nature medicine

Article

https://doi.org/10.1038/s41591-023-02332-5

A deep learning algorithm to predict risk of pancreatic cancer from disease trajectories

In the format provided by the authors and unedited

Supplementary Tables and Notes

Supplementary tables

Supplementary table 1. Description of the patient cohorts used in this study (DK).

Population Metadata (n=8,110,706 persons)		
Gender	Male	Female
Total Count	4,030,504 (49.69%)	4,080,202 (50.31%)
Alive	2,754,152 (33.96%)	2,827,021 (34.86%)
Dead	1,276,352 (15.74%)	1,253,181 (15.45%)
After continuity and length filtering	2,938,248 (36.23%)	3,239,989 (39.95%)
Age at last record [0-10)	216,329 (2.67%)	204,774 (2.52%)
Age at last record [10-20)	332,326 (4.10%)	314,445 (3.88%)
Age at last record [20-30)	322,802 (3.98%)	298,219 (3.68%)
Age at last record [30-40)	283,200 (3.49%)	305,470 (3.77%)
Age at last record [40-50)	323,811 (3.99%)	380,730 (4.69%)
Age at last record [50-60)	368,686 (4.55%)	419,100 (5.17%)
Age at last record [60-70)	373,220 (4.60%)	402,625 (4.96%)
Age at last record [70-80)	394,789 (4.87%)	408,890 (5.04%)
Age at last record [80-90)	258,193 (3.18%)	342,174 (4.22%)
Age at last record [90-100)	63,470 (0.78%)	156,154 (1.93%)
Age at last record [100, ∞)	1,422 (0.02%)	7,398 (0.09%)

Pancreatic Cancer Patients (n=23,985)		
	Male	Female
Total Count	11,880 (49.53%)	12,105 50.47%
Age at pancreatic cancer diagnosis [0,30)	13 (0.05%)	19 (0.08%)
Age at pancreatic cancer diagnosis [30-40)	92 (0.38%)	93 (0.39%)
Age at pancreatic cancer diagnosis [40-50)	474 (1.98%)	417 (1.74%)
Age at pancreatic cancer diagnosis [50-60)	1,626 (6.78%)	1,304 (5.44%)
Age at pancreatic cancer diagnosis [60-70)	3,585 (14.95%)	2,950 (12.30%)
Age at pancreatic cancer diagnosis [70-80)	4,017 (16.75%)	4,076 (16.99%)
Age at pancreatic cancer diagnosis [80-90)	1,925 (8.03%)	2,751 (11.47%)
Age at pancreatic cancer diagnosis [90, ∞)	148 (0.62%)	495 (2.06%)

Supplementary table 2. Hyperparameter search for machine learning models.

To comprehensively test different types of neural networks and the corresponding hyperparameters, we conducted a large parameter search for each of the network types. The different types of models include simple feed-forward models (LR, MLP) and more complex models that can take the sequential information of disease ordering into consideration (RNN, GRU and Transformer). The hyperparameters of the best performing model (DK-DNPR) are in **bold**.

	Type of ML model			
Hyper-parameters	Bag of words	MLP	GRU	Transformer
Dropout	0	0,0.1	0,0.1	**0**, 0.1
Weight decay	0.001	0,0.001	0,0.001	0, **0.001**
Only prior knowledge diseases	False, True	False	False	**False**, True
Dimension of hidden layer	-	32, 128, 256	32, 64, 128, 256	32, **256**
Number of hidden layers	-	1, 2	1, 2, 4	**1**, 2, 4
Age input	None	None	None, positional embedding	None, **positional embedding**
Time input	None	None	None, positional embedding	None, **positional embedding**
Number of Heads	-	-	-	8, **16**, 32

Supplementary table 3. Performance of exclusion experiments - DK dataset and US-VA dataset

A summary of performance of different models trained with different data exclusion intervals for different prediction intervals. In order to estimate the uncertainty of the performance metrics, 95% confidence interval (CI) were computed using 200 resamples (bootstrapping with replacement); these time intervals may be slightly too narrow due to the estimated small number of trajectories from a single patient in a particular sample, but provide a reasonable guide. Specificity, precision, and recall are for the F1-optimal operational point that maximizes the F1 score, which is the harmonic mean of recall and precision [1].

Summary of Tables S3

Table S3A	Performance summary DNPR (AUROC)
Table S3B	Performance summary DNPR (Specificity/Precision/Recall)
Table S3C	Performance summary DNPR models applied to US-VA (AUROC)
Table S3D	Performance summary DNPR models applied to US-VA (Specificity/Precision/Recall)
Table S3E	Performance summary US-VA, independent training (AUROC)
Table S3F	Performance summary US-VA, independent training (Specificity/Precision/Recall)
Table S3G	Performance summary US-VA, independent training above 50 (AUROC)
Table S3H	Performance summary US-VA, independent training above 50 (Specificity/Precision/Recall)
Table S3I	Performance summary DNPR above 50 (AUROC)
Table S3J	Performance summary DNPR above 50 (Specificity/Precision/Recall)

Table S3A Performance summary DNPR (AUROC)

Model	Prediction Interval (months) →	0 - 3	0 - 6	0 - 12	0 - 36	0 - 60
	Exclusion Interval (months)					
Bag-of-words	0	0.794 (0.791-0.797)	0.800 (0.797-0.803)	0.807 (0.805-0.809)	0.807 (0.805-0.809)	0.799 (0.797-0.800)
	3	-	0.815 (0.808-0.821)	0.823 (0.819-0.826)	0.812 (0.810-0.814)	0.798 (0.796-0.800)
	6	-	-	0.826 (0.821-0.830)	0.810 (0.807-0.812)	0.794 (0.792-0.797)
MLP	0	0.876 (0.873-0.879)	0.871 (0.869-0.873)	0.864 (0.861-0.866)	0.845 (0.843-0.847)	0.832 (0.830-0.834)
	3	-	0.836 (0.830-0.841)	0.832 (0.828-0.836)	0.838 (0.836-0.840)	0.828 (0.827-0.830)
	6	-	-	0.838 (0.833-0.842)	0.830 (0.828-0.833)	0.824 (0.822-0.825)
GRU	0	0.917 (0.914-0.919)	0.903 (0.900-0.905)	0.883 (0.881-0.885)	0.852 (0.850-0.854)	0.836 (0.834-0.837)
	3	-	0.859 (0.854-0.866)	0.852 (0.848-0.855)	0.832 (0.830-0.835)	0.820 (0.818-0.822)
	6	-	-	0.848 (0.844-0.852)	0.827 (0.824-0.829)	0.815 (0.812-0.816)
	12	-	-	-	0.814 (0.811-0.817)	0.803 (0.801-0.805)
Transformer	0	0.934 (0.932-0.937)	0.923 (0.920-0.925)	0.908 (0.906-0.911)	0.879 (0.877-0.880)	0.861 (0.860-0.863)
	3	-	0.866 (0.860-0.870)	0.862 (0.857-0.866)	0.843 (0.841-0.844)	0.830 (0.828-0.831)
	6	-	-	0.834 (0.830-0.838)	0.829 (0.827-0.832)	0.817 (0.816-0.819)
	12	-	-	-	0.827 (0.825-0.830)	0.816 (0.814-0.818)
Transformer - Known risk factors	0	0.850 (0.847-0.852)	0.850 (0.847-0.852)	0.850 (0.848-0.851)	0.838 (0.837-0.840)	0.832 (0.831-0.833)

Table S3B Performance summary DNPR (Specificity/Precision/Recall)

