Surveillance in people at high risk of pancreatic cancer

A Guide for Australian Primary Care Practitioners

Australian Government
Cancer Australia

RACGP

Surveillance in people at high risk of pancreatic cancer: A Guide for Australian Primary Care Practitioners has been officially recognised as an Accepted Clinical Resource by The Royal Australian College of General Practitioners.

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Acknowledgment of Country
Cancer Australia acknowledges Aboriginal and Torres Strait Islander people as the Traditional Custodians of Country throughout Australia. We pay our respects to Elders, past and present.
We celebrate the ongoing connections of Aboriginal and Torres Strait Islander peoples to Country, culture, community, family and tradition and recognise these as integral to health, healing and wellbeing. Cancer Australia acknowledges great diversity among Aboriginal and Torres Strait Islander peoples, and the contribution of the many voices, knowledge systems and experiences that guide all efforts to create a culturally safe and responsive cancer system that is equitable to all.

Contents

1 Purpose

The purpose of this clinical resource is to provide core principles and practice points for general practitioners (GPs) regarding surveillance in: (i) people who have a family history or pathogenic germline variant (gene mutation) that puts them at high risk of developing pancreatic adenocarcinoma (high-risk individuals; HRIs); and (ii) people with a cystic lesion of the pancreas discovered incidentally. The aims are to help GPs identify patients who would be classified as a HRI and provide advice regarding referrals for possible surveillance.

Details of the development of this resource are shown in Appendix 1. Briefly, the resource was developed by a working group of clinical experts and researchers, convened by the University of Queensland, as part of Cancer Australia's implementation of the National Pancreatic Cancer Roadmap. The working group considered the strength of the evidence in making these recommendations, but did not apply formal grading criteria.

2 Core principles

Principle 1: **Informed decision making**

People at high risk of developing pancreatic cancer (high risk individuals: HRIs) should be offered the opportunity to discuss the potential benefits and harms of surveillance so they can make an informed decision about whether this is an appropriate pathway for them. There is currently limited evidence about whether the benefits of surveillance outweigh the harms so HRIs who would like to consider surveillance should be referred to a genetic counsellor, gastroenterologist with a special interest in diseases of the pancreas, or hepato-pancreatico-biliary (HPB) surgeon who can provide comprehensive information about this issue.

Principle 2: **Appropriate expertise in diagnosis**

Surveillance should be undertaken by clinician/s with a high level of expertise in diagnosing and managing diseases of the pancreas, ideally with access to a multidisciplinary team who can ensure optimal interpretation of imaging and management decisions. This will reduce the likelihood that high-risk lesions will be missed and that inappropriate surveillance or pancreatic resection will be performed for low-risk lesions.

Principle 3: **Choice of imaging modality**

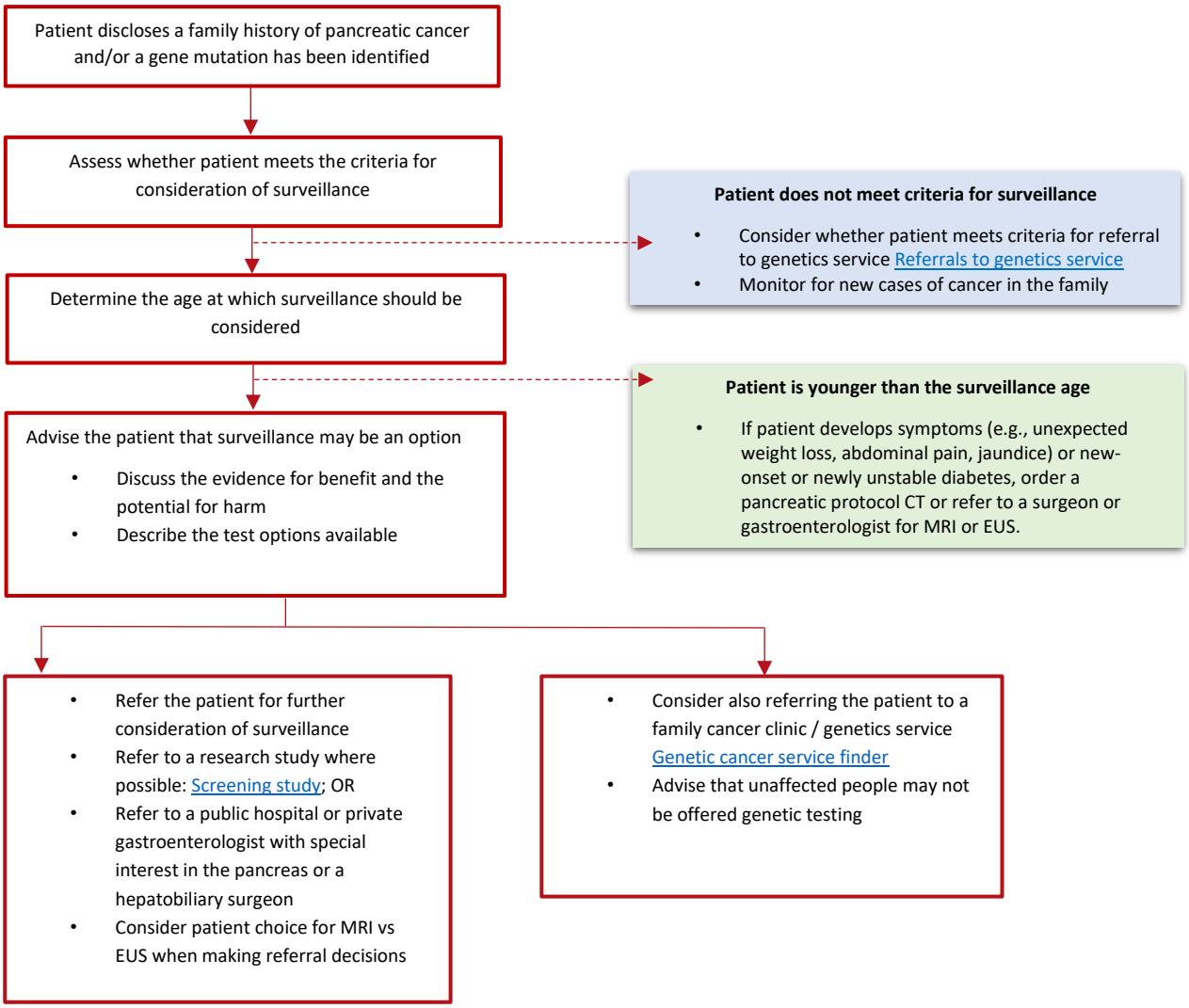
There are several imaging modalities that can be used for surveillance, each with strengths and weaknesses. HRIs should be included in decisions about which imaging modality will be used. They should be advised about the relative sensitivity, potential harms, out-of-pocket costs, and ease of access (including potential waiting times) of each of the options.

