Consensus Guideline on Screening for Pancreatic Cancer within Te Manawa Taki Midlands Region, Aotearoa New Zealand

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Introduction:

Pancreatic ductal adenocarcinoma (herein referred to as pancreatic cancer) continues to be one of the malignancies with the worst prognosis, often presenting late, with advanced disease. It is also one of the few cancers whose incidence is increasing.[1] Often it is asymptomatic until it is advanced precluding attempts at curative management.[2]

Pancreatic cancer is a relatively rare malignancy with an age-standardised annual incidence in Aotearoa New Zealand (AoNZ) of 7.9 per 100,000,[3] and a lifetime risk 1.3%.[4] . In 2020 there were 683 new cases. Only 15-20% of cases are resectable at time of diagnosis. Those that present with stage I disease have a 5-year survival of around 70-80%, compared to a survival of 9-13% at 5 years for all cases.[5,6] The goal of a surveillance program is to detect pancreatic cancer at an early stage to improve survival from this devastating disease.

The low incidence of pancreatic cancer in the general population necessitates a highly selected population for an effective surveillance program. This is in contrast to other malignancies, such as breast, cervical, and bowel cancer, where whole population screening programs have been employed.

Within AoNZ Māori patients had a 12% excess mortality compared non-Māori after being diagnosed with pancreatic cancer. Notably, when these patients were stratified by comorbidity, Māori patients with no comorbidity still had a 30% excess mortality in comparison to non-Māori.[7] The reasons for this have not been elucidated, but this disparity was only present in non-comorbid Māori patients with advanced disease, not present in non-comorbid Māori patients with early disease. Implementing a surveillance program has been shown to detect pancreatic cancer at an earlier stage[8–10] and thus we would expect an improvement in the current inequity seen with implementation of this surveillance program.

Although there have been previous concerns about the benefit of pancreatic cancer surveillance there is mounting evidence from pancreatic cancer surveillance programs of a highly selected population within the US that pancreatic cancers detected as part of surveillance have a significant improvement in long term survival compared to those detected outside of a surveillance program.[8,10]

The goal of this document is to provide a consensus statement regarding the role of pancreatic cancer surveillance within the Te Manawa Taki Midlands Region in AoNZ, after reviewing the international literature and guidelines on surveillance for pancreatic cancer in high-risk populations. The International Cancer of the Pancreas Screening (CAPS) Consortium has published updated guidelines for the management of patients with an increased risk of pancreatic cancer, referred to as high risk individuals (HRIs).[11] Our consensus guidelines aim to adapt and contextualize the CAPS recommendations to the healthcare landscape of AoNZ specifically within Te Manawa Taki Midlands Region, incorporating other international guidelines as well as the latest available literature. Our

goal is to service the entire Te Manawa Taki Midlands Region using these guidelines, and will expect our surveillance cohort to be drawn from Waikato, Taranaki, Lakes, Tairāwhiti, and Bay of Plenty catchments. Currently Te Manawa Taki Midlands Region services 1,007,405 people, including 280,170 Māori (28%), which equates to roughly 20% of AoNZ's population.

These guidelines can also be used as a framework to advocate for increased investment in surveillance for pancreatic cancer to improve both overall mortality and inequity. Implementing a surveillance program in the public healthcare setting for a rare disease requires a highly selected, high-risk population to minimise further stressors on the healthcare system and maximise benefit, which we are cognizant of in the current healthcare climate.

1. Risk Stratification

The lifetime incidence of pancreatic cancer is low, so screening of the general population is not recommended.[9] An estimated 10% of pancreatic cancer cases arise in those with a strong family history of pancreatic cancer or in carriers of germline mutations known to increase the risk of pancreatic cancer.[12] These individuals are referred to as high-risk individuals (HRIs). Those at increased risk of pancreatic cancer are predominantly individuals with a strong family history of pancreatic cancer, with an unidentified genetic susceptibility. These patients make up around 7% of those with pancreatic cancer. The genetic risk factors in these patients are not yet delineated so the most important tool for identifying those at increased risk and quantification of that risk is an accurate family history. The remaining 3% have specific identifiable mutations which place them at very high risk of developing pancreatic cancer during their lifetime.[13] We are proposing offering surveillance to these HRIs.

Familial History Assessment

Clinicians should obtain comprehensive personal and family histories of all types of cancer to identify individuals with familial cancer syndromes who are at increased risk of pancreatic cancer. It is essential to confirm the exact type of cancers i.e. pancreatic ductal adenocarcinoma, rather than carcinoid, neuroendocrine tumours, pancreatoblastoma etc. Number of first- and second-degree relatives (FDRs and SDRs) with pancreatic cancer should be sought to accurately quantify risk.[11] Age of diagnosis of pancreatic cancer is another important factor to consider, with earlier onset pancreatic cancer in a first degree relative being associated with higher risk of development of pancreatic cancer. Individuals with one or more FDR diagnosed before 40 years of age have an estimated cumulative lifetime risk of 15%.[14] This decreases to 7.1% if the youngest age of diagnosis in the affected family member is 60 years of age, and decreases further to 3.1% if the age of youngest diagnosis is 80 years of age.[14] Thus we recommend only family members who developed pancreatic cancer under the age of 80 years of age be included when assessing family history to determine risk.

Pancreatic Cancer Risk Categories	Risk for this group by age 80 years	Lifetime risk
General Population	-	1.3%[4]
2 affected FDRs	8-12%[15]	
3 affected FDRs	16-30%[15]	
3 affected FDRs, one of which <40 years at age of diagnosis	39%[14]	

Table 1: Adapted from https://www.eviq.org.au/cancer-genetics/adult/risk-management/1517-pancreatic-cancer-increased-risk-risk-man#lifetime-risk-of-cancer-tumour[16]

Genetic Counselling and Testing:

Individuals with a strong family history of pancreatic cancer or a known hereditary/familial syndrome associated with increased risk of pancreatic cancer should be referred for genetic counselling and testing, particularly if the family history suggests a familial cancer syndrome. Funded genetic testing should be available for individuals with a family history of one of the familial cancer syndromes which increases the risk of pancreatic cancer. If the individual does not have the culprit genetic mutation implicated in other members of their family, they do not need to be included in the surveillance program.[17] If no culprit gene is identified within the family, they would be included in the surveillance program based on number of relatives affected and ages of diagnosis.[17]

As with most genetic testing, risks and benefits should be discussed with patients prior to testing as there is potential risk of harm with over investigation, and psychological distress to consider with each individual.

2. Screening Modalities

Endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI) are considered to be the most accurate diagnostic tools for assessing the entire pancreas without exposure to ionising radiation.[4] They also have excellent concordance for cystic pancreatic lesions and outperform CT in this setting.[18]

Endoscopic Ultrasound (EUS)

EUS is one of the two preferred screening modalities for individuals at increased risk due to familial pancreatic cancer syndromes or hereditary cancer syndromes. It is most sensitive for solid lesions.[19]

Magnetic Resonance Imaging (MRI)

MRI with cholangiopancreatography (MRCP) can be considered as an alternative and/or complementary screening modality, particularly in individuals who are unable to undergo EUS or in settings where EUS capacity is limited. This is particularly important within Te Manawa Taki Midlands Region where several Te Whatu Ora/Health New Zealand provinces or hospitals have limited access to EUS. MRI is also more sensitive for cystic lesions compared to EUS.[19]

Computed Tomography (CT) pancreatic protocol

CT could be considered in those unable to undergo MRCP or EUS, however, strong preference remains for MRCP or EUS given their superior performance at identifying small (<1cm) cysts as well as the lack of ionising radiation. CT could be considered to further investigate solid lesions identified by MRCP or EUS although there is no consensus on this.[4]

Positron emission tomography

Not recommended in the AoNZ setting.

