Diagnostic methods for pancreatic cancer and their clinical applications (Review)

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Abstract. Pancreatic cancer (PC) is often considered one of the most aggressive and deadly types of cancer, distinguished by its swift advancement and unfavorable prognosis. This reality highlights the vital necessity for early detection to improve patient survival rates. In recent years, notable advancements in medical technology have catalyzed the development of various diagnostic approaches, including imaging modalities, tumor markers, tissue biopsy, liquid biopsy, volatile organic compounds and nanomaterials. However, despite the promising progress in these diagnostic tools, numerous challenges persist, particularly concerning the sensitivity and specificity of these methods, as well as the complexities involved in their practical implementation in everyday clinical practice. The present review article aims to produce a thorough analysis of the applicability of each diagnostic method available for PC, highlighting their respective strengths and limitations while providing clinical recommendations aimed at enhancing the early identification of this formidable disease.

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1. Introduction

Pancreatic cancer (PC), particularly pancreatic ductal adenocarcinoma (PDAC), continues to be one of the most fatal cancers, marked by a poor prognosis and an elevated mortality rate. The American Cancer Society reports that PC is the 10th most common cancer in men and the 8th in women in terms of newly diagnosed cases. Furthermore, it is recognized as the fourth leading cause of mortality associated with cancer (1). Patients diagnosed with stage IV metastatic PC exhibit a 5-year survival rate of 3%. By contrast, patients presenting with stage I PC can expect a notably higher 5-year survival rate, reaching as much as 44% (2). Patients diagnosed with stage IA PC can attain a 5-year disease-free survival rate of 80% (3). This disease often presents without symptoms in its early stages, leading to advanced stage diagnoses where therapeutic options are limited and less effective (4). Consequently, timely identification and precise diagnosis are paramount to improving patient outcomes and survival rates.

The array of diagnostic techniques available for PC includes various modalities, each presenting distinct benefits and drawbacks. Imaging techniques such as ultrasound, computed tomography (CT), magnetic resonance imaging (MRI) and endoscopic ultrasound (EUS) are pivotal in the initial detection and staging of pancreatic lesions (5). These modalities provide critical anatomical and functional information that guides clinical decision-making. Biopsy techniques, such as percutaneous core-needle biopsy, EUS-guided fine-needle aspiration (FNA) and fine-needle biopsy, remain the gold standard for definitive diagnosis. These methods allow for histopathological and molecular analyses, providing essential information for personalized treatment strategies (6). However, challenges such as sample adequacy and procedural complications persist, highlighting the need for optimization

and standardization (7). Tumor markers, particularly carbohydrate antigen 19-9 (CA19-9), play a significant role in the biochemical diagnosis of PC. Although CA19-9 is the most widely used serum marker, its specificity and sensitivity are suboptimal, necessitating the exploration of additional biomarkers to enhance diagnostic accuracy (8). Emerging diagnostic technologies, including liquid biopsy and advanced genomic and molecular techniques, are revolutionizing the field. Liquid biopsy, which analyzes indicators in the blood or other body fluids, offers a minimally invasive alternative for early detection and real-time monitoring of disease progression (9). Previous advances have identified several potential indicators, including circulating tumor cells (CTCs), circulating tumor (ct)DNA and exosomes, which hold promise for non-invasive diagnosis and monitoring (10). Additionally, genomic and molecular profiling of pancreatic tumors can uncover actionable mutations and guide targeted therapies, thereby enhancing precision medicine approaches (11). The metabolic changes within tumor cells have revealed that these cells release specific volatile organic compounds (VOCs), which could serve as potential indicators for the early identification of PC (12-14). Furthermore, the incorporation of nanomaterials into pre-existing technologies, such as sensors and biosensors, has resulted in notable improvements in both detection sensitivity and specificity (Fig. 1) (15).

The present review aims to discuss the latest research on imaging techniques, tumor markers, biopsy methods and novel diagnostic technologies, providing a holistic overview of their clinical applications and potential for integration into standard practice, offering insights into their efficacy, limitations and future directions.

2. Imaging techniques

Ultrasound, CT, MRI and EUS represent the cornerstone of non-invasive PC diagnostics. CT and MRI, with their superior anatomical resolution, have proven invaluable in pancreatic cancer staging and surgical planning. However, their sensitivity in detecting early-stage PC remains suboptimal. EUS, with its high-resolution images and potential for guided biopsies, has emerged as a critical tool (16). Artificial intelligence (AI) and machine learning (ML) algorithms are also being investigated to enhance diagnostic precision and optimize clinical workflows by analyzing complex data sets from imaging and molecular diagnostics (17).

Ultrasound examination. Transabdominal ultrasonography (TUS) examination is a widely used initial imaging modality for the diagnosis of PC due to its non-invasive nature, accessibility and cost-effectiveness. It employs high-frequency sound waves to produce images of the pancreas and surrounding structures. Despite its advantages, the sensitivity and specificity of ultrasound in detecting PC are relatively low, particularly for small lesions or pancreatic tail tumors (17). The accuracy of ultrasound can be significantly affected by obesity and bowel gas, which can obscure the pancreas. Previous studies have indicated that the presence of dilation and stenosis in the main pancreatic duct, pancreatic cyst formation, as well as localized adipose tissue alterations within the pancreas, as observed through imaging techniques, are distinctive features associated with the early stages of PDAC (18,19). Kanno *et al* (20) reported that the rate of tumor identification in stage I PC was 67.3% and the rate of main pancreatic duct dilation was 74.3% using TUS. Advancements in ultrasound technology, such as contrast-enhanced ultrasound (CEUS) and elastography, have improved diagnostic performance. CEUS enhances the visualization of vascular patterns within the tumor, aiding in the differentiation between benign and malignant lesions (21). CEUS has high diagnostic value in evaluating vascular invasion in patients with PDAC, especially invasion into the celiac artery and its branches (22). Elastography measures tissue stiffness, providing additional information that can help in the characterization of pancreatic masses (23).

