Should we be studying family communication tools to improve cascade testing in genomics? A value-of-information analysis in Lynch syndrome

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Abstract

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Purpose: To estimate the potential value of family communication tools to improve cascade screening in Lynch syndrome and the expected value of additional research to reduce uncertainty in their effectiveness.

Methods: We developed a decision tree and Markov model, which consists of four states: well, colorectal cancer (CRC) (year 1), CRC (years 2-5+) and death. A preliminary estimate of the effectiveness of a communication tool was based on a pilot RCT of a tool we previously developed, FamilyTalk. Clinical probabilities, utilities, and costs were derived from published

literature and secondary databases. Value-of-information (VOI) analysis was used to estimate the expected value of additional evidence generated from future research.

Results: The communication tool led to a difference in costs ranging from -$1,608 to $4,632 and a difference in quality-adjusted life-years (QALYs) from -0.26 to 0.83. The estimated value of future research specifically on the effectiveness of a communication tool was $52 million. In contrast, further research on reducing the uncertainties of adherence to or effectiveness of annual colonoscopy did not contribute to decreased decision uncertainty.

Conclusion: A family communication tool to improve Lynch syndrome cascade screening of even moderate effectiveness likely provides good economic value, but further research is warranted.

Background:

Lynch syndrome (LS) is an autosomal dominant cancer predisposition syndrome, conferring a strong susceptibility to colorectal cancer (CRC), endometrial cancer and other cancers [1,2]. Genetic testing to identify LS carriers with subsequent annual CRC screening is a recommended strategy to improve health outcomes [3]. Furthermore, previous studies have shown that genetic testing is a cost-effective strategy for newly diagnosed CRC patients, and the number of family members tested is a key driver of value [4].

Family communication of genetic test results is a complex process [5]. Communicating information about genetic tests results to relatives can provide them with useful information for their own health decision making but could be complicated because people may not want to know their genetic risks [6,7]. We recently conducted a small randomized control trial to explore the effectiveness of an innovative online communication tool (FamilyTalk) designed to increase family communication about CRC and Polyp (CRCP) risk and screening [8]. The FamilyTalk RCT recruited 189 patients eligible for clinical CRCP sequencing and showed greater communication of CRC risk was associated with better family functioning. However, the number of patients with positive findings was too low to reliably estimate the impact of the tool on family communication of positive LS results. Although the effectiveness of a family communication tool is highly plausible, given the importance of family communication of genetic test results in LS screening versus the uncertainty of its effectiveness to date, the value of further research on this topic unclear.

The objective of our study was to quantify the value of conducting additional research on the effectiveness of the communication tool between newly diagnosed CRC patients and their first-degree relatives (FDRs). Value of information is an approach to research prioritization that uses Bayesian methods to estimate the potential benefits of gathering further information – additional research - before making a decision. We utilized cost effectiveness analysis (CEA) and VOI analysis to examine whether use of a communication tool is a cost-effective intervention and whether society should invest in additional research to develop and test the family communication tool. To our knowledge, this is the first study to examine the cost effectiveness and the expected value of additional evidence that considers a communication tool in cascade screening as an intervention.

Methods:

Overview

We developed a decision tree and Markov model to project outcomes of use of an online communication tool between newly diagnosed CRC patients and their FDRs. We evaluated outcomes in life years gained, Quality-adjusted life-years (QALYs) gained, and incremental healthcare cost. We used cost-utility analysis to assess the potential economic value of use of a communication tool and VOI to estimate the expected value of gathering additional evidence to reduce the chance of making inappropriate decision about the use of such a tool.

Model structure

Our model consists of two components. First, we designed a decision tree (Figure 1) that compares two strategies: 1) patients using the communication tool; 2) patients not using the communication tool. In the first strategy, when the patient completes the communication tool, the

patient has two choices – to communicate with FDRs or not. If a patient communicated with their FDRs, the FDRs would decide whether or not to undergo genetic testing. If the FDRs underwent genetic testing, annual colonoscopy was recommended if the result was positive, and every 10-year colonoscopy was recommended if the result was negative. If FDRs refused annual colonoscopy, we assumed they received every 10-year colonoscopy. If FDRs did not undergo the genetic testing, every 10-year colonoscopy was recommended. In the second strategy (patients who did not complete the communication tool), the structure was similar, although the probability of communication with FDRs differed.

In the long-term component of the model, we designed a Markov model to estimate CRC related morbidity and mortality in FDRs (Figure 2). The Markov model consisted of four health states: well, CRC (year 1), post CRC (year 2-5+) and dead. Each person starts from the well state and can either move to the dead state or CRC (year1) state. The CRC (year1) patient could either move to the dead state or post-CRC (year 2-5+) state.

Within the CRC states in the Markov model, we assumed a weighted average of cancer stages, which differed between CRC detected by annual vs. 10-year colonoscopy. Cancer stages were classified as stage I-IV [9], and survival and mortality were assumed to depend on cancer stage.

We assumed that an individual developed CRC only once in his or her lifetime and FDRs progressed to the post-CRC state when they had survived CRC for more than 5 years. The model used a 1-year cycle length and a lifetime time horizon. We used 3% as discount rate; the model was implemented in Microsoft Excel version 16.36.