Ultrasound

Not recommended. The sensitivity of ultrasound is only 70% for pancreatic abnormalities and this modality is frequently unable to image the entire pancreas.[4,20,21]

3. Surveillance Initiation and Frequency

Who to screen:

Age, family history, germline mutation status, and comorbid status should all be considered when determining eligibility for entering a pancreatic cancer surveillance program. The cut-offs we have adopted in terms of defining a HRI are a lifetime risk of 5% or a relative risk of ≥5 which is in keeping with international guidelines.[4,11] All HRIs should be considered for surveillance. For the purposes of this document, wherever 'relative' is referred to this indicates being genetically related. We recommend the following patients should undergo surveillance:

- Individuals with a family history, known as kindreds, which comes under the category Familial Pancreatic Cancer (FPC)
    - Prospective studies have demonstrated a relationship between the number of affected relatives and the risk of developing pancreatic cancer as detailed in Table 1.[4]
    - Individuals with two or more affected relatives with pancreatic cancer who are on the same side of the family, with at least one these being a FDR, should be considered for surveillance.[11,22]
    - For families with multiple members affected by pancreatic cancer due to a specific genetic mutation as detailed in Table 1, individuals within these families should be tested for the genetic mutation implicated. Those that do not possess the mutation, as determined by genetic testing, do not require surveillance as they are not at increased risk of pancreatic cancer.[17]
    - We expect the majority of our surveillance population to be sourced from the FPC indication, between 51%-84% based on other surveillance programs.[8,10]
- Peutz-Jeghers syndrome
    - All patients with Peutz–Jeghers syndrome (STK11 mutation), regardless of family history, should be considered for surveillance. Lifetime incidence of pancreatic cancer in patients with Peutz–Jeghers syndrome is 11–36%.[23]
    - Surveillance should begin at 40 years of age as median age of pancreatic cancer diagnosis in Peutz-Jeghers is 54 years old.[24]
- Familial Atypical Multiple Mole Melanoma (FAMMM)
    - All patients with FAMMM (CDKN2A/p16 mutation) should be screened for pancreatic cancer regardless of family history. Studies show p16 gene mutation carries a relative risk of 13-22 times the normal population risk.[25–27] Lifetime risk of developing pancreatic cancer is 16-20%.[28] A prospective study in the Netherlands has shown improved survival in those with CKDN2A mutations undergoing surveillance.[29]
    - Surveillance should start at 40 years of age
- Hereditary pancreatitis

    - Those with hereditary pancreatitis have an estimated lifetime risk of pancreatic cancer of 40%.[30]
    - There are established international guidelines recommending surveillance in those with hereditary pancreatitis due to PRSS1 mutation.[31] This should be limited to those with recurrent pancreatitis rather than all PRSS1 mutation carriers.
    - Other mutations do not meet the threshold for surveillance
    - Surveillance should start at 40 years of age or 20 years after the first pancreatitis attack, whichever comes first.
- Hereditary Breast Ovarian Cancer Syndrome
    - BRCA2 mutation carriers with ≥1 affected FDR with pancreatic cancer or ≥2 affected family members on the same side (without a FDR) should be considered for surveillance.[11]
        - Germline BRCA2 mutations have been identified in 5-17% of familial pancreatic cancer and make up the largest portion of known causes of familial pancreatic cancer.[32–34]
        - Some guidelines advise screening all patients with BRCA1 and BRCA 2 mutations.[35] With our review of the literature and employing a cut off of lifetime risk 5% or RR ≥5, we recommend only those BRCA2 mutations patients with a first degree relative with pancreatic cancer or 2 affected blood relatives on the same side of the family should be offered surveillance
        - Some predictive models have shown that screening BRCA2 individuals with 1 or fewer affected FDRs might actually lead to a decrease in life expectancy, thought to be due to the risks of surveillance including false positives.[36] With two or more FDRs affected, modelling shows an increase in life expectancy. Real world studies are needed to assess this further.
- Lynch Syndrome
    - Patients with Lynch syndrome (mutations in MLH1, MSH2, MSH6, or PMS2) and one affected FDR should be considered for surveillance. Those with Lynch syndrome without a family history have a 3.7% lifetime risk of developing pancreatic cancer[37,38] so we have opted to only include those individuals with ≥1 FDR in our surveillance criteria.
- ATM mutation carriers should undergo surveillance if they have a FDR with pancreatic cancer. They have an estimated lifetime risk of pancreatic cancer of 5-10%.[39]

Who we do not recommend screening:

- Hereditary Breast Ovarian Cancer Syndrome
    - BRCA 1
        - BRCA1 mutations have a lower risk of developing pancreatic cancer than those with BRCA2 mutations.[28] Patients with BRCA1 mutations do not reach the 5% lifetime risk or fivefold relative risk thresholds.[28] ASGE guidelines recommend BRCA1 surveillance based on small studies which showed high rates of pancreatic abnormalities on

pancreatic imaging of BRCA1 and BRCA2 patients in retrospective studies.[40,41] These studies however were small and retrospective, with cross sectional imaging reviewed when available. This is likely to give selection bias given these patients were not imaged solely for screening, and instead are more likely to be symptomatic as the indication for the imaging.

        - The latest CAPS guidelines show only 69.% of experts agreeing or strongly agreeing with surveillance in BRCA1 mutation carriers.[11] In the interest of not overwhelming the surveillance program, as well as the lower overall risk of developing pancreatic cancer, we have opted not to include patients with BRCA1 mutations in our surveillance population, though this will be regularly revisited as further data becomes available.
    - PALB2 mutation carriers do not reach the threshold of RR ≥5 or lifetime risk ≥5% so are not recommended to be screened at this stage. International consensus guidelines recommend surveillance these patients if they have a FDR with pancreatic cancer. This could be revisited in our population once surveillance is established.
- Familial adenomatous polyposis
    - Incidence of pancreatic cancer in those with mutations of APC is around 2% so surveillance of these individuals is not recommended.[42]
- Cystic Fibrosis (CF) patients
    - Although a recent systematic review has shown a significantly increased risk of pancreatic cancer in cystic fibrosis patients (pooled standardised incidence ratio of 6·18, 1·31–29·27; p=0·022;) there was significant heterogeneity between the four studies analysed. Authors felt this was likely due to a heterogenous mixed population of transplanted and untransplanted CF patients.[43]
    - We feel at present further data is needed to confirm which CF patients would benefit from surveillance. This will need to be regularly revisited as the life expectancy of CF patients continues to improve.[43]

Estimated Numbers Needing Surveillance

It is difficult to be able to provide exact estimates as to how many patients will require surveillance, however if we look at national surveillance programs in Spain, Germany, and the US in comparison to their populations, we would expect fewer than 200 patients to be enrolled in surveillance in AoNZ.[8,44,45] The largest of these programs, the US based CAPS-5 surveillance program, is based off the National Familial Pancreas Tumor Registry, which captures 4000 familial kindreds within the US and screens over 1700 HRIs.[8] Extrapolating to AoNZ's population, we would only expect 62 familial kindreds requiring surveillance via the FPC category. Within this cohort FPC makes up 56.7% of their population. Extrapolating to AoNZ, this would then mean we expect around 47 patients requiring surveillance for genetic mutations.[8]

Initiation Age:

- Surveillance should generally commence at age 50 or 10 years earlier than the youngest age of pancreatic cancer diagnosis in the family,[4,11] whichever comes first, with a few exceptions:
    - In patients with Peutz-Jegher syndrome or CKDN2A mutations earlier surveillance should be considered as these patients tend to develop pancreatic cancer earlier. Our recommendation would be to start surveillance at 40 years of age for these cohorts, or 10 years younger than the youngest diagnosis of pancreatic cancer within the family.[11]
    - Those with hereditary pancreatitis should also be screened earlier, our recommendation is to begin surveillance at 40 years of age or 20 years after first pancreatitis attack due to a younger average age at diagnosis in these patients.[31]

Cessation age:

- There is no agreed upon age that surveillance should be stopped in international guidelines but if an individual would not be a surgical candidate they should no longer be surveilled.[4]
- Our recommendation would be to screen until 75 years of age with the following justifications:
    - This age cut off is in keeping with the bowel cancer screening program; the breast cancer screening program is also in the process of extending their cessation age to 75 years of age.
    - Average age at diagnosis is 68-71 years of age for those with familial pancreatic cancer so it would be logical to continue to age 75[14,46,47]
    - 90% of surveillance detected pancreatic cancers were detected in those under 75 years of age
- Potentially very fit 75-80 year old individuals could be considered to continue surveillance until 80 years of age, with decisions regarding when to stop surveillance made on a case by case basis. This is given there is still a significant number of pancreatic cancers diagnosed in this age group.

