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Consensus Guidelines in the Management of Branch Duct Intraductal Papillary Mucinous Neoplasm: A Cost-Effectiveness Analysis

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Abstract

Background and Aims—Based on consensus guidelines, surgical resection of branch duct intraductal papillary mucinous neoplasm (BD-IPMN) is indicated in patients with symptoms of cyst size ≥ 30 mm, intramural nodules, or dilated main pancreatic duct greater than 6 mm. The aim of this study was to determine the cost effectiveness of consensus guideline implementation in the management of BD-IPMN.

Methods—We developed a decision analytic model to compare the costs and effectiveness of three management strategies for a cohort of 60-year-old patients with branch duct IPMN: (1) surveillance using consensus guidelines for surgical resection (surveillance strategy), (2) surgical resection based on symptoms without surveillance (no surveillance strategy), and (3) immediate surgery (surgery strategy). The primary outcomes were quality-adjusted life years (QALYs), cost, and incremental cost-effectiveness ratio (ICER). Sensitivity analysis was performed over a wide ranges of estimates.

Results—The no surveillance strategy was the least costly, but also the least effective, while the surgery strategy was the most costly and most effective. Compared to the no surveillance strategy, the surveillance strategy cost an additional \$20,096 per QALY. The incremental cost-effectiveness ratio of the surgery strategy compared with the surveillance strategy was \$132,436 per QALY. In a probabilistic sensitivity analysis, if society was willing to pay \$50,000 per quality-adjusted life year gained, then 88.1% of patients using the surveillance strategy would be within budget.

Conclusions—Immediate surgery is the most effective, but may be prohibitively expensive. The surveillance strategy is a cost-effective option compared to no surveillance.

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Keywords

IPMN; Branch duct IPMN; Consensus guidelines; Cost effectiveness; Pancreatic cysts; Malignancy; Surgery

Introduction

Intraductal papillary mucinous neoplasm (IPMN) is characterized by precancerous mucin-producing epithelial cells causing dilatation of the pancreatic duct. In the setting of newer high-resolution imaging techniques, IPMNs have been increasing in prevalence, representing 1% of all pancreatic exocrine neoplasms [1]. Depending on the location of the dilatation, these lesions are further classified into three types—main duct, branch ducts, or mixed—and are known to progress to cancer. The frequency of malignancy (carcinoma in situ and invasive cancer) differs among the types of IPMN. Main duct IPMNs have a 57–92% risk of malignancy compared to branch duct IPMNs, which range from 6 to 46% [2–10]. In addition, invasive cancer has a poor prognosis. The overall 5-year survival is 36–67% with invasive cancer compared to 77–100% without [7,9,11–14].

Due to its higher risk of malignant transformation, patients with main duct IPMNs typically undergo surgical resection if they are operative candidates [15]. In comparison, the natural history of branch duct IPMN suggests slower progression to cancer [16–18]. Tanno et al. followed 82 patients with branch duct IPMN and found 13 patients with cystic duct enlargement or development of intramural nodules after a median 59-month follow-up [19]. Of those, seven patients underwent surgery, and only one had carcinoma-in situ. In another large cohort, Levy et al. calculated a 5-year actuarial risk of developing high-grade dysplasia or invasive cancer in branch duct IPMNs to be 15% compared to 63% in main duct IPMN [20]. This has led to many authors recommending conservative management using surveillance imaging of branch duct IPMN [21,22].

In 2006, the International Association of Pancreatology developed consensus guidelines for the management of IPMN. They recommended resection for IPMN with symptoms, cysts greater than 30 mm in size, intramural nodules, or dilation of main pancreatic duct greater than 6 mm [15]. Two follow-up studies evaluated the validity of these recommendations retrospectively for the detection of malignancy. Both studies found the consensus guidelines to have a sensitivity of 100% in diagnosing malignancy. However, the specificity of the guidelines was only 23–31%, which represented a relatively high resection rate for those without malignancy and raised concerns that the consensus guidelines were too aggressive [23,24]. As these guidelines become widely adopted, these effects may be magnified.

The aim of this study was to investigate the cost effectiveness of the consensus guidelines in the management of branch duct IPMN in comparison to no surveillance and immediate surgery.

