

Enhancing Early Detection of Pancreatic Cancer in Genetically Predisposed Individuals: Integrating Advanced Imaging Modalities with Emerging Biomarkers and Liquid Biopsy

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Purpose: Pancreatic cancer is one of the most lethal malignancies, with a five-year survival rate rarely exceeding 10%. Due to its asymptomatic onset, it is frequently diagnosed at an advanced and often inoperable stage. This review assesses current strategies for early detection, including genomic testing, advanced imaging technologies, and biomarker-based platforms, with a focus on their clinical utility and integration into surveillance protocols.

Methods: This narrative review synthesizes findings from published literature on germline genetic testing (GGT), imaging modalities such as endoscopic ultrasound (EUS) and magnetic resonance imaging (MRI), and the latest advancements in biomarker discovery and molecular diagnostics for early pancreatic cancer detection. International guidelines and emerging evidence were assessed to explore their clinical implementation and challenges.

Results: Although EUS and MRI show promise for detecting early pancreatic lesions, both require specialized expertise and are limited by accessibility and cost. Emerging blood-based biomarkers and molecular platforms, however, may offer a more scalable, non-invasive alternative for detecting pancreatic cancer at earlier, treatable stages.

Conclusion: Early detection of pancreatic cancer is pivotal to improving survival outcomes. While imaging techniques and genetic screening have enhanced risk stratification and early diagnosis in high-risk populations, novel biomarker and molecular testing platforms offer an accessible and scalable solution. Future efforts should focus on validating these assays in large-scale prospective cohorts and integrating them into screening protocols, particularly for individuals with genetic susceptibility.

Keywords: pancreatic cancer, screening, early detection, EUS, liquid biopsy, biomarkers

Introduction

Pancreatic ductal adenocarcinoma (PDAC) is one of the most devastating and challenging cancers worldwide. It is characterized by late diagnosis and aggressive biology that often leads to therapeutic failure.¹ Median survival is 6–12 months while the 5-year overall survival (OS) is less than 10%.^{2,3} The number of pancreatic cancer cases has been increasing steadily, with over 510,000 new cases diagnosed and more than 467,000 deaths estimated in 2020 worldwide.^{4,5} In the United States (US), pancreatic cancer is ranked the third leading cause of cancer-related

deaths following lung and colorectal cancer.⁶ The poor prognosis of PDAC is attributed to advanced stage at diagnosis and inherent chemoresistance.^{7,8} Current treatment options, include local management with surgery and/or radiation therapy and systemic treatment with chemotherapy, immunotherapy, and targeted therapies, have yielded only minimal improvements in overall survival.⁹

The pathogenesis of PDAC involves a cascade of molecular events, including activation of oncogenes (notably *KRAS*),¹⁰ inactivation of tumor suppressor genes (*TP53*, *CDKN2A*, *SMAD4*),¹¹ and disruptions in DNA damage repair pathways. *KRAS* mutations, present in over 90% of cases, play a central role in tumor initiation, progression, and resistance mechanisms through their influence on cell proliferation, survival, and the tumor microenvironment. Although most mutations are somatic, germline mutations are present in around 9% of patients.¹²

Giving the complex heterogeneity of pancreatic cancer, investigators attempted to focus on patient-derived models including patient-derived xenografts (PDXs),¹³ patient-derived organoids (PDOs),¹⁴ and patient-derived explants (PDEs),¹⁵ as superior platforms for studying tumor biology, drug response, and intercellular communication. Additionally, single-cell analyses that deepen our insights into mechanisms of resistance and tumor progression may help support personalized therapeutic strategies.^{16,17}

Early detection of pancreatic cancer, particularly PDAC, remains a significant challenge. Given the low incidence of pancreatic cancer in the general population, current guidelines and research focus on high-risk group, as general population screening is not feasible or cost-effective. As such, the US Preventive Services Task Force recommends against screening for pancreatic cancer in average risk adults.¹⁸ However, recent studies have focused on several biomarkers and genetic mutations, exploring their potential for early detection and thus better treatment outcomes.¹⁹ Circulating tumor DNA (ctDNA) levels in plasma samples from patients with early-stage PDCA, are used in several studies.²⁰

This review synthesizes available evidence on early detection strategies in genetically predisposed individuals, focusing on the integration of advanced imaging, biomarker assays, and genomic platforms into clinical surveillance protocols. The goal is to explore current best practices, limitations, and future directions aimed at reducing mortality through timely and targeted detection.

