Supplemental Figures and Tables

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Managing incidental pancreatic cystic neoplasms with integrated mutational profiling is a cost-effective strategy

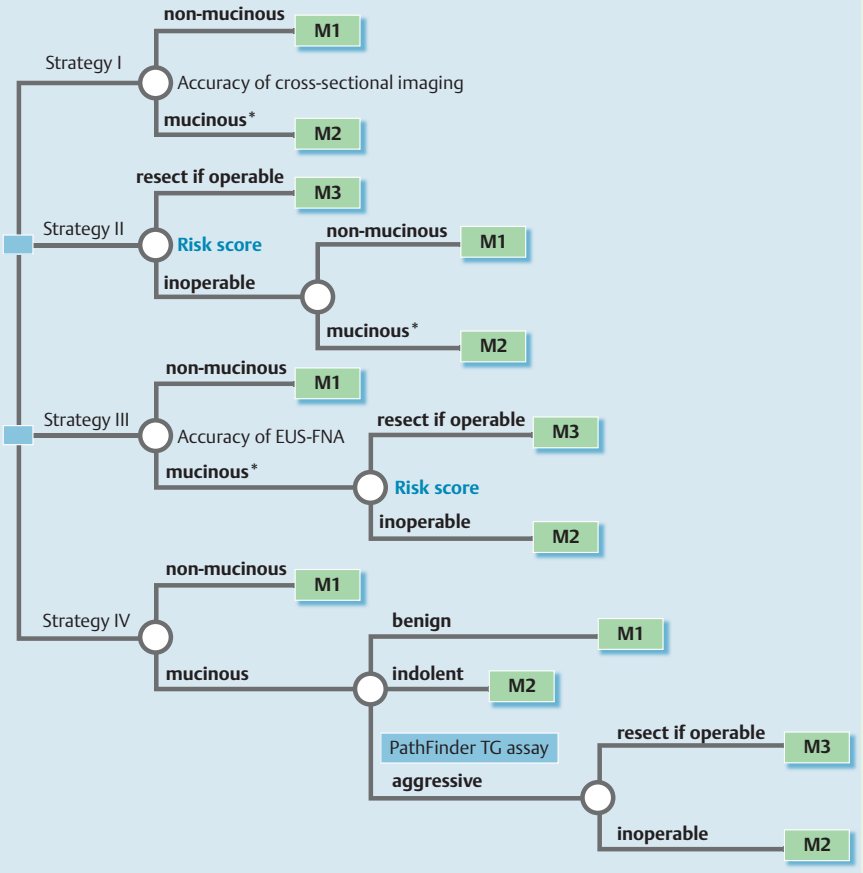

Fig. S1 Decision showing the different strategies. In simulations, each patient is taken through all 4 strategies. The circles labeled M1-M3 indicate Markov process, or an annually repeated simulation of any change in the state of the patient's cyst such as development of symptoms or emergence of malignancy.
Abbreviations: EUS-FNA, endoscopic ultrasound fine needle aspiration; M1-M3, Markov process.

