


# Development of a stratification tool to identify pancreatic intraductal papillary mucinous neoplasms at lowest risk of progression

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## Summary

**Background:** Because most pancreatic intraductal papillary mucinous neoplasms (IPMNs) will never become malignant, currently advocated long-term surveillance is low-yield for most individuals.

**Aim:** To develop a score chart identifying IPMNs at lowest risk of developing worrisome features or high-risk stigmata.

**Methods:** We combined prospectively maintained pancreatic cyst surveillance databases of three academic institutions. Patients were included if they had a presumed side-branch IPMN, without worrisome features or high-risk stigmata at baseline (as defined by the 2012 international Fukuoka guidelines), and were followed  $\geq 12$  months. The endpoint was development of one or more worrisome features or high-risk stigmata during follow-up. We created a multivariable prediction model using Cox-proportional logistic regression analysis and performed an internal-external validation.

**Results:** 875 patients were included. After a mean follow-up of 50 months (range 12–157), 116 (13%) patients developed worrisome features or high-risk stigmata. The final model included cyst size (HR 1.12, 95% CI 1.09–1.15), cyst multifocality (HR 1.49, 95% CI 1.01–2.18), ever having smoked (HR 1.40, 95% CI 0.95–2.04), history of acute pancreatitis (HR 2.07, 95% CI 1.21–3.55), and history of extrapancreatic malignancy (HR 1.34, 95% CI 0.91–1.97). After validation, the model had good discriminative ability (C-statistic 0.72 in the Mayo cohort, 0.71 in the Columbia cohort, 0.64 in the Erasmus cohort).

**Conclusion:** In presumed side branch IPMNs without worrisome features or high-risk stigmata at baseline, the Dutch-American Risk stratification Tool (DART-1) successfully identifies pancreatic lesions at low risk of developing worrisome features or high-risk stigmata.

Djuna L. Cahen and Marco J. Bruno should be considered joint senior authors.

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## 1 | INTRODUCTION

Pancreatic cystic lesions are a common, often incidental finding. Recent large studies using magnetic resonance cholangiopancreatography revealed a remarkably high prevalence in the general population,<sup>1,2</sup> of up to 49% and even up to 60% for persons over 70 years.<sup>2</sup> Many of these lesions are neoplastic mucinous cysts, a subgroup with a varying risk of malignant progression, depending on pathological subtype and extent of pancreatic duct involvement.

Of all neoplastic cysts, side branch intraductal papillary mucinous neoplasms (SB-IPMN) are the most common and deemed to bear the lowest risk of harbouring malignancy or progressing to malignancy. Risk estimations were initially based on small, retrospective series, evaluating mainly resected SB-IPMN in tertiary referral centres.<sup>3–6</sup> They reported a risk of invasive carcinoma ranging from 11%<sup>6</sup> to 29%.<sup>3</sup> However, several recent studies indicate a much lower risk for incidentally found SB-IPMN. In 2015, a meta-analysis was published including 2177 patients under surveillance for SB-IPMN, of which only 82 (3.7%) developed a pancreatic malignancy.<sup>7</sup> Since then, several additional studies, each including at least 300 patients with at least 5 years of follow-up, reported a pancreatic cancer risk of only 0%–1.6% for small asymptomatic cysts.<sup>2,8–12</sup> However, all these studies were retrospective and the actual, long-term risk is yet to be determined by large and prospective studies.

Pending definite answers, the European,<sup>13</sup> AGA,<sup>14</sup> ACG,<sup>15</sup> and international Fukuoka<sup>16</sup> guidelines recommend surveillance with magnetic resonance imaging/magnetic resonance cholangiopancreatography and/or endoscopic ultrasound for all IPMNs, including small unsuspected cysts, in an attempt to detect pancreatic cancer in an early or even premalignant stage. These recommendations pose a considerable burden on patients and health care resources, whereas the clinical benefit with regard to survival remains to be proven.

There are currently no tools to distinguish IPMNs that do not warrant surveillance, or that are helpful in selecting a tailored and optimal surveillance interval. Previous prediction models have focused on identifying high-risk IPMNs to improve patient selection for surgery.<sup>17–24</sup> Although these models are valuable and necessary, the vast majority of SB-IPMNs do not progress. Therefore, we aimed to develop a prediction model that identifies patients with SB-IPMN at lowest risk of developing worrisome features or high-risk stigmata. Such a stratifying tool is needed to prevent redundant surveillance and reduce the burden for patients and health care systems.

