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Projected Effect of Fecal Immunochemical Test Threshold for Colorectal Cancer Screening on Outcomes and Costs for Canada using the OncoSim Microsimulation Model

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Highlights

- The effect of FIT threshold on colorectal cancer screening outcomes is modelled
- Modelling uses reported results on FIT threshold and clinical sensitivity
- Lower FIT thresholds are predicted to result in reduced cancer mortality
- Cost effectiveness increases with declining FIT threshold

ABSTRACT

BACKGROUND: Immunochemical faecal testing (FIT) is used in Canada for colorectal cancer (CRC) screening. The threshold for FIT abnormality is under operator control and this study uses a simulation model to predict the effect of threshold selection on outcomes

including years-of-life gained, CRC incidence and mortality, and direct health system costs.

METHOD: The OncoSim Model was used to predict outcomes of biennial screening between ages 50-74 years in a cohort aged 45 years followed until death for eight FIT threshold values between 50 and 225 ng/ml. The literature on FIT performance was reviewed and seven parameter sets of sensitivity and specificity values by FIT threshold were created to span published variation in test performance in subjects with CRC, adenomas or no colorectal neoplasia.

RESULTS: Reducing the FIT threshold reduced both projected CRC incidence and mortality for all parameter sets, although cost impacts and cost-effectiveness varied compared to no screening. Biennial FIT was projected to be cost-effective at all thresholds considered with a maximum of CAD$ 5,400 per QALY over the seven parameter sets and a maximum of CAD$ 6,800 per QALY for a one level change in the eight threshold levels considered. Demand for colonoscopy varied strongly with FIT threshold and was greatest for the lowest threshold (50 ng/ml) but the magnitude varied across the 7 parameter sets.

CONCLUSIONS: Compared to no screening, all thresholds of FIT examined were predicted to be cost-effective in the prevention and management of CRC. Threshold choice strongly influences predicted demand placed upon colonoscopy resources.

INTRODUCTION

Colorectal cancer (CRC) is the second most common cancer and cancer cause of death in Canada (1) and the fourth most common worldwide (2). Screening has been found to be effective in reducing incidence and mortality of the disease (3-9). Consequently, CRC screening programs have been implemented in a number of countries (10), including Canada (11).

All 10 Canadian Provinces have instituted screening programs which vary somewhat in their implementation (12). Provinces separate their populations by CRC risk for the purposes of screening policy. High-risk subjects are those with a predisposition to CRC by virtue of a strong family history or genetic alterations. Elevated risk definitions vary

and are based upon age, a personal history of adenomas or a moderate family history of CRC or adenomas. Average risk for screening consists of the population between ages of 50 and 74/75 who are not classified as high or elevated risk (12). The proportion classified as average risk in each Province will depend upon the definition of the elevated risk group but generally exceeds seventy-five per-cent of the population. Screening of the average risk is based upon self-collected biennial faecal occult blood testing with eight provinces utilising Faecal Immunochemical Tests (FIT) and two guaiac (gFOBT) based tests. Currently, colonoscopy is used for the evaluation of abnormal faecal test results (13) and has been recommended for screening of those at elevated and high risk (12).

Despite widespread adoption of FIT there is no supporting randomized control trial (RCT) evidence proving that FIT results in reduction of CRC incidence or mortality, although observational evidence has been reported (14). Motivation for use of FIT derives from its increased acceptability compared to gFOBT (15), reduction in colorectal cancer mortality associated with gFOBT testing (16,17), the demonstrated ability of FIT to identify subjects who have adenomatous polyps, the adenoma-carcinoma sequence (18) of CRC development, and RCT demonstration that removing polyps results in reduced subsequent risk of CRC (7-9,19,20). (7,7-9,9) However, these lines of evidence do not directly indicate the magnitude of long term benefits of screening with FIT. Furthermore, several commercially available FIT tests are quantitative, thus permitting the operator to determine the threshold for abnormality and influence the sensitivity and specificity of the resulting testing. The relative effect of threshold choice on longer-term outcomes has not been observed and this is of interest since thresholds of 50, 75, 100 and 175 ng/ml are used within Canada (12).

A way to project long-term benefits of CRC screening options is through micro-simulation modelling of the population incorporating the natural history of CRC development and screening options. This approach was used in the planning and implementation of CRC screening services in the Netherlands (21). Such a model can simulate the effect of various thresholds within a framework calibrated to appropriate incidence, survival, mortality and health costs. The OncoSim model (formerly named the Cancer Risk Management Model,

or CRMM) which has been developed by the Canadian Partnership Against Cancer, is an example of a decision-making tool that can be used to evaluate the impact of interventions aimed at reducing the impact of cancer (22). OncoSim-CRC has been previously described, validated, and used to compare different modalities and options for CRC screening (23). Here we use OncoSim-CRC to undertake an analysis of the effect of FIT threshold, incorporating a sensitivity analysis to reflect uncertainty in the underlying parameters, on projected long-term CRC outcomes. The perspective taken is third party payer.

