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Cost-Effectiveness of Colorectal Cancer Screening in the Average Risk Population

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Abstract. Colorectal cancer (CRC) is a leading cause of cancer death in North America and in Israel. Risk of CRC increases exponentially with age starting at the age of 50 years. Therefore, people older than 50 years are being considered as an average risk population for CRC. The objective of this study was to obtain an improved assessment of the cost-effectiveness analysis of screening for CRC in the average risk population by using a more accurate technique, namely the Partially Observed Markov Decision Process (POMDP). We conducted a cost-effectiveness analysis within the specific probability rates and costs in Israel.

This study revealed that it is highly cost-effective to screen average-risk asymptomatic individuals.

Keywords: carcinoma of colon and rectum, screening, cost-effectiveness analysis, partially observed Markov decision process

1. Introduction

Colorectal cancer (CRC) is a major health concern. It was predicted that in the year 2001, over 1,000,000 new cases will be diagnosed worldwide and that a total of 510,000 will die (personal communications from David Liberman, Oregon Health Sciences University, USA). CRC is the second leading cause of cancer death in North America resulting in approximately 56,600 deaths in 1999 [1,2]; in Israel, CRC is the leading cause of death from cancer (in 2001 there were 3000 new cases of CRC and approximately 1500 deaths).

The risk for CRC depends on several parameters. Three major groups of risk level are recognized – the *increased risk* group, the *moderate risk* group, and the *average risk* group. The *increased risk* group, where a genetic factor is predominant, includes people with familial polyposis syndrome (FAP), hereditary nonpolyposis colon cancer (HNPCC, or Lynch's syndrome) and people with inflammatory bowel disease (ulcerative colitis and Crohn's disease). The life time risk for CRC in people with FAP is 100% and in people with HNPCC it is approximately 80%. The moderate risk group includes people having a first degree family history of CRC or a personal history of CRC; in this group, the life time risk for CRC is estimated at 10–15%. In people older than 50 years of age the incidence for neoplasm or polyps in the colon increases exponentially. Therefore, people older than 50 years are considered to have an average risk for CRC. In people older than 50 years of age, the lifetime risk of developing CRC has been estimated at approximately 5–6% [1]. In this study we focus on the average risk group population.

There is now clear evidence that early age screening of average-risk asymptomatic individuals, can reduce mortality through removal of the precursor lesion and detection of malignancy at an earlier stage. The natural history of the multistep process of CRC provides a unique opportunity for earlier intervention as patients undergoing polypectomy usually are kept cancer free.

A recent panel recommended that average-risk individuals begin screening at the age of 50 with one of the following strategies: annual fecal occult blood testing (FOBT), flexible sigmoidoscopy (SIG) every 5 years, annual FOBT plus SIG every 5 years, or colonoscopy[1] every 10 years [3]. Colorec-

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[1] Fecal Occult Blood Testing (FOBT) is a qualitative chromogen tests, which rely on the oxidative conversion of a colorless compound to a colored one in the presence of the pseudoperoxidase activity of hemoglobin, have been standardized employing guaiac-impregnated paper and developing solutions (hydrogen peroxide in denatured alcohol) and have been widely studied and utilized clinically (e.g., Hemoccult). These are commercially available, convenient, and inexpensive (the total cost of a FOBT test ranges between 5 and 35 US $). Dietary restriction to exclude peroxidase- and heme-rich foods is especially important before having the test. Colorectal cancers and adenomas bleed intermittently, and detection of fecal occult blood by Hemoccult test depends on the degree of blood loss.

Colonoscopy is performed by passing a flexible colonoscope through the anal canal into the rectum and colon. Although a willing patient and a skilled examiner can complete the procedure without sedation in many cases, conscious sedation is usually given before colonoscopy. The cost of colonoscopy in the US is between 550 to 1500 US $.

Flexible sigmoidoscopy is similar to colonoscopy but visualizes only the rectum and a variable portion of the left colon, typically to 60 cm from the

tal cancer screening tests vary considerably in terms of their performance characteristics, complication rates, acceptability, and cost. Moreover, only the effectiveness of FOBT has been established by randomized clinical trial [4–7].

Health care policy makers recognize the benefits of screening, but ask if society can afford it. When analyzing the cost of CRC, it is important to consider CRC screening as a program. The program begins with the initial screening test. If negative, the test may need to be repeated at intervals to be effective. The screening test is being used to identify patients with a higher risk of CRC; a positive test warrants an evaluation of the entire colon. If the colon evaluation is normal and the patient is asymptomatic, the patient may not need further screening for 10 years. If neoplasia is found during the colon evaluation, polypectomy or surgery is appropriate. Such patients are known to have a 30–40% risk of recurrent polyps within three years, and are generally entered into colonoscopic surveillance programs with exams every three to five years. If cancer is discovered, the cost of care becomes an additional financial burden to the program.

Models have been developed to analyze the cost-effectiveness (C/E) of screening [8–16]. Most of the models were based on a Markov process model; other studies used simulation models to compare the cost-utility of no screening and age-based strategies employing one-time colonoscopic screening. The objective of this study was to obtain an improved assessment of the cost-effectiveness analysis of screening for CRC by using a more accurate technique. We used the Partially Observed Markov Decision Process (POMDP), also called the Hidden Markov Model (HMM), instead of the Markov process model. We study the cost-effectiveness within the specific probability rates and costs in Israel.