## 2 | MATERIALS AND METHODS

### 2.1 | Study design

We included pancreatic cyst surveillance data from prospectively maintained databases of three academic institutions, namely the Erasmus University Medical Center, Rotterdam, the Netherlands; Columbia University Medical Center, New York, USA; and the Mayo Clinic Florida, Jacksonville, USA. At the Erasmus UMC, the study was exempt from institutional review board review (MEC-2018-1285). The

study received IRB approval at Columbia UMC (AAA08260(M01Y04)) and at the Mayo Clinic (14-007100). The need for written informed consent was waived by the Erasmus UMC and Columbia UMC. At the Mayo Clinic Florida, verbal informed consent was obtained from each participant before enrolment. The study was performed according to the declaration of Helsinki and the manuscript complies with the statement for the transparent reporting of a multivariable prediction model for individual prognosis or diagnosis (TRIPOD).<sup>25</sup>

### 2.2 | Participants

The databases contain all consecutive patients under surveillance for a pancreatic cyst since 2004 (Erasmus University Medical Center), 2003 (Columbia University Medical Center), and 2000 (Mayo Clinic Florida). From these databases, we selected patients with a radiologically presumed SB-IPMN who had been followed-up for at least 12 months. A subset of these patients have been described previously.<sup>26</sup> We excluded individuals with one or more worrisome features or high-risk stigmata at baseline, as defined in the 2012 international Fukuoka guidelines<sup>27</sup> (Figure 1).

### 2.3 | Endpoint and candidate predictors

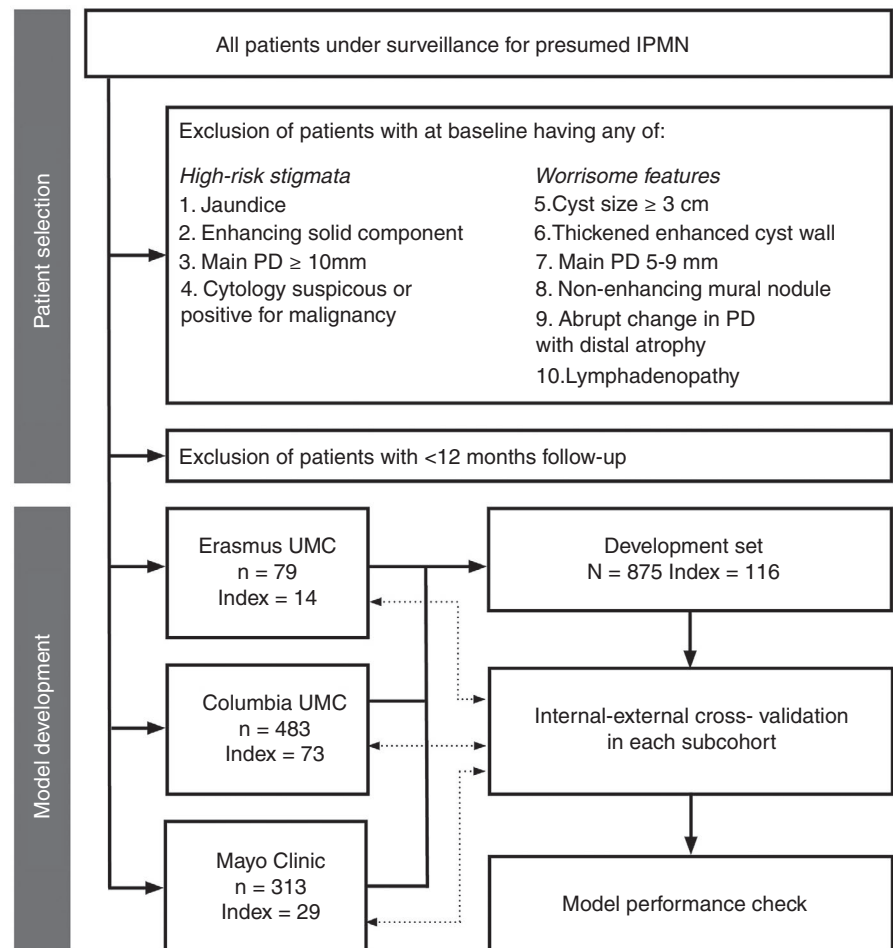
The endpoint was defined as the development of one or more worrisome features or high-risk stigmata according to the 2012 International Fukuoka guidelines. Candidate predictors were chosen based on prior publications and medical reasoning. Included in the analysis were age, personal history of diabetes mellitus (defined as having a previous diagnosis in electronic medical records), body mass index, ever having smoked personal history of acute pancreatitis, personal history of any type of extrapancreatic malignancy, family history of pancreatic ductal adenocarcinoma, multifocality of the cyst, and the diameter of the largest cyst. All variables were assessed at the time of cyst diagnosis.

