Few cancer outcomes.

Lifetime RR of pancreatic cancer

For the outcome of lifetime RR of pancreatic cancer in individuals with the *BRCA1* pathogenic variant, we included 4 studies in our meta-analysis.[73,76-78] The pooled estimate of RR was 1.93 (95% CI, 1.01-2.84; $P = .28$ and $I^2 = 21.0$) (Table 7 and Fig. 10). When we used this estimate, the cumulative lifetime risk of pancreatic cancer to age 80 was estimated to be 3.5%. While assessing the certainty of evidence of this outcome using the GRADE approach, we judged the quality of evidence to be low.

Lifetime SIR of pancreatic cancer

For the outcome of lifetime SIR of pancreatic cancer in individuals with the *BRCA1* pathogenic variant, we included 3 studies in our meta-analysis.[79-81] The pooled estimate of SIR was 3.69 (95% CI, 2.54-4.84; $P = .45$ and $I^2 = .0$) (Table 7 and Fig. 10). When we used this estimate, we estimated the absolute lifetime risk of pancreatic cancer to age 80 to be 3.8%. While assessing the certainty of evidence of this outcome using the GRADE approach, we judged the quality of evidence to be low.

Mortality

No studies reported on all-cause or pancreatic cancer–related mortality in screen-detected pancreatic cancer in individuals with the *BRCA1* pathogenic variant compared with unscreened individuals.

Yield of screening for high-risk lesions

See the same section in question 3a, above.

Yield of screening for resectable and borderline-resectable lesions

No studies reported on the yield of resectable and borderline-resectable lesions during screening in individuals with the *BRCA1* pathogenic variant.

Psychological benefits of screening

No studies reported on the psychological benefits of screening specific to individuals with the *BRCA1* pathogenic variant. See the same section under question 1, above.

Harms from screening

No studies reported on the harms from screening specific to individuals with the *BRCA1* pathogenic variant. See the same section under question 1, above.

Other considerations

Gender. Our analysis did not show any significant difference in risk of pancreatic cancer between males and female with the *BRCA1* pathogenic variant. The pooled risk estimate was 3.09 (95% CI, 1.86-5.15) for *BRCA1* males compared with 5.52 (95% CI, 2.96-8.08) for *BRCA1* females, based on SIR.

Family history of pancreatic cancer and other risk factors. See corresponding section under question 3a, above.

Discussion

We noted that the magnitude of association between pancreatic cancer and *BRCA1* was less consistent when compared with *BRCA2* because fewer individuals with *BRCA1* pathogenic variants were included in studies and very few *BRCA1*-related pancreatic cancers were noted in these studies. The risk of selection bias mentioned in the *BRCA2* panel discussion was also applicable to *BRCA1* studies. We discussed the possibility that the lower risk of pancreatic cancer reported with *BRCA1* compared with *BRCA2* may be unrelated to biologic differences between the 2 pathogenic variants but related to selection and other biases in the literature. It was also noted that historically, before 2012, the association between pancreatic cancer

TABLE 6. Continued

Certainty assessment			Effect			
Other considerations	Screening	No screening	Relative [95% confidence interval]	Absolute [95% confidence interval]	Certainty	Importance
BRCA2*: Lifetime relative risk of PDAC*						
None			Relative risk 5.1 [3.9-6.3]	Absolute lifetime risk of PDAC 5.2%	⨁⨁◯◯ Low	Critical
BRCA2*: Lifetime SIR of PDAC*						
None			SIR 7.2 [1.5-13.0]	Absolute lifetime risk of PDAC 7.4%	⨁◯◯◯ Very low	Critical
*Cumulative yield of screening for high-risk lesions (*BRCA1/2*)*						
None			8.6% [4.5-16.0]		⨁◯◯◯ Very low	Critical

TABLE 7. Summary of RR, SIR, and cumulative lifetime risk of pancreatic cancer to age 80 among *BRCA1* and *BRCA2* carriers

	BRCA1		BRCA2	
	RR	SIR	RR	SIR
Estimate	1.93 (1.01-2.84)	3.69 (2.54-4.84)	5.14 (3.95-6.33)	7.24 (1.51-12.97)
Lifetime risk to age 80, %	3.5	3.8	5.2	7.4

Values in parentheses are 95% confidence intervals.
RR, Relative risk; *SIR*, standardized incidence ratio.

and *BRCA1* was largely ignored, thus further limiting long-term data on the subject. One oncologist noted that there were no differences in response to chemotherapy between *BRCA1*- and *BRCA2*-related pancreatic cancers.

As with *BRCA2*, it was evident from the literature that patients with *BRCA1* were at increased risk of pancreatic cancer; however, quantification of risk estimate was imprecise. The panel reviewed literature showing that tumors with homologous recombination repair gene abnormalities such as *BRCA1/2* are responsive to platinum-based chemotherapeutic agents and poly(adenosine diphosphate-ribose) polymerase inhibitors.[90-93] A landmark randomized, placebo-controlled trial showed improved progression-free survival in patients with metastatic pancreatic cancer when treated with the poly(adenosine diphosphate-ribose) polymerase inhibitor olaparib.[93] Patients with *BRCA1/2* with borderline-resectable pancreatic cancers have also been shown to have higher rates of complete pathologic response to neoadjuvant platinum-based chemotherapy.[94] The panel recognized this as an opportunity to identify patients who may benefit for such treatments and therefore chose to accept a lower threshold to recommend pancreatic cancer screening than the widely accepted threshold of pancreatic cancer lifetime risk or a relative risk >5 (also see the discussion under question 6 in Summary and Recommendations article).[95] Of note, even though the point estimate of RR and lifetime risk of pancreatic cancer in *BRCA1* did not cross the RR ≥5 or lifetime risk ≥5% threshold, the 95% CIs were close to these thresholds.