METHODS

Model

OncoSim-CRC has been calibrated using disease patterns and health care costs for the Canadian population. Users are able to view and change model parameter values but are provided with a suggested set (base case). The OncoSim-CRC includes a natural history model for the development of CRC (Appendix File Figure 1). CRC is assumed to develop from adenomatous polyps that spontaneously arise and can grow or regress through three size groupings: 0-5mm, 6-9mm, 10+mm. Colorectal cancer may develop from any size of adenoma according to specific rate parameters. New CRCs are all assumed to initially be Stage I preclinical (no symptoms) and can progress to higher stages and remain preclinical or become clinical (detected) according to specified parameters. Adenomas or cancers in a preclinical stage are assumed be potentially detectable by screening. The likelihood of a positive FIT test is assumed to be determined by a subject's most advanced lesion. The probability a lesion will be identified by diagnostic follow-up is assumed to be independent of any other lesions present. The model was calibrated to replicate the prevalence of adenomas (by age, sex and size) taken from the literature (23) and the age- and sex-specific CRC incidence and mortality rates for the Canadian population. Subjects were assumed to be at risk from all-cause mortality using Canadian age-, sex- and year-of-birth-specific mortality rates. Stage-specific treatment pathways for colon and rectal cancers were obtained using expert opinion and a review of medical records (24) and costs and utilisation

rates were obtained from Canadian sources (22). Survival distributions were based upon cases diagnosed in the Ottawa region of Ontario (24). Costs were taken from the Ontario Health Insurance Plan and Ontario Case Costing Initiative (25) and base-case screening parameters (sensitivity and specificity) were obtained from the literature.

Summarizing Test Performance and Variability by Threshold

Test performance is captured by the sensitivity and specificity for disease states within the model. To simplify presentation, we will use the general term test positivity rates (TPR), which are the FIT sensitivity rate in subjects with disease (CRC or adenoma) and the false-positive rates in subjects without neoplasia. It was anticipated that there would be variability in the TPR's taken from different studies and it was desired to capture this for a sensitivity analysis of projections made using OncoSim. However, studies are not uniform in the threshold levels considered and disease categories assessed. By construction, the TPR for each disease state is non-decreasing with declining threshold within any study. This property holds for coherent descriptions of the relationship between threshold and TPR. Therefore, we elected to use a mathematical form (logistic model) which had this property to describe the relationship between threshold and TPR. The logistic model with a single covariate (threshold value) contains two parameters for a given disease state: location and scale. The scale parameter measures the (logistic) rate of change of response (TPR) with changes in threshold whereas the location relates to the TPR at a fixed threshold. For simplicity we selected the location parameter to indicate the response at a threshold of 100 ng/ml, so that

$$logit\ (TPR) = \alpha + \beta(T - 100),$$

where, α (location) determines the response at 100 ng/ml, T is the threshold and β is the rate of change with threshold (scale). This description also allows the calculation of relative rates comparing two or more threshold values. The formulation using the logistic function permitted sensitivity analysis across all thresholds simultaneously by varying the two parameters, rather than undertaking a separate sensitivity analysis at each threshold.

Estimating the Logistic Parameters

Several different FIT tests are manufactured and for liquid based tests, measured blood concentrations have traditionally been expressed as nanograms per millilitre (ng/ml) based upon buffer volume. These units were retained here as most publications reviewed expressed them in this form although currently they may be more recently expressed as nanograms per milligram of faecal material (26). Studies published prior to 2014 were identified from previously conducted systematic reviews (27,28) and associated bibliographies. To be eligible for inclusion here studies had to report, observed yields of adenoma's and CRC's in asymptomatic subjects for, a minimum of 3 threshold FIT values, including 100 ng/ml. In interpreting results, no distinction was made by stage of CRC. Reported results for advanced adenomas (AA) were allocated to the 10+mm category in the model. Many of the reviewed reports did not detail results for smaller (<10mm) adenomas or included them in an all-adenomas category: where possible smaller adenomas were separated in the data available. Several studies included colonoscopy of all subjects so that assessment of disease status was available independent of FIT result. Such studies provide direct calculation of specificity, or sensitivity in different disease categories, by threshold. In others studies only those with a FIT result above the study-specific lowest threshold received colonoscopy. These studies suffer from detection bias and only permit the calculation of relative sensitivity between the different threshold levels utilized within each study, where relative sensitivity is the ratio of cases with a positive test result at each threshold.

To provide a sensitivity analysis of the effect of parameter choices for the TPR function choices were to be selected to span the strength of the observed relationships between threshold and the relative sensitivity (scale parameter). Three scale parameter values were estimated for each disease state: strong (greater than base effect per unit threshold change), base and weak (lesser than base effect per unit threshold change). Similarly, three choices were made for each disease state to reflect overall level of response at the 100 ng/ml level (location parameter): high (greater than base TPR at 100 ng/ml), base and weak (lesser than base TPR at 100 ng/ml). These values were chosen to span the range of values reported in the studies reviewed. These parameter were then combined to provide base, strong, weak,

high and low sets of assumed parameters for each of the disease states for use in the simulations. Other sets would be added for particular circumstances as described in the results.

Structure of Simulations

The OncoSim-CRC model used for the evaluation of the effect of different thresholds is available for examination and use on a publicly available website hosted by the Canadian Partnership Against Cancer (29). The OncoSim-CRC used in evaluating different colorectal screening scenarios is described elsewhere (23). For the present manuscript simulations of screening scenarios were performed assuming a cohort of individuals aged 45 years in 2014 who were followed until their death. The ratio of men to women was the same as in the Canadian population in 2014. The model is calibrated to historical patterns of screening in the Canadian population but going forward from 2014 it was assumed that screening was as specified in the scenario under consideration (including no screening). All FIT screening scenarios explored assumed biennial testing with the first scheduled test at age 50 and the last at age 74. Screening scenarios varied in the choice of threshold value selected for FIT test abnormality and the parameters α, β for the sensitivity analysis (base, strong etc.).