EUS integrates endoscopy and ultrasound to provide high-resolution images of the pancreas and surrounding structures. EUS is valuable for detecting small pancreatic tumors and assessing local invasion and lymph node involvement (24). It allows for FNA of lesions, providing tissue samples for cytological examination and molecular analysis (25). The sensitivity of EUS in detecting PC is reported to be as high as 94%, with a specificity of 89% (26). Contrast-Enhanced Harmonic Imaging EUS (CEH EUS) has emerged as a superior tool for the early detection of smaller lesions, with studies showing 95.6% sensitivity compared to 82.7% for standard EUS (27). EUS is also valuable in guiding therapeutic interventions such as celiac plexus neurolysis for pain management in patients with PC (28). However, the accuracy of EUS can be operator-dependent, and the procedure is invasive, requiring sedation and carrying risks such as pancreatitis and infection.

CT and MRI. CT is considered the benchmark for the assessment and staging of PC. It offers comprehensive cross-sectional images of the pancreas, facilitating the evaluation of tumor size, location and involvement of adjacent structures. Multidetector CT with pancreatic protocol enhances the identification and characterization of pancreatic tumors (29). The sensitivity of CT in identifying PC is 76-92%, while the specificity is 85-95% (30). CT accurately detects PDAC at 98% for stage III but is less effective for stage I tumors (31). CT is also valuable in evaluating the resectability of the tumor by assessing vascular involvement, which is crucial for surgical planning. However, small tumors and those with isoattenuating characteristics may be missed on CT, necessitating the use of additional imaging modalities (32).

MRI is another essential imaging modality for the diagnosis and staging of PC. MRI offers enhanced contrast for soft tissues compared with CT, making it particularly useful for characterizing pancreatic lesions and detecting liver metastases (33). MRI techniques such as magnetic resonance cholangiopancreatography and diffusion-weighted imaging enhance the visualization of the pancreatic ductal system and tumor cellularity, respectively (34). Wiest *et al* (35) reported a sensitivity of 88-100%, a specificity of 63.4-94%, a positive predictive value (PPV) of 71.4-96.2% and a negative (N) PV of 68.5-100% for MRI. The sensitivity and specificity of MRI for detecting PC are comparable to those of CT, with some studies suggesting slightly higher sensitivity for small lesions (10,36). Additionally, MRI does not utilize ionizing radiation, which renders it a safer alternative for specific groups of patients. Positron emission tomography/CT (PET/CT) and positron

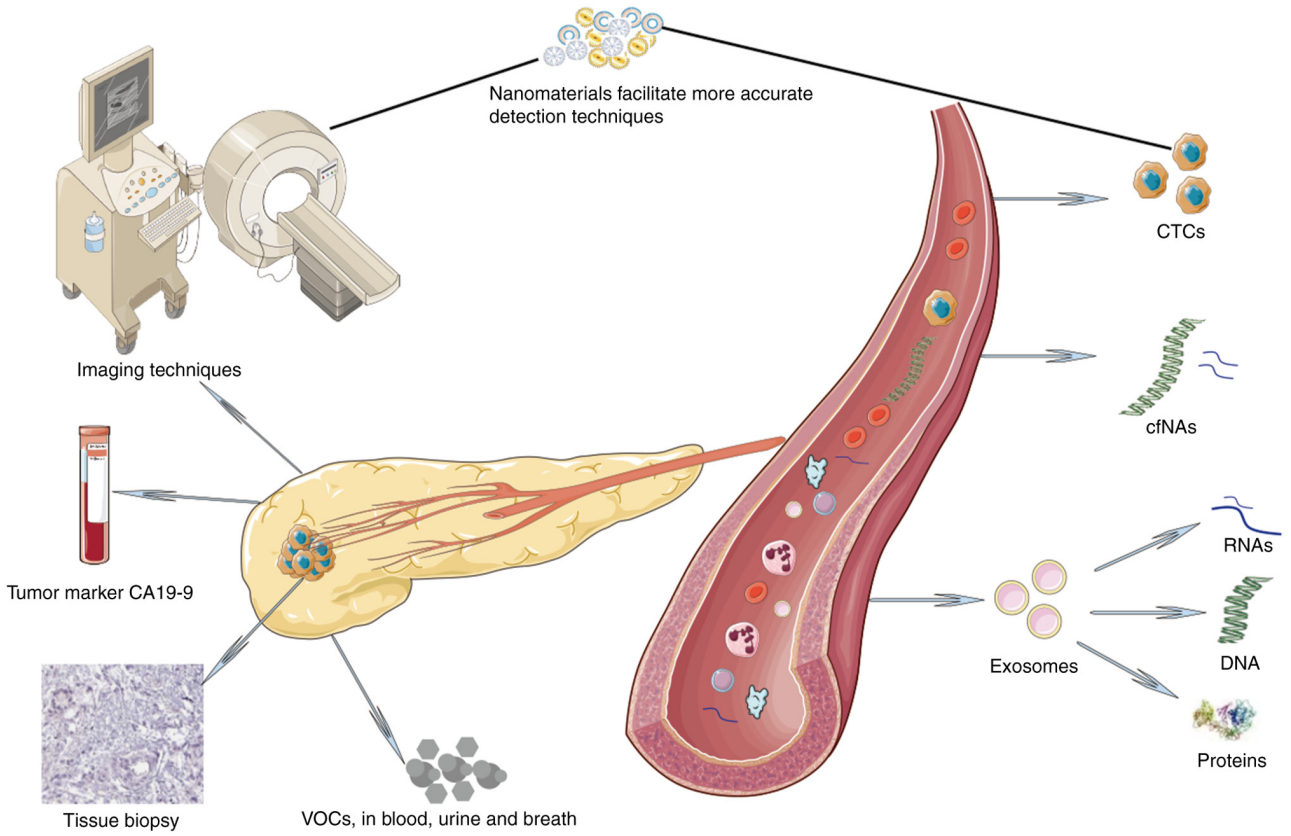

Figure 1. Diagnostic methods for pancreatic cancer. The contemporary diagnostic approach for pancreatic cancer generally includes initial imaging such as ultrasound, computed tomography, magnetic resonance imaging and endoscopic ultrasound, tumor marker CA19-9 detection, followed by a definitive histopathological assessment of fine-needle aspirates guided by endoscopic ultrasound. Liquid biopsies are employed to detect tumor-derived biomarkers present in peripheral blood, which include CTCs, cfNAs, circulating tumor exosomes and VOCs. Nanomaterials facilitate more accurate detection techniques. CTCs, circulating tumor cells; cfNAs, circulating free nucleic acids; VOCs, volatile organic compounds.

emission tomography/MRI (PET/MRI) are not routinely used in the staging of patients with PDAC, may aid in detecting suspected pancreatic tumors (37).