Most if not all CRC screening studies models use Markov models. A POMDP is a generalization of the Markov model, which presents more properly the natural history of colorectal neoplasia. We constructed an analytical decision model based on POMDP to evaluate the cost-effectiveness of CRC screening in average-risk individuals. Prior models have shown CRC screening to be economically attractive. Ness et al. [16] found that one-time colonoscopic screening between 50 and 54 years of age is cost-effective compared to no screening, or screening at older ages. Sonnenberg et al. [14] found that colonoscopy represents a cost-effective means of screening for CRC and that low compliance rates render colonoscopy every 10 years the most cost-effective primary screening strategy for CRC. Frazier et al. [13] found that even in the setting of imperfect compliance, using FOBT every year with sigmoidoscopy every 5 years is more effective than other strategies and that 60% compliance with an every-5-years schedule of screening was roughly equivalent to 100% compliance with an every-10-years schedule. Today the trend in the world is for colonoscopy screening, from once in a life-time (Italy, Poland) to every 5–10 years (USA) [personal communication from Professor Massimo Crespi, National Cancer Institute "Regina Elena", Rome, Italy, Professor Eugeniusz Butruk, Pharmacia Polska, Medical Centre for Postgraduate Education, Poland, and David Liberman, Oregon Health Sciences University, USA].

anal verge. This procedure causes abdominal cramping, but it is brief and is almost always performed without sedation. Sigmoidoscopy costs between 200 to 400 US $.

2. Material and methods

2.1. Model overview

We used the Partially Observed Markov Decision Process (POMDP) to simulate the evolution from normal colonic epithelium to adenomatous polyp to malignancy.

In this section we briefly describe the general characteristic of the POMDP model compared to the Markov model (for a detailed survey of the POMDP model see [17,18]). In a Markov model, the world being modeled is broken into a series of states, defined so that an individual may be in one and only one of the states at a given time. Markov processes assume that the time is broken into discrete intervals (cycles) and the transition between states occurs only once at the end of each cycle. These transitions are governed by a set of transition probabilities, which are the probabilities of being in a given state in the next cycle, conditioned on membership in a particular state in the current cycle. Usually, in health applications, decisions are not allowed within a Markov cycle, whereas in a more general setting decisions are allowed and are usually being made at time points referred to as decision epochs which correspond to the beginning of a cycle. At each cycle, the individual occupies a *health state*. At every cycle, the decision maker observes health state s, and he may choose an action; in the health care framework actions are usually a finite set of treatments or procedures. As a result of choosing an action a in a health state s at decision epoch t, the decision maker receives a reward $r_t(s,a)$ and the health state of the individual at the next decision cycle is determined by the transition probability distribution $p(\cdot|s,a)$. In some cases the reward depends also on the health state of the system at the next decision epoch. The non-negative function $p_t(s'|s,a)$ denotes the probability that the system is in health state s' at time $t+1$, when the decision maker chooses action a in health state s at time t. This is known as the transition probability function.

Partially Observed Markov Decision Processes (POMDP), also called the Hidden Markov Models (HMM), differ from the Markov process in that the decision maker does not always know the health state with certainty prior to making a decision (as in our case of screening for CRC). In addition to health states, actions, rewards, and transition probabilities, the POMDP model contains an observation or an indication space Y, and a probability function $q(y|s)$ which represents the probability that the decision maker receives an indication y, given that the unobserved health state is s.

The POMDP model represents more realistically the natural history of screening for colorectal cancer. In many epochs the decision maker does not know the true health state,

e.g., a negative FOBT test is a mere indication of the true health state of the patient. In a POMDP the core process is completely described by the transition probability distribution (which may not be stationary, i.e., it depends on time) P_t and the initial distribution over the states. The core process is not directly observable. Associated with the health states is a random variable Y_t, which takes on values in a finite "indication" or "signal" space. By observing y_t at time t, information regarding the true health state is obtained by the probabilistic relationship between the indication y and the true health state s. The probabilistic relationship is given by $Q_{t,s,y}$, where $Q_{t,s,y}$ is the probability of observing indication $Y = y$ at time t given that the true health state is s.

The stochastic process Y_t is called the observation process. A decision structure is now defined which incorporates the core and observation processes. In screening for colorectal cancer the decision maker can control both the observation and core processes by choosing various actions. A formal description of the POMDP model used in this study is given in the appendix.

The following passage presents the various health states and actions used in our model.

Persons representative of the 50-year-old Israel population were placed into the following health states: "normal colonic epithelium", "low-risk polyp", "high-risk polyp", "localized cancer", "regional CRC", "distant CRC", "death". The low risk polyp is defined as a single adenomatous polyp of size less than 1 cm and with tubular histology. A high-risk polyp is defined as any of the following: villous or tubulo-villous histology, size greater than 1 cm, multiple adenomas, high-grade dysplasia. The cycle length between epochs is one year. The population transitioned through the different health states and the transition probability from the observed indication to the true health state is estimated from the literature.