Model		Prediction Interval (months) : →	0 - 3	0 - 6	0 - 12	0 - 36	0 - 60
	Exclusion Interval (months)	Metric					
Bag-of-words	0	specificity	98.64% (96.31%-98.83%)	98.07% (95.42%-98.85%)	98.18% (97.50%-98.80%)	95.55% (94.86%-98.01%)	95.06% (94.09%-95.75%)
	0	precision	0.3% (0.3%-0.4%)	0.4% (0.4%-0.5%)	0.6% (0.6%-0.7%)	0.9% (0.8%-0.9%)	1.0% (0.9%-1.0%)
	0	recall	5.4% (4.6%-13.4%)	8.0% (4.9%-17.5%)	7.7% (5.3%-9.9%)	16.6% (8.1%-18.6%)	16.5% (14.6%-19.2%)
	3	specificity	-	99.91% (99.80%-99.91%)	99.72% (99.15%-99.80%)	97.04% (94.91%-99.70%)	94.82% (93.27%-97.03%)
	3	precision	-	0.2% (0.1%-0.3%)	0.4% (0.3%-0.5%)	0.6% (0.6%-0.9%)	0.7% (0.7%-0.7%)
	3	recall	-	1.0% (0.7%-2.1%)	2.0% (1.4%-4.9%)	11.7% (1.8%-19.4%)	17.2% (10.2%-22.2%)
	6	specificity	-	-	99.73% (99.19%-99.74%)	99.71% (97.11%-99.72%)	96.72% (93.37%-97.43%)
	6	precision	-	-	0.2% (0.2%-0.3%)	0.7% (0.5%-0.8%)	0.6% (0.6%-0.7%)
	6	recall	-	-	2.1% (1.7%-5.2%)	1.7% (1.6%-11.6%)	10.8% (8.5%-20.7%)
MLP	0	specificity	99.74% (99.68%-99.82%)	99.73% (99.66%-99.82%)	99.79% (99.66%-99.82%)	99.69% (99.53%-99.74%)	99.54% (99.43%-99.61%)
	0	precision	2.7% (2.4%-3.0%)	3.4% (3.0%-3.9%)	4.3% (3.6%-4.7%)	4.8% (4.1%-5.3%)	4.5% (4.2%-4.9%)
	0	recall	9.0% (6.9%-11.1%)	9.1% (7.0%-11.1%)	7.3% (6.6%-9.8%)	7.3% (6.5%-9.4%)	7.9% (7.1%-9.0%)
	3	specificity	-	99.85% (99.72%-99.87%)	99.83% (99.71%-99.84%)	99.75% (99.50%-99.76%)	99.43% (99.39%-99.56%)
	3	precision	-	0.5% (0.4%-0.6%)	1.0% (0.9%-1.2%)	2.0% (1.5%-2.1%)	1.8% (1.7%-2.0%)
	3	recall	-	3.5% (2.8%-5.4%)	3.3% (2.9%-4.8%)	3.7% (3.4%-5.9%)	5.1% (4.3%-5.6%)
	6	specificity	-	-	99.80% (99.80%-99.82%)	99.64% (99.62%-99.92%)	99.61% (99.59%-99.64%)
	6	precision	-	-	0.3% (0.3%-0.4%)	1.0% (0.9%-1.9%)	1.3% (1.2%-1.4%)
	6	recall	-	-	2.0% (1.5%-2.4%)	3.1% (1.3%-3.5%)	2.8% (2.6%-3.1%)
GRU	0	specificity	99.95% (99.93%-99.95%)	99.92% (99.89%-99.94%)	99.89% (99.87%-99.91%)	99.82% (99.77%-99.87%)	99.76% (99.74%-99.81%)
	0	precision	15.1% (13.1%-15.9%)	14.0% (11.7%-15.9%)	13.1% (12.0%-14.6%)	11.6% (10.2%-13.5%)	10.4% (9.8%-11.5%)
	0	recall	12.7% (11.9%-14.0%)	12.6% (11.4%-14.7%)	12.6% (11.4%-13.5%)	10.8% (9.5%-12.0%)	10.0% (9.1%-10.5%)
	3	specificity	-	99.97% (99.93%-99.97%)	99.94% (99.91%-99.95%)	99.86% (99.83%-99.89%)	99.84% (99.79%-99.86%)
	3	precision	-	2.8% (2.2%-3.4%)	5.2% (4.1%-6.0%)	5.5% (4.9%-6.2%)	5.8% (5.0%-6.3%)
	3	recall	-	4.9% (4.2%-7.1%)	6.1% (5.3%-7.6%)	6.0% (5.1%-6.7%)	5.1% (4.7%-5.7%)
	6	specificity	-	-	99.93% (99.85%-99.96%)	99.88% (99.85%-99.93%)	99.84% (99.78%-99.85%)
	6	precision	-	-	1.7% (1.3%-2.2%)	4.3% (3.5%-5.5%)	4.3% (3.7%-4.7%)
	6	recall	-	-	3.8% (2.8%-5.6%)	4.4% (3.5%-5.3%)	4.2% (3.9%-4.8%)
	12	specificity	-	-	-	99.67% (99.58%-99.89%)	99.79% (99.47%-99.84%)
	12	precision	-	-	-	1.1% (0.9%-1.3%)	1.7% (1.2%-1.9%)
	12	recall	-	-	-	4.4% (2.0%-5.1%)	2.6% (2.2%-4.6%)
Transformer	0	specificity	99.95% (99.92%-99.96%)	99.93% (99.91%-99.94%)	99.92% (99.90%-99.93%)	99.88% (99.87%-99.90%)	99.87% (99.83%-99.88%)
	0	precision	18.6% (15.6%-22.5%)	18.8% (16.9%-19.7%)	19.4% (17.8%-21.6%)	18.1% (17.1%-19.9%)	18.0% (15.2%-18.9%)
	0	recall	16.5% (14.4%-19.4%)	17.0% (16.1%-18.5%)	15.6% (14.7%-16.5%)	12.3% (11.7%-12.9%)	10.2% (9.8%-11.2%)
	3	specificity	-	99.92% (99.91%-99.98%)	99.92% (99.92%-99.93%)	99.87% (99.86%-99.91%)	99.63% (99.56%-99.64%)
	3	precision	-	1.7% (1.4%-3.0%)	4.3% (3.8%-4.8%)	5.4% (4.9%-6.6%)	2.7% (2.5%-2.9%)
	3	recall	-	5.9% (2.4%-7.2%)	6.5% (6.0%-7.2%)	5.2% (4.5%-5.6%)	5.3% (5.0%-6.0%)
	6	specificity	-	-	99.41% (98.21%-99.42%)	99.51% (99.47%-99.52%)	99.34% (95.82%-99.38%)
	6	precision	-	-	0.2% (0.1%-0.2%)	0.7% (0.7%-0.8%)	0.8% (0.7%-0.9%)
	6	recall	-	-	3.4% (2.7%-8.4%)	3.2% (2.9%-3.5%)	3.2% (3.0%-16.0%)
	12	specificity	-	-	-	99.44% (99.43%-99.45%)	99.41% (94.87%-99.42%)
	12	precision	-	-	-	0.5% (0.4%-0.5%)	0.6% (0.5%-0.7%)
	12	recall	-	-	-	3.1% (2.8%-3.5%)	2.7% (2.5%-18.3%)
Transformer - Known risk factors	0	specificity	99.96% (99.92%-99.97%)	99.92% (99.91%-99.93%)	99.91% (99.91%-99.92%)	99.87% (99.76%-99.88%)	99.79% (99.73%-99.88%)
	0	precision	11.6% (7.4%-12.7%)	9.2% (8.6%-10.0%)	10.3% (9.7%-10.8%)	3.6% (2.6%-3.9%)	2.8% (2.4%-4.0%)
	0	recall	6.9% (6.3%-9.7%)	9.2% (8.5%-9.7%)	8.3% (7.9%-8.7%)	2.5% (2.3%-3.2%)	2.4% (1.9%-2.8%)

Table S3C Performance summary DNPR models applied to US-VA (AUROC)

Model	Prediction Interval (months) →	0 - 3	0 - 6	0 - 12	0 - 36	0 - 60
	Exclusion Interval (months)					
Transformer	0	0.881 (0.878-0.883)	0.833 (0.830-0.835)	0.790 (0.788-0.792)	0.710 (0.708-0.712)	0.685 (0.683-0.687)
	3	-	0.665 (0.661-0.670)	0.641 (0.638-0.643)	0.626 (0.624-0.628)	0.627 (0.625-0.629)
	6	-	-	0.593 (0.590-0.598)	0.615 (0.612-0.616)	0.609 (0.607-0.610)

Table S3D Performance summary DNPR models applied to US-VA (Specificity/Precision/Recall)

