Enriching New-onset Diabetes for Pancreatic Cancer (ENDPAC): external validation using English sentinel network

Claire A Price, Hugh Claridge, Simon de Lusignan, Natalia Khalaf, Freda Mold, Nadia AS Smith, Martyn Winn and Agnieszka Lemanska

Abstract

Background

Pancreatic cancer has a very low survival rate due to late diagnosis. Symptoms are often non-specific, thereby complicating early detection in primary care. The Enriching New-onset Diabetes for Pancreatic Cancer (ENDPAC) algorithm uses weight change, glycaemic control, and age at diabetes onset to identify patients with new-onset diabetes (NOD) who are at increased risk of pancreatic cancer. It was developed in the US and has not been validated in the UK.

Aim

To validate ENDPAC in a UK primary care population and assess its predictive utility.

Design & setting

Retrospective cohort study using ORCHID, a national primary care sentinel network.

Method

Adults aged ≥50 years with NOD, requisite glycated haemoglobin (HbA1c), and weight data were included. ENDPAC scores were calculated and model performance was evaluated via discrimination, calibration, sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV). The Youden index identified optimal cut-offs. Sensitivity analyses were used to assess measurement timing, repeat HbA1c testing, and multiple values.

Results

Among 70 050 individuals, 185 (0.26%) developed pancreatic cancer. These people were older, and had higher HbA1c and greater weight-loss levels at diagnosis than those who did not develop pancreatic cancer. ENDPAC achieved an area under the curve of 0.734. An optimal ENDPAC score cut-off of ≥3 classified 27.8% of individuals as high risk, with 62.6% sensitivity, 72.5% specificity, 0.6% PPV, and 99.9% NPV. Sensitivity analyses showed similar performance across measurement windows and handling of multiple values.

Conclusion

ENDPAC shows moderate discrimination in UK primary care. Although it had a relatively low PPV, integration into routine systems as part of a sequential diagnostic pathway could provide scalable, low-cost, automated risk stratification, thereby identifying people with NOD who are at a higher risk of developing pancreatic cancer.

Keywords

early diagnosis; pancreatic cancer; routine healthcare data; general practice; primary health care; algorithms.

Introduction

Pancreatic cancer is often a devastating disease due to its high mortality rate and a very low 5-year survival rate of 3%–15%.[1–6] It has been reported as being the 14th most common cancer globally and accounting for 3% of all new cancer cases in 2020, with nearly half a million cases worldwide.[7] The high mortality of pancreatic cancer means that it is the fifth major cause of cancer mortality in the UK.[8]

The need for prompt diagnosis and early detection of pancreatic cancer is widely recognised.[9–11] Early detection is the focus of a recent NHS drive to improve current very low survival rates;[12] although, even with improved detection, advances in treatments will also be required to improve survival.[13] There are currently no widely available screening or biomarker tests for pancreatic cancer and diagnosis depends on presentation with symptoms to a GP. This is challenging as a full-time GP will only see one case every 5 years,[14] and especially difficult as pancreatic cancer often presents with non-specific symptoms. Symptoms also vary between patients, making diagnosis challenging for clinicians;[14–16] therefore, it is vital to provide GPs with innovative and practical ways to facilitate early detection. This includes data-driven approaches to flag for further investigation those people who are at high risk of having pancreatic cancer.

How this fits in

Pancreatic cancer is often a devastating disease that is hard to diagnose. The Enriching New-onset Diabetes for Pancreatic Cancer (ENDPAC) algorithm has been developed in the US to help clinicians identify people at risk of having undiagnosed pancreatic cancer. These people can be referred for an imaging investigation to diagnose or rule out cancer. This study validated ENDPAC using UK primary care data, which is an important first step to enabling it to be utilised in clinical practice in the UK. ENDPAC showed moderate discrimination for pancreatic cancer among people with new-onset diabetes in UK primary care but most people classified as high risk did not have the disease. It is therefore suited to risk enrichment within a staged diagnostic pathway and not to use as a stand-alone indication for referral.

People aged ≥50 years with new-onset diabetes (NOD) have the highest risk of developing non-familial — also known as sporadic — pancreatic cancer.[17,18] Diabetes is a recognised risk factor[19–21] and 30%–65% of patients with pancreatic cancer develop diabetes.[22–26] The risk of developing pancreatic cancer is greatest within 3 years of NOD, at ~1%,[18,27] which represents a 6–8-fold increase on the risk for the general population.[17,18,28,29] These facts led to the development of a simple, but promising, data-driven algorithm for the earlier detection of pancreatic cancer in the US. The Enriching New-onset Diabetes for Pancreatic Cancer (ENDPAC) algorithm[20] uses changes in weight and blood-glucose levels to calculate someone's risk of developing pancreatic cancer. The aim of the algorithm is to increase or 'enrich' the probability of finding individuals who are at high risk of developing pancreatic cancer in the larger population of people with NOD. ENDPAC's clear clinical rationale means that it is easily explainable to GPs and primary care teams, as well as patients. Its relative simplicity and use of measures that are routinely collected in primary care could make ENDPAC well suited for implementation in the UK primary care setting.

One marked advantage of ENDPAC is that it targets early detection as it is based on glucose and weight changes; in contrast, other data-driven risk assessment algorithms[15,19,30–36] incorporate symptoms such as back pain and jaundice, which typically manifest in the later stages of pancreatic cancer. Given that pancreatic cancer is often diagnosed too late for treatment to be effective, leading to high mortality rates, the ability of ENDPAC to identify cases earlier in the disease progression trajectory could potentially save lives. Furthermore, ENDPAC stands out for its use of a relatively small number of routinely collected measurements, thereby addressing concerns about data availability that arise with other algorithms.