Detecting of altered human DNA in stool to detect tumor-associated mutations in the stool is a new screening strategy (three genetic targets – TP53, BAT26, and K-RAS – as a screening strategy have also been examined [19,20]). We examined and compared the following strategies (starting at 50 years of age):

- no screening,
- one-time colonoscopic screening (COL),
- colonoscopy, followed by a 10-year interval of follow-up with colonoscopy (COL-10),
- annual FOBT (FOBT),
- annual FOBT and SIG in a 5-year interval (FOBT + SIG),
- annual detection of altered human DNA in stool.

Persons with any positive screening test result (e.g., FOBT) underwent surveillance colonoscopy. The surveillance colonoscopy is as follows: if no polyps or malignancy were detected during colonoscopy there is no follow-up except in the case where the screening strategy is colonoscopy every 10 years. If during colonoscopy a low-risk polyp is diagnosed, then polypectomy is performed and a surveillance colonoscopy is done after 3 years. If a high-risk polyp or a colorectal carcinoma is detected then polypectomy or surgical resection is performed and surveillance colonoscopy is done a year later. A patient is referred to a colonoscopy whenever he presents with an alarm symptom for CRC, e.g., change of bowel habits or unexplained iron deficiency anemia.

Although one of the screening strategies recommended by the panel a few years ago [3] was flexible sigmoidoscopy every 5 years, we decided to omit it as a strategy, because new studies revealed that there has been a significant proximal shift in the distribution of CRC over recent decades [21,22] and therefore flexible sigmoidoscopy will become less successful as a screening tool.

Because of the exponential increase in the incidence rate of adenomatous polyp or CRC with age after the age of 50 years, it seems reasonable that a screening program should start at the age of 50. This assumption could be examined by our analysis, however Ness et al. [16] already found that screening between 50 and 54 years of age is cost-effective compared to screening at older ages, hence we decided to examine the various screening strategies with people aged 50 years. The time horizon for the study was life-time. In Israel, the life expectancy of a person aged 50 is about 29 years. If hypothetically we could eliminate all mortality cases caused by CRC the general life expectancy would not significantly change, i.e., on average people die from other causes than from CRC at the age of 79–80. We assumed the life time horizon to be until 79 years of age and further assumed that screening and/or surveillance continued until 79 years of age. Sensitivity analyses were conducted to determine the effect of different time horizon periods on the cost effectiveness of the screening strategies.

Incremental analyses were performed by rank ordering the strategies by increasing effectiveness after eliminating those that were more costly and less effective than an alternative. Effectiveness was measured in 3 ways: (i) life expectancy in each strategy, (ii) mortality rate from CRC, and (iii) comparing the cumulative distributions of the CRC mortality rate. We then calculated the incremental average cost-effectiveness (CE) ratio for each strategy (additional expected cost divided by additional expected effectiveness) compared with the next least expensive strategy. Strategies were ruled out by simple dominance, i.e., those strategies that were more costly and less effective than an alternative [23]. Sensitivity analyses were performed to assess the stability of the results to plausible ranges of uncertain parameters. Future costs and life-years were discounted at an annual rate of 3% [23]. The model was programmed in MATLAB software (MathWorks Inc. Natick, MA).

2.2. Clinical data and parameter estimation

Table 1 presents selected parameter estimates. The parameter estimation was based on the current literature. The age specific prevalence of adenomatous polyps was based on the literature [24–48] and was adjusted to the prevalence of adenomatous polyps in studies based on the local Israeli pop-

Table 1
Baseline assumption and ranges tested in the sensitivity analysis

Incidence and prevalence of polyps	Baseline and ranges
Prevalence of localized CRC at age 50	0.5% (0.1–1.5%)
Prevalence of polyps at age 50	10% (5–30%)
Percentage of high-risk polyp out of all polyps	33% (25–40%)
Percentage of lesions (polyps) in the lower colon	60% (40–90%)
Sensitivity and specificity of the tests	
Sensitivity of colonoscopy	95%
Specificity of colonoscopy	100%
Sensitivity of detection of altered human DNA in stool for cancer	91% (70–92%)
Sensitivity of detection of altered human DNA in stool for low-risk polyp	70% (70–80%)
Sensitivity of detection of altered human DNA in stool for high-risk polyp	82% (70–85%)
Specificity for detection of altered human DNA in stool test	90% (80–93%)
Sensitivity of FOBT for cancer	50% (35–80%)
Sensitivity of FOBT for polyps	10% (5–45%)
Specificity of FOBT	90%
Sensitivity of SIG for high-risk polyps	95%
Sensitivity of SIG for low-risk polyps	85%
Specificity of SIG	100%
Rate of major complications	0.23% of colonoscopies
Rate of death	1 out of 5000 colonoscopies
Effectiveness in treatment	
Effectiveness in treatment for localized CRC (%)	90% (70–95%)
Effectiveness of treatment for regional CRC (%)	70% (40–85%)
Annual transition probability	
Transition probability from low-risk polyp to high risk polyp	2%
Transition probability from high-risk polyp to regional CRC	5%
Transition probability from localized CRC to regional CRC	28% (20–35%)
Transition probability from high-risk polyp to localized CRC	5% (2–10%)
Transition probability from regional CRC to distant CRC	63% (50–70%)
Probability of diagnosing a localized CRC due to symptoms	25%
Rate of annual CRC mortality	
Localized CRC	0.2% (0.1–0.4%)
Regional CRC	3% (1–5%)
Distant CRC	55% (40–65%)
Discount rate	3%
Rate of life discount	3%
Time horizon for the study	Life-time horizon
Costs (in New Israeli Shekel NIS)	*NIS*
Cost of colonoscopy with polypectomy	1000
Cost of colonoscopy	800
Cost of major complication (10 hospitalization days)	15,000
Cost of treatment of localized CRC (estimated lifetime costs)	44,000 (30,000–50,000)
Cost of treatment of regional CRC (estimated lifetime costs)	85,000 (50,000–95,000)
Cost of treatment of distant CRC (estimated lifetime costs)	170,000
Cost of DNA test	300 (50–300)
Cost of FOBT	40 (25–60)
Cost of SIG	450