Methods

We developed a decision analytical model using TreeAge 2008 (TreeAge Software Inc., Williamstown, MA) for a hypothetical cohort of 60-year-old patients diagnosed with branch duct IPMN in the head of the pancreas. Patients were managed according to one of three competing strategies: (1) surveillance using consensus guidelines for surgical resection (surveillance strategy), (2) immediate surgery after initial diagnosis of branch-duct IPMN (surgery strategy) and (3) surgical resection only on development of symptoms (no surveillance strategy). Details of each strategy are explained in the Electronic Supplementary Material.

The primary endpoints of this model were quality-adjusted life years (QALYs), cost in 2008 US dollars, incremental cost-effectiveness ratios (ICER), and incremental cost per life year gained. The secondary endpoints were death from cancer, surgical mortality, and proportion of patients undergoing surgery.

For each strategy, simulated patients entered a Markov model with either malignant or benign branch-duct IPMN and were followed over a lifetime horizon. Each patient transitioned every 6 months between relevant health states.

Base Case Patients

The base case cohort entering the model was comprised of 60-year-old patients found to have branch duct IPMN in the head of pancreas on either computed tomography (CT) or magnetic resonance imaging (MRI) with or without symptoms. Based on the literature, we estimated that 15% of the initial cohort would have malignant branch IPMN, of which 59% and 41% would be carcinoma in situ (CIS) and invasive cancer, respectively [15]. We assumed patients with non-invasive IPMN (i.e., adenoma, dysplasia, and CIS) would all have resectable disease. However, patients with invasive cancer were assumed to have resectable disease 80% of the time based on expert opinion (CFC, WRB) and the literature [25].

In the postoperative period, we modeled only those with invasive cancer for recurrence of cancer. According to the literature, patients with non-invasive IPMN have a low recurrence rate of cancer and have no disease-specific mortality in long-term follow-up, so for simplicity, we did not model recurrence of cancer in these patients [10,22,26]. Patients with invasive cancer who developed a first recurrence of cancer would undergo total pancreatectomy if resectable and would then develop postoperative diabetes. During each surgery, patients had a potential risk for complication or death from surgery. Patients with second recurrences of cancer were deemed unresectable. Figures 1 and 2 show the simplified Markov models.

Transition Probabilities

All transition probabilities with the exception of natural progression of IPMN were estimated from published literature and assumed a beta distribution [27]. We used published meta-analysis studies for estimates if available. Table 1 lists the base case estimates and ranges tested in the sensitivity analyses.

Costs

We analyzed our model from a societal perspective that included direct medical costs and indirect costs to patients during surgery (Table 2) [28]. We obtained the professional fees from 2008 Medicare reimbursement rates corresponding to the appropriate American Medical Association Current Procedural Terminology (CPT) [29]. The costs of hospitalization and surgical complications were derived from median hospitalization costs using diagnosis-related groups (DRG) based on the Nationwide Inpatient Sample [30]. We estimated societal costs of work productivity lost to both surgery and its complications using the 2008 US Census Bureau average household income adjusted for the total time off for surgery and its complications [31]. We estimated the average length of stay and recovery would be 4 weeks for a Whipple and an additional 4 weeks for surgical complications [32,33].

Cost estimates for all health states were derived from published literature that itemized direct inpatients and outpatient costs [34–36]. A log-normal distribution was used [27]. We converted all costs to 2008 US dollars by using the medical care component of the consumer price index and discounted all future costs at 3% per year [28].

Quality of Life

We derived our quality of life (QoL) estimates for each health state based on the available literature (Table 2). In patients with asymptomatic IPMN, we assumed an age-adjusted utility [37]. In postoperative states, studies have reported long-term quality of life and health utilities that were remarkably similar before and after the Whipple procedure, and accordingly, we did not adjust for these health states [38]. However, we made one-time utility reduction for surgical procedures and immediate postoperative period by assuming that post-procedure QoL utility would be 70% of pre-procedure [39]. A similar method was used for surgical complications, where we used a 4-week adjustment following a Whipple procedure and 4 additional weeks for surgical complications [32,33].

We assumed patients who had total pancreatectomy would have a similar QoL utility as patients with diabetes [40]. Patients with unresectable cancer would have the utility of terminal cancer [40,41]. We discounted all utilities at 3% per year [28].

