

Revolutionizing Pancreatic Cancer Detection: The Promise of PAC-MANN for Early Diagnosis and Real-Time Monitoring

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Abstract

Globally, Pancreatic cancer, especially Pancreatic ductal Adenocarcinoma, currently stands as the 12th most common cancer in both sexes and the 6th most common cause of cancer-related death with a prediction of it moving up in ranks in the nearest future. The incidence and mortality rates have been observed to increase steadily over the years and although this cancer has not received as much spotlight as others, it remains one of the most lethal malignancies with its late diagnosis being a major contributor to its poor prognosis and increasing mortality rate. The typically asymptomatic nature of the disease especially in its early stages as well as the rapidity of its progression underscore the urgency for early detection. In response to this urgent need, PAC-MANN stands out as a revolutionary innovation which serves to facilitate early, accurate, non-invasive and cost-effective detection of pancreatic cancer. This review dives into the already established screening measures of Pancreatic cancer, their limitations and disadvantages and the transformative potential of PAC-MANN in bringing revolution into pancreatic cancer diagnosis, real time monitoring and improving patient care and outcomes through early intervention.

Keywords: Pancreatic cancer; Pancreatic ductal adenocarcinoma (PDAC); Cancer epidemiology; Mortality rate

Introduction

Pancreatic Ductal Adenocarcinoma [PDAC] is a highly invasive neoplasm arising from the pancreatic ductal epithelial cells and has become one of the leading causes of cancer-related deaths worldwide. It is ubiquitous and accounts for more than 90% of all pancreatic malignancies [1]. PDAC is very aggressive, has early metastasis and highly resistance to multiple treatment, this distinguishes it from other pancreatic malignancies which are rare, slow-growing and responsive to immunotherapy. With a 5-year survival rate of 5-10%, PDAC remains quite lethal despite the numerous studies, research and clinical trials.

It primarily affects the head of the pancreas in about 60-70% of cases and other cases affecting the body or tail of the pancreas [3]. Involvement with the head has a better prognosis since clinical presentations are seen earlier than others with tumors of the body and tail having worse prognosis.

PDAC is notorious for its challenging early identification due to ambiguous and non-specific symptoms. It may manifest clinically as jaundice, unexplained weight loss, abdomen or back discomfort, gastrointestinal disturbances, nausea, and vomiting, with less frequent symptoms including new-onset diabetes or exacerbation of pre-existing diabetes and thromboembolic incidents.

The majority of PDAC is non-hereditary and associated with mutation in known driver genes like KRAS oncogene, and CDKN2A, TP53, and SMAD4 tumor suppressor gene, seen in both early-stage and advanced tumors [2].

KRAS activating mutation accounts for 90% of all pancreatic neoplasms.

PDAC typically progress from precursor lesions such as PanIN [4]. PanINs are microscopic, non-invasive lesions that develop

in the pancreatic ducts. They are classified into different grades based on their increasing degree of cellular and architectural atypia (dysplasia). While PanINs are relatively common, especially as people age, most will never progress to invasive cancer. However, the presence of higher-grade PanINs significantly increases the risk of PDAC development.

The progression of PanIN to PDAC plays out as follows: normal pancreatic ductal epithelium – PanIN-1 (low grade) – PanIN-2 (intermediate-grade) – PanIN-3 (high-grade carcinoma in situ) – Invasive PDAC

Early detection PDAC remains one of the most formidable challenges in oncology today.

One of the fundamental challenges is vague presentation and the anatomical location of the pancreas, retroperitoneal positioning creates a perfect spot for hiding during routine examination [5].

Limitations in early diagnosis is noted in the ineffectiveness of the routine biomarker test, serum carbohydrate antigen [CA 19-9]. This widely used biomarker for detection of PDAC is neither sensitive nor specific enough as it only elevated in late stages of disease. Studies show that sensitivity for early-stage PDAC can be low as 50-60% meaning significant of cases go undetected with this marker alone. It can be falsely increased in non-cancerous conditions like pancreatitis, gallstones, cholangitis, cirrhosis, and cystic fibrosis. Approximately 5-10% of population are Lewis antigen-negative and cannot synthesize CA 19-9, so they will false negative even when they have disease [6,7]. PDAC tumors are also high heterogenic and vary between individuals and within a single tumor, meaning no single biomarker is reliable enough for early detection.