AI-assisted diagnostic methods. In recent years, there has been a notable rise in the application of AI and ML within the healthcare sector (38). Similar to various other malignancies, screening, diagnosing and formulating treatment strategies for PDAC can be enhanced by AI models and ML algorithms. AI-driven analysis shows notable potential for enhancing the capabilities of imaging techniques in the early identification and characterization of PC (39). The present study consolidates current literature and a summary of a set of recent AI studies focused on the detection and diagnosis of PDAC, along with details regarding the models, datasets and evaluation metrics (40-63) (Table I).

3. Tissue biopsy

Percutaneous biopsy. Percutaneous biopsy, particularly CT-guided percutaneous FNA biopsy (FNAB), is widely used for diagnosing PC. This technique involves the insertion of a needle through the skin to obtain tissue samples from the pancreas, guided by imaging techniques such as CT or ultrasound. The accuracy of CT-guided percutaneous FNAB had a diagnostic accuracy rate of 95.1% in a study involving 84 patients with peritoneal lesions (64). The procedure is generally safe, with complications such as bleeding and ascite leakage occurring in a small percentage of cases (64). The high diagnostic yield and safety profile make percutaneous biopsy a valuable tool in the diagnostic arsenal for PC, especially when other less invasive methods fail to provide a definitive diagnosis.

Endoscopic-guided biopsy. EUS-guided FNAB (EUS-FNAB) has emerged as a preferred technique for obtaining tissue from pancreatic lesions. This technique integrates endoscopy and ultrasound to facilitate real-time imaging and precise needle placement. EUS-FNAB is especially advantageous for diagnosing PC, as it enables the sampling of lesions that are not easily accessible by percutaneous methods. Lee *et al* (65) have shown that EUS-FNAB has a high diagnostic accuracy, with sensitivity and specificity rates often >90%. Additionally, EUS-FNAB can be used to establish patient-derived PC organoids, which serve as valuable models for research and personalized treatment planning (32). Despite its high accuracy, there are instances where EUS-FNAB may fail to provide a definitive diagnosis, necessitating alternative methods such as serial pancreatic juice aspiration cytological examination (66).

FNAB. FNAB uses a thin needle to extract cells from a lesion for cytological examination. The procedure is often guided by ultrasound or CT to ensure accurate needle placement. FNAB has demonstrated efficacy in the diagnosis of PC, with study

Table I. Applying artificial intelligence-based imaging techniques in the diagnosis of PC.

First author, year	Sample size, n	Imaging	Groups	Efficiency	(Refs.)
Udristoiu *et al*, 2021	65	EUS	PDAC vs. CPP vs. PNET	AUC, 0.99	(40)
Tong *et al*, 2022	558	EUS	PDAC vs. CP	AUC, 0.99	(41)
Tonozuka *et al*, 2021	1,390	EUS	PDAC vs. CP	AUC, 0.94	(42)
Marya *et al*, 2021	583	EUS	AIP vs. PDAC vs. CP vs. NP	AUC, 0.98	(43)
Kuwahara *et al*, 2023	933	EUS	PDAC	AUC, 0.90	(44)
Ma *et al*, 2020	190	CT	PC vs. NP	AUC, 0.96	(45)
Liu *et al*, 2019	338	CT	PC vs. NP	AUC, 0.96	(46)
Si *et al*, 2021	319	CT	PC vs. NP	AUC, 0.87	(47)
Qiu *et al*, 2021	312	CT	PDAC vs. NP	AUC, 0.88	(48)
Qureshi *et al*, 2022	72	CT	PDAC vs. NP	AUC, 0.86	(49)
Ebrahimian *et al*, 2022	103	CT	PC vs. NP	AUC, 0.94	(50)
Chu *et al*, 2019	380	CT	PDAC vs. NP	AUC, 0.99	(51)
Mukherjee *et al*, 2022	420	CT	PDAC vs. NP	AUC, 0.98	(52)
Li *et al*, 2022	97	CT	PDAC vs. AIP	AUC, 0.97	(53)
Ziegelmayer *et al*, 2020	86	CT	PDAC vs. AIP	AUC, 0.90	(54)
Cao *et al*, 2023	6,239	CT	PDAC vs. NP	AUC, 0.99	(55)
Chen *et al*, 2023	546	CT	PDAC vs. NP	AUC, 0.96	(56)
Tayebi *et al*, 2024	1,625	CT	PDAC vs. NP	AUC, 0.95	(57)
Liang *et al*, 2020	40	MRI	PDAC segmentation	DSC, 0.71	(58)
Li *et al*, 2022	267	MRI	PC segmentation	DSC, 0.62	(59)
Chen *et al*, 2023	73	MRI	PC segmentation	DSC, 0.66	(60)
Li *et al*, 2018	80	PET/CT	PC vs. NP	AUC, 0.96	(61)
Liu *et al*, 2021	112	PET/CT	PDAC vs. AIP	AUC, 0.97	(62)
Zhang *et al*, 2019	111	PET/CT	PDAC vs. AIP	AUC, 0.93	(63)

PDAC, pancreatic ductal adenocarcinoma; CPP, chronic pseudotumoral pancreatitis; PNET, pancreatic neuroendocrine tumor; CP, chronic pancreatitis; AIP, autoimmune pancreatitis; NP, normal pancreas; PC, pancreatic cancer; AUC, area under the curve; DSC, dice similarity coefficient; EUS, endoscopic ultrasound; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography.

reporting high sensitivity (93%) and specificity rates (91%) (67). However, the diagnostic yield of FNAB can be influenced by factors such as the skill of the operator and the quality of the obtained sample. In cases where FNAB results are inconclusive, additional diagnostic methods or repeat biopsies may be necessary (68). The integration of molecular techniques, such as immunocytochemistry and genomic profiling, can enhance the diagnostic accuracy of FNAB and provide valuable information for personalized treatment planning (69).