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 should be performed**
> (*conditional recommendation, very low quality of evidence*).

We did not find any studies that reported patient outcomes based on screening intervals. We therefore used 2 methods to determine the frequency of pancreatic cancer screening. First, we reviewed screening intervals used within each of the 25 studies included in the systematic review to determine existing practices regarding screening frequency (Fig. 1). Sixteen studies did not report a screening interval or reported results of a 1-time screening. Of the remaining 9 studies, 7 used a 1-year screening interval.[13,15,16,19,29,30,96] The screening interval of Mocci et al[24] varied between 3 months and 1 year based on

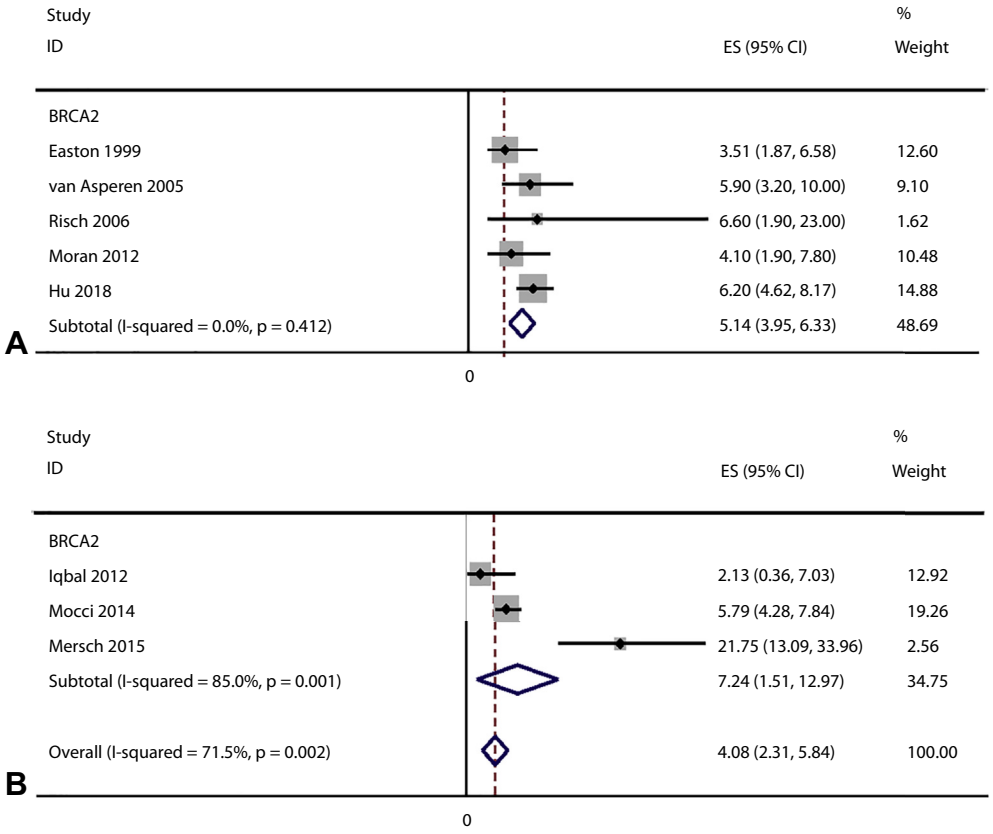

Figure 8. Forest plots of the 8 studies showing the (A) relative risk and (B) standardized incidence ratios for pancreatic cancer among individuals with *BRCA2* pathogenic variants. *CI*, Confidence interval; *ES,* effect size.

genetic condition and of Sheel et al[31] varied between 1 and 3 years based on results of duodenal aspirate analysis and previous tests. No study reported on mortality or yield of screening based on length of screening interval.

Second, we reviewed models on the progression time of pancreatic cancers. A quantitative analysis of the timing of genetic evolution of pancreatic cancer predicted at least a decade and a half between the occurrence of the initiating mutation and acquisition of metastatic ability.[97] Although this model suggests ample opportunity for early intervention, it is likely that for much of its life cycle the tumor is too small to be clinically detected by current screening tests like EUS or MRI. To understand the timing of cancer progression, Yu et al[98] compared the mean age of patients with pancreatic cancer at different stages. They found that patients with stage 1 cancer were only 1.3 years younger than those with stage IV cancer, whereas patients with T1 cancer were 1.06 years younger than those with T3 and 1.19 years younger than those with T4 cancers. In another study, Gangi et al[99] retrospectively reviewed CTs that were done in the months leading to a diagnosis of pancreatic cancer. Lesions that were definitive or suspicious for pancreatic cancer were noted in up to 50% of CTs done within 18 months before cancer diagnosis but were rarely noted on CTs done more than 18 months before. Taken together, these studies suggest once the tumor becomes clinically apparent, the progression from localized to advance stage may occur within a year, and we therefore concluded that screening should be done at yearly intervals for cancer to be detected at an early stage.

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 underlying genetic condition**
(*conditional recommendation, very low quality of evidence*).