Another challenge in early detection is poor identification on standard scans like Computed Tomography [CT] and Magnetic Resonance Imaging [MRI], early-stage PDAC often present with subtle textural and morphological changes, blending with the surrounding tissues making are difficult to discern by radiologist [1]. Endoscopic ultrasound provides detection of smaller lesion but its invasive, operator-dependent and not suitable for large scale screening [1,8].

Chemoresistance itself is a major inevitable obstacle in treatment of PDAC and contributes its poor prognosis. PDAC is resistant to the standard chemotherapy through interwoven mechanism of tumor cells aggression and the tumor microenvironment. The dense desmoplastic stroma which surrounds the tumor blocks the chemotherapy drugs from effectively penetrating [9]. Other factors like metabolic reprogramming and tumor-associated macrophages infiltrate further propagate the chemoresistance of the cancer cells [10].

PDAC has a high mortality and high mortality-incidence ratio indicating that a large number of individuals who are diagnosed will eventually die. The high mortality rate is a complex of issue stemming from combination silent progression, diagnostic ambiguity, limited screening tools, aggressive tumor biology, and resistance to current therapies.

Epidemiology

Worldwide, pancreatic cancer is the 12th most common cancer and the sixth leading cause of death in both males and fe-

males [11,15]. It is more common in males than in females and increases with age. The most recent data in 2025 estimate 67,440 new cases, accounting for about 3.3% of all new cancer cases. Estimated deaths in 2025 are 51,980, representing about 8.4% of all cancer deaths. [12] Countries with a higher Human Development Index typically have incidence rates four to five times higher per unit population [11]. The age-standardized incidence rate increased significantly from 5.0 per 100,000 people in 1990 to 5.7 per 100,000 in 2017, resulting in a 2.3-fold increase in deaths for both sexes over the same period. People aged 50–69 and 70 and above significantly contribute to the annual rise in new cases [13].

In 2018, GLOBOCAN reported 458,918 registered cases of pancreatic cancer, with an approximately 8% increase by 2020, and a male-to-female ratio of 1.0:1.1. Western Europe had the highest incidence rate at 8.6/100,000, while South-Central Asia had the lowest at 1.2/100,000 [13]. According to 2022 data, there were 510,992 new cases and 467,409 deaths, with the highest incidence and mortality rates in China, the US, and Japan [15]. This reflects a significant increase from 2020 statistics, which recorded 496,000 cases and 466,000 deaths, primarily in regions like Europe, Northern America, and Australia/New Zealand [11].

Recent data indicate that countries with rising prevalence of obesity, diabetes, and alcohol consumption, alongside improvements in diagnostic and registration practices, have stable or slightly increased incidence or mortality rates [11]. Migration may also affect cancer risk, particularly among individuals with similar genetic backgrounds moving to countries with different developmental stages. Factors such as residential environments, access to medical care, genetic susceptibility, and dietary habits can significantly alter incidence rates across age groups, genders, and regions [13].

Compared to declining breast cancer rates, projections based on studies of 28 European countries suggest that pancreatic cancer will surpass breast cancer as the third leading cause of cancer death by 2025 [11].

Prognosis

Pancreatic cancer is associated with a dismal prognosis, with a 5-year survival rate of less than 10% as of 2020.

[3] Surgical resection of early-stage Pancreatic Ductal Adenocarcinoma (PDAC) followed by adjuvant chemotherapy offers the best hope for improving survival rates. However, long-term survival post-surgery is achieved by only a subset of patients, with up to 20% surviving 5 years and approximately 10% surviving past 10 years, according to a 2016 article [15]. Most surgically resected patients have a median survival of less than 20 months, and the factors responsible for long-term survival are poorly understood.

Although the prognosis remains poor, the 5-year survival rate increased from 4% in 1997 to 12% in 2018 for all stages, attributed to advancements in multidisciplinary care and multimodality therapies, including surgical resection, radiation, chemotherapy, immunotherapy, and targeted therapy [16].

Clinical studies suggest that low disease stage, negative surgical margins, and negative lymph nodes are predictors of a more

favorable prognosis. However, 20–40% of patients surviving at least 5 years post-surgery had nodal disease and/or positive resection margins, indicating that pathological staging is not the sole determinant of long-term survival [15].