Syndrome	Gene(s) Implicated	Cumulative PC Risk	PC Relative Risk	To be screened?	Age to Initiate Surveillance*	AoNZ Population Prevalence	Estimated Number of Patients to be screened within AoNZ
Familial pancreatic cancer (FPC)	–	≥3 FDR with PC: 16%-40% cumulative risk[70] 2 FDR with PC: up to 12% cumulative risk[70] 1 FDR with PC: up to 6%[15]	3 FDR with PC: 32-fold[15] 2 FDR with PC: 6 fold[15] 1 FDR with PC: 2–5 fold[71]	3 FDR – Yes 2 FDR – Yes 1 FDR + 1 SDR or FDR - Yes 1 FDR – No	50	Unknown	<60** Estimated 57% of the total surveillance population[Δ8]
Peutz Jeghers syndrome (PJS)	*STK11/LKB1*	8-11% at 70 years 36% lifetime risk[23,48–50]	132 fold[23,48]	Yes - all	40	1 in 100,000 [51]	20-25[51]
Hereditary pancreatitis (HP)*	*PRSS1,SPINK1, PRSS2, CTRC*	Up to 53% at 75 years of age[30,52,53]	26–87 fold[31,54–57]	Yes – all with PRSS1 mutations	40	0.3 in 100,000 [53]	5-10[53]
Familial atypical multiple mole melanoma (FAMMM)	*P16/CDKN2A*	17% at 75 years of age[58]	13–46.6 fold[59,60]	Yes - all	40	Unknown	5-10[Δ] Estimated 4.7% of our total surveillance population[Δ8]
Hereditary breast-ovarian cancer syndrome (HBOC)	*BRCA1, BRCA2, PALB2*	BRCA1: 2.2-3% BRCA2: 3-7%[61] PALB2: up to 4%[62]	BRCA1: 2.26-3 fold[63] BRCA2: 3.5–22 fold[61,64,65] PALB2: 2.37 fold[63]	BRCA1 - No BRCA2 if ≥1 FDR PALB2 - No	50	BRCA 1: 0.04%[66] BRCA2: 0.4% [66] PALB2: 0.19%[67]	BRCA1: N/A BRCA2: 30-35[Δ] PALB2: N/A
Lynch syndrome (LS)	*MLH1, MSH2, MSH6, PMS2*	3.7% at 70 years of age[37]	8.6 fold[37]	Yes if ≥1 FDR	50	1 in 279[68]	5-10[Δ]
Ataxia telangiectasia (AT)	*ATM*	6.3% by 70 years of age 9.5% by 80 years of age[39]	6.5 fold[39]	Yes if ≥1 FDR	50	1 in 40,000 to 1 in 100,000[69]	10-15[Δ]
Familial adenomatous polyposis syndrome (FAP)	*APC*	1.7% at 80 years of age[42]	4.5 fold[72]	No	-	-	-
Li-Fraumeni syndrome (LFS)	*TP53*	<5%[73,74]	-	No	-	-	-
Cystic fibrosis (CF)	*CFTR*	<5%[42]	5.3 fold[75]	No	-	-	-

Table 2 *adapted from Llach et al summarising genetic syndromes with increased risk of pancreatic cancer and our recommendations around surveillance these populations, estimated number of individuals within the entire AoNZ population estimated from Statistics NZ Infoshare taking into account age of initiation.[13,76] (PC, pancreatic cancer.)*

**Or 10 years younger than the youngest affected blood relative*

***Based on Spanish and German screening whole population programs and the National Familial Pancreas Tumor Registry based in the United States of America (US)[8,44,45]*

Δ *Estimates extrapolated from the CAPS study population in America*

Frequency and configuration:

- Annual surveillance is recommended for individuals at increased risk if no abnormalities or non-concerning abnormalities are seen on previous surveillance imaging.
    - There is limited evidence regarding the best interval to screen, current consensus is 12-months.[11]
    - HRIs with advanced pancreatic cancer diagnosed after prior normal/indeterminate imaging usually presented ≥12 months later.[77,78]
- Our recommendation is to alternate between MRCP and EUS with annual surveillance. This will help to limit resource constraints that might be seen if only one modality is recommended, and is also in keeping with international surveillance programs.[8]
- Some research has shown if there is no abnormality on initial screening the following surveillance can be safely undertaken in 3 years time, as there were no difference in outcomes between this and annual surveillance in non-CDKN2A mutations but further data is needed to definitively prove this.[79] Some protocols also suggest if initial surveillance MRCP + EUS are completely normal then the interval can be extended to surveillance every 2 years though the data is not conclusive about the safety in doing this.[79] The vast majority of individuals in whom a clinically relevant lesion developed during follow-up had pancreatic abnormalities at baseline screening. [77,80] Until further data is available regarding the safety of this we recommend annual surveillance.
- Three or six months surveillance interval is suggested for concerning abnormalities if surgery is not indicated, based on already established guidelines for radiologically detected pancreatic abnormalities.[4,11]

Other Aspects of Surveillance:

- **CA19-9**
    - The role of CA19-9 in surveillance those at high risk is unclear and requires further study.
    - Expert consensus opinion is that it should be employed in those with worrisome features on their surveillance imaging.[11]
    - This recommendation may change with time as further data is available.
- **Diabetes Screening:**
    - Consensus opinion is that it would be reasonable to screen for new onset diabetes with either a fasting blood glucose or HbA1c annually in HRIs, and diagnosis of new onset diabetes in a HRI in the surveillance program should prompt interval investigations.[11]
    - New onset diabetes in a HRI should prompt initiation of surveillance regardless of age.
- **Lifestyle Advice:**
    - All patients in the surveillance program should be advised to quit smoking and avoid heavy alcohol use given both smoking and heavy alcohol use (binge drinking or more than 3 drinks per day) are associated with modest increased

risk for pancreatic cancer. Likewise increased physical activity, and diets high in folate, fruit and vegetables have been shown to be associated with a lower risk of pancreatic cancer and patients should be counselled around this.[28,31] We do not advocate for changing the surveillance recommendations based on smoking status of the patient.

4. Surveillance and Management of Screen-Detected Lesions:

The main targets of our surveillance are stage I pancreatic cancers and precursors with high-grade dysplasia, either in Pancreatic Intraepithelial Neoplasm (PanIN) or Intraductal Papillary Mucinous Neoplasm (IPMN).