Model		Prediction Interval (months): →	0 - 3	0 - 6	0 - 12	0 - 36	0 - 60
	Exclusion Interval (months)	Metric					
Transformer (cross evaluation)	0	specificity	99.94% (99.92%-99.97%)	99.92% (99.91%-99.92%)	99.91% (99.91%-99.92%)	99.90% (99.90%-99.91%)	99.90% (99.90%-99.90%)
	0	precision	6.8% (5.9%-9.3%)	6.1% (5.8%-6.4%)	6.4% (6.2%-6.7%)	6.2% (6.0%-6.4%)	6.3% (6.1%-6.4%)
	0	recall	13.3% (9.1%-17.7%)	12.9% (12.4%-13.4%)	9.7% (9.2%-10.0%)	5.9% (5.7%-6.1%)	4.9% (4.7%-5.0%)
	3	specificity	-	99.90% (99.90%-99.90%)	99.90% (99.90%-99.90%)	99.90% (99.90%-99.90%)	99.86% (99.72%-99.86%)
	3	precision	-	0.4% (0.4%-0.5%)	0.8% (0.7%-0.9%)	1.3% (1.2%-1.4%)	1.4% (1.1%-1.5%)
	3	recall	-	2.8% (2.5%-3.0%)	1.9% (1.8%-2.2%)	1.4% (1.3%-1.5%)	1.6% (1.6%-2.4%)
	6	specificity	-	-	99.94% (99.94%-99.94%)	81.89% (67.42%-81.94%)	81.89% (79.61%-81.95%)
	6	precision	-	-	0.1% (0.1%-0.1%)	0.1% (0.1%-0.1%)	0.2% (0.2%-0.2%)
	6	recall	-	-	0.2% (0.2%-0.3%)	26.1% (25.8%-45.7%)	26.4% (25.9%-29.5%)

Table S3E Performance summary US-VA, independent training (AUROC)

Model	Prediction Interval (months) →	0 - 3	0 - 6	0 - 12	0 - 36	0 - 60
	Exclusion Interval (months)					
Transformer	0	0.899 (0.895-0.903)	0.857 (0.854-0.862)	0.825 (0.822-0.828)	0.775 (0.772-0.778)	0.762 (0.760-0.765)
	3	-	0.783 (0.779-0.786)	0.761 (0.758-0.764)	0.758 (0.756-0.761)	0.745 (0.741-0.747)
	6	-	-	0.627 (0.622-0.630)	0.678 (0.676-0.680)	0.678 (0.676-0.680)

Table S3F Performance summary US-VA, independent training (Specificity/Precision/Recall)

Model		Prediction Interval (months) →	0 - 3	0 - 6	0 - 12	0 - 36	0 - 60
	Exclusion Interval (months)	Metric					
Transformer	0	specificity	99.96% (99.96%-99.97%)	99.96% (99.95%-99.96%)	99.95% (99.94%-99.95%)	99.91% (99.88%-99.95%)	99.89% (99.88%-99.91%)
	0	precision	11.5% (10.5%-13.2%)	11.1% (10.4%-12.1%)	12.0% (10.9%-12.7%)	8.9% (7.8%-12.2%)	8.0% (7.6%-9.1%)
	0	recall	15.4% (13.4%-16.8%)	13.0% (11.6%-13.7%)	10.6% (10.0%-11.3%)	7.9% (6.6%-9.3%)	7.3% (6.7%-7.5%)
	3	specificity	-	99.95% (99.93%-99.96%)	99.94% (99.93%-99.97%)	99.90% (99.89%-99.90%)	99.90% (99.77%-99.90%)
	3	precision	-	2.9% (2.4%-3.7%)	2.8% (2.4%-4.2%)	2.9% (2.7%-3.2%)	2.9% (2.0%-3.2%)
	3	recall	-	3.6% (2.8%-4.2%)	2.8% (2.1%-3.4%)	2.9% (2.6%-3.1%)	2.4% (2.2%-3.5%)
	6	specificity	-	-	97.18% (96.95%-99.60%)	96.59% (96.52%-96.99%)	96.60% (96.52%-97.07%)
	6	precision	-	-	0.2% (0.2%-0.2%)	0.3% (0.3%-0.3%)	0.3% (0.3%-0.3%)
	6	recall	-	-	7.8% (1.2%-8.6%)	8.3% (7.4%-8.7%)	7.8% (6.8%-8.3%)

Table S3G Performance summary US-VA, independent training above age 50 (AUROC)

Model	Prediction Interval (months) →	0 - 3	0 - 6	0 - 12	0 - 36	0 - 60
	Exclusion Interval (months)					
Transformer	0	0.900 (0.895-0.904)	0.857 (0.853-0.862)	0.825 (0.821-0.829)	0.775 (0.772-0.778)	0.762 (0.760-0.765)
	3	-	0.782 (0.778-0.787)	0.760 (0.758-0.764)	0.756 (0.754-0.759)	0.744 (0.741-0.746)

Table S3H Performance summary US-VA, independent training above age 50 (Specificity/Precision/Recall)

Model		Prediction Interval (months) →	0 - 3	0 - 6	0 - 12	0 - 36	0 - 60
	Exclusion Interval (months)	Metric					
Transformer	0	specificity	99.96% (99.96%-99.97%)	99.95% (99.95%-99.97%)	99.95% (99.94%-99.95%)	99.89% (99.88%-99.95%)	99.89% (99.88%-99.90%)
	0	precision	11.8% (11.0%-12.5%)	11.2% (10.4%-12.7%)	12.0% (11.2%-12.6%)	8.2% (7.8%-12.5%)	8.2% (7.7%-8.6%)
	0	recall	15.7% (14.7%-16.9%)	13.1% (11.5%-13.9%)	10.8% (10.1%-11.6%)	8.9% (6.8%-9.4%)	7.5% (6.9%-7.7%)
	3	specificity	-	99.96% (99.95%-99.96%)	99.96% (99.93%-99.97%)	99.90% (99.85%-99.90%)	99.82% (99.81%-99.90%)
	3	precision	-	3.6% (2.8%-4.1%)	3.7% (2.7%-4.6%)	2.9% (2.5%-3.1%)	2.3% (2.1%-3.1%)
	3	recall	-	3.4% (3.1%-4.0%)	2.5% (2.2%-3.2%)	2.9% (2.7%-3.4%)	2.9% (2.3%-3.2%)

Table S3I Performance summary DNPR above age 50 (AUROC)

Model	Prediction Interval (months): ->	0-3	0-6	0-12	0-36	0-60
	Exclusion Interval (months)					
Bag-of-words	0	0.600 (0.594-0.605)	0.611 (0.606-0.615)	0.622 (0.618-0.627)	0.621 (0.618-0.624)	0.605 (0.603-0.608)
	3	-	0.646 (0.636-0.656)	0.653 (0.646-0.660)	0.633 (0.629-0.637)	0.609 (0.606-0.612)
	6	-	-	0.655 (0.648-0.662)	0.631 (0.626-0.635)	0.605 (0.601-0.609)
MLP	0	0.758 (0.752-0.763)	0.747 (0.742-0.751)	0.727 (0.723-0.731)	0.690 (0.687-0.694)	0.665 (0.662-0.668)
	3	-	0.686 (0.676-0.696)	0.672 (0.666-0.680)	0.662 (0.659-0.666)	0.644 (0.641-0.648)
	6	-	-	0.654 (0.645-0.662)	0.642 (0.639-0.646)	0.631 (0.628-0.635)
GRU	0	0.854 (0.850-0.858)	0.827 (0.823-0.831)	0.777 (0.774-0.781)	0.717 (0.714-0.720)	0.686 (0.683-0.690)
	3	-	0.733 (0.725-0.744)	0.710 (0.703-0.715)	0.667 (0.663-0.671)	0.645 (0.641-0.648)
	6	-	-	0.694 (0.686-0.703)	0.652 (0.648-0.656)	0.629 (0.625-0.633)
	12	-	-	-	0.629 (0.622-0.634)	0.610 (0.606-0.614)
Transformer	0	0.876 (0.872-0.880)	0.853 (0.850-0.857)	0.821 (0.819-0.825)	0.753 (0.750-0.756)	0.717 (0.714-0.720)
	3	-	0.739 (0.728-0.746)	0.722 (0.715-0.727)	0.674 (0.671-0.678)	0.651 (0.648-0.654)
	6	-	-	0.661 (0.655-0.668)	0.646 (0.642-0.650)	0.623 (0.620-0.627)
	12	-	-	-	0.638 (0.632-0.643)	0.615 (0.611-0.620)
Transformer - Prior knowledge disease	0	0.664 (0.659-0.671)	0.669 (0.665-0.675)	0.669 (0.664-0.673)	0.638 (0.635-0.641)	0.626 (0.623-0.628)

