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# Recommendations, evidence and sustainability of screening for pancreatic cancer in high-risk individuals

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ABSTRACT

Pancreatic cancer is a highly lethal malignancy and is predicted to become the second leading cause of cancer-related deaths by 2030. Early detection significantly improves outcomes, but general population screening remains infeasible due to the low prevalence of the disease and lack of specific biomarkers. This review evaluates current recommendations for pancreatic cancer surveillance in high-risk individuals, synthesises evidence from recent studies and explores the sustainability of current imaging-based surveillance programmes. Challenges such as overdiagnosis, economic feasibility and disparities in access highlight the need for targeted, cost-effective strategies. Collaborative initiatives and consortia are needed to advance biomarker research and refine risk stratification. By integrating evidence-based recommendations with sustainable approaches, this review outlines pathways to improve early detection and reduce mortality from pancreatic cancer.

## 1. Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most lethal malignancies and is projected to become the second leading cause of cancer-related death in the United States by 2030 [1]. Despite advances in oncology, the prognosis of PDAC remains dismal, with a five-year survival rate of less than 10 % [2]. The majority of PDACs are detected at a late, unresectable stage, further contributing to poor outcomes [3]. Early detection is critical to improving survival, as resectable disease at diagnosis results in significantly better outcomes. However, screening the general population for PDAC is currently not feasible due to the relatively low lifetime risk (~1.5 %) and the low positive predictive value when current screening tools are applied to low risk populations [4,5]. This would result in false-positive findings, resulting in potential psychological distress and procedural risks, but would also make screening economically unsustainable [6].

Conversely, targeted screening, also referred to as surveillance of high-risk individuals (HRIs) has emerged as a promising strategy to detect and treat PDAC earlier in a selected population [7]. Numerous studies have been published in the last decade and various guidelines and recommendations being developed on this topic [7–9]. This review evaluates the latest literature on the recommendations, evidence, and sustainability of pancreatic cancer surveillance strategies for HRIs. By synthesizing recent advances in risk stratification, imaging modalities, biomarker discovery and clinical outcomes, it highlights both the progress and continuing challenges in the field. In addition, the review identifies key gaps in current knowledge and suggests directions for future research aimed at improving early detection and survival outcomes of pancreatic cancer in high-risk populations.

## 2. Recommendations for pancreatic cancer surveillance

In recent years, several guidelines, including those from the International Cancer of the Pancreas Screening (CAPS) Consortium [7], the American Gastroenterological Association (AGA) [9], and the American Society for Gastrointestinal Endoscopy (ASGE) [10], have provided evidence-based frameworks for identifying HRIs and implementing structured surveillance protocols. The overall consensus is to offer pancreatic cancer surveillance to those with an estimated lifetime risk of >5 % [11].

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### 2.1. Who to enrol in pancreatic surveillance?

Table 1 summarises the main high-risk groups, their genetic basis, associated lifetime risks, and guideline-recommended surveillance strategies. Individuals at high risk for PDAC fall into two main categories: those with an identifiable germline pathogenic variant (PV) who have an inherited cancer syndrome, and those with familial pancreatic cancer (FPC). FPC is characterised by the clustering of pancreatic cancer within a family without evidence of a known hereditary cancer syndrome [12]. The risk of developing pancreatic cancer increases significantly with the number of affected family members, rising to a cumulative risk of 12 % by age 75 years in those with ≥3 affected FDRs [13,14]. In addition, an early-onset pancreatic cancer in a family member further increases the risk [15]. Although FPC is not associated with an inherited cancer syndrome, it is likely that in some cases undetected or as yet unknown germline PVs contribute to the increased risk of pancreatic cancer [16]. In addition, gene-environment interactions may also play a role in the increased risk in these individuals [17].

Among hereditary cancer syndromes, the highest risk of PDAC is seen in individuals with Peutz-Jeghers syndrome (PJS), an autosomal dominant disorder caused by a PV in the STK11 gene [18]. It is associated with a lifetime risk of PDAC in excess of 40 %, which is approximately 132 times that of the general population and warrants the initiation of surveillance as early 30–40 years of age [19–21]. Similarly, carriers of a germline CDKN2A PV associated with hereditary melanoma, also known as familial atypical multiple mole/melanoma syndrome (FAMMM) have an estimated lifetime risk of PDAC of 20–25 % [22–25]. For these HRIs, surveillance is recommended to begin at age 40. Importantly, surveillance is recommended for both STK11 and CDKN2A PV carriers regardless of family history [7,9,10].

Groups at relatively lower risk of PDAC include individuals with hereditary breast and ovarian cancer (HBOC) caused by PVs in the BRCA1 and BRCA2 genes [7,9,10]. While reported lifetime risks have varied, with BRCA2-associated risks as high as 7 % in some studies [26,27], recent research involving more than 5000 families suggests that these risks may be significantly lower, around 2.5 % for both BRCA1 and BRCA2, regardless of sex [28]. Another recent study involving more than 8000 individuals, demonstrated a lifetime risk of PDAC of 2.2 % for BRCA1-and 2.7 % for BRCA2 carriers [29]. The CAPS and AGA guidelines recommend surveillance in individuals with HBOC who have at least one affected first-degree relative (FDR) with pancreatic cancer in order to meet the >5 % lifetime risk threshold [7,9]. However, recent studies have questioned whether a positive family history is required in BRCA1/2 carriers. Several studies have found no association between a positive family history of PDAC and an increased risk of PDAC in these carriers [30,31]. The most recent study by Laish et al. [32] reported a diagnostic yield of 2.6 % (3/116) in BRCA1/2 carriers with a positive family history and 1.6 % (1/64) in carriers without a family history. This finding adds to the debate about whether family history should be a determinant for surveillance in these HRIs. As a result, the more recent 2022 ASGE guidelines no longer include family history as a criterion for initiating surveillance in BRCA1 and BRCA2 [10].

In addition, Lynch syndrome (LS), a major contributor to hereditary colorectal cancer, has also been associated with an increased risk of PDAC [33]. The lifetime risk varies depending on the specific PV [34], with MLH1 PVs showing the strongest association, conferring a risk of 6.2 % by the age of 75 [33]. Both the CAPS and AGA guidelines recommend surveillance for individuals with LS who have at least one FDR affected by PDAC, as this meets the >5 % lifetime risk threshold [7,9]. In addition, the ASGE guideline recommends that LS with either a FDR or a second-degree relative (SDR) with PDAC should initiate surveillance [10].