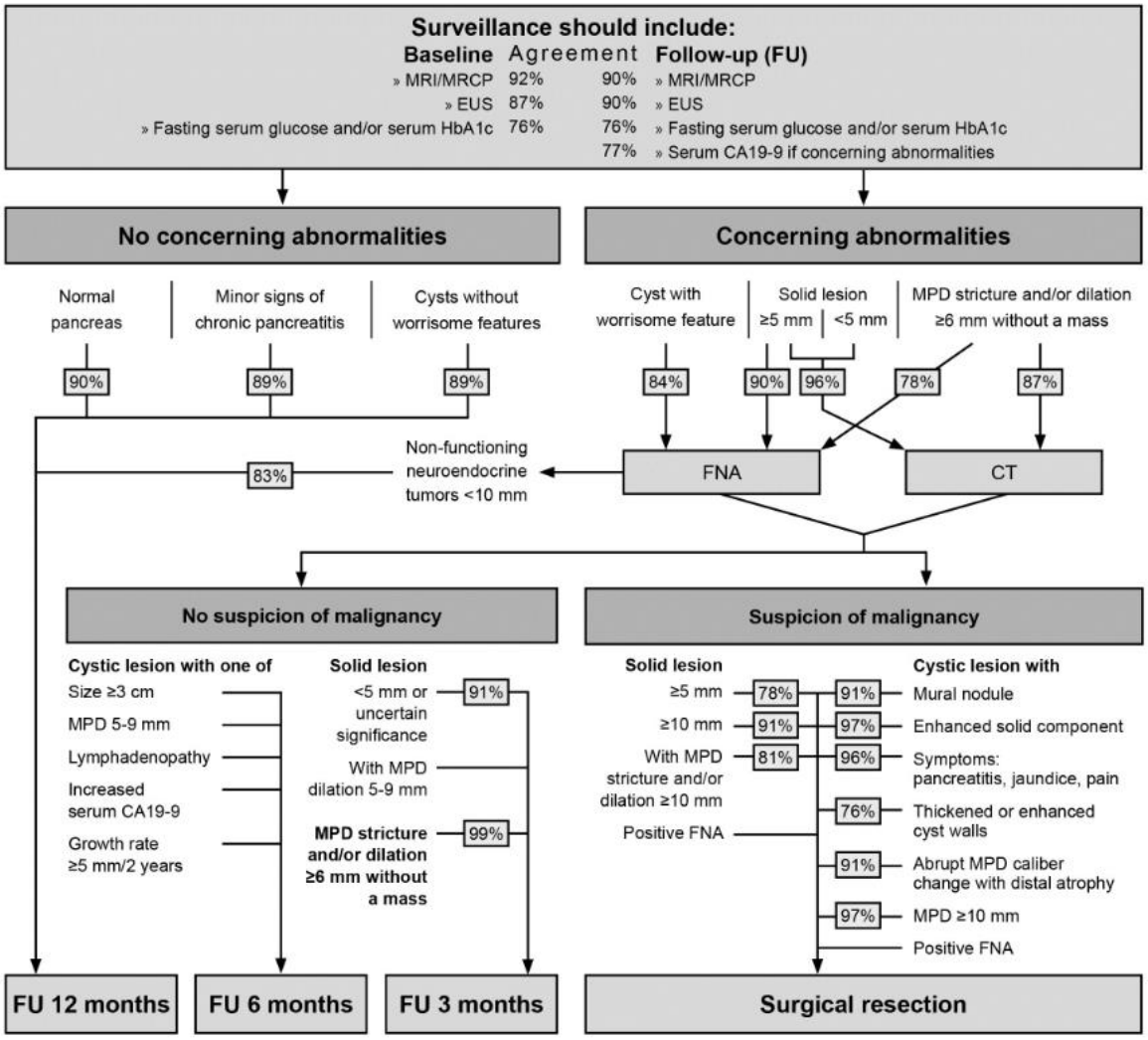

Figure 1: *suggested management protocol of surveillance-detected lesions, taken from Goggins et al.*[11] *EUS, endoscopic ultrasound; FNA, fine-needle aspiration; MPD, main pancreatic duct; MRCP, magnetic retrograde cholangiopancreatography.*

No abnormality detected on initial surveillance MRCP + EUS:

- Continue annual surveillance[11]

Abnormality detected on surveillance MRCP/EUS:

- HRIs will commonly have minor abnormalities on their surveillance imaging including cysts and non-specific parenchymal changes not fitting into the below mentioned criteria. In these patients we recommend annual surveillance.

- Broadly, we suggest FNA/FNB if a solid lesion or a cystic lesion with worrisome features is found +/- further imaging such as CT for solid lesions
- If pancreatic cancer is detected and confirmed, we recommend following current guidelines for sporadic pancreatic cancers to guide decisions regarding resection, as well as adjuvant and neoadjuvant chemotherapy.
- Where the diagnosis of pancreatic cancer is not confirmed but there are abnormalities detected:
    - Broadly speaking, resection should be undertaken for similar indications as non-HRIs as per current guidelines
    - Solid lesions
        - All solid lesions should be further investigated with a CT with pancreas protocol
        - A solid lesion ≥10mm should be considered for resection. If it is not for resection, FNA/FNB should be undertaken as well as follow up imaging in 3 months.
        - Management of solid lesions <10mm is controversial. We currently recommend CT pancreas, EUS with FNA/FNB as well as short-interval (3 months) follow up imaging. Solid lesions of indeterminate pathology that are >5 mm should be considered for pancreatic resection if FNA/FNB does not yield a definitive preoperative diagnosis. If resection is not undertaken follow up imaging should be in 3 months.[4]
    - Intraductal Papillary Mucinous Neoplasms
        - We recommend following the latest IPMN management guidelines if these are detected.[81]
        - In those being screened, IPMNs should be considered for resection if they fulfil any of the following worrisome features:
            - A mural nodule
            - An enhanced solid component
            - Symptoms (pain, pancreatitis, jaundice)
            - Thickened/enhanced cyst walls
            - Abrupt change in MPD with distal pancreatic atrophy
            - An MPD ≥10 mm
        - Most cystic lesions detected via surveillance are low-risk branch-duct IPMNs
            - In an unselected population with suspected BD-IPMNs, resection is considered if the patient has symptoms attributable to the cyst(s), if the cysts are >3 cm in size, or if the cysts contain mural nodules.[81–83]
            - Given these guidelines are from an unselected population, and our screened population will be high risk for pancreatic cancer, we recommend considering resection of cysts ≥2cm as based on the CAPS guidelines.[4]
            - There have been high-grade PanIN lesions (previously referred to as PanIN-3) found within IPMNs that were smaller than 1cm and high grade dysplasia has been found in resection specimens in patients with small BD-IPMNs[18,80,84,85] but

currently there is not enough evidence to make a recommendation about these subsets of patients[4]
        - Patients with a cystic branch-duct lesions without worrisome features should be re-evaluated at intervals depending on size, using accepted international consensus guidelines for sporadic BD-IPMNs[4,81]
    - Main pancreatic duct (MPD) stricture:
        - If an asymptomatic MPD stricture with associated suspicious mass is detected we recommend FNA/FNB and resection
        - If an indeterminate MPD stricture without suspicious mass is detected, a CT scan and EUS FNA/FNB should be performed. If this is not resected, repeat imaging should be performed within 3 months[4]
    - If concerning pancreatic abnormalities are detected in *CDKN2A* mutation carriers that do not warrant immediate surgery they should have EUS/fine-needle aspiration, and multidisciplinary review. If the findings still do not warrant surgery after this, we recommend close follow-up imaging in 3–6 months. Examples for when this might apply include mild main pancreatic duct dilation and stricture without mass[11]
- Despite annual surveillance, interval advanced cancers may still occur given estimates for the time to progress from a T1 tumour to T4 is a little over a year.[86] Monitoring for interval cancer development in the screening cohort should be undertaken to assess how common this is.
- Surveillance can periodically identify small PanNETs. The majority of incidentally detected small (<1cm) PanNETs have low malignant potential and should have annual surveillance.[10,18,77,78,80,84,87,88] For other PanNETs surveillance/treatment is recommended as per international guidelines.[89]

Surgical Management

- Determination of when surgery is required should be individualised with a multidisciplinary approach for every case
- Surgical resections should be performed at centres that have demonstrated acceptable post-operative outcomes following pancreatectomy in keeping with international standards
- Given the high morbidity and mortality associated with pancreatic resection, prophylactic resection is not recommended[11]
- Broadly speaking we recommend resection in keeping with guidelines for patients without mutations/family history i.e. sporadic cancers or IPMNs. If there are multiple lesions then resection decisions should be based on the most concerning lesion.[83,90–92]
- We would not advocate for a total pancreatectomy solely because of genetic/family risk factors over a Whipples as there is currently inadequate evidence this is beneficial. If there are concerning regions in multiple areas in the pancreas a total pancreatectomy may be the more appropriate resection.[11]

- We recommend ongoing surveillance for those who have had partial pancreatectomy.[11]

5. Addressing Controversies and Reservations

There are several reservations that are held when it comes to surveillance of HRIs for pancreatic cancer.

- Efficacy
    - Recent studies show increased rates of resectability and improved mortality in screened populations. Despite this, concerns about whether surveillance in these HRIs results in improved survival persists.
    - A recent meta-analysis shows that, of those with pancreatic cancer detected in surveillance populations, 60% were detected at 'resectable' or 'borderline resectable', compared to general population data where only 20% of patients were diagnosed at this stage.[9]
    - The median survival time of HRIs who were diagnosed during surveillance was significantly higher than those who had stopped surveillance or were surveilled late (5.3 years (IQR, 1.2–11.1 years) vs 1.4 years (IQR, 0.39–3.5 years) ($P < .0001$)).[10]
    - A recent review of a HRI surveillance group in the US detected predominantly stage I cancers (77.8%) and has found a median survival of 9.8 years. This is significantly better than pancreatic cancers found outside of the surveillance group, which presents with metastatic disease in >50% of cases.[8]
    - Resectability rates are much higher in surveillance cohorts than in symptomatic sporadic pancreatic cancer, with 71% of pancreatic cancers being resectable in one screened cohort but only 15-20% of symptomatic patients being resectable[10]
    - There is evidence of improved mortality in screened populations with overall 3-year survival rate of HRIs with pancreatic cancer was substantially higher than that of patients with pancreatic cancer in the US (57% vs 8.9%).[5,10]
    - Overall large, prospective, longer term studies are still required to further evaluate the full benefit of pancreatic cancer surveillance in HRIs but there is currently adequate evidence that surveillance in HRIs improves mortality from pancreatic cancer to advocate for initiating a surveillance program in Te Manawa Taki Midlands Region.
- Risks of overdiagnosis
    - Some patients within surveillance programs have had resections for concerning screening results with histology coming back as benign pathologies, without evidence of malignancy or high grade dysplasia, termed low-yield pancreatic surgery. This illustrates the potential harms of a surveillance program and is especially pertinent in this setting as pancreatectomy comes with significant risk of morbidity and mortality.[4]
    - The overall rate of low-yield pancreatic surgery was low on a recent meta-analysis, estimated at 2.8% of all screened HRIs, comprising 181 patients. Of the 181 patients who had pancreatic surgery as a result of surveillance, 46.6% underwent low-yield pancreatic surgery, defined as no evidence of malignancy or high grade dysplasia on histological assessment. Within this group of patients that underwent low-yield pancreatic surgery, the pooled rate of adverse events was high close to 20%.[35] This is a high proportion of