Table S3J Performance summary DNPR above age 50 (Specificity/Precision/Recall)

Model		Prediction Interval (months): ->	0-3	0-6	0-12	0-36	0-60
	Exclusion Interval (months)	Metric					
Bag-of-words	0	specificity	96.05% (90.42%-97.10%)	95.10% (92.06%-96.09%)	95.82% (92.13%-96.33%)	90.42% (88.67%-94.49%)	89.09% (87.19%-90.67%)
	0	precision	0.4% (0.3%-0.4%)	0.5% (0.4%-0.5%)	0.7% (0.6%-0.7%)	0.9% (0.9%-1.0%)	1.0% (1.0%-1.1%)
	0	recall	7.3% (5.5%-16.3%)	9.6% (7.6%-15.1%)	8.5% (7.4%-14.9%)	17.1% (10.2%-19.7%)	17.4% (15.0%-20.2%)
	3	specificity	-	99.79% (99.54%-99.80%)	99.32% (95.53%-99.52%)	94.59% (88.20%-95.38%)	87.88% (85.36%-93.80%)
	3	precision	-	0.2% (0.2%-0.3%)	0.4% (0.3%-0.5%)	0.6% (0.6%-0.7%)	0.8% (0.7%-0.8%)
	3	recall	-	1.0% (0.7%-1.8%)	2.2% (1.5%-10.5%)	10.5% (9.0%-21.7%)	19.6% (10.6%-23.5%)
	6	specificity	-	-	99.36% (96.63%-99.39%)	94.91% (89.44%-99.33%)	89.80% (85.63%-94.72%)
	6	precision	-	-	0.3% (0.2%-0.3%)	0.5% (0.5%-0.8%)	0.7% (0.6%-0.7%)
	6	recall	-	-	2.2% (1.7%-8.9%)	9.7% (1.7%-19.5%)	16.1% (8.8%-22.2%)
MLP	0	specificity	99.65% (99.42%-99.68%)	99.65% (99.42%-99.68%)	99.64% (99.43%-99.67%)	99.43% (99.08%-99.52%)	99.10% (98.88%-99.26%)
	0	precision	3.6% (3.1%-4.0%)	4.6% (3.9%-4.9%)	5.5% (4.6%-5.9%)	5.6% (4.6%-6.3%)	5.0% (4.6%-5.5%)
	0	recall	7.9% (7.1%-10.9%)	7.9% (7.1%-10.1%)	7.3% (6.8%-8.9%)	7.2% (6.4%-9.5%)	7.8% (6.8%-8.8%)
	3	specificity	-	99.76% (99.74%-99.80%)	99.72% (99.47%-99.73%)	99.08% (98.81%-99.53%)	98.81% (98.43%-99.01%)
	3	precision	-	0.7% (0.5%-0.8%)	1.3% (1.0%-1.5%)	1.7% (1.5%-2.2%)	1.8% (1.6%-1.9%)
	3	recall	-	3.4% (2.7%-4.6%)	3.2% (2.8%-4.9%)	5.2% (3.2%-6.2%)	5.0% (4.4%-6.1%)
	6	specificity	-	-	99.63% (99.62%-99.66%)	99.62% (99.25%-99.86%)	99.55% (98.89%-99.63%)
	6	precision	-	-	0.4% (0.3%-0.5%)	1.3% (1.0%-2.5%)	1.5% (1.1%-1.9%)
	6	recall	-	-	2.0% (1.6%-2.5%)	2.0% (1.2%-3.2%)	1.9% (1.5%-3.1%)
GRU	0	specificity	99.90% (99.83%-99.91%)	99.82% (99.78%-99.87%)	99.77% (99.73%-99.81%)	99.58% (99.55%-99.68%)	99.55% (99.53%-99.58%)
	0	precision	17.9% (14.0%-19.2%)	14.8% (13.4%-17.8%)	14.7% (13.2%-16.5%)	12.2% (11.6%-13.6%)	12.1% (11.6%-12.9%)
	0	recall	13.0% (12.3%-15.9%)	14.2% (12.2%-15.9%)	13.4% (12.4%-14.5%)	12.1% (11.0%-12.8%)	10.2% (9.7%-10.6%)
	3	specificity	-	99.94% (99.87%-99.95%)	99.88% (99.84%-99.91%)	99.71% (99.70%-99.76%)	99.70% (99.56%-99.71%)
	3	precision	-	3.9% (2.7%-4.6%)	6.4% (5.4%-7.5%)	6.4% (6.0%-7.1%)	6.9% (5.6%-7.4%)
	3	recall	-	5.4% (4.4%-8.5%)	6.9% (5.9%-8.0%)	6.4% (5.8%-6.9%)	5.1% (4.8%-5.9%)
	6	specificity	-	-	99.88% (99.76%-99.91%)	99.75% (99.69%-99.87%)	99.55% (99.39%-99.72%)
	6	precision	-	-	2.3% (1.8%-2.9%)	4.3% (3.8%-6.3%)	3.9% (3.3%-5.1%)
	6	recall	-	-	4.4% (3.4%-6.4%)	4.6% (3.5%-5.1%)	4.5% (3.6%-5.3%)
	12	specificity	-	-	-	99.29% (98.96%-99.47%)	99.23% (98.60%-99.63%)
	12	precision	-	-	-	1.0% (0.9%-1.2%)	1.3% (1.1%-1.7%)
	12	recall	-	-	-	4.0% (3.2%-5.3%)	3.2% (2.0%-4.8%)
Transformer	0	specificity	99.85% (99.83%-99.91%)	99.85% (99.81%-99.86%)	99.82% (99.80%-99.86%)	99.75% (99.72%-99.78%)	99.72% (99.62%-99.75%)
	0	precision	18.1% (16.5%-23.4%)	20.3% (18.1%-21.5%)	20.9% (19.7%-23.6%)	19.1% (17.9%-20.9%)	18.7% (15.9%-20.0%)
	0	recall	18.6% (15.6%-20.0%)	17.5% (16.4%-19.1%)	15.9% (14.8%-16.6%)	12.5% (11.7%-13.1%)	10.5% (10.0%-11.7%)
	3	specificity	-	99.82% (99.79%-99.96%)	99.82% (99.81%-99.84%)	99.72% (99.69%-99.80%)	99.13% (98.98%-99.22%)
	3	precision	-	1.8% (1.4%-3.1%)	4.5% (4.0%-4.9%)	5.6% (5.2%-6.7%)	2.7% (2.5%-2.9%)
	3	recall	-	6.2% (2.5%-7.7%)	6.9% (6.2%-7.5%)	5.5% (4.8%-5.8%)	5.6% (5.3%-6.2%)
	6	specificity	-	-	98.98% (98.96%-99.03%)	98.83% (98.74%-98.86%)	98.46% (90.54%-98.63%)
	6	precision	-	-	0.2% (0.2%-0.3%)	0.7% (0.7%-0.8%)	0.8% (0.7%-0.9%)
	6	recall	-	-	3.1% (2.4%-3.7%)	3.3% (3.0%-3.6%)	3.4% (3.0%-16.5%)
	12	specificity	-	-	-	98.83% (98.82%-98.84%)	98.74% (98.73%-98.80%)
	12	precision	-	-	-	0.5% (0.5%-0.6%)	0.7% (0.7%-0.8%)
	12	recall	-	-	-	3.3% (3.0%-3.6%)	2.9% (2.6%-3.2%)
Transformer - Prior knowledge disease	0	specificity	99.91% (99.79%-99.92%)	99.80% (99.78%-99.82%)	99.79% (99.78%-99.80%)	99.68% (99.65%-99.70%)	99.67% (99.33%-99.69%)
	0	precision	12.0% (7.5%-13.0%)	9.5% (8.9%-10.4%)	10.6% (10.1%-11.1%)	3.6% (3.3%-4.0%)	3.6% (2.4%-4.0%)
	0	recall	7.3% (6.7%-10.5%)	9.8% (8.9%-10.3%)	8.8% (8.4%-9.3%)	2.6% (2.4%-2.8%)	2.2% (2.0%-2.9%)

Supplementary table 4. Known risk factor disease codes.