To determine which genetic conditions should undergo pancreatic cancer screening, we took into consideration the risk threshold at which pancreatic screening is usually recommended, available literature on pancreatic cancer risk for each genetic condition, patient population enrolled in studies included in our pancreatic cancer screening meta-analysis, and pancreatic cancer screening

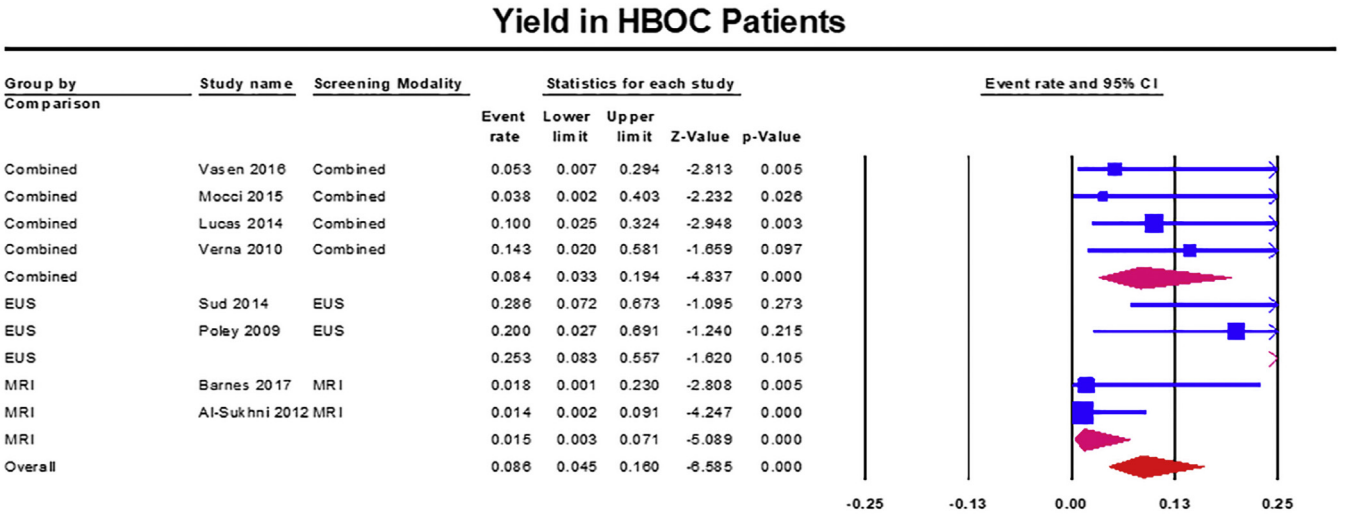

Figure 9. Forest plot of the 8 studies showing the cumulative yield (ie, pancreatic cancer, high-grade dysplasia, grade III pancreatic intraepithelial neoplasia) of screening among individuals with *BRCA2* and *BRCA1* pathogenic variants. *HBOC*, Hereditary breast ovarian cancer; *CI,* confidence interval; *MRI*, magnetic resonance imaging.

recommendations made by others (a table summarizing these recommendations can be found in Appendix 2, available online at www.giejournal.org).

A lifetime risk of pancreatic cancer >5% or RR >5 has been proposed as the threshold to define individuals at high risk for pancreatic cancer.[60] This threshold was initially proposed based on expert opinion and that screening for other cancers like colon cancer that had an equivalent lifetime prevalence was widely practiced.[60] This threshold has now been widely accepted and acknowledged by guidelines and clinical practice updates to determine when pancreatic cancer screening is recommended.[61,64,65,100] Corral et al[39] performed an economic analysis and found pancreatic cancer screening to be cost-effective at this threshold.

We reviewed the patient population enrolled in each of the 25 studies in our systematic review and, when reported, categorized the population by individual genetic condition. When all studies were considered together, the enrolled patient population was as follows: FPC = 1780, familial atypical multiple mole melanoma (FAMMM) syndrome = 393, *BRCA2* pathogenic variant = 219, *BRCA1* pathogenic variant = 50, *PALB2* pathogenic variant = 11, *BRCA* pathogenic variant not further specified = 88, hereditary pancreatitis = 42, Peutz-Jeghers syndrome = 41, Lynch syndrome = 20, and (ataxia-telangiectasia mutated) *ATM* pathogenic variant = 18. For several rare conditions (ie, FPC, FAMMM syndrome, Peutz-Jeghers syndrome, Lynch syndrome, hereditary pancreatitis, *PALB2*, and *ATM* pathogenic variant) only limited data were available to estimate pancreatic cancer risk, influence of family history of pancreatic cancer on pancreatic cancer risk, age at cancer onset, and outcomes of screening. These conditions were therefore not subjected to a systematic review of the literature, meta-analysis, or GRADE methodology. To make recommendations including age to initiate screening, the panel relied on existing literature, national and international guidelines, and the following principle: Conditions that moderately increased the risk of pancreatic cancer, defined as a lifetime risk of pancreatic cancer <10%, the panel generally recommended screening only in those who also had a family history of pancreatic cancer and to start screening at an age 1 standard deviation before the mean age of the pancreatic cancer diagnosis reported in that population. For conditions that significantly increased the risk of pancreatic cancer, defined as a lifetime risk of pancreatic cancer ≥10%, the panel generally recommended screening regardless of family history of pancreatic cancer and to start screening at an age 2 standard deviations before the mean age of pancreatic cancer diagnosis reported in that population. Below is a summary of evidence used to determine age at screening based on genetic susceptibility condition.

BRCA2 pathogenic variant: age 50

Four studies (97 patients) reported the age at diagnosis of pancreatic cancer in *BRCA2* carriers with a mean age of 59.8 years (Iqbal et al[79]), 62.9 ± 11.7 years (Kim[101]), 60 years (Van Asperen et al[75]), and 63.1 ± 11.0 years (Mocci et al[80]), with a range from 33 to 87 years. The mean age at diagnoses is lower in *BRCA2* than in the general U.S. population reflected in the SEER database of 70 years.[102]

BRCA1 pathogenic variant: age 50

Three studies reported on the age at diagnosis of pancreatic cancer (103 patients) in *BRCA1* carriers. The mean age at diagnoses is lower in *BRCA1* than in the general U.S. population reflected in the SEER database of 70 years.[102]

TABLE 8. Evidence profiles for question 3b: Should individuals with the *BRCA1* pathogenic variant undergo screening for pancreatic cancer?

