Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium

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ABSTRACT

Background and aim The International Cancer of the Pancreas Screening Consortium met in 2018 to update its consensus recommendations for the management of individuals with increased risk of pancreatic cancer based on family history or germline mutation status (high-risk individuals).

Methods A modified Delphi approach was employed to reach consensus among a multidisciplinary group of experts who voted on consensus statements. Consensus was considered reached if ≥75% agreed or disagreed.

Results Consensus was reached on 55 statements. The main goals of surveillance (to identify high-grade dysplastic precursor lesions and T1N0M0 pancreatic cancer) remained unchanged. Experts agreed that for those with familial risk, surveillance should start no earlier than age 50 or 10 years earlier than the youngest relative with pancreatic cancer, but were split on whether to start at age 50 or 55. Germline *ATM* mutation carriers with one affected first-degree relative are now considered eligible for surveillance. Experts agreed that preferred surveillance tests are endoscopic ultrasound and MRI/magnetic retrograde cholangiopancreatography, but no consensus was reached on how to alternate these modalities. Annual surveillance is recommended in the absence of concerning lesions. Main areas of disagreement included if and how surveillance should be performed for hereditary pancreatitis, and the management of indeterminate lesions.

Conclusions Pancreatic surveillance is recommended for selected high-risk individuals to detect early pancreatic cancer and its high-grade precursors, but should be performed in a research setting by multidisciplinary teams in centres with appropriate expertise. Until more evidence supporting these recommendations is available, the benefits, risks and costs of surveillance of pancreatic surveillance need additional evaluation.

INTRODUCTION

Pancreatic cancer is a deadly disease and early detection is considered the most effective way to improve survival. The International Cancer of the Pancreas Screening (CAPS) Consortium first met in Baltimore in 2011 to establish consensus guidelines for surveillance of individuals with familial and/or inherited risk of developing pancreatic cancer. The 2013 CAPS Consortium guidelines were based on the first decade or so of experience with pancreatic surveillance.[1–12] More recent evidence includes two studies showing evidence of improved outcomes for high-risk individuals in a pancreatic surveillance programme, highlighting the potential for pancreatic surveillance to affect overall survival.[7 10]

Individuals with a strong family history and/ or genetic susceptibility have an increased risk of developing pancreatic cancer that manifests over several decades. To help ensure the benefits of pancreatic surveillance, clinicians should select those most likely to benefit, counsel patients on the risks and benefits of surveillance and optimally manage patients with lesions identified by surveillance. The International CAPS Consortium met in Baltimore in April 2018 to update its recommendations for pancreatic surveillance.

METHODS

Consensus development process

Conference chairs (Professors Canto, Goggins and Bruno) selected a multidisciplinary team of experts to participate in the guideline update. Guideline development used a modified Delphi approach.[13] Delphi uses multiple iterations of a questionnaire with feedback, enabling individual reassessment of opinion to generate convergence within the panel. Participants were asked to review literature ahead of an in-person meeting to discuss areas of consensus and controversy and to reach consensus on guideline questions. After the meeting, experts
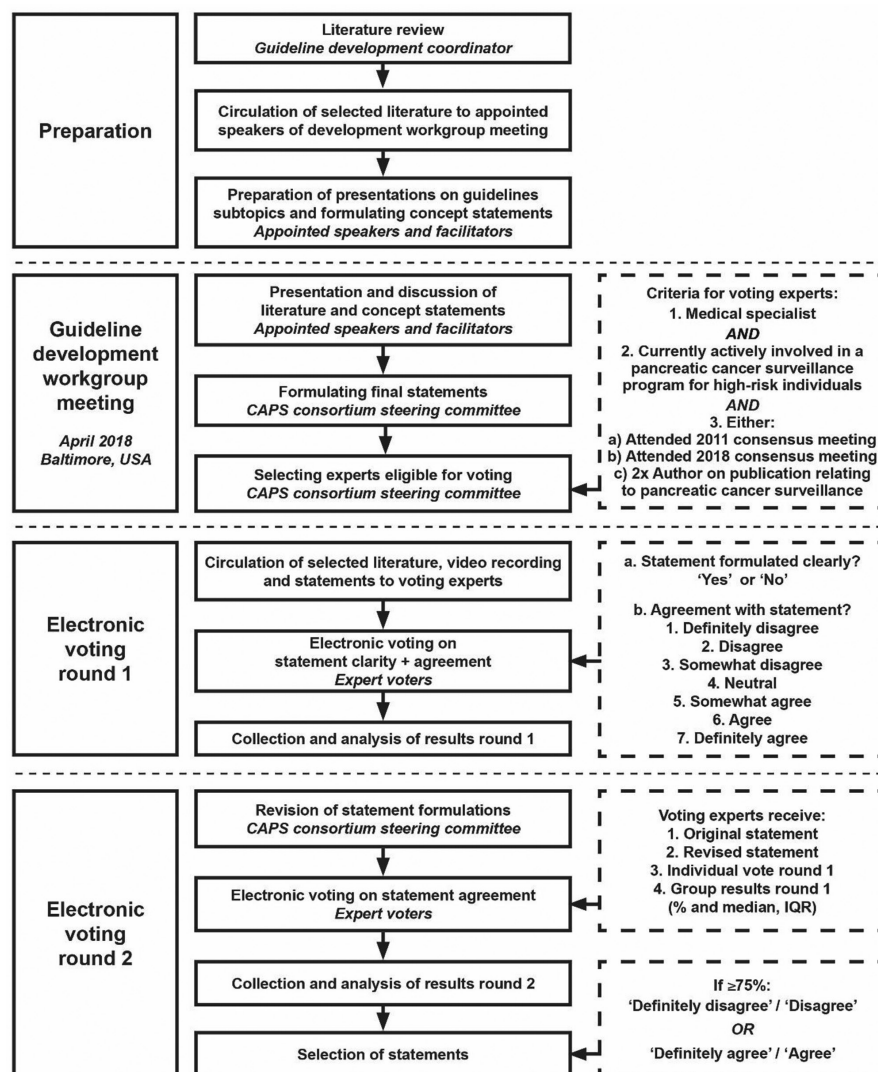
Figure 1 Flow chart of consensus development process. CAPS, Cancer of the Pancreas Screening consortium.