ulation [36–39]. For example, the prevalence of polyps for men aged 50 years in Israel was estimated at 10%, of which 67% were low risk and 60% were in the distal portion of the colon. The percentage of lower lesions (that could be detected by sigmoidoscopy) was based on the current literature [21,40,41]. Moreover, McCallion et al. [21] have shown that when the distribution of colorectal cancers in Northern Ireland reported from 1990 to 1997 was compared with those reported from 1976 to 1978, a significant proximal shift had occurred; whereas only 23.5% of cancers were found proximal to the splenic flexure in the early time period, this number grew to 36.7% in the 1990s. Prevalence of CRC and stage distribution at 50 years of age were obtained from SEER data and the local epidemiological data in Israel [36–39]. The transition probabilities were based on the literature and on previous studies. Sensitivity and specificity of detection of altered human DNA in stool for cancer, low-risk polyp, and high-risk polyp were based on [19,20]. The rates of complication and mortality caused by the risk of perforation were assigned to the endoscopic procedures.

Table 2
Lifetime costs and life expectancy, compliance 100%

Strategy	Lifetime cost per person (NIS)	Life expectancy	Incremental days of life gained	Incremental C/E ratio (NIS per life-year gained)
COL	1407	19.143		
FOBT + SIG	1447	19.174	11.57	1268
Annual FOBT	2023	19.152	(Dominated)	–
COL-10	2481	19.172	(Dominated)	–
No screening	2573	18.992	(Dominated)	–
Annual detection of altered human DNA in stool	2942	19.171	(Dominated)	–

Table 3
Mortality rates and reduction of mortality rates (compared to "no screening")

Strategy	Mortality rate	Reduction (%) of mortality rate (compared to "no screening")
No screening	3.10%	–
COL	1.25%	59.5%
FOBT	0.73%	76.5%
Annual detection of altered human DNA in stool	0.58%	81.3%
FOBT + SIG	0.50%	83.8%
COL-10	0.20%	93.7%

2.3. Costs

The costs of CRC treatment by stage and time period (initial, continuing, and terminal care) were obtained from two sources: (i) The Israel health ministry official costs, and (ii) the actual average costs paid by a large HMO data in Israel [49]. These costs include all costs of medical personnel and supplies to provide the service as well as overhead costs, such as administration, charting, and automated information systems. Tests costs were obtained from the same health maintenance organization. The stage-specific costs of annual treatment for CRC were obtained using the actual costs paid by a large HMO. All costs were updated to year 2000 New Israeli Shekels (NIS) (with US $1 equal to 5 NIS).

2.4. Effectiveness

Effectiveness was measured in three ways: (i) the average life expectancy, (ii) mortality rate from CRC, and (iii) the cumulative distributions of the mortality CRC rate. In the cost-effectiveness analysis, effectiveness was measured by the life expectancy in each strategy, and by the mortality rate from CRC in each strategy as an index of effectiveness.

Table 1 presents the baseline assumption in the analysis.

3. Results

Table 2 presents the life expectancy and marginal life expectancy for compliance rates of 100% for all strategies. Note that life-years were discounted at an annual rate of 3%. Annual FOBT and sigmoidoscopy during a 5-year interval (FOBT + SIG) is the best strategy with respect to life expectancy of 19.174 years. The "no screening" strategy results in the worst life expectancy of 18.992 years. Only two strategies ("FOBT + SIG" and "one time colonoscopic screening") were on the cost-effective frontier. FOBT + SIG had a C/E ratio of 1268 NIS ($250) per life-year saved compared to "one time colonoscopic screening". Other strategies were eliminated by simple dominance.

Mortality rates for each strategy and the reduction of mortality rates compared to "no screening" are presented in table 3. We found different ranks of the different screening strategies with respect to life expectancy and mortality rate.