Materials and Methods

Literature Search Strategy

We conducted a literature search using multiple academic databases, including PubMed, Scopus, Google Scholar and Web of Science® database. We applied specific exclusion and inclusion criteria to select relevant studies. We searched for articles published between 2000 and 2025, using the following keywords: pancreatic cancer, hereditary pancreatitis, familial pancreatic cancer, *BRCA1*, *BRCA2*, *STK11*, *CDKN2A*, germline genetic testing, hereditary cancer syndromes, Lynch syndrome, Peutz-Jeghers syndrome, hereditary breast and ovarian cancer syndrome, familial atypical multiple mole melanoma (FAMMM) syndrome, Li-Fraumeni syndrome, surveillance, early detection, biomarker, liquid biopsy. Articles were considered for inclusion if they met the following criteria: (1) published in peer-reviewed journals, (2) relevant to germline genetic testing, (3) written in English.

Data Extraction and Synthesis

After identifying and selecting the relevant studies, we extracted key information such as methodology, study design, sample size, and main findings. The data were then synthesized into common themes to facilitate comparison across different research efforts including imaging, biomarkers and liquid biopsy.

Limitations

The review is not without limitations, including language bias, since only English-language studies were included, and the possibility of publication bias, since negative studies might not be published.

High-Risk Groups

Several factors, both inherited and environmental, are known to increase the risk of pancreatic cancer. Understanding the characteristics of high-risk groups is crucial to the development of tailored screening and early detection programs.

Familial Pancreatic Cancer (FPC)

Individuals with a family history of pancreatic cancer are considered at higher risk. Familial Pancreatic Cancer (FPC) is defined as families with two or more first-degree relatives with pancreatic cancer.²¹ Studies suggest that the risk of developing pancreatic cancer is approximately 3–5 times higher in these individuals compared to the general population. The relative risk increases with the number of affected family members, with a lifetime risk of 8–12% for those with two first-degree relatives and up to 40% for those with three or more.^{22,23}

Hereditary Cancer Syndromes

Numerous inherited genetic syndromes predispose individuals to pancreatic cancer.²⁴ These include hereditary breast and ovarian cancer syndrome (*BRCA1*, *BRCA2* mutations), Lynch syndrome, familial atypical multiple mole melanoma (FAMMM) syndrome, Peutz-Jeghers syndrome and Li-Fraumeni syndrome.

Lynch Syndrome

Hereditary Nonpolyposis Colorectal Cancer (HNPCC), also known as Lynch syndrome, is an autosomal dominant hereditary cancer syndrome primarily associated with an increased risk of various cancers, mostly colorectal and endometrial.²⁵ It is caused by germline mutations in DNA mismatch repair (MMR) genes, including *MLH1*, *MSH2*, *MSH6*, *PMS2* and *EPCAM*.²⁶ The syndrome is also associated with an increased risk of other cancers, including small intestine, stomach, biliary tract, pancreas, ovary, urinary tract, and brain tumors. Endometrial cancer is the most common extracolonic cancer in Lynch syndrome, with a lifetime risk of up to 60%.²⁷ One study reported an 8.6-fold increase in risk (95% CI, 4.7–15.7) for pancreatic cancer in individuals with Lynch syndrome with a cumulative risk of 3.7% by age 70.^{28,29}

Hereditary Breast and Ovarian Cancer (HBOC) Syndromes

HBOC syndromes are known for their increased risk of developing breast and ovarian cancers, among other malignancies. These syndromes are primarily associated with pathogenic variants in both *BRCA1* and *BRCA2* genes. HBOC syndromes are known for their autosomal dominant inheritance pattern. Individuals with *BRCA1*, *BRCA2*, and *PALB2* genes are also at higher risk for pancreatic cancer, with relative risks ranging from 2.26 to 6.2.³⁰

Hereditary Pancreatitis (HP)

HP is an inherited condition, is autosomal dominant, and is usually associated with mutations in the *PRSS1* gene. Other genetic mutations that have been implicated include *SPINK1*, *CFTR*, *CPAI*, and *CTRC*, although these are less common.³¹ HP is characterized by repeated episodes of pancreatitis, which can be acute, recurrent, or chronic and can result in complications such as diabetes mellitus (DM), pancreatic exocrine insufficiency and an increased risk of pancreatic cancer.^{32,33} Compared to the general population, the risk of pancreatic cancer in individuals with hereditary pancreatitis is significantly elevated. Studies have shown varying cumulative risks, with some estimates suggesting a risk as high as 40% by age 70.³⁴ The risk is particularly high in individuals with *PRSS1* mutations, and it is further increased by factors such as alcohol use, smoking and a family history of cancer.