Tissue biopsies, including percutaneous, endoscopic and FNA techniques, provide definitive histopathological diagnosis. However, the invasive nature and associated risks, such as pancreatitis and tumor seeding, limit their widespread use. Advances in biopsy techniques and the integration of molecular profiling could enhance diagnostic accuracy and guide personalized treatment strategies.

4. Tumor marker detection - CA19-9

CA19-9 is recognized as the most commonly utilized serum biomarker for PC. Despite its widespread use, CA19-9 has limitations, such as 80% sensitivity and 75% specificity, particularly in the early stages of PC (70). CA19-9 levels are elevated in ~80% of patients with advanced PC, but it can also be elevated in cholangitis, cirrhosis and other gastrointestinal malignancies, which complicates its diagnostic utility (10). Moreover, ~5-10% of patients with PC lack the Lewis antigen, which is necessary for CA19-9 expression, rendering this biomarker ineffective for these individuals (71). Its role in early detection remains limited, highlighting the necessity for supplementary biomarkers to enhance the precision of diagnostics. Joint detection of carcinoembryonic antigen (CEA), CA125, CA242 and CA19-9 may enhance the diagnostic efficiency for PC, increasing sensitivity to 90.4% and specificity to 93.8%, obviously higher than single detection of those markers in diagnosis of pancreatic cancer (72). Joint detection of MUC5AC and CA19-9 demonstrated enhanced performance and increased specificity in distinguishing PC from control groups, achieving an area under the curve (AUC) of 0.894, sensitivity of 0.738 and specificity of 0.886 (73). Combination of trefoil factors (TFFs) with CA19.9 emerged as a promising strategy for discriminating early-stage PC from benign controls (BC) ($AUC_{TFF1 + TFF2 + TFF3 + CA19.9}$=0.93) as well as chronic pancreatitis (CP) ($AUC_{TFF1 + TFF2 + TFF3 + CA19.9}$=0.93) (74). Combination of serum CA19-9 and serum glycoproteomics (IL.17E, B7.1 and DR6) can differentiate

stage I PC from healthy controls (HCs; AUC=0.988; 100% sensitivity at 90% specificity) (75). However, these results still need to be further verified with large-scale, retrospective and prospective clinical studies. Given the limitations of CA19-9, research has focused on identifying additional biomarkers that could enhance the early identification and diagnosis of PC. The heterogeneity of PC and the lack of a universal biomarker underscore the necessity for a multimodal approach in biomarker-based diagnostics.

5. Emerging diagnostic technologies

Genomics and molecular biology techniques have revolutionized the field of cancer diagnostics, providing comprehensive understanding of the genetic and molecular characteristics of tumors. In PC, these techniques have facilitated the detection of specific genetic mutations and alterations that drive tumorigenesis. Next-generation sequencing has been instrumental in identifying actionable mutations in PC, guiding targeted therapy and personalized treatment approaches (76). Molecular biology techniques such as polymerase chain reaction (PCR) and digital droplet PCR (ddPCR) have also been employed to detect specific genetic alterations in PC. These techniques offer high sensitivity and specificity, allowing for the detection of low-abundance mutations in circulating free DNA (cfDNA) and exosomal DNA. ddPCR, in particular, has shown promise in detecting KRAS mutations in PC, providing valuable information for diagnosis and monitoring (77). The combination of CTCs, circulating free nucleic acids (cfNAs) and exosomes with advanced genomic analysis provides a comprehensive and non-invasive approach to PC diagnosis and monitoring (78).

Liquid biopsy is an innovative and minimally invasive diagnostic method that has shown promise in the early detection and monitoring of PC. This technique involves the analysis of CTCs, cfNAs and exosomes in bodily fluids. Studies have demonstrated the existence of CTCs associated with disease stage and prognosis (79,80). ctDNA, which refers to the diminutive segments of DNA that are emitted by neoplastic cells into the circulatory system, offers another promising avenue as it can provide information on genetic mutations, tumor burden and treatment responses (81). Exosomes, small extracellular vesicles containing proteins, lipids and nucleic acids, have also been recognized as promising biomarkers. Exosomal RNA and proteins can reflect the molecular characteristics of the tumor and have been shown to have diagnostic and prognostic value (82).

Diagnostic role of CTCs in PC. CTCs are malignant tumor cells present in the blood, which can either shed directly from primary tumor cells after undergoing epithelial-mesenchymal transition (EMT) or enter the bloodstream through the lymphatic system to reach secondary sites. They provide critical information regarding the genetic and phenotypic characteristics of the tumor, aiding in the diagnosis and monitoring of PC. Study has demonstrated that CTCs can be detected in patients with PC with varying sensitivity and specificity, making them a valuable tool for early diagnosis and prognosis (83). In a suitable environment, CTCs settle and proliferate, forming metastatic tumors, and are considered the 'seeds' of malignant tumor metastasis (84). CTCs are used as non-invasive assessment indicators for disease progression and prognosis in breast, colorectal and prostate cancer (85,86). In PC, patients with PDAC with positive CTCs have a poorer overall survival (OS) (HR, 1.23; 95% CI, 0.88-2.08; P<0.001) (87,88). Ankeny *et al* (89) found that the number of peripheral blood CTCs can serve as a biomarker for the diagnosis and staging of PC. However, there is still controversy regarding the use of CTCs for early detection of PDAC. Bidard *et al* (90) discovered that the detection rate of CTCs is low in the early stages of malignant tumors, with only 11% of patients with locally advanced PC having detectable levels of circulating CTCs. Tien *et al* (91) found that 68% of patients with PDAC had detectable CTCs in portal vein blood, while only 40% had detectable CTCs in peripheral blood, suggesting that portal vein blood may serve as a more effective alternative sample. However, currently, reliable separation and detection of CTCs remain technically challenging. On one hand, CTCs have a short half-life in peripheral blood (1-2.4 h) and low concentration (100,000-1,000,000/ml). On the other hand, CTC detection and enrichment rely on the utilization of highly specific biomarkers to attain the required levels of specificity and sensitivity. Furthermore, the high heterogeneity and plasticity of tumor cells complicate the selection of CTC marker detection (92).