Hereditary pancreatitis, most commonly caused by PRSS1 PVs, represents a unique category of HRIs due to the chronic inflammatory state of the pancreas, resulting in a cumulative PDAC risk that can be as high as 40 % or more. Guidelines recommend starting surveillance at 40 years of age or 20 years after the first episode of pancreatitis [7,9,10].

**Table 1**
Overview of groups at increased risk for pancreatic cancer and corresponding recommendations for surveillance from the CAPS, AGA, and ASGE guidelines.

| High-risk group | Lifetime risk | Starting age and family history criteria | | | | | |
|---|---|---|---|---|---|---|---|
| | | CAPS 2019 | | AGA 2020 | | ASGE 2022 | |
| FPC[a] | 3–12 % | 50 or 55 | ≥2 FDR | 50 | ≥2 FDR | 50 | ≥2 FDR |
| ATM (Ataxia teleangiectasia) | 9.5 % | 45 or 50 | ≥1 FDR | 50 | ≥1 FDR | 50 | ≥1 FDR or ≥1 SDR |
| BRCA1/BRCA2 (HBOC) | 2.2%–7.0 % | 45 or 50 | ≥1 FDR | 50 | ≥1 FDR | 50 | – |
| CDKN2A (Hereditary melanoma) | 19.0%–25.0 % | 40 | – | 40 | – | 40 | – |
| STK11/LKB1 (PJS) | 11.0%–36.0 % | 40 | – | 35 | – | 35 | – |
| MLH1/MSH2/MSH6 (LS)[b] | 3.7%–6.2 % | 45 or 50 | ≥1 FDR | 50 | ≥1 FDR | 50 | ≥1 FDR or ≥1 SDR |
| PALB2 (HBOC) | 4.0 % | 45 or 50 | ≥1 FDR | 50 | ≥1 FDR | 50 | – |
| PRSS1/SPINK1 (Hereditary pancreatitis) | 7.2%–53.3 % | 40 | – | 40 | – | 40 | – |

*Adapted with permission from Klatte* et al. *Hereditary Pancreatic Cancer. Best Pract Res Clin Gastroenterol. 2022 Jun-Aug;58-59:101783.* Abbreviations: FDR, first-degree relative; FPC, familial pancreatic cancer; HBOC, hereditary breast and ovarian cancer; LS, Lynch syndrome; PJS, Peutz-Jeghers syndrome; SDR, second-degree relative.

[a] FPC is defined as a kindred with pancreatic cancer occurring in 2 or more FDRs that does not meet criteria for other hereditary cancer syndromes. The estimation of lifetime risk depends on the number of affected FDRs. A cumulative risk of 12 % was estimated for individuals with 3 or more affected FDRs [14].

[b] A cumulative incidence at 75 years of age of 6.2 % has been reported by Møller et al. Gut 2017 [33].

### 2.2. How to perform pancreatic surveillance

Surveillance of HRIs involves a structured approach to imaging, follow-up intervals, and decision-making based on the likelihood of malignancy in a multidisciplinary approach. Current guidelines emphasise the use of magnetic resonance imaging (MRI) with magnetic resonance cholangiopancreatography (MRCP) and endoscopic ultrasound (EUS) as the cornerstone imaging modalities [7,9,10]. In addition, fine-needle aspiration or biopsy can be performed during EUS to confirm malignancy [7,9,10]. MRI/MRCP and EUS are complementary tools for PDAC surveillance, each with distinct advantages, which are discussed further in Section 3.4 [35,36].

Computed tomography (CT) can be used for staging and assessment of resectability but is not suitable for routine surveillance because of its limited sensitivity for small lesions and the cumulative risks associated with radiation exposure [7].

Annual imaging is usually sufficient for HRIs with a normal pancreas or benign findings, while shorter intervals are recommended for lesions with worrisome or high-risk features. Intermediate-risk lesions, such as cystic lesions ≥30 mm, generally require follow-up every six months. For high-risk findings, including solid lesions <5 mm or cystic lesions with enhancing solid components, more frequent surveillance at three-month intervals is recommended. EUS-guided tissue sampling should be performed to further evaluate suspicious lesions, while surgical

resection is indicated for solid lesions larger than ≥10 mm or cystic lesions with enhancing solid components. In addition, new-onset diabetes in HRI should lead to additional imaging and a shortening of the surveillance interval [7,9]. Fig. 1 shows a proposed decision algorithm for surveillance.

Pancreatic cancer surveillance is complex and requires careful management of indeterminate findings and the risk of false positive or false negative results, which can lead to unnecessary interventions or missed diagnoses. This highlights the need for management in expert centres with access to multidisciplinary teams. These teams, which include gastroenterologists, radiologists, surgeons, pathologists and genetic counsellors, play a critical role in ensuring accurate interpretation of findings, minimising procedural risks and facilitating personalised care. Multidisciplinary discussion is particularly important in determining appropriate interventions for high-risk lesions and optimising patient outcomes. In addition, expert centres provide comprehensive support for HRIs, addressing the psychological and logistical challenges associated with long-term surveillance and improving adherence to recommended protocols.

### 2.3. Recommendations for germline genetic testing

Germline genetic testing is essential for identifying individuals with an inherited predisposition to PDAC and related malignancies. It allows selection of candidates for surveillance and informs at-risk family members of their potential cancer risk. However, determining eligibility for testing can be challenging due to the diverse syndromes associated with PDAC and overlapping cancer risks.

Eligibility for genetic testing is typically based on a detailed personal and family cancer history. The gold standard is a three-generation pedigree documenting tumour types and ages at diagnosis in first- and second-degree relatives [37]. Factors such as early-onset cancer, multiple affected relatives, or multiple primary tumours in organs such as the pancreas, breast, or colon often indicate a genetic predisposition.

A recent National Comprehensive Cancer Network (NCCN) guideline recommends universal germline testing for all individuals diagnosed with PDAC, regardless of family history [38]. This approach recognises that up to 11 % of PDAC cases carry pathogenic PVs, many of which would be missed by traditional family history-based criteria. Subsequent cascade testing of relatives of PV carriers allows for enrolment in pancreatic cancer surveillance programmes. However, uptake remains low due to logistical and awareness barriers [39,40]. Addressing these challenges through education, streamlined processes, and improved access to genetic counselling is essential to maximize the benefits of genetic testing.