Principle 4: **Ongoing data collection**

In light of the current lack of high-quality evidence for benefits and harms of surveillance, ongoing data collection is critical. HRIs who decide to undergo surveillance should be encouraged to do so within the context of a research study, following a standardised research protocol, where possible. Irrespective of whether or not HRIs participate in a formal research study, all people who are found to be at high risk should have data captured in a registry. Information about any imaging that occurs, outcomes of surveillance, lesions that arise between planned surveillance imaging, cancers that occur in people who do and do not undergo surveillance, morbidity and mortality should be captured.

Patients should be asked to provide informed consent for data linkage to enable complete long-term follow-up.

Decision flow chart: patients at high risk of pancreatic cancer



1. Link to eviQ guidelines: Guidelines for referral to genetics services
2. For enquiries about the research study, please contact EC-APRISE@epworth.org.au
3. Link to genetic service finder: Genetics services
4. Variant refers to a pathogenic or likely pathogenic change in a gene using American College of Medical Genetics Criteria (https://www.ncbi.nlm.nih.gov/pubmed/25741868)

3 Practice points for surveillance in high-risk individuals

3.1 Definition of high risk and age at which surveillance should be considered

Patients can be classified as being at high risk on the basis of family history or the presence of a known pathogenic germline variant. Table 1 shows how to classify an individual as being at high risk and the age from which surveillance should be considered.

See Appendix 2 (Sections 5.2 and 5.3) for more information about the risk associated with each criterion and the age from which surveillance should be considered.

Table 1: Criteria for defining risk and age to begin surveillance

Criteria to define patients at high risk	Age to start considering routine surveillance
Two or more FDRs[1] or one FDR and one SDR[2] (who are FDRs to one another) affected by pancreatic cancer	50 years or 10 years younger than the age at diagnosis of the youngest family member affected *(whichever is youngest)*
BRCA1 / BCRA2 variant[3] (familial breast and ovarian cancer syndrome) **and** one FDR affected by pancreatic cancer	
PALB2 variant **and** one FDR affected by pancreatic cancer	
MLH1, MSH2, MSH6 variant (Lynch Syndrome) **and** one FDR affected by pancreatic cancer	
ATM variant (ataxia telangiectasia) **and** one FDR affected by pancreatic cancer	
CDKN2A variant (familial melanoma)	40 years
STK11 variant (Peutz Jeghers syndrome)	
Hereditary pancreatitis (irrespective of gene involved)	40 years or 20 years after the first pancreatitis attack *(whichever is youngest)*

[1] FDR=first-degree relative (biologically related parents, children, and siblings)

[2] SDR=second-degree relative (biologically related grandparents, grandchildren, aunts, uncles, nieces, nephews, and half-siblings)

[3] Variant refers to a pathogenic or likely pathogenic change in a gene using American College of Medical Genetics Criteria[1]

3.2 Aboriginal and Torres Strait Islander people at high risk of pancreatic cancer

The Optimal care pathway for Aboriginal and Torres Strait Islander people with cancer provides detailed information about how to care for Aboriginal and Torres Strait Islander people.[2] Of additional relevance to surveillance for pancreatic cancer, clinicians should be aware that the concept of family is not limited by blood relationships so clinicians need to ensure they specify the types of relationships that are relevant to risk of pancreatic cancer. In addition, discussing family members who may be part of the Stolen Generation may be distressing for Aboriginal and/or Torres Strait Islander peoples. It is essential that GPs approach these conversations with cultural sensitivity.

3.3 Advising high-risk individuals about the potential benefits and harms of surveillance

When a person with a family history or pathogenic germline variant that places them at high risk has been identified, they should be advised that surveillance has potential benefits and harms and that the balance of these is not yet well established.

Patients should be informed that the yield of pancreatic cancer in patients under surveillance is low (approximately 5 pancreatic cancers per 1000 people under surveillance per year).

There is some evidence that surveillance leads to diagnosis of pancreatic cancer at an early stage when it is potentially amenable to surgical resection. Observational studies suggest that up to approximately two thirds of pancreatic cancers diagnosed during surveillance are resectable, compared with <20% of those in the general population. However, due to a lack of randomised controlled trials (RCTs) it is not known whether this leads to reduced mortality. Patients should understand that people under surveillance can still be diagnosed with advanced-stage disease.

There are potential harms of surveillance. Benign or low-risk lesions can be misinterpreted as high risk resulting in unnecessary investigations and treatment that can have adverse sequalae. That is, though uncommon, tissue acquisition can cause complications (e.g., haemorrhage or pancreatitis) in approximately 2% of patients.[3] Up to 2% of patients under surveillance may undergo resection for low-risk lesions, with potential sequalae including post-operative morbidity or mortality, and diabetes and/or exocrine insufficiency.

Patients who would like to consider surveillance should be referred to a gastroenterologist with expertise in pancreatic disease or a specialist HPB surgeon or who can help them make an informed decision about whether to proceed with surveillance.