patients undergoing unnecessary surgery with significant risk of adverse events, which needs to be weighed against the extremely poor prognosis of advanced pancreatic cancer and the high risk of developing pancreatic cancer in this cohort. Overall the total number of screened HRIs undergoing low yield surgery is low. The surveillance risks and benefits should be discussed frankly with each patient before enrolment in any surveillance program.

    - Concerns about quality of life (QoL) after unnecessary pancreatectomy also form part of the reluctance to implement pancreatic cancer surveillance programs. An observational study assessing QoL post-duodenopancreatectomy found patients had a similar QoL to post-cholecystectomy patients and control patients, predominantly in those who had duodenopancreatomy for benign pathologies. However post-operative QoL was lower in the analysis of subgroups with pancreatic cancer and chronic pancreatitis.[93] A meta-analysis of 13 studies assessing psychological outcomes in post-pancreatectomy patients shows a decrease in QoL in the immediate post-operative period, with some improvements seen at later timepoints in follow up. Their conclusion is that more research is required to fully elucidate the effects seen post-operatively in these patients.[94]

- Psychological impact of surveillance
    - A meta-analysis including six cohort and one cross-sectional study explored the psychological impact of surveillance for pancreatic cancer in HRIs. The studies included were heterogenous in their assessed outcomes looking at cancer perceived risk, cancer-related concerns or distress, participants' view on surveillance, anxiety, depression, and general distress. Some used standardised, validated questionnaires and others used study specific questionnaires. Acknowledging the heterogeneity of these studies, overall the psychological impact of surveillance was found to be positive.[95]
    - MRI and EUS were found to be equally burdensome amongst surveillance cohorts, mainly related to claustrophobia and inadequate sedation respectively.[95]
    - Qualitative data has shown patients who have had family members affected by pancreatic cancer prefer more invasive surveillance procedures, as long as the test had good performance[96]
- Cost effectiveness
    - Several papers have modelled cost-effectiveness of surveillance, both EUS and MRI, in HRIs and found surveillance to be cost-effective in this cohort. MRI appeared to more cost effective in lower risk HRIs while EUS appeared to be more cost-effective in the highest risk patients.[97–100]
- Healthcare System Strain
    - Our estimates based on available prevalence and incidence data indicates that the number of patients which would require annual surveillance would not be large with the current criteria we have proposed, though exact numbers are unable to be estimated as there are no published data on rates of HRIs within a general population, and it is difficult to estimate how many of those with genetic mutations associated with increased risk of pancreatic cancer would have a FDR/SDR with pancreatic cancer to include in the surveillance group. We would monitor the number of patients enrolled into

the surveillance program and the workload this generates. If the numbers are beyond what we are predicting we would re-assess entry criteria to ensure we are servicing populations at the highest risk with the most potential benefit from surveillance.

- A recent meta-analysis has shown the number needed to screen of 253–281 to prevent 1 pancreatic cancer death, which is significantly smaller than other screening modalities, such as mammography (1887) or faecal occult blood (880), accepting that the screening tests proposed here are more involved and invasive than either of these other tests.

6. Goals and Monitoring Success

- Our primary goal is to detect pancreatic cancer and high risk precursor lesions early to allow for resection, with an overall goal of improving mortality and increasing survival in HRIs.
    - Within this goal we also specifically want to improve the current inequity evident with our Maori population given the excess mortality. This will involve ensuring that access to surveillance modalities does not depend on geographical location. This would potentially involve supporting travel to larger centres if necessary to ensure rural populations are not disadvantaged.
- Every HRI should be collated in a central database, with this database being used to monitor outcomes, with regular review of outcomes including but not limited to surveillance tests, cancer detection rate, missed cancers, and low-yield surgery.

7. Potential Areas of Future Research

There are several promising areas of future research which will need to be reviewed at regular intervals to determine whether they need to be incorporated into these recommendations.

The pathogenesis of pancreatic cancer usually involves development of PanIN as an interim step prior to development of invasive cancer. Currently our diagnostic imaging options are often not able to detect the subtle parenchymal changes that are seen with PanIN. This remains a potential avenue to explore to improve the performance of surveillance programs as our imaging technique advance further. This could be an area where artificial intelligence might be able to be employed to improve performance of diagnostic tests we currently have available.[28,101]

There are retrospective studies that show decreasing muscle mass and adipose tissue detectable on imaging in the 6-12 months preceding the diagnosis of pancreatic cancer. Further studies are needed to see whether incorporating muscle mass and adipose tissue measures in surveillance and risk stratification improves detection of high-risk lesions in HRIs.[102]

Testing for circulating tumour DNA (ctDNA) has been used to predict recurrence and survival in laboratory settings, as well as prognostication of known pancreatic cancer, but further research is required to assess performance in surveillance for pancreatic cancer in HRIs in real world settings.[103]

8. **Conclusion:**

These consensus guidelines provide a framework for the surveillance and management of individuals at increased risk of familial pancreatic cancer within Te Manawa Taki Midlands Region Aotearoa New Zealand healthcare system. By implementing these recommendations, healthcare providers can contribute to the early detection of pancreatic cancer in at-risk populations. There is increasing evidence of the survival benefit in surveillance HRIs for pancreatic cancer, though the surveillance is not without risk and patients should be fully informed of both the benefits and the risks of surveillance. Regular updates and revisions to these guidelines are essential to incorporate advancements in surveillance modalities, genetic testing technologies, and as more data comes to hand about the outcomes of those within surveillance programs.

References

1. Gaddam S, Abboud Y, Oh J, Samaan JS, Nissen NN, Lu SC, et al. Incidence of Pancreatic Cancer by Age and Sex in the US, 2000-2018. JAMA. 2021 Nov 23;326(20):2075.
2. Takaori K, Bassi C, Biankin A, Brunner TB, Cataldo I, Campbell F, et al. International Association of Pancreatology (IAP)/European Pancreatic Club (EPC) consensus review of guidelines for the treatment of pancreatic cancer. Pancreatology. 2016 Aug;16(1):14–27.
3. Te Whatu Ora. Te Whatu Ora Cancer Data Web Tool. https://tewhatuora.shinyapps.io/cancer-web-tool/. 2023.
4. Canto MI, Harinck F, Hruban RH, Offerhaus GJ, Poley JW, Kamel I, et al. International Cancer of the Pancreas Screening (CAPS) Consortium summit on the management of patients with increased risk for familial pancreatic cancer. Gut. 2013 Aug;62(3):339–47.
5. National Cancer Institute. SEER cancer statistics review, 1975-2014. https://seer.cancer.gov/archive/csr/1975_ 2014/. National Cancer Institute. 2018.
6. Blackford AL, Canto MI, Klein AP, Hruban RH, Goggins M. Recent Trends in the Incidence and Survival of Stage 1A Pancreatic Cancer: A Surveillance, Epidemiology, and End Results Analysis. JNCI: Journal of the National Cancer Institute. 2020 Nov 1;112(11):1162–9.
7. Gurney J, Stanley J, McLeod M, Koea J, Jackson C, Sarfati D. Disparities in Cancer-Specific Survival Between Māori and Non-Māori New Zealanders, 2007-2016. JCO Glob Oncol. 2020 Aug;(6):766–74.
8. Dbouk M, Katona BW, Brand RE, Chak A, Syngal S, Farrell JJ, et al. The Multicenter Cancer of Pancreas Screening Study: Impact on Stage and Survival. Journal of Clinical Oncology. 2022 Oct 1;40(28):3257–66.
9. Sawhney MS, Calderwood AH, Thosani NC, Rebbeck TR, Wani S, Canto MI, et al. ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations. Gastrointest Endosc. 2022 May;95(5):817–26.
10. Canto MI, Almario JA, Schulick RD, Yeo CJ, Klein A, Blackford A, et al. Risk of Neoplastic Progression in Individuals at High Risk for Pancreatic Cancer Undergoing Long-term Surveillance. Gastroenterology. 2018 Aug;155(3):740-751.e2.
11. Goggins M, Overbeek KA, Brand R, Syngal S, Del Chiaro M, Bartsch DK, et al. Management of patients with increased risk for familial pancreatic cancer: updated recommendations from the International Cancer of the Pancreas Screening (CAPS) Consortium. Gut. 2020 Jan;69(1):7–17.
12. Kamisawa T, Wood LD, Itoi T, Takaori K. Pancreatic cancer. The Lancet. 2016 Jul;388(10039):73–85.
13. Llach J, Carballal S, Moreira L. Familial Pancreatic Cancer: Current Perspectives. Cancer Manag Res. 2020 Aug;Volume 12:743–58.
14. Brune KA, Lau B, Palmisano E, Canto M, Goggins MG, Hruban RH, et al. Importance of Age of Onset in Pancreatic Cancer Kindreds. JNCI Journal of the National Cancer Institute. 2010 Jan 20;102(2):119–26.
15. Klein AP, Brune KA, Petersen GM, Goggins M, Tersmette AC, Offerhaus GJA, et al. Prospective Risk of Pancreatic Cancer in Familial Pancreatic Cancer Kindreds. Cancer Res. 2004 Apr 1;64(7):2634–8.