In the examples presented we assumed 60% compliance to recommended FIT screening which did not vary by threshold or sensitivity analysis. Initial test results were assumed to not influence future compliance, other than that recommended. Inflation and discounting were assumed at 2% and 3% per-annum respectively and results expressed in 2014 Canadian Dollars (CAD$). Results for each screening scenario were summarized based upon 10 million simulated lives.

RESULTS

Review of Studies of FIT Threshold and Colorectal Neoplasia

Review yielded 8 studies (30-37) that met the criteria of FIT being performed in individuals who were stated as being asymptomatic and that reported FIT results for at least 3 threshold levels, including 100 ng/ml, as well as separately for CRC and advanced adenomas (AA). Relative sensitivities were calculated from the published tables with 100 ng/ml set as the reference point. Results are summarized for colorectal cancer and advanced adenomas (Table 1). The study results varied in the thresholds included and the tables were constructed to include most thresholds used. Results for colorectal cancer (Table 1) generally had little fine detail due to small numbers of detected cancers which frequently lead to adjacent thresholds having the same relative sensitivity. Results for advanced adenomas (Table 1) display finer separation. Visual comparison appeared to indicate that the relationship with threshold was stronger for advanced adenomas than for CRC's although no formal tests of comparison were conducted.

Separate reporting of results for adenomas smaller than 10mm was infrequent. The results from Park (33) indicate that the ratio of smaller (<10mm) to larger adenomas is higher at 75ng/ml than at 100 ng/ml providing no indication that the relative sensitivity relationship is weaker for adenomas 6-9 mm.

Table 2 provides TPR for the different states as reported for studies in which colonoscopy evaluation of all subjects was conducted (33-37). The contributing studies grouped

subjects with smaller adenomas (<10mm) with those without any colorectal neoplasms so that reported TPR's likely overestimate the rates in subjects free of colorectal neoplasia. Within each study TPR's were lower for AA's compared to CRC's at each level of the threshold evaluated.

Parameters Used in Sensitivity Analysis

Using the logistic formulation, the relationship between TPR and threshold sets of parameters were constructed to span differences in relationships. As a conservative assumption, since data was sparse, we assumed that the TPR in subjects with 0-5mm

adenomas would be the same as that in subjects without colorectal neoplasia at all thresholds and for all sensitivity analyses. This is similar to the assumption made by Wilschut et al. in their model (38). Also, again because of sparse data, we assumed the same logistic parameter for the gradient (β) in relative sensitivity for the 6-9 mm and the 10+mm adenomas and subject them to the same sensitivity assumptions.

The assumed base, strong, and weak (β varied) and high and low (α varied) TPR`s are provided in Appendix File Table 3 for each of the modelled threshold values. As earlier noted there were few published estimates of TPR`s for small adenomas (0-5mm and 6-9mm). In order to provide a separate sensitivity analysis of the effect of assumed TPR`s for small adenoma two additional parameter sets were included:

Base1: TPR's were the same as for the Base case except that for adenomas 6-9mm the rates were the same as for those no neoplasia in the Base Case at all thresholds

Low-Base1 TPR's were assumed to be the same as for Base1 except that the rates from the Low set were used for adenomas 1-5 and non-neoplasia.

Results of Simulations

Table 3 provides the projected proportional cumulative CRC incidence compared to a no screening scenario in the cohort lifetime by parameter set and FIT threshold. All combinations of parameter sets and FIT threshold resulted in predicted reductions in CRC incidence. As may be anticipated the largest differences in projected CRC reduction between each parameter set occurred at the highest and lowest FIT thresholds where modelled variation was greatest. Table 3 also provides similar predictions for CRC deaths. Proportional reductions in deaths exceeded proportional reductions in incidence at the same combination of parameter set and threshold. Compared to the conventionally used threshold of 100ng/ml dropping the threshold to 50ng/ml increased the demand for screening related colonoscopy by between 20% and 77% depending upon the parameter set, with the smallest increase for the weak set and the largest for the strong set. Compared to 100ng/ml, increasing the threshold to 225ng/ml decreased the demand for screening related colonoscopy by between 13% and 40% depending upon parameter set with the smallest relative reduction for the weak set and the largest for the strong set.

Direct lifetime costs of screening and treatment were projected for the cohort for the different FIT thresholds and parameter sets with future costs discounted at 3%. Similarly, quality-of-life adjusted life-years (QALY) were also calculated and discounted at the same rate. The resulting gains, with respect to no screening, in QALY and costs incurred are displayed in Figure 1. Within each of the parameters sets used for the sensitivity analysis predicted costs decreased and QALY's increased with declining
threshold from the highest (225ng/ml) so that it was always dominated by some lower thresholds. Consequently, the least cost-effective screening scenario occurred at
the 225ng/ml threshold and was for the "low" parameter set which assumed lowest TPR's at all thresholds. Most parameter sets lead to predicted costs and QALY's that were closely clustered with one another (Figure 1) except for the Low parameter set which had substantially higher predicted net costs and lower predicted QALY's than the other parameter sets. Predicted net costs behaved slightly differently between parameter sets For all parameter sets, at any of the thresholds considered, the predicted cost-effectiveness is high with none exceeding CAD$5,600 per QALY compared to no screening. Figure 2 provides incremental cost-effectiveness ratios (ICERs) for the seven parameter sets where the plotted value is that where the threshold is reduced from the next higher level (e.g. that at the 75 ng/ml level represents the change from 100 ng/ml) and that plotted for 225 ng/ml is versus no screening. The plotted ICERs for reductions in threshold are mostly negative and for any of the parameter sets considered CAD$6,800 per QALY was the maximum.

