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ORIGINAL RESEARCH

Cost-Effectiveness and Clinical Utility of Pancreatic Cancer Non-Invasive Test in New-Onset Diabetes

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Importance: Most pancreatic cancer (PC) cases are diagnosed at a late stage, leading to poor prognosis. New-onset diabetes (NOD) increases the risk of PC by 6- to 8-fold within the first 3 years of diagnosis. This study aims to assess the clinical utility and economic benefits of early detection of PC in patients with NOD using a cell-free DNA (cfDNA) epigenomic blood test (Avantect; ClearNote Health, CA).

Design: A Markov model compares two primary strategies: no testing and testing higher-risk NOD patients using the cfDNA epigenomic test. Using the enriching new-onset diabetes for pancreatic cancer (END-PAC) criteria ≥3, approximately 20% of the NOD patients were at higher risk for PC. The cfDNA epigenomic test has a sensitivity of 68% and a specificity of 97%.

Results: The cfDNA test is robustly cost-effective in NOD high-risk patients, with an Incremental Cost-Effectiveness Ratio (ICER) of $56,564 at a Willingness-to-Pay (WTP) threshold of $100,000; its cost-effectiveness is superior to the standard of care, ie, no testing. In a modeled cohort of 10,000 NOD patients, the no-testing strategy would result in 1% of PC cases, with only 7.1% being eligible for potentially curative surgery. By contrast, cfDNA testing identified 71 cases of PC, with 32.4% of these cases being eligible for surgical resection. Early-stage detection through this approach more than quadruples surgical eligibility and significantly enhances the chances of a cure.

Conclusions and Relevance: These findings underscore the transformative clinical and economic value of early PC detection in high-risk patients with NOD. Implementing cfDNA testing during the first three years following diabetes onset has the potential to shift the diagnosis paradigm, leading to early interventions and meaningful improvements in expected survival, while remaining cost-effective.

Keywords: pancreatic cancer, new-onset diabetes, early detection, cost effectiveness, cell-free DNA, epigenomics

Introduction

Pancreatic cancer (PC) is a leading cause of cancer mortality around the globe. PC is the third most common cause of cancer-related deaths in the US, and it is predicted to be the second-leading cause by 2030.[1] In the US, the 5-year survival expectancy after diagnosis is only 13.3%.[1] Currently, over 50% of PC cases are diagnosed as "distant" (Stage IV) with a 5-year survival rate of approximately 3%.[1] In contrast, diagnosing the disease at Stage IA improves the expected 5-year survival rate to approximately 80%.[2] Therefore, early detection is crucial in reducing the burden of pancreatic cancer.[3]

PC usually refers to a ductal adenocarcinoma of the pancreas, which represents approximately 85% of all pancreatic neoplasms. There are several subtypes of ductal adenocarcinoma; most have a similar poor long-term prognosis, except for colloid carcinomas, which have a better prognosis, and adenosquamous cancers, which have a worse prognosis than other subtypes. In general, all are treated similarly. The more inclusive term "exocrine pancreatic neoplasms" encompasses all tumors arising from the pancreatic ductal and acinar cells and their stem cells.[4]

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More than 95% of malignant neoplasms of the pancreas arise from the exocrine elements. Neoplasms arising from the endocrine pancreas (ie, pancreatic neuroendocrine [islet cell] tumors) comprise no more than 5% of pancreatic neoplasms.[4] Key PC risk factors include a strong family history of the disease, some germline mutations, and newly diagnosed type 2 diabetes.[5–8]

According to US professional guidelines, PC surveillance is recommended for individuals with a family history of PC or genetic risk factors, or those with cystic neoplasms of the pancreas.[7–9] In such individuals, annual MRI or endoscopic ultrasound imaging (EUS) is standard and has been demonstrated to be cost-effective.[10] However, imaging approaches are a limited resource and not suitable for large-scale surveillance. Moreover, CA19-9 and CEA serum biomarkers are neither sensitive nor specific enough for the early detection of PC.[11]

Sensitive, accurate, non-invasive testing could address the need for early detection when imaging modalities are scarce or not routinely used. Use of this type of test may also lead to increased compliance with testing. Analysis of cell-free DNA (cfDNA) in blood has proven to be a powerful platform for developing non-invasive testing. Data first published by Guler et al show differences in the distribution of the epigenomic marker 5-hydroxymethylcytosine (5hmC) in cfDNA samples from patients with PC compared to healthy individuals.[12] The authors used cfDNA isolated from patients' peripheral blood to determine 5hmC-DNA profiles using a proprietary 5hmC enrichment workflow and Next-Generation Sequencing (NGS). This approach has been validated, demonstrating that the test, combining 5hmC enrichment, copy number analysis, and DNA fragment size differences, can detect PC at an early stage with high sensitivity and specificity.[13,14] This technology is the basis for the commercially available Avantect Pancreatic Cancer Test (cfDNA test).