Beyond risk stratification, germline testing has therapeutic implications. Identification of PVs in genes such as BRCA1, BRCA2, or PALB2 can guide the use of PARP inhibitors or platinum-based therapies. In addition, mismatch repair deficiencies, such as those seen in LS, may provide access to immunotherapies [41].

## 3. Evidence for pancreatic cancer surveillance

In recent years, several large studies of pancreatic cancer surveillance have published their outcomes (Table 2). The Wilson and Jungner criteria for screening emphasise that effective screening requires not only a reliable and acceptable test, but also the availability of a treatment that is more effective when administered during the early (pre-symptomatic) stage of detected disease [42]. For pancreatic cancer, it is clear that detection and treatment in an early stage has far more favourable outcomes. However, it is important that pancreatic surveillance programmes provide more benefits than potential harms.

### 3.1. Benefits

A multicentre study by Dbouk et al. [43] evaluated the effectiveness of pancreatic cancer surveillance in 1731 HRIs and reported a diagnostic yield of 2.1 % (36/1731). An extension of this study further assessed the added value of surveillance versus no surveillance by comparing the 26 surveillance-detected PDAC cases with 1504 matched controls from the Surveillance, Epidemiology, and End Results (SEER) dataset [44]. Surveillance detected 31 % of all cases at stage I, whereas only 10 % of individuals who did not undergo surveillance were diagnosed at stage I [44]. In addition, the 5-year survival rate for those who underwent surveillance was 50 %, compared with only 9 % for those who did not [44]. Another study by Klatte et al. [24]. evaluated the largest CDKN2A cohort under surveillance over a 20-year period and detected 36 (10.4 %) of PDAC cases in 347 individuals. A follow-up study compared cancer stage and survival outcomes between the surveillance cohort and a matched general population cohort, adjusting for lead time bias [45]. The surveillance group showed a higher detection rate of stage I PDAC (38.7 % vs. 5.8 %), increased resectability (71.0 % vs. 18.7 %) and an improved 5-year survival rate (32.4 % vs. 4.3 %) [45]. Of note, this study was conducted in a cohort of individuals with a CDKN2A PV only and it remains unclear whether the same benefits can be extrapolated to other germline PVs [24].

### 3.2. Concerns in FPC surveillance

Offering surveillance to individuals with FPC has been the subject of recent debate, with emerging evidence suggesting its ineffectiveness in its current form. While a large 2018 study by Canto et al. [46] reported a diagnostic yield of 5.2 % (13/344) in an FPC cohort, this population was not all confirmed PV-negative for the known PDAC risk genes. In comparison, Overbeek et al. [47] conducted a study in a PV-negative confirmed FPC cohort and reported a diagnostic yield of 0 % (0/201). In addition, the authors mention that their FPC cohort was relatively young and that the risk of developing PDAC increases with age [47]. However, based on this, the authors suggest that the starting age for these individuals should be increased to 55 or 60 years [47]. Another recent study from 2024 by Maurer et al. [48]. evaluated their FPC cohort after genetic testing and found that 74/337 (22 %) individuals had an underlying PV in a PDAC risk gene, while the remaining 263/337 (78 %) individuals were PV-negative. The diagnostic yield for the PV-carriers cohort was 13.5 % (10/74), 0.7 % (1/151) for PV-negative FPC individuals with two first-degree relatives and 0.9 % (1/110) for PV-negative FPC individuals with three first- or second-degree relatives. These recent studies raise concerns about whether surveillance for these individuals should be modified by increasing the age criteria (currently set at 45/50 years) or whether it should be discontinued altogether [7,9,10,49]. Addressing these issues, together with identifying new underlying PDAC risk genes in FPC families, is an important avenue for future research.

### 3.3. Harms of surveillance

#### 3.3.1. Overtreatment

Although there are benefits to pancreatic cancer surveillance, one of the main concerns is the risk of overdiagnosis, which may lead to overtreatment [50]. A meta-analysis by Paiella et al. [51] evaluated the outcomes of pancreatic cancer surveillance in FPC individuals and found that 68.1 % of all surgeries performed were subsequently deemed unnecessary. In another study, Canto et al. [52] evaluated their surveillance cohort and reported that 24 out of 48 individuals (50 %) who underwent surgery were operated on low-grade dysplasia. Similarly, Overbeek et al. [47] found that 11/21 surgeries (50 %) were performed for non-malignant lesions and Klatte et al. [24] found that 6/36 (16.7 %) individuals from the CDKN2A cohort underwent unnecessary surgery. Unnecessary surgery carries significant risks, as pancreatic resection is associated with considerable mortality and morbidity [53,54]. Mortality rates for these procedures can be as high as 10 % in low- and middle-income countries and up to 5 % in high-income countries [53].