Tumors in the body and tail of the pancreas are associated with a worse prognosis. Patients with metastatic pancreatic cancer also face a poor prognosis, with less than 20% surviving past first year [3]. Factors such as distinct genetics, epigenetics, or other biological factors, including changes in the tumor micro-environment or enhanced immune response, may contribute to less aggressive phenotypes [15].

Diagnostic Limitations

Early detections offer significant benefits, but diagnosing pancreatic cancer early remains a formidable challenge [17]. Unlike mammograms, Pap smears, or colonoscopies for breast, cervical, or colon cancer, respectively, pancreatic cancer lacks a routine screening test [18]. Despite being a leading cause of cancer-related death, screening the general population is not recommended due to the lack of cost-effective tests, limited availability, and invasiveness of some tests like endoscopic ultrasound (EUS). CA-19-9 has low utility due to low sensitivity and specificity. Screening for high-risk populations, especially those with an inherited risk, has been employed and deemed effective. Symptoms of pancreatic ductal adenocarcinoma (PDAC) are often non-specific. Vague clinical Presentations at early stages, such as epigastric or back pain, nausea, fatigue, and bloating, can lead to misdiagnosis with less serious conditions. Typical symptoms like jaundice, weight loss, main pancreatic duct obstruction, or cholangitis usually appear at advanced, non-respectable stages. The rapid growth and progression of pancreatic cancer, spanning months to a few years, contribute to its aggressive nature, increasing the likelihood of diagnosis at a less treatable or more advanced stage.

Importance of Early Detection

Early detection makes resection more feasible. When the cancer is confined to the pancreas or has spread only to nearby areas, it can be removed surgically. The most ideal approach is complete tumor removal, as partial removal reduces the chance of long-term survival. Surgery is indicated only if the entire cancer can be removed [18].

Development of PAC-MANN

The research team from Oregon Health & Science University has developed and is continuing to validate a model of a non-invasive, rapid, high-throughput assay called PAC-MANN (Protease-ACTivated MAGnetic NaNosensor) that can detect early-stage pancreatic ductal adenocarcinoma. The test uses a small blood sample to detect changes in the activity of a type of protein called protease, which is a key indicator of PDAC. The research behind PAC-MANN was inspired by the pressing need for a reliable, non-invasive tool to detect pancreatic cancer at its earliest stages. Recognizing the limitations of current diagnostic techniques, the team at Oregon Health & Science University explored the use of altered protease activity—biochemical markers present in cancer patients' blood.

By combining these insights with AI, they aimed to develop a scalable, personalized diagnostic approach that could significantly improve survival outcomes. [19][20] The research was led by Dr. Jared Fischer, an assistant professor of molecular and medical genetics, and Dr. Jose L. Montoya Mira, a research

engineer at OHSU's CEDAR, who started the research around 2020. According to Dr. Fischer, the institution focused on pancreatic cancer for multiple reasons: it is extremely deadly when caught late, and it is almost always caught late. Also, there are currently no tests approved for early detection. He expressed that he wanted the test to be fast, cheap, accurate, and to meet all necessary metrics. From the onset of the research, the PAC-MANN assay progressed, culminating in its publication on February 12, 2025. [21]

Scientific Principle

The scientific principle behind PAC-MANN is based on the detection of abnormal protease activity in a blood sample. Proteases are enzymes that break down proteins by cleaving peptide bonds. Proteases play roles in digestion, immune response, signaling, tissue remodeling, and more. Protease activities are highly regulated under normal physiological processes. In cancers, protease activities are dysregulated. Different forms of cancer show increased activity of specific proteases. In pancreatic cancer, the increased protease activity aids cancer growth by breaking down the extracellular matrix and connective tissue, causing local invasion. It also facilitates angiogenesis, which could lead to metastasis. [22]

Test Methodology and Time Efficiency (Results in 45 Minutes)

According to Dr. Jared Fischer, PAC-MANN was invented because he wanted a fast, cheap, and accurate test for the early detection of pancreatic cancer [21]. The test requires about 8 microliters of blood (less than a drop of blood), into which protease-sensitive nanosensors are introduced. Synthetic peptides are attached to magnetic iron oxide nanoparticles. These synthetic peptides are designed to be cleaved by pancreatic cancer-associated proteases.