Model input

Clinical inputs

The risks of developing CRC in the general population were derived from Surveillance, Epidemiology and End Results (SEER) data [10], and mortality data for the general population were obtained from United States Life Tables, 2015 [11]. We estimated the cumulative risks of developing CRC among LS carriers as 1% (95% CI: 0 to 1%) at age 30, 18% (95% CI:11% to 25%) at age 50 and 53% (95% CI: 37% to 64%) at age 70 from a study by Choi and colleagues[12] that provided population-based estimates of the risks of CRC by gender and mutation type from the Ontario population, including 199 first-degree and 421 second-degree relatives (Table 1). These estimates have been used in several previous cost effectiveness studies of screening for LS among persons newly diagnosed with CRC and their relatives [13-15].

The effectiveness of annual surveillance colonoscopy in CRC patients with LS was derived from a study by Stupart and colleagues [18], which provided relative risk of CRC incidence for patients with LS who adhered to annual colonoscopy, compared with a non-surveillance group. This study was also used by several previous economic modeling studies [13,19,20]. Among 178 subjects, CRC was diagnosed in 14/129 (11%) subjects in the surveillance group and 13/49 (27%) in the non-surveillance group (P = 0.019, relative risk 0.42, 95% CI 0.21 to 0.82). Moreover, colorectal cancers in the surveillance group were at an earlier stage than in the non-surveillance group. Specifically, seven patients out of total 14 patients from the surveillance group were in Duke's stage A, while only one of 13 patients from the non-

surveillance group was in Duke's stage A. The effectiveness of every 10-year colonoscopy in CRC patients with LS was obtained from Wang and colleagues' study; the relative risk of CRC incidence for patients with LS who adhered to every 10-year colonoscopy, as compared with the non-surveillance group was 0.9.

In order to model stage shift - earlier stage CRC diagnosed in patients who participated in the surveillance group - we calculated the weighted average survival stratified by age groups. For example, we calculated the weighted average survival by multiplying each survival rate in the set by its weight in each cancer stage, then added up the products and divided the products' sum by the sum of all weights.

Given both the *a priori* expectation that a communication tool would increase family communication and the uncertainty of the effectiveness of the tool from the FamilyTalk trial (relative risk of 0.9, CI (95% CI 0.4 to 2.2)), we assumed the relative increase of communication (compared with no tool) was 1.1 with range from 0.75 to 1.5.

We assumed the prevalence of LS mutation among FDRs was 50%, which reflects the autosomal dominant inheritance. According to several cost effectiveness studies of screening for LS among persons newly diagnosed with CRC and their relatives [13-17, 19, 20], we assumed four FDRs for each new CRC diagnosed proband with range from 2 to 8. We also assumed 70% (50% to 90%) adherence to colonoscopy and 70% (30 to 90%) uptake of genetic testing in FDRs who were aware of a positive test results in their family member [15].

Costs

Healthcare costs included direct expenses associated with colonoscopy, genetic testing, communication tool (user fee), and colorectal cancer care, which varied by different colonoscopy strategies (annual vs. every 10-year colonoscopy) and risks. We assumed the cost of annual colonoscopy of $1,000 ($900 to $1100) [14] and we divided it by 10 years to derive the annual cost of every 10-year colonoscopy equal to $100 ($90 to $110).

We assumed the cost of genetic testing was $500 and ranged from $200 to $1,000, generally based on Mvundura and colleagues' previous economic study [20]. Mvundura obtained list prices for laboratory tests from three large, commercial laboratories (City of Hope, Mayo Medical Laboratories, and Myriad Genetic Laboratories Inc.) and calculated the median price. For the cost of the communication tool, we consulted with several experts who were responsible for developing the communication tool in the FamilyTalk trial, and we used $100 ($50, $250) in the model.

CRC cancer treatment costs by stage were based on Wang's study [13]. For example, the CRC treatment costs were relatively lower for patients who underwent an annual colonoscopy since their CRC was diagnosed at an earlier stage. We adjusted costs from published sources to 2019 US dollars (Table 1).

Utilities

We assumed the utility for the well condition was 0.91 (0.84 to 1.0) based on McCaffrey's study [21] that estimates health-related quality of life (HRQoL) normative values

for the EQ-5D-5L preference-based measure in a large, randomly selected, community sample (2,908 adults). Utility related to LS with CRC (first year) was obtained from Wang's study [14]. For the utility of post-CRC, when patients survived longer than 5 years, we assumed patients would have a utility as 0.91. We calculated the mean utility for post CRC (year 2-5+) as 0.84, assuming a 10% disutility from the baseline value of 0.91.

Analysis

Outcomes

The model outputs were life years, quality-adjusted life-years (QALYs), cost, incremental QALYs gained, incremental costs, and the incremental cost effectiveness ratio (ICER). Results were discounted by 3% annually per guidelines. [22]

Sensitivity analysis

We performed deterministic one-way sensitivity analyses on all inputs to assess how robust our results were to changing one input parameter at a time across predefined ranges. We also conducted a probabilistic sensitivity analysis (PSA) with 1,000 iterations. The input parameters were assigned distributions by fittings lognormal distribution for costs and parameters associated with risks, and beta distributions for utilities, effectiveness of tests and tests adherence.