Data-driven algorithms, such as electronic risk assessment tools (eRATs) and QCancer,[37,38] are showing promise in aiding clinical decisions and expediting referrals.[39–41] Before ENDPAC can be added to these tools in clinical practice, it requires validation in the UK. As ENDPAC was developed in the US, validation in the UK is necessary due to notable differences between the healthcare systems and measurement standards for healthcare records of the two countries.[42–45] Furthermore, previous validations of ENDPAC[35,46,47] have also included secondary care data. Validation of the ENDPAC algorithm is also necessary for its application in UK primary care due to how blood glucose is commonly recorded: ENDPAC was developed in the US using fasting blood-glucose levels but, in UK primary care, glycated haemoglobin (HbA1c) is recorded and used to diagnose diabetes. As such, validation that is specific to primary care settings in the UK is essential to ensure the algorithm's suitability for use with such data.

This study aimed to validate the ENDPAC algorithm using UK primary care data.

Method

Study design and data source

This retrospective cohort study involved data on adults who had NOD between January 2006 and December 2017. They were followed up for 3 years after their first elevated HbA1c reading. The authors used 2006 as the beginning of the study period because coding of metabolic markers, such as weight and HbA1c, in primary care improved significantly from 2004 with the introduction of the Quality and Outcomes Framework and the pay-for-performance incentive scheme.[48,49] The 2006 cut-off was set to improve data completeness for at least 2 years before the index date (defined below). As the dataset was censored in May 2021, using 2017 as the end of the study period ensured that 3 years' follow-up data were available for each participant.

Data from the Oxford Clinical Informatics Digital Hub (ORCHID) database was used (https://healthdatagateway.org). This is a nationally representative database[50] that downloads electronic healthcare records from GP practices that belong to the Oxford-RCGP Research and Surveillance Centre. The network comprises 1800 practices (27.2% of the 6609 GP practices in England in May 2021[51]) serving >15 million people. In May 2021,

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using the Systematised Nomenclature of Medicine Clinical Terms (SNOMED CT) system,[52] the authors curated a cohort of people with NOD. A dataset was extracted that included demographic information, age at diagnoses of diabetes and pancreatic cancer (where present), as well as all measurements of weight and HbA1c as recorded in 2001 or later.

Diabetes status

In the UK, two elevated glycaemic values are required to diagnose diabetes; however, in this study — as in other ENDPAC studies[35,46,47] — NOD was defined using the first elevated HbA1c (≥48 mmol/mol) measure. The date of this HbA1c data was set as the index date for the study and encompasses new-onset biochemically defined hyperglycaemia and diabetes (glycaemic onset). In the UK, glycaemic control is most commonly measured with HbA1c in mmol/mol,[53] so those tests and units were utilised in this study.

ENDPAC

The authors replicated the ENDPAC model,[20] which combines age at NOD with changes in blood glucose and weight over the year before NOD to produce a risk score for developing pancreatic cancer. The final ENDPAC score was calculated using three sub-scores: A (Δ blood-glucose category) + B (Δ weight category) + C (age category at diabetes diagnosis, Table 1). The total ENDPAC score was then categorised as one of three outcomes: low (≤0), intermediate (1-2), or high risk (≥3) of having pancreatic cancer.

Study cohort

Study participants were aged ≥50 years, who had NOD diagnosed between 2006 and 2017. Eligible patients were required to have:

- an HbA1c reading of ≥48 mmol/mol at the index date, preceded by at least one HbA1c reading of <48 mmol/mol in the previous 3–24 months;
- no HbA1c reading of ≥48 mmol/mol before the index date;
- no history of pancreatic cancer before the index date;
- weight documented on the index date (±30 days); and
- weight documented prior to the index date (between 10 years and 3 months prior).

If multiple readings for weight or HbA1c readings were available, the flowchart by Sharma *et al*[20] was followed to select the readings that should be used to calculate the ENDPAC score.

Statistical analysis

Descriptive statistics. Baseline demographic statistics (sex, ethnicity, and Index of Multiple Deprivation [IMD] quintile) were analysed with descriptive statistics, means ± standard deviations (SDs), counts, and percentages. All counts were rounded to the nearest five as per the rules of statistical disclosure.

Predictors. The study included three risk factors, as defined by the ENDPAC model. These were: age at index date, change in body weight (kg), and change in HbA1c (mmol/mol).

Outcome identification. The outcome was the diagnosis of pancreatic cancer within 3 years after the index date. Pancreatic cancer diagnosis was defined based on the SNOMED CT clinical coding system, using the code 363418001 for malignant tumour of pancreas (disorder) and all sub-codes, excluding codes related to cancers that have metastasised to the pancreas (94164003, 94212002, 94325008, 94354002, 94459006, 94460001, 94618007, and 285614004).[52]

Missing data. This study was a validation of the ENDPAC model. ENDPAC scores were only calculated for people who had the required information (complete cases).

Model validation. The positive predictive value (PPV), negative predictive value (NPV), sensitivity, and specificity were calculated for ENDPAC scores from ≤0, through 1 to 5, and ≥6. The percentage to be referred for further investigation at each score was calculated as the number of people with a score greater than or equal to the score divided by the whole cohort population multiplied by 100.

Calibration (predicted probability matches with observed outcomes) was assessed using calibration plots of the slope of the observed proportion of events against the predicted risk. The model's discrimination (ability to distinguish between those with and without pancreatic cancer) was assessed by area under the receiver operating characteristic curve (AUC).