Sensitivity Analysis

We performed a tornado analysis to determine the variables our model was most sensitive to and the thresholds where the most cost-effective strategy would change. Probabilistic sensitivity analysis was also performed to introduce simultaneously variability in all parameter estimates (see Electronic Supplementary Material).

Model Verification

Given the uncertainty of multiple parameters and our model structure, we compared published outcomes not used in our analysis to the outcomes from our model to verify our model output and search for any additional influential factors our model may not have accounted for. Specifically, we compared the survival curves of postoperative patients with and without invasive cancer.

Results

Model Verification

Our model predicted an overall 5-year survival of 41% among a cohort of 60-year-old postoperative patients with invasive IPMN compared with a mean 5-year survival of 46% with a range from 36% to 67% based on the literature [7,11–14,42]. For postoperative patients without invasive IPMN, our model predicted an overall 5-year survival of 94%. The literature reports a mean overall 5-year survival of 87% with a range from 77% to 100% [7,11–14,42]. Our model yielded 5-year survival curves similar to those of previously published studies.

Base Case Results

Table 3 shows the results of our base case analysis. We found that the no surveillance strategy was the least effective with 10.930 QALYs, but also the least costly at \$222,593. Compared to the no surveillance strategy, the surveillance strategy had an incremental effectiveness of 0.193 QALYs and incremental cost of \$3881, resulting in an ICER of \$20,096 per QALY. The surgery strategy was the most effective, but also the most costly with an incremental 0.151 QALYs and incremental cost of \$20,019 over the surveillance strategy, which resulted in an ICER of \$132,436 per QALY. In unadjusted life years, the surveillance strategy cost \$16,042 per life year gained compared with the no surveillance strategy.

Our base case showed that over an entire lifetime, death from invasive cancer and surgery was 11.2% and 4.4%, respectively, in the no surveillance strategy. This was compared to 9.7% of

patients in the surveillance strategy dying from invasive cancer and 4.5% from surgery. For the surgery strategy, 4.7% died from surgery, and 5.4% of patients died from invasive cancer.

Sensitivity Analysis

Based on the tornado analysis, the five most influential variables, in descending order, were age, cost of non-diabetic care, cost of postoperative care, annual discount rate, and quality of life utility value of the post-Whipple procedure. Using a \$50,000 willingness-to-pay threshold, we found that age, sensitivity, and specificity of consensus guidelines, and annual progression rate from adenoma to dysplasia/CIS have threshold values where strategies would change (Table 4). The surveillance strategy is cost effective at age below 78, sensitivity of consensus guidelines above 69.7%, and specificity above 13.6% compared to the no surveillance strategy. The surgery strategy became cost effective at annual progression rates from adenoma to dysplasia/CIS above 6.88% when compared to the surveillance strategy. We also performed additional one-way sensitivity analysis on costs and utilities (see Table 1 of Electronic Supplementary Material).

The results of the probabilistic sensitivity analysis are displayed as acceptability curves in Figure 3. Our simulated trials randomly sampled each parameter's probability distribution for each microstimulation. The median ICER between the no surveillance and surveillance strategies was \$23,802 per QALY (2.5 and 97.5 percentile, \$9,083 per QALY and \$58,763, respectively). The percentage of trials in the surveillance strategy that were within the willingness-to-pay threshold at \$25,000, \$50,000, and \$100,000 were 56.0%, 88.1%, and 99.4%, respectively. For example, if society was willing to pay \$50,000 per QALY for surveillance, then 88.1% of the patients in this simulation would be within budget. In addition, the net health benefit (NHB) becomes positive at a WTP threshold of \$20,291 for the surveillance strategy.

Discussion

The results of our analysis suggest that surveillance as recommended by the consensus guidelines may be a cost-effective strategy in the management of 60-year-old patients with a branch duct IPMN in the head of the pancreas in comparison to no surveillance. Despite having similar outcomes in terms of surgical mortality rates and the likelihood of receiving surgical intervention, patients in the surveillance arm had a 13.3% lower risk of death rate over their lifetime from invasive IPMN than patients in the no surveillance arm (9.7% vs. 11.2%). This resulted in an additional \$20,096 for each additional QALY gained with respect to no surveillance. Although immediate surgery may result in more QALYs and life expectancy, this gain came at a relatively high cost. The ICER of the surgery strategy compared to the surveillance strategy was \$132,436 per QALY, which would be considered expensive. In unadjusted life years, the surveillance strategy costs \$16,042 per additional life-year gained compared to the no surveillance strategy, which compares favorably to other screening practices such as mammography (\$34,000–\$88,000 per life-year gained) and colorectal screening (\$10,000–\$25,000 per life-year gained) [43,44].