DISCUSSION

The CRMM-CRC model provides results calibrated to the Canadian population on risks of CRC incidence and death, and reproduces the general findings of models from other jurisdictions of the effectiveness of several approaches to preventing development and death from CRC (23). It provides projected estimates of the effect of measures on the Canadian population so that clinical and administrative stakeholders can assess the value of interventions in a number of different dimensions. Literature review revealed uncertainty in the TPR's (sensitivity and specificity) with FIT threshold and in particular

for small adenomas where information was sparse. TPR variability was captured using models of the threshold-detection curve for FIT threshold with parameterizations which spanned observed results. The simulations indicated that outcomes were relatively insensitive to assumptions about the TPR for small adenomas. Also the steepness of the relationship between FIT threshold, for a given parameter set, and TPR had a modest effect on predicted disease and cost outcomes but strongly influenced colonoscopy demand. The parameter set which assumed low sensitivity for large adenomas and CRC at all thresholds was the only one which produced a substantially different predicted effectiveness and cost-effectiveness indicating the influence of test performance in these lesions on long term outcomes. Nevertheless, for all parameter sets considered, effectiveness increased with reduced FIT threshold and for no parameter set was cost-per-QALY substantially higher at lower thresholds.

As for any calculation which predicts outcomes over a period exceeding forty years there is considerable uncertainty in the resulting predictions. In this paper we only examined uncertainty in TPR, related to the sensitivity of the FIT test at select thresholds. Uncertainty exists in other parameters within the model with potentially the most important (for this application) being those which relate to the speed with which adenomas progress to adenocarcinomas (39). However, these parameters are constrained by measured prevalence of adenomas and the incidence of colorectal cancer so that within a model of this type they cannot vary greatly. As illustrated, estimates of TPR differ between studies, as does the strength of the relationship between FIT threshold and TPR. The majority of these studies are in populations in which the screening history of participants is not well documented. Thus, it is unclear whether the relationships presented represent first or subsequent screen results or results in individuals previously screened in other ways. Several studies (40-43) have found that population overall TPR's are higher for first screens than for subsequent screens. Additionally, it is unclear whether lower rates on the second round are only due to the reduced prevalence of adenomas or also by lower false-positive rates in subjects who were not positive at the first screen. Declining false-positive test rates at increasing screening rounds would impact the overall requirement for colonoscopy and the costs of screening. Age-and-sex is known to influence the likelihood

of an adenoma (44) and also the incidence of CRC varies in different countries (45). The present study did not attempt to adjust for differences in the age and sex composition and location of studies used to inform TPR's so that true differences in TPR performance are likely overestimated since variation in the composition of the population will have been included as uncertainty in the TPR`s. Studies included used a single test type (OC Sensor®) and it is known that variation exists between tests (28,46-49). In common with other models of screening cost-effectiveness, the time scale required for consideration is very long so that projected future treatment costs, even after discounting, affect predicted cost-effectiveness. Detailed and thorough assessment of current screening and treatment costs will likely reduce but not eliminate this future uncertainty. Sessile serrated polyps (SSP's) are believed to be the origin of 20-30% of CRC's (50) and are relatively more common in the right colon where the relative performance of colonoscopy is lower (51-53). SSP's have limited surface vascularisation (50,54) and the performance of FIT for detecting such lesions is unclear but may be poor (55).

Many models have examined the effectiveness and cost-effectiveness of CRC screening (56). Generally, the findings of these studies indicate that most CRC screening options are cost-effective (57-59) and also that FIT is cost-effective (23,38,60-62). One versus two sample FIT testing has been compared (61). At the same threshold two samples lead to increased sensitivity when, as is usual practice, screen-positive is declared if either test is positive. However, reducing the FIT threshold also increases the sensitivity without the added cost of collecting and processing a second sample. Van Rossum (60) examined the effect of altered FIT thresholds within the context of screening in the Netherlands. They found that lowered threshold increased the effectiveness and cost-effectiveness of FIT based screening.

A concern which arises in many countries contemplating or delivering population based FIT screening, is the availability, quality, and timeliness of endoscopy services for those with a positive screening test. Colonoscopy capacity in the health system influences the ability to deliver screening. The FIT threshold used has a considerable effect on colonoscopy demand, especially in the short term. It can be anticipated that the rate of

screen positivity will decline with increasing screening rounds so that a policy of reducing the FIT threshold in future rounds may achieve many of the long-term advantages of a lower threshold without requiring large increases in endoscopy capacity.

