Early Pancreatic Cancer Detection via Extracellular Vesicle-Based Classifier: A Blinded Cohort Analysis

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Introduction

- Pancreatic ductal adenocarcinoma (PDAC) is among the most aggressive malignancies, with a five-year survival rate below 12%. Late-stage diagnoses significantly limit curative treatment options, making early detection a critical unmet need. Additionally, the presence of heterogeneous benign pancreatic conditions complicates risk stratification and differentiation from malignancy.
- Advances in liquid biopsy have introduced minimally invasive methods for cancer detection, with EV-based diagnostics offering unique advantages.
- A previously established exosome-based proteomic classifier demonstrated strong performance in distinguishing early PDAC cases from healthy controls (Hinestrosa et al. *Commun. Med.* **2023**, *3*, 146).
- This study evaluates the classifier in a blinded, real-world cohort, including high-risk benign pancreatic conditions, to assess its clinical utility and identify the most informative biomarkers for risk stratification.

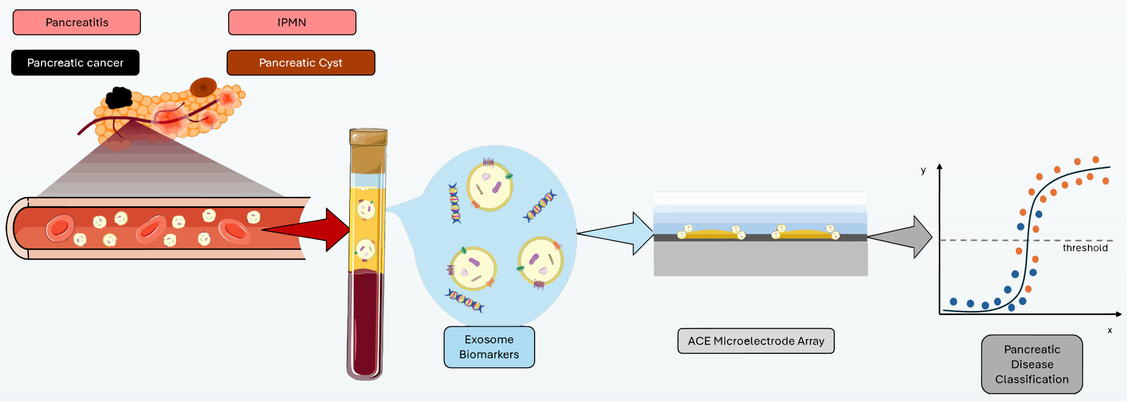

Figure 1. Overview of the test workflow. Blood samples from patients with PDAC, high-risk pancreatic diseases, and healthy controls contain useful biomarkers on the EVs. Plasma-derived EVs were isolated using an ACE microelectrode array, and their proteomic signals were analyzed to classify for pancreatic cancer.

Cohort and Study Design

Blood samples were collected from patients at OHSU under an IRB-approved protocol. Blood samples were drawn into K_2EDTA tubes. The cohort included patients with confirmed PDAC diagnoses, individuals with high-risk benign pancreatic conditions, and healthy controls to provide a comprehensive evaluation of the EV classifier performance across different patient groups.