The optimal ENDPAC cut-off value (set to identify people at high risk of pancreatic cancer, previously set at ≥3 during model derivation) was determined, using the Youden index, which maximises both the sensitivity and specificity of the model.[54] The performance of the model was compared with other published models for the detection of pancreatic cancer using the χ^2 test for the models' sensitivity and specificity. To account for multiple comparisons, statistical significance was set at $P<0.01$.

Subgroup analyses

Risk-score stratification was utilised to explore the differences in cancer rates between the risk-score categories (low, intermediate, and high risk). Model sensitivity was also investigated for different time windows before the index date (3 to <6 months, 6 to <9 months, 9 to <15 months, 15 to <18 months, 18 to <21 months and 21 to <24 months) of HbA1c measurements and for the same windows plus an additional window of 24 months to 10 years for weight measurements. Sensitivity analysis was conducted to investigate whether the predictions changed when using the highest, lowest, or mean readings where multiple weight or HbA1c readings were available. The effect of using a single elevated HbA1c reading as the definition of diabetes, instead of requiring people to have a second HbA1c reading within 90 days, was also investigated.

Software and reproducibility

The database was managed in Structured Query Language Server Management Studio (version 18.9.1). Data analyses were conducted using RStudio (version 2023.03.0+386, code-named 'Cherry Blossom').

Results

A total of 70 050 people from 669 GP practices met the inclusion criteria.

Table 1. ENDPAC score parameters with blood-glucose (HbA1c) categories equivalent to fasting blood-glucose categories[a]

FBG categories, mg/dl, BG range	HbA1c BG categories, mmol/mol, BG range	Score	Δ BG category score (NOD score – 1 year score): A
BG category at ~1 year			+1–+4
<100	<42	1	
≥100–<110	≥42–<44	2	
≥110–<126	≥44–<48	3	
BG category at glycaemically defined NOD			
≥126–<160	≥48–<60	4	
≥160	≥60	5	
Δ Weight category, kg			**Δ Weight score: B**
≤–6.0		+6	–6–+6
>–6.0–≤–4.0		+4	
>–4.0–≤–2.0		+2	
>–2.0–<+2.0		0	
≥+2.0–<+4.0		–2	
≥+4.0–<+6.0		–4	
≥+6.0		–6	
Age at glycaemically defined NOD, years			**Age score: C**
<60		-1	–1–+1
≥60–<70		0	
≥70		+1	
Total score			**A+B+C**

[a]Based on American Diabetes Association blood–glucose levels for healthy, prediabetes, diabetes, and uncontrolled diabetes. Table adapted from Sharma et al.[20] BG = blood–glucose. Δ = change in measurement. FBG = fasting blood glucose. HbA1c = glycated haemoglobin. NOD = new-onset diabetes.

Figure 1 illustrates how the final cohort was reached. Participants in the final cohort had a mean age of 68 years (SD 9.9 years) and 57.2% were male (Table 2). Pancreatic cancer occurred in 185 (0.26%) individuals.

Table 2 summarises the demographic and clinical characteristics of the whole cohort and, separately, those participants with and without pancreatic cancer. Participants with pancreatic cancer were older at the index date than those without: 72.4 years (SD 8.4 years) versus 68.0 years (SD 9.9 years), respectively (P<0.001). They also had a higher HbA1c reading at the index date (57.0 mmol/mol [SD 15.8 mmol/mol] versus 53.2 mmol/mol [SD 9.2 mmol/mol], P<0.001), and a greater HbA1c increase from before the index date (mean increase of 13.5 mmol/mol versus 9.0 mmol/mol), lower weight at the index date (82.1 kg [SD 19.8 kg] versus 88.0 kg [SD 19.9 kg], P<0.001), and greater weight loss (mean change of –2.5 kg versus +1.2 kg).

Table 3 presents ENDPAC sub-scores for age, HbA1c readings, weight, and total scores at the index date for the whole cohort, as well as for participants with and without pancreatic cancer. ENDPAC scores were significantly higher in participants with pancreatic cancer than those without (4.10 [SD 3.57] versus 1.04 [SD 3.34], P<0.001), with a striking difference in a higher weight sub-score (1.61 [SD 3.28] versus –0.77 [SD 3.10], P<0.001).

The AUC of the ENDPAC model (Figure 2a) was 0.734. Calibration plots showed a slope of 0.256, intercept of -0.003, and a Brier score of 0.265 (Figure 2b). When calibration plots were repeated around decision thresholds only, the metrics were largely unchanged (slope of 0.27, intercept of -0.004 and Brier score of 0.249) (data not shown).

Table 4 presents the numbers of participants at each ENDPAC score, sensitivity, specificity, PPV, and NPV. The proportion of individuals from the whole cohort that would be flagged as requiring referral for cancer investigation if the score was used as the cut-off for high risk is also presented, as well as the Youden index used to define the optimal cut-off. The highest number of participants — 29 240 people (41.7%) — had an ENDPAC score of ≤0 and, using cut-offs from the original model derivation, would be classified as low risk. A total of 21 315 people (30.4%) had ENDPAC scores of 1 and 2, and would be classified as intermediate risk; 19 500 people (27.8%) had ENDPAC scores of ≥3 and would be classified as high risk. The Youden index was the highest at 0.35 for ENDPAC score 3, identifying this as the optimal threshold and confirming it as the cut-off for high risk; this level achieved a sensitivity of 62.6%, specificity of 72.5%, a PPV of 0.6%, and an NPV of 99.9%. Using this threshold, 27.8% of individuals would have an ENDPAC score of ≥3 and would be referred for further investigation for pancreatic cancer. This is equivalent to roughly 29 referrals per practice over the 12-year study period, or approximately two to three referrals per practice per