### 2.4 | Statistical analysis

Missing data were imputed using multiple imputation by chained equations (MICE) based on the posterior distributions with five datasets with the MICE package in R software.<sup>28</sup> We used a Cox-proportional logistic regression analysis to develop a multivariable prediction model. A linear relation was the best approximation of the relationship between the endpoint and the continuous predictors. A backward stepwise selection procedure was performed with Akaike's Information Criterion as stopping rule, to limit overfitting and to prevent exclusion of important predictors. The final model with the best predictive ability was presented with hazard ratios, and 95% CIs calculated using a parametric approach, to indicate the individual predictor effects. The Cox-proportional hazard assumption was checked and showed nonsignificant results, indicating that proportional hazards can be assumed.

We first performed an internal validation with bootstrap resampling with 500 replications to shrink the model's coefficients to

**FIGURE 1** Flow-chart of patient selection and model development process



minimise overfitting.<sup>29</sup> Subsequently, we performed an internal-external validation of the final model, in which each subcohort was in turn omitted from the development set and subsequently used as validation set (Figure 1). Model performance in terms of discriminative ability was described with the Harrell's concordance statistic (C-statistic), which varies between 0.5 (a non-informative model) and 1.0 (a perfect model). The coefficients were used to calculate the probability of developing worrisome features or high-risk stigmata within three years and within 5 years, which is presented in a score chart. We used SPSS Statistics 22 (IBM Corporation, Armonk, New York, USA) and R Software version 3.3.5 (R foundation for statistical computing, Vienna, Austria) for the statistical analysis.

### 3 | RESULTS

#### 3.1 | Participants and clinical outcome

We included 875 patients. The mean age was 66 (SD 11.2) years, 37% (321) were male, 74% (648) Caucasian, and the mean body mass index was 27 (SD 4.9). At baseline, multifocal cysts were observed in 335 (38%) patients and the average diameter of the largest cyst was 12 mm (SD 6.4, see Table 1 for all baseline characteristics). After a mean follow-up of 50 months (SD 28.5, range 12-157) and a total follow-up of 3649 person-years, 116 (13.2%) patients developed one

or more worrisome features or high-risk stigmata. Table 2 shows the baseline characteristics according to outcome.

In the group who developed a worrisome feature, surgery was performed on 36 (31%) patients. Pathology showed an invasive carcinoma in three patients, high-grade dysplasia in six patients, low or moderate grade dysplasia in 22 patients, a neuroendocrine tumour in one patient, and a mucinous cystic neoplasm in four patients. In the group without a worrisome feature during follow-up, surgery was performed on 20 (2.6%) patients. Reasons for this included the presence of symptoms (other than jaundice or current pancreatitis), minor growth of a cyst smaller than 3 cm, an increased cyst fluid carcinoembryonic antigen level, a pancreatitis episode in the past (but not at the moment of cyst detection), the patient's wishes, or a combination of these reasons. In these cases, pathology showed only low or moderate grade dysplasia (18) or a mucinous cystic neoplasm (2). Of the non-operated patients, none were diagnosed with pancreatic cancer during follow-up.

#### 3.2 | Missing data and model specification

None of the patients had missing data for the endpoint, age, cyst multifocality, or initial cyst size. There was ≤ 5% missing data for smoking behaviour (4.5%), personal history of diabetes (0.6%), personal history of acute pancreatitis (2.1%), personal history of extrapancreatic malignancy (1.0%), and family history of pancreatic