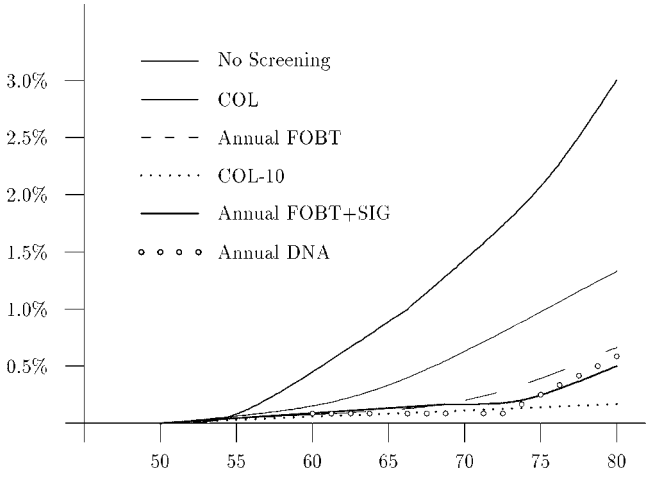

Figure 1. Cumulative CRC mortality.

Although one would expect the procedure with the highest life expectancy to also be associated with the lowest mortality rate, we found the opposite. Specifically, we found that "COL-10" was superior to "FOBT + SIG" with respect to mortality rate; however, with respect to life expectancy, "COL-10" was inferior to "FOBT + SIG".[2]

Figure 1 presents the cumulative CRC mortality for the various strategies. There is no stochastic dominance between the strategies; i.e., using the stochastic dominance rules the cost-effective frontier includes all strategies [50].

[2] Below we prove that the rank order can be different with respect to life expectancy and mortality rate even without applying a discount rate to saved life-years. Let n be the number of cycles, and denote by p_i the probability of staying alive at cycle i given that the subject was alive at cycle $i-1$. If a subject died during cycle i, varying assumption about how long into each cycle he lived. We assume that the subject lived on average halfway through the cycle. We calculate that life expectancy as $\frac{1}{2}(1-p_1)+1\frac{1}{2}p_1(1-p_2)+2\frac{1}{2}p_1p_2(1-p_3)+\cdots+(n-\frac{1}{2})p_1p_2\cdots p_{n-1}(1-p_n) = \frac{1}{2}+p_1+p_1p_2+p_1p_2p_3+\cdots+p_1\cdots p_{n-1}-(n-\frac{1}{2})p_1\cdots p_n = \frac{1}{2}+\sum_{k=1}^{n-1}\prod_{j=1}^{k}p_j-(n-\frac{1}{2})\prod_{i=1}^{n}p_i$. The probability that a subject will stay alive until the end of cycle n is $\prod_{i=1}^{n}p_i$, therefore the mortality rate is given by $1-\prod_{i=1}^{n}p_i$. Take two strategies with probabilities $p_1,\ldots,p_n$ and, respectively, $q_1,\ldots,q_n$. For example, choose $n=2$, if the first strategy has a better life expectancy but is inferior related to mortality rate we have that $\frac{1}{2}+p_1-1\frac{1}{2}p_1p_2 > \frac{1}{2}+q_1-1\frac{1}{2}q_1q_2$ and $1-p_1p_2 < 1-q_1q_2$ (note that we don't require that $p_1+p_2=1$). But this can be easily be satisfied, take, for example, $p_1=1$, $p_2=\frac{2}{5}$, $q_1=\frac{1}{2}$, and $q_2=\frac{2}{5}$.

Table 4
Sensitivity analyses

Variable	Sensitivity analysis values	Incremental C/E ratio of FOBT + SIG compared with COL (NIS per life-year gained)
Cost of colonoscopy with polypectomy (NIS)	800	1308
	1000	1268
	1350	1198
Cost of complication of colonoscopy (NIS)	10,000	1568
	15,000	1268
	25,000	667
Cost of treatment of localized CRC (estimated lifetime costs)	35,000	1924
	44,000	1268
Cost of treatment regional CRC (estimated lifetime costs)	70,000	1111
	85,000	1268
	100,000	2053
Effectiveness in treatment for localized CRC (%)	70%	2146
	90%	1268
Effectiveness of treatment for regional CRC (%)	60%	1634
	70%	1268
Cost of SIG	450	1268
	500	2576
Probability of major complication due to colonoscopy	0.10%	1777
	0.23%	1268
	0.30%	994
Compliance with follow-up colonoscopy	40%	5780
	60%	4984
	100%	1268
Prevalence of polyps at age 50 years	5%	1616
	10%	1268
	17%	847
Percentage of lesions (polyps) in the lower colon	40%	1333
	60%	1268
	80%	1203
Time horizon (in years)	30	1802
	32.5	2734
	35	3945

3.1. Sensitivity analysis

One-way and two-way sensitivity analyses were performed over most settings of the variables. In most scenarios we examined, the ranking of the strategies was stable and did not change. Table 4 presents the incremental C/E ratio of COL compared with FOBT + SIG (NIS per life-year gained) for different variable settings. When the cost of complications of colonoscopy increases to 25,000 NIS, the incremental C/E ratio decreases from 1268 NIS to 667 NIS, and when the cost of sigmoidoscopy increases to 500 NIS (instead of 450 NIS) the incremental C/E ratio increases from 1268 NIS to 2576 NIS. The incremental C/E ratio of FOBT + SIG compared to COL was most influenced by compliance with follow-up by colonoscopy. For example, changing the compliance with follow-up rate to 40% (instead of 100%) the incremental C/E ratio increased to 5780 NIS (instead of 1268 NIS). The annual detection of altered human DNA in stool becomes the optimal strategy if the cost of the test decreases to approximately 105 NIS (about $20 US).