Type 2 diabetes (T2D), and especially new-onset diabetes (NOD), is a significant risk factor for PC. Pancreatogenic diabetes occurs when damage to the pancreas reduces the production of insulin or glucagon.[15] However, the differential diagnosis of pancreatogenic diabetes can be challenging, and it is therefore often diagnosed as T2D.[15] Multiple retrospective studies have demonstrated an elevated risk of PC within two to three years of NOD diagnosis, an association confirmed across racial and ethnic groups.[16] Nearly 25% of patients with PC are diagnosed with diabetes six months to 36 months before the diagnosis of PC.[17] Individuals 50 years of age and older with glycemically defined NOD have a six- to eight-fold higher risk of PC within three years of meeting the criteria for NOD, with approximately 1% of these individuals developing PC during this time.[5] Analysis of an extensive real-world database of administrative claims has further confirmed the association of NOD with a subsequent PC diagnosis.[18] Importantly, recently published prospective data from a large NOD cohort further confirm these findings.[19] Testing for cancer at the time of T2D diagnosis and for the subsequent 36 months may lead to the identification of PC at an earlier stage, when treatment may significantly increase the chances of survival.[5,20]

Our study aims to extend the understanding of the clinical benefits and cost-effectiveness of PC testing by developing a clinical utility and cost-effectiveness model for PC detection using a blood-based, non-invasive cfDNA test (Avantect Pancreatic Cancer Test).

Methods

We developed a Markov model to simulate the risk of developing pancreatic cancer in individuals with NOD, adhering to the guidelines of the Panel on Cost-Effectiveness in Health and Medicine for conducting and reporting a reference case analysis.[21,22]

For the initial analysis, we evaluated competing strategies in 50-year-old cancer-free NOD patients from the viewpoint of clinical interventions employed by treating physicians and third-party payer coverage and reimbursement, considering a lifetime time horizon.

Study Definitions

NOD was identified in patients who had two consecutive or simultaneous hyperglycemia indicators (fasting blood sugar $\geq$ 126 mg/dl, random blood sugar $\geq$ 200 mg/dl, and hemoglobin A1c $\geq$ 6.5) without previous diabetic treatment and who had at least one normal glucose test in the prior 3–18 months. Surveillance candidacy in these patients was determined

using an END-PAC score of ≥ 3.[20] Patients with high-risk familial or genetic susceptibility for pancreatic cancer were excluded.

Markov Model and Clinical Probabilities

The Markov model was constructed with six transitional states: NOD, low-risk lesion, high-risk lesion, pancreatic cancer, diabetes, and death, as depicted in Figure 1. This model was converted into a decision tree using TreeAge Pro software (TreeAge Software, Inc., Williamstown, Mass). We derived clinical probabilities from various sources, including the SEER database for pancreatic adenocarcinoma distribution and a systematic review of surveillance test results (EUS or MRI) (Table 1). Mortality data during pancreatic cancer treatment also came from SEER, while baseline complication probabilities were sourced from published studies.[10,23]

Surveillance Strategies

We compared five surveillance strategies in the baseline analysis, applied after entry into the decision model:

- Strategy I, No Surveillance, no cfDNA testing.
- Strategy II, MRI-based Surveillance with once-a-year MRI for 3 years.
- Strategy III, cfDNA-based Surveillance with once-a-year testing for 3 years.
- Strategy IV, EUS-based Surveillance with once-a-year EUS for 3 years.
- Strategy V, all patients with NOD had cfDNA testing at entry into the mo if the cfDNA testing was negative, no further testing was undertaken; if the test was positive and the patient had an END-PAC score of < 3, an initial EUS followed by cfDNA testing was done for 3 years; if the cfDNA test was positive and the patient had an END-PAC score of ≥3, annual EUS-based surveillance was continued for 3 years.

Surveillance commenced upon diagnosis of diabetes in individuals aged 50 or above and continued for three years. In strategies II to IV, patients with an END-PAC score of less than 3 were not tested. Smoking status did not affect the initiation of surveillance. CT scans were not considered for surveillance per CAPS guidelines. In strategies II through V,