**TABLE 1** Baseline patient and cyst characteristics

	Erasmus UMC (n = 79)	Columbia UMC (n = 483)	Mayo Clinic Florida (n = 313)
Patient characteristics			
Age, mean (SD), y	61 (11.0)	65 (11.9)	68 (9.5)
Male gender	20 (25.3)	197 (40.8)	104 (33.2)
Race			
Caucasian	64 (81.0)	295 (61.1)	289 (92.3)
Asian	2 (2.5)	20 (4.1)	3 (1.0)
Black	4 (5.1)	30 (6.2)	16 (5.1)
Other	4 (5.1)	16 (3.3)	1 (0.3)
Unknown	5 (6.3)	122 (25.3)	4 (1.3)
Diabetes mellitus	10 (12.7)	119 (24.6)	46 (14.7)
Body mass index, mean (SD)	27 (5.6)	27 (5.0)	27 (4.8)
Smoking ever	27 (34.2)	189 (39.1)	126 (40.3)
Alcohol ever	38 (48.1)	198 (41)	136 (43.5)
History of acute pancreatitis	9 (11.3)	48 (9.9)	13 (4.2)
History of extrapancreatic malignancy	12 (15.2)	195 (40.4)	84 (26.8)
Family history of PDAC	10 (12.7)	50 (10.4)	30 (9.6)
Cyst characteristics			
Location dominant cyst			
Head	52 (65.8)	188 (38.9)	141 (45.0)
Body	22 (27.8)	188 (38.9)	103 (32.9)
Tail	4 (5.1)	106 (21.9)	68 (21.7)
Multifocality	43 (54.4)	188 (38.9)	104 (33.2)
Largest diameter, mean (SD), mm	13 (6.6)	11.5 (6.5)	12 (6.1)

Note: Values presented as n (%) unless otherwise indicated.

Abbreviations: PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation.

ductal adenocarcinoma (4.3%). For body mass index, data were missing for 200 (23%) patients.

The model with the best fit included cyst size (HR 1.12, 95% CI 1.09-1.15), cyst multifocality (HR 1.49, 95% CI 1.01-2.18), ever having smoked (HR 1.40, 95% CI 0.95-2.04), history of acute pancreatitis (HR 2.07, 95% CI 1.21-3.55), and history of extrapancreatic malignancy (HR 1.34, 95% CI 0.91-1.97). The hazard ratios and 95% CI of each predictive variable in both univariable and multivariable analysis are shown in Table 3.

### 3.3 | Model performance

Bootstrap resampling showed limited optimism in the C-statistic of 0.02. In the internal-external validation, model performance varied between the three subcohorts. The model showed the best discriminative ability in the cohorts of Mayo Clinic Florida (C-statistic 0.72, 95% CI 0.61-0.84) and Columbia UMC (C-statistic 0.71, 95% CI 0.66-0.80). The performance within the Erasmus UMC cohort was 0.64 (95% CI 0.57-0.88).

### 3.4 | Score chart and example

The Dutch-American Risk stratification Tool (DART-1) visualises the estimated 3-year and 5-year risk of developing one or more worrisome features or high-risk stigmata for all possible predictor combinations (Figure 2A,B). A web-based application has been developed and is available at <https://rtools.mayo.edu/DART/> (Figure 3). When using the DART-1, a patient with a unifocal cyst smaller than 1 cm, without a history of acute pancreatitis, extrapancreatic malignancy or smoking, has an estimated 3-year risk of  $\leq 2\%$  and 5-year risk of  $\leq 5\%$  to develop one or more worrisome features or high-risk stigmata.

## 4 | DISCUSSION

In this international multicentre study, we describe the development of DART-1, the first version of a prediction model that does not focus on identifying IPMNs at high risk of malignancy, but on those at low risk instead. It is based on patient and cyst characteristics that

**TABLE 2** Patient and cyst characteristics separated on study endpoint

	Total (N = 875)	No development of WF or HRS (n = 759)	Development of WF or HRS (n = 116)
Centre			
Erasmus UMC	79 (9.0)	65 (8.6)	14 (12.1)
Columbia UMC	483 (55.2)	410 (54.0)	73 (62.9)
Mayo Clinic Florida	313 (35.8)	284 (37.4)	29 (25.0)
Patient characteristics			
Age, mean (SD), y	66 (11.2)	65 (10.9)	67 (12.8)
Male gender	321 (36.7)	271 (35.7)	50 (43.1)
Race			
Caucasian	648 (74.1)	568 (74.8)	80 (69.0)
Asian	25 (2.9)	22 (2.9)	3 (2.6)
Black	50 (5.7)	41 (5.4)	9 (7.8)
Other	21 (2.3)	18 (2.4)	3 (2.6)
Unknown	131 (15.0)	110 (14.5)	21 (18.1)
Diabetes mellitus	175 (20.0)	148 (19.5)	27 (23.3)
Body mass index, mean (SD)	27 (4.9)	27 (4.9)	27 (5.3)
Smoking ever	342 (39.1)	288 (37.9)	54 (46.6)
Alcohol ever	372 (42.5)	319 (42.0)	53 (45.7)
History of acute pancreatitis	70 (8.0)	54 (7.1)	16 (13.8)
History of extrapancreatic malignancy	291 (33.3)	246 (32.4)	45 (38.8)
Family history of PDAC	90 (10.3)	80 (10.5)	10 (8.6)
Cyst characteristics			
Location dominant cyst			
Head	381 (43.5)	329 (43.3)	52 (44.8)
Body	313 (35.8)	274 (36.1)	39 (33.6)
Tail	178 (20.3)	153 (20.2)	25 (21.6)
Multifocality	335 (38.3)	280 (36.9)	55 (47.4)
Largest diameter, mean (SD), mm	12 (6.4)	11 (6.0)	17 (6.7)

Note: Values presented as n (%) unless otherwise indicated.

