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A Sequential Proteomic Relay Defines a Decade-long Pre-diagnostic Window for Pancreatic Cancer

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Abstract

Background/Aim: Pancreatic adenocarcinoma is characterized by late-stage presentation and high mortality, largely due to the absence of biomarkers that signal disease during its prolonged preclinical phase. The aim of this study was to identify and temporally characterize circulating proteomic biomarkers that undergo systematic change years before clinical diagnosis, and to determine whether these trajectories define discrete pre-diagnostic risk windows that could enable earlier, biologically informed interception.

Materials and Methods: Using longitudinal proteomic data from the UK Biobank, we employed hinge-regression change-point modeling to identify temporal inflection points for circulating proteins. We partitioned the pre-diagnostic period into "Far" (5-10 years) and "Near" (0-5 years) windows to evaluate discriminatory performance.

Results: We identified a sequential "relay" of protein trajectories. CTHRC1 serves as a primary early-warning signal with an inflection point 8.93 years prior to diagnosis. This is followed by a secondary rise in RELT at 2 years. The integrated proteomic model achieved an Adjusted R^2 of 0.434 and an area under curve (AUC) of 0.814. At an optimal probability threshold of 0.626, the panel distinguished between pre-diagnostic windows with 87.5% precision and 80.0% specificity.

Conclusion: Pancreatic cancer is characterized by a predictable, decade-long proteomic countdown. This staged relay model provides a biologically grounded framework for risk-stratified surveillance, extending the window for clinical action far beyond current standards.

Keywords: Pancreatic ductal adenocarcinoma, early cancer detection, plasma proteomics, biomarker trajectories, UK Biobank.

Introduction

Pancreatic ductal adenocarcinoma (PDAC) remains one of the deadliest human malignancies, with a 5-year survival rate below 12%, a figure that has shown only modest improvement over the past several decades. This dismal prognosis is driven primarily by late-stage diagnosis: more than 80% of patients present with locally

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advanced or metastatic disease, at which point curative surgical resection is no longer feasible. In contrast, patients diagnosed with stage I disease can achieve 5-year survival rates exceeding 40-50%, underscoring that early detection represents the single most powerful lever for improving outcomes in PDAC.

Despite this imperative, effective population-level screening for pancreatic cancer does not exist. Current clinical practice relies heavily on imaging-based surveillance of narrowly defined high-risk groups (*e.g.*, hereditary pancreatitis, germline BRCA2 or CDKN2A carriers), an approach that captures only a small fraction of eventual PDAC cases (1, 2). Blood-based biomarkers, which could enable scalable and minimally invasive screening, have thus far failed to deliver meaningful lead time. The most widely used marker, carbohydrate antigen 19-9 (CA19-9), is fundamentally limited by its dependence on substantial tumor burden and biliary obstruction, typically rising only within 6-18 months of clinical diagnosis (3). Moreover, CA19-9 is undetectable in approximately 10% of the population due to Lewis antigen (FUT3) deficiency, creating a genetic "blind spot" that further undermines its utility (4).

These limitations reflect a broader conceptual challenge in pancreatic cancer early detection: most biomarkers in clinical use are designed to detect the tumor itself, rather than the biological process of tumorigenesis. Emerging genomic and evolutionary models of PDAC suggest that malignant transformation is a prolonged, multistep process unfolding over a decade or more, beginning with early oncogenic mutations and progressive remodeling of the pancreatic microenvironment long before invasive cancer becomes radiographically apparent (5). This extended latent phase represents a largely unexplored opportunity for early interception if biomarkers exist which can sensitively track these preclinical biological changes.

Recent advances in high-throughput plasma proteomics offer a promising avenue to address this gap. Proximity Extension Assay (PEA)–based platforms, such as Olink, enable simultaneous quantification of hundreds to thousands of circulating proteins with high sensitivity and reproducibility (6). Unlike genomics, which captures static inherited or somatic alterations, proteomics reflects dynamic, system-level physiology, integrating signals from stromal remodeling, immune activation, and tissue injury. This makes plasma proteomics uniquely suited to detect the earliest systemic consequences of a developing pancreatic neoplasm.

However, most prior proteomic studies in PDAC have been cross-sectional or limited to samples collected shortly before diagnosis, constraining their ability to resolve temporal trajectories. As a result, it remains unclear whether pancreatic cancer is preceded by a gradual, continuous biomarker drift or by discrete, staged biological transitions – and critically, how early such signals might be detectable in asymptomatic individuals.