Value of information (VOI)

We applied VOI to our cost-effectiveness model in order to determine whether more research on reducing uncertain parameters is justified in regard to decision making. We calculated the net benefit (NB) by multiplying the effectiveness (QALY) by a $100,000 per QALY gained for willingness to pay (WTP) and subtracting the cost. The maximum NB represented the expected benefit under current information and was derived from the PSA on all the uncertain parameters in the model. The difference between the maximum NB with perfect information and the maximum NB with current information is called the Expected Value of Perfect Information (EVPI), which provides an estimate of the expected value of additional evidence to eliminate all uncertainty. We further calculated the expected value of partial perfect information (EVPPI) for four key parameters that had the greatest influence on cost and effectiveness: percentage of family members undergoing the genetic test, percentage adherent with annual colonoscopy, relative increase in communication with use of the communication tool vs. no tool, and the risk of developing CRC in LS carriers. EVPPI can highlight the specific areas that future research should focus on where the elimination of uncertainty has the greatest value.

We estimated the EVPI and EVPPI for the population that could benefit from more research. To calculate the population EVPI, we estimated the effective lifetime of the communication tool to be ten years. The annual patient population that could benefit from future research was newly diagnosed CRC patients (approximately 140,000 cases annually) who were LS positive (2.8% of new CRC cases annually) [23,24]. We assumed 50% of them completed the genetic test; the effective population over ten years was 17,221 patients. We also conducted scenario analyses in which we increased the affected population by 50% (n=25,831) and 100% (n=34,442).

Results:

Base case QALYs, Cost and ICER

In the base analysis, compared with no tool, the communication tool yielded 0.12 QALY on average, ranging from an increase of 0.83 QALYs to a decrease of 0.26 QALY. The tool was associated with a $625 increased in cost, ranging from savings of $1,608 to an increase of $4,632. The incremental cost-effectiveness radio (ICER) was $5,399/QALY in the base case (Table 2).

One-way sensitivity analysis

Figures 3a and Figure 3b show the influence of inputs in one-way sensitivity analyses (OWSA). The most influential variables were the relative increase in communication (effectiveness of the communication tool), the percentage of FDRs undergoing the genetic test, adherence to annual colonoscopy, and the risk of CRC in LS carriers.

Probabilistic sensitivity analysis

Figure 4 shows the cost-effectiveness acceptability curve (CEAC) for the communication tool vs. no tool. At a WTP threshold of $7,000/QALY gained, the communication tool has a 50% probability of being cost-effective, and at WTP threshold of $18,000/QALY gained, the probability of being cost effective increased to 70%. However, after $20,000/QALY WTP, the CEA curve for communication tool became flat at 70% of being cost effective regardless the WTP thresholds, which mainly due to the uncertainty in clinical effectiveness (incremental QALYs).

Value of Information

At a WTP of $100,000/QALY (a commonly cited threshold in the US), the population EVPI indicates that the value of collecting future data to eliminate all uncertainty in the decision about using a communication tool would yield a monetary benefit of $62 million. In other words, conducting sufficient research to eliminate all uncertainty in the decision problem, all of the model parameters, would provide a value of $62 million by reducing the probability of making an incorrect decision about the use of a communication tool in Lynch syndrome. Figure 5 shows the results for our three estimated population sizes. The result of the partial EVPI calculations showed the value of conducting research on specific parameters such as the parameter for the relative increase in communication accounted for the greatest expected opportunity loss caused by uncertainty (and thus the highest value of future research, $52 million), while the other three key parameters had essentially no value associated in future research in comparison.

Discussion:

We developed a decision analytic model to estimate the potential cost-effectiveness of a communication tool to improve cascade screening in LS. The communication tool was potentially of high economic value, but results were highly uncertain. Sensitivity analyses showed that the most influential variables were the relative increase in communication (communication tool vs. no tool), the percentage of FDRs undergoing the genetic test, adherence to annual colonoscopy, and the risk CRC in LS carriers. However, VOI analyses suggest that the value of future research in reducing decision uncertainty was focused solely on future studies of communication tool effectiveness.

Implications

Our results suggest that a family communication tool to improve cascade screening in LS could be a highly cost-effective intervention. However, the uncertain effectiveness of a communication tool – recognizing the small but real possibility of a decrease in communication – warrants caution before the routine use of such tools can be recommended. Our results further suggest that future research on communication tools should be prioritized over better understanding the uptake of testing in relatives who are aware of a family member's positive finding, the adherence to annual colonoscopy, or the risk of CRC in LS patients.

Limitations

Our study had a number of limitations. First, to capture the effect of CRC annual colonoscopy surveillance on cancer stage shift we used a weighted mortality and cost to define different types of CRC based on screening frequency. While a more complex model could capture more nuances in stage shift, given the relatively limited data in LS patients we felt the model complexity was appropriate. Second, we did not differentiate the utility of CRC cancer stage shifting, although the impact of this simplification likely biases our results against the intervention. Third, we assumed 100% sensitivity and specificity for the genetic test given the high accuracy of next generation sequencing platforms increasingly being used in clinical practice. While this assumption may favor the intervention, the relative impact on outcomes was likely small in relation to the uncertainty in the effectiveness of the communication tool. Fourth, for the base case analysis, we assumed the relative increase in communication (communication tool vs. no tool) was 1.1; however, the pilot RCT did not provide statistically significant results regarding to the effectiveness of the communication tool, and we therefore used a wide range from 0.5 to 2. We addressed this uncertainty by performing OWSA and PSA, and most importantly VOI analyses to assess the value of reducing this uncertainty. Finally, the cost of the communication tool in clinical practice is difficult to estimate given the research setting for its development and use; we thus conducted one-way sensitivity analysis with a wide range of costs from $50 to $250.