For information about the evidence for benefits and harms see Appendix 2 (Sections 5.4 to 5.6).

3.4 Identifying high-risk individuals

The RACGP Guidelines for preventive activities in general practice (Red Book)[4] recommends that family history be updated every 3 years. GPs should ask about cancer history in first- and second-degree relatives. In patients known to have mutations in genes that could increase risk of pancreatic cancer (see Table 1 above) patients should be asked about new pancreatic cancer diagnoses in first and second-degree relatives annually.

3.5 Imaging options for surveillance

There are three imaging options that can be used for surveillance in HRIs: magnetic resonance imaging (MRI), endoscopic ultrasound (EUS), and computed tomography (CT). There are no RCTs comparing imaging options in HRIs. However, the evidence suggests that there is high concordance between EUS and MRI but lower concordance between EUS/MRI and CT.

There are benefits and harms of each option, and their cost and accessibility differ. Patients' imaging preference may inform referral pathways, so an initial discussion of the available options may be needed in primary care.

Magnetic Resonance Imaging: is an accepted radiological approach for imaging the pancreas and, with consideration of access, benefits, and potential harm, is the most appropriate test for initial surveillance imaging in HRIs. The quality of MRI images and interpretation is unit/operator dependent so a facility with appropriately advanced MRI equipment and expert radiology reporting should be engaged, or images should be transmitted for centralised review by a multidisciplinary team.

Endoscopic Ultrasound: EUS is slightly superior to MRI for detecting small (<1 cm) and solid lesions that may be indicators of high-grade premalignant lesions or early-stage pancreatic cancer. However, EUS requires sedation, is less accessible than other imaging modalities (particularly outside major cities), and is operator dependent. EUS has the advantage of enabling tissue acquisition of suspicious lesions at the time of initial imaging.

NB: Patients with hereditary pancreatitis should not be imaged using EUS, as calcification prevents adequate assessment with EUS and assessment of calcification in relation to parenchymal change is better undertaken with MRI/CT.

- **Computed tomography:** CT (pancreatic protocol) exposes patients to radiation (31 mSv multiphase abdominopelvic CT compared to 1.5 mSv in a low-dose chest CT),[5] which should be avoided in asymptomatic patients, particularly in younger people who may have repeated scans over many years. It should only be used for surveillance in HRIs if: (i) EUS or MRI are not possible for clinical reasons; or (ii) MRI is contraindicated and the patient chooses not to undergo EUS (e.g., for reasons of accessibility or to avoid sedation).

See Appendix (Section 5.7) for information about the sensitivity and harms of the surveillance options.

3.6 Referring high-risk individuals for consideration of surveillance

Patients who would like to consult a gastroenterologist or HPB surgeon about surveillance should be referred to:

(1) A pancreatic cancer screening study;
(2) A high-volume public hospital or privately to a clinician (gastroenterologist with expertise in pancreatic disease/hepato-pancreatico-biliary surgeon) that manages patients in a high-volume hospital/clinic with access to high-quality MRI/EUS and a multidisciplinary team;
(3) A clinician (gastroenterologist with expertise in managing pancreatic disease or HPB surgeon) who practises outside a high-volume setting and has access to a multidisciplinary team that can provide expert interpretation of MRI/EUS scans.

Patient preference should be considered. In particular, cost to patients (public vs private) and patient preference regarding travel or a particular imaging approach should be considered when making referral decisions.

3.7 Referring patients for genetic counselling

GPs should consider referring high-risk patients *who meet the eviQ criteria* (eviQ referral guidelines) to a clinical genetics service or family cancer clinic. The criteria differ from those that are used to determine eligibility for surveillance and are as follows:

(i) Have a blood relative with a pathogenic variant (e.g., BRCA1, BRCA2, PALB2, MLH1, MSH2, MSH6, PMS2, APC, or other);
(ii) Have a strong family history on the same side of the family; i.e.,
   a. Three FDRs or SDRs with the same/related* cancers OR
   b. Two FDRs or SDRs with the same/related* cancers, where one is diagnosed at younger than 50 years.

* Related cancers include breast / ovarian / pancreatic; Lynch syndrome-associated cancers include colorectal, endometrial, ovarian, renal, gastric, small bowel, pancreas, brain, and liver.

Patients should be aware that diagnostic genetic testing for familial cancer in people without a diagnosis of the relevant cancer is not funded by Medicare or offered in most genetics services. The

likelihood of identifying a pathogenic germline variant is low in unaffected people (irrespective of their family history) and there is a risk that variants of uncertain significance could be identified, for which there is no clinical action.

If a HRI has an affected family member who is still alive, genetic testing in the affected relative may be offered, with government funding available.

Irrespective of whether a person will be offered a diagnostic genetic test, genetic counselling may be beneficial.

GPs can refer patients to a genetics service alongside referrals to gastroenterologists or surgeons. Alternatively, patients may prefer to consider their genetic risk before making a decision about a referral to a gastroenterologist or HPB surgeon for surveillance.

3.8 Investigations of the pancreas in high-risk individuals diagnosed with diabetes

Pancreatic cancer can cause diabetes. If a HRI is diagnosed with diabetes, imaging of the pancreas should be performed, irrespective of the age at which diabetes arises. Similarly, the development of unstable diabetes in a HRI with previously well-managed diabetes should alert clinicians to the possibility of pancreatic cancer.

If a HRI has not yet begun surveillance a pancreatic protocol CT is an appropriate diagnostic test, in line with recommendations for diagnostic testing in symptomatic patients.

If a HRI is already undergoing surveillance additional imaging should be considered in people with newly diagnosed or newly unstable diabetes. GPs should advise these patients to make an appointment with the clinician who is overseeing their surveillance or order a pancreatic protocol CT.

See Appendix 2 (Section 5.9) for more information about diabetes and pancreatic cancer.