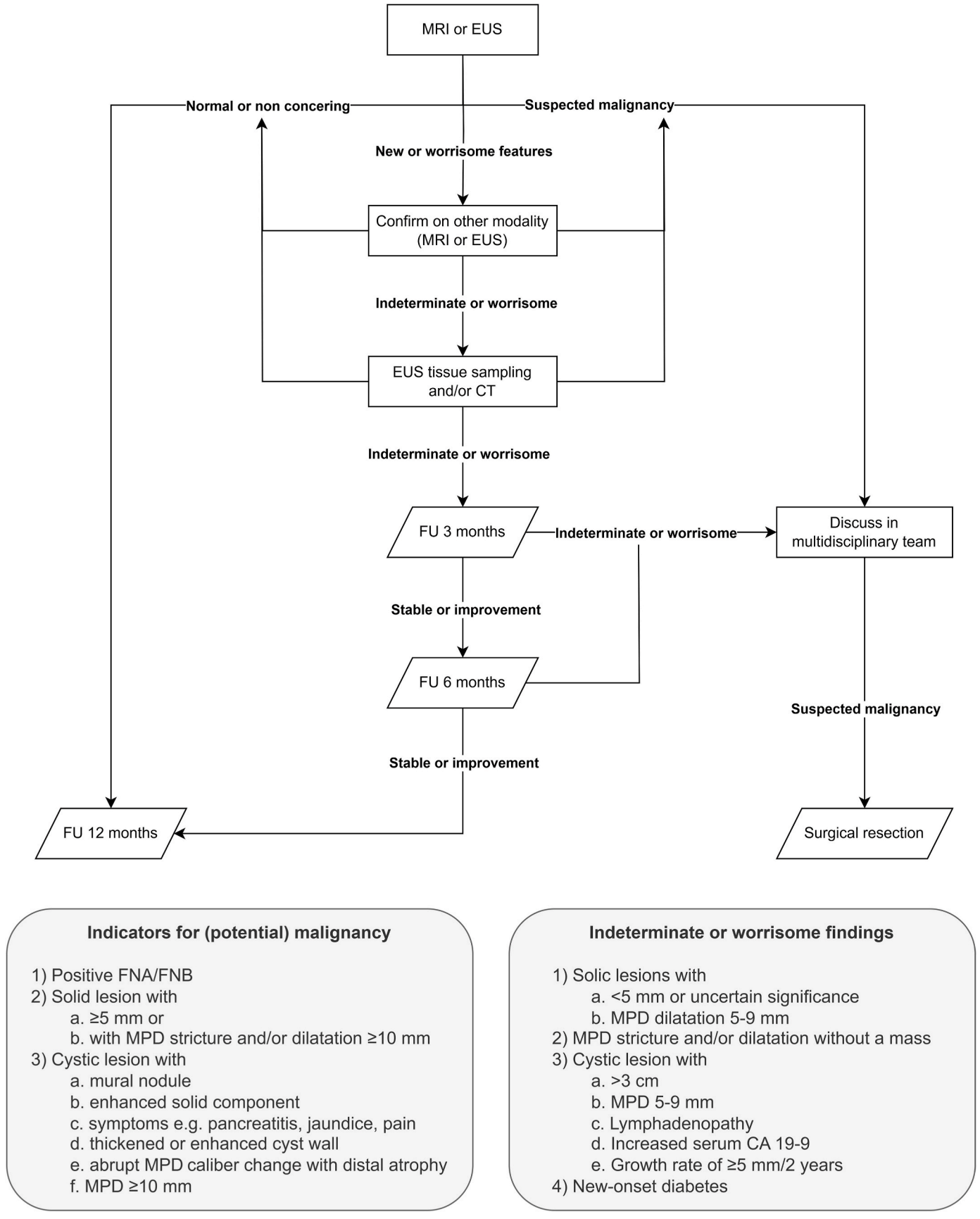


**Fig. 1.** Proposed algorithm for pancreatic cancer surveillance.
Abbreviations: CT, computed tomography; EUS, endoscopic ultrasound; FNA, fine-needle aspiration; FNB, fine-needle biopsy; FU, follow-up; MPD, main-pancreatic duct; MRI, magnetic resonance imaging.

**Table 2**
Overview of recently published (2018–2024) outcomes of pancreatic cancer surveillance studies.

| Author | Age at start, years | Cohort composition (N) | Sex, female (%) | Follow-up, duration, months | Resected/total PDAC cases (%) | PDAC stage | Diagnostic yield[a] | Unnecessary surgery rate[b] | Median survival, months |
|---|---|---|---|---|---|---|---|---|---|
| Maurer et al. (2024), Germany | 49 | 337 total<br>263 PV-negative FPC<br>27 BRCA2<br>13 PALB2<br>8 ATM<br>8 CDKN2A<br>4 BRCA1<br>14 others | 197 (58.5 %) | 64 | 4/4 (100 %) | 1 stage II<br>3 stage III | 13.5 % (PV-cohort)<br>0.7 % (FPC2)<br>0.9 % (FPC3) | 3.6 % | 28 |
| Overbeek et al. (2022), The Netherlands | 54 | 366 total<br>201 FPC<br>96 CDKN2A<br>45 BRCA2<br>9 STK11/LKB1<br>15 others | 209 (57.1 %) | 63 | 6/10 (60 %) | 4 stage I<br>1 stage II<br>3 stage III<br>2 stage IV | 6.1 % (PV-cohort)<br>0 % (FPC) | 3 % | 18 |
| Dbouk et al. (2022), United States | 59.2 | 1731 total<br>981 FPC<br>285 BRCA2<br>96 ATM<br>76 BRCA1<br>73 CDKN2A<br>64 PALB2<br>58 MLH1/MSH2/MSH6/PMS2 and EPCAM<br>26 STK11<br>72 others | 1095 (63.3 %) | 33.6 | 18/26 (69.2 %) | 12 stage I<br>3 stage II<br>4 stage III<br>7 stage IV | 2.1 % | Not reported | 117.6 |
| Klatte et al. (2022), The Netherlands | 48.6 | 347 total, all CDKN2A | 201 (57.9 %) | 67.2 | 27/36 (75 %) | 12 stage I<br>11 stage II<br>9 stage III<br>4 stage IV | 10.4 % | 2 % | 26.8 |
| Canto et al. (2018), United States | 56.4 | 354 total<br>297 FPC<br>41 BRCA1/BRCA2/PALB2<br>10 STK11/LKB1<br>6 others | 186 (52.5 %) | 67.2 | 9/10 (90 %) | 1 stage I<br>7 stage II<br>2 stage IV | 5.6 % | 6.5 % | 63.6 |

NOTE. Age at start of surveillance and follow-up duration depicts either mean or median.
[a] The diagnostic yield was calculated by dividing the number of significant lesions (*all* stages of PDAC, high-grade IPMN, and PanIN3) by the total cohort.
[b] To calculate the unnecessary surgery rate, we considered surgeries conducted for insignificant findings (e.g. PanIN and IPMN with low-grade dysplasia) divided by the total number of participants in the surveillance cohort.

In addition, these procedures are associated with an overall complication rate of up to 68.7 %, with the most common complications being pancreatic fistula (24.9 %), infection (21 %), and delayed gastric emptying (18.9 %) [53]. Moreover, long-term complications such as post-operative diabetes or exocrine dysfunction, requiring enzyme replacement therapy are important concerns to consider [55].