Conclusion

We developed a decision analytic model to estimate the potential cost-effectiveness of a communication tool to improve cascade screening in LS and the value of future research in this area. We found that if a family communication tool can improve communication about LS positive genetic test results to first degree relatives to a reasonable degree, it is likely highly cost effective. However, given current uncertainty in the effectiveness of a family communication tool in LS, the return on investment for additional research is high.

Table1: Model inputs

Parameters	Base-case value	Ranges	References
Relative risks (RR)			
Uncertainty of LS penetrance	1	(0.9, 1.1)	Choi 2009 [12]
LS carrier risk of developing CRC (annual colonoscopy vs. no colonoscopy)	0.42	(0.35, 0.7)	Wang 2012 [13]
LS carrier risk of developing CRC (every 10 year colonoscopy vs. no colonoscopy)	0.90	(0.85, 0.95)	Wang 2012 [13]
RR_CRC_Survival (1 yr for age 20-64, LS+ annual colonoscopy vs. general population)	1.0045	(1, 1.015)	Choi 2009 [12], Wang 2012 [13]
RR _CRC_Survival (1 yr for age>=65, LS+ annual colonoscopy vs. general population)	1.0093	(1, 1.01)	Choi 2009 [12], Wang 2012 [13]
RR_CRC_Survival (1 yr for age 20-64) (LS+10yrs colonoscopy vs. general population)	0.91	(0.85, 0.95)	Choi 2009 [12], Wang 2012 [13]
RR_CRC_Survival (1 yr for age>=65) (LS+10yrs colonoscopy vs. general population)	0.83	(0.75, 0.9)	Choi 2009 [12], Wang 2012 [13]
Relative increase of communication (communication tool vs. no tool)	1.10	(0.75, 1.50)	Expert opinion
RR-Post CRC_Death for age20-64 (LS+ annual colonoscopy vs. general population)	0.95	(0.8, 1)	Choi 2009 [12], Wang 2012 [13]
RR-Post CRC_Death for age>=65 (LS+ annual colonoscopy vs. general population)	0.99	(0.85, 1)	Choi 2009 [12], Wang 2012 [13]
RR-Post CRC_Death for age20-64 (LS+10yrs colonoscopy vs. general population)	2.2	(1.8, 2.8)	Choi 2009 [12], Wang 2012 [13]

RR-Post CRC_Death for age>=65 (LS+10yrs colonoscopy vs. general population)	1.85	(1.65, 2.15)	Choi 2009 [12], Wang 2012 [13]
Percentage of communication (without communication tool)	0.7	(0.6, 0.8)	Expert opinion
Percentage undergoing genetic test	0.7	(0.3, 0.7)	Wang 2012 [13]
Percentage adherence to annual colonoscopy	0.7	(0.5, 0.9)	Wang 2012 [13]
Average number of FDRs	4	(2, 8)	Collins 2007 [16], Wang 2012 [13]
Costs			
Cost of well state annual colonoscopy	$1,000	($900, $1100)	Wang 2012 [13]
Cost_well_every 10yrs colonoscopy	$100	($90, $110)	Wang 2012 [13]
Cost_CRC (LS+ annual colonoscopy) 1st year	$42,556	($38301, $46812)	Wang 2012 [13]
Cost_CRC (LS+10yrs colonoscopy) 1st year	$48,981	($44083, $53879)	Wang 2012 [13]
Cost_CRC (avg) 1st year	$49,052	($44147, $53958)	Wang 2012 [13]
Cost_survival (LS+ annual colonoscopy) 2-5years	$11,469	($10322, $12615)	Wang 2012 [13]
Cost_survival (LS+10yrs colonoscopy) 2-5years	$12,723	($11451, $13995)	Wang 2012 [13]
Cost_survival (avg) 2-5years	$12,665	($11399, $13932)	Wang 2012 [13]
Cost of communication tool	$100.00	($50, $250)	Expert opinion
Cost of genetic testing	$500.00	($200, $1000)	Mvundura 2010 [20]
Utilities			
Utility_well	0.91	(0.84, 1)	McCaffrey 2016 [21]
Utility_Colorectal cancer	0.6	(0.54, 0.66)	Wang 2012 [13]
Utility_postCRC	0.84	(0.76, 0.91)	Expert opinion
Utility_Dead	0		McCaffrey 2016 [22]

Table2

	Communication tool	No tool	Incremental
Total cost	$103,574	$102,949	$625
QALYs	78.36	78.24	0.12
Life Years gained	86.63	86.51	0.12
ICER	$5,399/QALY gained		