Peutz-Jeghers Syndrome (PJS)

PJS is a rare inherited autosomal dominant disorder. Mutations in the *STK11* gene are the key genetic alteration that may lead to an increased risk of various cancers. It is categorized by hamartomatous gastrointestinal polyps, especially in the small intestine, and pigmented spots on the skin and mucous membranes. People with PJS face higher cancer risks, including colorectal, ovarian and breast cancers. Individuals with this syndrome have a significantly elevated risk of pancreatic cancer, with a relative risk (RR) of 132, while the lifetime risk of developing pancreatic cancer ranges from 11% to 36%.^{35,36}

Familial Atypical Multiple Mole Melanoma (FAMMM) Syndrome

FAMMM is an inherited disorder characterized by the presence of multiple atypical moles (nevi). Individuals with FAMMM have a higher likelihood of melanoma at an earlier age, often due to alterations in the *CDKN2A* gene. Regular skin checks and sun protection are crucial for management. Additionally, patients with FAMMM syndrome carry a relative risk of 13–39 for pancreatic cancer.^{37,38}

Pancreatic Adenocarcinoma in Adolescents and Children

Pancreatic adenocarcinoma is a very rare malignancy in children and adolescents, with only a few reported cases in the literature.³⁹ Similar to adults, prognosis is very poor due to delayed diagnosis.⁴⁰ The McGill Interactive Pediatric Onco Genetic Guidelines (MIPOGG) criteria emphasize that adult-type cancers in children warrant screening for cancer predisposition syndromes.⁴¹ Germline mutation studies in pediatric cases are lacking, but evidence from adult-onset PDAC suggests an association with hereditary conditions.⁴² Thus, genetic counseling and surveillance in at-risk individuals is helpful in early identification and management of hereditary cancer risks.⁴³

Current Screening Modalities

Unfortunately, there is no universally accepted screening method for pancreatic cancer. However, several imaging studies, biomarker assays and molecular tests are being evaluated for their effectiveness in high-risk populations. These techniques primarily aim to diagnose pancreatic cancer at an early stage, ideally prior to the development of symptoms and local invasion or metastasis.

Imaging Studies

Imaging plays a vital role in identifying pancreatic abnormalities. Endoscopic ultrasound (EUS) is considered one of the most effective methods for detecting small pancreatic lesions. This technique allows for high-resolution imaging and the ability to perform biopsies of suspicious lesions. EUS has shown promise in high-risk individuals, but its invasiveness, cost, and the need for particular equipment and skilled personnel make it less suitable for general screening.

Magnetic resonance imaging (MRI) and MR cholangiopancreatography (MRCP) are non-invasive imaging methods that provide detailed images of the pancreas and its ducts. MRI and MRCP have been investigated as screening tools, but their specificity and sensitivity for early-stage pancreatic cancer are not high enough. Both EUS and MRI have been shown to detect asymptomatic precursor lesions, such as pancreatic intraepithelial neoplasia (PanIN), intraductal papillary mucinous neoplasms (IPMNs) and in high-risk individuals.⁴⁴ However, one study showed that nearly half of high-risk individuals (n=2552) under surveillance, who developed high-grade dysplasia or pancreatic cancer (n=28) during a median follow-up of 29 months after baseline, had no prior lesions detected by imaging. All participating programs in this study used EUS, MRI/MRCP, or both, at each visit, or they alternated between the two imaging studies, with additional diagnostic tests performed as indicated, such as computed tomography (CT) and fine-needle aspiration (FNA).⁴⁵ CT scans are commonly used for diagnosing pancreatic cancer, but their role in screening is less clear. CT may detect advanced disease but is less sensitive for identifying smaller lesions or early-stage tumors.