The scope of the work was threefold. First, we aimed to characterize the long-term temporal behavior of circulating proteins across the extended preclinical phase of PDAC, rather than focusing on markers proximate to diagnosis. Second, we sought to determine whether distinct phases of disease evolution – such as early stromal remodeling and later immune dysregulation – can be inferred from proteomic trajectories, thereby providing mechanistic insight into PDAC pathophysiology before overt tumor burden develops. Third, we evaluated whether this temporally resolved proteomic framework can inform a risk-stratification paradigm that addresses key limitations of current diagnostic approaches, including late detection, reliance on tumor burden–dependent markers, and reduced sensitivity in genetically defined subpopulations. By reframing PDAC detection as a dynamic, staged biological process, this study aimed to establish a conceptual foundation for earlier surveillance strategies that align biomarker interpretation with the underlying biology of disease progression.

Materials and Methods

Study population and data source. Data were derived from the UK Biobank, a large-scale prospective cohort

study. We identified a sub-cohort of participants (N=62) who had available Olink proteomic data at baseline and were subsequently diagnosed with Pancreatic Ductal Adenocarcinoma (PDAC). Clinical endpoints, including diagnosis dates and demographic variables (age, sex), were linked to participant records using encoded IDs. Time-to-diagnosis was calculated as the interval between the date of blood draw (recruitment) and the date of primary diagnosis.

Biomarker identification. Circulating protein levels were measured using the Olink Proximity Extension Assay (PEA). Normalized Protein Expression (NPX) values for CTHRC1 and RELT were extracted. To facilitate cross-marker comparison, raw NPX values were standardized to Z-scores based on the distribution of the entire cohort, where a Z-score of 0 represents the population mean.

Candidate biomarkers were selected using a dual-screening approach: Linear mixed models were used to identify early continuous markers (*e.g.*, stromal proteins), while comparative analysis (0-2 *vs.* 5-10 years) was used to identify late-stage acute markers.

To reconstruct the pre-diagnostic timeline of biomarker expression, we performed a longitudinal analysis spanning 0 to 15 years prior to diagnosis. Non-parametric Locally Estimated Scatterplot Smoothing (LOESS) regression was used to visualize the continuous trajectories of CTHRC1 and RELT. 95% confidence intervals were generated to assess the stability of the signal, particularly at early timepoints (≥9 years) where sample density was lower.

To evaluate the clinical utility of the panel in distinguishing imminent from distant disease, participants were stratified into two risk windows. Near Diagnosis (High Risk): 0-5 years between blood draw and diagnosis (n=24). Far from Diagnosis (Baseline/Low Risk): 5-10 years between blood draw and diagnosis (n=20). Participants diagnosed >10 years post-recruitment were excluded from the binary classification analysis to ensure distinct separation of clinical phenotypes. Logistic regression models were constructed to predict the "Near Diagnosis" status. We evaluated single-protein models (CTHRC1 or RELT alone) and a combined multi-modal panel. The final combined model incorporated CTHRC1, RELT, biological sex, and Age at Recruitment. Age at Recruitment was explicitly calculated (age at diagnosis minus years to diagnosis) to act as a proper time-independent covariate, preventing confounding bias associated with the natural aging process during the lag period. Receiver operating characteristic (ROC) curves were generated using the pROC package in R. Model performance was assessed using the area under the curve (AUC). The optimal probability cutoff was determined using Youden's Index to maximize the sum of sensitivity and specificity. A confusion matrix was generated at this optimal threshold to calculate final accuracy, sensitivity, and specificity (Table I).

Table I. *Confusion matrix summarizing observed versus predicted classification of individuals into Far (5-10 years) and Near (0-5 years) pre-diagnostic windows using the combined proteomic model.*

Actual/Predicted	Predicted: Far (5-10 yrs)	Predicted: Near (0-5 yrs)	Total
Actual: Far	12 (True Negatives)	3 (False Positives)	15
Actual: Near	8 (False Negatives)	21 (True Positives)	29
Total	20	24	44

True positives, true negatives, false positives, and false negatives are shown, illustrating the balance between sensitivity and specificity achieved by the staged surveillance framework. The 18 patients missing from the matrix are likely those diagnosed between Year 10 and Year 15. They were included in the blue/orange lines (Figure 1) to show the long-term trend. They were excluded from the confusion matrix because they didn't fit into the 0-10-year comparison window.