The combination of the nanosensors and blood is incubated, allowing proteases to cleave the peptide (if positive for the cancer). Then, a magnet is used to remove the unreacted nanosensors from the solution, leaving only the fluorescent tags. The fluorescent tags are read and analyzed to correlate with the level of protease activity to determine the presence of pancreatic cancer enzymes. The entire testing process takes approximately 45 minutes. According to Dr. Jose L. Montoya Mira, the test could easily be used in rural and underserved settings where traditional tests are not available. He also stated that it could be used in people at high risk for pancreatic cancer, which cannot be identified by current tests [19,23].

Pancreatic Ductal Adenocarcinoma (PDAC): Diagnostic Advances with PAC-MANN

Pancreatic Ductal Adenocarcinoma (PDAC) stands as one of the most lethal malignancies globally, consistently ranking among the leading causes of cancer-related mortality. A primary factor contributing to its dismal prognosis is the frequent diagnosis at advanced stages, at which point effective treatment options are severely limited, and patient survival rates are exceptionally low [19]. The imperative for earlier detection cannot be overstated, as it is widely recognized as the most critical avenue for expanding therapeutic possibilities and significantly enhancing patient survival outcomes.

Limitations of Current Diagnostic Tests

Current diagnostic approaches for PDAC face considerable limitations. Carbohydrate Antigen 19-9 (CA 19-9), while the most extensively validated serum biomarker for pancreatic cancer, is primarily approved and utilized for monitoring dis-

ease progression and indicating prognosis in diagnosed patients [24]. However, it consistently demonstrates insufficient sensitivity for the crucial task of early-stage detection, often failing to identify the disease when it is most treatable [24]. This diagnostic gap underscores an urgent need for novel, more effective tools capable of identifying PDAC at its nascent stages.

PAC-MANN: A Novel Diagnostic Tool

PAC-MANN, an acronym for "Protease Activity-based Assay using a Magnetic Nanosensor" emerges as a promising liquid biopsy designed to address these critical unmet needs [21]. By identifying early signs of cancer-related activity in the blood, PAC-MANN aims to provide clinicians with a tool that can detect the disease much earlier, thereby expanding treatment options and offering a better chance of survival for patients [25].

Reported Diagnostic Accuracy

In a blinded retrospective study, the PAC-MANN assay demonstrated robust performance in identifying PDAC samples. When used as a standalone test, it achieved a high specificity of 98% and a sensitivity of 73% across all stages of PDAC [19]. This high specificity is particularly valuable in a screening context, as it indicates a low rate of false positives, thereby minimizing unnecessary follow-up procedures and patient anxiety. Furthermore, the test exhibited an exceptional ability to differentiate PDAC from non-cancerous pancreatic conditions, achieving 100% distinction in the study cohort [19]. This strong discriminative power is a critical attribute for any diagnostic tool aimed at early detection. The diagnostic accuracy for PAC-MANN alone in distinguishing PDAC from controls was reported at $79 \pm 6\%$ [19].

However, the most compelling results emerged when PAC-MANN was combined with the clinical biomarker CA 19-9. This combined approach significantly enhanced the detection of early-stage disease, demonstrating 85% sensitivity for Stage I PDAC with a specificity of 96% [19]. This combined strategy was consistently reported to spot early-stage cancer with an overall accuracy of 85% [24]. It is important to note that some variations in reported metrics exist across different sources. For instance, some reports indicated 90% overall accuracy for PAC-MANN alone, with 72.7% sensitivity and 97.6% specificity [20], while another study presented 78% sensitivity and 86% specificity for PAC-MANN alone, and 84% sensitivity with 100% specificity for the combined assay [26].