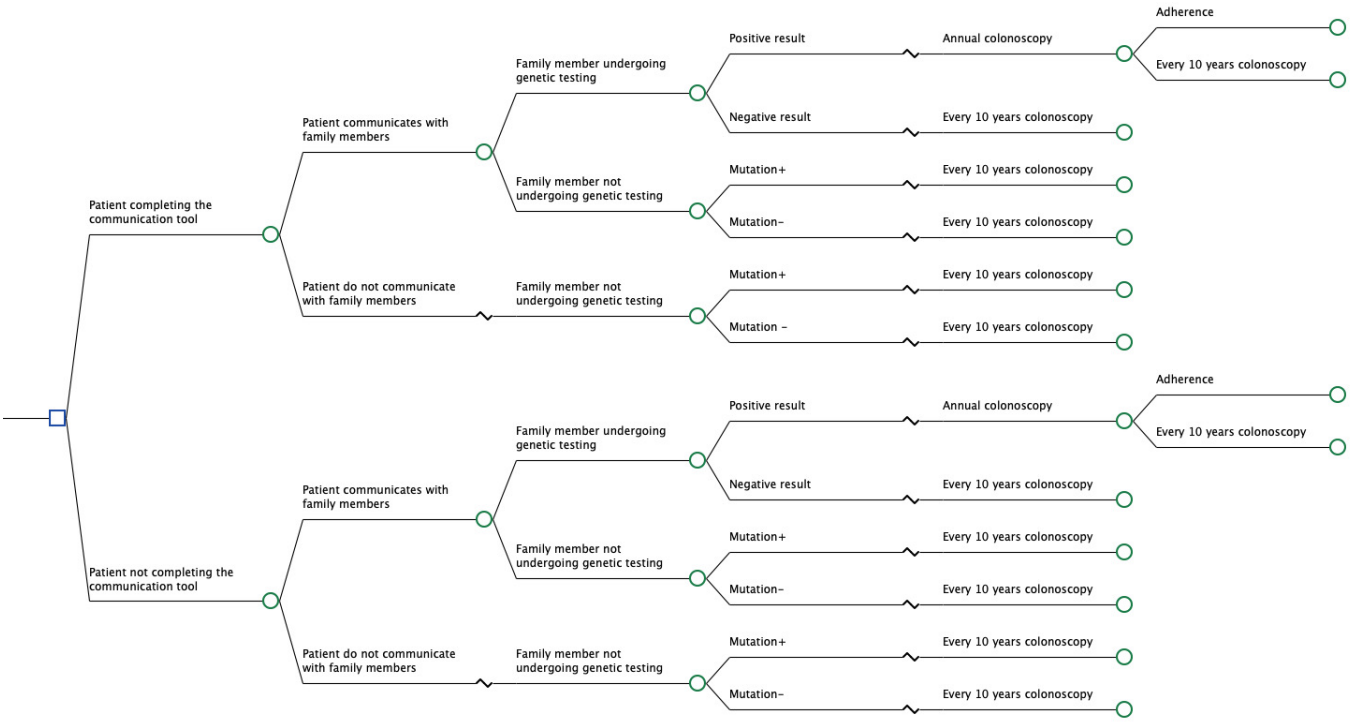

Figure 1: Overview of decision tree. The decision tree contained two strategies: 1) patients completing the communication tool; 2) patients not completing the communication tool. In the first strategy, when the patient completes the communication tool, the patient has two choices – to communicate with FDRs or not. If a patient communicated with their FDRs, the FDRs would decide whether or not to undergo genetic testing. If the FDRs underwent genetic testing, annual colonoscopy was recommended if the result was positive, and every 10-year colonoscopy was recommended if the result was negative. If FDRs refused annual colonoscopy, they would receive every 10-year colonoscopy. If FDRs did not undergo the genetic testing, every 10-year colonoscopy was recommended. In the second strategy (patients who did not complete the communication tool), the structure was similar, although the probability of communication with FDRs differed.