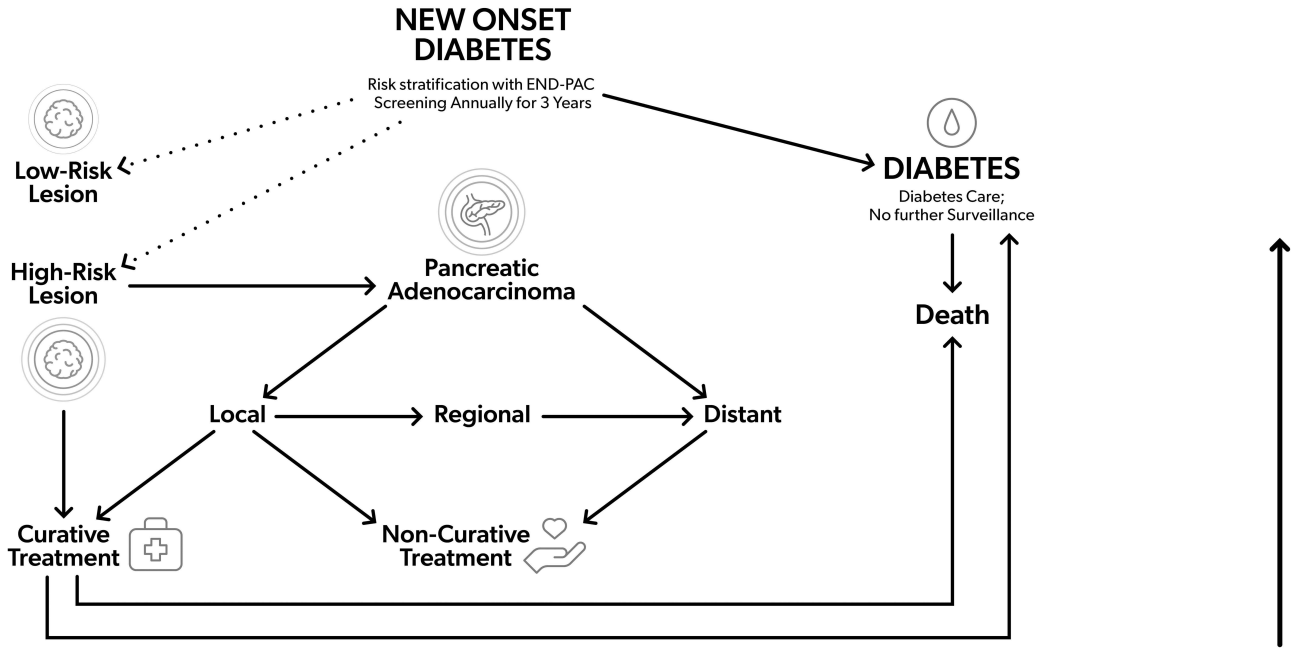

Figure 1 A simplified model of different Markov states. Patients with new-onset diabetes remain in the diabetic state and undergo annual surveillance tests, stratified by the END-PAC risk score. A single arrowhead indicates a transition from one state to another in the direction of the arrowhead. Solid lines indicate the primary transition path between states; dotted lines indicate alternative scenarios.

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Table 1 Selected Clinical Probabilities and Cost Estimates Used in the Decision Analysis (Modified from Previous publication)[6]

Clinical Probabilities and Utility Estimates	Description	Baseline	Range
Age	Age of entry into the model	50 years	50-80 years
Age-specific mortality for a healthy person	US life tables[24,25]	Life expectancy (age + stage)	0-0.002323
Probability of local (resectable) stage PC detected without surveillance	SEER data[26]	0.1	0.05–0.2
Probability of regional (un- or borderline resectable) stage PC detected without surveillance	SEER data[26]	0.3	0-0.5
Probability of regional stage cancer detected during surveillance	Previous systematic review[10]	0.2	0-0.2
Probability of local stage cancer detected during surveillance	Previous systematic review[10]	0.75	0-0.75
Probability of long-term cure with local stage PC detected with surveillance	Survival data from SEER[26]	0.1	0.05–0.2
Probability of dying from advanced-stage PC	Survival data from SEER[26]	0.5	0.1–0.7
Probability of dying from regional stage PC	Survival data from SEER[26]	0.34	0.1–0.5
Probability of dying from local stage PC	Survival data from SEER[26]	0.21	0.1–0.5
Operative mortality of PC surgery/total pancreatectomy	Stauffer et al,[29] Yeo et al[30] Balcom et al[31]	0.02	0-0.04
Probability of healthy (average risk) person developing PC without surveillance	DevCan data from SEER[23]		0-0.0004
Probability of high-risk lesion with EUS surveillance; stage dependent	Previous systematic review[10]	If (stage >1; 0.0013–0.0067)	0-0.0067
Probability of low-risk lesion with EUS surveillance	Previous systematic review[10]	0.1	0-0.1
Probability of PC on EUS surveillance	Previous systematic review[10]	If (stage >1; 0.0008–0.0038)	0-0.0038
Probability of abnormal EUS findings in high-risk patients undergoing EUS	Authors' consensus	0.1	0-0.2
Probability of abnormal EUS findings in high-risk patients undergoing MRI	Authors' consensus	0.1	0-0.1
Prevalence of abnormal cfDNA test in patients with new-onset diabetes	Authors' consensus	0.1	0-0.2
Sensitivity of EUS in detecting abnormal lesions	Banafea et al,[32] Best et al[33]	0.9	0.8–0.95
Specificity of EUS in detecting abnormal lesions	Banafea et al,[32] Best et al[33]	0.9	0.85–0.99
Sensitivity of MRI in detecting abnormal lesions	Best et al[33]	0.8	0.7–0.9
Specificity of MRI in detecting abnormal lesions	Best et al[33]	0.8	0.75-0.99
Sensitivity of cfDNA in detecting pancreatic cancer in patients with new-onset diabetes	Haan et al and Chowdhury et al[13,14]	0.68	0.65–0.90
Specificity of cfDNA in detecting pancreatic cancer in patients with new-onset diabetes	Haan et al and Chowdhury et al[13,14]	0.97	0.75–0.99
Utility of patient undergoing MRI	Previous systematic review[10]	1	0.98–1.0
Utility of EUS (includes disutility related to adverse events of bleeding, perforation and pancreatitis; no mortality)	Previous systematic review[10]	0.985	0.95–0.985
Utility associated with PC under treatment	Previous systematic review[10]	0.9	0.75–0.95
Utility of healthy patient who is not undergoing surveillance	Previous systematic review[10]	0.98	0.95-1
Utility of DM	Rubenstein et al,[34] Billings et al[35]	0.92	0.9–0.99
Costs			
Cost of cfDNA testing	Personal communication	$1,160	$500-$1,500
MRI pancreas, including MRCP	CMS data (2024)	$500 for 60%; $1,125 for 40% Averaged: $750	$500-$1,000