3.9 The age at which surveillance should not be considered or should cease

When a patient's age or comorbidities make pancreatic resection contraindicated, surveillance should not commence. If a patient has already begun surveillance it should cease or be paused if age or comorbidities suggest pancreatic resection would be contraindicated. This decision should be made in discussion with the patient, and with referral for a specialist opinion if indicated.

3.10 Referring patients with cystic lesions identified incidentally

With increasing use of abdominal imaging, cystic lesions of the pancreas may be identified incidentally. The vast majority of these will not progress to cancer. However, patients with cystic lesions of the pancreas should be referred for further investigation, unless a radiologist specifically advises that the size, location, or characteristics of the lesion indicate that further imaging is **not** required or the patient has co-morbidities that preclude surgery.

Most international guidelines recommend that MRI be used preferentially to characterize pancreatic cysts, and that multiphase CT be used if MRI is unavailable or contraindicated. Patients should be referred to a high-volume public hospital HPB clinic, or privately to a gastroenterologist with a special interest in diseases of the pancreas or a HPB surgeon.

For more information about cystic lesions, see Appendix 2 (Section 5.10).

4 Appendix 1: Development of the clinical resource

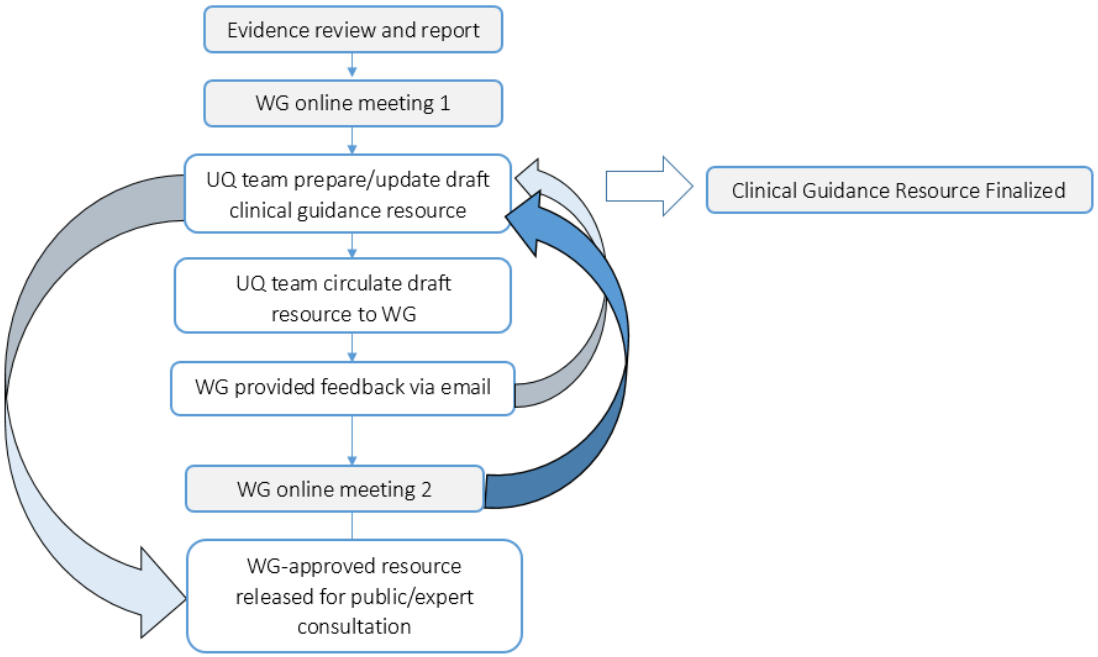
The development process of the clinical resource involved three main components: i) establishing the working group (Appendix 1, Table 1); ii) evidence review; and iii) preparation and approval of the clinical resource

Appendix 1 Figure **1**).

i) Establishing the working group: members of the working group were selected according to the specialties required; i.e., general practitioners, genetic counsellors, clinical geneticists, medical oncologists, gastroenterologists and surgeons.

ii) Evidence review: the evidence review involved a rapid desktop review to identify existing national and international guidelines and supporting evidence. A search of the grey literature using Google was performed, using the search string 'pancreatic cancer surveillance guidelines', and the PubMed database was searched using the terms ('pancreatic cancer' and 'surveillance' and 'guidelines'). Two reviewers extracted information from relevant guidelines regarding definitions of high risk and age to begin screening. Additional information was drawn from meta-analyses/systematic reviews where available, and studies published since the most recent meta-analysis/systematic review. The evidence was summarised and sent to members of the working group to prepare for the meeting.

iii) Preparation and approval of the clinical guidance resource: The working group participated in two online meetings. In preparation for first meeting, the working group received the evidence report and an online survey. After the initial meeting, working group members provided individual feedback in questions related to their expertise. A draft of the principles of the clinical guidance document was circulated to the WG and supported the discussions in the second meeting. A new version of the document was circulated to the WG members for review and approval. This document, following approval from Cancer Australia, was released for public consultation.



Appendix 1 Figure 1. Development process of the clinical resource for the National Pancreatic Cancer Roadmap Priority 1

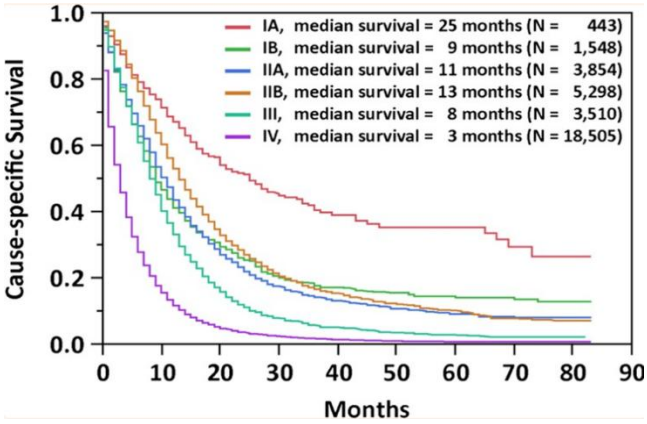
Appendix 1 Table 1: Members of the Working Group