were asked to vote electronically and provide feedback on first-round questions; responses were incorporated into second-round electronic voting (figure 1).

Literature search and development workgroup meeting
One author (KAO) performed a systematic Medline search for relevant literature published since the 2011 meeting (online supplementary table S1). Speakers and facilitators were selected to discuss major guideline topics focusing on recent literature. Live audio-stream was available for experts not present in person, and the meeting was recorded. After the meeting, the steering committee (MG, KAO, DLC, MIC and MB) formulated voting statements based on 2013 guideline statements, new scientific insights, the meeting presentations and discussions. These statements were incorporated in an electronic survey.

Electronic voting rounds
International experts within the field of pancreatic cancer surveillance were invited to participate if they met the following criteria: a clinician actively involved in an institutional review board-approved pancreatic cancer surveillance programme for high-risk individuals, who attended either the 2011 or 2018 guideline development workgroup meeting or had been author

on two or more scientific publications relating to pancreatic cancer surveillance since 2011. All invited experts were given the recent literature summary and the workgroup meeting video.

In round 1, experts were asked to vote on statements on a seven-point Likert scale, ranging from 'strongly disagree' to 'strongly agree'. They could also opt-out from answering statements if they lacked expertise. After round 1, the steering committee revised statements deemed unclear by >5% of respondents.

In round 2, experts voted again and given (1) the original consensus statements and any revisions; (2) first-round voting for each question; and (3) their own voting. Voting was anonymous. Only the guideline coordinator (KAO) had access to voting results.

Statistical analysis, accepting and grading of statements
First-round group results, including distribution of answers with median and IQR, were given to voters. Statements were accepted as having reached consensus if after second-round voting ≥75% of experts disagreed ('strongly disagree' or 'disagree'), or agreed ('strongly-agree' or 'agree'). Non-votes were not included in consensus tabulations. All statistics were performed using SPSS v22 (IBM, Armonk, New York, USA). Strength of consensus

Table 1 Definition of high-risk individuals eligible for pancreatic cancer surveillance.

Gene mutation	PDAC family history criteria	Agreement	Grade
LKB1/STK11 (Peutz-Jeghers syndrome)	Regardless of family history	99%	1
CDKN2A p16* (FAMMM)	With at least one affected FDR	99%	1
CDKN2A p16* (FAMMM)	Regardless of family history	77%	1
BRCA2	If at least one affected FDR, or at least two affected relatives† of any degree	93%	2
PALB2	If at least one affected FDR	83%	2
MLH1/MSH2/MSH6 (Lynch)	If at least one affected FDR	84%	2
ATM	If at least one affected FDR	88%	2
BRCA1	If at least one affected FDR	69.6%‡	3
Regardless of gene mutation status	If at least three affected relatives† on the same side of the family, of whom at least one is an FDR to the individual considered for surveillance	97%	2
Regardless of gene mutation status	If at least two affected relatives† who are FDR to each other, of whom at least one is an FDR to the individual considered for surveillance	93%	2
Regardless of gene mutation status	If at least two affected relatives† on the same side of the family, of whom at least one is an FDR to the individual considered for surveillance	88%	2

*Only encompassing CDKN2A mutations leading to changes in the p16 protein.
†Wherever relative is stated, this indicates blood relatives only.
‡An additional 20.3% somewhat agreed with surveillance (total 89.9%).
ATM, ataxia telangiectasia mutated; BRCA2, breast cancer 2; CDKN2A, cyclin-dependent kinase inhibitor 2A; FAMMM, familial atypical multiple mole melanoma; FDR, first-degree relative; GRADE, Grading of Recommendations, Assessment, Development, and Evaluations; HBOC, hereditary breast and ovarian cancer; LKB1/STK11, liver kinase B1/serine/threonine kinase 11; Lynch syndrome, MLH1, mutL homolog 1; MSH2, mutS homolog 2; MSH6, mutS homolog 6; PALB2, partner and localizer of BRCA2; PDAC, pancreatic ductal adenocarcinoma.

was based on Grading of Recommendations Assessment, Development and Evaluation (GRADE)[14] definitions for quality improvement and guideline development: 1 (strong)='definitely do it', 2 (weak)='probably do it', 3 (no recommendation), 4 (weak)='probably don't do it', and 5 (strong)='definitely don't do it'.

RESULTS
Participants
Ninety-one experts met selection criteria and were invited to vote. Eighty-two completed the first round, 76 completed the second round (response rate 84%). The 76 final responders included 37 gastroenterologists, 16 surgeons, 7 pathologists, 6 radiologists, 5 geneticists, 3 oncologists, and two epidemiologists, from 11 countries and four continents; 70 (92%) worked in a university hospital setting. They had practised their profession for a median of 22 (IQR 15) years, and had been involved in a pancreatic cancer surveillance programme for a median of 10 (IQR 12) years.