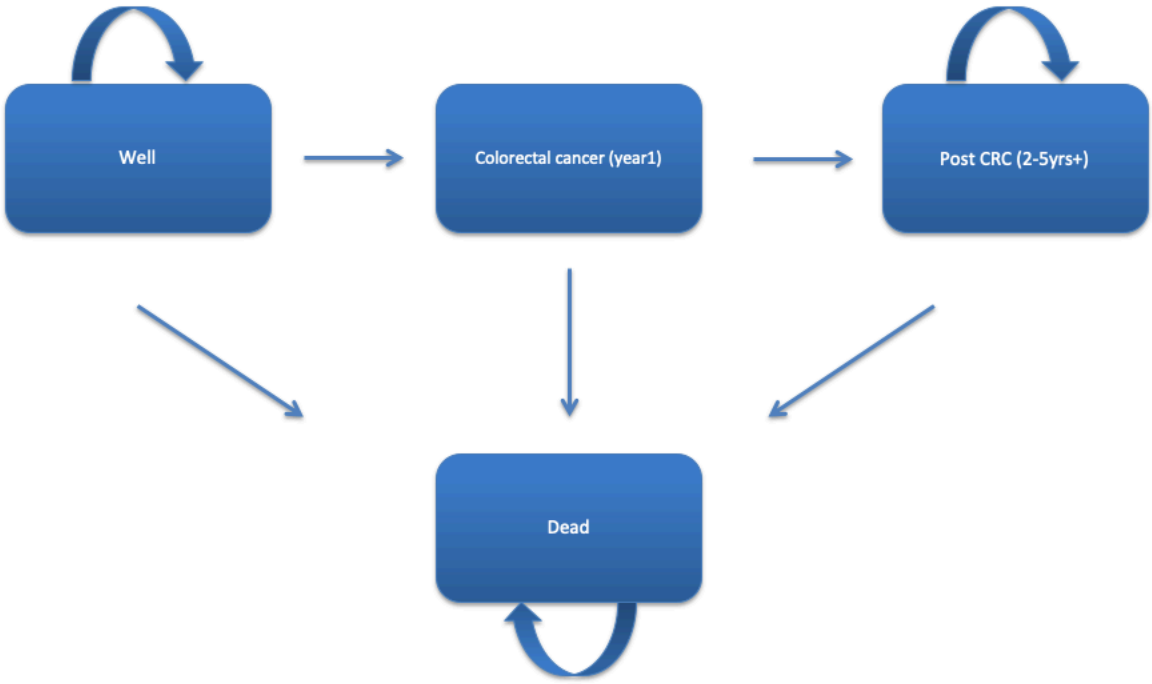

Figure 2: Markov model. Markov model was used to estimate CRC related morbidity and mortality in FDRs, which consisted of four health states: well, CRC (year 1), post CRC (year 2-5+) and dead.

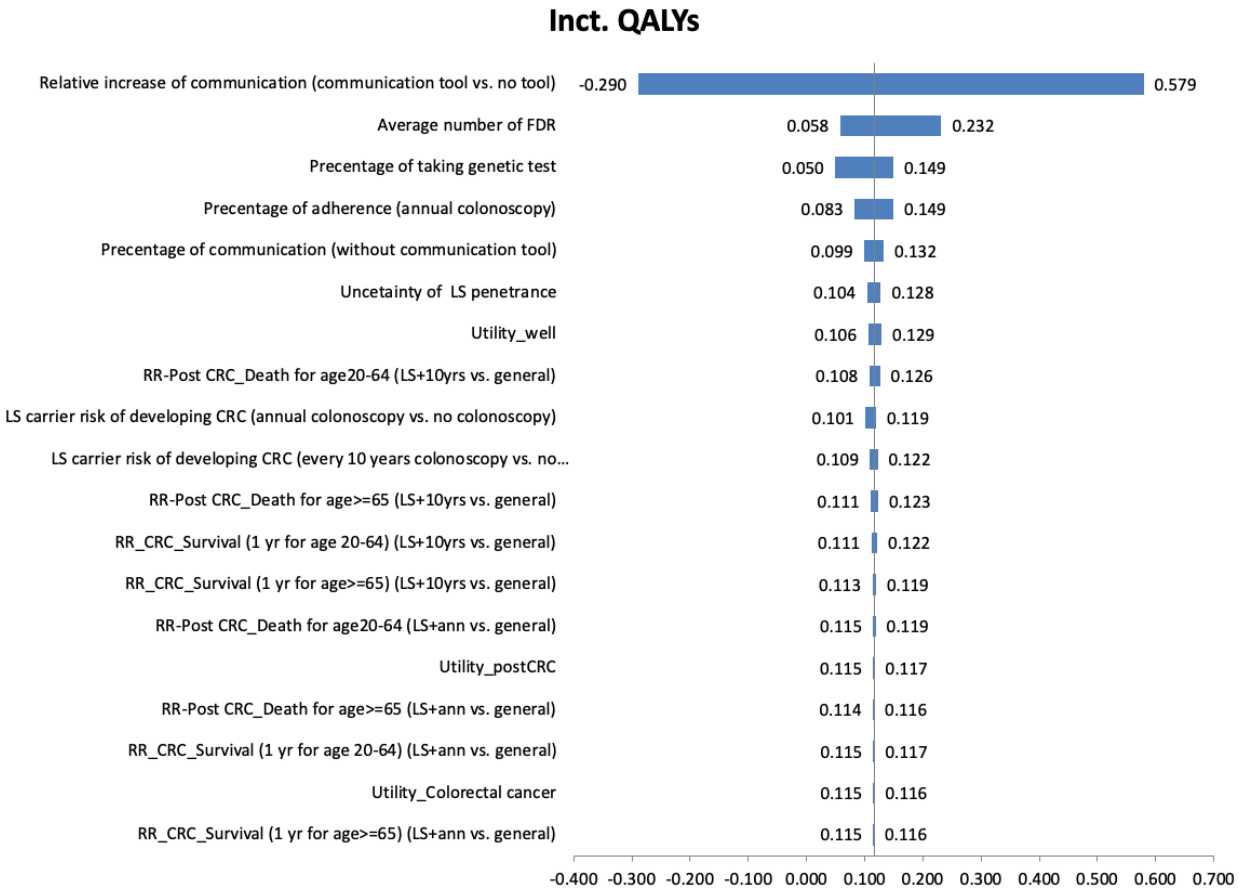

Figure 3a: One-way sensitivity analysis for incremental QALYs. The results of a one-way sensitivity analysis systematically varying all input parameters across wider intervals. on the outcome of incremental QALYs.