Diagnostic role of cfNAs in PC. cfNAs, including ctDNA and ctRNA, are another component of liquid biopsy. These nucleic acids are released into the circulatory system from apoptotic and necrotic tumor cells. cfNAs can offer an extensive genetic characterization of the tumor, encompassing details such as mutations, variations in copy number and patterns of methylation. Previous advancements have improved the sensitivity and specificity of cfNA detection, making it a powerful tool for the early detection of PC (93). cfDNA released through tumor cell apoptosis, necrosis or active release is termed ctDNA, which accounts for a small portion of total cfDNA (94). ctDNA encompasses not only mutations that mirror those found in neoplastic cells but also demonstrates analogous epigenetic configurations, including DNA methylation, histone modifications and chromatin remodeling, which are consistent with gene expression and tumor characteristics (95). In the blood, ctDNA is swiftly eliminated from the bloodstream via the activity of endonucleases and exonucleases, in addition to renal excretion, exhibiting a half-life that varies between several minutes to 2 h (96). Therefore, it can reflect the actual condition of malignant tumors and the dynamic molecular changes during tumor development. Consequently, ctDNA has been used to understand the mutation status of malignant tumors, including PC (97). Additionally, ctDNA can also serve as a diagnostic method for diseases. Research has shown that the sensitivity and specificity of ctDNA for diagnosing PDAC are 65 and 75%, respectively, while the combined sensitivity and specificity of ctDNA, CA199 and CTCs increase to 78 and 91%, respectively. Combining ctDNA with CA199, CEA, hepatocyte growth factor and osteopontin can enhance the sensitivity to 64% and specificity to 99.5% of PDAC diagnosis, respectively (98). Zill *et al* (99) compared ctDNA samples from 26 patients with PC with tumor tissue sequences and assessed 54 gene mutations, finding that ctDNA mutations

in genes including KRAS, TP53, APC, FBXW7 and SMAD could accurately detect PDAC. Li *et al* (100) have reported significant variability in the frequency of detected ctDNA mutations, such as KRAS in patients with PDAC ranging from 30 to 92%. Another option for detecting DNA mutations may be to examine variations in DNA methylation. Li *et al* (101) compared differentially methylated regions of cfDNA between patients with PC and HCs and developed a diagnostic prediction model incorporating MAPT, SIX3, MIR663, EPB41L3, FAM150A, TRIM73, LOC100128977 and LOC100130148, which serve as potential non-invasive diagnostic indicators for PC. Eissa *et al* (102) found that the ctDNA ADAMTS1 and BNC1 methylation could be used as diagnostic markers for early detection of PC with an AUC of 0.95 (sensitivity, 97.4%; specificity, 91.6%). However, ctDNA sequencing technology requires very high sensitivity and specificity to overcome the low concentration of ctDNA in the early stages of malignant tumors and the potential for false positives from cfDNA present in normal individuals (103).

miRNA is a non-coding RNA, consisting of ~21-25 nucleotides, that can affect the post-transcriptional expression of target genes. It is crucial for various essential biological functions, including development, proliferation and apoptosis. Studies have shown that miRNAs are present in saliva, serum, plasma and urine, with circulating miRNAs in the blood showing potential roles in the diagnosis of cancer. In the diagnosis of PC, Słotwiński and Slotwinska (104) found that plasma miR-16 and miR-196a combined with CA199 can better distinguish PC from HCs. In addition, Wang (105) discovered that serum miR-133a can differentiate PC from HC (AUC, 0.893; sensitivity, 90.6%; specificity, 87.2%). Furthermore, Wei *et al* (106) found that serum miR-1290 and miR-1246 combined with CA199 can effectively distinguish PC from HC (AUC, 0.97).

Due to the low abundance and fragility of circulating miRNAs in the bloodstream, they are easily degraded by RNase degradation in the bloodstream, leading to loss and/or damage during the extraction process. With advancements in research, it has been found that serum exosomes may serve as important carriers for circulating miRNAs. Exosomes can package miRNAs, protecting them from RNA enzyme digestion, and their high stability and ease of enrichment also address the challenges of enriching circulating miRNAs (107).

Diagnostic role of exosomes in PC. Exosomes are lipid-based vesicles released by cells into the extracellular environment, with a diameter of 40-160 nm and a phospholipid bilayer membrane structure. They encompass various bioactive components derived from the source cells, such as miRNA, mRNA, transcription factors, cytokines, growth factors and lipids. All cells can secrete exosomes, which can be found in various bodily fluids such as blood, urine, saliva, breast milk and bile. Initially, exosomes were considered to be a means for cells to release unwanted substances. However, subsequent research has revealed their significant role in facilitating intercellular communication and contributing to tumor advancement. The bioactive components contained within exosomes are closely related to the parent cells from which they originate, and thus, differences or specific expressions of some bioactive components in exosomes may make them potential biomarkers for the diagnosis of PC (108-145) (Table II).

Diagnostic role of exosomal RNA and DNA in PC. miRNAs in exosomes are relatively stable under various physicochemical conditions due to the protective membrane structure of exosomes, which shields them from ribonuclease digestion (146). Zhou *et al* (110) found that serum exosomal miR-122-5p and miR-193b-3p were upregulated in PC compared with HCs, while miR-221-3p was downregulated. Goto *et al* (111) compared 32 PC, 29 intraductal papillary mucinous neoplasm (IPMN) and 22 HC samples, and found that serum exosomal miR-191, miR-21 and miR-451a were upregulated in both PC and IPMN. Exosomal miRNAs could distinguish HCs from stage I and IIA PC, with miR-21 achieving a diagnostic accuracy of 80.8%. Additionally, exosomal miRNAs from other bodily fluids have shown potential diagnostic value for PC, such as salivary exosomal miR-1246 and miR-4644, which could serve as candidate biomarkers for diagnosing cholangiocarcinoma (AUC, 0.833). Yoshizawa *et al* (114) found that the proportion of miR-3940-5p to miR-8069 in urinary exosomes from patients with PDAC was elevated, achieving sensitivities and specificities of 93.0 and 78.4%, respectively, when combined with CA199 for diagnosing PDAC. To date, multiple studies have demonstrated that exosomal miRNAs, either individually or in conjunction, can serve as potential biomarkers for diagnosing PC (115,116).