Recommendation statements
A summary of the statements that reached consensus is provided in tables 1 and 2. All voting statements and results are provided

in online supplementary table S2. A summary of the main consensus recommendations is provided in table 3.

Who should be screened?
Age, family history and germline mutation status are the major criteria for determining eligibility for pancreatic surveillance. The number of first- and second-degree relatives with pancreatic cancer can be used to quantify pancreatic cancer risk.[15] For example, the estimated lifetime risk of developing pancreatic cancer for an individual with two first-degree relatives with pancreatic cancer is ~8%.[15 16] Family history of pancreatic cancer is also a risk factor for patients identified as having incidentally detected pancreatic cysts.[17] Current surveillance recommendations for a family history (generally in one blood relative) are the same as for those without a family history.[18 19]

Consensus on family history recommendations for pancreatic surveillance (ie, having at least one first-degree relative and one second-degree relative with pancreatic cancer) were the same as in the 2013 guidelines. Obtaining a comprehensive cancer family history from newly diagnosed patients with pancreatic cancer can help to identify family members who may benefit from surveillance. The average lifetime risk of developing pancreatic cancer (~1 in 64 in the USA) is too low for population-based screening.[20 21]

Germline mutation carriers
Pancreatic surveillance is recommended for carriers of germline deleterious variants in cancer susceptibility gene,[22–26]: BRCA2, ATM, BRCA1, PALB2, CDKN2A, STK11, MLH1 and MSH2. Recommendations for age and family history vary by gene. Surveillance for CDKN2A and STK11 (Peutz-Jegher syndrome) mutation carriers is recommended irrespective of patients' family history of pancreatic cancer, because of their high lifetime risk. Since the previous consensus, ATM mutation carriers have been added to the list recommended for surveillance. For carriers of mutations in ATM, BRCA2 and PALB2, the consensus among experts was to recommended surveillance for mutation carriers who have a blood relative with pancreatic cancer. Consensus on family history criteria for BRCA1 mutation carriers was not reached (table 1), but consensus was reached for recommending that BRCA1 mutation carriers undergo surveillance (online supplementary table S2).

Surveillance is recommended for patients with hereditary pancreatitis, with most experts recommending age 40 or 20 years after the first pancreatitis attack (online supplementary table S2), irrespective of gene status. The pancreatitis susceptibility genes, PRSS1, CPA1 and CTRC, are associated with significantly increased risk of developing pancreatitis.[27–30] Deleterious variants in CPA1 and CPB1 associated with pancreatic cancer risk may not always progress through a clinical syndrome of pancreatitis.[31]

Deleterious variants in the known pancreatic cancer susceptibility genes account for ~10–20% of the familial clustering of pancreatic cancer.[26 32 33] Deleterious variants have also been reported in ~5–10% of patients with apparently sporadic pancreatic cancer.[34–39] These variants also confer risk for other cancers.[40] Therefore, germline testing should be considered for individuals eligible for pancreatic cancer surveillance.[41 42] Recent National Comprehensive Cancer Network (NCCN) guidelines recommend offering gene testing for patients with newly diagnosed pancreatic ductal adenocarcinoma; this recommendation did not reach consensus among CAPS experts (online supplementary table S2). American Society of Clinical Oncology guidelines