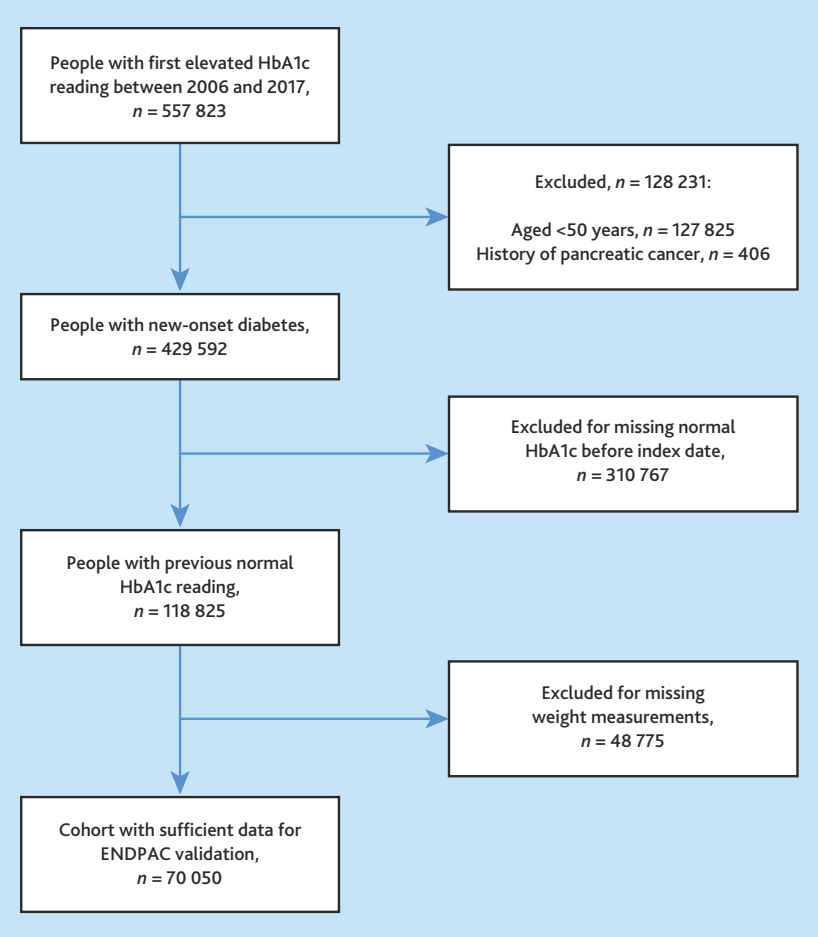

Figure 1. CONSORT flowchart diagram of cohort population. ENDPAC = Enriching New-onset Diabetes for Pancreatic Cancer. HbA1c = glycated haemoglobin.

year. If data completeness increases (for example, through routine recording of weight and/or HbA1c levels), these referral numbers are likely to increase.

The mean time after the index date to pancreatic cancer diagnosis was 416 days (SD 308 days; median 379.5 days; interquartile range 145.25–669.25 days). Of these cases, 25 (13.5%) occurred in the low-risk group, 40 (21.6%) in the intermediate-risk group, and 120 (64.9%) in the high-risk group. The prevalence of pancreatic cancer in the high-risk group was 0.6%, representing a 2.2-fold enrichment from the whole cohort prevalence of 0.26% (Table 4).

Sensitivity analysis

Measurement lead times. The majority of people had HbA1c (n = 41 615, 59.4%) and weight (n = 40 845, 58.3%) readings taken in the 9–15 months before the index date (see Supplementary Table S1). Sensitivity was highest when HbA1c measurements were taken 9–15 months pre-index (65.1% sensitivity; 75.6% specificity). For weight readings, sensitivity was highest for readings taken 18–21 months pre-index (66.7%; specificity 84.2%).

Second elevated HbA1c within 90 days. Of the 70 050 people, 11 110 (15.9%) had a second elevated HbA1c reading within 90 days of their first elevated result; 55 of these individuals (0.5%) were diagnosed with pancreatic cancer. When the analysis was restricted to this subgroup, the model's AUC was 0.741 and was not statistically significantly different from the main model (P = 0.76). The optimal cut-off identified by the Youden index (0.37) was an ENDPAC score of 4, yielding a sensitivity of 61.1%, specificity of 76.3%, PPV of 1.2%, and NPV of 99.8%. For comparison, using the whole cohort cut-off of 3 for this subset of people yielded a sensitivity of 68.5%, specificity of 68.8%, PPV of 1.1%, and NPV of 99.8% (data not shown).

Multiple HbA1c values. After selecting HbA1c readings according to the time windows specified in Sharma *et al*,[20] 1255 (1.8%) people had multiple eligible HbA1c readings. When the analysis was repeated using different approaches to these multiple values, the AUCs were nearly identical and not statistically significantly different (P = 0.97): 0.734 when using the highest HbA1c, 0.732 when using the lowest, and 0.732 when using the mean. The Youden index (0.35 for all analyses) identified an optimal cut-off of 3 across all approaches. At this cut-off, the three models produced the same sensitivity (62.6%), PPV (0.6%), and NPV (99.9%), with specificity differing marginally (72.5%, 72.1%, and 72.3%, respectively) (data not shown).

Comparison with other models. The χ^2 test comparing AUCs showed no statistically significant difference between the results of our study and those obtained for ENDPAC in other cohorts (see Supplementary Table S2). However, when compared with other models, significant differences in the AUC were observed for the studies by Boursi *et al*[32] (P<0.001) and Malhotra *et al*[19] (P = 0.002).