PAC-MANN vs. CA 19-9

Sensitivity and Specificity Comparison

CA 19-9, while widely used, is generally not sensitive enough for early-stage PDAC detection [24]. Its reported sensitivity for symptomatic patients ranges from 72% to 81%, with specificity varying between 82% and 90% [27]. Notably, CA 19-9 is elevated in only approximately 50% of pancreatic adenocarcinomas that are smaller than 3 cm [27], further underscoring its limitations in detecting truly early-stage disease. In contrast, PAC-MANN alone demonstrates a sensitivity of 73% across all stages with a high specificity of 98% [19]. The most significant enhancement in diagnostic performance occurs when PAC-MANN is combined with CA 19-9, achieving 85% sensitivity for Stage I PDAC with 96% specificity [19]. This comparison highlights PAC-MANN's inherently superior specificity and its ability to significantly improve early-stage sensitivity when integrated with CA 19-9.

Performance in CA 19-9 Non-Secretors (~5-10% of Population)

One of the most significant limitations of CA 19-9 as a universal biomarker is its unreliability in a notable portion of the population. Approximately 5-10% (or up to 10-20% in some reports) of individuals are Lewis antigen-negative (Lewis (a-b-) phenotype) [28]. These individuals lack the specific enzyme (α 1-3,4 fucosyltransferase) required for CA 19-9 biosynthesis, resulting in undetectable or very low serum CA 19-9 levels (typically below 1 U/mL) [28]. This genetic predisposition leads to false-negative results, severely limiting CA 19-9's utility as a screening or diagnostic tool in this subgroup [28].

There are, however, some nuanced and even contradictory findings regarding CA 19-9 expression in Lewis-negative patients. While several sources indicate that CA 19-9 is not useful in Lewis-negative individuals, one study reported that not all Lewis-negative PDAC patients are complete non-secretors. This study found that 27.4% of Lewis-negative patients with PDAC still had elevated CA 19-9 levels (>37 U/mL), and CA 19-9 maintained diagnostic utility (Area Under the Receiver Operating Characteristic curve of 0.842) in this subgroup [29]. This suggests that the relationship between Lewis status and CA 19-9 expression can be more complex than a simple binary, indicating a need for a more nuanced understanding and potentially genetic testing alongside CA 19-9 measurements. Regardless of these complexities, PAC-MANN offers a fundamental advantage in this context.

Its detection mechanism is based on measuring cancer-associated protease activity, which is entirely independent of the Lewis antigen system [19]. This inherent independence means that PAC-MANN bypasses the "blind spot" of CA 19-9 in non-secretors, providing a reliable diagnostic tool for this significant patient subgroup. This is particularly critical because Lewis-negative PDAC patients have been associated with poorer outcomes and higher metastatic rates, emphasizing the urgent need for alternative early detection methods that are effective across the entire population, irrespective of their Lewis phenotype [30].

Prognostic Utility

CA 19-9's established clinical role lies primarily in prognostication and monitoring disease progression or recurrence in patients already diagnosed with PDAC [24]. A decline in CA 19-9 levels following treatment is associated with prolonged survival [27]. However, CA 19-9 levels alone are considered poor predictors of overall survival [31], and clinical guidelines advise against making treatment decisions based solely on changes in CA 19-9 levels [32]. In contrast, PAC-MANN demonstrates a more dynamic potential for prognostic utility. Research indicates that the protease cleavage signal detected by PAC-MANN significantly decreases (by $16 \pm 24\%$) following the surgical removal of the primary tumor [19]. This observed reduction directly reflects a decrease in cancer-associated biological activity. The level of protease activity measured by PAC-MANN also correlates with tumor burden [21]. This correlation implies that PAC-MANN can serve as a real-time, dynamic biomarker for assessing treatment response. This dynamic monitoring capability is a significant advancement in oncology. It provides clinicians with a tool to monitor patient progress and guide future therapeutic options in real-time [24]. Unlike CA 19-9, which offers more of a retrospective prognos-

tic indicator, PAC-MANN's reflection of active protease activity linked to tumor burden provides a more immediate biological readout of disease activity.

Advantages of non-invasiveness and cost-effectiveness

Beyond its promising diagnostic performance, PAC-MANN possesses several practical advantages that significantly enhance its suitability for widespread clinical integration, particularly in the context of early Pancreatic Ductal Adenocarcinoma (PDAC) detection and ongoing patient management. PAC-MANN is a non-invasive liquid biopsy, requiring only a small blood sample of 8 microliters [24]. This minimal invasiveness represents a substantial advantage over traditional diagnostic methods for pancreatic cancer, such as endoscopic ultrasound or surgical biopsies, which are significantly more burdensome for patients, carry inherent risks, and require specialized medical infrastructure [24]. The test primarily relies on the measurement of serum protease activity [19] and does not explicitly require complex imaging data, extensive laboratory panels (beyond the protease assay itself), or detailed clinical records for its execution. While a comprehensive diagnostic workup would still involve these elements, PAC-MANN's minimal data input for the test itself simplifies its application.