Guidelines

Table 2 Statements that reached consensus

Statement	Agreement grade	grade
At what age should pancreatic surveillance begin?		
1. For patients with a familial risk (no known germline mutations or PJS), screening should begin by the age of…	10.3%	4
	67.6%	2
▶ 45 years or 10 years younger than the youngest relative with PDAC	22.1%	2
▶ 50 years or 10 years younger than the youngest relative with PDAC		
▶ 55 years or 10 years younger than the youngest relative with PDAC		
2. For germline mutation carriers (excluding PJS), screening should begin 5 years earlier than for high-risk individuals with defined familial pancreatic cancer	74.7%	2
3. For patients with PJS, screening should begin at least by the age of…	14.9%	4
▶ 30 years or 10 years younger than the youngest relative with PDAC	17.9%	4
▶ 35 years or 10 years younger than the youngest relative with PDAC	67.2%	2
▶ 40 years or 10 years younger than the youngest relative with PDAC		
4. New-onset diabetes in a high-risk individual should lead to initiation of screening, regardless of age.	82.4%	2
How should high-risk individuals be screened?		
5. *Baseline* pancreatic screening tests should include (multiple answers allowed)	86.8%	2
▶ EUS	92.1%	2
▶ MRI/MRCP	19.7%	4
▶ CT	2.6%	5
▶ Abdominal ultrasound		
6. Follow-up pancreatic screening tests should include (multiple answers allowed)	89.5%	2
▶ EUS	89.5%	2
▶ MRI/MRCP	15.8%	4
▶ CT	1.3%	5
▶ Abdominal ultrasound		
7. CA19-9 should be used as an additional surveillance test for individuals with worrisome features on imaging	76.5%	2
8. Routine testing for diabetes mellitus with fasting blood glucose and/or haemoglobin A1c should be performed.	76.1%	2
Surveillance questions		
9. In the absence of pancreatic abnormalities, the recommended surveillance interval is 12 months	90.4%	2
10. For patients with small (<1 cm), non-functioning neuroendocrine tumours, the recommended surveillance interval is 12 months	82.6%	2
11. For patients with low-risk findings (ie, pancreatic lobulation or a cyst without worrisome features), the recommended surveillance interval is 12 months	88.6%	2
12. For *CDKN2A p16* mutation carriers with newly detected pancreatic abnormalities that are concerning but do not lead to surgery (mild MPD dilation, stricture without mass), repeat imaging should be performed within 3–6 months	98.5%	2
13. A diagnosis of new-onset diabetes* in an HRI under surveillance, prompts immediate investigations	90.3%	2
14. Smoking status does not affect the surveillance interval	76.8%	2
15. When a cystic lesion with worrisome features (ie, mural nodule, solid component, duct dilation, etc) is detected, EUS-FNA should be performed.	84.3%	2
16. When a solid lesion is detected, CT should be performed	95.7%	1
17. At detection of a solid lesion, EUS-FNA should be performed…	70.1%	2
▶ Always	19.4%	1
▶ If ≥5 mm	4.5%	1
▶ If ≥10 mm	6.0%	5
▶ Never		
18. When a solid lesion of uncertain significance is newly detected and the patient is not referred for surgery, imaging should be repeated after 3 months	91.2%	1
19. Standardised nomenclature should be used to define chronic pancreatitis-like abnormalities	98.6%	2
20. When an asymptomatic MPD stricture with an associated suspicious mass is detected…	75.7%	1
▶ EUS-FNA should be performed	81.2%	2
▶ Surgery should be performed		
21. When an asymptomatic MPD stricture of unknown aetiology (without a mass) is detected…	86.6%	1
▶ CT should be performed	77.9%	1
▶ EUS-FNA should be performed		
22. When a patient with an MPD stricture is not referred for surgery, repeat imaging should be performed within 3 months	98.5%	1

Goggins M, *et al. Gut* 2020;**69**:7–17. doi:10.1136/gutjnl-2019-319352

Table 2 Continued

Statement	Agreement grade	grade
When should surgery be performed?		
23. A solid lesion, detected by EUS (except biopsy-proven or highly suspicious to be neuroendocrine, autoimmune or other benign conditions) should be resected…	64.7%	4
▶ Regardless of size	77.9%	1
▶ When ≥5 mm	91.2%	1
▶ When ≥10 mm		
24. In an HRI undergoing pancreatic screening, an IPMN should be resected in case of…	91.0%	1
▶ A mural nodule	97.0%	1
▶ An enhanced solid component	95.5%	1
▶ Symptoms, including pancreatitis, jaundice, pain	76.1%	1
▶ Thickened/enhanced cyst walls	91.0%	1
▶ Abrupt change in MPD with distal pancreatic atrophy	97.0%	1
▶ An MPD ≥10 mm		
25. Pancreatic resections should be performed at specialty centres	95.9%	1
26. In cases of suspected PC, an oncological radical resection is indicated	92.9%	1
27. When an HRI undergoes surgery for suspected small PC (max. 1 cm, T1M0N0 on imaging), a partial pancreatectomy is suitable	89.6%	2
Goals of surveillance		
28. Detection and treatment of the following pathological lesion should be considered a 'success' of a screening programme:	96%	1
▶ Resected cancer, confined to the pancreas, with negative margins, at baseline	85%	1
▶ Resected cancer, confined to the pancreas, with negative margins, at follow-up	99%	2
▶ Multifocal PanIN-3	97%	2
▶ Unifocal PanIN-3	97%	1
▶ IPMN with high-grade dysplasia	75%	2
▶ Pancreatic neuroendocrine tumour ≥10 mm		

CA19-9, carbohydrate antigen 19–9; CDKN2A, cyclin-dependent kinase inhibitor 2A; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; HRI, high-risk individual; IPMN, intraductal papillary mucinous neoplasm; MPD, main pancreatic duct; MRI/MRCP, magnetic resonance imaging/magnetic retrograde cholangiopancreatography; PanIN-3, pancreatic intraepithelial neoplasia-3; PC, pancreatic ductal adenocarcinoma; PDAC, pancreatic ductal adenocarcinoma; PJS, Peutz-Jeghers syndrome.

also consider the role of gene testing for patients with pancreatic cancer.[43] The average lifetime risk of developing pancreatic cancer has been estimated in prospective studies for carriers of deleterious variants in *BRCA2, BRCA1, CDK2NA, PRSS1, MLH1* and *MSH2*,[12 25 29 44–46] and odds of developing pancreatic cancer from case/control analysis for *ATM, PALB2* and *TP53*.[35] Many individuals undergo gene testing because a germline mutation was identified in a blood relative who developed cancer. The risk of pancreatic cancer in *ATM/BRCA/PALB2* mutation carriers without a pancreatic cancer family history is not well defined. A study of *BRCA* mutation carriers found no difference in pancreatic cyst prevalence by family history; although the authors suggested pancreatic surveillance is appropriate for *BRCA* mutation carriers irrespective of family history, more evidence on this question is needed.[47] Although family history remains an important risk assessment tool,[48] pedigrees are often small and family histories incomplete. Further research is needed to better define how family history of pancreatic cancer in mutation carriers influences their risk of developing the disease.

At what age should pancreatic surveillance begin?