Name	Specialty	Affiliation
Paul Grogan	Policy, implementation	University of NSW / Cancer Council NSW
Rachel Neale (Project Lead)	Epidemiology	University of Queensland / QIMR Berghofer Medical Research Institute
Susan Jordan	Epidemiology, General Practice	University of Queensland
Joel Rhee	General Practice	University of New South Wales
Heba Azer	General Practice	University of New South Wales
Warren Jennings	General Practice	Inala Centre of Excellence (Indigenous Health) / University of Queensland
Benedict Devereaux	Gastroenterology, ERCP, EUS	University of Queensland / Royal Brisbane and Women's Hospital
Alina Stoita	Gastroenterology, EUS	St Vincent's Hospital, Sydney
Ian Yusoff	Gastroenterology, HPB	Sir Charles Gairdner Hospital, Perth
Yu Xin Liew	HPB surgery	Fiona Stanley Hospital, Perth
Manju Chandrasegaram	HPB surgery	University of Queensland / The Prince Charles Hospital
Luke Bradshaw	HPB surgery	St Vincent Hospital, Peter McCallum and Box Hill, Melbourne
Richard Turner	General/ GI Surgery	University of Tasmania / Royal Hobart Hospital
Aideen McInerney-Leo	Genetic counselling	University of Queensland
Sibel Saya	Genetic counselling	University of Melbourne
Nicola Poplawski	Clinical Geneticist	Royal Adelaide Hospital
John Zalcberg	Medical oncology	Monash University / Alfred Health
Dagmara Poprawski	Medical oncology	Riyadh's King Faisal Specialist Hospital and Research Centre, Saudi Arabia
Anthony Gill	Anatomical pathology	University of Sydney
Claire Nightingale	Public health, implementation	University of Melbourne
Will McGahan	Consumer representative, surgery trainee	University of Queensland
Kylee Elvin	Consumer representative	The Australian Pancreatic Cancer Foundation (Pankind)
Michelle Stewart	Consumer advocacy	The Australian Pancreatic Cancer Foundation (Pankind)
Manil Chouhan	Radiologist	University of Queensland / The Princess Alexandra Hospital
Christina Bernardes	Public health, Project manager	University of Queensland / QIMR Berghofer Medical Research Institute

5 Appendix 2: Supporting evidence

5.1 Stage as a determinant of pancreatic cancer survival

Pancreatic cancer is the 8th most commonly occurring cancer in Australia (excluding keratinocyte cancer) but is the 4th most common cause of cancer death. Each year, ~4500 people are diagnosed with pancreatic cancer and ~3700 die from their disease.[6]



Appendix 2 Figure 1: Stage-specific survival for pancreatic cancer from SEER data

Stage is a very strong determinant of survival. In people diagnosed when the tumour is confined to the pancreas and less than 2 cm in size (stage 1A), the median survival is approximately 2 years, compared with only 3 months in those with metastatic disease (stage 4) at diagnosis (A2 Figure 1).[7]

Appendix 2 Table 1. Five-year survival by stage in the Surveillance, Epidemiology and End Results (SEER) Program, in the United States[8] and the stage distribution at diagnosis in New South Wales, Australia:

Stage of disease	Survival (%)	Resectable	Percent at diagnosis[1]
Stage IA	83.7 (95% CI= 78.6-89.2)	Yes	19.5
Stage IB	74.3 (95% CI= 68.0-81.3)	Yes	
Stage IIA	13.3 (95% CI= 11.0-16.1)	Yes	
Stage IIB	15.5 (95% CI= 13.2-18.1)	Yes	
Stage III	3.2 (95% CI= 2.1-4.9)	Borderline or no	18.0
Stage IV	2.8 (95% CI= 2.4-3.4)	No	40.7
Unknown			21.8

[1] Cancer Institute NSW[9]

Early detection through screening may detect premalignant lesions or increase the percentage of people who are diagnosed when their cancer is potentially curable. Population-wide screening is not feasible because the incidence of pancreatic cancer is too low, but surveillance may be appropriate in people with at least a fivefold increased risk of pancreatic cancer. This currently applies only to people who have a strong family history or a known gene mutation. Approximately 10% of pancreatic cancers arise in people who are at increased genetic risk (high-risk individuals; HRIs).

5.2 Risk of pancreatic cancer according to family history and pathogenic germline variants

Appendix 2 Table 2. Risks of pancreatic cancer in people with family history or pathogenic germline variants. Reproduced from McKay et al. (2016)[10] unless otherwise specified.

Risk group	Syndrome	Relative risk (95% ci)	Estimated lifetime risk (%)
General population			~1.5%
1 FDR pancreatic cancer	Familial pancreatic cancer	3.5 (2.5-4.8)[11]	7% (early onset[a]) 5% (late onset[b]) [11]
2 FDR pancreatic cancer	Familial pancreatic cancer	5.4 (4.1-7.3) [11]	12% (early onset[a]) [11] 9% (late onset[b])
≥3 FDR pancreatic cancer	Familial pancreatic cancer	10.8 (4.1-7.3) [11]	24% (early onset[a]) [11] 18% (late onset[b])
STK11 variant	Peutz Jegher syndrome	132 (44-261)	11-32%
PRSS1 variant	Hereditary pancreatitis	58 (23-105)	20-40%
CDKN2A variant	Familial melanoma	38 (10-97)	17%
BRCA2 variant	HBOC	4.9 (2.2-10.5) [12]	3-8%
BRCA1 variant	HBOC	3.0 (2.0-4.7) [12]	2%
MSH2 MLH1 MSH6, PMS2 variant	Lynch syndrome	8.6 (4.7-15.7)	4%
PALB2 variant	Familial pancreatic cancer	2.4 (1.2-4.5) [13]	2-3% [13]
ATM variant	Ataxia telangiectasia	Elevated but not defined	Elevated but not defined