### 3.3.2. *Late-stage detection*

While not inherently harmful, the detection of advanced-stage PDAC can lead to the view that surveillance is pointless because it fails to achieve its primary goal of detecting early-stage PDAC [7]. Although the detection of stage I PDAC cases is higher with surveillance compared to no surveillance, the detection of late-stage PDAC remains prevalent [44,45]. A meta-analysis of 13 pancreatic cancer surveillance studies identified 39 PDAC cases, of which 30 (76.9 %) were classified as late-stage PDAC (stage II or higher) [3]. Blackford et al. [44] pooled data from all CAPS cohorts and found that 16/26 (61.5 %) PDAC cases detected during surveillance were late stage PDACs. Similarly, the Dutch surveillance groups reported high rates, with 24/36 (66.7 %) late-stage PDAC cases being detected in the CDKN2A cohort and 7/10 (70 %) in the cohort of Overbeek et al. [45,47]. Taken together, these findings show that over 61.5 % of detected PDAC cases are still diagnosed at an advanced stage.

### 3.3.3. *Psychological wellbeing*

Another concern is the psychological wellbeing of individuals undergoing surveillance. Interestingly, studies have shown that participants undergoing surveillance do not exhibit higher levels of distress or depression compared to the general population [56]. However, this does not appear to be the case for younger individuals (age $\leq$44 years), who report higher levels of distress during surveillance compared with the general population [56]. Furthermore, evidence suggests that cancer-related distress is highest at the start of surveillance and decreases over time [57]. These studies suggest that younger individuals, particularly at their first visit, could potentially benefit from counselling to manage any additional distress associated with surveillance [56,57].

## 3.4. *MRI and EUS*

MRI and EUS are the main modalities used in the surveillance of pancreatic cancer. The choice between MRI and EUS has inherent advantages and disadvantages. Ultimately, however, both modalities are

complementary. The following section outlines their respective strengths and limitations.

#### 3.4.1. Operator dependency and learning curve

MRI is a highly standardizable technique, resulting in consistent images across different time points [58]. This uniformity facilitates comparison of consecutive MRI images in a surveillance setting. In contrast, EUS has variability in image and video acquisition and is operator-dependent, making accurate replication and subsequent comparisons more difficult [59]. In addition, EUS has a significant learning curve, which poses a challenge for trainees and practitioners in low-volume centres [60]. This reliance on experience highlights the need for EUS to be performed by experienced endoscopists. However, the recent developments in artificial intelligence (AI) may help to reduce this gap by decreasing the learning curve for trainees and improving the diagnostic accuracy for endoscopists in lower volume centres [60,61].

#### 3.4.2. Invasiveness and practical applications

Another advantage of MRI is its non-invasive nature and relative safety [62]. In contrast, EUS is invasive and may carry a higher risk of complications. The complication rate for any diagnostic EUS is generally low, ranging from 0.034 % to 0.22 % [63]. However, this risk increases with interventional EUS. A meta-analysis shows that the pooled complication risk for EUS-guided pancreatic biopsy is approximately 2.1 % [64]. Surprisingly, despite the invasiveness of EUS, it has been reported to be as burdensome as MRI (10 % vs 11 %, respectively), which may be explained by the use of sedation [65]. Claustrophobia was the main problem leading to discomfort with MRI, whereas inadequate sedation was the primary problem with the EUS [65].

EUS offers several practical advantages, including the ability to directly obtain tissue samples for malignancy confirmation, an essential step before proceeding with surgery or neoadjuvant therapy [38]. In addition, EUS allows for the collection of cyst fluid and pancreatic juice, which has gained interest for its diagnostic potential, discussed in section 4.2.

#### 3.4.3. Diagnostic accuracy

In terms of accuracy, a meta-analysis by Signoretti et al. [66] evaluated various pancreatic cancer surveillance programmes that used MRI and/or EUS and observed a non-statistically significant trend suggesting that EUS detected more solid lesions than MRI. EUS identified 5.2 % (95 % CI 3–9%; $I^2 = 60.6$ %) of solid lesions, compared to 4.1 % (95 % CI 2–9%; $I^2 = 83$ %) detected by MRI. The analysis also revealed a similar non-significant trend, with MRI detecting more cystic lesions than EUS, 22.4 % (95 % CI 15–32 %; $I^2 = 89.3$ %) and 16.6 % (95 % CI 10–27 %; $I^2 = 85.7$ %), respectively [66]. The high $I^2$ values indicate substantial heterogeneity across studies, suggesting that findings vary between surveillance programmes. This variability underscores that, while trends are observed, the accuracy of MRI and EUS may differ depending on the institution. Additionally, another meta-analysis by Corral et al. [67] observed a trend of EUS detecting more high-risk lesions (precursors with high-grade dysplasia (HGD), or PDAC) than MRI, with EUS detecting 1.07 (95 % CI, 0.05–2.09) high-risk lesions per 100 patient-years compared to 0.41 (95 % CI, 0.05–0.78) for MRI. However, this difference was not statistically significant [67].

Recent advances in MRI technologies, including optimized hardware, enhanced scan quality, and the integration of AI, have significantly improved its ability to detect small pancreatic lesions, particularly those under 10 mm, which are associated with a more favourable prognosis. Standardized imaging protocols may further enhance the role of MRI in early detection [35]. Ultimately, the choice between MRI and EUS should be guided by institutional expertise, clinician and patient preferences, and practical considerations to maximize diagnostic outcomes.

### 3.5. Cost effectiveness of pancreatic cancer surveillance

Evaluation of the cost-effectiveness of pancreatic cancer surveillance is critical to its feasibility according to the Wilson-Jungner criteria [42]. The challenges and recent evidence in this area are discussed below.

#### 3.5.1. Challenges in determining cost-effectiveness

Assessing cost-effectiveness is complex because of the considerable variability in factors that affect both costs and benefits [68]. Costs vary widely and are influenced by the price of individual EUS or MRI scans, which varies between countries [69], and differences in the frequency of imaging (e.g. annual versus biannual). The effectiveness of surveillance programmes also depends on cohort size, background risk for PDAC and institutional expertise, all of which contribute to variation in overall costs and outcomes [70,71].

Willingness to pay (WTP) per quality-adjusted life year (QALY) is another critical factor and is highly country-specific. For example, the Netherlands has a flexible threshold ranging from €20,000 to €80,000 depending on the burden of the disease [72], whereas in the US, the threshold is typically $100,000 [73]. High-income countries are more likely to spend more on health care, so cost-effectiveness in one setting does not guarantee its viability elsewhere. In addition, effectiveness depends on the accuracy of surveillance programmes and the heterogeneity of HRIs, who have different lifetime risks of PDAC [18,66].