For individuals who meet familial risk criteria (without a defined genetic mutation) the consensus was that surveillance should begin at age 50 or later; but some experts thought surveillance should begin at 50, others at age 55. Most pancreatic surveillance programmes lower the age at which surveillance is initiated for individuals with a first-degree relative with young-onset pancreatic cancer (age <50).[49] For mutation carriers, with a deleterious germline variant, the recommended age to initiate surveillance is generally age 50 (*BRCA2, ATM, PALB2*), though some groups would start surveillance at age 45 and earlier still

for the higher-risk genes; surveillance from age 40 is recommended for *CDKN2A* mutation carriers; 16% of p16-Leiden mutation carriers with pancreatic cancer were diagnosed at age <45[50] and at age 30–40 for those with Peutz-Jegher syndrome.[3] When to initiate pancreatic surveillance for these mutation carriers did not reach consensus (online supplementary table S2). To date, most pancreatic cancers in high-risk individuals with familial risk only (ie, no known susceptibility gene mutation) under surveillance are diagnosed after age 55.[10] The average age of pancreatic cancer diagnosis among individuals with a family history of pancreatic cancer is younger than for those with no family history, and mutation carriers who develop pancreatic cancer are diagnosed at a slightly younger age (~3–5 years) than those with sporadic forms of the disease.[34–36] The average age for diagnosis of pancreatic cancer is slightly younger in smokers (by several years) than in non-smokers.[51 52] The relative risk of pancreatic cancer among smokers is not considered sufficiently high to recommend surveillance in the absence of other risk factors. There was no consensus that the age at which surveillance begins should be modified for high-risk individuals who smoke. As pancreatic cancer risk factors become better defined, it should become possible to provide more accurate individualised risk assessment that can be used to provide personalised recommendations for pancreatic surveillance.[53]

What tests should be used for pancreatic surveillance?

Most pancreatic surveillance protocols for high-risk individuals use pancreatic imaging with MRI/magneticretrograde cholangiopancreatography (MRCP) and/or endoscopic ultrasound (EUS), with pancreatic-protocol CT reserved for individuals unable to have MRI or EUS. The preference for EUS and MRI/

Table 3 Summary of the main recommendations of the 2019 International Cancer of the Pancreas Surveillance (CAPS) Consortium

Who?

► All patients with Peutz-Jeghers syndrome (carriers of a germline *LKB1/STK11* gene mutation)
► All carriers of a germline *CDKN2A* mutation
► Carriers of a germline *BRCA2*, *BRCA1*, *PALB2*, *ATM*, *MLH1*, *MSH2*, or *MSH6* gene mutation with at least one affected first-degree blood relative
► Individuals who have at least one first-degree relative with pancreatic cancer who in turn also has a first-degree relative with pancreatic cancer (familial pancreatic cancer kindred)

When (at what age)?

► Age to initiate surveillance depends on an individual's gene mutation status and family history

Familial pancreatic cancer kindred (without a known germline mutation)	Start at age 50 or 55* or 10 years younger than the youngest affected blood relative
Mutation carriers: For *CDKN2A*†, Peutz-Jegher syndrome, start at age 40; *BRCA2,ATM, PALB2 BRCA1*, *MLH1/MSH2* start at age 45 or 50 or 10 years younger than youngest affected blood relative	

► There is no consensus on the age to end surveillance

How?

At baseline	► MRI/MRCP+EUS + fasting blood glucose and/or HbA1c	
During follow-up	► Alternate MRI/MRCP and EUS (no consensus if and how to alternate) ► Routinely test fasting blood glucose and/or HbA1c	
On indication	► Serum CA 19–9	► If concerning features on imaging
	► EUS-FNA only for	► Solid lesions of ≥5 mm ► Cystic lesions with worrisome features ► Asymptomatic MPD strictures (with or without mass)
	► CT only for	► Solid lesions, regardless of size ► Asymptomatic MPD strictures of unknown aetiology (without mass)

Intervals and surgery

12 Months	► If no abnormalities, or only non-concerning abnormalities (eg, pancreatic cysts without worrisome features)
3 or 6 Months	► If concerning abnormalities for which immediate surgery is not indicated (see figure 2 for details)
Surgery	► If positive FNA and/or a high suspicion of malignancy on imaging (see figure 2 for details)

► When surgery is indicated, perform an oncological radical resection at a specialty centre

Goals

The goal of surveillance is to detect and treat the following pathological lesions	► Stage I pancreatic cancer, confined to the pancreas, resected with negative margins ► Pancreatic cancer precursor lesions with high-grade dysplasia (PanIN or IPMN)

*Consensus as to when to start surveillance was not reached.
†Literature-based recommendation.
ATM, ataxia telangiectasia mutated; *BRCA2*, breast cancer 2; CDKN2A, cyclin-dependent kinase inhibitor 2A; CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; HbA1c, hemoglobin A1c; IPMN, intraductal papillary mucinous neoplasm; *MLH1*, mutL homolog 1; MPD, main pancreatic duct; MRI/MRCP, magnetic resonance imaging/magnetic retrograde cholangiopancreatography; *MSH2*, mutS homolog 2; MSH6, mutS homolog 6; *PALB2*, partner and localizer of *BRCA2*; PanIN, pancreatic intraepithelial neoplasia; STK11, serine/ threonine kinase 11.