The benefits of the surveillance strategy are its high sensitivity for the detection of malignancy compared to the no surveillance strategy and the reduction of some cases of unnecessary surgeries compared to the immediate surgery option. In many ways, the surveillance strategy can be considered as a hybrid or intermediate strategy between no surveillance and immediate surgical resection. However, the benefits of surveillance diminish based on age of the cohort, cost of postoperative care, and annual progression from adenoma to dysplasia/CIS.

We found that the ICER of the surveillance strategy compared to the no surveillance strategy increases with age. Although the willingness-to-pay threshold is ultimately a decision made

by society, hemodialysis has been used as the benchmark at \$50,000/QALY [45]. Using this threshold, our results show that at age below 78, the surveillance strategy is a cost-effective strategy when compared to the no surveillance strategy. However, at above age 78, the surveillance strategy surpasses the \$50,000 willingness-to-pay threshold. This would suggest that no surveillance can be considered as a management strategy for patients above this age as the benefits of early resection based on consensus guidelines are no longer cost effective.

In addition, as annual progression of adenoma to dysplasia/CIS increases, the surveillance strategy becomes less cost effective compared to the no surveillance strategy. The explanation for this somewhat paradoxical effect is that as progression to dysplasia/CIS increases, more cancers will be missed by the surveillance strategy as the interval between evaluations is fixed in the model. As a result, the surgery strategy becomes a more cost-effective strategy compared to the surveillance strategy. At annual progression rates above 6.88%, the surgery strategy becomes the most cost-effective strategy and dominates the surveillance strategy. This suggests that immediate surgery is the better management strategy if BD-IPMN adenoma progresses rapidly.

Our results also show that when sensitivity of consensus guidelines falls below 69.7%, the surveillance strategy dominates. In addition, when specificity of consensus guidelines is above 13.6%, the surveillance strategy becomes cost effective compared to the no surveillance strategy with ICER achieving the \$50,000/QALY threshold. Even though sensitivity was excellent in detecting cancer, the major drawback of the surveillance strategy was its poor specificity, which subjected a large number of patients to premature or unnecessary surgical intervention. In two recently published studies, the sensitivity and specificity of consensus guidelines were found to be 100% and 23–30%, respectively [23,24]. A specificity of 23–30% would mean 70–77% of patients would have a false-positive diagnosis of malignancy and therefore undergo unnecessary surgery. Our analysis reaffirmed this hypothesis, showing 76% of patients with non-invasive IPMN in the surveillance strategy eventually underwent surgery. We believe that the poor specificity of the consensus guidelines may be the result of the non-specific symptoms that arise from noninvasive IPMN at initial diagnosis, leading to unnecessary resection. The literature reports that 66% of patients with noninvasive IPMN have symptoms [46]. Because consensus guidelines also have symptoms as a criterion for resection, these symptomatic patients with non-invasive IPMN would undergo surgery. This would suggest that the specificity of the consensus guidelines may improve if symptoms were not used as one of the criteria for surgical resection. However, excluding symptoms as a criterion in the consensus guidelines will have to be considered carefully because the sensitivity of consensus guidelines may also be dramatically affected since 78% of invasive IPMN also have symptoms [46].

There are several limitations to this analysis. First, this study pertains to patients with a branch duct IPMN in the head of the pancreas. Applicability of our model to branch duct IPMN involving the body and tail of pancreas, small cysts, or multifocal branch duct IPMN may be limited. Second, there is uncertainty surrounding our parameter estimates. Specifically, there is a paucity of data on which to base estimates of parameters governing the natural history of IPMN. We estimated transition probabilities based on a calibration to the largest IPMN follow-up study known to date. To check our methodology and to validate these results, we verified the various transition rates by comparing our model predictions to outcomes from another study and corroborated our assumptions with experts. Third, our base case estimates are based on heterogeneous studies with varying study designs, patient populations and quality. In order to minimize these effects, we used systemic review whenever possible and performed both probabilistic and one-way sensitivity analysis over wide ranges of estimates. Fourth, our model is an oversimplification of reality. Each event can lead to a complex set of decisions and outcomes that may be difficult to model. To justify our simplification, we validated our model

and its assumptions using its predictions and comparing them to published results from the literature.