Although the QCancer (Pancreas)[14] model did not differ significantly from ENDPAC in terms of sensitivity (P = 0.93), there was a significant difference in specificity and AUC (P<0.001). QCancer (Pancreas) had higher specificity and AUC, indicating potentially increased accuracy; however, it also utilised imputation for missing data, so may not reflect a clinically meaningful difference. Insufficient data were available to compare sensitivity and specificity for other models (data not shown).

Discussion

Summary

In this large, nationally representative UK primary care cohort of >70 000 adults with NOD, the ENDPAC model was validated and performance was found to be consistent with previous studies.[35,46,47] ENDPAC demonstrated moderate discrimination, supporting its role as a risk-stratification aid rather than a standalone screening

Table 2. Summary of demographics and clinical characteristics for the whole cohort, and separately for participants with and without pancreatic cancer[a]

Characteristic	Whole cohort, *N* = 70 050	People with pancreatic cancer, *n* = 185	People without pancreatic cancer, *n* = 69 865	*P*-value[b]
Age, years, mean (SD)	68.0 (9.9)	72.4 (8.4)	68.0 (9.9)	<0.001
Sex, *n* (%)				0.66
Female	29 975 (42.8)	75 (40.5)	29 900 (42.8)	
Male	40 075 (57.2)	110 (59.5)	39 965 (57.2)	
Ethnicity, *n* (%)				0.057
Asian	3670 (5.2)	5 (2.7)	3670 (5.3)	
Black	1760 (2.5)	5 (2.7)	1750 (2.5)	
Mixed	360 (0.5)	5 (2.7)	360 (0.5)	
Other	330 (0.5)	5 (2.7)	330 (0.5)	
White	54 220 (77.4)	140 (75.7)	54 090 (77.4)	
Missing	9710 (13.9)	40 (21.6)	9670 (13.8)	
Index of Multiple Deprivation quintile, *n* (%)				0.52
1 (most deprived)	13 035 (18.6)	30 (16.2)	13 010 (18.6)	
2	13 240 (18.9)	40 (21.6)	13 200 (18.9)	
3	13 975 (20.0)	35 (18.9)	13 940 (20.0)	
4	14 205 (20.3)	45 (24.3)	14 165 (20.3)	
5 (least deprived)	13 355 (19.1)	35 (18.9)	13 315 (19.1)	
Missing	2240 (3.2)	10 (5.4)	2235 (3.2)	
HbA1c at index date, mmol/mol, mean (SD)	53.2 (9.3)	57.0 (15.8)	53.2 (9.2)	<0.001
HbA1c before index date, mmol/mol, mean (SD)	44.2 (3.0)	43.5 (3.2)	44.2 (3.0)	0.003
Body weight at index date, kg, mean (SD)	88.0 (19.9)	82.1 (19.8)	88.0 (19.9)	<0.001
Body weight before index date, kg, mean (SD)	86.8 (19.1)	84.6 (20.1)	86.8 (19.1)	0.13

[a]All counts were rounded to the nearest five to comply with the rules of statistical disclosure. Percentages are calculated from the rounded counts and the column totals shown, so rounded counts may not sum to the column totals. [b]P-values were calculated from the unrounded data using Welch t-tests for continuous variables and χ^2 tests for sex and Index of Multiple Deprivation. A Fisher-Freeman-Halton exact test was used for ethnicity because expected counts were <5 in several cells. HbA1c = glycated haemoglobin. SD = standard deviation.

or diagnostic tool.[55] However, PPV was relatively low and calibration was poor, with a shallow slope indicating overestimation of absolute risk. Sensitivity analyses showed robust performance across HbA1c measurement timing, handling of multiple values, and paired hyperglycaemic readings.

The baseline prevalence in the cohort (0.26%) was lower than in prior validation studies (0.7% to 0.8%),[35,46,47] although a similar 2.2-fold enrichment was observed. Consequently, the PPV was lower, reflecting either a lower underlying population incidence or how cancers are reported in primary care.[56] However, ENDPAC effectively increased or enriched risk prediction, increasing the probability of finding individuals with NOD who are at high risk of having pancreatic cancer. Individuals with a score of ≥3 accounted for 62.2% of cancer cases, which more than doubled the prevalence compared with the overall cohort of people with NOD, equating to an expected two to three additional referrals per practice annually.

Strengths and limitations

A key strength of this study is the use of a large, nationally representative primary care dataset, enabling real-world evaluation of ENDPAC; the study represents the largest validation of ENDPAC and is reflective of data available in the UK primary care system. Inclusion of practices within a vetted research network ensures high data quality.[49] Defining NOD using HbA1c minimises misclassification and reflects real-world practice, as many people lack a confirmatory reading within 90 days.[57] Comprehensive sensitivity analyses demonstrated robust and consistent discrimination across measurement timing and multiple values. Stratified analyses further allowed for an evaluation of performance across patient sub-groups, informing a potential refinement of risk thresholds.