(*Continued*)

Table 1 (Continued).

Clinical Probabilities and Utility Estimates	Description	Baseline	Range
EUS (includes sedation, professional and facility fees, pathology cost)	CMS data (2024)	$1,575 for 60% $3,550 for 40% Averaged: $2,365	$1,500-$3,500
Total preventive pancreatectomy	CMS data (2024)	$80,000	$60,000- $100,000
Initial treatment of PC including diagnostic workup	SEER Cost of Cancer Project[36]	$92,000	$50,000- $150,000
Dying from terminal PC	SEER Cost of Cancer Project[36]	$113,115	$75,000- $150,000
Dying from complication of PC surgery	SEER Cost of Cancer Project[36]	$47,565	$20,000- $80,000
Annual cost of diabetes care after total pancreatectomy	SEER Cost of Cancer Project[36]	$13,139	$3,000-$11,764
Subsequent care after initial treatment of PC annually up to 5 years	SEER Cost of Cancer Project[36]	$17,800	$5,000-$20,000

Abbreviations: CMS refers to the Centers for Medicare & Medicaid Services; MRCP stands for magnetic resonance cholangiopancreatography; MRI stands for Magnetic Resonance Imaging; EUS refers to Endoscopic Ultrasound. cfDNA means cell-free DNA.

if imaging showed a low-risk lesion, EUS-guided fine-needle aspiration (EUS-FNA) was performed. If the EUS-FNA result is negative, EUS would be repeated in 6 months. If a high-risk lesion or cancer were found on surveillance and were confirmed by EUS-FNA, surgery would be performed. All patients enrolled in the surveillance program were considered surgical candidates.

Cost Estimates

Cost data were primarily sourced from the SEER database and the Centers for Medicare & Medicaid Services (CMS), with adjustments made for geographic cost variations (Table 1). We considered direct costs only, adjusted for inflation, and discounted at an annual rate. An inflation rate of 3% and a discount rate of 3% were applied annually.

Clinical Health Outcomes Estimates

Outcomes were measured in quality-adjusted life years (QALYs), with incremental cost-effectiveness ratios (ICERs) calculated considering expected lifetime quality adjustments for the diabetic state and postoperative conditions. The postoperative state was calculated using utility values of short-term states (eg, chronic abdominal pain, medication intake [pancreatic enzyme replacement], and diabetes).[10] Mortality from surgery or cancer was accounted for by assigning a utility value of 0.

Sensitivity and Threshold Analysis

We tested model robustness using sensitivity and threshold analyses to assess the impact of various clinical probabilities and cost factors. A probabilistic sensitivity analysis was conducted in a simulated cohort of 10,000 patients to estimate risk reductions and determine necessary surveillance measures. Sensitivity analysis was performed with the performance characteristics of cfDNA testing and imaging (ie, EUS, MRI, or a combination of both), costs, surveillance interval (ie, every year vs every three years), and surveillance duration. Threshold analysis determined a cost limit beyond which EUS and MRI became cost-effective. Similarly, we calculated an age limit at which surveillance costs exceeded QALYs gained.

Net Health Benefit and Willingness to Pay (WTP)

We assessed cost-effectiveness across a Willingness-to-Pay (WTP) range of $100,000 to $200,000, using net health benefit calculations rather than ICERs.

Statistical Considerations and Other Assumptions

We incorporated half-cycle corrections and assumed diminished follow-up test positivity after an initial negative result. Sensitivity and specificity were considered for cfDNA testing and both EUS and MRI. For pancreatic cancer patients who had advanced disease, treatment costs were limited for 1 or 2 years, followed by death. Expertise was assumed for both procedural and interpretive tasks, and surgeries were restricted to high-volume centers performing the Whipple Procedure, opting for total pancreatectomy to preempt further cancer development. Any discrepancies in the data were resolved through consensus among the authors.