Several studies have tried to address the clinical impact of surveillance imaging among higher-risk individuals. Studies are very heterogeneous, including different population groups with various risks and variable surveillance methodology. In one multicenter prospective study, the CAPS5 (Cancer of Pancreas Screening-5), high-risk individuals underwent an annual pancreas imaging surveillance protocol. Individuals were considered high risk if they had family history of $\geq$ one first-degree and one second-degree relative with pancreatic cancer, or they carried pathogenic/likely pathogenic (P/LP) variants of *CDKN2A*, *ATM*, *BRCA1*, *BRCA2*, *STK11*, *MSH2*, *MLH1*, *MSH6*, *EPCAM*, or *PALB2*. Among the 1461 individuals enrolled, 10 patients were diagnosed with pancreatic cancer; 7 were with stage I disease. Compared to patients diagnosed outside of the surveillance protocol, median OS was significantly better in patients diagnosed with screening-detected pancreatic cancer, (9.8 years vs 1.5 years, respectively; HR, 0.13; 95% CI, 0.03–0.50; P=0.003).⁴⁶ In another study, 411 symptomless individuals participated in a surveillance programs in three European centers including 214 individuals with FPC, 178 *CDKN2A* mutation carriers and 19 *BRCA2*, *BRCA1* or *PALB2* mutation

carriers. Pancreatic cancer was diagnosed in 13 (7.3%) of 178 *CDKN2A* mutation carriers. Resection rate was high at 75% and the 5-year survival rate was 24%.⁴⁷

A smaller comparative cohort study from several US centers compared 26 high-risk participants who underwent annual pancreas surveillance with EUS or MRI to 1504 matched unscreened controls from the SEER database. Patients were considered at risk because of their family history, or because they carried a P/LP germline variant associated with increased risk of pancreatic cancer including *BRCA1*, *BRCA2*, *PALB2*, *ATM*, *CDKN2A*, and *STK11*. Median primary tumor size in the individuals who underwent screening was smaller compared to the control SEER group; 2.5 cm versus 3.6 cm, respectively, $P < 0.001$. Additionally, the stage at diagnosis was lower ($P < 0.001$), and survival outcomes were better, compared to the controls.⁴⁸

Another relatively large prospective study from Netherland included 347 carriers of a germline P/LP *CDKN2A* variants who participated in a 20-year pancreatic cancer surveillance study. After a median follow-up of 5.6 years, 36 cases of pancreatic cancer were diagnosed in 31 (8.9%) patients, majority (83.3%) were resectable, and one-third were diagnosed as stage I. Five-year OS in patients who underwent resection was 44.1% (95% CI, 27.2–71.3).⁴⁹ These studies and a few others are shown in Table 1.^{50–52}

Table 1 Summary of Clinical Studies Evaluating Surveillance by Imaging in High-Risk Individuals

Study (Year of Publication)	Number of Patients	High-Risk Criteria	Clinical Outcomes	
Dbouk M et al CAPS5 Study (2022) ⁴⁶	1461	1. Family history of $\geq$ one 1 st degree and one 2 nd degree relative with pancreatic cancer, or 2. P/LP variants of <i>CDKN2A</i> , <i>STK11</i> , <i>ATM</i> , <i>BRCA1</i> , <i>BRCA2</i> , <i>MSH2</i> , <i>MLH1</i> , <i>MSH6</i> , <i>EPCAM</i> , or <i>PALB2</i>	10 patients were diagnosed with pancreatic cancer (7 were stage I)	Median OS: Surveillance group: 9.8 years No Surveillance: 1.5 year HR, 0.13, (95% CI, 0.03–0.50) $P = 0.003$
Vasen H et al (2016) ⁴⁷	411	1. FPC (n=214) 2. <i>CDKN2A</i> mutation carrier (n=178) 3. <i>BRCA1</i> , <i>BRCA2</i> or <i>PALB2</i> mutation carriers (n=19)	PDAC detection rate: 1. FPC <1% 2. <i>CDKN2A</i> carriers: 7.3%	Resection rate: 75% 5-year survival rate: 24%
Blackford AL et al (2024) ⁴⁸	26	26 high-risk individuals 1. FPC 2. <i>ATM</i> , <i>BRCA1</i> , <i>BRCA2</i> , <i>CDKN2A</i> , <i>PALB2</i> , and <i>STK11</i> 1504 matched unscreened controls from the SEER database	Median primary tumor size in individuals who underwent screening was smaller (2.5 cm) compared to the control SEER group (3.6 cm), $P < 0.001$	Stage at diagnosis was lower ($P < 0.001$), and survival outcomes were better, compared to the controls
Klatte DCF et al (2022) ⁴⁹	347	Carriers of P/LP germline <i>CDKN2A</i>	1. After a median follow-up of 5.6 years, 36 cases of PDAC were diagnosed in 31 (8.9%) patients. 2. Out of the 36 pancreatic cancers diagnosed, 83.3% were resectable, and 33.3% were diagnosed as stage I 3. PDAC was diagnosed in 20.7% of patients by age 70.	Five-year OS in those who underwent resection was 44.1% (95% CI, 27.2–71.3).