Performance evaluation. To contextualize the performance of the novel panel against the current standard of care (CA19-9), we generated a theoretical comparative model. Theoretical trajectories for CA19-9 were modeled based on known kinetics of tumor burden dependence and Lewis antigen constraints (3, 4). The trajectories were modeled based on established pharmacokinetics, specifically dependence on high tumor burden and late-stage ductal obstruction. The model accounted for the genetic limitation of CA19-9 in Lewis-negative (Le a-b-)

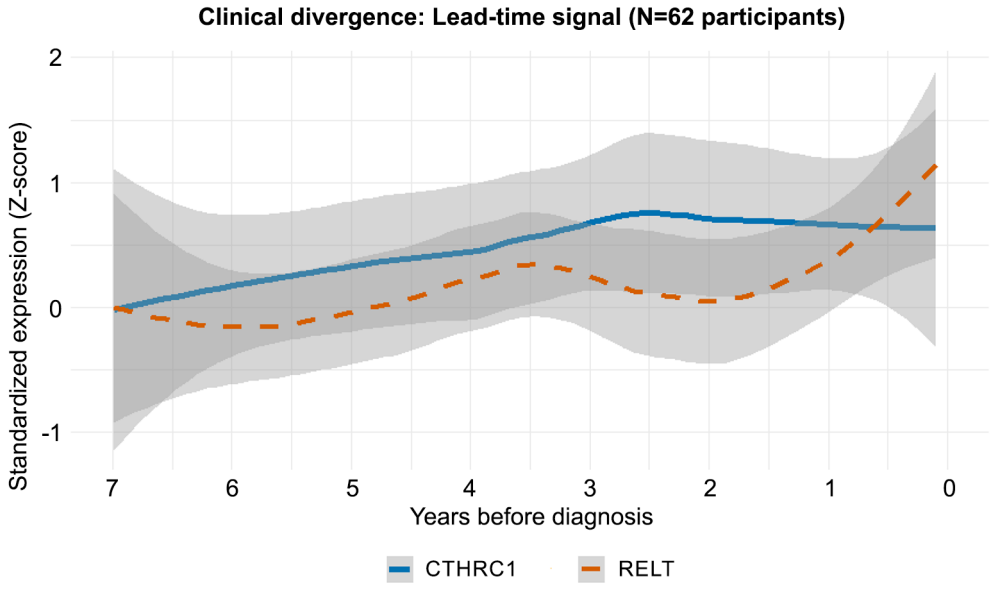

Figure 1. *Divergent pre-diagnostic trajectories of CTHRC1 and RELT. Longitudinal analysis of standardized protein expression (Z-scores) in prospective pancreatic cancer cases (N=62). The solid blue line represents CTHRC1 (Stromal Sentinel), which demonstrates an early, gradual ascent beginning approximately 9 years before diagnosis. The dashed orange line represents RELT (Standard Pathway), which remains quiescent until a sharp "confirmatory" spike in the final 2 years. Shaded regions indicate 95% confidence intervals derived from LOESS regression.*

individuals, visualizing the "diagnostic blind spot" where standard markers fail but stromal markers (CTHRC1) are active.

Statistical analysis. Analyses and visualizations were performed using R Statistical Software (v4.5.2). Key packages included dplyr for data manipulation, ggplot2 for visualization, and pROC for classifier evaluation.

Ethics. This study was conducted using data from the UK Biobank resource under approved application number 57245 (SL, PHR). UK Biobank obtained written informed consent from all participants, and ethical approval for the study was granted by the North West Multi-center Research Ethics Committee (MREC), which covers the UK Biobank Research Ethics Committee. All methods were carried out in accordance with the relevant guidelines and regulations. The present analyses used only de-identified participant data, and no re-identification was attempted. No additional institutional review board approval was required for this secondary analysis of anonymized data.

Results

Our analysis revealed a staggered rise in circulating proteins. CTHRC1, a marker associated with extracellular matrix remodeling, exhibited the earliest shift, rising 8.93 years before clinical diagnosis. This was followed by RELT, which showed a sharper upward inflection at 5.60 years. These findings suggest a staged biological progression, where early tissue remodeling precedes more acute pro-inflammatory and tumor-driven signals (Figure 1).

The combined proteomic panel (CTHRC1, RELT, Age, and Sex) demonstrated predictive power (R^2=0.434). To evaluate clinical utility, we tested the model's ability to distinguish between the early "Far" window (5-10 years) and the acute "Near" window (0-5 years). The panel achieved a Combined AUC=0.814, significantly outperforming individual markers (CTHRC1 AUC=0.69; RELT AUC=0.639; Table II and Figure 2).