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Conflicts of Interest: none

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Titles and Legends to Figures

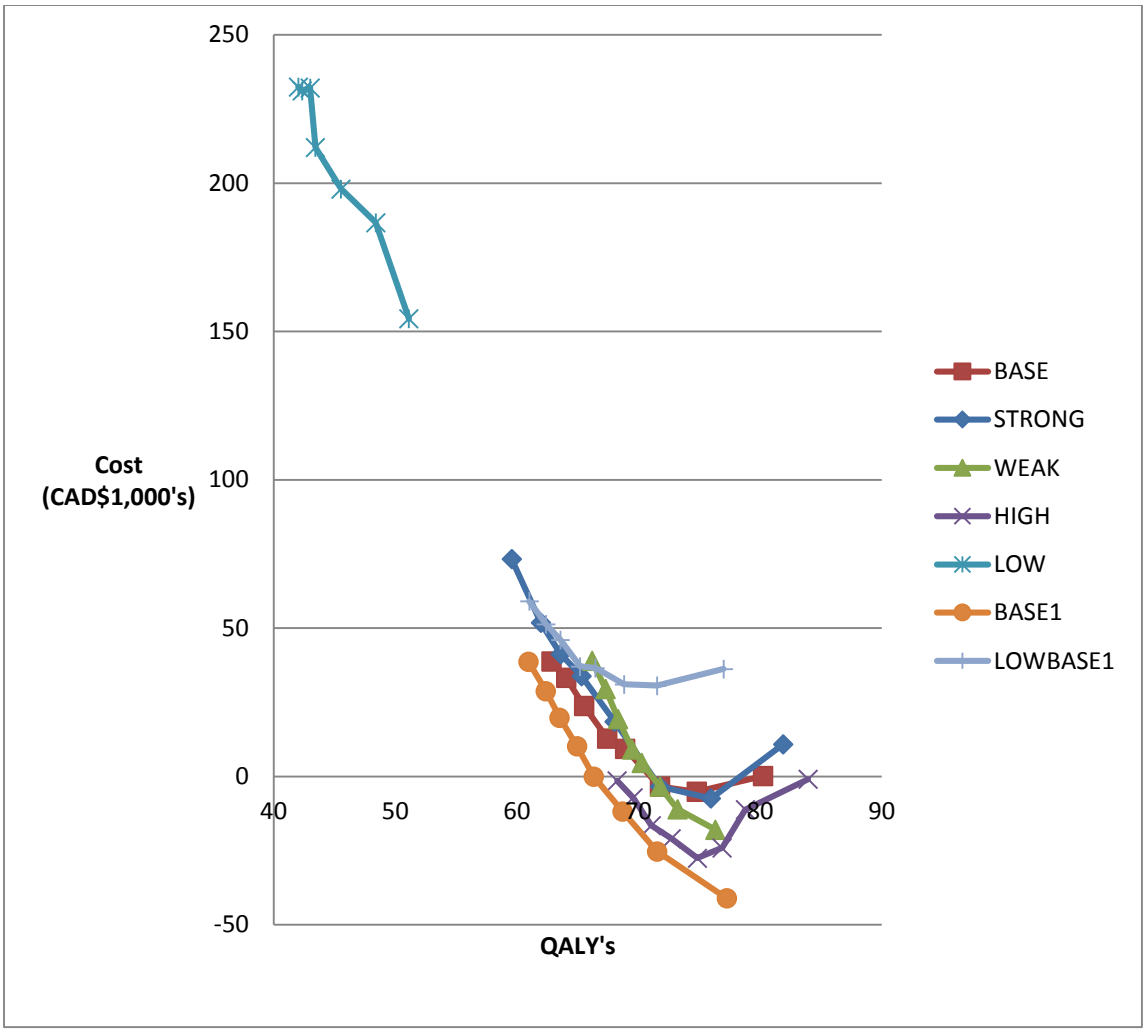


Figure 1: Increase in Discounted Quality Adjusted Life-Years Versus Discounted Cost for Seven Parameter Set and FIT Threshold* per 1,000 Subjects

*FIT thresholds for each parameter set are connected by lines with the leftmost point being the highest threshold 225 ng/ml and moving to the right through 200, 175, 150, 125, 100, 75 and 50 ng/ml.