In conclusion, our analysis demonstrates that surveillance with current guidelines is a cost-effective strategy in the management of branch duct IPMN in the head of pancreas when compared to no surveillance. These findings are dependent on the underlying age of the population, specificity and sensitivity of consensus guidelines, and progression from adenoma to dysplasia/CIS. Although surgery could be more effective, it may be prohibitively expensive from a policy perspective. Future research should focus on natural history of IPMN progression and methods to improve the specificity of the consensus guidelines.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations

IPMN	Intraductal papillary mucinous neoplasm
QALY	Quality-adjusted life year
QoL	Quality of life
ICER	Incremental cost-effectiveness ratio
MRCP	Magnetic resonance cholangiopancreatography

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Fig. 1.

Simplified Markov decision tree for the surveillance and no surveillance strategies. All patients start from the BD-IPMN health state. In the surveillance strategy, patients transition to post-resection based on consensus guidelines, and in the no surveillance strategy, patients transition to post-resection based on symptoms. All other patients enter natural progression. Each semi-circular arrow represents a person remaining in that state. Patients continue between health states in 6-month cycles until death occurs

Fig. 2.

Simplified Markov decision tree for the surgery strategy. All patients start from the BD-IPMN health state and undergo surgery. Each semi-circular arrow represents a person remaining in that state. Patients continue between health states in 6-month cycles until death occurs

Fig. 3.

Acceptability curve of no surveillance versus surveillance strategies. Based on willingness-to-pay threshold (\$ per QALY) on the horizontal axis, the axis showed the proportion of our simulated trials in the Monte Carlo probabilistic sensitivity analysis that would fall within budget. For example, at \$50,000 willingness-to-pay (WTP) threshold, 88.1% of the simulated trials in the surveillance strategy were within budget. In addition, net health benefit (NHB) becomes positive at a WTP threshold of \$20,291 for the surveillance strategy

Table 1

Base case estimates

Variable	Base case estimate	Range tested	References
Age	60	40–80	
Probability of malignancy (CIS and invasive cancer)	15%	1–50%	[2–8,14,15,24]
Probability of malignancy being invasive	41%	15–80%	[2,3,7,8,15]
Consensus guidelines in detecting malignancy			
Sensitivity	99%	65–100%	[23,24]
Specificity	25%	10–50%	[23,24]
Pancreaticoduodenectomy			
Perioperative mortality	4.6%	1–10%	[32,47,48]
Perioperative morbidity	35%	20–65%	[32,47,48]
Annual probability of recurrence for invasive cancer	29%	15–40%	[11,49–51]
Cancer resectability			
Patient with missed invasive cancer	56%	25–80%	[9]
Patient with diagnosed invasive cancer	80%	50–100%	*, [25]
Annual probability			
Adenoma to dysplasia/CIS	2.93%	0.5–20%	[17], See Electronic Supplementary Material
Dysplasia/CIS to invasive cancer	30.5%	5–65%	[17], See Electronic Supplementary Material
Symptoms			
Invasive cancer	78%	50–100%	[46]
Noninvasive IPMN (adenoma, dysplasia/CIS)	66%	40–90%	[46]
Annual progression of symptoms in noninvasive IPMN	10%	1–20%	*
Annual probability of developing indication for resection	4%	0–10%	[17]

* Expert opinion (CFC, WBB from Massachusetts General Hospital—see acknowledgement)