The economic profile of PAC-MANN is particularly noteworthy. The estimated material cost for running a single PAC-MANN test is remarkably low, at less than one cent per sample [24]. This exceptionally low cost, combined with a rapid turnaround time of approximately 45 minutes per test [24], significantly contributes to its overall cost-effectiveness. Furthermore, the assay's high-throughput capability, allowing for the analysis of 300-500 samples per day with minimal personnel and equipment [21], underscores its scalability. These attributes collectively render PAC-MANN highly accessible, holding immense potential for widespread implementation, especially in low-resource and rural settings where advanced diagnostic infrastructure is often limited or entirely absent [24].

The ability to perform such a critical screening test quickly and affordably could democratize access to early cancer detection, potentially transforming global health outcomes by enabling screening programs in regions currently underserved by conventional diagnostics. PAC-MANN is specifically designed and highlighted for its potential to significantly enhance early PDAC detection in high-risk individuals [19]. High-risk populations typically include individuals with a strong family history of PDAC, those with chronic pancreatitis, or patients with new-onset diabetes [21]. The non-invasive nature, low cost, and rapid turnaround time of PAC-MANN allow for more frequent screening intervals than currently feasible with more invasive and expensive methods like endoscopic ultrasound [24]. This capability to perform frequent, low-cost surveillance in high-risk groups represents a paradigm shift in PDAC management. Given the rapid progression of pancreatic cancer, regular monitoring is crucial for detecting the disease when it is still resectable. PAC-MANN's attributes directly address the barriers to such proactive surveillance programs, offering a practical and sustainable solution for catching cancers at their earliest, most treatable stages, thereby transforming reactive diagnosis into proactive disease management.

Broader Implications for Cancer Screening

PAC-MANN is a blood test developed to detect pancreatic ductal adenocarcinoma at early stages. The PAC-MANN as-

say's potential in resource-limited areas lies in its capacity for early and accurate pancreatic cancer detection [34].

Considering the challenges that low-to-middle-income countries face in delivering intensive modern neoadjuvant therapies, a reliable early detection method like PAC-MANN could be invaluable [35]. In resource-constrained settings, where access to advanced imaging and specialized medical care may be limited, a simple blood test that can identify high-risk individuals could significantly impact patient outcomes [36].

Here are some specific ways PAC-MANN could be beneficial in resource-limited areas:

- **Early Detection:** Pancreatic cancer is often diagnosed late due to its vague symptoms and the difficulty in imaging the pancreas [37]. PAC-MANN aims to detect the disease earlier [33], which is crucial because early-stage PDAC is more amenable to treatment [38].
- **Non-invasive and Quick:** PAC-MANN uses a simple blood sample and provides results in 45 minutes with a fluorescent readout [21]. This makes it a potentially accessible diagnostic tool even in settings with limited resources.
- **Improved Accuracy:** The PAC-MANN test has shown promising accuracy rates when used with the CA-19 blood test [36].
- **Targeted Screening:** Instead of widespread screening, which can be expensive and logistically challenging, PAC-MANN could be used to screen high-risk populations, such as those with a family history of pancreatic cancer or those with certain genetic mutations [34].
- **Improved Triage:** In settings where access to specialized care is limited, PAC-MANN could help triage patients, ensuring that those most likely to have pancreatic cancer are prioritized for further evaluation and treatment.
- **Cost-Effectiveness:** While the initial cost of the PAC-MANN test may be a barrier in some resource-limited settings, its potential to reduce the need for more expensive and invasive diagnostic procedures could make it a cost-effective solution in the long run.

Due to the poor prognosis of pancreatic cancer, early detection remains a major goal [39]. Identifying pancreatic cancer at earlier stages may lead to improved survival outcomes [40]. The PAC-MANN assay holds promise for revolutionizing early cancer screening methods, particularly for pancreatic cancer, by addressing key limitations of existing approaches [33].