16. eviQ - NSW Government. Pancreatic cancer (increased risk) – risk management. https://www.eviq.org.au/cancer-genetics/adult/risk-management/1517-pancreatic-cancer-increased-risk-risk-man#evidence-for-risk-management-guidelines. 2023.
17. Overbeek KA, Levink IJM, Koopmann BDM, Harinck F, Konings ICAW, Ausems MGEM, et al. Long-term yield of pancreatic cancer surveillance in high-risk individuals. Gut. 2022 Aug;71(6):1152–60.
18. Canto MI, Hruban RH, Fishman EK, Kamel IR, Schulick R, Zhang Z, et al. Frequent Detection of Pancreatic Lesions in Asymptomatic High-Risk Individuals. Gastroenterology. 2012 Aug;142(4):796–804.
19. Harinck F, Konings ICAW, Kluijt I, Poley JW, van Hooft JE, van Dullemen HM, et al. A multicentre comparative prospective blinded analysis of EUS and MRI for screening of pancreatic cancer in high-risk individuals. Gut. 2016 Sep;65(9):1505–13.
20. Long EE, Van Dam J, Weinstein S, Jeffrey B, Desser T, Norton JA. Computed tomography, endoscopic, laparoscopic, and intra-operative sonography for assessing resectability of pancreatic cancer. Surg Oncol. 2005 Aug;14(2):105–13.
21. Moutinho-Ribeiro P, Coelho R, Giovannini M, Macedo G. Pancreatic cancer screening: Still a delusion? Pancreatology. 2017 Aug;17(5):754–65.
22. Kimmey MB, Bronner MP, Byrd DR, Brentnall TA. Screening and surveillance for hereditary pancreatic cancer. Gastrointest Endosc. 2002 Aug;56(4):S82–6.
23. van Lier MGF, Wagner A, Mathus-Vliegen EMH, Kuipers EJ, Steyerberg EW, van Leerdam ME. High Cancer Risk in Peutz–Jeghers Syndrome: A Systematic Review and Surveillance Recommendations. American Journal of Gastroenterology. 2010 Aug;105(6):1258–64.
24. Korsse SE, Harinck F, van Lier MGF, Biermann K, Offerhaus GJA, Krak N, et al. Pancreatic cancer risk in Peutz-Jeghers syndrome patients: a large cohort study and implications for surveillance. J Med Genet. 2013 Aug;50(1):59–64.
25. de Snoo FA, Bishop DT, Bergman W, van Leeuwen I, van der Drift C, van Nieuwpoort FA, et al. Increased Risk of Cancer Other Than Melanoma in CDKN2A Founder Mutation (p16-Leiden)-Positive Melanoma Families. Clinical Cancer Research. 2008 Nov 1;14(21):7151–7.
26. Lynch HT, Fusaro RM, Lynch JF, Brand R. Pancreatic cancer and the FAMMM syndrome. Fam Cancer. 2008 Mar 9;7(1):103–12.
27. Goldstein AM, Chan M, Harland M, Hayward NK, Demenais F, Timothy Bishop D, et al. Features associated with germline CDKN2A mutations: a GenoMEL study of melanoma-prone families from three continents. J Med Genet. 2006 Aug 11;44(2):99–106.
28. Stoffel EM, Brand RE, Goggins M. Pancreatic Cancer: Changing Epidemiology and New Approaches to Risk Assessment, Early Detection, and Prevention. Gastroenterology. 2023 Apr;164(5):752–65.
29. Klatte DCF, Boekestijn B, Wasser MNJM, Feshtali Shahbazi S, Ibrahim IS, Mieog JSD, et al. Pancreatic Cancer Surveillance in Carriers of a Germline CDKN2A Pathogenic Variant: Yield and Outcomes of a 20-Year Prospective Follow-Up. Journal of Clinical Oncology. 2022 Oct 1;40(28):3267–77.
30. Lowenfels AB, Maisonneuve P, DiMagno EP, Elitsur Y, Gates LK, Perrault J, et al. Hereditary Pancreatitis and the Risk of Pancreatic Cancer. JNCI Journal of the National Cancer Institute. 1997 Aug;89(6):442–6.
31. Greenhalf W, Lévy P, Gress T, Rebours V, Brand RE, Pandol S, et al. International consensus guidelines on surveillance for pancreatic cancer in chronic pancreatitis. Recommendations from the working group for the international consensus guidelines for chronic pancreatitis in collaboration with the International Association of