Table 2

Cost and utilities estimates

Variable	Base case estimate	Range	References
Annual costs ^a			
MRI	\$544	\$250–\$1,500	[29]
Physician visit	\$44	\$10–\$100	[29]
Diabetes mellitus health care	\$12,131	\$3,000–\$25,000	[34]
Non-diabetic mellitus health care	\$5,263	\$500–\$15,000	[34]
Pancreaticoduodenectomy	\$61,807	\$25,000–\$120,000	[29,30]
Surgical complications	\$23,709	\$10,000–\$55,000	[29,30]
Postoperative care	\$6,858	\$1,000–\$15,000	[34,36]
End-of-life costs	\$32,547	\$10,000–\$60,000	[35]
Utilities ^b			
Post-Whipple procedure	100%	70–100%	[38]
Unresectable cancer	69%	30–80%	[41]
Diabetes	88%	60–100%	[40]
Penalty toll for pancreaticoduodenectomy (4 weeks) ^c	–30%	10–60%	[39]
Penalty toll for surgical complications (4 weeks) ^c	–30%	10–60%	[39]
Annual discount rate	3%	1–5%	[28]

^a Adjusted to 2008 US dollars

^b Calculated as percent of age-adjusted utility [37]

^c QoL reduction for surgery and complications were subtracted as percent of pre-surgery, pre-complications utility [39]

Table 3

Results of cost effectiveness from base case analysis

Strategy	Cost ^a	Effectiveness ^b	Incremental cost/effectiveness ^c
No surveillance	\$222,593	10.930	–
Surveillance	\$226,474	11.123	\$20,096
Surgery	\$246,493	11.274	\$132,436

^a Average discounted lifetime cost per patient in 2008 US dollars^b Discounted QALYs^c For surveillance strategy, incremental cost-effectiveness compared to non-surveillance strategy. For surgery strategy, incremental cost-effectiveness compared to surveillance strategy

Table 4

Calculated ICER from one-way sensitivity analysis on selected parameters

Variable (base case estimate)	Range	Surveillance versus no surveillance ^d	Surgery versus surveillance ^d
Age (60 years old)	40	\$16,482	\$54,605
	50	\$17,322	\$74,551
	60	\$20,096	\$132,436
	78	\$50,000 ^b	Dominated
	80	\$63,056	Dominated
Sensitivity of consensus guidelines (99%)	65%	Dominated	\$69,423
	69.7%	\$50,000 ^c	\$69,954
	80%	\$22,496	\$82,248
	90%	\$20,711	\$101,479
	99%	\$20,096	\$132,436
Specificity of consensus guidelines (25%)	100%	\$20,049	\$137,365
	10%	\$56,500	\$129,371
	13.6%	\$50,000 ^c	\$128,609
	25%	\$20,096	\$132,436
	40%	<i>_d</i>	\$134,236
Annual progression from adenoma to dysplasia/CIS (2.93%)	50%	<i>_d</i>	\$134,848
	0.5%	\$10,395	Dominated
	1%	\$12,696	\$3,757,306
	6.88%	\$28,567	\$50,000 ^e
	10%	\$31,180	\$35,099
Post-Whipple utility (100%)	20%	Dominated	\$24,400
	70%	\$27,937	Dominated
	80%	\$24,721	Dominated
	90%	\$22,170	Dominated
	95%	\$21,082	\$315,233
Probability of malignancy (15%)	100%	\$20,096	\$132,436
	1%	\$11,944	\$137,072
	5%	\$18,609	\$135,851
	15%	\$20,096	\$132,436
	35%	\$20,547	\$123,505
Surgical mortality (4.6%)	50%	\$20,650	\$113,965
	1%	\$20,069	\$98,146
	2%	\$20,076	\$105,73
	4.6%	\$20,096	\$132,436
	5%	\$20,100	\$139,753
Surgical morbidity (35%)	10%	\$20,149	\$342,772
	20%	\$20,016	\$129,450
	30%	\$20,069	\$131,494

Variable (base case estimate)	Range	Surveillance versus no surveillance ^a	Surgery versus surveillance ^a
	35%	\$20,096	\$132,436
	50%	\$20,175	\$135,275
	65%	\$20,254	\$138,135

^a ICER—\$/QALY

^b Age at which surveillance strategy reaches \$50,000 willingness-to-pay threshold

^c Sensitivity and specificity of Consensus Guidelines at which surveillance strategy reaches \$50,000 willingness-to-pay threshold

^d No surveillance strategy dominated

^e Annual progression at which surgery strategy reaches \$50,000 willingness-to-pay threshold