Abbreviations: HRS, high-risk stigmata; PDAC, pancreatic ductal adenocarcinoma; SD, standard deviation; WF, worrisome feature.

can be assessed at the time of diagnosis, and predicts the 3-year and 5-year risk of developing worrisome features or high-risk stigmata as defined by the 2012 international Fukuoka guidelines. Such a model is important, as pancreatic cysts are diagnosed with increasing frequency and yearly imaging is generally recommended, even though the majority of lesions are at low risk of malignant progression. Using a stratifying tool, clinicians can make evidence-based risk estimations for progression in individual patients and identify those at lowest risk. The ultimate goal would be to decrease the burden of surveillance on patients, but also on health care resources by either

optimising surveillance intervals or, in selected cases, discontinue surveillance.

In our cohort, multivariable analysis resulted in five predictors for progression: cyst size, cyst multifocality, ever having smoked history of acute pancreatitis, and history of extrapancreatic malignancy. Cyst size being an independent predictor of progression comes as no surprise, given that a size of 3 centimetres or greater is defined as a worrisome feature<sup>27</sup> and therefore incorporated in our composite endpoint. However, it has been shown in other cohorts that initial cyst size is a predictor of cyst growth,<sup>30-32</sup> development

**TABLE 3** Candidate predictors with associated hazard ratios

Predictor	Univariable		Final multivariable model	
	HR	95% CI	HR	95% CI
Age	1.01	0.99-1.03	NA	NA
Body mass index	1.01	0.96-1.05	NA	NA
Smoking, ever	1.42	0.98-2.05	1.40	0.95-2.04
History of diabetes mellitus	1.37	0.89-2.12	NA	NA
History of acute pancreatitis	1.76	1.04-2.99	2.07	1.21-3.55
History of extrapancreatic malignancy	1.21	0.83-1.76	1.34	0.91-1.97
Cyst multifocality	1.65	1.14-2.41	1.49	1.01-2.18
Largest cyst diameter, per mm	1.12	1.09-1.15	1.12	1.09-1.15

Abbreviations: CI, confidence interval; HR, hazard ratio; NA, not applicable, was not included in the model with the best fit.

of other worrisome features,<sup>31,33</sup> and malignancy.<sup>12</sup> The predictive value of cyst multifocality has been described less often, but is not a new finding. Crippa et al followed 144 patients with SB-IPMN for 5 years, and found that an increase in the number of lesions was associated with the development of worrisome features or high-risk stigmata (OR 6, 95% CI 1.7-20.8).<sup>33</sup> It was also identified as predictor in an earlier analysis of a subset of our cohort.<sup>26</sup> A history of smoking and of acute pancreatitis are well-established risk factors for pancreatic cancer,<sup>34-37</sup> but not for the development of worrisome features in IPMN. Some studies suggest smoking accelerates progression of IPMN, and that it predicts invasive IPMN or concomitant pancreatic cancer in resected IPMN, but results are conflicting.<sup>38-41</sup>

A history of extrapancreatic malignancy has not been described as a predictor for progression in other cohorts. In the previous analysis of a subset of our cohort, a history of any extrapancreatic malignancy was not an independent predictor, but a history of prostate cancer was. This difference is most likely attributable to the difference in sample size. Retrospective studies have reported an increased incidence of extrapancreatic malignancies in patients with IPMN, but prospective studies were unable to confirm this.<sup>8,42</sup> Crippa et al did not find an association between extrapancreatic tumors and the development of worrisome features,<sup>33</sup> but because their cohort consisted of 144 patients of which only 26 developed worrisome features or high-risk stigmata, this may be due to a lack of power. The predictive value of a history of an extrapancreatic malignancy on progression of IPMN has to be confirmed by studies in other cohorts.