3.2. Compliance

A major factor determining which test to use for screening is its compliance rate. We analyzed the ranking of incremental cost per life-year saved in various settings of compliance rates of the various tests. We found that when the compliance rate for FOBT is 75% every year, and the compliance rate for colonoscopy is 25%, then COL dominates FOBT + SIG; i.e., it is less costly and more effective. Another setting revealed that if we assume a compliance rate of 70% for FOBT for the first year and then a compliance rate of 90% for FOBT for each consecutive year compared to 35% for COL, then COL also dominates FOBT + SIG. When the compliance rate for Colonoscopy is 60% and the compliance rate for Colonoscopy for surveillance is 80%, the incremental C/E ratio of COL-10 compared to COL is 42900 NIS, and the incremental C/E ratio of COL-10 compared to FOBT + SIG is 40,100 NIS. We can conclude that compliance rates play a major role in the cost-effectiveness analysis, and one should consider the compliance rate as an important factor in determining the preferred strategy for screening for CRC.

4. Summary and conclusions

CRC is the second leading cause of cancer death in North America and the leading cause of death from cancer in Israel. Six strategies were evaluated using a Partially Observed Markov Decision Process (POMDP) to simulate the evolution from normal colonic epithelium to adenomatous polyp to malignancy. A POMDP is a generalization of Markov models, where the POMDP presents more properly the natural history of colorectal neoplasia.

When compliance was assumed to be 100% for all tests, the cost-effective efficient frontier included FOBT + SIG and COL. When effectiveness was measured by the mortality reduction rate we found that COL-10 resulted in the best outcome, reducing the mortality rate by 94% compared to "no screening". The next best strategy regarding reduction in mortality rate was FOBT + SIG, with an 84% reduction of the mortality rate compared to "no screening". The COL strategy reduces the mortality rate by 59% compared to "no screening". This study revealed that it is highly cost-effective to screen average-risk asymptomatic individuals beginning at age 50. COL or FOBT + SIG would be the preferred test for screening, starting screening at that age.

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Appendix A

In this appendix we give a formal description of the POMDP model. Let X_t be a random variable defined on a sample space Ω, where $t \in I$, and $I = \{0, 1, 2, \ldots, n\}$; where X_t presents the *health state* of an individual at time t and n is a finite time horizon. Denote the set of *health state* by $\mathcal{S} = \{s_1, \ldots, s_k\}$, then X_t takes values in the finite set $\mathcal{S} = \{s_1, \ldots, s_k\}$. The stochastic process $\{X_t, t \in I\}$, called the *core process*, assumes to be a finite state Markov chain with $k \times k$ transition probability matrix P_t, where $P_t(i, j) = \Pr(X_{t+1} = s_j | X_t = s_i)$. The core process is completely described by P_t and the initial distribution over $\mathcal{S}$, denoted by $\pi(0) = (\pi_1(0), \ldots, \pi_k(0))$, where $\pi_i(0) = \Pr\{X_0 = s_i\}$, $i = 1, \ldots, k$. The core process is not directly observable; that is, the realization of X_t, is not determinate with certainty at time t.

Associated with X_t is a random variable Y_t, which takes on values in a finite "indication" space $\mathcal{Y} = \{y_l, \ldots, y_m\}$. By observing Y_t at time t, information regarding the true value of X_t is obtained. The probabilistic relationship between X_t, and Y_t, is known to the decision maker. Suppose that if $X_t = s$, an observation will have indication y with probability Q_{sy}, i.e.,

$$Q_{sy} = \Pr\{Y_t = y | X_t = s\}, \quad \text{for } s \in \mathcal{S}, y \in \mathcal{Y}. \tag{A.1}$$

Define the $n \times m$ *information matrix* as $Q = [q_{sy}]$, $s \in \mathcal{S}$, $y \in \mathcal{Y}$. The stochastic process $\{Y_t, t \in I\}$ is called the *observation process*.

In this study, $\mathcal{S}$, the set of health states is given by $\mathcal{S} = \{$*"normal colonic epithelium", "low-risk polyp", "high-risk polyp", "localized cancer", "regional CRC", "distant CRC", "death"*$\}$ and $\mathcal{Y}$, the set of indications is given by the various results of the different tests like FOBT, or colonoscopy. The set of indications also includes different symptoms related to CRC, e.g., unspecified change in bowel habits, rectal bleeding and others. The *information matrix* is calculated by using the sensitivity and specificity of every test.

Assume that the decision maker can control both the observation and core processes by choosing actions. Let $\mathcal{A}$ be a finite set denoting all of the actions available to the decision maker. In our study, $\mathcal{A}$ includes various treatments or surgical procedures, e.g., polypectomy, surgical removal of the tumor, chemotherapy, radiation, etc. Let $P_t(a)$ denote the transition matrix of the core process when action $a \in \mathcal{A}$ is chosen. That is, if s_i is the current state and action a is chosen, the core process moves to a new state s_j with probability $P_t(a)(i, j)$, $s_i, s_j \in \mathcal{S}$. Similarly, let $Q(a)$ denote the relationship between the observation and core processes when $a \in \mathcal{A}$ is chosen.