A subset of 23 diseases (subset of the 2000 level 3 ICD codes) that have been considered as risk factors for pancreatic cancer [2,3] were chosen for the "known risk factor" analysis. Indeed, most of these are flagged by the IG feature extraction method to make a significant contribution to the machine learning prediction of cancer occurrence (Figure 4). These risk factors were used to train a separate time-series model 'Transformer - known risk factors' for comparison to the model trained on all ICD codes (Figure 3).

ICD codes	Diseases
C18	Malignant neoplasm of colon
C34	Malignant neoplasm of bronchus and lung
C50	Malignant neoplasm of breast.
C61	Malignant neoplasm of prostate
E10, E11	Type I/II diabetes mellitus
E66	Obesity
E78	High Cholestrol
E84	Cystic fibrosis
F32	Depression
I10	Hypertension
I82	Venous embolism and thrombosis
K05	Periodontal disease
K21	GERD
K27	Peptic Ulcer Disease
K50, K51, K52	Inflammatory bowel disease
K85	Acute Pancreatitis
K86	Chronic Pancreatitis
R17	Jaundice
R63	Weight loss
Z92	Personal history of medical treatment

Supplementary table 5. Disease attribution after training with 3 months data exclusion - Denmark DNPR & US-VA

In order to discover the top diseases that contribute to our model's risk prediction, we calculated the contribution score for all input features using integrated gradients (IG), an attribution method for neural networks. The IG contribution score (arbitrary units) was calculated for trajectories with cancer occurrence in the time windows 0-6 months, 6-12 months, 12-24 months and 24-36 months for DNPR and US-VA data, both with 3 months data exclusion. - A list with features without data exclusion is in Figure 5. - We mapped ICD9 diagnosis codes to ICD10 for the US-VA dataset to keep the description comparable, and therefore multiple code descriptions might be listed for a given ICD9 code.

DNPR - Denmark Healthcare system

Disease contribution to the risk assessment of cancer occurrence at different times between assessment and actual occurrence of cancer (DK-DNPR)

Diseases contribution at different time to cancer (DNPR)

Cancer in 0-6 months	Cancer in 6-12 months	Cancer in 12-24 months	Cancer in 24-36 months
Other diseases of biliary tract (32.3335)	Other diseases of biliary tract (25.4905)	Other diseases of biliary tract (26.2387)	Non-insulin-dependent diabetes mellitus (11.9299)
Unspecified jaundice (14.3137)	Other diseases of pancreas (11.5739)	Non-insulin-dependent diabetes mellitus (17.4123)	Other diseases of biliary tract (11.2389)
Other diseases of pancreas (13.5165)	Unspecified jaundice (10.1354)	Medical observation and evaluation for suspected diseases and conditions (13.7912)	Other diseases of pancreas (8.8495)
Non-insulin-dependent diabetes mellitus (9.1564)	Non-insulin-dependent diabetes mellitus (8.7353)	Other diseases of pancreas (11.5773)	Medical observation and evaluation for suspected diseases and conditions (8.5102)
Diseases of pancreas (8.8114)	Medical observation and evaluation for suspected diseases and conditions (7.5375)	Abdominal and pelvic pain (4.8105)	Unspecified jaundice (4.2823)
Abdominal and pelvic pain (8.1039)	Diseases of pancreas (5.4421)	Diseases of pancreas (4.2698)	Benign neoplasm of colon, rectum, anus and anal canal (3.2988)
Acute pancreatitis (5.7806)	Abdominal and pelvic pain (3.3334)	Acute pancreatitis (3.2563)	Abdominal and pelvic pain (3.1899)
Malignant neoplasm of stomach (4.6699)	Malignant neoplasm of bronchus and lung (2.2486)	Unspecified jaundice (2.9892)	Gastritis and duodenitis (2.8434)
Medical observation and evaluation for suspected diseases and conditions (3.6176)	Benign neoplasm of colon, rectum, anus and anal canal (2.1298)	Benign neoplasm of colon, rectum, anus and anal canal (2.7481)	Gingivitis and periodontal diseases (2.7876)
Other anaemias (3.1611)	Diabetes mellitus (1.9986)	Other anaemias (2.5468)	Malignant neoplasm of bronchus and lung (2.4107)
Diabetes mellitus (2.5442)	Abnormal involuntary movements (1.6557)	Gastro-oesophageal reflux disease (2.2908)	Gastro-oesophageal reflux disease (1.9136)
Gastro-oesophageal reflux disease (2.4501)	Other anaemias (1.6202)	Disorders of sphingolipid metabolism and other lipid storage disorders (2.0459)	Acute pancreatitis (1.7894)
Dyspepsia (2.1679)	Other symptoms and signs involving the digestive system and abdomen (1.5917)	Malignant neoplasm of bronchus and lung (1.9628)	Malignant neoplasm of other and unspecified parts of biliary tract (1.6697)
Bacterial pneumonia, not elsewhere classified (2.0704)	Gastritis and duodenitis (1.5842)	Diabetes mellitus (1.8423)	Other anaemias (1.5393)
Malignant neoplasm of bronchus and lung (1.6351)	Cholelithiasis (1.4921)	Enlarged lymph nodes (1.7293)	Diabetes mellitus (1.2959)
Cholelithiasis (1.5319)	Gastro-oesophageal reflux disease (1.4884)	Other intervertebral disc disorders (1.6947)	Angina pectoris (1.2408)
Benign neoplasm of colon, rectum, anus and anal canal (1.3892)	Secondary malignant neoplasm of respiratory and digestive organs (1.4277)	Bacterial pneumonia, not elsewhere classified (1.5436)	Dyspepsia (1.0569)
Dislocation, sprain and strain of joints and ligaments of head (1.3044)	Mental and behavioural disorders due to use of tobacco (1.416)	Gastritis and duodenitis (1.4928)	Malignant neoplasm of stomach (1.0218)
Malignant neoplasm of small intestine (1.2895)	Malignant neoplasm of stomach (1.4045)	Other functional intestinal disorders (1.4278)	Diseases of pancreas (1.0155)
Pneumonia, organism unspecified (1.1685)	Osteoporosis without pathological fracture (1.3343)	Dyspepsia (1.4028)	Mental and behavioural disorders due to use of tobacco (0.9639)
Osteoporosis without pathological fracture (1.1565)	Other diseases of gallbladder and biliary (1.2574)	Delirium, not induced by alcohol and other psychoactive substances (1.1866)	Delirium, not induced by alcohol and other psychoactive substances (0.9083)
Other symptoms and signs involving the digestive system and abdomen (1.1477)	Acute pancreatitis (1.1292)	Hyperparathyroidism and other disorders of parathyroid gland (1.164)	Other intervertebral disc disorders (0.8991)
Malignant neoplasm of other and unspecified parts of biliary tract (1.1396)	Dyspepsia (1.1197)	Insulin-dependent diabetes mellitus (1.1136)	Disorders of pancreatic internal secretion other than diabetes mellitus (0.895)
Malignant neoplasm without specification of site (1.133)	Bacterial pneumonia, not elsewhere classified (1.0645)	Chronic ulcer of skin (1.087)	Dislocation, sprain and strain of joints and ligaments of shoulder girdle (0.8586)

Sequelae of poisoning by drugs, med icaments and biological substances (1.087)	Aortic aneurysm and dissection (1.0609)	Malignant neoplasm of stomach (1.0713)	Bacterial pneumonia, not elsewhere classified (0.8422)
Gastritis and duodenitis (1.0649)	Dislocation, sprain and strain of j oints and ligaments of shoulder girdle (0.8825)	Postprocedural respiratory disorder s, not elsewhere classified (1.0706)	Open wound of wrist and hand (0.8262)
Umbilical hernia (1.049)	Enlarged lymph nodes (0.7821)	Cholelithiasis (1.0693)	Special screening examination for n eoplasms (0.8235)
Malignant neoplasm of cervix uteri (0.9971)	Postprocedural respiratory disorder s, not elsewhere classified (0.7585)	Secondary malignant neoplasm of res piratory and digestive organs (0.9917)	Insulin-dependent diabetes mellitus (0.8152)
Noninflammatory disorders of ovary, fallopian tube and broad ligament (0.974)	850 (0.6887)	Benign mammary dysplasia (0.9914)	Paralytic ileus and intestinal obst ruction without hernia (0.8109)