Ethical Considerations

This study was conducted in accordance with the principles outlined in the Declaration of Helsinki. As this research employed computational economic modeling and decision analysis based on previously published aggregate data from the literature, SEER database, and Centers for Medicare & Medicaid Services (CMS), it did not involve direct human participants, identifiable medical records, human tissues, or animal subjects. Therefore, this study was considered exempt from formal institutional review board (IRB) approval under applicable research ethics regulations. All model inputs were derived from publicly available data sources and peer-reviewed published literature.

Results

Baseline analysis of a cohort with new-onset diabetes and an END-PAC score of ≥3 showed that the cfDNA-based surveillance strategy is cost-effective compared to the no-test surveillance strategy, with an ICER of $56,564, which is well below the usual WTP threshold ($100,000-$200,000). Our analysis showed that the cfDNA-based strategy yielded a higher QALE compared to the MRI-based strategy over the no-test strategy. In a direct comparison of the cfDNA-based strategy with MRI-based surveillance, although the MRI-based strategy was less costly, it yielded less QALE. EUS-based surveillance was prohibitively expensive, with an ICER of almost $122 million. cfDNA testing done at entry, without considering the END-PAC score, was absolutely dominated, as it was more expensive and yielded fewer QALYs compared to no surveillance. The results of the baseline cost-effectiveness analysis are shown in Table 2.

Sensitivity and Threshold Analyses

Sensitivity analyses confirm that although the model's results are influenced by the costs and performance characteristics of the tests, the cfDNA-based strategy remains cost-effective within the range documented in the literature. A tornado diagram illustrates that this strategy withstands variations in most modeled parameters. (Figure 2) The age of entry into the model significantly impacts cost-effectiveness, with cfDNA-based surveillance maintaining affordability across a broad age range (40–80 years). Notably, between the ages of 64 and 72, this strategy is unequivocally dominant, both less expensive and more effective. Moreover, the difference between the Net Medical Benefit (NMB) in US dollars of the cfDNA test and the No Test strategy is in the cfDNA test's favor for all ages of entry evaluated (Figure 3).

Table 2 Results of the Baseline Analysis

Category	Strategy	Cost	Incremental Cost	Effectiveness (QALE)	Incremental Effectiveness(QALE)	ICER ($/QALE)	NMB
Undominated	No Testing	$169,861		11.75006			$2,180,150
Undominated	MRI	$170,374	$513	11.79719	0.04713	10,881.00	$2,189,065
Undominated	cfDNA	$170,576	$202	11.80076	0.00357	56,564.00	$2,189,577
Undominated	EUS	$219,964	$49,388	11.80117	0.00040	22,412,529.00	$2,140,269
Abs Dominated	cfDNA-all NOD	$228,226	$8,262	11.79503	−0.00613	−1,347,170.00	$2,130,781

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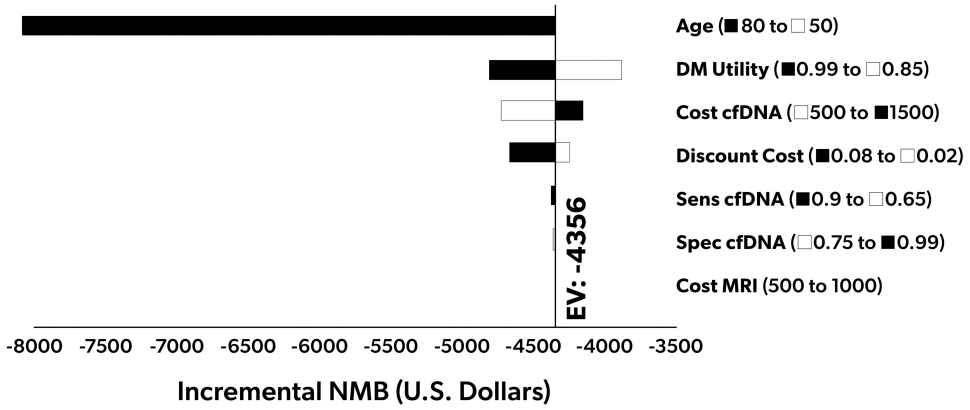

Figure 2 The Tornado diagram illustrates the results of one-way sensitivity analyses using important variables and the range of change in Incremental Net Medical Benefit (NMB) with each variable, with respect to the WTP. Age at entry into the model has the most significant impact on NMB followed by health utility of diabetes and the cost of cfDNA test.