Limitations include incomplete and opportunistic recording of weight and HbA1c, with variable measurement intervals that may particularly affect the weight-loss component. Pancreatic cancer diagnoses were extracted from primary care records, rather than cancer registry linkage, thereby potentially missing or miscoding cases,[58–60] although primary care generally receive reliable cancer notifications.[61] Calibration was limited, which is expected in low-prevalence settings, where limited event counts can constrain the reliability of calibration assessment, particularly in external validation contexts.[62,63] However, a model with good discrimination may retain clinically useful ranking ability, even in the presence of imperfect calibration.[64]

Additionally, some patients may present with advanced diabetes, as the disease is frequently undiagnosed: ~2% of UK adults have undiagnosed diabetes, and 30% of cases of diabetes remain undiagnosed.[65] This limits the window for early cancer detection. The absence of cancer-staging data also prevented assessment of performance in early versus late disease. As with

Table 3. Mean ENDPAC scores and sub-scores with statistical significance (*P*-value) of the difference between people with and without pancreatic cancer

	ENDPAC score and sub-score, mean (SD)			
Sub-score category	Whole cohort, *N* = 70 050	People with pancreatic cancer, *n* = 185	People without pancreatic cancer, *n* = 69 865	*P*-value
Age	0.22 (0.79)	0.59 (0.63)	0.21 (0.79)	<0.001
HbA1c	1.59 (0.83)	1.89 (0.94)	1.59 (0.83)	<0.001
Weight	-0.76 (3.11)	1.61 (3.28)	-0.77 (3.10)	<0.001
Total	1.04 (3.35)	4.10 (3.57)	1.04 (3.34)	<0.001

ENDPAC = Enriching New-onset Diabetes for Pancreatic Cancer. HbA1c = glycated haemoglobin. SD = standard deviation.

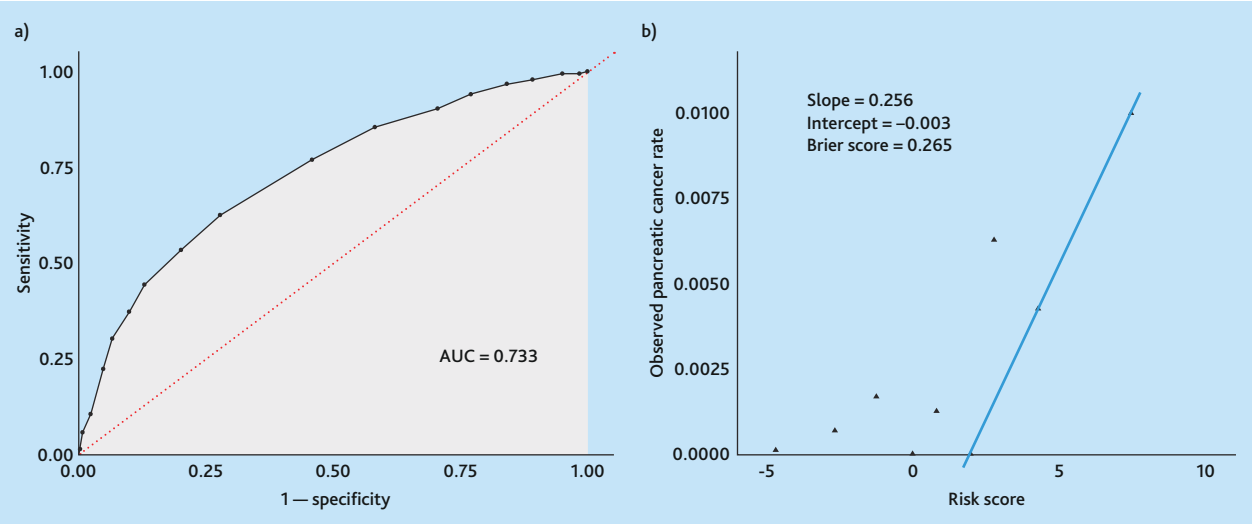

Figure 2. Model performance plots: a) area under the receiver operating characteristic curve; and b) calibration plot. Triangles show the observed proportion of people diagnosed with pancreatic cancer within groups of ENDPAC risk score and the blue line is the fitted calibration line.

Table 4. People with an ENDPAC score, sensitivity, specificity, PPV, NPV, and percentage of the whole cohort who would require referral if the score was used as the cut-off for individuals at high risk of having pancreatic cancer (*N* = 70 050)[a]

Risk score	People, *n* (%)	People to be referred if ENDPAC score used as cut-off, *n* (%)	Pancreatic cancer cases, *n* (%), *n* = 185	Sensitivity, %	Specificity, %	PPV, %	NPV, %	Youden index
≤0	29 240 (41.7)	[b]	25 (13.5)	14.4	58.2	9.23	99.5	0.20
1	8595 (12.3)	40 815 (58.3)	15 (8.1)	85.6	41.7	0.39	99.9	0.27
2	12 720 (18.2)	32 220 (46.0)	25 (13.5)	77.0	53.9	0.45	99.9	0.31
3[c]	**5410 (7.7)**	**19 500 (27.8)**	**15 (8.1)**	**62.6**	**72.5**	**0.60**	**99.9**	**0.35**
4	5030 (7.2)	14 090 (20.1)	15 (8.1)	53.5	79.9	0.71	99.8	0.33
5	2030 (2.9)	9060 (12.9)	15 (8.1)	44.4	87.1	0.92	99.8	0.32
≥6	7030 (10.0)	7030 (10.0)	70 (37.8)	37.4	90.0	1.00	99.8	0.27

[a]Counts were rounded to the nearest five for statistical disclosure control and may therefore not sum to the column totals (n = 70 050 people and n = 185 cancer cases). [b]As the table is truncated with scores of ≤0 grouped together, a percentage of people to be referred cannot be calculated as this would include the whole cohort. [c]The optimal cut-off of ≥3 (as determined by the highest Youden index) is highlighted in bold. ENDPAC = Enriching New-onset Diabetes for Pancreatic Cancer. NPV = negative predictive value. PPV = positive predictive value.

all retrospective analyses, selection and information bias are possible.