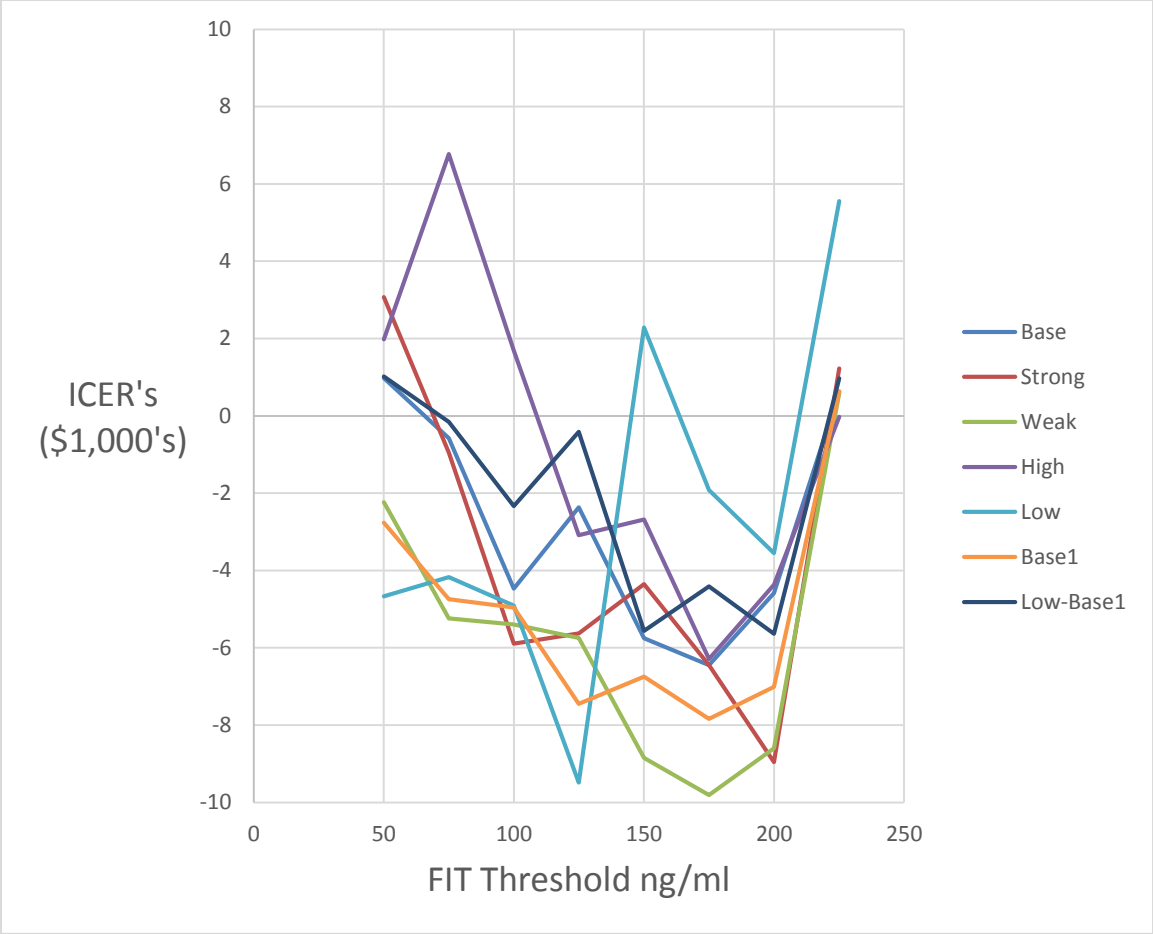


Figure 2: Incremental Cost Effectiveness Ratio's, discounted CAD$ per QALY, for a change in threshold by one level for the Seven Parameter Sets*

*The values plotted at 225 ng/ml represent a comparison with no screening and other points are those based upon a change from the next higher threshold

Table 1: Relative sensitivity (100ng/ml =1.0) for Colorectal Cancer and Advanced Adenoma by study and by FIT threshold

State	Study	FIT Threshold ng/ml							
		50	**75**	**100**	**125**	**150**	**175**	**200**	**225**
CANCER	van Rossum [28]	1.17	1.13	1.0	1.0	1.0	1.0	1.0	0.96
	Hol [29]	1.21	1.07	1.0	1.0	0.93	0.93	0.86	
	Grazzini [30]		1.14*	1.0	0.93*				
	Park [31]	1.0	1.0	1.0	0.92	0.92			
	Terhaar sive Droste [33]	1.03	1.01	1.0	0.94	0.92		0.90	
	Rozen [32]	1.15	1.08	1.0	0.92	0.85		0.85	
	de Wijkerslooth [34]	1.17	1.0	1.0					
	Hernandez [35] †	1.0	1.0	1.0	1.0†	0.80		0.80	
ADVANCED ADENOMA	van Rossum [28]	1.33	1.13	1.0	0.93	0.88	0.80	0.74	0.70
	Hol [29]	1.35	1.10	1.0	0.95	0.95	0.87	0.84	
	Grazzini [30]		1.04*	1.0	0.98*				
	Park [31]	1.30	1.10	1.0	0.85	0.80			
	Terhaar siveDroste [33]	1.10	1.06	1.0	0.97	0.91		0.82	
	Rozen [32]	1.38	1.17	1.0	0.85	0.85		0.82	
	de Wijkerslooth [34]	1.21	1.07	1.0					
	Hernandez [35] †	1.14	1.04	1.0	0.93	0.89		0.89	

* Levels used 80 (put in 75 column), 100 and 120 (put in 125 column).

† 115 ng./ml.

Table 2: Reported Positivity Rates of FIT by Threshold for Disease States for studies using the OC Sensor® test with Colonoscopy Evaluation of all Subjects

Study	Disease State	FIT Threshold (ng/ml)							
		50	**75**	**100**	**125**	**150**	**175**	**200**	**225**
Park [31]	Cancer	92.3	92.3	**92.3**	84.6	84.6			
	AA	44.1	37.3	**33.9**	28.8	27.1			
	<AA+C†	10.2	8.7	**7.9**	7.0	6.4			
Terhaar sive Droste [33]	Cancer	92.4	91.1	**89.9**	84.8	82.3		81.0	
	AA	41.1	39.4	**37.3**	36.0	33.9		30.5	
	<AA+C†	10.1	7.8	**6.5**	5.7	4.9		4.2	
Rozen [32]	Cancer	75.0	70.0	**65.0**	60.0	55.0		55.0	
	AA	36.4	31.0	**26.4**	22.5	22.5		21.7	
	<AA+C†	6.7	4.8	**3.7**	3.3	2.7		2.3	
de Wijkerslooth [34]	Cancer	88	75	**75**					
	AA	35	31	**29**					
	<AA+C†	6.7	4.3	**3.0**					
Hernandez [35]	Cancer	100	100	**100**	100*	80		80	
	AA	32.0	29.0	**28.0**	26.0*	25.0		25.0	
	<AA+C†	5.0	4.0	**4.0**	3.0*	3.0		3.0	