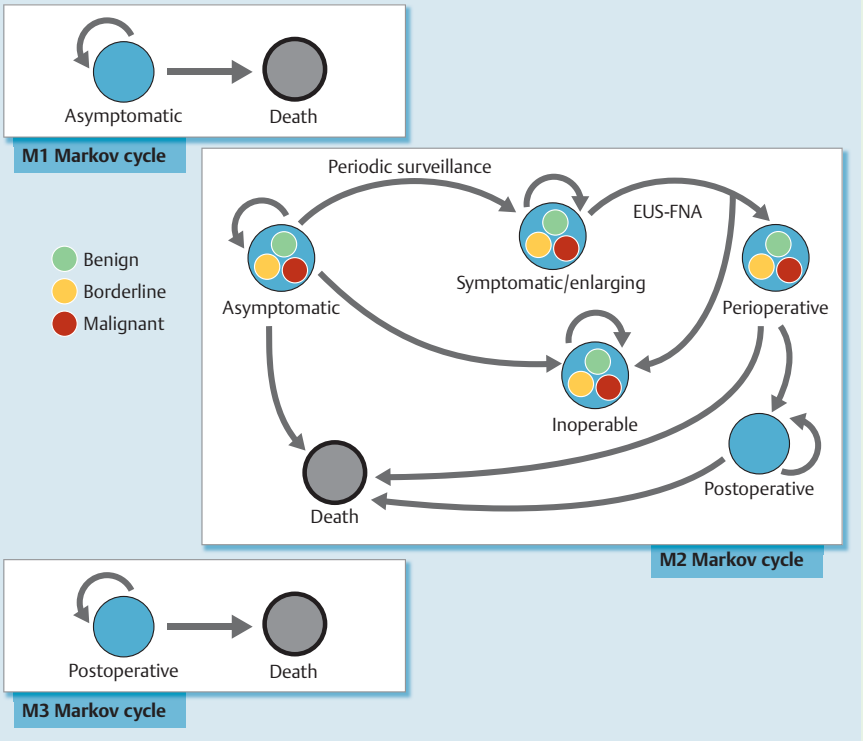

Fig. S2 Details of the Markov cycles M1-M3. M1 is used for non-mucinous lesions – these are assumed in the model to stay asymptomatic until the patient's ultimate (unrelated) death. Similarly M3 is used for patients' postoperative years, in which no further progression of the PCN occurs, and patients are assumed to have no further complications or death from the surgery. M2 is used for mucinous lesions, which may become symptomatic, enlarge (or develop similar high risk stigmata), transition to malignancy, and the patient may die from causes related or unrelated to the PCN.
Abbreviations: EUS-FNA, endoscopic ultrasound fine needle aspiration; M1-M3, Markov process.

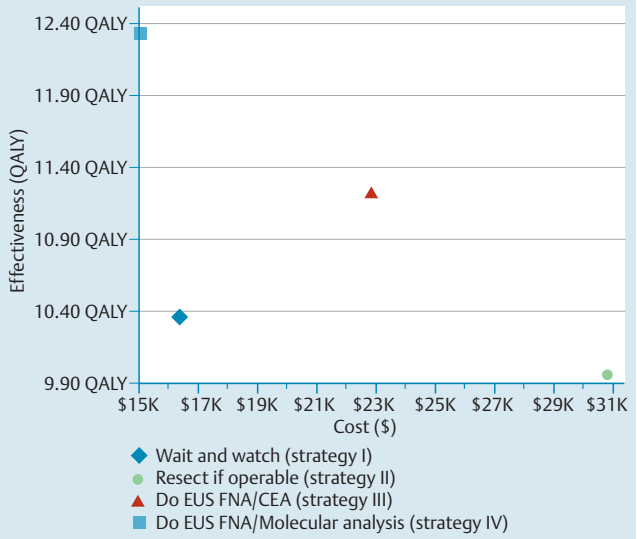

Fig. S3 Result of the baseline analysis showing cost (X-axis) and effectiveness (Y-axis) of the different strategies. Strategy IV is the most effective at equivalent cost to Strategy I is the preferred strategy. Conversely, Strategy II, the most expensive and least effective in term of QALY, is the least favored approach for management of these cysts.