Pancreatology, the American Pancreatic Association, the Japan Pancreas Society, and European Pancreatic Club. Pancreatology. 2020 Jul;20(5):910–8.
32. Murphy KM, Brune KA, Griffin C, Sollenberger JE, Petersen GM, Bansal R, et al. Evaluation of candidate genes MAP2K4, MADH4, ACVR1B, and BRCA2 in familial pancreatic cancer: deleterious BRCA2 mutations in 17%. Cancer Res. 2002;62(13):3789–93.
33. Hahn SA, Greenhalf B, Ellis I, Sina-Frey M, Rieder H, Korte B, et al. BRCA2 Germline Mutations in Familial Pancreatic Carcinoma. JNCI Journal of the National Cancer Institute. 2003 Aug;95(3):214–21.
34. Couch FJ, Johnson MR, Rabe KG, Brune K, de Andrade M, Goggins M, et al. The Prevalence of BRCA2 Mutations in Familial Pancreatic Cancer. Cancer Epidemiology, Biomarkers & Prevention. 2007 Aug;16(2):342–6.
35. Sawhney MS, Calderwood AH, Thosani NC, Rebbeck TR, Wani S, Canto MI, et al. ASGE guideline on screening for pancreatic cancer in individuals with genetic susceptibility: summary and recommendations. Gastrointest Endosc. 2022 May;95(5):817–26.
36. Pandharipande P V, Jeon A, Heberle CR, Dowling EC, Kong CY, Chung DC, et al. Screening for Pancreatic Adenocarcinoma in BRCA2 Mutation Carriers: Results of a Disease Simulation Model. EBioMedicine. 2015 Aug;2(12):1980–6.
37. Kastrinos F. Risk of Pancreatic Cancer in Families With Lynch Syndrome. JAMA. 2009 Oct 28;302(16):1790.
38. Win AK, Young JP, Lindor NM, Tucker KM, Ahnen DJ, Young GP, et al. Colorectal and Other Cancer Risks for Carriers and Noncarriers From Families With a DNA Mismatch Repair Gene Mutation: A Prospective Cohort Study. Journal of Clinical Oncology. 2012 Mar 20;30(9):958–64.
39. Hsu FC, Roberts NJ, Childs E, Porter N, Rabe KG, Borgida A, et al. Risk of Pancreatic Cancer Among Individuals With Pathogenic Variants in the ATM Gene. JAMA Oncol. 2021 Nov 1;7(11):1664.
40. Chahla E, Cheesman A, Mahon SM, Garrett RW, Bradenham BP, Schwartz TL, et al. Frequency and Significance of Abnormal Pancreatic Imaging in Patients with BRCA1 and BRCA2 Genetic Mutations. Scientifica (Cairo). 2016;2016:1–6.
41. Roch AM, Schneider J, Carr RA, Lancaster WP, House MG, Zyromski NJ, et al. Are BRCA1 and BRCA2 gene mutation patients underscreened for pancreatic adenocarcinoma? J Surg Oncol. 2019 Aug;119(6):777–83.
42. Giardiello FM, Offerhaus GJ, Lee DH, Krush AJ, Tersmette AC, Booker S V, et al. Increased risk of thyroid and pancreatic carcinoma in familial adenomatous polyposis. Gut. 1993 Oct 1;34(10):1394–6.
43. Yamada A, Komaki Y, Komaki F, Micic D, Zullow S, Sakuraba A. Risk of gastrointestinal cancers in patients with cystic fibrosis: a systematic review and meta-analysis. Lancet Oncol. 2018 Aug;19(6):758–67.
44. Bartsch DK, Matthäi E, Mintziras I, Bauer C, Figiel J, Sina-Boemers M, et al. The German National Case Collection for Familial Pancreatic Cancer (FaPaCa). Dtsch Arztebl Int. 2021 Mar 12;
45. Mocci E, Guillen-Ponce C, Earl J, Marquez M, Solera J, Salazar-López MT, et al. PanGen-Fam: Spanish registry of hereditary pancreatic cancer. Eur J Cancer. 2015 Sep;51(14):1911–7.
46. Petersen GM. Familial pancreatic cancer. Semin Oncol. 2016 Aug;43(5):548–53.
47. Aslanian HR, Lee JH, Canto MI. AGA Clinical Practice Update on Pancreas Cancer Screening in High-Risk Individuals: Expert Review. Gastroenterology. 2020 Aug;159(1):358–62.

48. Giardiello FM, Brensinger JD, Tersmette AC, Goodman SN, Petersen GM, Booker S V., et al. Very high risk of cancer in familial Peutz–Jeghers syndrome. Gastroenterology. 2000 Dec;119(6):1447–53.
49. Lim W, Olschwang S, Keller JJ, Westerman AM, Menko FH, Boardman LA, et al. Relative frequency and morphology of cancers in STK11 mutation carriers1 ☆. Gastroenterology. 2004 Jun;126(7):1788–94.
50. Hearle N, Schumacher V, Menko FH, Olschwang S, Boardman LA, Gille JJP, et al. Frequency and Spectrum of Cancers in the Peutz-Jeghers Syndrome. Clinical Cancer Research. 2006 May 15;12(10):3209–15.
51. Kopacova M, Tacheci I, Rejchrt S, Bures J. Peutz-Jeghers syndrome: Diagnostic and therapeutic approach. World J Gastroenterol. 2009;15(43):5397.
52. Howes N, Lerch MM, Greenhalf W, Stocken DD, Ellis I, Simon P, et al. Clinical and genetic characteristics of hereditary pancreatitis in Europe. Clinical Gastroenterology and Hepatology. 2004 Mar;2(3):252–61.
53. Rebours V, Lévy P, Ruszniewski P. An overview of hereditary pancreatitis. Digestive and Liver Disease. 2012 Jan;44(1):8–15.
54. Raimondi S, Lowenfels AB, Morselli-Labate AM, Maisonneuve P, Pezzilli R. Pancreatic cancer in chronic pancreatitis; aetiology, incidence, and early detection. Best Pract Res Clin Gastroenterol. 2010 Jun;24(3):349–58.
55. Rebours V, Boutron-Ruault MC, Schnee M, Férec C, Maire F, Hammel P, et al. Risk of Pancreatic Adenocarcinoma in Patients With Hereditary Pancreatitis: A National Exhaustive Series. Am J Gastroenterol. 2008 Jan;103(1):111–9.
56. Shelton CA, Umapathy C, Stello K, Yadav D, Whitcomb DC. Hereditary Pancreatitis in the United States: Survival and Rates of Pancreatic Cancer. American Journal of Gastroenterology. 2018 Sep;113(9):1376.
57. Lowenfels AB, Maisonneuve P, Cavallini G, Ammann RW, Lankisch PG, Andersen JR, et al. Pancreatitis and the Risk of Pancreatic Cancer. New England Journal of Medicine. 1993 May 20;328(20):1433–7.
58. Vasen HFA, Gruis NA, Frants RR, van der Velden PA, Hille ETM, Bergman W. Risk of developing pancreatic cancer in families with familial atypical multiple mole melanoma associated with a specific 19 deletion ofp16 (p16-Leiden). Int J Cancer. 2000 Sep 15;87(6):809–11.
59. Lynch HT. Foreword. Fam Cancer. 2008 Mar 30;7(1):1–2.
60. de Snoo FA, Bishop DT, Bergman W, van Leeuwen I, van der Drift C, van Nieuwpoort FA, et al. Increased Risk of Cancer Other Than Melanoma in CDKN2A Founder Mutation (p16-Leiden)-Positive Melanoma Families. Clinical Cancer Research. 2008 Nov 1;14(21):7151–7.
61. van Asperen CJ, Brohet RM, Meijers-Heijboer EJ, Hoogerbrugge N, Verhoef S, Vasen HFA, et al. Cancer risks in BRCA2 families: estimates for sites other than breast and ovary. J Med Genet. 2005 Sep 1;42(9):711–9.
62. Yang X, Leslie G, Doroszuk A, Schneider S, Allen J, Decker B, et al. Cancer Risks Associated With Germline PALB2 Pathogenic Variants: An International Study of 524 Families. Journal of Clinical Oncology. 2020 Mar 1;38(7):674–85.
63. Wong W, Raufi AG, Safyan RA, Bates SE, Manji GA. BRCA Mutations in Pancreas Cancer: Spectrum, Current Management, Challenges and Future Prospects. Cancer Manag Res. 2020 Apr;Volume 12:2731–42.
64. Breast Cancer Linkage Consortium T. Cancer Risks in BRCA2 Mutation Carriers. JNCI Journal of the National Cancer Institute. 1999 Aug 4;91(15):1310–6.