* 115 ng/ml, † All subjects without advanced adenoma (AA) or CRC

Table 3: Projected Proportional CRC Incidence and Mortality for Biennial FIT Screening versus No Screening by Parameter Set and FIT Threshold

FIT Threshold (ng/ml)	Case						
	Base	Strong[1]	Weak[1]	High[2]	Low[2]	Base1[3]	Low-Base1[4]
	Ratio CRC Incidence (Versus No Screening)						
50	49.4	47.6	53.5	46.3	65.9	54.0	54.5
75	54.1	53.3	55.5	51.4	71.1	58.0	58.5
100	56.7	56.7	56.7	53.6	73.3	60.4	60.9
125	59.1	59.6	57.7	55.6	75.5	62.3	62.6
150	60.4	61.8	58.3	57.0	77.4	63.4	63.8
175	61.7	63.0	59.1	58.2	77.7	64.4	64.8
200	63.3	64.5	60.0	59.5	78.1	65.4	65.7
225	64.0	66.6	60.8	60.5	78.3	66.2	66.5
	Ratio CRC Mortality (Versus No Screening)						
50	37.6	36.0	40.9	34.8	51.8	41.1	41.3
75	41.7	40.7	42.8	38.4	57.2	45.0	45.0
100	43.7	43.7	43.7	40.5	59.5	46.8	46.9
125	45.9	46.3	44.8	42.0	61.7	48.7	49.0
150	47.0	48.3	45.4	43.4	63.6	49.6	50.0
175	48.6	49.6	46.1	44.4	64.0	50.8	51.1
200	49.7	51.0	46.8	45.6	64.6	51.5	51.6
225	50.5	52.6	47.4	46.8	64.9	52.6	52.8

1. Strong and Weak refer to greater and lesser (compared to base) gradient TPR by threshold

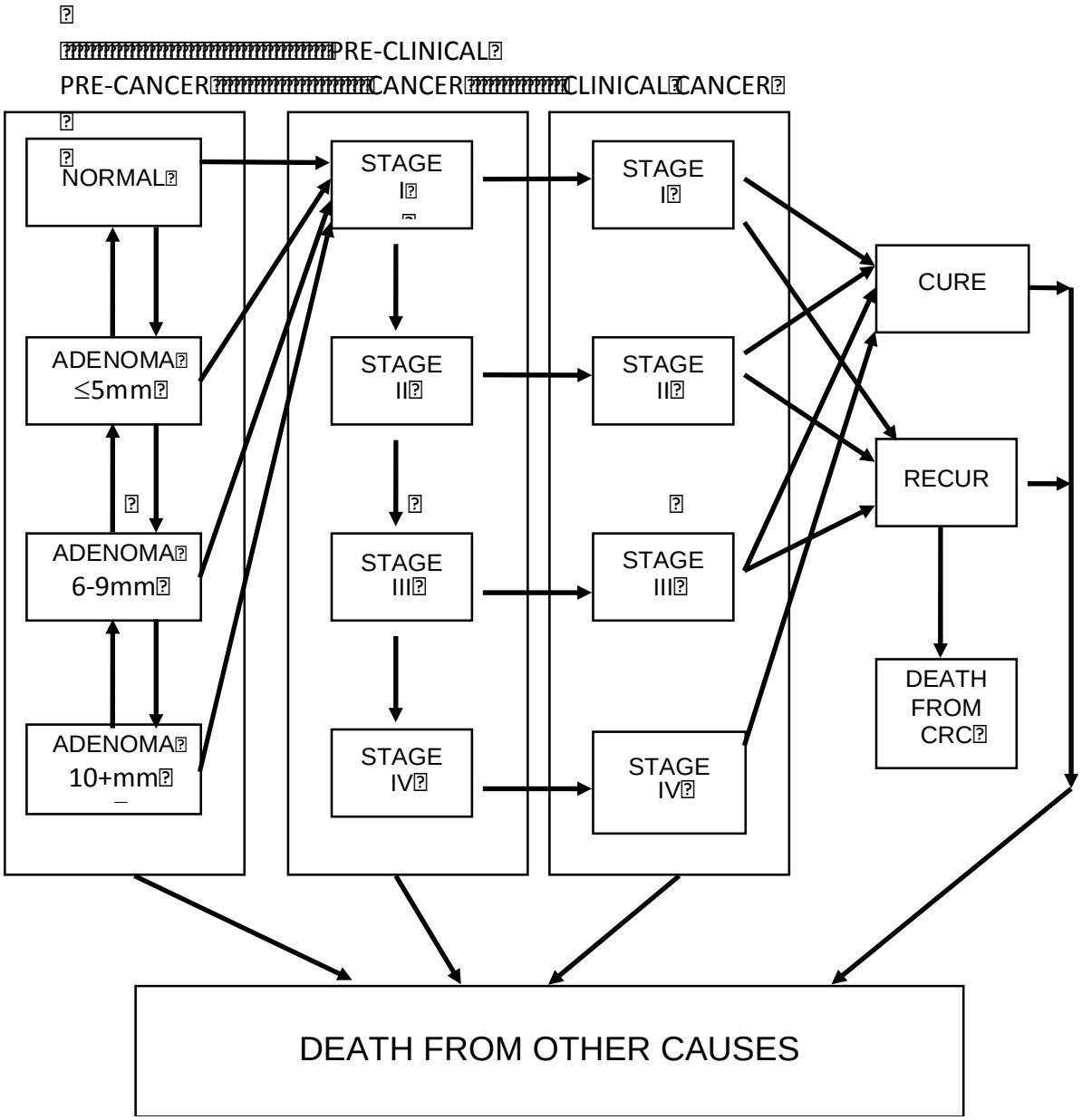
2. High and Low refer to higher and lower TPR (compared to base) at 100ngéml