#### 3.5.2. Recent insights

The CAPS consortium set a 5 % lifetime risk threshold for HRIs to qualify for surveillance in 2013 [7], which has since become the standard. However, a recent review suggests that this threshold may need to be adjusted, as surveillance may only be cost-effective for individuals with a lifetime risk above 10 % [74].

A 2023 European study found that surveillance was cost-effective (less than €50,000 per QALY) for individuals with a lifetime risk of PDAC of at least 10 % [71]. A US study further distinguished between MRI and EUS and found that surveillance was cost-effective (less than $100,000 per QALY) for individuals with a relative risk (RR) of 5–20, corresponding to a lifetime risk of 8.5–34 % [70]. In this cohort, MRI was the most cost-effective strategy. For those with an RR above 20 (lifetime risk >34 %), EUS was the more cost-effective strategy. Another study concluded that combined MRI/EUS screening may be a cost-effective approach for individuals with an RR > 12, such as those with CDKN2A and STK11 PVs. However, for those at moderate risk (RR 5–12), surveillance would only be cost-effective at higher WTP thresholds (e.g., $200,000 per QALY) [75]. These findings highlight the need to tailor surveillance strategies to individual risk profiles and economic considerations.

## 4. Sustainability of pancreatic cancer surveillance

### 4.1. What are the current challenges?

#### 4.1.1. Early phases of the disease

The poor prognosis of PDAC highlights the need for the implementation of effective, sustainable and cost-effective screening programmes to facilitate earlier detection. The prognosis is significantly improved with early diagnosis, with a sixfold increase in one-year survival when the disease is detected at stage I/II [76]. However, the low prevalence of PDAC in the general population makes widespread screening infeasible [50], and early-stage disease is often asymptomatic or presents with non-specific symptoms, making diagnosis difficult.

The goal of early detection strategies is to identify PDAC at its earliest stages, ideally through the detection of high-grade precursor lesions (PRLs). The two main PRLs are pancreatic intraepithelial neoplasia (PanIN) and cystic lesions known as intraductal papillary mucinous neoplasms (IPMNs). The progression from PanINs and IPMNs to high-grade lesions or early invasive cancer may span over a decade,

thereby offering a window of opportunity for early detection, particularly in the surveillance of HRIs [50].

Detection of high-grade PRLs is critical to improving outcomes, as these lesions have the most favourable prognosis. However, current imaging-based surveillance modalities are often inadequate to visualise and characterise these lesions, resulting in missed diagnoses [77]. However, even if PanIN is suspected, it is difficult to obtain accurate biopsies to determine the degree of dysplasia. IPMNs are directly visible on imaging, but it is often difficult to distinguish those with low-grade dysplasia from those with high-grade dysplasia. There are currently no specific early detection biomarkers approved or used in clinical practice to facilitate screening.

#### 4.1.2. Enrichment of high-risk cohorts

To broaden the impact of pancreatic cancer surveillance, efforts must extend beyond those with a hereditary predisposition to include those at increased risk due to other factors. Most PDAC patients within the general population have relevant symptoms and multiple general practitioner (GP) consultations within two years before diagnosis, highlighting an opportunity for earlier detection. A promising approach in this domain is risk stratification using clinical decision support tools (CDSTs) implemented by GPs during consultations [78].

CDSTs integrate data such as symptoms, biomarker test results, demographics, and risk factors (e.g., new-onset diabetes (NOD)) to assess whether a patient exceeds a predefined risk threshold. These tools may assist clinicians in identifying HRIs, guiding decisions for further investigation or referral, and improving early detection. Despite their potential, further validation of CDST models is needed, along with improved accessibility and evaluation of their clinical impact, acceptability, and cost-effectiveness in real-world settings. Improved sharing of electronic health records between primary and secondary care is also essential to facilitate timely referrals and streamline screening programmes.

Pancreatic cancer has the lowest early detection rate among major cancers, highlighting the urgent need for better diagnostic strategies. Current efforts are focused on advancing biomarkers, improving imaging modalities, and refining surveillance programmes targeting high-risk populations, including those with chronic pancreatitis, NOD, or a family history of pancreatic cancer. These advances aim to improve early detection and improve outcomes, as described in the next section.

#### 4.1.3. Advances in biomarkers and imaging for early detection of pancreatic cancer

There are currently no clinically approved biomarkers for the early detection of pancreatic cancer. However, preclinical biomarker studies have demonstrated potential for further evaluation and have shown promising performance in differentiating PDAC cases from controls [76]. It is important to emphasise the relevance of comparing appropriate control groups with PDAC cases to ensure the clinical significance of research findings. This should include treatment-naïve early-stage PDAC versus symptomatic and HRIs, rather than just healthy controls. In addition, potential confounding factors should be taken into account.

Biomarkers collected using non-invasive methods such as blood or urine are essential to ensure patient acceptability, healthcare sustainability, and participation in screening and surveillance programmes. Currently, **carbohydrate antigen 19–9 (CA19–9)** is the only biomarker routinely used in the management of PDAC. Elevated blood levels of CA19-9 are commonly observed in pancreatic cancer cases, including prediagnosis samples. However, its utility for early detection is limited due to suboptimal specificity (78 %) and sensitivity (74 %) [76]. CA19-9 levels can also be elevated in benign conditions such as pancreatitis, gallbladder disease, and liver disorders. In addition, 5–10 % of the population lack the Lewis antigen required for CA19-9 production, resulting in undetectable levels even in pancreatic cancer patients. Therefore, CA19-9 can assist in the diagnosis of pancreatic cancer when combined with imaging and treatment monitoring, though it is not reliable as a standalone test.

Recent research is exploring the combination of CA19-9 with other biomarkers and advanced imaging techniques to improve specificity [79]. In the clinical setting, another glycoprotein, **carcinoembryonic antigen (CEA)**, is often measured alongside CA19-9 to improve diagnostic accuracy [80]. Although CEA is elevated in some PDAC cases, it lacks specificity (e.g. it is also elevated in colorectal cancer and benign inflammatory diseases) and has low sensitivity. Other biomarker tests that could be used in clinical practice include glucose, haemoglobin A1c (HbA1c) and neutrophil-to-lymphocyte ratio, which could be combined with clinical features and CA19-9.

A comprehensive review of candidate biomarkers for the early detection of pancreatic cancer is beyond the scope of this article, but it is important to highlight several novel biomarkers that show promise.