Certainty assessment				
No. of studies	**Study design**	**Risk of bias**	**Inconsistency**	**Indirectness**
BRCA1*: Lifetime relative risk PDAC*				
4	Observational studies	Not serious	Not serious	Not serious
BRCA1*: Lifetime SIR PDAC*				
3	Observational studies	Not serious	Not serious	Not serious
Cumulative yield for screening for high risk lesions for BRCA1/2				
8	Observational studies	Not serious	Not serious	Not serious

PDAC, Pancreatic ductal adenocarcinoma; *SIR*, standardized incidence ratio.
*Few cancer outcomes.

PALB2 pathogenic variant: age 50

At the time of our systematic review, no studies addressed the lifetime risk of pancreatic cancer in individuals with the *PALB2* pathogenic variant in sufficient numbers or detail. Across the studies included in our systematic review of pancreatic cancer screening studies, only 11 carriers had the *PALB2* pathogenic variant. A study published after the conduct of our systematic review that included 524 families of 976 individuals from 21 countries estimated the RR of pancreatic cancer to be 2.37 (95% CI, 1.24-4.50), which translated to an absolute risk to age 80 of 2.2% (95% CI, 1.2-4.2) for females and 2.8% (95% CI, 1.5-5.3) for males in their model.[103]

FPC: age 50 years, or 10 years earlier than the youngest relative with pancreatic cancer, whichever comes first

FPC kindreds are defined as those having at least 1 pair of first-degree relatives with pancreatic cancer without an association with a known hereditary cancer syndrome.[104-108] Although the putative gene for FPC has not been identified, modeling studies suggest autosomal-dominant inheritance of a rare allele as the likely etiology.[109] In a prospective registry-based study, SIR for pancreatic cancer was significantly elevated in FPC kindreds (9.0; 95% CI, 4.5-16.1).[104] Pancreatic cancer risk in FPC kindreds was elevated in individuals with 3 (32.0; 95% CI, 10.2-74.7), 2 (6.4; 95% CI, 1.8-16.4), or 1 (4.6; 95% CI, .5-16.4) affected first-degree relative. FPC kindreds who smoked were at higher risk for pancreatic cancer (SIR, 19.2; 95% CI, 7.7-39.5). Another study using the same registry found that the lifetime risk of pancreatic cancer increased with decreasing age at pancreatic cancer onset in the kindred (hazard ratio, 1.55; 95% CI, 1.19-2.03 per year).[110] In this registry the mean age at diagnosis for pancreatic cancer for men was 69.5 ± 8.5 years and for women was 68.4 ± 14.3 years. No incident pancreatic cancer was found in individuals <45 years of age.

In our systematic review, 1780 patients with FPC syndrome underwent screening, of which 32 were diagnosed with pancreatic cancer. The mean age at cancer diagnosis was 63.6 ± 10.2 years (median, 62.5; range, 44-82). Only 3 cancers were diagnosed before age 50.

Patients who have a family history of pancreatic cancer but do not meet the criteria for FPC are also at increased risk of developing pancreatic cancer. A meta-analysis of 7 case-control and 2 cohort studies involving 6568 pancreatic cancer patients found an overall RR for pancreatic cancer of 1.80 (95% CI, 1.48-2.12) for these patients.[111] No significant difference in cancer risk was noted between those with a first-degree or a second-degree relative with pancreatic cancer (RR, 3.3 [95% CI, 1.8-6.1] vs 2.9 [95% CI, 1.3-6.3]) or between those with early- or late-onset pancreatic cancer in the index case (RR, 2.69 [95% CI, .56-4.82] vs 3.41 [95% CI, .79-6.03]). Another report using data from the National Familial Pancreas Tumor Registry found the SIR for pancreatic cancer in those with a family history of pancreatic cancer who did not meet the criteria for FPC to be 2.41 (95% CI, 1.04-4.47).[110] No difference in risk was noted between those with young and later-onset kindred with pancreatic cancer (2.74 [95% CI, .05-15.30] vs 2.36 [95% CI, .95-4.88]).

Taken together, these data suggest that 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. The degree of relatedness and age at onset of pancreatic cancer in the index patient does not appear to affect cancer risk. Pancreatic cancer screening is recommended for those in whom RR of pancreatic cancer exceeds 5 or the lifetime risk of pancreatic cancer exceeds 5%. Pancreatic cancer risk for patients with a family history of pancreatic cancer who do not meet criteria for FPC are likely to fall below this threshold and may not benefit from screening. Of note, a consensus guideline also recommended screening for individuals with 3 or more blood relatives with pancreatic cancer with at least 1 affected first-degree relative and for

TABLE 8. Continued

Certainty assessment			Effect			
Imprecision	Other considerations		Screening	Certainty	Importance	
BRCA1: *Lifetime relative risk PDAC*						
Not serious	None		Relative risk 1.9 [1.0-2.8] Absolute lifetime risk of PDAC 3.5%	⨁⨁◯◯ Low	Critical	
BRCA1: *Lifetime SIR PDAC*						
Not serious	None		SIR 3.69 (2.54-4.84) Absolute lifetime risk of PDAC 3.8%	⨁⨁◯◯ Low	Critical	
Cumulative yield for screening for high risk lesions for BRCA1/2						
Serious *	None		8.6% [4.5-16.0]	⨁◯◯◯ Very low	Critical	

those with 2 affected blood relatives with pancreatic cancer with at least 1 first-degree relative.[60,61]

FAMMM syndrome: age 40, or 10 years earlier than the youngest relative with pancreatic cancer