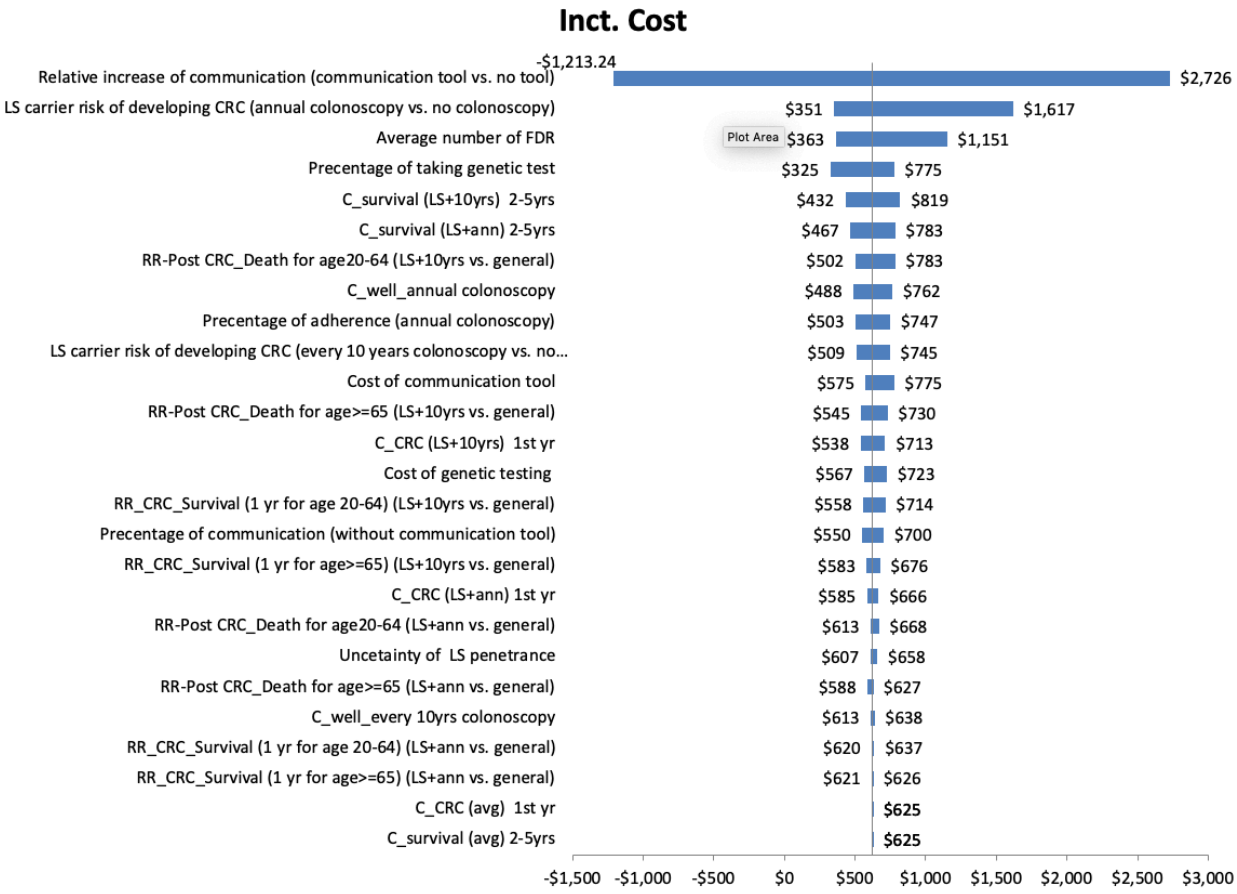

Figure 3b: One-way sensitivity analysis for incremental costs. The results of a one-way sensitivity analysis systematically varying all input parameters across wider intervals. on the outcome of incremental costs.