Comparison with existing literature

Consistent with the original derivation study,[20] an ENDPAC score of ≥3 identified patients at high risk of developing pancreatic cancer. Performance metrics aligned with prior work,[35,46,47] showing modest discrimination with AUCs between 0.70 and 0.75, and a modest PPV of between 1.7% and 2.6%. This supports ENDPAC's transportability across health systems and its reproducibility and risk-enrichment capability. Routine longitudinal metabolic changes may, therefore, function as practical, low-cost, early detection signals for pancreatic cancer, with a high score identifying individuals who are at risk several months prior to clinical presentation.[20] However, heterogeneity in sensitivity, specificity, and optimal cut-off across populations (for example, the validation by Khan *et al*[46] reports an optimal cut-off of >1) highlights the importance of validation and calibration for each population.[55,66]

As observed in prior studies,[35,46,47] low pancreatic cancer prevalence limits PPV. This reflects a fundamental epidemiological constraint: even in enriched populations, most flagged individuals will not develop cancer. This highlights the limitations of population-level screening based solely on NOD status, limiting the clinical utility of the model as a stand-alone screening tool. Nonetheless, the present results support the potential role of ENDPAC as a risk-enrichment tool within a multi-step diagnostic pathway, helping clinicians prioritise a subset of patients with NOD for further investigation, who may have pancreatogenic hyperglycaemia that is otherwise difficult to recognise in primary care.[14,67]

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ENDPAC has the advantage of simplicity, relying on just three routinely recorded variables. Other models[15,19,31–34,36] achieve comparable AUCs but differ in sensitivity and specificity, illustrating trade-offs between false positives and false negatives. They also often require additional data inputs that may limit feasibility of use in routine practice. ENDPAC also differs from models such as QCancer (Pancreas),[15] which uses cross-sectional symptoms, demographics, and comorbidities to flag undiagnosed pancreatic cancer at the population level. In contrast, ENDPAC operates within a higher-risk NOD population, improving pre-test probability but limiting applicability to non-NOD presentations. These approaches are therefore complementary: population-level models support broad triage, while ENDPAC enriches risk within a clinically defined high-risk subgroup.

Other approaches, such as those by Clift *et al*[68] and the UK Biobank,[69] suggest that combining clinical, biochemical, and genetic data may improve risk stratification. However, missing data remain a challenge across all modelling strategies, particularly in routinely collected datasets where information is generated for clinical rather than research purposes.[70,71] While multiple imputation is often recommended, complete-case analysis remains common in external validation due to concerns about transportability of imputation models.[64,72] For ENDPAC, imputation has shown minimal benefit[73] and may introduce additional uncertainty.

Even with the parsimony of ENDPAC, a score could only be calculated in 16.3% of individuals presenting with NOD. As in other validation studies,[35,46,47] the original requirement for a confirmatory raised HbA1c at diagnosis was omitted, which increased the proportion of individuals eligible for scoring from 2.6% to 16.3%. Although when using the smaller cohort the PPV increased to 1.2%, there is little clinical utility in having a model that can only be applied to a few people.[74,75] Therefore, data completeness remains a key constraint. This reflects a broader limitation of routine data-based models, where increasing predictor complexity typically reduces usable sample size. Ultimately, sufficient routinely recorded information is required to generate meaningful predictions, which must be considered when designing early detection strategies for pancreatic cancer in primary care.

Implications for research and practice

Further research should move beyond retrospective validation to determine whether ENDPAC-guided risk stratification improves meaningful clinical outcomes, such as earlier pancreatic cancer diagnosis and survival. Prospective studies, such as those being undertaken by Chari *et al*[76] and Oldfield *et al*,[77] which include linkage to imaging and cancer registry endpoints, are needed to evaluate effectiveness, safety, and cost–benefit balance in routine care. These should be accompanied by health-economic evaluation of imaging demand, missed-case trade-offs, and equity impacts, alongside implementation research assessing usability, acceptability, and workflow integration, given that predictive tools often fail to translate into practice.[78,79]

Evidence from primary care suggests that underuse of National Institute for Health and Care Excellence (NICE) referral guidance remains a barrier to early diagnosis[68,80] and a possible gap in care quality, which contributes to diagnostic delay and poorer outcomes than many European countries.[81,82] In response, an NHS initiative launched in 2025 aims to improve referral pathways for high-risk abdominal imaging.[12] This will evaluate how NICE guidelines (which like ENDPAC focus on age and weight loss for people with NOD) are incorporated into early detection pathways. A randomised controlled trial in the US is currently testing whether referral strategies based on age, glycaemic change, and weight loss improve early detection.[76] Parallel work is assessing embedding ENDPAC-like tools directly into primary care systems.[83] This UK validation therefore represents an early step in translating model development into practice.

Ultimately, successful implementation requires integration into primary care workflows,[55,78,84,85] not just accurate validation, and should be understood within the broader context of diagnostic strategy design. The authors envision ENDPAC being integrated into clinical workflows in the same way eRATs are utilised,[86] to support early cancer detection by flagging patients with elevated risk based on routinely collected data. These tools,

including QCancer, have demonstrated value in supporting decision making and improving alignment with NICE NG12 referral guidance for suspected cancer.[15,37,86,87] However, they are most effective when embedded in a multi-step pathway rather than used in isolation. Clinical judgement remains essential, with risk scores acting as a triage mechanism supported by symptom review and patient history to avoid unnecessary referrals, particularly in low-incidence cancers where PPV is inherently constrained.