Having a history of diabetes was predictive in the univariable analysis but did not contribute significantly to the multivariable model and was therefore omitted from DART-1. The association between diabetes and pancreatic cancer is well-known,<sup>43-46</sup> but the association with IPMN is less established. Some studies have reported an increased risk for patients with diabetes to develop

IPMN,<sup>1,47</sup> but in another large population-based study, this association disappeared after correcting for age and body mass index.<sup>2</sup> Morales-Oyarvide et al showed that in patients with resected IPMN, preoperative diabetes is associated with high-grade dysplasia and invasive carcinoma,<sup>48</sup> suggesting diabetes has a proliferative effect on the cyst. However, to the best of our knowledge, there have been no studies that demonstrate that diabetes is associated with the development of worrisome features and high-risk stigmata. Although diabetes did not contribute to the predictive ability of the model in our cohort, it should be included in validation studies and future updates of DART-1, to further establish its value.

We encountered some minor differences between the subcohorts, the most noticeable being a higher prevalence of diabetes and personal history of extrapancreatic malignancy in the Columbia cohort, and more multifocal cysts in the Erasmus cohort. However, any meaningful differences between the subcohorts were ruled out by the internal-external validation. In this type of validation, each subcohort is in turn left out from the development set and used as a validation set. The final model is then based on all available data. Such an internal-external cross-validation can be used to demonstrate external validity of a prediction model, with the additional advantage that sample size is retained.<sup>49</sup> DART-1 performed similarly in the total cohort before validation (apparent performance), the Columbia cohort, and the Mayo cohort. The slight decrease in performance within the Erasmus cohort was expected and is attributable to this cohort's smaller sample size.

DART-1 shows promise, but should be interpreted with some caution. Foremost, prediction models are developed to augment, and not replace clinical judgment, and the given risks are estimates that therefore hold some extent of uncertainty. Also, it is crucial that DART-1 is validated in other cohorts before it is implemented in clinical care. We expect DART-1 will be highly generalisable because our development set encompasses three centres, each located in a different geographical region, and each collecting patient data in slightly different time periods. Also, our cohort consists of patients without complex cysts, and is therefore likely to be comparable to the patient population in the primary or secondary care setting. Additionally, we observed limited optimism in the C-statistic and, therefore, a good external performance is likely.

The main limitation of this prediction model is that it uses a composite, surrogate endpoint. Ideally it would predict development of malignancy. However, given the low cancer risk of SB-IPMNs, it would require extremely large cohorts to reach adequate numbers for statistical modeling. Although we collected one of the largest low-risk SB-IPMN cohorts, it did not yield enough pancreatic cancer cases for this purpose, and we are unable to make predictions on the development of malignancy. However, the ultimate objective of DART-1 is not to identify high-risk IPMNs, but those unlikely to develop into malignancy. Although it has been shown that worrisome features and high-risk stigmata accurately stratify for malignancy risk,<sup>50</sup> it is also known that a substantial number of IPMNs with a worrisome feature do not harbor high-grade dysplasia or invasive carcinoma,<sup>21-23</sup> which is supported by our own results. IPMNs



3-year risk of developing one or more worrisome features or high-risk stigmata									
(A)	Unifocal cyst				Cyst size (mm)	Multifocal cyst			
	Non-smoker		Current or former smoker			Non-smoker		Current or former smoker	
Acute pancreatitis history	25	31	32	39	28	33	41	42	50
	21	26	27	33	26	28	35	36	44
	17	22	22	28	24	24	29	30	37
	14	18	19	24	22	20	25	26	32
	12	15	16	20	20	16	21	21	27
	10	13	13	16	18	14	17	18	23
	8	10	11	14	16	11	14	15	19
	7	9	9	11	14	9	12	12	16
	5	7	7	9	12	8	10	10	13
	4	6	6	8	10	6	8	8	11
	4	5	5	6	8	5	7	7	9
	3	4	4	5	6	4	5	6	7
No acute pancreatitis history	2	3	3	4	4	3	5	5	6
	2	3	3	4	2	3	4	4	5
	14	18	18	23	28	19	24	25	31
	11	15	15	19	26	16	20	21	26
	9	12	12	16	24	13	17	17	22
	8	10	10	13	22	11	14	14	18
	6	8	8	11	20	9	11	12	15
	5	7	7	9	18	7	9	10	13
	4	6	6	7	16	6	8	8	10
	4	5	5	6	14	5	6	7	9
	3	4	4	5	12	4	5	5	7
	2	3	3	4	10	3	4	4	6
2	3	3	3	8	3	4	4	5	
2	2	2	3	6	2	3	3	4	
1	2	2	2	4	2	2	2	3	
1	1	1	2	2	2	2	2	3	
No		Yes			No		Yes		
History of extrapancreatic malignancy									

**FIGURE 2** The Dutch-American Risk stratification Tool (DART-1) to identify side branch intraductal papillary mucinous neoplasms (SB-IPMN) at low probability (%) of developing one or more worrisome features or high-risk stigmata within 3 y (A) or within 5 y (B)

without worrisome features harbour an even lower risk of developing pancreatic cancer, which strengthens the usefulness of DART-1 as a negative prediction tool that can be used to identify those SB-IPMNs that require less intense surveillance.