FDR=first-degree relative; HBOC=hereditary breast and ovarian cancer

[a]At least one family member diagnosed at <50 years; [b] All family members diagnosed at ≥50 years

5.3 The age at which surveillance should be considered

Family history: In patients with a family history of pancreatic cancer, the age at diagnosis is similar to that in the general population (~65 years).[14]

Hereditary pancreatitis: For those with hereditary pancreatitis there are relatively little data available; in a series of 246 patients from the United States, Europe, and Japan, 8 patients developed pancreatic cancer at a mean age of 57 years.[15]

CDKN2A variants: In a prospective study of 347 people with germline pathogenic *CDKN2A* variants, pancreatic cancer was diagnosed in 31 patients at a median age of 60 years.[16]

Peutz-Jeghers syndrome: The age of pancreatic cancer diagnosis in those with Peutz Jeghers syndrome is relatively young; in a series of 144 patients with Peutz Jeghers syndrome, 7 people developed pancreatic cancer at a median age of 54 years.[17]

Smoking: Smoking status may influence age at diagnosis. The risk of pancreatic cancer associated with family history of pancreatic cancer was approximately 3-fold higher among ever-smokers compared with never smokers.[18] Additionally, people who smoke appear to develop pancreatic cancer approximately 10 years earlier than non-smokers.[19,20]

International recommendations: The International Cancer of the Pancreas Screening (CAPS) Consortium recommends that for HRIs other than those with high-risk mutations 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.[21] For patients with Peutz Jegher syndrome or CDKN2A mutations surveillance should start at age 40.

5.4 Evidence for the benefits of surveillance

There are no randomised controlled trials (RCTs) of surveillance in high-risk individuals, so the effects of surveillance on mortality are not known. The Cancer of the Pancreas Screening Consortium has defined the goal of pancreatic cancer surveillance as detection of T1N0M0* pancreatic cancers, high-grade IPMNs, PanIN-3, and pancreatic neuroendocrine tumours (PanNETs) ≥10 mm. However, diagnosis of early stage tumours does not necessarily translate into a mortality benefit.

*T1N0M0: tumour is confined to the pancreas and less than 2 cm in size, no lymph node involvement, no distant metastases.

5.5 Cohort studies demonstrating outcomes of surveillance

Multi-country surveillance study

In an analysis of 2552 individuals who were enrolled in surveillance in 16 centres in 7 countries (including Australia) 122 (4.8%) people had pancreatic lesions identified (Appendix 2 Table 3).[22] Of these, 65 (53%) were benign, 22 (18%) were considered successes (pancreatic cancer confined to the pancreas or high-grade precursor lesions), and 35 (29%) were surveillance failures (non-resectable=14; resected with spread beyond the pancreas=21). *Of the total 2552 people who were enrolled in surveillance and followed for a median of 3.4 years, approximately 1% potentially benefited (i.e., high-risk pancreatic lesions identified were resectable).* The longer-term benefit is not yet known.

Appendix 2 Table 3. Outcomes of surveillance in the multi-country analysis

		N (%)[1]
	Individuals who underwent surveillance	2552
1	**Total PDAC**	**41 (1.6)**
2	**Unresectable PDAC**	**14 (0.5)**
3	Detected at baseline	2
4	Detected at follow-up (median 34 months)	12
5	**Total resections**	**108 (4.2)**
6	PDAC	27 (25)
7	*Confined to pancreas with negative margins*	*6*
8	High-grade precursor lesions	16 (15)
9	Low-grade precursor lesions	46 (43)
10	Neuroendocrine tumour	14 (13)
11	No neoplasia	5 (4.6)
12	**Considered success[2]**	**22 (0.9)**
13	**Considered failure[3]**	**35 (1.4)**

[1] Denominator for calculation of percentages for rows 1, 2, 5, 12 and 13 is 2552; Denominator for rows 6-11 is 108
Successful early detection was defined according the goals of surveillance, as recommended by the CAPS consensus statements.
[2] Surveillance success was defined as malignancy confined to the pancreas with negative resection margins, PanIN-3, or IPMN with high-grade dysplasia;
[3] Surveillance failure was defined as malignancy spread beyond the pancreas as shown by imaging or the surgical specimen and therefore not likely to be successfully resected
Abbreviation: PDAC=Pancreatic ductal adenocarcinoma

United States surveillance studies

Two studies have been conducted in the United States, the Cancer of the Pancreas Screening (CAPS 1 to 4)[14] and (CAPS 5)[23] studies (Appendix 2 Table 4). Across both studies a total of 26 people had a diagnosis of PDAC over more than 20 years, corresponding to a detection rate of 5.15 PDACs diagnosed per 1000 person-years of surveillance; one individual was diagnosed with PDAC per year for every 194 screened. Nineteen PDACs were identified through surveillance; of these 13 (68%) were stage I or II (compared with <20% in the general population).

Overall, the two studies identified 26 individuals (n=26/1731=1.5%) with stage I or II disease or high-grade dysplasia who could be said to have benefited from surveillance.

Appendix 2 Table 4. Screen-detected PDAC or high-grade neoplasms in Cancer of Pancreas Screening (CAPS 1-5) studies

Characteristics	CAPS 1-4[14] (N=354)	CAPS 5[23] (N=1461)
Lesions resected		
Total number of lesions resected	44	16
Total number of PDAC resected	11	8
Total number of high-risk preneoplastic lesions resected	10	3
Total number of low-grade lesions resected	23	5
TOTAL PDAC (identified in and outside surveillance)	14	12
PDACs identified through surveillance	10	9
Stage I	2	7
Stage II	3	1
Stage III	4	1
Stage IV	1	-
PDACs identified outside surveillance	4	3*
Stage I	-	-
Stage II	3	-
Stage III	-	-
Stage IV	-	1
Stage not specified	1	2

*Two HRIs from CAPS 1-4 cohort stopped surveillance and then developed PDAC after the last report of that cohort are included[14]

Strength of evidence for benefits of surveillance: The working group considered the strength of evidence for benefits of surveillance vs no surveillance in high-risk individuals for reduction of mortality from pancreatic cancer or all-cause mortality to be low.