Recent evidence suggests that **NOD** may be an early manifestation of PDAC, especially when accompanied with weight loss [81]. Although NOD may occur when PDAC is still asymptomatic, providing a potential diagnostic window, there are currently no established guidelines or screening programmes for this group. One of the challenges is to distinguish type 3c (also known as pancreatogenic diabetes), from type 2 diabetes. Ongoing research by Oldfield et al. has shown that blood levels of adiponectin and interleukin-1 receptor antagonist (IL-1Ra) can distinguish between these two forms, facilitating its potential as an early detection marker [76].

Nené et al. used an ensemble learning model and proteomics to identify a panel of serum protein biomarkers (including von Willebrand factor and mucin-16) in combination with CA19-9 levels and clinical covariates for the early detection of PDAC [82]. The results are promising, but external and clinical validation is ongoing. It is also important to highlight the first commercially available blood-based test for the early detection of PDAC in HRIs under surveillance with promising performance, the IMMray PanCan-d, although large prospective studies are needed to prove its efficacy [83].

There have been promising developments in identifying specific blood **microRNAs** that can be upregulated or downregulated in progression of PDAC. These include miR-21, miR-155, miR-34a, among others, but clinical validation has not yet been performed [84]. Similarly, efforts have been made to evaluate cell-free DNA (cfDNA), such as **circulating tumour DNA** (**ctDNA**), to identify mutations and methylation patterns specific to PDAC. However, research is at an early phase and the utility of ctDNA in early detection is limited by the low concentration of ctDNA detected in early-stage disease. Its diagnostic potential as a multi-cancer screening test is being investigated in studies such as **CancerSEEK** [85], which combines ctDNA with 8 circulating proteins, but its sensitivity and specificity for detecting early-stage PDAC needs to be improved. Another example is the **GRAIL's Galleri® test**, but pilot studies have shown limited promise for PDAC screening.

Other studies suggest that abnormal **serum lipid levels**, including variations in total serum cholesterol levels and lipid ratios, may serve as early indicators of PDAC and have the potential to select HRIs from the general population, with some studies showing lower serum cholesterol levels more than a year before PDAC diagnosis [86,87]. More research is needed, but alterations in lipid metabolism may help identify individuals at high risk before other symptoms become apparent [88].

In addition to blood biomarkers, there are few studies of other non-invasive body fluids such as urine. Several research groups have identified a panel of urinary proteins (such as LYVE-1, REG1A/B and TFF1) as potential markers for the early detection of pancreatic cancer [89]. **Volatile organic compounds** (VOCs) have emerged as promising non-invasive biomarkers for the early detection of pancreatic cancer with early studies and trials showing specific VOC signatures (e.g. aldehydes, ketones, hydrocarbons, etc.), able to differentiate PDAC from other gastrointestinal disorders [90]. However, external factors like diet, medication, and environment can influence VOC levels, making standardization difficult. Larger, multicenter clinical trials, such as the

VAPOR trial at Imperial College London, are needed to confirm the diagnostic accuracy and reliability of VOCs [91].

Several studies have suggested that an increased risk of pancreatic cancer is associated with changes in the composition of the gut or pancreatic **microbiome** and microbial metabolites. Studies are beginning to explore the potential of microbiome signatures as biomarkers for early detection [92]. However, knowledge is still limited. Kartal et al. [93] identified certain microorganisms in stool samples that could help identify HRIs or even detect the disease at an early stage. A recent study by Irajizad et al. [94] using pre-diagnostic serum describes the performance of a risk prediction model, based on a 3-marker microbial-associated metabolite panel (combined with CA19-9) for assessing 5-year pancreatic cancer risk to identify HRIs who may benefit from surveillance. A limitation of this study is the limited sample size of PDAC cases. The microbiome holds great potential as a tool for early detection of pancreatic cancer, but more research is needed to validate the data and understand its practical application in clinical settings.

**Pancreatic juice** has also been used as a source of early detection biomarkers (e.g. mucins, interleukin-8), although its collection is more invasive, typically requiring endoscopic procedures [95], it can be implemented as part of the patient's surveillance plan. Studies have focused on the detection of genetic [96], proteomic, and metabolomic changes in pancreatic juice and, although promising, none of these markers have been clinically approved as their sensitivity needs to be improved. However, clinical trials are underway to evaluate the utility of pancreatic juice biomarkers in combination with advanced imaging and other diagnostic modalities to stratify HRIs.

**Polygenic risk scores (PRS)**, which combine the effect of multiple genetic variants identified by single-nucleotide polymorphism analysis to estimate an individual's predisposition or genetic risk of developing a disease, are promising emerging tools for refining risk stratification and identifying HRIs when combined with other clinical data [97]. PRS require further validation in large, independent cohorts to establish their accuracy and reliability in predicting pancreatic cancer risk [97].

**AI** has the potential to revolutionise imaging in pancreatic cancer surveillance by improving diagnostic accuracy and reducing observer variability. AI-powered algorithms can analyse complex imaging datasets from MRI and EUS and identify subtle **imaging biomarkers** indicative of precursor lesions or early-stage pancreatic cancer that may be missed by human observers. These systems are particularly valuable in distinguishing high-risk lesions, such as PanINs or IPMNs with malignant potential, from benign findings [98]. These algorithms can be combined with clinical and/or other biomarker data. In addition, AI has the potential to standardise imaging assessments across centres, helping less experienced radiologists and endoscopists to make accurate diagnoses. As research progresses, the integration of AI into imaging workflows could optimise surveillance protocols, improve early detection rates and ultimately reduce the burden of pancreatic cancer. However, rigorous validation and clinical integration are essential to realise its full potential.

In conclusion, to improve PDAC outcomes, we need to validate biomarker panels with higher sensitivity and specificity for early detection using appropriate sample sets and disease groups, and advance current imaging techniques to detect small premalignant lesions or small tumours. This is also key to risk stratification strategies. In the coming years, the integration of AI to analyse complex datasets of imaging, biomarker and genetic profiles may help to better identify subtle signs of early pancreatic cancer.