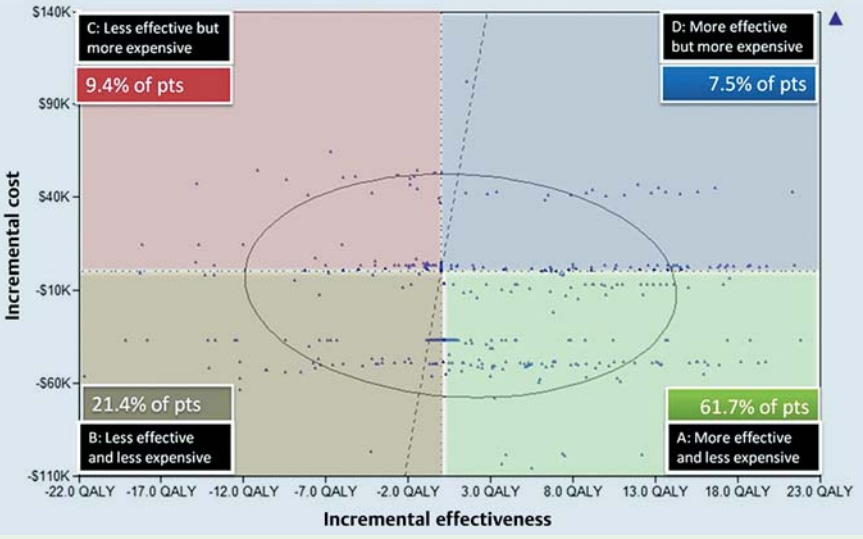

Fig. S4 (also shown as **Fig. 4** in the main manuscript) Results of a Monte Carlo simulation of 1000 patients. Each point represents the increase/decrease in cost (y axis) and QALY (x axis) for a particular patient when choosing Strategy IV over Strategy III. The lower right quadrant (A) represents patients for who Strategy IV was more effective than Strategy III and less expensive, so Strategy IV would clearly be preferred – 617 of the 1000 simulated patients fell into this quadrant. Conversely, in the upper left quadrant (C) Strategy IV was less effective but more expensive, in which case Strategy III would clearly be preferred – 94/1000 patients fell into this quadrant. Quadrants B (214/1000 patients) and C (75/1000 patients) correspond to more effective but more expensive and less effective but less expensive respectively, and thus determining the preferred strategy requires determining if extra cost is "worthwhile". When comparing incremental costs for different management strategies (via Incremental Cost Effectiveness Ratio), a key factor is societal Willingness to Pay (WTP), typically estimated at $ 50 K/QALY. This WTP level corresponds to a diagonal line, with points to the right of the line being considered "worth the cost" and those to the left, "not worth the cost"; a 95 % confidence ellipse is also shown. Thus one can see that most of the 75 patients falling in Quadrant D meet the WTP criteria, and in Quadrant B only a few do. However the patients included or excluded from Quadrant B and D are not enough to offset the high proportion of patients falling in Quadrant A (lower cost and more effective), which helps explain why Strategy IV was overall the most cost-effective.
Abbreviations: pts, patients.

Table S1 Estimates for model variables with supporting references.

Model variable	Strategies that use this variable	Baseline value	Range for sensitivity analyses	Supporting references
Development of malignancy (%)				
Cystic lesions that are non-mucinous (e. g., serous cystadenoma, pseudocyst)	All	30	10 – 60	[1 – 3]
Biological aggressiveness of mucinous cysts/ branch type IPMN (at presentation)	All			[2, 4 – 12]
Benign		65	0 – 100	
Borderline/indolent		20	0 – 100	
Malignant		15	0 – 100	
Probability of asymptomatic mucinous cyst or side-branch IPMN becoming symptomatic (years)	All			[5, 13 – 16]
Cyst is ≤ 3 cm		2	0 – 5	
Cyst is > 3 cm		10	1 – 15	
Probability of benign mucinous cystic lesion/branch type IPMN transitioning from benign to malignant (years)				[13 – 16]
Cyst is ≤ 3 cm		2.5	0 – 50	
Cyst is > 3 cm		5	0 – 50	
Probability of malignant cysts becoming symptomatic (annual)		25	0 – 100	Assumtion
Performance characteristics of diagnostic tests (%)				
Differentiating mucinous from non-mucinous cysts				
MRI/CT (sensitivity)	All	70	50 – 100	[2, 17]
CEA + cytology (sensitivity)	III, IV	80	50 – 100	[18 – 21]
CEA + cytology (specificity)	III, IV	65	0 – 80	
PathFinder TG + CEA + cytology (sensitivity)	IV	68	50 – 80	[22 – 25]
PathFinder TG + CEA + cytology (specificity)	IV	90	70 – 95	
Distinguishing aggressive from non-aggressive cysts				
PathFinder sensitivity	IV	82	70 – 90	[22 – 27]
PathFinder specificity	IV	85	70 – 90	
Mortality and utility (used in calculating QALY)				
Perioperative mortality		3	1 – 15	[28, 29]
Mortality from invasive malignant cysts (years)		10	0 – 5	[30, 31]
Utility of health states (years)				
Normal (%)		1.0	(N/A)	[32 – 34]
Incidental cyst (%)		1.0	0.75 – 1	
Symptomatic cyst (%)		0.95	0.7 – 1	
Postoperative state (%)		0.95	0.7 – 1	
Early cancer (%)		0.9	0.68 – 1	
Advanced cancer (%)		0.5	0.38 – 1	
Costs ($)				
Cross-sectional imaging (CT/ MRI)	All	1000	± 250	[30, 35 – 37]
EUS-FNA (including cost of sedation with monitored anesthesia care + CEA + cytology)	III, IV	1525	675 – 2675	
Pancreatic surgery		40 000	± 10 000	
Treatment for advanced malignancy – annual (e. g., chemotherapy and palliative care)		50 000	± 12 500	
PathFinder TG testing	IV	3100	2500 – 5000	Provieded by RedPath
Discount rate (%) (Correction for inflation/cost increases)		3	0 – 7	[38 – 39]

Abbreviations: MRI, magnetic resonance imaging; CT, computed tomography; CEA, carcinoembryonic antigen; EUS-FNA, endoscopic ultrasound fine needle aspiration.

Table S2 Surveillance intervals in the model.