5.6 Evidence for the harms of surveillance

Unnecessary surgery: Screening tests always have the potential for harm due to the risks of misdiagnosis (incorrectly identifying a non-malignant lesion as malignant) or overdiagnosis (identifying malignant cancers that are indolent and would not cause harm within a person's lifetime). Due to the lack of RCTs the risks of misdiagnosis and overdiagnosis are unknown, but there is evidence that some people undergo surgery for low-risk lesions. In a meta-analysis of people undergoing surveillance (23 studies, 5027 patients per study), 2.1% of patients underwent surgery with low-yield pathology

findings (i.e., PanIN1-2, low-grade IPMN, asymptomatic chronic pancreatitis, PanNETs, no detectable lesion).[24]

Endoscopic ultrasound: EUS requires sedation, and in the small number of cases in which tissue acquisition (fine-needle biopsy) is indicated there is a low risk of haemorrhage, infection, or pancreatitis.

There is relatively limited evidence about the harms of EUS specifically in HRIs undergoing surveillance. The United States Preventive Services Task Force summarized the risks of EUS in HRIs undergoing surveillance.[25] In eight studies[26-33] that reported on procedural harms from screening (n=675), no serious harms were reported from initial screening.

The harms of EUS-guided tissue acquisition, not restricted to HRIs, have been documented. A systematic review and meta-analysis of fine-needle aspiration (FNA) of pancreatic lesions documented complications from EUS-guided tissue acquisition in 246 of 11,652 patients (2%).[3] The most commonly adverse events occurring were bleeding (0.8%), pancreatitis (0.7%), and pain (0.3%). Other events occurred at a rate of <0.1%.

It is imperative to appreciate that EUS-guided tissue acquisition is only performed when an abnormality is detected during the EUS examination, raising concern of a high-risk lesion. Indeed, if a suspicious lesion is detected by MRI, the next appropriate diagnostic investigation is EUS +/- fine needle biopsy.

Magnetic resonance imaging: MRI needs extra consideration in patients who have pacemakers or metal insertions.[34] There are some concerns about deposition of gadolinium in the brain with repeated contrast MRIs. Gadolinium-based contrast agents commonly used for enhancement in MR imaging are deposited in tissues, including the brain. Currently there is no clinical evidence regarding the neurologic effects of gadolinium deposition, but clinicians are advised to use this agent with caution until further information is available.[35]

Computed tomography: Having a CT scan for surveillance of pancreatic cancer exposes people to radiation (31 mSv multiphase abdominopelvic CT compared to 1.5 mSv in a low-dose chest CT),[5] and there is consistent evidence that this this higher dose of radiation may increase the risk of cancer. A recent literature review and meta-analysis found that the cancer risk increased with cumulative radiation dose from CT scans, slowly with radiation dose below 55mSv, and rapidly with doses above 55mSv. An estimate of the cancer risk was calculated by comparing a control group (assumed to have received the global mean of 2.4mSv of background radiation dose) to a CT-exposed group (aged 18 years or older with ≥1 CT scan at a radiation dose per capita of 66.7 mSv (range 5.15 mSv to 122 mSv)). The incidence of cancer in the control group (42.7/100000 for men and 65.7/100000 for women) was approximately two-thirds of that in the CT-exposed group (68.8/100000 for men and 91.9/100000 for women).[36]

Psychological outcomes: In a study of 102 Australian HRIs undergoing surveillance, there was no negative psychological impact of screening. Rather, there was evidence of long-term benefit that emerged from one year after baseline (i.e., at the time of recruitment into the study). This benefit was observed, irrespective of whether abnormal findings were detected or not.[37]

Strength of evidence for harms of surveillance: The working group considered that there is insufficient evidence to establish the harms of surveillance vs no surveillance.

5.7 Evidence for the accuracy of different imaging modalities

There have been no RCTs of different imaging modalities in HRIs, so there is no information about how the use of different imaging approaches affects mortality from pancreatic cancer.

In a multicentre study, 216 HRIs were imaged using EUS, CT, and Magnetic resonance cholangiopancreatography (MRCP), with all tests occurring within a 2-day period. Thirty-six percent of HRIs had a normal pancreas according to all 3 imaging tests.[38] Of those with at least one lesion (n=93/216), 27% were able to be identified by CT, 81% by MRI and 93% by EUS. The concordance between EUS and MRI for detection of any neoplastic-type lesion was 91%, compared with 73% concordance for EUS and CT.

A number of studies have assessed the accuracy of different imaging modalities for diagnosis of the lesions of the pancreas. These are described below, but it should be noted that their relevance to surveillance in HRIs is unclear, as lesions diagnosed in symptomatic patients undergoing diagnostic investigations may not generalise to asymptomatic patients undergoing surveillance.