This has implications for how thresholds are defined. A single cut-off is unlikely to be optimal; instead, stratified thresholds tailored to clinical context and patient preference are more appropriate.[88] Shared decision making is essential as acceptable risk thresholds vary, with some evidence supporting referral at risks as low as 1% and higher thresholds (for example, 3%) prompting urgent pathways.[89] Decision curve analysis may help define these thresholds by balancing benefits and harms, and help to assess the probability of disease at which a patient would opt for treatment.[90]

Given the low incidence of pancreatic cancer (17.6 per 100 000 annually),[91,92] false positives from predictive models are unavoidable, making population-wide screening inappropriate due to downstream harms including unnecessary testing, psychological burden, and cost.[93,94] However, comparable trade-offs are accepted in other cancer screening programmes, where low PPVs are offset by earlier detection benefits. For example, QCancer for gastro-oesophageal cancer produces PPVs of 0.2% to 0.8%, with large numbers of false positives (only 405 cases from 53 529 women flagged as high risk).[95] Breast, prostate, and colorectal screening programmes also routinely accept false positive rates of 10% to 60%.[96] ENDPAC's estimated false positive rate (~99%) is also similar to low-dose computed tomography lung cancer screening (~96%).[97] In these contexts, benefits of earlier diagnosis are considered to outweigh harms when embedded in structured pathways.[97,98] Importantly, evidence suggests that the psychological impact of false positives on patients is generally transient and may even reduce anxiety or increase future screening engagement,[96,99] although clear communication and informed consent remain essential.

The potential value of earlier detection is reinforced by economic considerations. Pancreatic cancer treatment is expensive, with costs continuing to rise.[100,101] Therefore, while increased testing from false positives may strain services, earlier detection could reduce long-term treatment costs and improve outcomes by increasing the proportion of patients eligible for resection and curative treatment. For instance, estimates suggest that screening could increase resectability rates from 10%–15% to around 40%, and may remain cost-effective even with more modest improvements above 25%.[102] Currently, NHS spending on cancer diagnosis is around £1 billion annually.[103] This may be reduced through earlier detection reducing ongoing treatment costs, but although improved referral systems have been associated with survival gains,[104] robust cost-effectiveness data remain limited.[105]

Maximising benefit while limiting harm therefore requires embedding ENDPAC within a multi-step diagnostic pathway. Secondary triage using clinical review, biomarkers, and imaging can substantially reduce false positives. For example, Sharma *et al* demonstrated that additional review could halve false positives and increase the 3-year cancer risk from 3.6% to 10% in people flagged as high risk.[20] Such pathways also improve diagnostic specificity by identifying alternative explanations, such as steroid use or poorly controlled diabetes.

Further refinement could improve performance and clinical utility. ENDPAC was originally based on evidence that pancreatogenic diabetes is associated with more rapid glycaemic deterioration and higher HbA1c at diagnosis than type 2 diabetes.[23,106] Therefore, sensitivity analysis could be conducted to see if people with very high HbA1c at diagnosis (for example, ≥60) are at increased risk and whether this warrants further stratification of the model.

More broadly, incorporating additional risk modifiers could improve targeting. Evidence supports stratification by age, sex, ethnicity, deprivation (IMD), and lifestyle factors (for example, smoking and alcohol use), reflecting known variation in incidence and diagnostic timing (including later peak diagnosis in women and incidence variation by deprivation).[92,107,108] Further improvements could include using body mass index alongside weight loss to increase data availability and shifting from categorical to continuous variables to better distinguish risk within groups. These refinements would help target investigations for those most at risk, which is essential given the rarity of pancreatic cancer and the consequent low PPV of even highly accurate models.

Alongside model refinement, additional research should examine the influence of data completeness, measurement timing and frequency, as well as the relationship between diabetes onset and pancreatic cancer detection. The present findings reinforce the need for structured recording of weight and HbA1c in primary care, which would not only benefit pancreatic cancer detection but also identification of undiagnosed diabetes. This is itself a significant public health issue, with an estimated 1 million people in the UK living with undiagnosed diabetes, representing nearly a quarter of cases.[65,109]

Ultimately, routine clinical data offer opportunities for earlier detection across multiple conditions, but only where information is sufficiently complete and consistently recorded. Improving pancreatic cancer outcomes will therefore require not only better risk stratification tools and diagnostic pathways, but also advances in treatment and biomarkers, particularly given tumour heterogeneity. Within this broader framework, ENDPAC provides a structured and scalable approach to risk enrichment in primary care.

In conclusion, this study provides robust, real-world validation of ENDPAC within UK primary care. ENDPAC demonstrates consistent, moderate discrimination and can effectively enrich pancreatic cancer risk among individuals with NOD. While limitations related to calibration, data completeness,

and low disease prevalence restrict its use as a standalone tool, it reliably enriches a population of people with NOD to identify a high-risk subgroup for pancreatic cancer and performs consistently with existing literature. Its simplicity, reproducibility, and compatibility with routine clinical data means it has clear potential as part of a structured, multi-step early detection strategy. However, prospective evaluation, integration into clinical workflows, and careful management of trade-offs between early detection, false positives, and resource use are needed to determine whether ENDPAC-guided strategies can meaningfully improve diagnostic timeliness and clinical outcomes.

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Ethical approval

The study was approved by the University of Surrey Ethics Committee on 30 September 2022 (reference number: FHMS 21-22 269 EGA). Access to Research and Surveillance Centre (RSC) data was approved by the Royal College of General Practitioners (RCGP) under data request RSC_0420.

Data

Data will remain under the control of the Oxford Clinical Informatics Digital Hub (https://orchid.phc.ox.ac.uk) and can be accessed following all necessary approvals.

Provenance

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Competing interests

The authors have declared no competing interests.

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