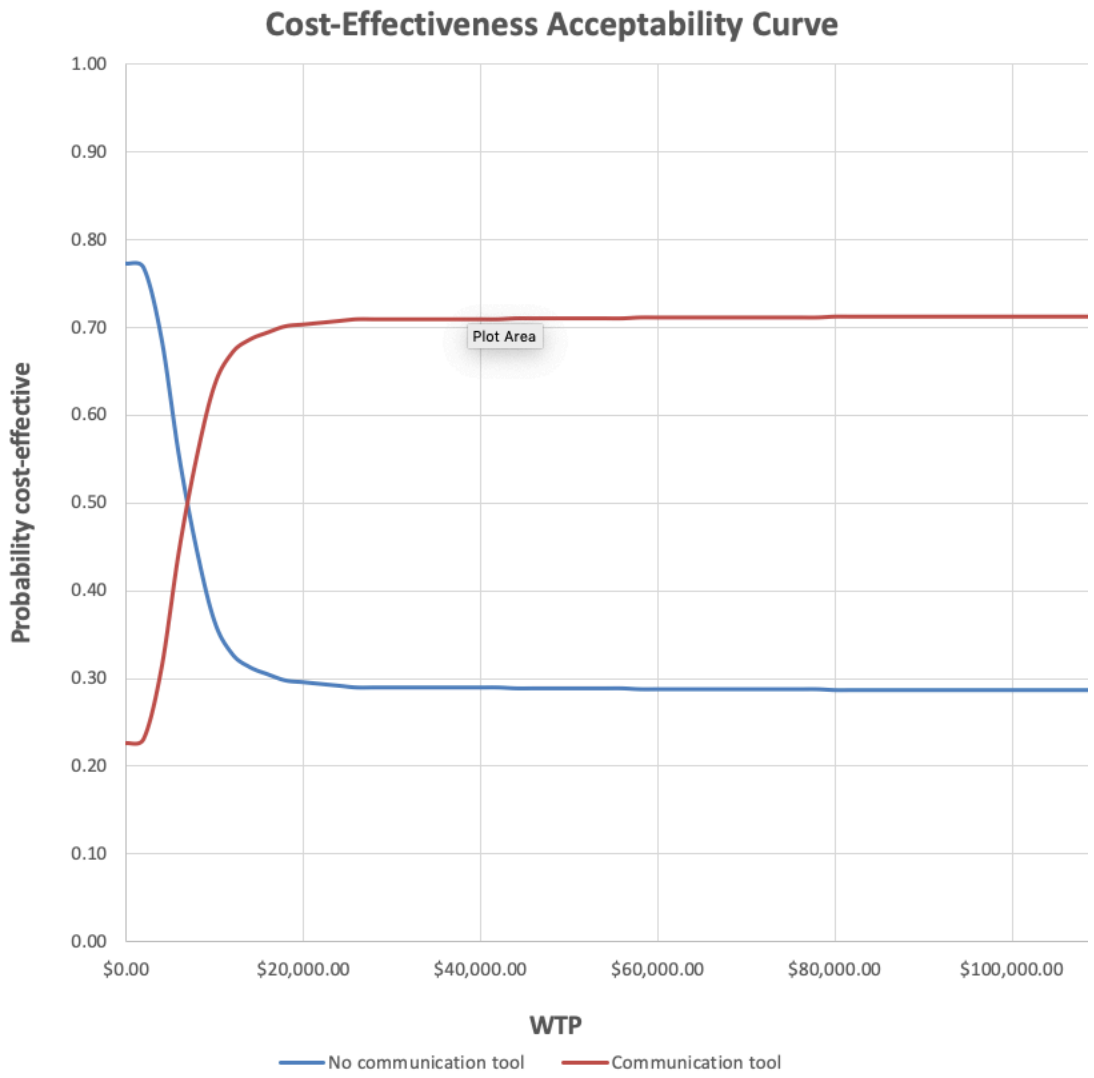

Figure 4: cost effectiveness acceptability curve (CEAC). CEAC for the communication tool in red line and the no communication tool in blue line.

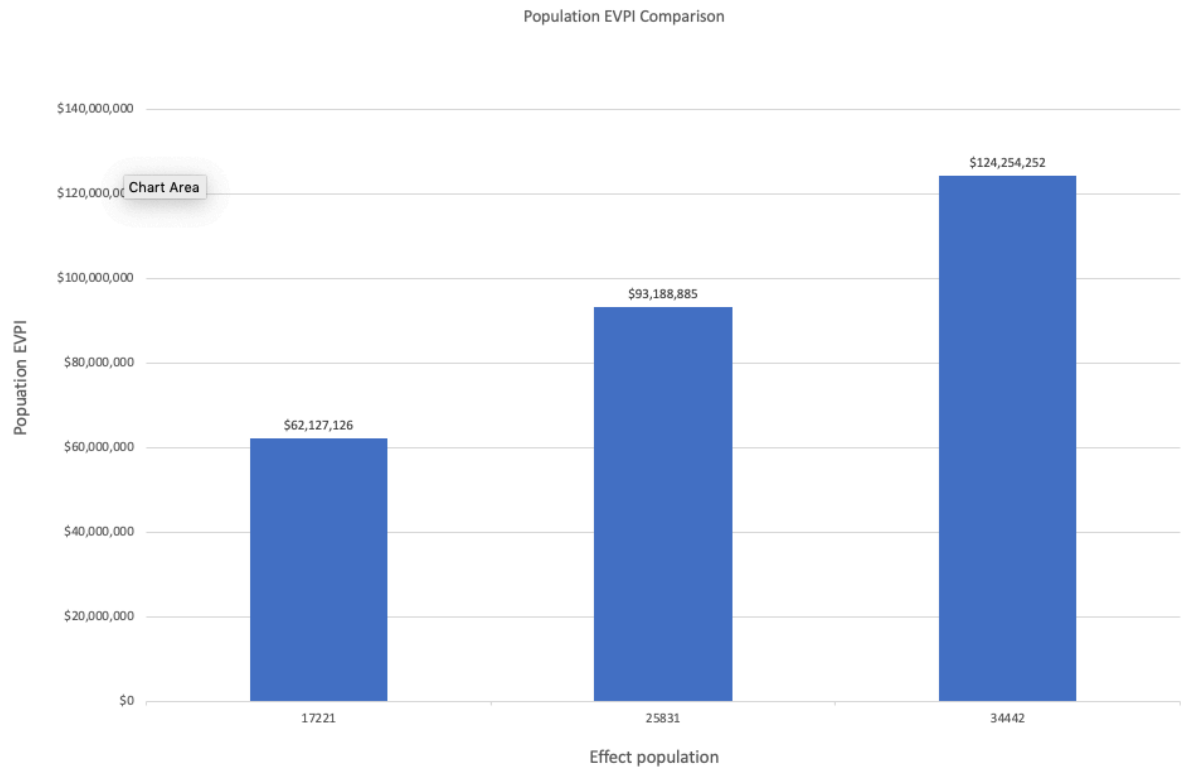

Figure 5: Population EVPI comparison. The results of population EVPI are associated with three estimated population sizes.

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