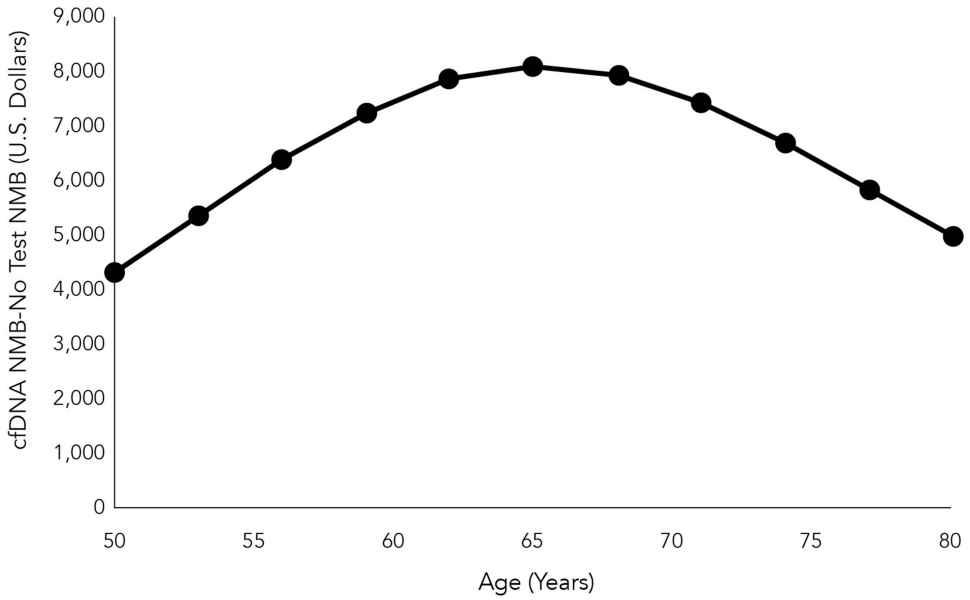

Figure 3 Result of 1-way sensitivity analysis with x-axis showing age at entry into model and y-axis showing corresponding difference between Net Medical Benefit (NMB) in US dollars of cfDNA test and No Test strategy. The surveillance strategy with cfDNA testing consistently yields higher NMB than the No Test strategy, although for both strategies, overall NMB decreases with age at entry.

The two-way sensitivity analysis, which varies the cost of cfDNA and MRI tests, further supports the preference for the cfDNA-based strategy in most scenarios, as illustrated in Figure 4.

A second-order Monte Carlo simulation of a hypothetical cohort of 10,000 patients with new-onset diabetes revealed that the no-surveillance strategy led to 99 pancreatic cancer diagnoses (with only 7.1% resectable) compared to 71 (with 32.4% resectable) in the cfDNA-tested group. Relative to no testing, cfDNA-based surveillance significantly reduced the risk of pancreatic cancer (Relative Risk, RR = 0.71; 95% CI, 0.53–0.97), and the number needed to test to prevent one case was 357 (95% CI, 187–3911). Similarly, for the diagnosis of pancreatic cancer at a resectable stage, with strategy II the estimated RR was 0.73 (95% CI, 0.61–0.86; p =0.002) and the number needed to test was 4 (95% CI, 2.8–6.9).

Strategies II and IV remained cost-effective across various willingness-to-pay values in most simulated scenarios. The acceptability curve from the Monte Carlo analysis (Figure 5) underscores this, showing that Strategy II is cost-effective in a high proportion of simulations based on WTP.

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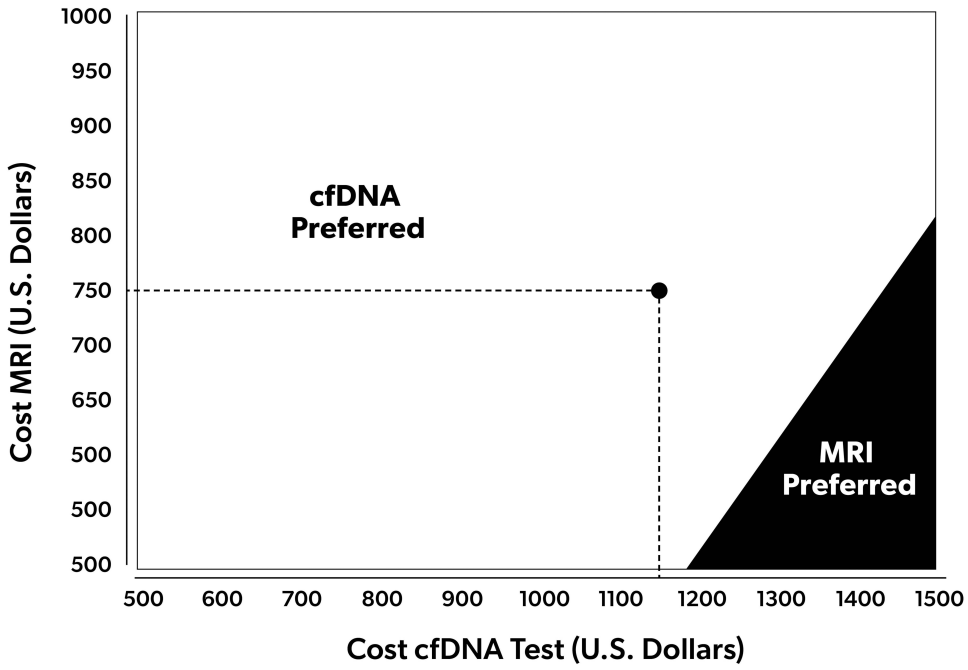

Figure 4 A 2-way sensitivity analysis with the cost of cfDNA testing along the X-axis and the cost of MRI along the Y-axis with the circle representing the point estimates used in the baseline analysis. For a wide range of point estimates, including the baseline scenario, strategy of surveillance with cfDNA testing is preferred over MRI-based surveillance in terms of net benefit.