(Continued)

Table 1 (Continued).

Study (Year of Publication)	Number of Patients	High-Risk Criteria	Clinical Outcomes	
Paiella S et al (2019) ⁵⁰	187	1. FPC 2. <i>BRCA1/2</i> , <i>CDKN2A</i> , <i>STK11</i> or <i>PRSS1</i> ,	1. MRCP: 28 (14.9%) presumed branch-duct intraductal papillary mucinous neoplasms (IPMN), one invasive carcinoma/IPMN and one low-grade mixed-type IPMN. 2. EUS: 4 invasive (2.1%): 1 was resected, 1 was found locally advanced intraoperatively, and 2 were metastatic.	
Laish I et al (2024) ⁵¹	180	Asymptomatic carriers of P/LP mutations including <i>BRCA1</i> (n=57, 31.7%) and <i>BRCA2</i> (n=121, 67.2%)	1. After a median follow-up of 4 years, PDAC was detected in 4 patients (all with <i>BRCA2</i>), and the disease was resectable in 3 of them.	
Canto MI et al (2018) ⁵²	354	1. Peutz-Jeghers syndrome, or mutation in the <i>STK11</i> gene, and who were at least 30 years' old 2. FPC 3. Lynch syndrome, <i>BRCA1</i> , <i>BRCA2</i> , <i>PALB2</i> , <i>PRSS1</i> , <i>CDKN2A</i> with at least 1 affected 1 st or 2 nd degree relative, and at least 50 years old, or 10 years younger than the youngest pancreatic cancer in the family.	1. Median follow-up: 5.6 years 2. Suspicious pancreas lesions in 68 (19%) 3. 24/354 (7%) had neoplastic progression over 16-year follow-up 4. Out of the lesions detected from screening, 90% were resectable	3-year OS rate was 85% in those with resectable lesions.

Abbreviations: P/LP: Pathogenic or likely pathogenic; FPC: Familial pancreatic cancer; CAPS5: Cancer of Pancreas Screening-5, PDAC: Pancreatic adenocarcinoma; MRCP: Magnetic resonance cholangiopancreatography; EUS: Endoscopic ultrasound.

Biomarkers

Biomarkers are molecules, mostly proteins, in blood, tissues or body secretions that may indicate the presence of pancreatic cancer. Several biomarkers have been investigated for their utility in the early detection of pancreatic cancer.

CA 19-9

CA 19–9 (carbohydrate antigen 19–9), a glycoprotein expressed by pancreatic cancer cells, is currently the only approved and widely used biomarker for pancreatic cancer diagnosis and monitoring.^{19,53} Elevated CA 19–9 correlate with pancreatic malignancies, making it a standard diagnostic test in clinical practice.⁵⁴ However, CA 19–9 has several limitations, mostly related to low specificity and sensitivity in early-stage pancreatic cancer. Benign conditions such as pancreatitis, cholestasis and obstructive jaundice may also be associated with high levels leading to false positives. Additionally, CA 19–9 is not tumor-type-specific; high levels can be observed in various malignancies, including colorectal, gastric, lung, breast, and liver, as well as in pancreatic neuroendocrine tumors.⁵⁵ Adding to its limited role as a screening tool, a significant percentage of patients with pancreatic cancer, particularly those with Lewis blood type-negative phenotype, do not have high CA 19–9 levels.

One of the most interesting new functions of CA19-9 is its ability to hasten the progression of pancreatic cancer by glycosylating proteins, binding to E-selectin, enhancing angiogenesis, and mediating the immunologic response.⁵⁶ This

makes CA19-9 a promising therapeutic target for cancer. Therapeutic approaches utilizing CA19-9 to treat pancreatic cancer include specific anti-CA19-9 monoclonal antibodies to initiate antibody-dependent cell-mediated cytotoxicity.⁵⁷

Mucin 1 (MUC1)

Mucin 1 is a cell-surface glycoprotein and has shown promise as an early marker for pancreatic cancer. Elevated MUC1 levels have been detected in patients with pancreatic cancer.⁵⁸ Serum levels of MUC1 increase in a stage-dependent manner in patients with PDCA and so MUC1 expression may be potentially used as biomarker for the diagnosis and monitoring of tumor load in such patients. It also allows clinicians to monitor response to treatment. In addition to its role as a cancer biomarker, MUC1, promoting PDAC carcinogenesis, may represent an opportunity to develop therapeutic targets including an MUC1-based cancer vaccine for cancer treatment.^{59,60}