Strategy	Scenario	Followup (Baseline)
I – Wait & watch	Asymptomatic	Annual for first 3 years, thereafter every 3rd year
	Symptomatic	Every 6 months
II – Resect if operable	Operable	Post-op surveillance every 3 years
	Non-operable	Surveillance without surgery
III – EUS-FNA Pos CEA	CEA Pos/Operable	post-op surveillance every 3 year
	CEA Pos/Non-operable	Every 3rd year
	CEA Neg/Asymptomatic	Annual for first 3 years, thereafter every 3rd year
	CEA Neg/Symptomatic	Increased surveillance (every 6 months)
IV - EUS + CEA + Cytology + Integrated Mutational Profiling	PFTG mucinous Pos/Benign/Asymptomatic	Annual for first 3 years, thereafter every 3rd year
	PFTG mucinous Pos/Benign/Symptomatic	Increased surveillance (every 6 months)
	PFTG mucinous Pos/Indolent/Asymptomatic	Annual for first 5 years, thereafter every 3rd year
	PFTG mucinous Pos/Indolent/Symptomatic	Increased surveillance (every 6 months)
	PFTG mucinous Pos/Aggressive/Operable	Post-op surveillance every 3 years
	PFTG mucinous Pos/Aggressive/Non-operable	Surveillance without surgery
	PFTG mucinous Neg/Asymptomatic	Annual for first 3 years, thereafter every 3rd year
	PFTG mucinous Neg/Symptomatic	Increased surveillance (every 6 months)

Abbreviations: CEA, carcinoembryonic antigen; Pos, positive; Neg, negative; PFTG, PathFinder TG.
Note: Surveillance in the model was based on the strategy and the diagnostic findings for the patient. The baseline surveillance regime was annual surveillance with cross-sectional imaging for 3 years and thereafter every third year. If symptoms emerged, the surveillance was increased to be twice as frequent as for asymptomatic cysts. After surgery, surveillance was done by cross-sectional imaging every 3 years.

Table S3 Patient operability score. **a** Components of patient operability score.

Components	Score
ASA score	
I	0
II	1
III	2
IV/V	10
Age score	
Age > 80 years1	3
Age 65 – 79 years	2
Age < 65 years	1
Location score	
Lesion in head of pancreas	3
Lesion in body of pancreas	2
Lesion in tail of pancreas	1
Size score	
Lesion size > 5 cm	1
Lesion size 4 – 5 cm	2
Lesion size ≤ 3 cm	3
Total operability score = ASA score + Age Score + Location Score + Size score	Maximum score: 3 Minimum Score: 19

Abbreviations: ASA, American Society of Anesthesiology.

Table S3 Patient operability score. **b** Probability of undergoing surgery corresponding to the total operability score.

Score	Probability
Score < 5	100
Score 5 – 7	66
Score 8 – 9	33
Score ≥ 10	0

Table S3 Patient operability score. **c** The American Society of Anesthesiologist classification system is used to stratify patients preoperatively by risk [40].

ASA	Patient's health	Status of underlying disease	Limitations on activities	Risk of death
I	excellent; no systemic disease; excludes persons at extremes of age	none	none	none
II	disease of one body system	well-controlled	none	none
III	disease of more than one body system or one major system	controlled	present but not incapacitated	no immediate danger
IV	poor with at least 1 severe disease	poorly controlled or end stage	incapacitated	possible
V	very poor, moribund		incapacitated	imminent

The total score defined the probability of an individual patient for undergoing surgical resection (**Table S3**) and also determined perioperative mortality in the patient. In our baseline analysis, a typical patient was considered to be in the age group of <65 years, with ASA score of III and with a 3 cm cystic lesion located in the tail of pancreas. The total score for such a patient would be 7 and the corresponding probability of this patient undergoing surgical resection was estimated at 66%.
In this manuscript, all cysts were in the head of the pancreas, so the Location Score was always 3, and the ASA score was always III by assumption.

Model assumptions

Primarily because of no or limited published information, several assumptions were made in this model.