Here's how:

- **Improved Sensitivity and Specificity:** Current tests like CA 19-9 lack the sensitivity needed for early-stage detection [33]. PAC-MANN aims to fill this gap by identifying signs of cancer-related activity in the blood earlier [33]. In one study, PAC-MANN demonstrated 85% accuracy when combined with the CA-19 blood test [36].
- **Non-invasive and Accessible:** PAC-MANN requires only a small blood sample and provides a quick fluorescent readout [33]. This makes it more accessible than invasive procedures like endoscopic ultrasound [41], potentially enabling wider screening.
- **Potential for Targeted Screening:** Given the relatively low prevalence of pancreatic cancer, general population screening is not always feasible [40]. PAC-MANN can be used to screen high-risk individuals [37], such as those with a family history or genetic predispositions, making screening efforts more efficient [40].

While challenges remain, such as the need for validation in larger cohorts and longitudinal studies [34], PAC-MANN's ability to detect early-stage pancreatic cancer with promising accuracy [37] positions it as a potential game-changer in early cancer screening [40].

Accessibility:

- **Low cost:** The test requires very little blood (8 microliters) and can be run quickly (45 minutes) at a low cost (less than a penny per sample) [33]. This makes it potentially usable in rural and underserved settings where traditional tests are not readily available [33].
- **Non-invasive:** As a blood test, PAC-MANN is non-invasive, which improves patient acceptance and facilitates repeated testing [36].
- **Point-of-care potential:** While not explicitly stated, the rapid turnaround time and simple readout suggest potential for point-of-care use, further enhancing accessibility.

Scalability:

- **High-throughput potential:** Some immunoassays powered by microfluidics have demonstrated rapid and multiplex capabilities [42]. It should be noted that PAC-MANN has an 85% accuracy rate when used with the CA-19 blood test [36].
- **Adaptability:** The PAC-MANN test could be used to screen high-risk individuals [34], such as those with a family history or genetic predispositions, making screening efforts more efficient.
- **Automation:** High-throughput assays with short turnaround times can incorporate machine learning for autonomous image analysis [42].

Therapeutic monitoring and real time applications

The PAC-MANN assay (Protease-Activated Cancer Magnetic Nanosensor) represents a significant advancement not only in early pancreatic cancer detection but also in monitoring treatment response and enabling personalized oncology. By targeting tumor-associated protease activity, PAC-MANN opens up new opportunities for real-time, noninvasive tracking of disease progression and therapeutic effectiveness.

Tracking protease activity during treatment

PAC-MANN can track the activity of protease to monitor treatment effectiveness for pancreatic cancer. This is achieved by measuring changes in protease activity in a blood sample, which can indicate how well a patient is responding to therapy. Proteases such as matrix metalloproteinases (MMPs) and cathepsins play key roles in tumor invasion and metastasis, and their activity levels tend to correlate with tumor burden and aggressiveness. PAC-MANN leverages this by using magnetic nanosensors that are activated upon cleavage by these proteases in the bloodstream. In a clinical pilot, patients with pancreatic cancer showed an average 16% decrease in PAC-MANN signal following surgical tumor resection, suggesting that the test could be used to track changes in protease activity during therapy and detect residual or recurring disease earlier than imaging or traditional biomarkers [1].

Real-Time Assessment of Treatment Response

Unlike imaging or serum CA 19-9 levels, which may lag behind actual tumor behavior, PAC-MANN can provide real-time updates on treatment effectiveness, detecting biochemical

changes in as little as one hour from a single drop of blood. This rapid response capability makes it ideal for use in monitoring ongoing therapy, such as chemotherapy, radiation, or immunotherapy.

If a patient shows early suppression of protease activity, their treatment may be working well. If protease levels don't drop or bounce back, it may indicate residual disease, tumor resistance, need to change or intensify therapy. PAC-MANN makes it possible to track this week by week or even day by day, just from a drop of blood.

The PAC-MANN test is quantitative and repeatable, showing protease signal reduction after tumor resection, which supports its potential use for tracking treatment response. Although formal responder vs. non-responder studies have not yet been published, the technology holds promise for such stratification in future trials [43].