3. Base1 has lower sensitivity (compared to base) for adenomas 6-9mm

4. Low-Base1 has lower TPR (compared to Base1) for adenomas 1-5mm and no neoplasia.

Appendix

Appendix Figure 1: Schematic of the OncoSim-CRC Model



Appendix Table 1: Assumed Relative Sensitivity for Cancer AA and 5-9mm Polyps: Base, Strong and Weak Cases

Case	State	Threshold of Fit							
		50	**75**	**100**	**125**	**150**	**175**	**200**	**225**
Base	Cancer	1.15	1.06	1.0	0.95	0.92	0.88	0.85	0.83
	AA	1.29	1.11	1.0	0.93	0.88	0.85	0.82	0.81
	Normal, 1-5 & 6-9 mm	2.0	1.32	1.0	0.79	0.68	0.59	0.53	0.48
Strong	Cancer	1.29	1.11	1.0	0.93	0.88	0.85	0.82	0.81
	AA	1.35	1.14	1.0	0.91	0.84	0.79	0.75	0.71
	Normal, 1-5 & 6-9 mm	2.40	1.40	1.0	0.79	0.66	0.57	0.50	0.45
Weak	Cancer	1.10	1.04	1.0	0.97	0.94	0.92	0.90	0.89
	AA	1.15	1.06	1.0	0.95	0.92	0.88	0.85	0.83
	Normal, 1-5 & 6-9 mm	1.29	1.11	1.0	0.93	0.88	0.85	0.82	0.81

Appendix Table 2: Assumed Base, High and Low TPR values at 100 ng/ml Threshold by Disease State.

Disease State	Case		
	Base	High	Low
Cancer	0.75	0.90	0.51
Advanced Adenoma	0.30	0.35	0.13
6-9 mm Adenoma	0.10	0.13	0.04
No neoplasm or 1-5mm adenoma	0.04	0.05	0.022

Appendix Table 3. TPR's for use in Simulation by Case, Disease State and FIT Threshold

Case	State	Threshold of FIT, ng/ml							
		50	**75**	**100**	**125**	**150**	**175**	**200**	**225**
Base	Cancer	0.86	0.80	0.75	0.71	0.69	0.66	0.64	0.62
	AA	0.39	0.33	0.30	0.28	0.27	0.26	0.25	0.24
	6-9 mm	0.20	0.13	0.10	0.08	0.07	0.06	0.05	0.05
	Normal, 1-5mm	0.08	0.053	0.04	0.032	0.027	0.024	0.021	0.019
Strong	Cancer	0.97	0.83	0.75	0.70	0.66	0.64	0.62	0.61
	AA	0.41	0.34	0.30	0.27	0.25	0.24	0.23	0.21
	6-9 mm	0.24	0.14	0.10	0.08	0.07	0.06	0.05	0.04
	Normal, 1-5mm	0.096	0.056	0.04	0.032	0.026	0.023	0.020	0.018
Weak	Cancer	0.83	0.78	0.75	0.73	0.71	0.69	0.68	0.67
	AA	0.35	0.32	0.30	0.29	0.28	0.27	0.26	0.25
	6-9 mm	0.13	0.11	0.10	0.095	0.092	0.088	0.085	0.083
	Normal, 1-5mm	0.052	0.044	0.04	0.037	0.035	0.034	0.033	0.032
High	Cancer	1.00	0.95	0.90	0.86	0.83	0.79	0.77	0.75
	AA	0.45	0.37	0.35	0.33	0.31	0.30	0.29	0.28
	6-9 mm	0.26	0.17	0.13	0.10	0.09	0.08	0.07	0.06

	Normal, 1-5mm	0.10	0.066	0.05	0.04	0.034	0.030	0.027	0.024
Low	Cancer	0.59	0.54	0.51	0.48	0.47	0.45	0.43	0.42
	AA	0.17	0.14	0.13	0.12	0.11	0.11	0.11	0.11
	6-9 mm	0.08	0.053	0.04	0.032	0.027	0.024	0.021	0.019
	Normal, 1-5mm	0.044	0.029	0.022	0.017	0.015	0.013	0.012	0.011

Appendix Table 3 cont. TPR's for use in Simulation by Case, Disease State and FIT Threshold

Case	State	Threshold of FIT, ng/ml							
		50	**75**	**100**	**125**	**150**	**175**	**200**	**225**
Base1	Cancer	0.86	0.80	0.75	0.71	0.69	0.66	0.64	0.62
	AA	0.39	0.33	0.30	0.28	0.27	0.26	0.25	0.24
	6-9 mm	0.08	0.053	0.04	0.032	0.027	0.024	0.021	0.019
	Normal, 1-5mm	0.08	0.053	0.04	0.032	0.027	0.024	0.021	0.019
Low-Base1	Cancer	0.86	0.80	0.75	0.71	0.69	0.66	0.64	0.62
	AA	0.39	0.33	0.30	0.28	0.27	0.26	0.25	0.24
	6-9 mm	0.08	0.053	0.04	0.032	0.027	0.024	0.021	0.019
	Normal, 1-5mm	0.044	0.029	0.022	0.017	0.015	0.013	0.012	0.011