PAC-MANN Assay

In a recent development, researchers at Oregon Health & Science University (OHSU), developed a non-invasive detection assay for pancreatic cancer based on serum protease activity that is usually increased in the peripheral blood of patients with pancreatic cancer. A single matrix metalloproteinase (MMP)-sensitive probe was identified with the capacity to distinguish PDAC from controls with $79 \pm 6\%$ accuracy. A rapid magnetic nano sensor assay, termed PAC-MANN (“protease activity-based assay using a magnetic nanosensor”), which uses Pancreatic Cancer Multi-Omics Analysis to measure serum protease cleavage, was also developed with a simple fluorescent readout. Researchers applied this assay on a group of patients undergoing surgical resection of the primary tumor; the probe cleavage signal was lowered by $16 \pm 24\%$ after surgery. In a separate blinded study, the PAC-MANN assay identified pancreatic cancer samples with 73% sensitivity and 98% specificity across all stages, and distinguished 100% of patients with non-cancer pancreatic disorders. The PAC-MANN assay, when combined with CA 19-9 was 85% sensitive for detection of stage I pancreatic cancer with 96% specificity.⁶¹

Liquid Biopsy

Circulating DNA (ctDNA)

Circulating DNA (ctDNA) and circulating tumor cells (CTC) may help detecting early-stage pancreatic cancer; however, large studies on diverse patient populations are needed to validate these molecular techniques.²⁰ Detection of ctDNA by next-generation sequencing (NGS) may provide insights into the molecular profile of pancreatic cancer and may help guide clinical decisions, particularly in the context of treatment response and prognosis.

In one prospective study from Northwestern Medicine in Chicago, 56 patients with PDAC were enrolled between October 2020 and October 2022 to study the correlation of disease burden and ctDNA. Targeted tumor-agnostic NGS at three timepoints: at diagnosis (pre-therapy), post-neoadjuvant (NAC) therapy and after surgery or local therapy, were performed on peripheral blood samples. ctDNA was detectable in 33% post-NAC and 41% after local therapy compared to 48% at diagnosis. Following the completion of NAC, patients with positive ctDNA had higher CA19-9 levels versus those without (78.4 vs 30.0, $P=0.02$). The presence of *KRAS* ctDNA at diagnosis was associated with worse progression-free survival (PFS) among patients treated with NAC.⁶²

However, the ctDNA detection sensitivity remains one of the limitations, especially in patients with a low tumor burden. The presence of ctDNA was associated with worse survival outcomes, and its detection can predict early tumor progression and recurrence. In a study that enrolled 61 patients with pancreatic cancer, the presence of ctDNA in initial molecular assessment predicted early tumor progression and identified a subgroup of patients who are more likely to benefit from chemotherapy.⁶³ In a separate study, digital-droplet PCR was employed to identify key PDAC-related somatic *KRAS* alteration in liquid biopsies. For clinical validation, 290 plasma samples (postoperative and preoperative) were collected from 59 PDAC patients. Preoperative ctDNA was identified in 29 (49%) of the patients and was identified as an independent predictor of reduced OS and recurrence-free survival (RFS). Patients who underwent NAC had a lower likelihood of having preoperative ctDNA compared to those who did not undergo neoadjuvant chemotherapy (21% vs 69%; $P < 0.001$). The persistence of ctDNA in the immediate postoperative period correlated with a higher recurrence rate and a poor median RFS of 5 months. ctDNA detection during follow-up predicted clinical recurrence with

a sensitivity of 90% (95% CI, 74–98%) and specificity of 88% (95% CI, 62–98%), with a median lead time of 84 days (interquartile range, 25–146). Post pancreatectomy, median OS had not yet been reached at 30 months for patients without detectable ctDNA, compared to 17 months in those with detectable ctDNA, $P = 0.011$.⁶⁴

In efforts to get better insight into the pathogenesis of pancreatic cancer, researchers at Johns Hopkins performed in 2008 the first comprehensive genetic analysis of 24 pancreatic cancers and found that these cancers contained an average of 63 genetic alterations, mostly point mutations that defined a core set of 12 cellular signaling pathways, and each was genetically altered in 67 to 100% of the tumors.⁶⁵ More recently conducted studies confirmed these findings and identified four major driver mutations including *KRAS*, *TP53*, *SMAD4* and *CDKN2A*.⁶⁶