Guidance of Personalised Therapy and Improved

By reflecting tumor-specific biology, PAC-MANN enables more precise adjustments to therapy regimens. For instance, patients showing early drops in protease levels may be good candidates for de-escalated treatment, while persistently high levels may prompt an intensification or switch in therapy. This real-time feedback loop aligns with the goals of precision oncology, potentially reducing overtreatment and improving patient outcomes. In future applications, PAC-MANN's serial measurements could potentially be integrated with AI-driven algorithms to detect evolving trends in protease activity—enabling prediction of treatment resistance or progression and guiding individualized care. While not yet studied directly with PAC-MANN, AI-assisted biomarker interpretation has shown promise in other cancer-monitoring platforms, and PAC-MANN's dynamic protease data could lend itself to similar computational approaches in the future.

Future Directions and Clinical Trials

While PAC-MANN was specifically developed for pancreatic cancer detection [38], the underlying technology and principles could potentially be adapted for detecting other cancers. Here's how:

- **Liquid Biopsy Approach:** PAC-MANN utilizes a liquid biopsy approach, analyzing cancer-related molecules in the blood [37]. This approach is applicable to other cancers, as circulating tumor DNA (ctDNA), RNA, proteins, and other biomarkers are present in the blood of patients with various types of cancer.
- **Protease Activity:** PAC-MANN recognizes specific proteins that break down other proteins (proteases) in the blood [37]. Since elevated protease activity is associated with the growth and spread of various cancers, this principle could be applied to develop tests for other malignancies.
- **Biomarker Identification:** The key to adapting PAC-MANN for other cancers lies in identifying specific biomarkers that are indicative of those cancers. By targeting different biomarkers, the same basic technology could be used to detect a range of malignancies [44]. For example, salivary exosomes containing specific proteins have shown promise as biomarkers for early diagnosis of oral squamous cell carcinoma [44].
- **Adaptation to other blood tests:** PAC-MANN has an 85% accuracy rate when used with the CA-19 blood test [36].

Regulatory Challenges:

- **Approval Pathway:** The specific regulatory pathway will depend on the jurisdiction (e.g., FDA in the US, EMA in Europe) and the classification of PAC-MANN. Gaining approval requires demonstrating both safety and efficacy through rigorous clinical trials [45]. The EU AI Act establishes a risk-based framework, requiring regulatory review based on device risk, with high-risk devices subject to stricter oversight [45].
- **Data Requirements:** Regulators will scrutinize the data used to train and validate the PAC-MANN assay, ensuring it is representative of the intended population and free from bias [45].
- **Continuous Learning and Adaptation:** If PAC-MANN incorporates AI or machine learning, regulators will need to address how the algorithm can be updated and improved over time while maintaining safety and efficacy [46].
- **Standardization:** Actions of third-party institutions in terms of standardization and security enhancements are required [47].

Implementation Challenges:

- **Cost and Reimbursement:** The cost of the PAC-MANN assay will be a major factor influencing its adoption, particularly in resource-limited settings. Securing reimbursement from insurance providers or government healthcare systems will be essential.
- **Infrastructure Requirements:** Implementing PAC-MANN may require investments in laboratory equipment, personnel training, and data management systems.
- **Integration with Existing Clinical Workflows:** Successfully integrating PAC-MANN into existing cancer screening and diagnostic pathways will require careful planning and coordination with healthcare providers.
- **Ethical Considerations:** Widespread screening raises ethical concerns about potential overdiagnosis, false positives, and patient anxiety. Clear guidelines and counseling services will be needed to address these issues.
- **Data Privacy and Security:** Protecting the privacy and security of patient data is paramount, especially given the sensitive nature of genetic information.
- **Physician and Patient Education:** Effective implementation requires educating physicians and patients about the benefits and limitations of PAC-MANN, as well as providing clear guidance on interpreting test results and making informed decisions.

Conclusion

PAC-MANN stands as a revolutionary tool and a transformative leap in the early detection and real time monitoring of pancreatic cancer and possibly many other lethal cancers. With its potential to ensure early detection and treatment, this test promises to improve survival rates of oncology patients worldwide and promote global health equity by providing a cost-effective means of diagnosis and monitoring treatment. It is highly recommended that continued research, collaboration and investment be placed in technologies like PAC-MANN as this is fundamental to the redefinition of the future of oncology.

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