FAMMM syndrome is an autosomal-dominant condition characterized by the presence of multiple moles and a strong predisposition for the development of melanoma and pancreatic cancer.[112,113] FAMMM syndrome is associated with mutations in the *CDKN2A* gene and rarely *CDK4* gene. In individuals with FAMMM syndrome, the SIR for pancreatic cancer is between 13.1 (95% CI, 1.5-47.4) and 21.8 (95% CI, 8.7-44.8).[114] The cumulative risk of developing pancreatic cancer by age 75 years is estimated to be 17%.[115]

In a study of 50 patients with pancreatic cancer with p16-Leiden founder mutation in the *CDKN2A* gene from the Netherlands, the median age at cancer diagnosis was 55 years, with a range of 21 to 76 years.[116] In a study of 22 patients with pancreatic cancer from 159 FAMMM syndrome families for whom the age at cancer diagnosis was known, the mean age at pancreatic cancer diagnosis was 59.2 ± 11.7 years (median, 58; range, 39-78).[117] Our systematic review included 393 patients with FAMMM syndrome of whom 19 were diagnosed with pancreatic cancer. The mean age at diagnosis was 57.6 ± 10.2 years (median, 57; range, 39-77). Only 1 of 19 cancers was diagnosed in a patient before age 45.

Peutz-Jeghers syndrome: age 35, or 10 years earlier than the youngest relative with pancreatic cancer

Peutz-Jeghers syndrome is an autosomal-dominant syndrome characterized by hamartomatous GI polyps and mucocutaneous pigmentation.[118] Peutz-Jeghers syndrome is associated with germline mutations in the *STK11* (*LKB1*) gene, and there in a marked increase in the risk of GI cancers including colorectal, small bowel, gastric, and pancreatic cancer and non-GI cancer such as breast cancer.[119,120]

A systematic review found that Peutz-Jeghers syndrome individuals were 132 times more like to develop pancreatic cancer compared with the general population.[120] In that report, the mean age at diagnosis was 52 years; however, the standard deviation and age range were not provided. The cumulative risk of developing pancreatic cancer to ages 65 to 70 years was estimated to be 11% to 36%.[121,122] In a study of 240 individuals with Peutz-Jeghers syndrome with germline mutations in *STK11*, 6 patients were diagnosed with pancreatic cancer. All pancreatic carcinomas were diagnosed between ages 34 and 49 years.[123] In another study of 144 Peutz-Jeghers syndrome patients, 7 pancreatic cancers were noted at a mean age of 50.9 ± 12.4 years (median, 54).[124] Based on 2 patients who developed cancer at the ages of 35 and 36 years, these authors suggested that screening in individuals with Peutz-Jeghers syndrome should start at age 30 years. In our meta-analysis, of 41 individuals with Peutz-Jeghers syndrome, 2 were diagnosed with pancreatic cancers at ages 47 and 66 years.

ATM heterozygotes with a first- or second-degree relative with pancreatic cancer: age 50, or 10 years earlier than the youngest relative with pancreatic cancer

Ataxia-telangiectasia is a rare autosomal-recessive disorder caused by mutations in the ataxia-telangiectasia mutated (*ATM*) gene.[125,126] Homozygotes for the *ATM* pathogenic variant develop progressive neurologic abnormalities like cerebellar ataxia and oculocutaneous telangiectasias. Up to 2% of all whites in the United States may be heterozygotes for the *ATM* pathogenic variant.[127,128] Although heterozygotes do not develop neurologic disease, they may be at increased risk of breast and pancreatic cancer.[129] Hu et al found an *ATM* pathogenic variant in 41 of 1213 patients with pancreatic cancer (carrier frequency of 3.8% vs .38% in control subjects) and computed an OR for pancreatic cancer of 8.96 (95% CI, 6.1-13). The age at diagnosis was not provided. Of note, 38.1% of patients with pancreatic cancer had a first- or second-degree relative with

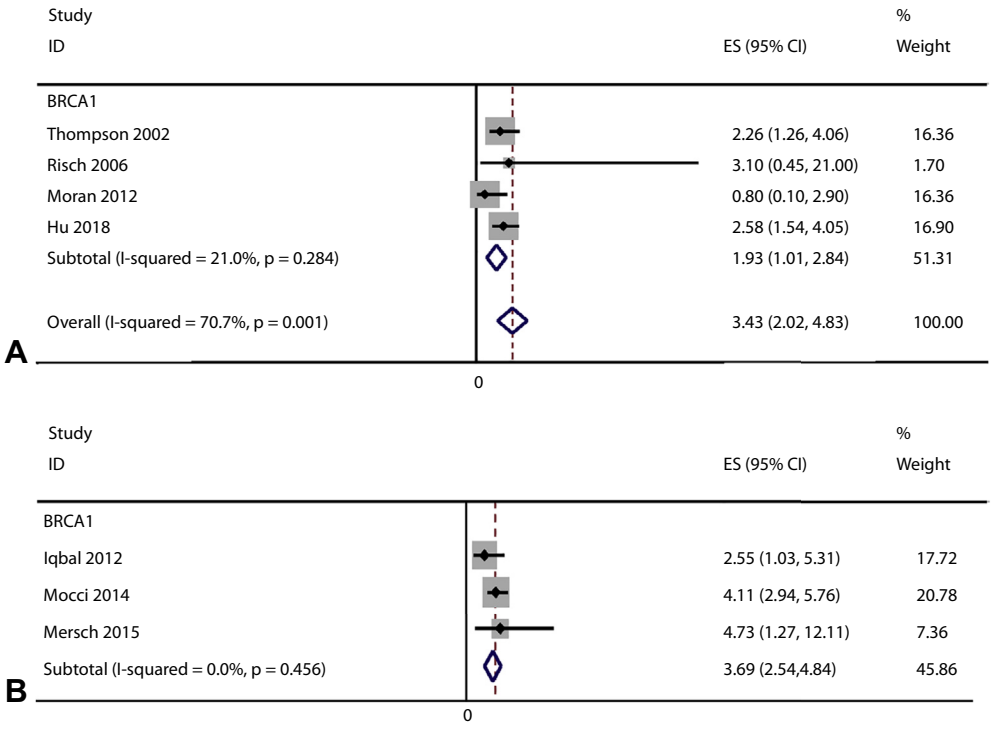

Figure 10. Forest plots of the 7 studies showing the (A) relative risk and (B) standardized incidence ratios for pancreatic cancer among individuals with *BRCA1* pathogenic variants. *CI*, Confidence interval; *ES*, effect size.

pancreatic cancer. Our systematic review did not yield any pancreatic cancers in *ATM* carriers.