MRCP rather than CT is based on their superiority at detecting subcentimetre pancreatic cysts, and avoidance of ionising radiation.[1] Subcentimetre pancreatic cysts are detected in up to 50% of high-risk individuals, depending on the age of the cohort.[10 54] However, pancreatic cysts have low malignant potential and although their detection can help risk stratification, the primary responsibility of pancreatic imaging tests is to detect pancreatic cancers. In this respect, EUS may be better for detecting small pancreatic ductal adenocarcinomas, although this evidence is based on studies of small numbers of individuals[55]; some centres use EUS as the primary test for pancreatic surveillance. EUS diagnostic yield is highly operator dependent.[56] EUS has previously been shown to be better at detecting small neuroendocrine tumours.[57] EUS also identifies subtle non-specific parenchymal abnormalities, which in a high-risk setting may represent the effects of pancreatic intraepithelial neoplasia (PanIN) with associated lobulocentric atrophy.[58–60]

Pancreatic-protocol CT can accurately detect early-stage pancreatic cancers and performs similarly to MRI in detecting evidence of cancer/high-grade dysplasia associated with intraductal papillary mucinous neoplasms (IPMN).[61] In addition, CT can, in principle, also be used to quantify changes in abdominal fat and lumbar muscle mass with the emergence of pancreatic cancer.[62 63] Observation of this early wasting could help to detect early pancreatic cancers, although this approach has not been tested in prospective studies. The availability of deep learning and advanced radiomics protocols may help radiologists to identify and quantify subtle abnormalities in the pancreas by CT.[64 65]

Based on current evidence, the consensus among experts is that MRI/MRCP and EUS should be the first-line tests for pancreatic surveillance, in part because of the cumulative radiation exposure with frequent CT, but developments in low-dose CT imaging may necessitate re-evaluation of the role of CT in surveillance. One European study examined the diagnostic yield of performing MRI/MRCP annually with EUS or limiting EUS to every third year unless there are significant changes in MRI scans. The authors found no significant difference in the diagnostic yield among the different surveillance protocols,[66] although a larger sample size and longer follow-up would be required to definitively answer this question. Less expensive, short-protocol MRI has been evaluated for cyst

surveillance.[67] Some Japanese centres have evaluated abdominal ultrasound as a screening modality,[68] as detailed pancreas sonographic images are feasible in thin individuals, but there was consensus that abdominal ultrasound should not be a first-line test for pancreatic surveillance.

The experts also considered the role of CA19-9 testing. Although the role of CA19-9 testing has not been studied in high-risk individuals with familial/genetic risk, its diagnostic performance characteristics have been extensively studied.[69–71] CA19-9 could have diagnostic value in individuals in whom the pre-test probability of pancreatic cancer is significant, although this question requires further investigation. For this reason, there was consensus that CA19-9 testing should be performed when there is concern about the possibility of pancreatic cancer, such as when worrisome features are found on pancreatic imaging.

Experts also reached consensus that glucose testing (fasting glucose or HbA1C) to detect new-onset diabetes was reasonable for high-risk individuals. There was also consensus that the emergence of new-onset diabetes in a high-risk individual should prompt additional investigation. Population guidelines recommend fasting glucose or HbA1c testing for individuals with risk factors for diabetes such as overweight or obesity,[72] although there are concerns about the potential to overtreat individuals with pre-diabetes. Epidemiological studies show that 0.4% to 0.8% of patients with new-onset diabetes aged ≥50 will be diagnosed with pancreatic cancer within 3 years.[62 73–75] A model incorporating weight loss, age and trend in glucose level can help to identify patients with new-onset diabetes more likely to have pancreatic cancer[76]; other models incorporating additional parameters are being evaluated.[77] One study estimated the average glucose level for a given tumour size, predicting that when glucose levels reach diabetic levels (126 mg/dL), pancreatic tumour volume is ~2–8 mL (~diameter of 1.6–2.5 cm).[76] There is no direct evidence that glucose monitoring is of additional value for improving detection of pancreatic cancer for individuals undergoing regular pancreatic imaging. Nonetheless, given the higher risk of pancreatic cancer in high-risk individuals compared with the general population, the consensus was that new-onset diabetes in a high-risk individual should prompt further testing for the presence of pancreatic cancer.

Experts discussed circulating tumour DNA (ctDNA) and its potential to contribute to pancreatic surveillance.[78–80] CtDNA testing is beginning to emerge as a clinical test[81]; further studies are needed to define its role for patients under pancreatic surveillance. Other biomarker tests are also undergoing evaluation for their potential for early detection,[63 82–84] but more study is needed to determine their diagnostic performance.

The experts recognised that many high-risk individuals meeting criteria for pancreatic surveillance (particularly mutation carriers) are at increased risk of developing other cancers; these individuals should undergo surveillance for other cancers tailored to their germline mutation status and cancer family history.