Let $y_t \in \mathcal{Y}$ and $a_t \in \mathcal{A}$ denote the value observed and the action taken at time t, respectively. The data available for decision making at time t is given by $(\pi(0), y_1, a_1, \ldots, a_{t-1}, y_t)$. Denote the set of all possible available data at time t by $\mathcal{D}_t$. Define $\pi_i(t) = \Pr\{X_t = s_i | (\pi(0), y_1, a_1, \ldots, a_{t-1}, y_t)\}$ and let

$$\pi(t) = \big(\pi_1(t), \ldots, \pi_k(t)\big),$$

where $\pi(t)$ is called the *information vector*. Using Bayes' formula, the transformation of the information vector from time t to $t + 1$ can be specified.

Assume that there is a reward function (and respectively a cost function), say $r_t : \mathcal{S} \times \mathcal{A} \to R$, where $r_t(s_i, a)$ is the reward that is earned at time t if the core process is in state s_i and action a is taken. In our model, the reward is the discounted life years earned and similarly for the costs.

For ease of notation let $r_t(a) = [r_t(s_1, a), \ldots, r_t(s_k, a)]$, then, if $\pi(t)$ is the *information vector* then the expected reward (and similarly costs) at time t is given by

$$\pi(t) \cdot r_t(a),$$

where "$\cdot$" denotes the usual inner product operator.

Let the function $\delta : \mathcal{D} \to \mathcal{A}$ denote a *decision rule* which indicates the action to take at time t when the data available for decision making at time t is given by $(\pi(0), y_1, a_1, \ldots, a_{t-1}, y_t)$. A policy (or strategy) δ, is defined as a sequence of decision rules, $\delta = \{\delta_1, \ldots, \delta_t, \ldots, \}$.

In this study we did not aim to find the best strategy, but we calculated the expected efficacy and costs for several prior defined strategies. Given strategy δ is employed and the process starts at $\pi(0)$, the prior distribution over the health states $\mathcal{S}$, the expected discounted finite horizon reward (and similarly for costs) of the POMDP is given by:

$$\sum_{t=0}^{n} \frac{\pi(t) \cdot r_t(a)}{(1+\beta)^t}, \tag{A.2}$$

where $0 \leqslant \beta < 1$ is the discount factor.

In this study we examined the following strategies: "no screening", "one-time colonoscopic screening (COL)", "colonoscopy, followed by a 10-year interval of follow-up with colonoscopy (COL-10)", "annual FOBT (FOBT)", "annual FOBT and SIG in a 5-year interval (FOBT + SIG)", "annual detecting of altered human DNA in stool".

We next provide the way we employed the POMDP in our case and give full details on how we computed the annual FOBT curve presented in figure 1. In the case of the "annual FOBT" strategy, the set of actions is given by $\mathcal{A} = \{a_1, a_2, a_3, a_4\}$, where $a_1 =$ "conduct a FOBT", $a_2 =$ "perform a colonoscopy with or without polypectomy", $a_3 =$ "treat for CRC", and $a_4 =$ "do nothing" and the health state space is given by $\mathcal{S} = \{s_1, s_2, \ldots, s_7\}$, where $s_1 =$ "normal colonic epithelium", $s_2 =$ "low-risk polyp", $s_3 =$ "high-risk polyp", $s_4 =$ "localized cancer", $s_5 =$ "regional CRC", $s_6 =$ "distant CRC", $s_7 =$"death". As the decision rule is a given and is dependent only by the observation of the indication (e.g., a positive FOBT yields a colonoscopy) to simplify we define a new health state space and a new "indication" space by a subset of the cartesian product of $\mathcal{S}$ with $\mathcal{A}$ and, respectively, for $\mathcal{Y}$ with $\mathcal{A}$, i.e., $\tilde{S} \subset \mathcal{S} \times \mathcal{A}$, $\tilde{Y} \subset \mathcal{Y} \times \mathcal{A}$.

The new health state space and the new "indication" space is given by:

$$\begin{aligned}\tilde{S} = \{&s_1 \times a_1, s_1 \times a_2, s_1 \times a_4, s_2 \times a_1, s_2 \times a_2, s_2 \times a_4,\\ &s_3 \times a_1, s_3 \times a_2, s_3 \times a_4, s_4 \times a_1, s_4 \times a_2, s_4 \times a_3,\\ &s_4 \times a_4, s_5 \times a_1, s_5 \times a_2, s_5 \times a_3, s_5 \times a_4, s_6 \times a_1,\\ &s_6 \times a_2, s_6 \times a_3, s_6 \times a_4, s_7\}.\end{aligned}$$

The indication space includes the indication obtained from the FOBT, colonoscopy, different symptoms that are related to CRC and the case where no indication is being observed, e.g., after performing a colonoscopy that yielded a "normal colonic epithelium" during the following years the patient does not undergo any observation and therefore no indication is being observed during this period of time.