A second limitation is that we have based our endpoint on the 2012 international Fukuoka guidelines,<sup>27</sup> whereas these were revised in 2017.<sup>16</sup> Similar to the European guidelines,<sup>13</sup> the updated version includes elevated serum carbohydrate antigen 19-9 levels as a worrisome feature, as well as cyst growth. In our cohorts, serum

carbohydrate antigen 19-9 levels and exact cyst growth were not routinely determined and recorded in the past, because they were under surveillance long before guidelines stressed the importance of these parameters. Because previous studies have shown that cysts not necessarily display a linear growth pattern<sup>31,32</sup> and that there is a variability in size measurement between imaging modalities<sup>51</sup> and between observers,<sup>52</sup> it was not possible to reliably assess growth rate retrospectively. Therefore, we could not use the updated guidelines, and fast-growing IPMNs that did not reach

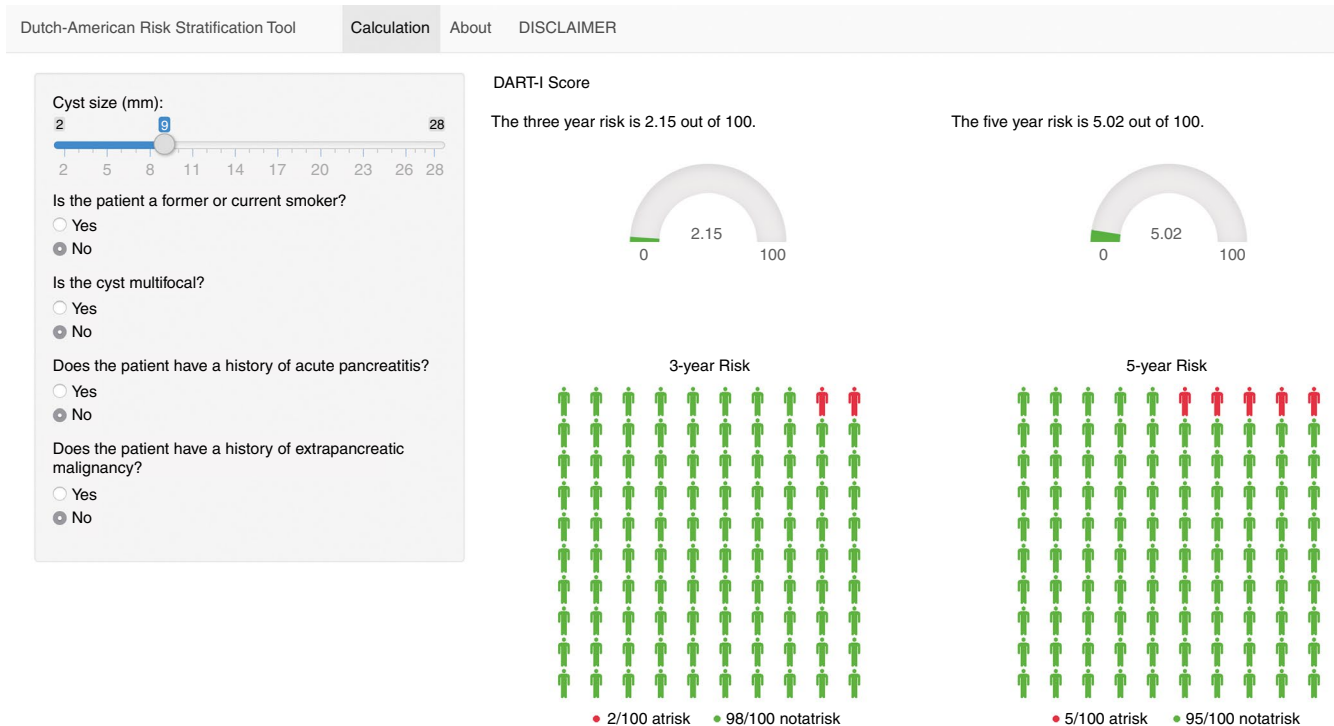
5-year risk of developing one or more worrisome features or high-risk stigmata									
(B)	Unifocal cyst				Cyst size (mm)	Multifocal cyst			
	Non-smoker		Current or former smoker			Non-smoker		Current or former smoker	
	No	Yes	No	Yes		No	Yes	No	Yes
Acute pancreatitis history	49	58	59	69	28	62	71	72	81
	42	51	52	62	26	54	64	65	74
	36	44	45	54	24	47	56	58	67
	31	38	39	47	22	41	49	50	60
	26	32	33	41	20	35	42	44	52
	22	27	28	35	18	29	36	37	46
	18	23	24	29	16	25	31	32	39
	15	19	20	25	14	21	26	27	33
	12	16	16	21	12	17	22	22	28
	10	13	14	17	10	14	18	19	24
	9	11	11	14	8	12	15	16	20
	7	9	9	12	6	10	13	13	17
	6	7	8	10	4	8	10	11	14
	5	6	6	8	2	7	9	9	11
No acute pancreatitis history	30	37	38	46	28	39	48	49	58
	25	31	32	39	26	34	41	42	51
	21	26	37	34	24	28	35	36	44
	17	22	23	28	22	24	30	31	38
	15	18	19	24	20	20	25	26	32
	12	15	16	20	18	17	21	22	27
	10	13	13	17	16	14	18	18	23
	8	11	11	14	14	11	15	15	19
	7	9	9	11	12	9	12	13	16
	6	7	7	9	10	8	10	10	13
	5	6	6	8	8	6	8	9	11
	4	5	5	6	6	5	7	7	9
	3	4	4	5	4	4	6	6	7
	3	3	3	4	2	4	5	5	6
History of extrapancreatic malignancy									