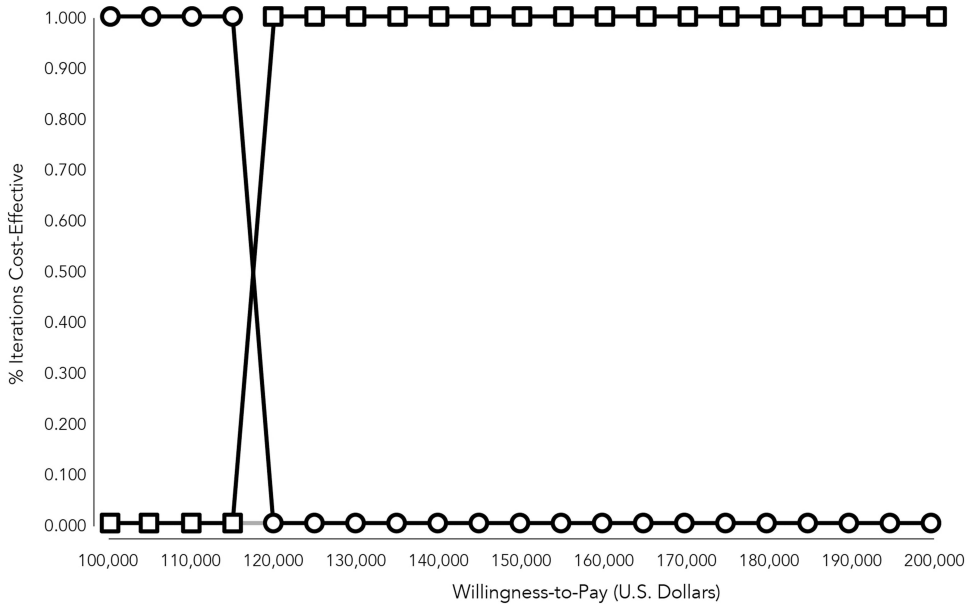

Figure 5 Cost-effectiveness Acceptability graph summarizes the results of the Monte Carlo simulations; above a WTP of approximately $115,000, the majority of the iterations favor the cfDNA-based strategy over the MRI-based strategy. Circles depict NOD surveillance using MRI, Squares depict NOD surveillance using the cfDNA test; the light gray line indicates the No Testing strategy.

Discussion

Risk stratification of NOD patients followed by testing with the cfDNA-based (Avantect®) test represents a powerful approach to improve outcomes in this high-risk population. Previous analyses evaluated imaging modalities to surveil for PC in NOD patients. To our knowledge, the current study is the first to assess the economic and clinical impact of PC testing in the NOD population using a cfDNA epigenomics-based test.

Currently, patients with genetic predisposition or family history of cancer are assessed for PC using imaging modalities, sometimes in conjunction with serum biomarkers.[4] However, NOD patients are not routinely tested for PC. Although imaging is effective, its use in large populations is limited by cost, resource constraints, and access disparities. CA19-9 and CEA are not recommended due to their suboptimal sensitivity and specificity.[11] In contrast, the cfDNA epigenomic test, with its high sensitivity and specificity, is highly effective for detecting PC in its early stages. The noninvasive nature of the cfDNA test also makes it well-suited for use in large patient populations.

This study developed a Markov model to compare several testing strategies, including non-surveillance, surveillance using imaging modalities, and surveillance of NOD patients using a cfDNA epigenomic test. Using criteria from Sharma et al, approximately 20% of the NOD patients were considered to be at higher risk for PC.[20] The baseline analysis shows that the cfDNA-based testing strategy of a risk-stratified NOD cohort is the most cost-effective compared to the standard of care (no testing for PC). cfDNA testing remains the preferred strategy when compared to imaging-based surveillance approaches. Although the MRI-based strategy was slightly lower in cost compared with CMS fee schedule rates (2024 fee schedule), it was a suboptimal strategy since it yielded lower QALYs. This interpretation is further supported when the real-world out-of-pocket cost of the MRCP test ($3,600 to $6,160) is used[37] In the context of NOD, where PC risk increases beginning at age 50 before most individuals in the US qualify for Medicare, this discrepancy becomes particularly important.

Our findings demonstrate that the cfDNA epigenomic test proves cost-effective in NOD patients at higher risk, with an ICER of $56,564 at a WTP of $100,000. Moreover, the model demonstrates the significant clinical utility of cfDNA testing in NOD patients. In a cohort of 10,000 NOD patients, a no-surveillance approach would identify only 1% of pancreatic cancer cases, with just 7.1% eligible for potentially curative surgery. In contrast, cfDNA testing is predicted to detect 71 cases of pancreatic cancer, with 32.4% of those patients eligible for surgical resection.