Insulin-dependent diabetes mellitus (0.9269)	Other noninflammatory disorders of vulva and perineum (0.6836)	Gingivitis and periodontal diseases (0.9797)	Observation, without need for furth er medical care (0.7409)
Secondary malignant neoplasm of res piratory and digestive organs (0.9135)	Chronic ulcer of skin (0.6428)	Other chronic obstructive pulmonary disease (0.9633)	Acute myocardial infarction (0.7025)
Other noninflammatory disorders of vulva and perineum (0.865)	Dislocation, sprain and strain of j oint and ligaments of hip (0.6387)	Aortic aneurysm and dissection (0.9152)	Obesity (0.6952)
Mental and behavioural disorders du e to use of tobacco (0.8545)	Dislocation, sprain and strain of j oints and ligaments of head (0.6196)	Paralytic ileus and intestinal obst ruction without hernia (0.8735)	Personal history of malignant neopl asm (0.6901)
850 (0.8509)	Other cerebrovascular diseases (0.6025)	Osteoporosis without pathological f racture (0.8014)	Other diseases of oesophagus (0.6649)
Delirium, not induced by alcohol an d other psychoactive substances (0.7508)	Malignant neoplasm without specific ation of site (0.5877)	Malignant neoplasm of other and uns pecified parts of biliary tract (0.8013)	Dislocation, sprain and strain of j oints and ligaments at ankle and foot level (0.6579)
Malignant neoplasm of gallbladder a nd bile ducts (0.7488)	Chronic renal failure (0.5764)	Disorders of globe (0.7984)	Benign neoplasm of urinary organs (0.6276)
Mental and behavioural disorders du e to use of alcohol (0.7157)	Malignant neoplasm of other and uns pecified parts of biliary tract (0.5745)	850 (0.794)	Dislocation, sprain and strain of j oints and ligaments at wrist and hand level (0.6254)
Complications and misadventures in operative therapeutic procedures (0.685)	Acute myocardial infarction (0.5735)	Open wound of wrist and hand (0.7659)	Hypotension (0.6154)
Enlarged lymph nodes (0.6249)	Malignant neoplasm of gallbladder a nd bile ducts (0.5688)	Neoplasm of unspecified nature of d igestive organs (0.7392)	Cerebral infarction (0.6125)
Other diseases of gallbladder and b iliary (0.6058)	Gastric ulcer (0.5565)	Other septicaemia (0.717)	Disorders of sphingolipid metabolis m and other lipid storage disorders (0.5905)
Phlebitis and thrombophlebitis (0.5884)	Other chronic obstructive pulmonary disease (0.5372)	Symptomatic heart disease (0.7164)	Cutaneous abscess, furuncle and car buncle (0.5888)
Benign neoplasm of other and ill-de fined parts of digestive system (0.5648)	Synovitis and tenosynovitis (0.5352)	Mental and behavioural disorders du e to use of tobacco (0.6664)	Transient cerebral ischaemic attack s and related syndromes (0.5777)
Other venous embolism and thrombosi s (0.5452)	Convulsions, not elsewhere classifi ed (0.519)	Abnormal involuntary movements (0.6605)	Cholelithiasis (0.5719)
Acute myocardial infarction (0.5372)	Other diseases of oesophagus (0.5127)	Diseases of vocal cords and larynx, not elsewhere classified (0.6412)	Aortic aneurysm and dissection (0.5665)
Other surgical follow-up care (0.5349)	Other coagulation defects (0.512)	Other symptoms and signs involving the digestive system and abdomen (0.6085)	Other disorders of bone density and structure (0.5537)
Other noninfective gastroenteritis and colitis (0.5322)	Obesity (0.5105)	Dislocation, sprain and strain of j oints and ligaments of head (0.6056)	Unspecified diabetes mellitus (0.5417)
Unspecified acute lower respiratory infection (0.5144)	Disorders of sphingolipid metabolis m and other lipid storage disorders (0.4908)	Hypotension (0.5991)	Phlebitis and thrombophlebitis (0.5181)
Other diseases of oesophagus (0.5117)	Heart failure (0.4866)	825 (0.5963)	Synovitis and tenosynovitis (0.502)
Gastro-enteritis and colitis, excep t ulcerative, of non-infectious origin (0.4643)	Alcoholic liver disease (0.4693)	Atrial fibrillation and flutter (0.5832)	Other diseases of intestine (0.4841)
Malignant neoplasm of connective an d other soft tissue (0.4607)	None (0.4646)	Chronic diseases of tonsils and ade noids (0.5745)	Umbilical hernia (0.4795)

US-VA Healthcare system

Disease contribution to the risk assessment of cancer occurrence at different times between assessment and actual occurrence of cancer (US-VA)

Cancer in 0-6 months	Cancer in 6-12 months	Cancer in 12-24 months	Cancer in 24-36 months
Acute pancreatitis Other diseases of pancreas	Non-insulin-dependent diabetes mellitus Insulin-dependent diabetes mellitus Other specified diabetes mellitus	Non-insulin-dependent diabetes mellitus Insulin-dependent diabetes mellitus Other specified diabetes mellitus	Mental and behavioral disorders due to psychoactive substances use
Non-insulin-dependent diabetes mellitus Insulin-dependent diabetes mellitus Other specified diabetes mellitus	Mental and behavioral disorders due to psychoactive substances use	Mental and behavioral disorders due to psychoactive substances use	Non-insulin-dependent diabetes mellitus Insulin-dependent diabetes mellitus Other specified diabetes mellitus
Other symptoms and signs involving the digestive system and abdomen	Persons encountering health services in other circumstances	Persons encountering health services in other circumstances	Persons encountering health services in other circumstances
Persons encountering health services in other circumstances	Other symptoms and signs involving the digestive system and abdomen	Other arthritis	Benign neoplasm of digestive system
Mental and behavioral disorders due to psychoactive substances use	Other arthritis	Other symptoms and signs involving the digestive system and abdomen	Symptoms and signs involving the digestive system and abdomen
Other diseases of biliary tract	Mental and behavioral disorders due to psychoactive substances use	Symptoms and signs involving the digestive system and abdomen	Malignant neoplasm of prostate
Symptoms and signs involving the digestive system and abdomen	Benign neoplasm of digestive system	Benign neoplasm of digestive system	Symptoms and signs involving the circulatory and respiratory systems
Benign neoplasm of digestive system	Other diseases of biliary tract	Malignant neoplasm of prostate	Other arthritis
Other arthritis	Malignant neoplasm of prostate	Mental and behavioral disorders due to psychoactive substances use	Other symptoms and signs involving the digestive system and abdomen
Symptoms and signs involving the circulatory and respiratory systems	Symptoms and signs involving the circulatory and respiratory systems	Abnormal findings on examination of blood, without diagnosis Other disorders of thyroid	Abnormal findings on examination of blood, without diagnosis Other disorders of thyroid
Other diseases of pancreas	Symptoms and signs involving the digestive system and abdomen	Symptoms and signs involving the circulatory and respiratory systems	Age-related cataract and Other cataract
Mental and behavioral disorders due to psychoactive substances use	Acute pancreatitis Other diseases of pancreas	Other diseases of biliary tract	Glaucoma
Age-related cataract and Other cataract	Viral hepatitis	Acute pancreatitis Other diseases of pancreas	Viral hepatitis
Viral hepatitis	Essential (primary) hypertension I169	Radiation-related disorders of the skin and subcutaneous tissue	Mental and behavioral disorders due to psychoactive substances use
Malignant neoplasm of prostate	Abnormal findings on examination of blood, without diagnosis Other disorders of thyroid	Age-related cataract and Other cataract	Radiation-related disorders of the skin and subcutaneous tissue