FIGURE 2 (Continued)

3 cm during the follow-up period, may have been misidentified as non-progressors. Now that serum carbohydrate antigen 19-9 levels and growth rates are routinely determined as per guidelines, it will be possible to include these variables as part of the study endpoint or as predictor in future updates. Another aspect that could not be completely ruled out, is if our dataset contained a bias by right censoring. However, the predictors in the model did not show an association with follow-up time, limiting the possible influence of this type of bias.

An issue of much debate is whether the risk of malignancy increases over time. Some recent studies have shown that even small SB-IPMN may evolve into malignancy after 5 or 10 years,<sup>11,12,33</sup> and that a stable cyst size for 5 years does not preclude future growth.<sup>53</sup> Because our study population has a mean follow-up of 50 months, we are not yet able to determine these long-term risks. At this point in time, this precludes us from stopping surveillance altogether, based on DART-1. Therefore, we do not advocate a complete stop of surveillance, but suggest a reduction of surveillance frequency for the





**FIGURE 3** Web-based application of the Dutch-American Risk stratification Tool (DART-1) with an example patient with low probability of developing one or more worrisome features or high-risk stigmata. The application can be found at <https://rtools.mayo.edu/DART/>

lowest risk SB-IPMNs, the ideal cut-off for which requires further calculation in external cohorts. It is essential to update DART-1 based on long-term, prospective data. Additional predictors should be explored, such as diabetes, glycated haemoglobin or serum fasting glucose, serum carbohydrate antigen 19-9 level, or other promising biomarkers. It may also be of interest to objectify smoking exposure, that is, using pack years as a predictor rather than a history of smoking. It is also conceivable that current smokers are at higher risk than former smokers. Cyst growth may also be a strong predictor, but including this will render the model unfit for use at the time of cyst diagnosis.

In conclusion, we have developed a prediction model that does not focus on detecting high-risk IPMNs, but identifies IPMNs at lowest risk of developing worrisome features or high-risk stigmata instead, by combining variables readily available at the time of cyst diagnosis. Even though DART-1 is the first version of this type of prediction model, it had a good performance in an internal-external validation, and high generalisability to other cohorts is expected. After DART-1 is externally validated by others, it can be used to explore varying surveillance strategies using looser follow-up policies for IPMNs at lowest risk. This very novel approach of stratifying IPMNs has the potential to protect patients with low-risk IPMNs from redundant medical interventions, and to reduce costs and the burden for the health care system.

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## AUTHORSHIP

**Guarantor of the article:** Marco J. Bruno.

**Author contributions:** MJB and DLC designed the study and initiated the collaboration. The study was supervised by them and by TAG and MBW. Data acquisition was performed by KAO, VG, PK, CB and PAR. Analysis of the data was performed by KAO and MA, and interpreted by them and MJB and DLC. The results were critically reviewed also by AS, TAG and MBW. The manuscript was drafted by KAO and MA, and critically reviewed by DLC and MJB. The final submitted manuscript including the authorship list was approved by all authors.

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