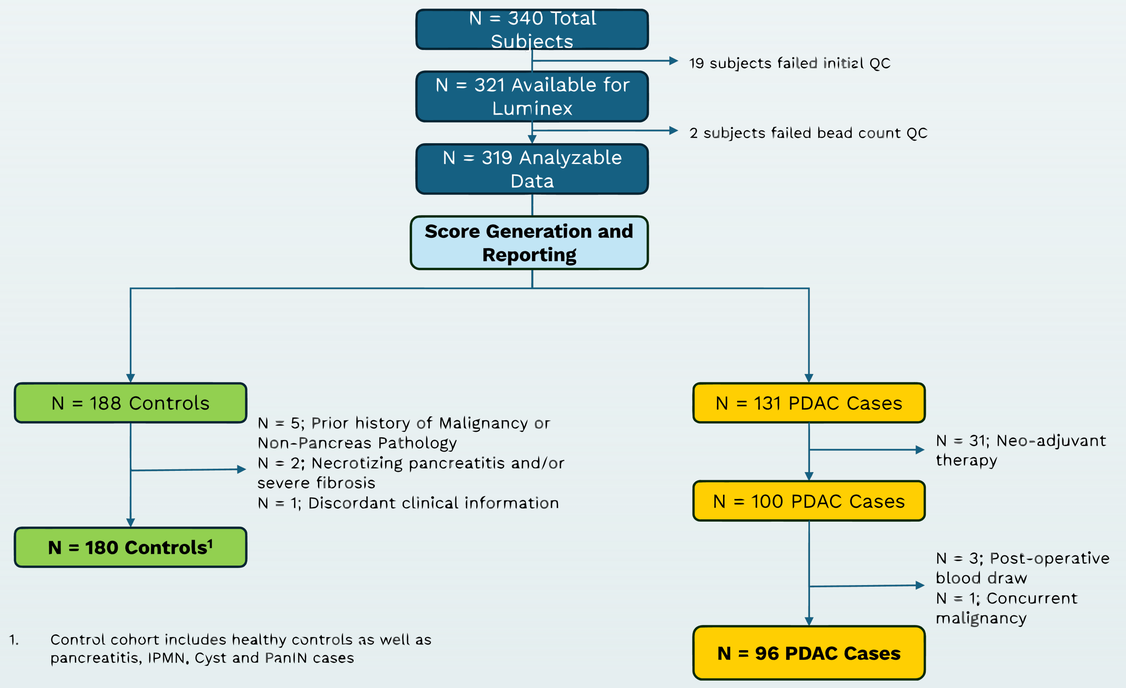

Figure 2. Study Analysis Process. Overview of the cohort composition with exclusion criteria applied after the unblinding of the patient information.

Table 1 shows the demographic information for study cohort with a breakdown of the control's conditions. High-risk conditions, such as pancreatitis, IPMN, and pancreatic cysts, comprised a significant portion of the control group.

Table 1. Cohort Information

	Controls	Cases
Total N	180	96
Age (Min / Med / Max)	18 / 59 / 89	37 / 69 / 87
Sex (F / M / Unknown)	86 / 93 / 1	47 / 49 / 0
Cancer Stage		
I		12
II		84
Control Breakdown		
Pancreatitis	93	
Pancreatic Cyst	47	
IPMN	22	
Healthy Normal	10	
Pancreatic Polyp	5	
Disorder of the bile duct	2	
Disorder of the liver	1	

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Results

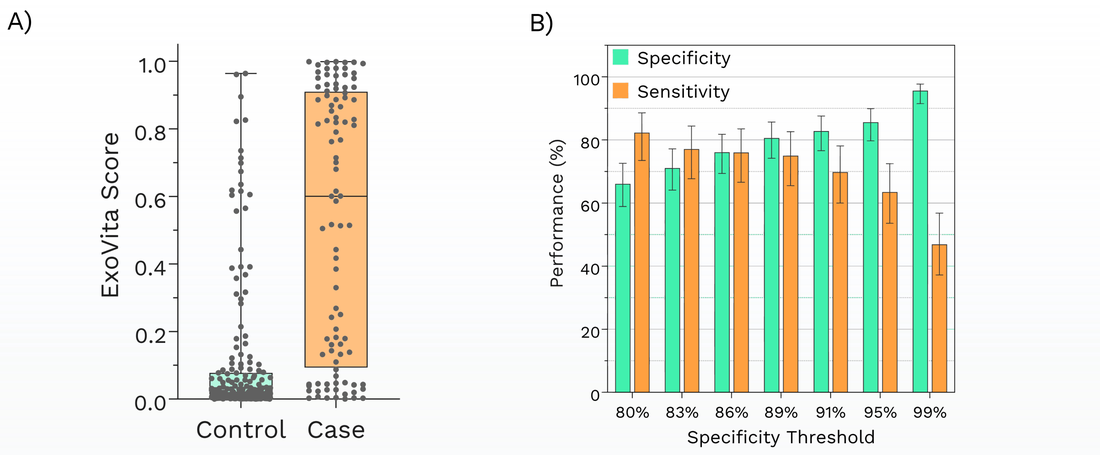

Figure 3. Risk Score and Overall Performance for blinded dataset at multiple specificity thresholds. A) Risk score calculated based on the EV Classifier where each dot represents a subject in the study. B) Specificity and Sensitivity performance at different specificity thresholds from the trained, published classifier. The error bars represent the two-side Wilson 95% confidence interval.

Biomarker Selection for High-Risk Conditions

Given the high prevalence of high-risk conditions in the dataset, we initiated a biomarker selection process to enhance stratification, improve detection rates, and optimize the algorithm.