Long noncoding RNAs (lncRNAs) are classified as noncoding RNAs that exceed a length of 200 nucleotides (147). Several studies have confirmed the abnormal expression of exosomal lncRNAs in PC (148). Takahashi *et al* (124) analyzed serum exosomal lncRNA-HULC in 20 cases of PDAC, 22 cases of IPMN and 21 HCs, finding that the expression of serum exosomal lncRNA-HULC in patients with PDAC was significantly increased compared with HCs and IPMN cases, showing good diagnostic performance (AUC, 0.920). Yu *et al* (126) studied 284 cases of PDAC, 100 cases of CP and 117 cases of HC, finding that a lncRNA group composed of FGA, KRT19, ITIH2, HIST1H2BK, MARCH2, CLDN1, MAL2 and TIMP1 showed high accuracy for the diagnosis of PDAC (AUC, 0.931). Circular RNA (circRNA) is also a noncoding RNA that has been discovered in recent years, and due to its closed-loop structure, exhibits higher stability compared with linear RNA (149). Li *et al* (127) conducted sequencing analysis of exosomal circRNA from the plasma of 8 patients with early-stage PDAC and 8 HCs, finding 155 circRNAs that were differentially expressed between PDAC and HC, which may be potential indicators for the early diagnosis of PDAC. In addition, small nucleolar RNA (snoRNA) is a non-coding RNA composed of ~60-300 nucleotides (150). Kitagawa *et al* (129) studied serum exosomes from 27 patients with stage I-II PDAC and 13 HCs, finding that SNORA74A and SNORA25l could serve as biomarkers for early detection of PDAC (AUC, 0.946 and 0.940, respectively). Kumar *et al* (132) sequenced serum exosomal mRNA and found that the expression of MMP8, TBX3, PDX1, CTSL and SIGLEC15 in serum exosomes obtained from PDAC samples was higher than that in HCs. Yang *et al* (131) found that the combination of circulating exosomal miR-409, CK18 mRNA, CD63 mRNA, circulating cfDNA concentration and CA19-9 had improved diagnostic efficacy for PC than CA19-9 testing alone (Table II).

Table II. Overview of exosome-based diagnosis for pancreatic cancer.

A, miRNA

First author, year	Fluid	Exosome isolation	Exosome markers	AUC	(Refs.)
Zou *et al*, 2019	Serum	Polymer-based precipitation	let-7b-5p, miR-192-5p, miR-19a-3p, miR-19b-3p, miR-223-3p, miR-25-3p,	0.91	(109)
Zhou *et al*, 2018	Serum	Polymer-based precipitation	miR-122-5p, miR-193b-3p	0.72, 0.65	(110)
Goto *et al*, 2018	Serum	Polymer-based precipitation	miR-191, miR-21, miR-451a	0.79, 0.83, 0.76	(111)
Pu *et al*, 2020	Plasma	Polymer-based precipitation	miR-21	0.72	(112)
Machida *et al*, 2016	Saliva	Polymer-based precipitation	miR-1246, miR-4644	0.83	(113)
Yoshizawa *et al*, 2020	Urine	Polymer-based precipitation	miR-3940-5p, miR-8069	0.73	(114)
Shao *et al*, 2021	Serum	Polymer-based precipitation	miR-483-3p	0.84	(115)
Wang *et al*, 2021	Serum	Polymer-based precipitation	miR-1226-3p	0.74	(116)
Nakamura *et al*, 2019	Pancreatic juice	Ultracentrifugation	miR-21, miR-155	0.90, 0.89	(117)
Chen *et al*, 2022	Serum	Membrane-based affinity	miR-451a	-	(118)
Wang *et al*, 2021	Plasma	Membrane-based affinity	miR-19b	0.94	(119)
Nakamura *et al*, 2022	Plasma	Ultracentrifugation	miR145-5p, miR200b-3p, miR429, miR1260b, miR145-3p, miR216b-5p, miR200a-3p, miR217-5p	0.99	(120)
Guo *et al*, 2021	Plasma	Ultracentrifugation	miR-95-3p, miR-26b-5p, CA19-9	0.95	(121)
Chen *et al*, 2025	Serum	Polymer-based precipitation	miR-7977, miR-451a	0.92	(122)
Taniguchi *et al*, 2024	Duodenal fluid	Ultracentrifugation	miR-20a	0.88	(123)

B, lncRNA

First author, year	Fluid	Exosome isolation	Exosome markers	AUC	(Refs.)
Takahashi *et al*, 2020	Serum	Ultracentrifugation	HULC	0.94	(124)
Kumar *et al*, 2020	Serum	Polymer-based precipitation	MALAT1, CRNDE	-	(125)
Yu *et al*, 2020	Plasma	Polymer-based precipitation	FGA, KRT1, HIST1H2BK, ITIH2, MARCH2, CLDN1, MAL2, TIMP1	0.95	(126)

C, circRNA

First author, year	Fluid	Exosome isolation	Exosome markers	AUC	(Refs.)
Li *et al*, 2018	Plasma	Polymer-based precipitation	circ-IARS	-	(127)
Hong *et al*, 2022	Plasma	Polymer-based precipitation	circ-0006220, circ-0001666	0.88	(128)

Table II. Continued.