Lynch syndrome with first- or second-degree relative with pancreatic cancer: age 50, or 10 years earlier than the youngest relative with pancreatic cancer

Lynch syndrome is an autosomal-dominant disorder that is caused by pathogenic germline variants in any of the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, *EPCAM*). Individuals with Lynch syndrome are at increased risk of colorectal, endometrial, ovarian, stomach, small bowel, skin, and pancreatic cancer.

In a prospective cohort of 446 unaffected individuals with a mismatch repair pathogenic variant who were followed for a median of 5 years, 2 pancreatic cancers were noted (SIR, 10.68; 95% CI, 2.7-47.7).[130] In another study using registries at the Dana Farber Cancer Institute and the University of Michigan with 6342 individuals with mismatch repair pathogenic variant,[131] the cumulative risk of pancreatic cancer was 1.3% (95% CI, .31-2.32) up to age 50 years and 3.7% (95% CI, 1.45-5.88) up to age 70 years. This pancreatic cancer risk was considered 8.6-fold (95% CI, 4.7-15.7) higher when compared with the general population. The median age at diagnosis and range for men was 51.5 years (19-85 years) and for women was 56.5 years (27-79 years). Fifty percent of cancers were diagnosed before age 50 years in men compared with 22% in women.

Hu et al reported on 1652 patients with pancreatic cancer who were identified from a 140,000-patient cohort undergoing multigene panel testing of predisposition genes. The authors found the *MSH2* pathogenic variant in 2 of 1190 patients with pancreatic cancer (carrier frequency of 0.17% vs .02% in control subjects) and computed an OR for pancreatic cancer of 7.1 (95% CI, 1.04-37.16). The authors found the *MSH6* pathogenic variant in 12 of 1190 patients with pancreatic cancer (carrier frequency of 1.01% vs .13% in control subjects) and computed an OR for pancreatic cancer of 7.79 (95% CI, 8.1-26.2). Of note, the association between *MSH2* and pancreatic cancer was based on a limited number of mutations detected among cancer cases. The age at diagnosis was not provided. Our systematic review did not yield any pancreatic cancers in Lynch syndrome patients.

Hereditary pancreatitis: age 40

Hereditary pancreatitis is defined as acute recurrent or chronic pancreatitis with a Mendelian pattern of inheritance, most often associated with mutations in the *PRSSI* gene.[132] Individuals with hereditary pancreatitis, especially those with the *PRSSI* pathogenic variant, are at increased risk for pancreatic cancer. Rebours et al[133] analyzed a French hereditary pancreatitis registry and found the median age at pancreatic cancer was 55 years (range, 39-78) and the cumulative risk of pancreatic cancer at ages 50, 60, and 75 years was 10%, 18.7%, and 53.5%, respectively. Howes et al[134] analyzed the European Registry of Hereditary

Pancreatitis and Pancreatic Cancer and found the overall cumulative risk of pancreatic cancer was 0% at 30 years, .5% at 40 years, 3.4% at 50 years, 9.8% at 60 years, 18.8% at 70 years, and 33.3% at 80 years (95% CI, 19.0%-47.5%). The cumulative risk of pancreatic cancer from symptom onset was 1.5% at 20 years, 2.5% at 30 years, 8.5% at 40 years, 14.6% at 50 years, 25.3% at 60 years, and 44.0% at 70 years. Lowenfels et al[135] invited members of the American Pancreatic Association and the International Association of Pancreatology to enroll their hereditary pancreatitis patients in a longitudinal study. Of the 246 hereditary pancreatitis patients enrolled, 8 pancreatic adenocarcinomas were noted with a mean age at cancer diagnosis of 56.9 ± 11.2 years during 8531 person-years of follow-up, yielding an SIR of 53. The estimated cumulative risk of pancreatic cancer to age 70 years was 40%. For patients with a paternal inheritance pattern, the cumulative risk of pancreatic cancer was approximately 75%. A study of 217 *PRSSI* pathogenic variant carriers from the United States found the SIR for pancreatic cancer to be 59 and the cumulative risk of pancreatic cancer by age 70 years to be 7.2%.[136]

The risk of pancreatic cancer in individuals with *SPINK1* and other mutations associated with hereditary pancreatitis is less well studied.[137] A study of 209 patients from France and England with the *SPINK1* pathogenic variant found a 12-fold increase in pancreatic cancer risk.[138] The cancer risk was .8% at 50 years, 11.9% at 60 years, 27.7% at 70 years, and 51.8% at 80 years.

In addition to recommendations from the National Comprehensive Cancer Network, American College of Gastroenterology, and Cancer of the Pancreas Screening (Appendix 2), screening recommendations were also made by a multisociety pancreatology group.[137] These guidelines recommend that screening should be considered for all affected individuals with an autosomal-dominant history of hereditary pancreatitis with and without known *PRSS1* pathogenic variants. Screening was not recommended in those with chronic pancreatitis associated with *SPINK1*, *CFTR*, *CTRC*, *CPA1*, or *CEL* pathogenic variants. Screening should start at age 40 years and be performed with CT or MRI. These guidelines also recommended against using EUS for screening, noting that early tumors may be obscured by fibrosis and calcifications.