#### 4.1.4. *Collaborative research programmes and longitudinal studies*

The vast majority (90–95 %) of patients who develop PDAC have no family history or associated PVs. Therefore, focusing on other high-risk groups is key to ensuring the sustainability of surveillance programmes, but the low incidence of PDAC makes sample availability for research a challenge. Societies such as the United European Gastroenterology (UEG) have published position papers summarising the challenges and opportunities in this area, highlighting that screening should be targeted at high-risk individuals. It is also important that well-established protocols for sample collection, processing and storage are used to ensure reliability of results and reproducibility. Making surveillance programmes affordable, cost-effective and accessible, especially to underserved populations, is essential [99]. This includes integrating screening into routine care for high-risk individuals and ensuring that the programme addresses ethnic disparities and reaches minority populations.

The previous section highlights the promising advances in biomarker research, but none have been validated for the early detection of PDAC. To improve surveillance strategies and accelerate progress, collaborative research programmes and longitudinal studies are actively collecting biospecimens and clinical data in diverse populations. In Europe, initiatives such as EUROPAC [100] (focusing on familial pancreatic cancer and hereditary pancreatitis), UK-EDI [101] (targeting NOD) and ADEPTS [102] (studying high-risk symptomatic and cancer cases) are making significant contributions. Meanwhile, in the USA, programmes such as CAPS [7] and the Pancreatic Cancer Early Detection Consortium (PRECEDE [103]) are expanding globally, involving larger and more diverse cohorts. These efforts aim to deepen our understanding of early PDAC and refine strategies for its early detection.

Longitudinal studies following patients over time to provide more robust data on progression from precursor lesions (e.g. PanINs, cysts, IPMNs) to pancreatic cancer are critical but also challenging, requiring long-term funding and resources. There is a need to establish clear, evidence-based guidelines for screening intervals and methodology, particularly for populations with chronic pancreatitis, NOD or pancreatic cysts.

#### 4.1.5. *Policy support and public awareness*

Policy support by governments and private organizations/institutions for the early detection of pancreatic cancer includes raising awareness, funding and establishing guidelines that prioritise earlier screening, improving access to advanced imaging tools, and integrating surveillance programmes and biomarker research into healthcare systems to improve survival. Efforts have been made by organizations and charities such as the World Pancreatic Cancer Coalition to raise global public and clinical awareness through scientific and educational initiatives about the symptoms and risk factors of pancreatic cancer and the benefits of early detection. Social and community support for pancreatic cancer patients is also key to improving quality of life and overall well-being, yet patients report high levels of unmet need for supportive care. Policies encourage screening in high-risk populations, and programmes and consortia such as EUROPAC, PRECEDE and CAPS emphasise a focus on hereditary cases. Greater advocacy is needed for health policies to fund screening/surveillance programmes and research into early detection technologies, and to address inequalities in access to care, which will reduce anxiety and distress in HRIs and improve acceptability.

### 4.2. *Future perspectives and directions*

All of the above underscores the importance of early detection surveillance programmes to improve PDAC outcomes and the high level of interest from the scientific and healthcare communities. To refine and expand these programmes, several key strategies are needed to overcome existing challenges, improve accessibility, increase diagnostic accuracy and integrate innovative research. Collaboration between clinicians, researchers, patient organizations and policy makers is essential for further refinement. Strategies must follow a multimodal diagnostic approach to improve sensitivity and specificity for early detection, integrating genetic testing (including PRS), clinical and environmental data, lifestyle risk factors, biomarkers (multi-omics) and advanced imaging tools to better identify HRIs and ensure sustainability. However, the balance between effectiveness, accessibility to all populations and cost-effectiveness remains critical for widespread implementation. The

use of AI to analyse complex datasets and stratify at-risk populations, as well as to identify lesions at an early or premalignant stage through AI-assisted imaging, may improve diagnostic accuracy, although more data are needed to understand the real benefits of these applications in screening and surveillance to avoid overdiagnosis, misdiagnosis or unnecessary interventions.

## 5. Summary

Pancreatic cancer surveillance for HRIs has evolved into a structured, multidisciplinary effort to identify precursor lesions or early-stage PDAC, offering a critical opportunity to improve outcomes. Current guidelines advocate surveillance in individuals with a lifetime risk of PDAC >5 %, using MRI and EUS as cornerstone modalities. Recent advances, such as artificial intelligence and optimized imaging protocols, will improve the detection of high-grade precursor lesions. However, key challenges remain, including the risk of overdiagnosis, late detection and the economic feasibility of surveillance programmes.

Biomarkers such as CA19-9 have limited utility as stand-alone tools for early detection, and further validation of novel candidates, including proteomic, metabolomic and microbial signatures, is needed. Collaborative initiatives such as PRECEDE and EUROPAC are expanding research on biomarkers and imaging technologies, promoting global participation and diversity in HRI cohorts.

The integration of risk stratification tools, including clinical decision support systems, holds promise for refining surveillance strategies. Future directions emphasise the combination of genetic, clinical and imaging data to improve early detection capabilities while addressing disparities in access to care. Sustained policy support and interdisciplinary collaboration will be essential to translate these advances into sustainable, effective programmes that reduce the burden of PDAC.

## 6. Practice points

- Pancreatic cancer surveillance is recommended for high-risk individuals with a lifetime risk greater than 5 %, with specific starting ages and criteria for each high-risk group
- Surveillance programmes require management in expert centres with multidisciplinary teams to ensure accurate interpretation of findings, personalised care and optimal outcomes
- Surveillance should use MRI or EUS, with the choice of modality based on institutional expertise, patient preference and clinical considerations
- While surveillance has demonstrated improved outcomes by enabling early detection, potential harms include overdiagnosis, false-positive results and unnecessary procedures

## 7. Research agenda

- Further research is needed to identify and validate novel biomarkers, including proteomic, metabolomic and microbial signatures, to improve early detection of PDAC and increase the accuracy of surveillance
- Efforts should focus on refining risk stratification methods, including establishing evidence-based inclusion criteria for surveillance programmes
- Expanding global collaborative initiatives, such as longitudinal studies that collect biospecimens and clinical data, is critical to deepen understanding of pancreatic cancer development, integrate diverse populations, and optimise surveillance strategies.

## CRediT authorship contribution statement

**Aleksander M. Bogdanski:** Conceptualization, Writing – original draft. **Pilar Acedo:** Conceptualization, Writing – original draft. **Michael B. Wallace:** Supervision, Writing – review & editing. **Monique E. van Leerdam:** Supervision, Writing – review & editing. **Derk C.F. Klatte:** Conceptualization, Supervision, Writing – original draft, Writing – review & editing.

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## Declaration of competing interest

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