Long term (current) drug therapy Encounters for other specific health care	Cellulitis	Viral hepatitis	Other disorders of urinary system
Special screening examination for other diseases and disorders	papulosquamous disorders	Other disorders of the skin and subcutaneous tissue	Other diseases of biliary tract
Symptoms and signs involving the skin and subcutaneous tissue	Non-insulin-dependent diabetes mellitus	Other disorders of urinary system	Cellulitis
Abnormal findings on examination of blood, without diagnosis Other disorders of thyroid	Age-related cataract and Other cataract	Follow-up examination after treatment for malignant neoplasms and others	Acute pancreatitis Other diseases of pancreas
Cellulitis	Other diseases of pancreas	Symptoms and signs involving the skin and subcutaneous tissue Oedema, not elsewhere classified Unspecified jaundice	Other disorders of the skin and subcutaneous tissue
Special screening examination for other diseases and disorders	Radiation-related disorders of the skin and subcutaneous tissue	Glaucoma	Other spondylopathies Dorsalgia Other dorsopathies, not elsewhere classified
Essential (primary) hypertension Hypertension Crisis	Symptoms and signs involving the skin and subcutaneous tissue Oedema, not elsewhere classified Unspecified jaundice	Dermatitis and eczema	Dermatitis and eczema
Overweight and obesity	Dermatophytosis	Special screening examination for other diseases and disorders	Cervical disc disorders Other intervertebral disc disorders Postprocedural musculoskeletal disorders, not elsewhere classified
Symptoms and signs concerning food and fluid intake	Special screening examination for other diseases and disorders	Other spondylopathies Dorsalgia Other dorsopathies, not elsewhere classified	Disorders of skin appendages
Other spondylopathies Dorsalgia Other dorsopathies, not elsewhere classified	Other spondylopathies Dorsalgia Other dorsopathies, not elsewhere classified	Heart disease	Symptoms and signs involving the skin and subcutaneous tissue Oedema, not elsewhere classified Unspecified jaundice
Paroxysmal tachycardia Atrial fibrillation and flutter Other cardiac arrhythmias Cardiac arrest Abnormalities of heart beat	Follow-up examination after treatment for malignant neoplasms and others	Cellulitis	Special screening examination for other diseases and disorders
Presence of other functional implants	Glaucoma	Diverticular disease of intestine	Heart disease
Other medical care	Other medical care	Encounters for other specific health care Long term (current) drug therapy	Follow-up examination after treatment for malignant neoplasms and others
Glaucoma	Other disorders of urinary system	papulosquamous disorders	Presence of other devices And other functional implants
Dermatophytosis	Other disorders of the skin and subcutaneous tissue	Other benign neoplasms of skin	Persons with potential health hazards related to socioeconomic and psychosocial circumstances

Follow-up examination after treatment for malignant neoplasms and others	Dermatitis and eczema	Cervical disc disorders Other intervertebral disc disorders Postprocedural musculoskeletal disorders, not elsewhere classified	Acquired deformities of fingers and toes
Other diseases of the urinary system	Cervical disc disorders Other intervertebral disc disorders Postprocedural musculoskeletal disorders, not elsewhere classified	Persons with potential health hazards related to socioeconomic and psychosocial circumstances	Other forms of heart disease
Symptoms and signs involving the skin and subcutaneous tissue Edema, not elsewhere classified Unspecified jaundice	Heart disease	Radiation-related disorders of the skin and subcutaneous tissue	Mental and behavioural disorders due to use of alcohol
Papulosquamous disorders	Persons with potential health hazards related to socioeconomic and psychosocial circumstances	Other malignant neoplasms of skin	Other malignant neoplasms of skin
Other disorders of the skin and subcutaneous tissue	Cholelithiasis	Acquired deformities of fingers and toes	Other benign neoplasms of skin
Other forms of heart disease	Symptoms and signs concerning food and fluid intake	Dermatophytosis	Diverticular disease of intestine
Diverticular disease of intestine	Other forms of heart disease	Other forms of heart disease	Nail disorders
Persons with potential health hazards related to socioeconomic and psychosocial circumstances	Corns and callosities	Pulmonary disease Chronic bronchitis	Varicose veins of lower extremities
Dermatitis and eczema	Diverticular disease of intestine	Mental and behavioral disorders due to use of alcohol	Symptoms and signs concerning food and fluid intake
Disorders of refraction and accommodation	Presence of other devices And other functional implants	Other diseases of digestive system	Other disorders of male genital organs
Cholecystitis Other diseases of gallbladder	Other diseases of digestive system	Varicose veins of lower extremities	Asthma Other chronic obstructive pulmonary disease
Other benign neoplasms of skin	Overweight and obesity	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere	Calculus of kidney and ureter
Varicose veins of lower extremities	Other disorders of male genital organs	Personal history of other diseases and conditions	Disorders of choroid and retina
Malignant neoplasm of trachea Malignant neoplasm of bronchus and lung	Acquired deformities of fingers and toes	Presence of other devices And other functional implants	Herpesviral [herpes simplex] infections
Cholelithiasis	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere	Other cerebrovascular diseases	Other venous embolism and thrombosis
Disorders of skin appendages	Other benign neoplasms of skin	Nail disorders	Dermatophytosis

Non-insulin-dependent diabetes mellitus	Encounters for other specific health care Long term (current) drug therapy	Other disorders of male genital organs	Angina pectoris
Mental and behavioral disorders due to use of alcohol	Nonrheumatic aortic valve disorders	Heart failure	Disorders of arteries, arterioles and capillaries in diseases classified elsewhere
Disorders of arteries, arterioles and capillaries in diseases classified elsewhere	Disorders of skin appendages	Non-insulin-dependent diabetes mellitus	Disorders of external ear in diseases classified elsewhere
Other disorders of male genital organs	Mononeuropathies of upper limb Other mononeuropathies	Disorders of external ear in diseases classified elsewhere	Inguinal hernia

Supplementary table 6: Checklist for supervised clinical ML study

Study design (Part 1)	**Completed:**	**page number**	**Notes if not completed**
The clinical problem in which the model will be employed is clearly detailed in the paper.	Y		
The research question is clearly stated.	Y		
The characteristics of the cohorts (training and test sets) are detailed in the text.	Y		
The cohorts (training and test sets) are shown to be representative of real-world clinical settings.	Y		
The state-of-the-art solution used as a baseline for comparison has been identified and detailed.	Y		

Data and optimization (Parts 2, 3)	Completed:	page number	Notes if not completed
The origin of the data is described and the original format is detailed in the paper.	Y		
Transformations of the data before it is applied to the proposed model are described.	Y		
The independence between training and test sets has been proven in the paper.	Y		
Details on the models that were evaluated and the code developed to select the best model are provided.	Y		
Is the input data type structured or unstructured?	X Structured	☐ Unstructured	

Model performance (Part 4)	Completed:	page number	Notes if not completed
The primary metric selected to evaluate algorithm performance (eg: AUC, F-score, etc) including the justification for selection, has been clearly stated.	Y		
The primary metric selected to evaluate the clinical utility of the model (eg PPV, NNT, etc) including the justification for selection, has been clearly stated.	Y		
The performance comparison between baseline and proposed model is presented with the appropriate statistical significance.	Y		

Model Examination (Parts 5)	**Completed:**	**page number**	**Notes if not completed**
Examination Technique 1[a]	Y		
Examination Technique 2[a]	Y		
A discussion of the relevance of the examination results with respect to model/algorithm performance is presented.	Y		
A discussion of the feasibility and significance of model interpretability at the case level if examination methods are uninterpretable is presented.	Y		
A discussion of the reliability and robustness of the model as the underlying data distribution shifts is included.	Y		
*Common examination approaches based on study type: * For studies involving exclusively structured data coefficients and sensitivity analysis are often appropriate * For studies involving unstructured data in the domains of image analysis or NLP: saliency maps (or equivalents) and sensitivity analysis are often appropriate			
Reproducibility (Part 6): choose appropriate tier of transparency			**Notes**
Tier 1: complete sharing of the code		X	

Tier 2: allow a third party to evaluate the code for accuracy/fairness; share the results of this evaluation	☐	
Tier 3: release of a virtual machine (binary) for running the code on new data without sharing its details	☐	
Tier 4: no sharing	☐	

PPV: Positive Predictive Value

NNT: Numbers Needed to Treat

[a] Common examination approaches based on study type: for studies involving exclusively structured data, coefficients and sensitivity analysis are often appropriate; for studies involving unstructured data in the domains of image analysis or natural language processing, saliency maps (or equivalents) and sensitivity analyses are often appropriate. Select 2 from this list or choose an appropriate technique, document each technique used on the appropriate line above.

Supplementary notes

Draft economic considerations for the design of clinical screening trial

Whether or not cancer is actually detected early in high-risk patients of course depends on the frequency and type of clinical tests performed in a surveillance program. Detailed deliberations with clinicians will be required to design the details of such a program, with considerations for minimizing cost and minimizing potential harm from invasive procedures. For cost considerations alone, we provide a hypothetical tradeoff algorithm (below). A surveillance program will also have to be supplemented with counseling, in analogy to genetic counseling, to provide patients with an informed choice and to minimize potential anxiety. The numerical estimates of performance of the risk assessment tool presented here are simply one of several considerations needed for the design of a surveillance program.