HEALTH DISPARITIES AND HEALTH EQUITY

For each of the PICOs, the panel addressed feasibility and health equity, acknowledging that many patients have limited access to high-quality medical care and differences in use of cancer screening among diverse socioeconomic and racial groups contribute to health disparities. Out-of-pocket costs for patients for cancer screening tests can vary considerably depending on the type of health insurance plan and can act as a barrier to screening, which could further augment disparities in cancer outcomes.[55] Furthermore, the panel noted racial disparities in the diagnosis and treatment of pancreatic cancer, with African Americans experiencing higher incidences of pancreatic cancer and more frequently presenting with advanced-stage disease.[139] African Americans are also less likely to receive some cancer screening tests (eg, colorectal and prostate cancer) when compared with white Americans, and this may have implications for pancreatic cancer screening.[140]

Although there is consensus that pancreatic screening and subsequent care should ideally be performed at high-volume centers with multidisciplinary expertise, many patients eligible for screening may not have access to such centers. A study using New York City area hospital discharge data found that even after adjusting for insurance type and comorbidities, nonwhite patients were more likely to be operated on by a low-volume surgeon at a low-volume hospital.[141] Another study using the Nationwide Inpatient Sample found that patients operated on by high-volume pancreatic surgeons were more likely to be men, white, and residents of high-income zip codes.[142] The panel cautioned that recommendations considered in this guideline had the potential to worsen health disparities depending on their implementation in clinical care. Therefore, every effort should be made to implement programs for pancreatic screening that are equitable and accessible for all who meet criteria for screening, with particular attention to specific groups at risk of experiencing disparities, such as African Americans or those with lower socioeconomic status.

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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.

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Abbreviations: ASGE, American Society for Gastrointestinal Endoscopy; ATM, ataxia-telangiectasia mutated; FAMMM, familial atypical multiple mole melanoma; FPC, familial pancreatic cancer; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IPMN, intraductal papillary mucinous neoplasm; MRI, magnetic resonance imaging; OR, odds ratio; PanIN, pancreatic intraepithelial neoplasia; PICO, population, intervention, comparator, and outcomes; RR, relative risk; SEER, Surveillance, Epidemiology, and End Results Program; SIR, standardized incidence ratio.

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APPENDIX 1

Search strategies for the population, intervention, comparator, and outcomes (PICO) questions 1 and 2 (screening; EUS vs magnetic resonance imaging) and PICO questions 3 and 4 (risk of pancreatic cancer in *BRCA1*, *BRCA2*, and *PALB2*) for pancreatic cancer screening in individuals at increased risk because of genetic susceptibility

Search strategies for pancreatic cancer screening in individuals at increased risk because of genetic susceptibility

Search date: March 21, 2020

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2020 March 20; Wiley Cochrane

Limits: English language, human, 2017 to current

Excluded: Case reports, letters, editorials, comments, notes

Ovid MEDLINE(R), Embase

No.	Searches	Results
1	exp *pancreas cancer/ use emczd or exp *pancreas tumour/ use emczd	91206
2	exp *Pancreatic Neoplasms/ use ppez	61606
3	((Pancreatic or pancreas) adj2 (adenocarcinoma* or cancer* or neoplasm*)).ti,ab,kw.	133029
4	or/1-3	196195
5	exp *mass screening/	151526
6	exp *Population Surveillance/ use ppez	24991
7	exp *health survey/ use emczd	29583
8	exp *"Early Detection of Cancer"/ use ppez	13729
9	exp *early cancer diagnosis/ use emczd or exp *early diagnosis/ use emczd	13256
10	(screen* or surveil*).ti,ab,kw.	2162951
11	or/5-10	2242284
12	4 and 11	10522
13	exp Endosonography/ use ppez	12454
14	exp endoscopic ultrasonography/ use emczd	7966
15	(endoscop* adj2 (ultrasound* or ultrasonograph*)).ti,ab,kw.	33961
16	(eus or endosonograph*).ti,ab,kw.	34316
17	exp nuclear magnetic resonance imaging/ use emczd	936957
18	exp Magnetic Resonance Imaging/ use ppez	444251
19	((Magnetic Resonance or MR) adj2 (cholangiopancreatography or Imaging)).ti,ab,kw.	610070
20	or/13-19	1550633
21	12 and 20	1680
22	limit 21 to english language	1584
23	limit 22 to yr="2017 -Current"	548
24	animals/ not (humans/ and animals/)	6021236
25	23 not 24	548
26	limit 25 to (case reports or comment or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) In-Process, Ovid MEDLINE(R) Publisher, Embase; records were retained]	36
27	Case Report/	4644397
28	25 not (26 or 27)	442
29	remove duplicates from 28	345

Wiley Cochrane

ID	Search	Hits
#1	MeSH descriptor: [Pancreatic Neoplasms] explode all trees	1673
#2	((Pancreatic or pancreas) NEAR/2 (adenocarcinoma* or cancer* or neoplasm*)):ti,ab,kw	4597
#3	#1 or #2	4627
#4	MeSH descriptor: [Mass Screening] explode all trees	3626
#5	MeSH descriptor: [Population Surveillance] explode all trees	499
#6	MeSH descriptor: [Early Detection of Cancer] explode all trees	1043
#7	(screen* or surveil*):ti,ab,kw	73697
#8	#4 or #5 or #6 or #7	74138
#9	#3 and #8	192
#10	MeSH descriptor: [Endosonography] explode all trees	327
#11	(endoscop* NEAR/2 (ultrasound* or ultrasonograph*)):ti,ab,kw	1109
#12	(eus or endosonograph*):ti,ab,kw	1375
#13	MeSH descriptor: [Magnetic Resonance Imaging] explode all trees	7394
#14	((Magnetic Resonance or MR) NEAR/2 (cholangiopancreatography or Imaging)):ti,ab,kw	21872
#15	#10 or #11 or #12 or #13 or #14	23889
#16	#9 and #15 with Cochrane Library publication date Between Jan 2017 and Jan 2020	14