KRAS Mutation

KRAS mutation is the most recognized oncogene with the highest mutation rate across all cancers, and has been used extensively in the diagnosis, treatment, and prognosis of PDAC in recent years.⁶⁷ *KRAS* mutations serve as a major driver of PDAC, and these mutations are critical for development and progression of PDCA, making *KRAS* a potential target for therapeutic interventions. Alterations in codon 12, specifically G12D and G12V, are commonly found in PDAC and are often associated with poor response to therapy and lower than expected OS, while G12R mutations have been linked to better survival.^{68,69} The development of small-molecule inhibitors targeting the *KRAS* pathway provides several treatment options for PDAC patients.⁷⁰

The use of *KRAS* mutations in liquid biopsy for the screening and early detection of pancreatic cancer, particularly PDAC, has been explored in several other studies. One study found that *KRAS* mutations in ctDNA were associated with early recurrence in resectable PDAC patients, indicating its potential as a prognostic marker.⁷¹ In another study, researchers analyzed matched plasma and tumor samples from 50 patients with pancreatic cancer, mostly (82%) with early stage (I and II) disease. DNA was extracted from plasma and tumor samples and tested for the common codon 12 mutations including G12D, G12V, and G12C by digital PCR. *KRAS* mutations were identified in 72% of the tumors. Examination of the mutations in matched plasma samples revealed mutation rates of 0% for G12C, 36% for G12D and 50% for G12V. The detection appeared to correlate with the number of tumor cells in the primary tumor. No *KRAS* mutations were detected in 20 samples of healthy control plasma.⁷²

Exosome-Derived DNA (exoDNA), as a source for detecting *KRAS* mutations, was compared to cfDNA in a study that reported a higher rate of *KRAS* mutations in exoDNA compared to cfDNA in early-stage PDAC patients. However, a significant minority of healthy controls also showed mutant *KRAS*, which may limit its utilization for broad screening.⁷³

KRAS Mutation in Duodenal Fluid

A very recent study from Japan demonstrated the utility of detecting *KRAS* alterations in duodenal fluid collected after secretin stimulation during esophagogastroduodenoscopy (EGD). Researchers demonstrated a high area under the curve (AUC) of 0.934 for differentiating between patients with early-stage resectable PDAC and healthy controls, with a sensitivity of 83.1% and a specificity of 100%. If confirmed in larger studies, *KRAS* mutations in duodenal fluid could be a promising marker for early detection of early-stage PDAC.⁷⁴ The importance of this approach is the ability to perform EUS in the same setting, thus enhancing detection rate.

In summary, *KRAS* alterations detected in liquid biopsies show potential for the early detection of pancreatic cancer in high-risk individuals. However, challenges remain in terms of specificity and sensitivity, especially for early-stage disease. Technological advancements, like duodenal fluid analysis, may help improve the utilization of *KRAS* mutation for early detection purposes.

Current International Guidelines

Several international guidelines have explored the limitations and potential benefits of screening for pancreatic cancer in high-risk individuals. The American Society for Gastrointestinal Endoscopy (ASGE),^{75,76} the American Society of Clinical Oncology (ASCO),⁷⁷ the American Gastroenterological Association (AGA),⁷⁸ the International Cancer of the Pancreas Screening Consortium⁷⁹ and the National Comprehensive Cancer Network (NCCN)³⁰ have published guidelines on testing, counseling and screening of individuals at high risk of PDAC (Table 2).

Table 2 Summary of Recommendations for Early Detection of Pancreatic Cancer for Individuals with Pathogenic Variants or Familial Disorders

Genetic Mutation	Guidelines		Tools
	ASGE, ^{75,76} ASCO, ⁷⁷ AGA ⁷⁸	NCCN ³⁰	
STK11 (Peutz-Jeghers syndrome)	At age 35, or 10 years earlier than the youngest relative with pancreatic cancer.		EUS EUS alternating with MRI MRI* (Annual)
BRCA1	At age 50, or 10 years earlier than the youngest relative with pancreatic cancer	Additional family history of pancreatic cancer (at least one first- or second-degree relative)	
BRCA2	At age 50, or 10 years earlier than the youngest relative with pancreatic cancer		
PALB2	At age 50 or 10 years earlier than the youngest relative with pancreatic cancer	Additional family history of pancreatic cancer (at least one first- or second-degree relative)	
ATM	At age 50, or 10 years earlier than the youngest relative with pancreatic cancer		
FPC	At age 50, or 10 years earlier than the youngest relative with pancreatic cancer		
CDKN2A (FAMMM)	At age 40, or 10 years earlier than the youngest relative with pancreatic cancer		
PRSS1 (Autosomal-dominant hereditary pancreatitis)	At age 40		
Lynch Syndrome (MSH2, MLH1, MSH6, EPCAM)	At age 50, or 10 years earlier than the youngest relative with pancreatic cancer	Additional family history of pancreatic cancer (at least 1 first- or second degree relative)	

Note: *Based on patients' preference and available expertise.