65. Mersch J, Jackson MA, Park M, Nebgen D, Peterson SK, Singletary C, et al. Cancers associated with BRCA1 and BRCA2 mutations other than breast and ovarian. Cancer. 2015 Jan 15;121(2):269–75.
66. Malone KE, Daling JR, Doody DR, Hsu L, Bernstein L, Coates RJ, et al. Prevalence and Predictors of BRCA1 and BRCA2 Mutations in a Population-Based Study of Breast Cancer in White and Black American Women Ages 35 to 64 Years. Cancer Res. 2006 Aug 15;66(16):8297–308.
67. Zhou J, Wang H, Fu F, Li Z, Feng Q, Wu W, et al. Spectrum of PALB2 germline mutations and characteristics of PALB2-related breast cancer: Screening of 16,501 unselected patients with breast cancer and 5890 controls by next-generation sequencing. Cancer. 2020 Jul 15;126(14):3202–8.
68. Boland PM, Yurgelun MB, Boland CR. Recent progress in Lynch syndrome and other familial colorectal cancer syndromes. CA Cancer J Clin. 2018 May 27;68(3):217–31.
69. Rothblum-Oviatt C, Wright J, Lefton-Greif MA, McGrath-Morrow SA, Crawford TO, Lederman HM. Ataxia telangiectasia: a review. Orphanet J Rare Dis. 2016 Dec 25;11(1):159.
70. Wang W, Chen S, Brune KA, Hruban RH, Parmigiani G, Klein AP. PancPRO: Risk Assessment for Individuals With a Family History of Pancreatic Cancer. Journal of Clinical Oncology. 2007 Apr 10;25(11):1417–22.
71. Matsubayashi H, Takaori K, Morizane C, Kiyozumi Y. Familial Pancreatic Cancer and Surveillance of High-Risk Individuals. Gut Liver. 2019 Sep 15;13(5):498–505.
72. Galiatsatos P, Foulkes WD. Familial Adenomatous Polyposis. Am J Gastroenterol. 2006 Feb;101(2):385–98.
73. Roberts NJ, Norris AL, Petersen GM, Bondy ML, Brand R, Gallinger S, et al. Whole Genome Sequencing Defines the Genetic Heterogeneity of Familial Pancreatic Cancer. Cancer Discov. 2016 Feb 1;6(2):166–75.
74. Leoz ML, Sánchez A, Carballal S, Ruano L, Ocaña T, Pellisé M, et al. Hereditary gastric and pancreatic cancer predisposition syndromes. Gastroenterología y Hepatología (English Edition). 2016 Aug;39(7):481–93.
75. Maisonneuve P, Marshall BC, Lowenfels AB. Risk of pancreatic cancer in patients with cystic fibrosis. Gut. 2007 Apr 5;56(9):1327–8.
76. https://infoshare.stats.govt.nz/. StatsNZ Infoshare. 2024.
77. Vasen HFA, Wasser M, van Mil A, Tollenaar RA, Konstantinovski M, Gruis NA, et al. Magnetic Resonance Imaging Surveillance Detects Early-Stage Pancreatic Cancer in Carriers of a p16-Leiden Mutation. Gastroenterology. 2011 Aug;140(3):850–6.
78. Al-Sukhni W, Borgida A, Rothenmund H, Holter S, Semotiuk K, Grant R, et al. Screening for Pancreatic Cancer in a High-Risk Cohort: An Eight-Year Experience. Journal of Gastrointestinal Surgery. 2012 Apr 30;16(4):771–83.
79. Bartsch DK, Slater EP, Carrato A, Ibrahim IS, Guillen-Ponce C, Vasen HFA, et al. Refinement of screening for familial pancreatic cancer. Gut. 2016 Aug;65(8):1314–21.
80. Canto MI, Goggins M, Hruban RH, Petersen GM, Giardiello FM, Yeo C, et al. Screening for Early Pancreatic Neoplasia in High-Risk Individuals: A Prospective Controlled Study. Clinical Gastroenterology and Hepatology. 2006 Jun;4(6):766–81.
81. Ohtsuka T, Castillo CF del, Furukawa T, Hijioka S, Jang JY, Lennon AM, et al. International evidence-based Kyoto guidelines for the management of intraductal papillary mucinous neoplasm of the pancreas. Pancreatology. 2023 Aug;
82. Tanaka M, Chari S, Adsay V, Castillo FDC, Falconi M, Shimizu M, et al. International Consensus Guidelines for Management of Intraductal Papillary Mucinous Neoplasms and Mucinous Cystic Neoplasms of the Pancreas. Pancreatology. 2006 Aug;6(1–2):17–32.

83. Tanaka M, Castillo CF del, Adsay V, Chari S, Falconi M, Jang JY, et al. International consensus guidelines 2012 for the management of IPMN and MCN of the pancreas. Pancreatology. 2012 Aug;12(3):183–97.
84. Schneider R, Slater EP, Sina M, Habbe N, Fendrich V, Matthäi E, et al. German national case collection for familial pancreatic cancer (FaPaCa): ten years experience. Fam Cancer. 2011 Jun 5;10(2):323–30.
85. Canto MI, Goggins M, Yeo CJ, Griffin C, Axilbund JE, Brune K, et al. Screening for pancreatic neoplasia in high-risk individuals: an EUS-based approach. Clinical Gastroenterology and Hepatology. 2004 Jul;2(7):606–21.
86. Yu J, Blackford AL, dal Molin M, Wolfgang CL, Goggins M. Time to progression of pancreatic ductal adenocarcinoma from low-to-high tumour stages. Gut. 2015 Nov;64(11):1783–9.
87. Pea A, Yu J, Marchionni L, Noe M, Luchini C, Pulvirenti A, et al. Genetic Analysis of Small Well-differentiated Pancreatic Neuroendocrine Tumors Identifies Subgroups With Differing Risks of Liver Metastases. Ann Surg. 2020 Mar;271(3):566–73.
88. Vasen H, Ibrahim I, Ponce CG, Slater EP, Matthäi E, Carrato A, et al. Benefit of Surveillance for Pancreatic Cancer in High-Risk Individuals: Outcome of Long-Term Prospective Follow-Up Studies From Three European Expert Centers. Journal of Clinical Oncology. 2016 Aug;34(17):2010–9.
89. Falconi M, Eriksson B, Kaltsas G, Bartsch DK, Capdevila J, Caplin M, et al. ENETS Consensus Guidelines Update for the Management of Patients with Functional Pancreatic Neuroendocrine Tumors and Non-Functional Pancreatic Neuroendocrine Tumors. Neuroendocrinology. 2016;103(2):153–71.
90. Crippa S, Bassi C, Salvia R, Malleo G, Marchegiani G, Rebours V, et al. Low progression of intraductal papillary mucinous neoplasms with worrisome features and high-risk stigmata undergoing non-operative management: a mid-term follow-up analysis. Gut. 2017 Mar;66(3):495–506.
91. Falconi M, Crippa S, Chari S, Conlon K, Kim SW, Levy P, et al. Quality assessment of the guidelines on cystic neoplasms of the pancreas. Pancreatology. 2015 Sep;15(5):463–9.
92. European Study Group on Cystic Tumours of the Pancreas. European evidence-based guidelines on pancreatic cystic neoplasms. Gut. 2018 May;67(5):789–804.
93. Huang JJ, Yeo CJ, Sohn TA, Lillemoe KD, Sauter PK, Coleman J, et al. Quality of Life and Outcomes After Pancreaticoduodenectomy. Ann Surg. 2000 Jun;231(6):890–8.
94. Lounis L, Aurran-Schleinitz T, Turrini O, Delpero JR, Bréjard V. Psychological Outcomes and Quality of Life in Relation to Pancreatectomy. Pancreas. 2019 Apr;48(4):471–9.
95. Cazacu I, Luzuriaga Chavez A, Saftoiu A, Bhutani M. Psychological impact of pancreatic cancer screening by EUS or magnetic resonance imaging in high-risk individuals: A systematic review. Endosc Ultrasound. 2019;8(1):17.
96. Lewis ZK, Frost CJ, Venne VL. Pancreatic Cancer Surveillance Among High-Risk Populations: Knowledge and Intent. J Genet Couns. 2009 Jun 5;18(3):229–38.
97. Corral JE, Das A, Bruno MJ, Wallace MB. Cost-effectiveness of Pancreatic Cancer Surveillance in High-Risk Individuals. Pancreas. 2019 Apr;48(4):526–36.
98. Joergensen MT, Gerdes AM, Sorensen J, Schaffalitzky de Muckadell O, Mortensen MB. Is screening for pancreatic cancer in high-risk groups cost-effective? – Experience from a Danish national screening program. Pancreatology. 2016 Jul;16(4):584–92.

99. Bruenderman E, Martin RCG. A cost analysis of a pancreatic cancer screening protocol in high-risk populations. The American Journal of Surgery. 2015 Sep;210(3):409–16.
100. Kumar S, Saumoy M, Oh A, Schneider Y, Brand RE, Chak A, et al. Threshold Analysis of the Cost-effectiveness of Endoscopic Ultrasound in Patients at High Risk for Pancreatic Ductal Adenocarcinoma. Pancreas. 2021 Jul;50(6):807–14.
101. Chhoda A, Vodusek Z, Wattamwar K, Mukherjee E, Gunderson C, Grimshaw A, et al. Late-Stage Pancreatic Cancer Detected During High-Risk Individual Surveillance: A Systematic Review and Meta-Analysis. Gastroenterology. 2022 Mar;162(3):786–98.
102. Sah RP, Sharma A, Nagpal S, Patlolla SH, Sharma A, Kandlakunta H, et al. Phases of Metabolic and Soft Tissue Changes in Months Preceding a Diagnosis of Pancreatic Ductal Adenocarcinoma. Gastroenterology. 2019 May;156(6):1742–52.
103. Groot VP, Mosier S, Javed AA, Teinor JA, Gemenetzis G, Ding D, et al. Circulating Tumor DNA as a Clinical Test in Resected Pancreatic Cancer. Clinical Cancer Research. 2019 Aug 15;25(16):4973–84.