Search strategies for risk of pancreatic cancer in individuals with *BRCA1*, *BRCA2*, and *PALB2* pathogenic variants

Search date: December 13, 2019

Databases searched: Ovid MEDLINE: Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE® Daily and Ovid MEDLINE® 1946-Present, Embase Classic+Embase 1947 to 2019 December 12; Wiley Cochrane

Limits: Human, English, 1990 to current

Excluded: Case reports, editorial, letters, notes, comments, and conference abstracts published before 2017

Ovid MEDLINE(R), Embase

No.	Searches	Results
1	exp Genes, BRCA1/ use ppez	5853
2	exp BRCA1 Protein/	23005
3	exp Genes, BRCA2/ use ppez	3792
4	exp BRCA2 Protein/	16930
5	exp Fanconi Anemia Complementation Group N Protein/ use ppez	283
6	(brca1 or brca2 or palb2 or fancn or Fanconi Anemia Complementation Group N).ti,ab,kf,kw.	41352
7	('hereditary breast and ovarian cancer syndrome*').ti,ab,kf,kw.	832
8	or/1-7	50562
9	exp Pancreatic Neoplasms/ use ppez	73615
10	exp pancreas tumor/ use emczd	144623
11	exp pancreas cancer/ use emczd	100198
12	(pancreas or pancreatic).ti,ab,kf,kw.	593570
13	or/9-12	641903
14	8 and 13	2171
15	animals/ not (humans/ and animals/)	5985793
16	14 not 15	2156
17	limit 16 to english language	2098
18	limit 17 to yr="1990 -Current"	2096
19	limit 18 to (case reports or comment or editorial or letter or note) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) In-Process, Ovid MEDLINE(R) Publisher, Embase; records were retained]	128
20	Case Report/ or case report.ti.	4653589
21	18 not (19 or 20)	1854
22	limit 21 to (congress or conference abstract) [Limit not valid in Ovid MEDLINE(R),Ovid MEDLINE(R) Daily Update, Ovid MEDLINE(R) In-Process, Ovid MEDLINE(R) Publisher, Embase; records were retained]	516
23	limit 22 to yr="1860 - 2017"	369
24	21 not 23	1485
25	remove duplicates from 24	1067

Wiley Cochrane
With Publication Year from 1990 to 2019, in Trials

#1	MeSH descriptor: [Genes, BRCA1] explode all trees	80
#2	MeSH descriptor: [BRCA1 Protein] explode all trees	61
#3	MeSH descriptor: [Genes, BRCA2] explode all trees	65
#4	MeSH descriptor: [BRCA2 Protein] explode all trees	47
#5	MeSH descriptor: [Fanconi Anemia Complementation Group N Protein] explode all trees	0
#6	(brca1 or brca2 or palb2 or fancn or Fanconi Anemia Complementation Group N):ti,ab	759
#7	('hereditary breast and ovarian cancer syndrome*'):ti,ab	24
#8	#1 or #2 or #3 or #4 or #5 or #6 or #7	793
#9	MeSH descriptor: [Pancreatic Neoplasms] explode all trees	1558
#10	(pancreas or pancreatic):ti,ab	10918
#11	#9 or #10	11106
#12	#8 and #11	32

APPENDIX 2. Screening recommendations made by others for individuals with genetic susceptibility to pancreatic cancer

	National Comprehensive Cancer Network	American College of Gastroenterology	International Cancer of the Pancreas Screening Consortium
Familial pancreatic cancer	≥2 FDRs with PC, or ≥3 relatives with PC on same side of family. Start at age 50 years, or 10 years earlier than youngest relative with PC.	≥2 relatives with PC of whom at least 1 is an FDR, or ≥3 relatives with PC. Start at age 50 years, or 10 years earlier than youngest relative with PC.	2 relatives with PC, with at least 1 an FDR. Start at age 50 or 55 years, or 10 years earlier than youngest relative with PC.
Familial atypical multiple mole melanoma syndrome	Start at age 40 years, or 10 years earlier than youngest relative with PC.	Start at age 50 years, or 10 years earlier than youngest relative with PC.	Start at age 40 years.
Peutz-Jeghers syndrome	30-35 years, or 10 years earlier than youngest relative with PC.	Start at age 35 years.	Start at age 40 years.
Ataxia-telangiectasia	First- or second-degree relative with PC. Screening should start at age 50 years, or 10 years earlier than youngest relative with PC.	First- or second-degree relative with PC. Screening should start at age 50 years, or 10 years earlier than youngest relative with PC.	First-degree relative with PC. Screening should start at age 45-50 years, or 10 years earlier than youngest relative with PC.
Lynch syndrome	First- or second-degree relative with PC. Screening should start at age 50 years, or 10 years earlier than youngest relative with PC.	First- or second-degree relative with PC. Screening should start at age 50 years, or 10 years earlier than youngest relative with PC.	First-degree relative with PC. Screening should start at age 45-50 years, or 10 years earlier than youngest relative with PC.
Hereditary pancreatitis	Pathogenic variants in *PRSS1* or other hereditary pancreatitis genes and consistent clinical phenotype. Start 20 years after onset of pancreatitis or age 40 years.	Age 50 years, or 10 years earlier than youngest relative with PC.	Failed to reach consensus but stated that most experts recommended screening at age 40, or 20 years after the first pancreatitis attack.

FDR, First-degree relative; *PC,* pancreatic cancer.