Surveillance questions

There was consensus that patients with normal pancreata, or without concerning lesions, should undergo annual pancreatic imaging surveillance. Surveillance of high-risk individuals occasionally identifies small (<1 cm) pancreatic neuroendocrine tumours (PanNETs)[1–11] although it is not certain if these lesions are more common in this population. Most incidentally detected PanNETs have low malignant potential.[85] There was consensus that patients with small (<1 cm diameter) PanNETs can also undergo annual surveillance detection and that treatment of PanNETs (>1 cm)

could be considered a success of surveillance. However, recent studies report small (<2 cm) PanNETs with low-risk characteristics on biopsy (eg, low Ki-67) can be safely followed up.[86–88] Current neuroendocrine neoplasms guidelines recommend surveillance of asymptomatic non-functional low-risk (by grade, Ki-67 by EUS-fine-needle aspiration) PanNETs (2 cm).[88]

Although patients in a high-risk programme commonly have pancreatic abnormalities (depending on age and other risk-factors, up to 50% will have pancreatic cysts; many also have subtle non-specific EUS parenchymal abnormalities), only a minority will develop concerning lesions. There was consensus that annual surveillance is appropriate for those with these abnormalities (figure 2). Furthermore, there was consensus that *CDKN2A* mutation carriers with concerning pancreatic abnormalities that do not lead to immediate surgery (eg, mild main pancreatic duct dilation, stricture without mass) should undergo additional testing such as EUS/fine-needle aspiration, and if they do not proceed to surgery after multidisciplinary review, should undergo close follow-up imaging in 3–6 months.

The predicted progression rate suggests that stage I pancreatic cancers can progress to stage IV disease within 1 year,[89] which may explain why interval pancreatic cancers are occasionally diagnosed despite annual surveillance, even in the absence of concerning lesions (worrisome features or solid lesions)[18 19] on prior scans.

Few studies have evaluated factors that influence compliance with long-term pancreatic surveillance; one such study found that many high-risk individuals drop out of regular surveillance.[90] Factors affecting long-term compliance with surveillance require further study.

When should surgery be performed?

Many factors are considered when deciding if surgical resection is appropriate for patients with concerning imaging findings, including a patient's estimated risk of pancreatic cancer based on their gene mutation status, family history, operative risk, comorbidities, life expectancy and compliance with surveillance. Decision-making is best undertaken by an experienced, expert multidisciplinary team. There was consensus that high-risk individuals should undergo pancreatic resection for broadly similar indications to individuals without known familial/genetic risk, based on established guidelines—for example, those with worrisome features.[18 19 91 92] Thus, generally, surgical resection in a patient with multifocal pancreatic cysts should manage the dominant, worrisome lesion. There was consensus that patients with solid lesions of indeterminate pathology and >5 mm should undergo pancreatic resection if additional evaluation does not yield a definitive preoperative diagnosis.

Some high-risk individuals develop multiple precursors throughout their pancreas, and those who undergo pancreatic resection for IPMN can have concomitant high-grade PanIN.[59] This raises the question of whether resection criteria for high-risk individuals should include less concerning lesions than for those with sporadic disease, or if total pancreatectomy should be considered. There is no evidence to support this approach unless there are concerning lesions affecting multiple regions of the gland. Total pancreatectomy is a major operation, although studies have reported that morbidity and mortality are similar to those of Whipple operations, and diabetes-related mortality, is quite rare.[93 94] There was also no consensus that surgical resection was indicated for less worrying lesions, such as suspected IPMN of 2 cm or with mild main pancreatic duct dilatation.

Consensus was also reached that the operative approach to a resectable pancreatic cancer should be the same for high-risk
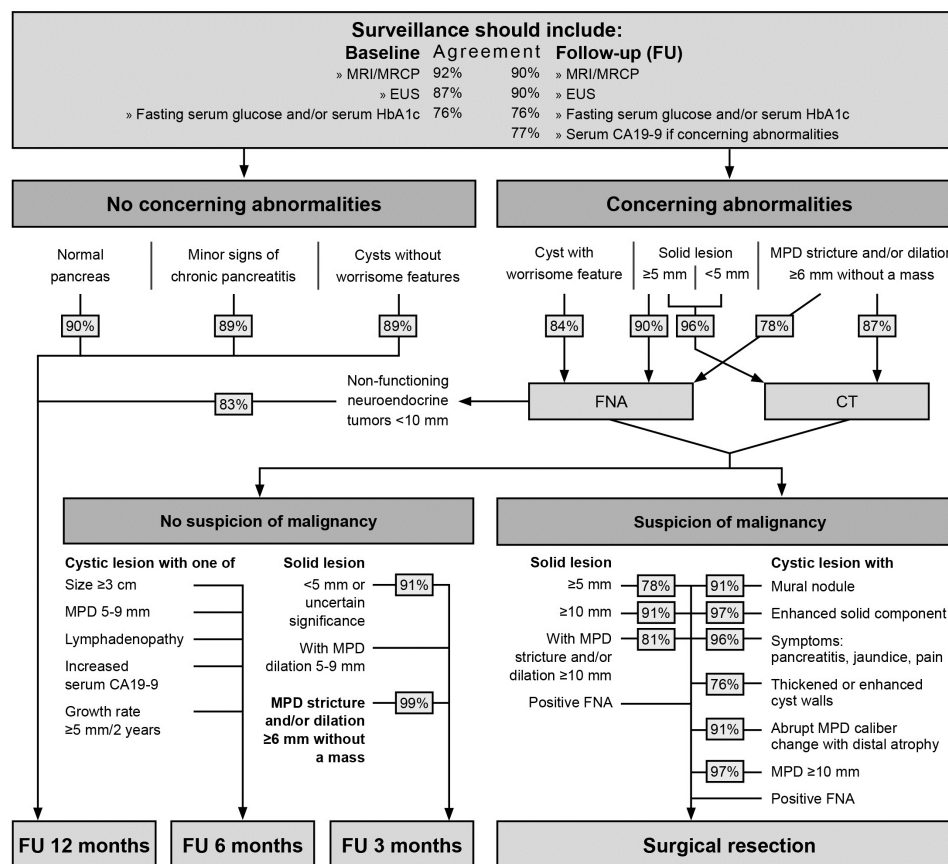
Figure 2 Decision flow-chart for the management of pancreatic abnormalities found during surveillance. EUS, endoscopic ultrasound; FNA, fine-needle aspiration; MPD, main pancreatic duct; MRCP, magnetic retrograde cholangiopancreatography.