Abbreviations: ASCO: American Society of Clinical Oncology, AGA: American Gastroenterological Association, ASGE: American Society for Gastrointestinal Endoscopy, NCCN: National Comprehensive Cancer Network. EUS: Endoscopic ultrasound, MRI: Magnetic resonance imaging.

Guidelines emphasize screening for individuals with genetic susceptibility, such as those with familial pancreatic cancer (FPC), Peutz-Jeghers syndrome, and Lynch syndrome, among others. The guidelines highlight that screening-detected pancreatic cancer tends to be diagnosed at an earlier stage and is associated with better outcomes.⁸⁰ However, the potential harms of screening, such as low-yield surgeries and associated adverse events, must be carefully considered.

Cost-Effectiveness of Surveillance for Hereditary Pancreatic Cancer

Advancements in early detection methods for pancreatic cancer, including imaging techniques, biomarkers, and liquid biopsy, hold significant promises for improving patient outcomes.^{81,82} However, the implementation of these technologies necessitates rigorous cost-effectiveness analysis to ensure their practical viability within healthcare systems. Recent studies have begun to address this need. The development of blood-based tests, such as the PAC-MANN assay, offers a low-cost approach for early pancreatic cancer detection, though comprehensive economic evaluations are required to assess their broader financial implications.^{61,83} Wang et al evaluated the cost-effectiveness of surveillance strategies for pancreatic cancer in individuals at hereditary risk, including those with a strong family history or pathogenic germline mutations. This review highlights that cost-effectiveness analysis is a critical tool for balancing healthcare expenditures with the benefits and risks of surveillance. Future research should focus on prospective large-scale studies that not only validate the clinical efficacy of these early detection methods but also provide detailed cost-benefit analyses. This approach will be crucial in informing policy decisions and optimizing resource allocation to integrate these technologies effectively into routine clinical practice.⁸⁴

Psychological Impacts

Genetic testing, in general and in pancreatic cancer in particular, in high-risk populations can have significant psychological impacts on patients and their close relatives. These impacts are mostly related to the absence of reasonable tools to prevent the occurrence of cancer or to detect it at an earlier stage.

Based on test results and personal and family history, the psychological effects of genetic testing can vary significantly. Both negative and positive psychological outcomes were observed following genetic testing. In one study, patients with PDAC who underwent genetic testing experienced similar levels of distress regardless of their test results, whether positive, negative, or variants of uncertain significance (VUS).⁸⁵ Another study conducted on individuals at risk for hereditary melanoma and pancreatic cancer concluded that genetic testing generally did not increase anxiety or depression over time. In fact, anxiety decreased significantly, and participants reported multiple perceived benefits from testing, such as increased knowledge and preventive behaviors.⁸⁶ This indicates that genetic testing can provide psychological benefits, including reassurance and empowerment through knowledge.⁸⁷ Another recent study reached similar conclusions.⁸⁸ Additionally, the AGA guidelines suggested that while screening in high-risk individuals can initially increase anxiety, it often leads to a reduction in cancer-related distress over time.

Conclusions and Future Directions

Pancreatic cancer remains a deadly cancer, frequently diagnosed at a late stage where treatment options are limited and outcomes are poor. Although considerable advances have been made in elucidating its molecular biology and identifying associated risk factors, effective strategies for early detection and screening remain elusive. While significant progress has been made in liquid biopsy, and next-generation sequencing and other cutting-edge technologies have helped identify potential biomarkers, challenges persist in their clinical implementation. The development of multi-biomarker panels that integrate several markers should help enhance sensitivity and specificity. Additionally, emerging imaging technologies, such as artificial intelligence (AI)-assisted imaging, are being explored to improve early detection.^{89–91}

Data Sharing Statement

Data used to generate this manuscript can be made available through the corresponding author upon reasonable request.

Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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