D, snoRNA

First author, year	Fluid	Exosomes isolation	Exosomes markers	AUC	(Refs.)
Kitagawa *et al*, 2019	Serum	Polymer-based precipitation	SNORA74A, SNORA25	>0.90	(129)

E, mRNA

First author, year	Fluid	Exosomes isolation	Exosomes markers	AUC	(Ref.)
Kitagawa *et al*, 2019	Serum	Polymer-based precipitation	WASF2, ARF6	0.94, 0.94	(129)
Hu *et al*, 2017	Serum	Ultracentrifugation	GPC1	1.00	(130)
Yang *et al*, 2020	Plasma	Track etched magnetic nanopore (TENPO) device	CK18, CD63	0.95	(131)
Kumar *et al*, 2020	Serum	Polymer-based precipitation	MMP8, TBX3, PDX1, CTSL, SIGLEC15	-	(132)
Wang *et al*, 2025	Plasma	-	ALB, FCER1G, KRT18, LCN2, PPDPF, SLC9A3R2, AGO2, CKS2, MALAT1, RAB32, S100A9, UBE2Q2	0.98	(133)

F, DNA

First author, year	Fluid	Exosomes isolation	Exosomes markers	AUC	(Refs.)
Allenson *et al*, 2017	Serum	Polymer-based precipitation	p53, KRAS mutation	-	(134)
Castillo *et al*, 2018	Plasma	Ultracentrifugation	CLDN4, EpCAM, CD151, LGALS3BP, HIST2H2BE, HIST2H2BF, KRAS Mutation	-	(135)

G, Protein

First author, year	Fluid	Exosomes isolation	Exosomes markers	AUC	(Refs.)
Jin *et al*, 2018	Serum	Polymer-based precipitation	ZIP4	0.89	(136)
Melo *et al*, 2015	Serum	Ultracentrifugation	GPC1	1.00	(137)
Xiao *et al*, 2020	Plasma	Ultracentrifugation	GPC1, CD82, CA19-9	0.94	(138)
Yang *et al*, 2017	Plasma	Ultracentrifugation	EGFRR, EpCAM, MUC1, GPC1, WNT2	1.00	(139)
Yang *et al*, 2021	Plasma	Ultracentrifugation	ALIX	0.91	(140)
Wei *et al*, 2020; Liang *et al*, 2017	Plasma	Nanoplasmon-enhanced scattering (nPES) assay	EphA2	0.96	(141,142)
Shin *et al*, 2019; Lux *et al*, 2019	Plasma	Ultracentrifugation	EGFR, ALPPL2, CKAP4, c-met, PD-L1, Eps8, ALIX	0.91	(143,144)
David *et al*, 2025	Plasma	Polymer-based precipitation	CD40, CD25, CA19-9	0.92	(145)

AUC, area under the curve; miR/miRNA, microRNA; CA19-9, carbohydrate antigen 19-9; lncRNA, long non-coding RNA; circRNA, circular RNA; snoRNA, small nucleolar RNA.

The genomic mutations of DNA in exosomes can also serve as biomarkers for diagnosing PC (151). Allenson *et al* (134) found that plasma exosomal KRAS mutations in HCs and patients with early-stage, locally advanced and late-stage

PDAC were 7.4, 66.7, 80.0 and 85.0%, respectively, with statistically significant differences. Furthermore, with the accumulation of exosomal analysis data, data mining identified 575 protein-coding genes, 26 RNA genes and 1 pseudogene directly related to PC (152). This exosome database established through pure bioinformatics methods serves as a valuable resource for the identification and confirmation of novel diagnostic combinations.

Diagnostic role of exosomal proteins and lipid components in PC. The diagnostic role of exosomal membrane proteins and the proteins contained within them in PC has also received considerable attention. GPC-1 is a proteoglycan located on the surface of cells that has been found to be significantly overexpressed in exosomes from prostate cancer cells and is considered a promising potential diagnostic marker in PDAC (153). Melo *et al* (137) extracted serum exosomes from HCs, benign pancreatic disease (BPD) and early to late-stage PDAC for mass spectrometry and nano-flow cytometry identification, finding that GPC-1$^+$ exosomes could act as a marker for detecting early PC (AUC, 1). Buscai *et al* (154) discovered that combining CD63$^+$GPC-1$^+$ exosomes from peripheral blood and portal vein blood with CA19-9 improved the diagnostic efficacy for PC, and demonstrated a positive correlation between GPC-1$^-$ exosome levels and CTCs, which were associated with progression-free survival(PFS) and OS of patients. However, Lai *et al* (155) indicate that GPC-1 cannot diagnose PDAC. These studies confirm that GPC-1$^+$ serum exosomes can act as potential diagnosis biomarkers for PC, but further research is needed for validation. Wei *et al* (141) found that serum exosomal Ephrin type-A receptor 2 (EphA2) could diagnose PC (AUC, 0.960). Additionally, exosomal proteins such as epidermal growth factor receptor (EGFR), alkaline phosphatase, placental like 2 (ALPPL2), cytoskeleton-associated protein 4 (CKAP4), cellular mesenchymal-epithelial transition factor (c-met), programmed death ligand 1 (PD-L1), epidermal growth factor receptor pathway substrate 8 (Eps8) and ALG-2-interacting protein X (ALIX) have also attracted the attention of researchers regarding their role in PC diagnosis (Table II) (140,143,144). Although further research is required for confirmation and there are differences in the types of proteins studied, the aforementioned studies indirectly suggest that exosomal membranes and contained proteins could serve as potential diagnosis biomarkers for PC.

Exosomes contain rich and complex lipid components such as cholesterol, sphingolipids and PS (156). Sharma *et al* (157) found that phosphatidylserine (PS) in plasma exosomes from patients with PC increased before histopathological confirmation of PC, suggesting it could be used for screening and ultra-early diagnosis of PC. Tao *et al* (158) applied liquid chromatography-mass spectrometry technology to analyze the lipid profiles of exosomes from the serum of patients with PC and HCs, identifying 37 differentially expressed lipid components. This suggests that these differentially expressed lipids may serve as potential biomarkers for diagnosing PC. However, there is currently limited research on exosomal lipids in the diagnosis of PC, making it difficult to evaluate their diagnostic efficacy.

The aforementioned research results indicate that circulating exosomal contents has potential value in the diagnosis and treatment of PC. However, due to the rich variety of exosomal contents, current studies are small-sample single-center studies, and there are differences in exosome extraction, content separation and sequencing methods. Additionally, body fluids are not uniform, and factors such as region, ethnicity and tumor staging can lead to differences in research results. Therefore, it is imperative to conduct large-sample multi-center studies after standardizing the technology, with the aim of finding suitable early diagnostic markers for PC.