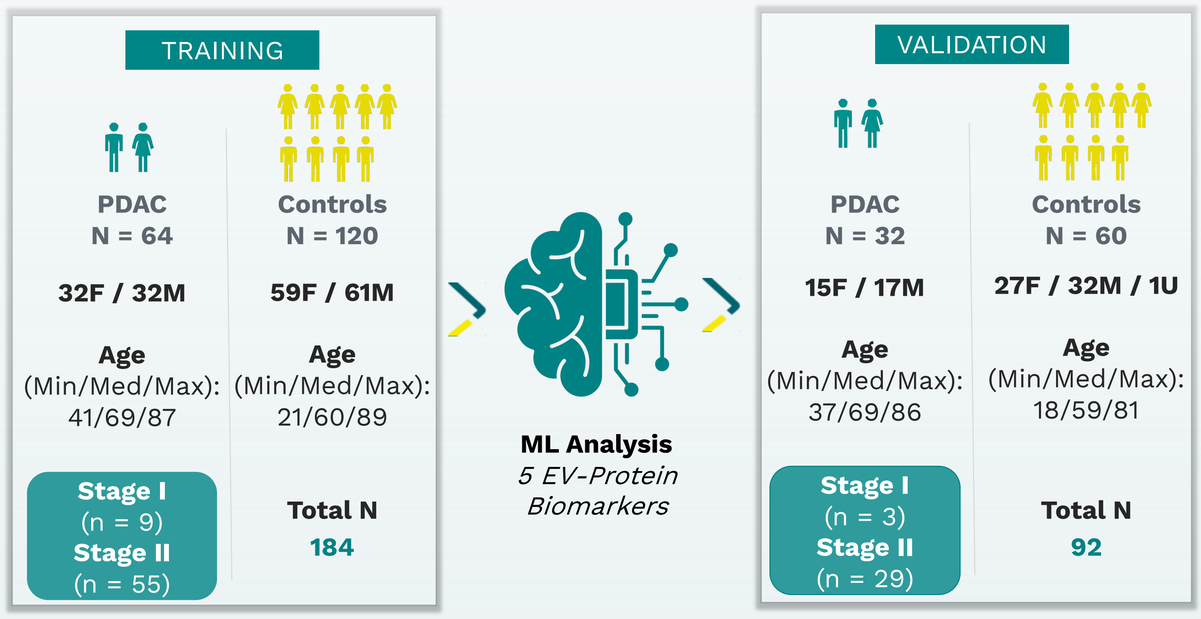

Figure 4. ML Modeling Approach. The training set is used for biomarker and algorithm development and the validation dataset is used for the model evaluation.

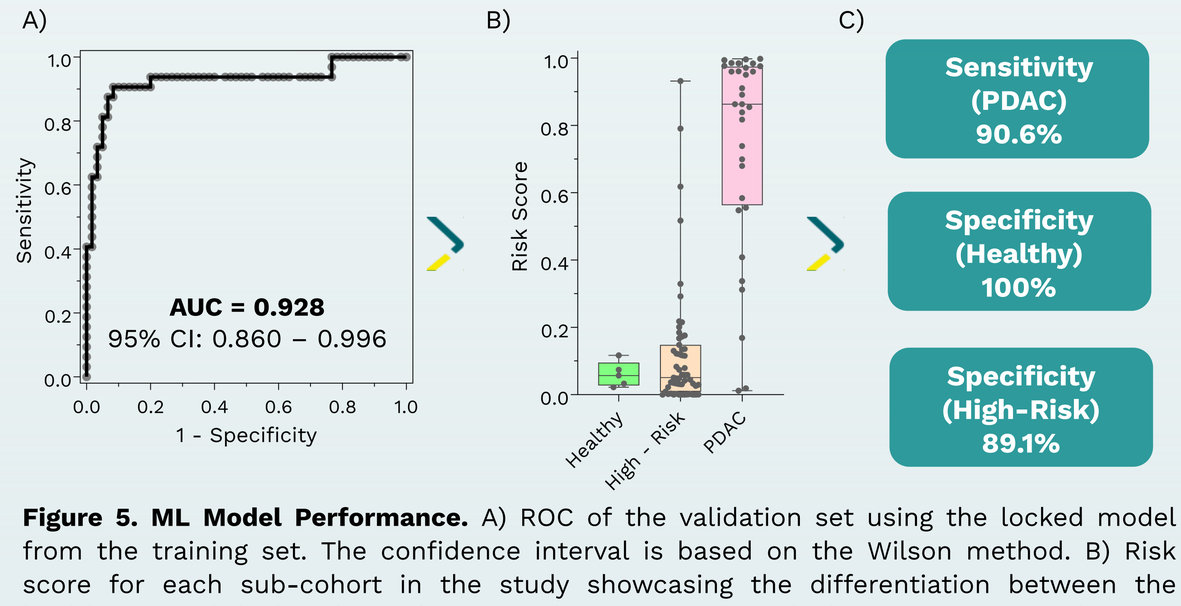

Figure 5. ML Model Performance. A) ROC of the validation set using the locked model from the training set. The confidence interval is based on the Wilson method. B) Risk score for each sub-cohort in the study showcasing the differentiation between the healthy control, high-risk conditions, and PDAC cases. Each dot represents a subject in the validation set. C) Performance of each major control sub-cohort.

Conclusions

- ✓ The sensitivity for Stage I and II PDAC was **90.6%.**
- ✓ The specificity for healthy controls was **100%,** while the specificity for the high-risk pancreatic conditions, was **89.1%**.
- ✓ Among PDAC cases, the classifier achieved a sensitivity of **93.1%** for stage II pancreatic disease.
- ✓ Biomarkers detected on extracellular vesicles (EVs) from patient plasma highlight the diagnostic versatility of this approach. At high specificity thresholds, the false positives can be minimized allowing for screening applications. In contrast, reducing the threshold enhances sensitivity supporting its potential role in risk stratification of high-risk populations.

Dynamic deployment of the EV-based classifier in clinical context enables pancreatic cancer detection early enough for meaningful intervention — and can lead to integration into existing diagnostic pathways.