individuals and those with sporadic pancreatic cancer. Patients with sporadic IPMN who have had partial pancreatectomy have a 5–10% risk of developing pancreatic cancer[95–98]; ongoing surveillance of these individuals is needed. Studies have identified factors associated with metachronous disease.[97 98] In some cases, metachronous disease represents re-emergence of a previously resected IPMN, raising the possibility that precancerous cells might spread through the main pancreatic duct.[98–100] In germline mutation carriers, particularly those at highest risk of pancreatic cancer, the possibility of multiple primary cancers should be considered.[101]

What are the goals of surveillance?
The primary goal of pancreatic surveillance is to prevent death from pancreatic cancer and prevent its emergence by identifying and treating precursor lesions. As with the first CAPS consensus guideline, there was consensus that the main pathological targets of surveillance are stage I pancreatic cancers and precursors with high-grade dysplasia either in PanIN or IPMN (online supplementary table S3). Since the last consensus meeting, the classification of pancreatic precursors has been slightly revised.[102]

Published studies of surveillance programmes reveal evidence of downstaging of pancreatic cancers, with most pancreatic cancers diagnosed as stage IIB or stage I.[7 10] The detection and management of high-grade dysplasia in PanIN and IPMN remains an important goal of surveillance; these lesions are not only more commonly detected by pancreatic imaging, they are more likely to have pancreatic precursor lesions than in patients without such a family history.[103]

The imaging characteristics of IPMN can be useful in identifying evidence of high-grade dysplasia within IPMN, but this is not the case for PanIN, most of which are microscopic lesions that cannot be identified with available technologies. Most pancreatic ductal adenocarcinomas are thought to arise from PanIN. This is thought to be true for patients with sporadic pancreatic cancers and also for those with a familial/inherited susceptibility to develop pancreatic cancer. Most pancreatic cancers from such individuals have genetic signatures consistent with PanIN origin,[26] and pancreatic cancers detected during surveillance often arise in areas of the gland separate from pancreatic cysts.[95 104] Indeed, many pancreatic cancers associated with IPMN are genetically distinct from the IPMN.[105] Since PanIN generally do not cause specific imaging abnormalities, high-grade PanIN (previously known as PanIN-3) is diagnosed only by surgical pathology review of pancreatic resections undertaken for other concerning imaging findings. In some cases, evidence of pancreatic neoplasia can be inferred by the presence of mutations detected in secretin-stimulated pancreatic fluid samples,[104 106] and multifocal PanIN lesions by imaging findings of lobulocentric atrophy,[59] but further investigation is needed to determine the value of these tests for patients under pancreatic surveillance.

Areas for future research
Emerging technologies such as CT detection of muscle and fat wasting as well as subtle changes in the pancreas using deep learning have yet to be applied to the high-risk setting. Similarly, the value of glucose monitoring in detecting new-onset diabetes for patients

already undergoing routine pancreatic imaging is not known. The development of non-invasive blood tests, such as tests for ctDNA, provides hope that these will eventually improve the early detection of pancreatic cancer. The emergence of interval (ie, presenting before their annual surveillance) advanced-stage pancreatic cancers in some patients under regular pancreatic imaging suggests that biological characteristics, such as early lymph node metastases and venous invasion even with small cancers,[107] make early detection efforts particularly challenging. The main factors used in clinical practice to assess the risk of pancreatic cancer in high-risk individuals remain family history, gene mutation status, age and pancreatic imaging abnormalities. Other known factors, such as diabetes and metabolic syndrome markers, smoking status, other cancer family history, gene variants identified through genome-wide meta-analysis,[108] and circulating biomarkers that predict future risk,[109] could help to improve risk stratification, particularly if models could be developed and validated.

Cost-effectiveness models of pancreatic surveillance have been reported. One recent paper estimated that MRI is more cost-effective in the USA overall, with EUS more cost-effective for highest-risk individuals (relative risk >20)[110]; cost-effective model results depend on cost estimates and MRI and EUS costs vary considerably. Ultimately, pancreatic surveillance programmes need to demonstrate better evidence that survival from pancreatic cancer can be improved by surveillance or even that the detection and treatment of high-grade dysplasia can lower the incidence of pancreatic cancer.[111] Indeed, the US Preventive Services Task Force recommended that pancreatic screening should not be carried out,[21 112 113] although it excluded the study by Vasen et al,[7] because it focused on mutation carriers and completed its literature review before the recent CAPS study was published.[10] These two studies show that pancreatic surveillance of high-risk individuals can lead to downstaging of pancreatic cancers diagnosed. Such downstaging is associated with better survival compared with historical controls, particularly when surveillance detects stage I cancers. The need to evaluate long-term outcomes necessitates pancreatic surveillance be undertaken in academic settings. Efforts to implement a pancreatic surveillance programme need to be balanced with its costs. This is a difficult balance to achieve since the harms of overdiagnosis can take many years to become evident, as is the case for other cancers.[114–116] The evaluation of long-term outcomes of high-risk individuals participating in pancreatic surveillance programmes,[7 95 96 117] including the potential for harm, should continue.

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