Two previous studies have been published on the economics of testing NOD patients for PC[38,39] Schwartz et al reported their findings using the END-PAC PC risk model to risk-stratify NOD patients. The authors developed an integrated decision tree and Markov state-transition model to evaluate the cost-effectiveness of PC testing in patients aged 50 years or older with NOD using CT imaging versus no testing[38] Their analysis predicted a cost per QALY gained of under $50,000 and under $100,000 in 34% and 99% of the simulations, respectively.[38]

Wang and collaborators compared PC early detection strategies targeting NOD patients aged ≥50 years at various minimal predicted PC risk thresholds (0.5% to 5.0%) vs standard of care in a Markov state–transition decision model. The authors utilized the risk stratification model published by Boursi et al to define risk thresholds within the model population.[40] In Wang et al's approach, the patients deemed to be at high risk underwent one-time diagnostic testing with abdominal MRI/magnetic resonance cholangiopancreatography (MRCP), and those with positive MRI underwent EUS/fine-needle aspiration (FNA). The low-risk group did not receive PC early detection testing (standard of care). The authors concluded that, at a WTP threshold of $150,000 per quality-adjusted life-year, the early detection strategy targeting patients with a minimum predicted 3-year PC risk of 1% was cost-effective, with an ICER of $116,911. At a WTP threshold of $100,000 per quality-adjusted life year, the early detection strategy at the 2% risk threshold was cost-effective (ICER: $63,045).

Findings from both studies agree that PC testing of NOD patients within three years of diabetes diagnosis can be cost-effective if testing is done in NOD patients at a higher risk for PC.

In contrast to the studies by Schwartz et al, which utilized contrast CT scans, and Wang and collaborators, which employed MRCP as the primary surveillance modality in high-risk patients, our study evaluated a cfDNA epigenomic test for surveillance purposes. Despite differences in the surveillance tests, all three studies employed broadly comparable methodologies, model input estimates, and assumptions. Each study reached similar conclusions, ie, (1) a risk-stratified PC surveillance strategy is cost-effective in patients with NOD and (2) there is clear clinical utility by enabling earlier detection and intervention. Notably, the cfDNA blood test-based surveillance was found to be significantly more cost-effective, with an ICER of only $56,564, compared to $65,076 for contrast CT imaging (Schwartz) and $116,911 per QALY for MRCP-based surveillance (Wang).

Implications and Future Directions

According to the Centers for Disease Control and Prevention (CDC), over 1.2 million individuals receive a new T2D diagnosis each year, with over 75% of them aged 45 years or older.[27] Based on our model, a significant number of these individuals could benefit from pancreatic cancer surveillance.

The United States Preventive Services Task Force (USPSTF; 2019) recommends against surveillance for PC in the general population[28] The USPSTF explicitly recommends against testing NOD patients for PC[28] However, this recommendation is based primarily on the assumption that there is no sensitive and accurate test amenable to use in a large number of at-risk individuals. The availability of non-invasive, sensitive, and accurate testing modalities, such as the cfDNA test, is expected to have a significant impact during the next round of evidence evaluation by the USPSTF. This would be a welcome development, as evidence accumulated for the last 15 years shows that NOD patients are at a significantly higher risk of PC compared to the general population.[2] This change in surveillance recommendations would be expected to have a substantial impact on the stage of detection and survival, as demonstrated by recently published data on the impact of active surveillance of individuals at high-risk for pancreatic cancer due to genetic predisposition and/or family history.[9]

Our study has inherent limitations. In the absence of published long-term health outcomes data on patients with NOD and PC detected by surveillance, we relied on data from surveillance programs targeting genetically predisposed high-risk individuals. Despite these limitations, our economic analysis also possesses several methodological strengths. To address the inherent uncertainty in the validity of input parameters, we conducted a comprehensive search of all published data. We used the most plausible range of estimates for sensitivity analyses. Furthermore, we employed advanced second-order Monte Carlo simulation techniques to account for these uncertainties, simulating real-life clinical practice and deriving robust statistical measures of effectiveness, such as relative risk and number needed to treat (NNT). We also applied the concepts of incremental net health benefit and willingness to pay, which are considered more appropriate indicators of cost-effectiveness than the ICER in analyses from a third-party payer perspective.

This analysis indicates that cfDNA epigenomic testing of risk-stratified NOD patients within three years of diabetes diagnosis is cost-effective and predicts strong clinical utility. Surveillance strategies employing a cfDNA-based test (Avantect®) offer a compelling, non-invasive alternative for monitoring patients with NOD at risk for pancreatic cancer, providing the potential for early detection and improved clinical outcomes.

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Disclosure

Dr Adrian Vilalta was paid by ClearNote Health to lead the data analysis and to write the manuscript. Dr Ananya Das reports consulting fees from ClearNote, during the conduct of the study. Dr Michael Wallace reports personal fees from ClearNote, during the conduct of the study.

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