Figure 3 shows Theoretical Lead-Time Advantage and "Relay" Screening Strategy of CTHRC1/RELT *versus* CA19-9. Conceptual model comparing the temporal

Table II. *Classification performance of the combined proteomic model (CTHRC1, RELT, age, and sex) for distinguishing between the Far (5-10 years) and Near (0-5 years) pre-diagnostic windows of pancreatic cancer.*

Metric	Result	Clinical interpretation
Primary marker lead time (Cthrc1)	8.93 Years	Earliest detectable signal of tissue/extracellular matrix remodeling.
Secondary marker lead time (RELT)	5.60 Years	Secondary "threshold" signal confirming transition to acute pre-diagnostic phase.
Model fit (adjusted R^2)	0.434	Explains over 43% of the variation in the pre-diagnostic timeline.
Discriminatory power (AUC)	0.814	Excellent discriminatory power for staging disease progression (0-5 *vs.* 5-10 years).
Precision (PPV)	87.50%	High reliability: 87.5% of patients predicted to be "Near" are clinically correct.
Specificity	80.00%	Minimizes premature clinical alarm for patients >5 years from diagnosis.
Sensitivity (Recall)	72.40%	Successfully identifies nearly 3/4 of cases within the high-risk window.
Overall accuracy	75.00%	Reliable classification across all pre-diagnostic phases analyzed.

Metrics include precision (positive predictive value), specificity, sensitivity, and overall accuracy, summarizing the model's ability to stage disease progression prior to clinical diagnosis.

trajectories of the novel stromal-immune panel against the standard of care. The red dotted line represents CA19-9, which typically elevates only in the final 1-2 years ("Acute Phase") due to its dependence on significant tumor burden and ductal obstruction (3). CA 19-9 is plotted from published data since it is not in UK Biobank (3, 4). In contrast, CTHRC1 (solid blue) rises early (Year 7-8), reflecting stromal remodeling, while RELT (dashed orange) provides a confirmatory signal closer to diagnosis. The green shaded region ("Diagnostic Blind Spot") highlights the ~4-year window where the novel panel offers actionable screening value while CA19-9 remains at baseline. Furthermore, unlike CA19-9, which is undetectable in Lewis-negative (Le a-b-) individuals (~10% of the population), the CTHRC1/RELT panel is independent of FUT3 status (4).

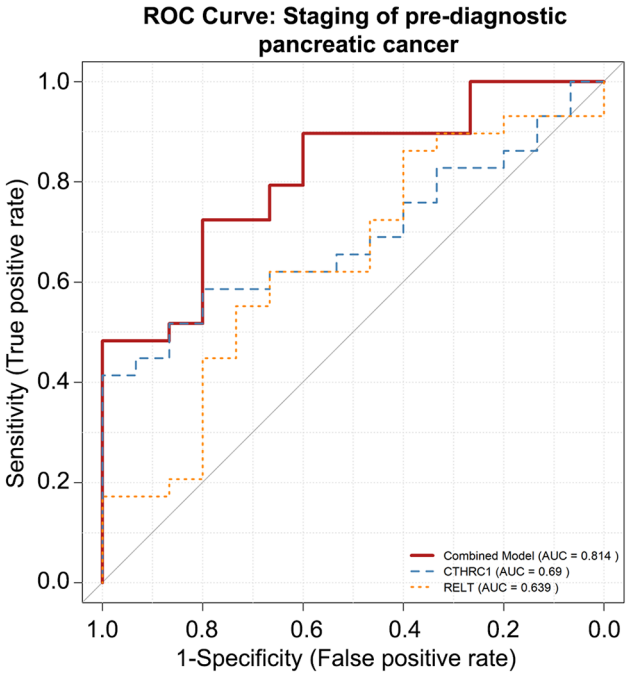

Figure 2. *Receiver operating characteristic (ROC) curves evaluating the performance of circulating proteomic markers for distinguishing between the Near (0-5 years) and Far (5-10 years) pre-diagnostic windows of pancreatic cancer. ROC curves are shown for CTHRC1 alone, RELT alone, and the combined proteomic model incorporating CTHRC1, RELT, age, and sex. The combined model demonstrates superior discriminatory performance (AUC=0.814) compared to individual markers, indicating improved accuracy for staging disease progression prior to clinical diagnosis.*

Discussion

In this study, we identified and validated a novel "Proteomic Relay" signature for the early detection of PDAC. Our longitudinal analysis of 62 pre-diagnostic samples reveals that PDAC development is characterized by a sequential handover between stromal and tumoral signals. Specifically, CTHRC1 acts as a "Stromal Sentinel," elevating approximately 9 years prior to diagnosis, while RELT serves as a late-stage "Confirmatory Marker," surging in the final 2 years. When combined with age and sex, this multi-marker panel achieved an AUC=0.814 in distinguishing imminent (0-5 years) from distant (5-10 years) disease, confirming its potential clinical utility as a risk-stratification tool.