1. It was assumed an incidental solitary pancreatic cystic lesion would be categorized into three main type viz. non-mucinous cystic lesion including serous adenoma, mucinous cystic lesion and branch type IPMN. Main duct or combined main and branch duct IPMT (mixed type) are quite distinctive histopathological entities with readily distinguishable imaging features and often require different clinical management. Other unrelated entities such as pseudocysts, simple cysts and cystic neuroendocrine tumor as well solid pseudopapillary lesions were not considered in this model.
2. In this model, we considered solitary lesions only and this limitation has been mentioned the discussion part of the revised manuscript. One objective was to keep the model as straight-forward as possible. Multiple lesions which are not uncommon present more difficult management decisions and is usually made on a case by case basis.
   Multiple cystic lesions in the pancreas are commonly seen with side branch or mixed type IPMN (which is considered to be at a lower risk of malignancy compared to MCN or main duct IPMN) and presence of multiple lesions usually discourages surgical intervention (because of need for extensive resection). In case surgical intervention is decided up on, it is usually based on symptoms related to a dominant lesion.
3. Although there have been a handful of reports of malignant transformation of serous adenoma, in this model, we considered them to have a benign natural history that did not mandate resection [2,41].
4. It was assumed that patients who would be selected for surgery and undergo surgery uneventfully would be expected to have complete resection of the cystic lesion but would undergo surveillance by cross-sectional imaging every 3 years. Although a recent report suggested that patients with pancreatic cystic lesions are at considerably high risk for developing pancreatic cancer in regions remote from cystic lesion, this was not considered in the model [42].
5. For cost and mortality estimates, it was assumed that all patients undergoing surgery would undergo laparotomy and resection would be done with either a Whipple procedure for lesions in the head of pancreas or distal pancreatectomy for body/tail lesions. No emerging surgical techniques such as laparoscopic distal pancreatectomy were considered.
6. With respect to EUS FNA, it was assumed that EUS FNA would be feasible in all patients. For simplicity, no complications related to EUS-FNA were considered in the model.[21,43] Complication rates related to EUS- FNA of pancreatic cysts are low and usually mild [43].
7. Endoscopic therapy of neoplastic pancreatic cysts by ablation of cystic epithelium has been reported but was not considered in this model because efficacy of such intervention has not been determined [44].
8. Due to lack of objective data, potential adverse impact of patient anxiety with respect to malignant potential of PCN on quality of life was not taken account into this model [45].

Sensitivity analysis

The robustness of the model was tested by performing sensitivity analysis with the important clinical probabilities and cost estimates. Given that the natural history of incidental pancreatic cystic lesions are not well-described, one-way and multi-way sensitivity analyses were performed using clinical variables such as the probability of borderline and malignant cystic lesion at presentation in patients with incidental pancreatic cysts and rates of progression from benign to borderline and malignant states in patients undergoing conservative follow up. In a hypothetical cohort of 1000 patients with incidentally diagnosed solitary pancreatic cystic lesion, a second-order Monte Carlo simulation was performed for a probabilistic sensitivity analysis. Monte Carlo simulation recalculates a model multiple times and incorporates uncertainties into an analysis in keeping with real-life situations [46]. In this method, sampling probability values from probability distributions (specifically, triangular distribution) of important variables (rather than from a single range defined by upper and lower bounds) places greater weight on likely combination of parameter values, and simulation results quantify the total impact of uncertainty on the model in terms of the confidence that can be placed in the analysis results. Tracker variables were used to compare the numbers of patients with unresectable malignant pancreatic cystic lesions and/or had undergone surgery among different strategies.

Outcomes and statistical methods

The primary outcomes compared among the three strategies were incremental cost-effectiveness ratio (ICER), and Net health Benefit (NHBI) Incremental cost-effectiveness ratio (ICER) was calculated as the difference in costs divided by the difference in outcome (life years) between the strategies (ICER = [Cost Strategy I –Cost Strategy II]/[Effectiveness Strategy I-Effectiveness Strategy II]). The ICER is a measure of the added cost for each additional life years gained by Strategy II. Also, the net health benefit (NHB) of an alternative option, which is increasingly being used in economic evaluation of healthcare intervention, was calculated using a formula: NHB = E - C/WTP, where E represents effectiveness, C represents cost, and WTP is the willingness to pay (i.e., the decision maker's threshold ICER).[47,48] The NHB is the health-effect of the treatment minus the benefit that one would have obtained by investing the resources spent on a marginally effective treatment. Incremental net health benefit (INHB) was calculated as the difference of two NHB. NHB is often preferred to ICER as a measure of cost-effectiveness because of its direct interpretation as the average health gained per patient who undergoes the alternative treatment adjusted for cost and willingness to pay. Also, unlike ICER, the NHB is a monotonic function of both health and cost. Higher values of NHB are always better. Health policymakers should favor a strategy for which the NHB takes the greatest positive value in relation to values of "willingness to pay" that seem reasonable with respect to known public policy. For analysis of the results of the Monte Carlo analysis, relative

risk with 95% confidence intervals and number needed to treat (NNT) were calculated.

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