In conclusion, emerging diagnostic technologies such as liquid biopsy and advanced genomic techniques hold significant promise for the early detection of PC. These methods offer a non-invasive, sensitive and specific approach to diagnosing PC. However, the integration of such sophisticated technologies into routine clinical practice poses challenges, including cost, accessibility and the need for specialized expertise. Further research and clinical validation are needed to fully realize the potential of these technologies in routine clinical practice.

6. Diagnostic role of VOCs in PC

VOCs are a diverse group of organic chemicals characterized by their elevated vapor pressure at ambient temperatures, which allows them to easily evaporate into the atmosphere. The unique metabolic activities of cancer cells can result in the production of specific VOCs that may serve as indicators of malignancy. The ability to detect these compounds in non-invasive biofluids such as breath, urine and saliva presents a significant advantage over traditional diagnostic methods, which often require invasive procedures such as biopsies. Research has shown that the presence and concentration of certain VOCs can correlate with the presence of pancreatic tumors, making them potential candidates for early diagnostic tools. Daulton *et al* (14) have shown that certain VOCs such as 2,6-dimethyl-octane and nonanal are significantly elevated in the urine of patients with PC compared with HCs, suggesting their potential as biomarkers for early detection (AUC, 0.85). Martínez-Moral *et al* (13) found that the serum VOC butoxymethylbenzene may be a suitable PC biomarker candidate (AUC, 0.98). Tiankanon *et al* (159) found that the VOCs, acetone dimers have the potential to be new biomarkers for PDAC detection (AUC, 0.91). A rapid, non-invasive and effective diagnostic method is particularly suitable for use in primary healthcare settings as a preliminary screening instrument, demonstrating significant patient acceptability and practicality. In the assessment of hepatobiliary conditions and PC, VOCs exhibited a sensitivity of 0.79 and a specificity of 0.81. These findings are notably encouraging and could offer a viable approach for the early identification and management of cancer (160).

7. Diagnostic role of nanomaterials in PC

The emergence of nanotechnology has paved the way for the development of sophisticated diagnostic tools, particularly through the implementation of nanomaterials. Nanomaterials can be engineered to target specific biomarkers linked to PC, facilitating more accurate detection techniques that could revolutionize the field of PC diagnostics (161).

Caputo and Caracciolo (162) demonstrated that blood tests utilizing nanoparticles were capable of distinguishing patients with PDAC from healthy individuals through a comprehensive alteration in the nanoparticle-protein corona. Electrochemical biosensors utilizing nanomaterials have exhibited exceptional sensitivity for the detection of microRNAs and other biomarkers pertinent to PC, presenting opportunities for timely diagnosis (163).

Moccia *et al* (164) presented an economically viable paper-based electrochemical biosensor utilizing peptide nucleic acid for the identification of miRNA-492, a recognized biomarker associated with PDAC (164). The incorporation of nanomaterials into imaging technologies has markedly advanced the domain of medical diagnostics and treatment. The physicochemical attributes of nanomaterials, including their dimensions, morphology, surface chemistry and functionalization potential, contribute to enhanced imaging contrast, targeted delivery and heightened therapeutic effectiveness. For example, superparamagnetic iron oxide nanoparticles have been harnessed to target specific tumor markers, thereby enhancing the specificity of MRI for cancer identification (165). Gold nanoparticles have been utilized in photoacoustic imaging, wherein they absorb light and convert it into thermal energy, resulting in the generation of ultrasound signals that can be detected and visualized. This imaging technique has demonstrated potential in tumor imaging, offering deeper tissue penetration and superior resolution compared with conventional optical imaging methods (166). In summary, the future outlook for PC diagnostics appears promising with the emergence of nanomaterials. Ongoing research concentrating on developing efficient nanomaterial systems, combined with the integration of contemporary technologies and patient-centered methodologies, is crucial for advancing early detection and precision treatment.

8. Optimization of clinical pathways

Optimizing clinical pathways for PC diagnosis involves integrating multiple diagnostic modalities to enhance early detection and treatment planning. The combination of imaging techniques with tumor marker analysis and liquid biopsies can streamline the diagnostic process, reducing the time to diagnosis and improving patient outcomes. For example, a clinical pathway that incorporates initial imaging (CT or MRI) followed by EUS-FNA for suspicious lesions and concurrent CA19-9 testing, can provide a comprehensive diagnostic approach (10). Additionally, incorporating liquid biopsy techniques, such as ctDNA, exosome and VOCs analysis, can offer non-invasive options for monitoring disease progression and treatment response (167), and has become an essential instrument in improving the processes of screening, identifying, diagnosing, treating and monitoring PDAC (39). However, nanomaterials facilitate more accurate detection techniques, and thus implementing these integrated diagnostic pathways requires multidisciplinary collaboration and continuous evaluation to ensure they are tailored to individual patient needs and clinical settings (168). Through the integration of diverse diagnostic approaches and cutting-edge technologies, clinical pathways can be refined to enhance the rates of early detection and improve outcomes for patients with PC (10). An extensive diagnostic approach that combines imaging techniques, biomarker assessment and molecular characterization shows potential for enhancing early diagnosis and patient prognosis. Subsequent investigations should aim to concentrate on the validation of novel biomarkers, refinement of imaging techniques and the development of standardized protocols for liquid and molecular biopsies.

9. Conclusion

In the intricate landscape of PC diagnosis, it is evident that while notable strides have been made, there remains a critical need for advancements to enhance early identification and improve patient outcomes. The current diagnostic modalities, such as imaging techniques, tumor biomarker detection and tissue biopsies, each offer unique strengths but also present inherent limitations in sensitivity, specificity and clinical utility. Ultimately, the future of PC diagnosis is rooted in a multidisciplinary approach, leveraging advancements in technological innovations and enhanced comprehension of tumor biology. By addressing the current challenges and fostering collaborative research, progress can be made toward achieving early diagnosis and, consequently, improve prognoses for patients afflicted by PC.

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Authors' contributions

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Competing interests

The authors declare that they have no competing interests.

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