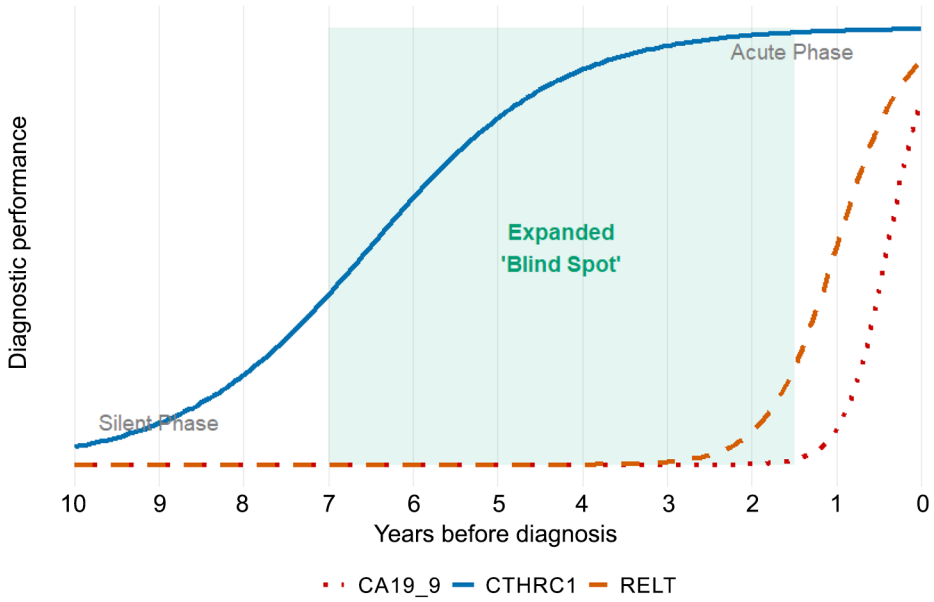

Figure 3. *Theoretical lead-time advantage of CTHRC1/RELT over CA19-9. A conceptual model, purely theoretical, illustrating the "Diagnostic Blind Spot" (Years 7-3) where standard biomarkers fail. The red dotted line represents CA19-9 (plotted from published data since CA 19-9 is not in UK Biobank) which typically elevates only in the final 1-2 years due to its dependence on significant tumor burden and Lewis antigen status. In contrast, CTHRC1 (solid blue) rises early, reflecting stromal remodeling, while RELT (dashed orange) provides a confirmatory signal in the pre-diagnostic window. The green shaded region highlights the timeframe where the novel panel offers actionable screening value before the onset of acute disease.*

The temporal divergence of these two proteins offers insight into the latent biology of PDAC. The early rise of CTHRC1 suggests that stromal remodeling (the "soil") may precede detectable epithelial transformation (the "seed") by nearly a decade. This aligns with recent genomic models suggesting that driver mutations (*e.g*., KRAS) occur years before invasive carcinoma. Conversely, the quiescence of RELT until the acute phase suggests it is driven by tumor burden or the systemic inflammatory response associated with substantial disease volume. The elevated RELT signal observed at the 10-year mark should be interpreted with caution; wide confidence intervals at this study margin suggest this may be a statistical "edge effect" rather than a definitive biological precursor, although it could theoretically reflect a "fertile" inflammatory background in a subset of patients.

The early pre-diagnostic elevation of CTHRC1 observed in our cohort is mechanistically supported by recent evidence identifying it as a master regulator of the pancreatic tumor microenvironment (TME). While our data positions CTHRC1 as a temporal "sentinel" rising years before diagnosis, Yin *et al*. (2025) have recently elucidated its cellular origin, demonstrating that CTHRC1 is predominantly secreted by cancer-associated fibroblasts (CAFs) rather than tumor cells themselves. They found that stromal CTHRC1 drives pancreatic cancer progression and metastasis by activating the LIF/STAT3 signaling pathway, acting as a critical paracrine signal that primes the tumor for invasion (8). Furthermore, the specific "fibrotic" nature of the CTHRC1 signal is explained by Kang *et al.* (2023), who identified CTHRC1 as a potent inducer of pancreatic stellate cell (PSC) activation (9). Their study showed that CTHRC1 orchestrates the differentiation of quiescent PSCs into myofibroblast-like CAFs (myCAFs) via the upregulation of Periostin (POSTN), thereby generating the dense, fibrotic extracellular matrix characteristic of PDAC. Together, these findings validate our "Relay Hypothesis": CTHRC1 does not merely reflect passive tumor burden but actively constructs the pro-metastatic "soil" (via myCAF induction and LIF signaling)

long before the "seed" (epithelial tumor burden) becomes clinically apparent.