A meta-analysis of the accuracy of MRI, CT, and EUS for diagnosis of lesions in the pancreas found that the sensitivity of CT (72%) was lower than that for MRI (76%) and EUS (75%), and the overall diagnostic accuracy of MRI, CT and EUS for differentiating benign and malignant cystic pancreatic lesions was 85%, 75% and 81%, respectively (Appendix 2 Table *5*).[39]

Appendix 2 Table 5. Accuracy of MRI, CT, and EUS for diagnosing pancreatic lesions[39]

Accuracy Measure	CT (9 Studies)	MRI (17 Studies)	EUS (5 Studies)
Sensitivity	0.72 [0.57-0.83]	0.76 [0.67-0.84]	0.75 [0.53-0.89]
Specificity	0.74 [0.69-0.79]	0.80 [0.74-0.85]	0.75 [0.62-0.85]
Positive likelihood ratio	2.5 [2.2-3.6]	3.8 [2.9-4.9]	3.0 [1.7-5.3]
Negative likelihood ratio	0.38 [0.23-0.60]	0.30 [0.21-0.42]	0.33 [0.15-0.73]
Diagnostic odds ratio	7 [4-15]	13 [8-21]	9 [3-32]
Area under ROC curve	0.75 [0.71-0.79]	0.85 [0.82-0.88]	0.81 [0.77-0.84]

95% confidence interval in parentheses. Note the confidence intervals were derived from meta-analysis and not from direct comparison meta-regression. ROC: receiver operating characteristic

Another study, in which the sensitivity according to different lesion types was investigated, found that EUS was most sensitive for diagnosis of PDAC and cystic lesions, including intraductal papillary mucinous neoplasms that can be precursors to pancreatic cancer, although sample sizes were small (Appendix 2 Table *6*).[40]

Appendix 2 Table 6. Sensitivity of cross-sectional imaging per postoperative diagnosis[40]

Postoperative diagnosis	CT n (%)	MRI n (%)	EUS-FNA/B n (%)
A. Solid lesions (n= 118)			
PDAC (n= 35)	27/34 (79)	7/10 (70)	20/22 (91)
pNET (n= 41)	28/34 (82)	9/14 (64)	17/23 (74)
Metastasis other (n= 4)	3/4 (75)	1/1 (100)	2/3 (67)
SPN (n=7)	3/7 (43)	1/2 (50)	2/4 (50)
Pancreatitis (n= 25)	19/25 (76)	9/10 (90)	10/17 (59)
Other lesions (n= 6)[a]	1/4 (25)	1/3 (33)	0/5 (0)
Total correct solid	81/108 (75)	28/40 (70)	51/74 (69)
B. Cystic lesions (n= 63)			
Cystic PDAC (n= 9)	5/6 (83)	4/6 (67)	6/7 (86)
pNET (n= 3)	0/3 (0)	0/2 (0.0)	0/3 (0)
IPMN (n= 20)	8/13 (61)	12/15 (80)	17/19 (89)
MCN (n= 22)	13/18 (72)	7/10 (70)	11/14 (79)
SCN (n= 6)	3/5 (60)	1/3 (33)	1/3 (33)
Pseudocyst (n= 1)	0/1 (0)	-	1/1 (100)
Other lesions (n= 2)[b]	0/1 (0)	0/1 (0)	0/1 (0)
Total correct cystic	29/47 (62)	23/37 (62)	36/48 (75)
Overall correct	110/155 (71)	51/77 (66)	87/122 (71)

Abbreviations: CT: computed tomography; EUS: endoscopic ultrasound; IPMN: intraductal papillary mucinous neoplasm; MCN: mucinous cystic neoplasm; MRI: magnetic resonance imaging; n: number of patients; PDAC: pancreatic ductal adenocarcinoma; pNET: pancreatic neuroendocrine tumor; SPN: solid pseudopapillary neoplasm; SCN: serous cystic neoplasm.

[a] One patient had no detectable lesion, two patients had small inflammatory changes, one patient had a granular tumor, one patient had ectopic spleen tissue and one patient had pancreatic intraepithelial neoplasia (PanIN).

[b] One patient had no detectable lesion and one patient had a retention cyst.

Strength of evidence for recommending different surveillance approaches: The working group considered the strength of evidence for recommending EUS vs MRI to be low. The working group considered the evidence for recommending EUS or MRI vs CT to be moderate.

5.8 What surveillance interval is optimal?

There have been no RCTs of different surveillance intervals, so the optimal surveillance interval is unknown. International guidelines recommend annual surveillance with EUS or MRI, with more frequent follow-up if concerning lesions are identified.[21,41-43]

5.9 Diabetes as an indicator of pancreatic cancer

Pancreatic cancer can cause diabetes mellitus (diabetes), and the diabetes can arise several years before symptoms lead to diagnosis of pancreatic cancer. However, in the general population (of those aged <50 years) pancreatic cancer is the cause of diabetes in only 0.5-1% of people;[44-47] there is no way to determine whether new-onset diabetes is type 2 diabetes or pancreatogenic diabetes (Type 3c). There is no information about the risk of pancreatic cancer in high-risk individuals with new-onset diabetes. There is no evidence, in the general population or in high-risk individuals, that surveillance imaging in people with new-onset diabetes reduces mortality from pancreatic cancer.

Strength of evidence that diagnosis of new-onset diabetes should influence surveillance in high-risk individuals: The working group considered the strength of evidence for recommending early or additional surveillance in high-risk individuals diagnosed with new-onset diabetes to be low.

5.10 Cystic lesions identified incidentally

The prevalence of pancreatic cystic lesions varies considerably, depending on the imaging modality used. It is lower with CT than with MRI. A review of 2832 contrast-enhanced multi-detector CT scans in the United States identified 73 pancreatic cystic lesions (2.6%).[48] The American Gastroenterology Association (AGA) notes that pancreatic cysts are identified in approximately 15% of patients undergoing abdominal MRI for other indications.[49] The high prevalence of cystic lesions and low incidence of pancreatic cancer highlights the low malignant potential of these lesions; the AGA estimated that a cyst seen incidentally on MRI has a 27/100,000 chance of being an invasive malignancy.[49]

A number of guidelines for cyst management have been developed. While there is some inconsistency across management recommendations, most recommend MRI/MRCP as the preferred imaging modalities for cyst characterisation due to their superior ability to assess cyst-duct communication and the avoidance of ionising radiation.[50] Pancreatic protocol CT is the imaging modality of choice for patients who are unable to have an MRI scan for medical reasons.

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