We propose a toy estimate of a practical scenario for a screening trial, taking into account typically available real-world data, the accuracy of prediction on such data, the estimated cost of a screening trial, the cost of clinical screening methods and the overall potential benefit of treatment.

The detailed design of a prediction-surveillance program, to be explored in a clinical setting, depends on the organization of a particular health care system. In a ‘walk in’ scenario, in approximate analogy to colonoscopic screening for colorectal cancer, patients older than, e.g., age 50 would be invited for assessment of their risk by the prediction tool on a yearly basis and, if identified as high-risk, offered a series of follow-up visits with extensive clinical testing. In a ‘national system’ scenario, possible in centralized health systems with location-independent centralized aggregation of electronic health records, risk assessment could be done on an ongoing basis, possibly for each patient whenever a new disease event occurs. If a high-risk prediction is triggered, the responsible physician would receive an alert. With a diversity of scenarios, it is reasonable to propose a clinical prediction-surveillance program tailored to the health system in a particular country.

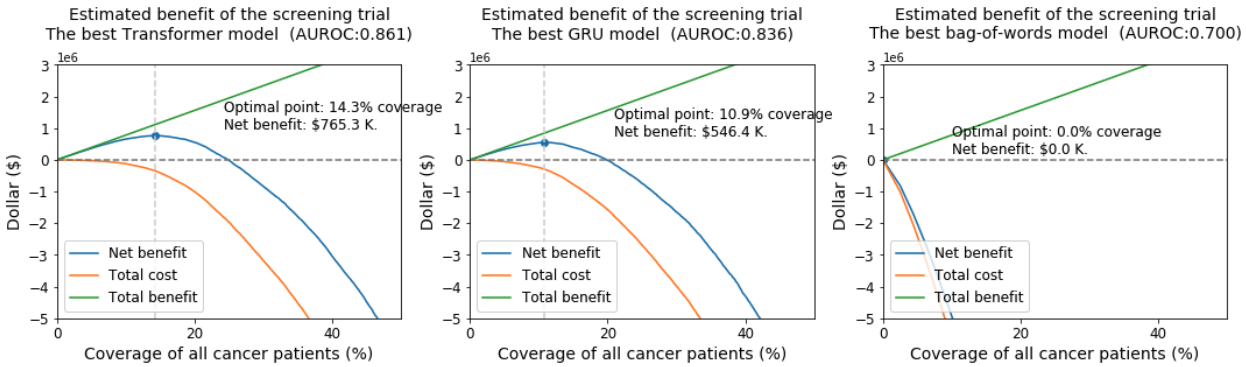
To illustrate the economic benefits of such a screening and to stimulate discussion regarding the optimal design of a prediction-surveillance program, we have made a first-order-estimate for a clinical screening trial of 10,000 people using the best model (the transformer model). For simplicity, we have made no assumptions regarding age distribution. In the calculation below, the cost of running the software on the entire population has been neglected, as it is marginal compared to the rest of the expenses (the algorithm can easily assess the risk using computers available in the hospitals, e.g., in less than an hour of run time on a single computer). Here is a simple economic model.

Net Benefit = Average benefit for each correctly identified cancer patient * TP

− Monitoring expense for each high-risk patient * P

− Basic cost per enrollee * N

where the screening cohort is N=10,000 and TP is the number of true positives, i.e., the number of correctly identified high-risk patients, and P is the number of actual positive patients, which we estimated using cancer incidence of the DNPR dataset. In our cost-benefit estimate, we arbitrarily set the screening trial cost at $200 per enrollee, the additional monitoring expense for a patient predicted at high risk by screening at $10,000 and the extra cost saved for advanced treatment for each monitored patient at $200,000, averaged over those in which cancer is detected (savings in excess of $200,000) and those in which it is not detected (no savings).



Estimate of financial benefits for different models. We analyzed each possible operational point and calculated the corresponding cost and benefit, using ballpark estimates. We plotted the net benefits as a function of coverage of cancer patients, i.e. recall or sensitivity. Covering more cancer patients plausibly leads to a larger total benefit, but the total cost also increases. The optimal point is picked for maximal net benefit.

An optimal decision threshold has to balance the cost of assessment and testing against the potential financial benefit for reducing treatment cost. Using this simplified model, we estimated the net benefits of different models with all possible operational points. Such a screening trial for 10,000 people would have $760,000 net benefit by choosing the balance between true and false positives such that the net benefit is optimal. This corresponds to a precision of 14.0% and a specificity of 99.7%. In contrast, a less good model GRU would have $540K net benefits but a bag-of-words model (baseline) would have no net benefits for any operational point because of the low incidence of pancreatic cancer.

The proposed concrete but hypothetical design of a screening trial is intended to guide the debate and ultimate decisions regarding implementation with clinicians and healthcare professionals. However, this calculation is based on roughly estimated numbers and does not reflect real-world cost analysis. Nor does this economic model

reflect the non-monetary benefits to patients' quality of life, which should be the dominant factor in the design of prediction-surveillance and early intervention programs. In a real-world scenario, clinicians and payers in a particular health system have the opportunity to optimize the design of such trials with realistic cost-benefit parameters, as well as consideration of communication ethics and the non-financial aspects of patient benefit.

A key challenge for future realistic economic estimates is the mapping between ICD (diagnosis) codes to CPT (billing) codes that are used for expense calculations and reimbursements. In addition, in the US, there is substantial geographical variability in reimbursement even for the same CPT/billing codes.

Comparison with surveillance programs based on family history and germline variants

Interestingly, the relative risk as reported in this study is comparable to that reported for patients with genetic risk factors such as mutations in the BRCA2, ATM, PALB2 and other genes or those with a high value of a polygenic risk score [3,4]; and, those with family history of pancreatic cancer are reported to have a 9x higher risk of pancreatic cancer (relative risk). But these criteria cover only a small fraction of the total population, as genetic or detailed family history data is available only in a relatively small number of patients and heritability is estimated to explain only 4-5% of all pancreatic cancers. In this work, complementary to established surveillance programs for patients with elevated risk based on germline variants or family history, the focus is on the application to the entire real-world patient population. The real-world AI approach casts a much wider net and supports application in practice in that running the prediction program routinely on, say, 1 million patients - is relatively inexpensive (see Result S1). In planning the scope of a realistic surveillance program, in addition to prediction performance, the cost of screening is a key leading factor in determining the fraction of high-risk patients nominated for a screening program in any particular health care system.

Information contribution as a function of time gap between of assessment and cancer occurrence

The exclusion of trajectories ending very close to pancreatic cancer removes the influence of disease codes that represent late symptoms of pancreatic cancer or are otherwise easily attributable to pancreatic cancer. However, data exclusion of such late events alone does not quantify the influence of longer term risk factors on prediction. We therefore computed the recall rate of prediction as a function of the time-to-cancer, defined as the time between the end of disease trajectory and the occurrence of cancer (Figure 5A, C). As expected, recall levels decrease with longer time-to-cancer, from 8% for cancer occurring about 1 year after assessment to a recall

of 4% for cancer occurring about 3 years after assessment (DNPR, Figure 5A). This suggests that the model not only learns from symptoms very close to pancreatic cancer but also from longer disease history, albeit at lower accuracy.

Survival curves for DNPR and US-VA datasets.

For the Danish dataset, five-year survival was 23% for Stage I, 8.3% for Stage II, 2.3% for Stage III, and 0.8 for Stage IV. Median survival was 645 days for Stage I, 483 days for Stage II, 262 days for Stage III, and 81 days for Stage IV.

For the US-VA dataset, five-year survival was 19.4% for Stage I, 8.8% for Stage II, 3.2% for Stage III, and 1.3% for Stage IV. Median survival was 424 days for Stage I, 330 days for Stage II, 243 days for Stage III, and 91 days for Stage IV.

Ordered for comparison:

Median survival [days]	*DNPR*	*US-VA*
Stage I	*645*	*424*
Stage II	*483*	*330*
Stage III	*262*	*243*
Stage IV	*81*	*91*

The uneven distribution of sex in the VA database may contribute to the differences in survival. The overall similarity of the survival curves in the two datasets adds some confidence to the quality of the data, as selected for the study.

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