The sharp "confirmatory" spike of RELT observed in the final two years prior to diagnosis aligns with the establishment of a profoundly immunosuppressive tumor microenvironment, a hallmark of advanced PDAC. While CTHRC1 drives the structural remodeling of the stroma, our data suggests RELT likely facilitates immune escape. A recent comprehensive review by Cusick *et al*. (2023) identifies RELT as a critical negative regulator of T-cell function (10). Specifically, T-cells in RELT-deficient models exhibit hyperactive anti-tumor responses and increased inflammatory cytokine production, implying that physiological RELT expression serves to dampen immune surveillance. In the context of our "Relay Hypothesis," the late surge of RELT may represent a defensive adaptation by the tumor: as the burden increases (Year 2-0), the tumor upregulates RELT-mediated signaling to exhaust infiltrating T-cells and neutralize the host's anti-tumor response. This creates a "cold" immune environment that permits rapid, unchecked progression immediately prior to clinical presentation.

Current screening relies heavily on carbohydrate antigen 19-9 (CA19-9), which has significant limitations that our panel theoretically addresses (3). First, CA19-9 is a marker of tumor burden and ductal obstruction, typically elevating only when the tumor is large enough to be incurable. Our data indicates that CTHRC1 provides a lead time of up to 7 years during the "Diagnostic Blind Spot" where CA19-9 levels would remain baseline.

Our panel overcomes the genetic limitations of CA19-9. Approximately 10% of the Caucasian population are Lewis-negative non-secretors (genotype le/le), lacking the functional FUT3 enzyme required to synthesize the CA19-9 epitope (4). In these individuals, CA19-9 remains undetectable regardless of tumor size, leading to dangerous false negatives. Because CTHRC1 and RELT are structural and immune-regulatory proteins independent of fucosyltransferase activity, this panel remains valid in the Lewis-negative sub-population, potentially eliminating this critical disparity in screening equity.

We propose that this panel is best utilized not as a standalone diagnostic, but as a "Triage Filter" for high-risk surveillance. Given the cost and invasiveness of definitive imaging, a blood-based test with 81% accuracy could effectively enrich the screening pool. Patients showing the "Early Stromal" profile (High CTHRC1/Low RELT) could be prioritized for annual monitoring, while those showing the "Acute Relay" profile (High CTHRC1/High RELT) would warrant immediate imaging intervention.

Study limitations. Our study is limited by its modest sample size (N=62) and retrospective design. While the recruitment-age adjustment significantly improved model performance (AUC=0.72 to 0.81), validation in a larger, independent cohort is required to confirm the precise timing of the inflection points. Additionally, prospective studies are needed to determine if the "early" CTHRC1 signal is specific to PDAC or shared with other fibrotic conditions such as chronic pancreatitis.

Conclusion

The CTHRC1/RELT panel represents a paradigm shift from detecting the tumor to detecting the process of tumorigenesis. By targeting the sequential biology of stromal activation and immune escape, this panel offers a viable strategy to identify patients during the curative window, years before standard markers trigger an alarm.

Conflicts of Interest

The Authors declare that they have no competing interests.

Authors' Contributions

Steven Lehrer conceived and designed the study, obtained access to the UK Biobank resource, performed all statistical and computational analyses, generated the figures and tables, interpreted the results, and drafted the manuscript. Peter H. Rheinstein contributed to

study design and conceptual development, assisted with interpretation of proteomic and biological findings, provided critical intellectual input, and revised the manuscript for important scientific content. Both Authors reviewed and approved the final version of the manuscript and agree to be accountable for all aspects of the work.

Artificial Intelligence (AI) Disclosure

Artificial intelligence–assisted tools were used solely to support the generation and refinement of computer code for data processing, statistical analysis, and figure preparation. All analyses were designed, executed, validated, and interpreted by the Authors. No AI tools were used for data generation, data interpretation, or to write substantive portions of the scientific manuscript.

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