In our case the matrix $P_t(i, j)$ is time dependent and has 22 rows and 22 columns. The $Q(i, j)$ matrix is independent in time and has 22 rows (the number of "health state") and 10 columns (the number od "indications"). For simplicity we present only the first 4 rows and columns of the two matrices. The first column of the Q matrix is for the indication $y_1 =$ "FOBT resulted with a positive FOBT", the second column is for the indication $y_2 =$ "FOBT resulted with negative FOBT", the third column is the indication $y_3 =$ "colonoscopy resulted with normal colonic epithelium", the forth column is the indication $y_4 =$ "colonoscopy resulted with low risk polyp" and so on.

Thus the *information matrix* Q is given by

$$Q = \begin{matrix} s_1 \times a_1 \\ s_1 \times a_2 \\ s_1 \times a_4 \\ s_2 \times a_1 \\ \vdots \end{matrix} \begin{pmatrix} 0.1 & 0.9 & 0 & 0 & \dots \\ 0 & 0 & 1 & 0 & \dots \\ 0 & 0 & 0 & 0 & \dots \\ 0.1 & 0.9 & 0 & 0 & \dots \\ \vdots & \vdots & \vdots & \vdots & \end{pmatrix}, \tag{A.3}$$

which is based on our basic assumptions, i.e.,

$$Q = \begin{pmatrix} \begin{matrix}1-\text{specificity}\\ \text{of FOBT}\end{matrix} & \begin{matrix}\text{specificity}\\ \text{of FOBT}\end{matrix} & 0 & 0 & \dots \\ 0 & 0 & \begin{matrix}\text{specificity of}\\ \text{colonoscopy}\end{matrix} & 0 & \dots \\ 0 & 0 & 0 & 0 & \dots \\ \begin{matrix}\text{sensitivity}\\ \text{of FOBT}\\ \text{for polyps}\end{matrix} & \begin{matrix}1-\text{sensitivity}\\ \text{of FOBT}\end{matrix} & 0 & 0 & \dots \\ \vdots & \vdots & \vdots & \vdots & \end{pmatrix}.$$

The initial distribution $\pi(0)$, is given by $\pi(0) = (0.895, 0, 0, 0.067, 0, 0, 0.033, 0, 0, 0.005, 0, \dots, 0)$, i.e., in the first cycle all people perform a FOBT (assuming compliance rate of 100%), 89.5% of the population will have a "normal colonic epithelium", 6.7% will have a low-risk polyp, 3.3% will have "high risk polyp" and 0.5% will have localized CRC.

We present the first 4 rows and columns of the transition matrix P_t for $t = 1$ of the core process, where the compliance rate is 100%.

$$P_1 = \begin{matrix} s_1 \times a_1 \\ s_1 \times a_2 \\ s_1 \times a_4 \\ s_2 \times a_1 \\ \vdots \end{matrix} \begin{pmatrix} 0.887 & 0.1 & 0 & 0.013 & \dots \\ 0 & 0 & 0.986 & 0 & \dots \\ 0 & 0 & 0.986 & 0 & \dots \\ 0 & 0.095 & 0 & 0.0986 & \dots \\ \vdots & \vdots & \vdots & \vdots & \vdots \end{pmatrix}. \tag{A.4}$$

In the computerized model all variables are incorporated into the transitional matrix such that sensitivity analysis could be conducted. For example the first row and the second column in P_1 is the result of a false negative FOBT, where the patient is referred to perform a colonoscopy. Note that some of the transition probabilities are time dependent.

We have

$$\begin{aligned}\pi_i(t) &= \Pr(X_t = s_i),\\ Q(i, j) &= \Pr(Y_t = y_j | X_t = s_i)\end{aligned}$$

and

$$P_t(i, j) = \Pr(X_{t+1} = s_i | X_t = s_j).$$

We need to update the distribution over the health states or the information vector $\pi(t + 1)$ given $\pi(t)$. Using Bayes' formula, the transformation of the information vector from time t to $t + 1$ is specified as:

$$\begin{aligned}&\Pr(X_{t+1} = s_i | Y_{t+1} = y_j)\\ &\quad= \frac{\Pr(Y_{t+1} = y_j | X_{t+1} = s_i) \Pr(X_{t+1} = s_i)}{\Pr(Y_{t+1} = y_j)}\\ &\quad= \frac{Q(i, j) \sum_k \Pr(X_{t+1} = s_i | X_t = s_k) \Pr(X_t = s_k)}{\Pr(Y_{t+1} = y_j)}\\ &\quad= \frac{Q(i, j) \sum_k P_t(k, i)\pi_k(t)}{\sum_l \Pr(Y_{t+1} = y_j | X_{t+1} = s_l) \Pr(X_{t+1} = s_l)}\\ &\quad= \frac{Q(i, j) \sum_k P_t(k, i)\pi_i(t)}{\sum_l Q(l, j) \sum_k P_t(k, l)\pi_l(t)}.\end{aligned}$$

Thus we have:

$$\begin{aligned}\pi_i(t + 1) &= \Pr(X_{t+1} = s_i)\\ &= \sum_j \Pr(X_{t+1} = s_i | Y_{t+1} = y_j) \Pr(Y_{t+1} = y_j)\end{aligned} \tag{A.5}$$

or

$$\pi_i(t + 1) = \sum_j Q(i, j) \sum_l Q(l, j)\pi_l(t). \tag{A.6}$$

Finally, to compute the annual FOBT curve presented in figure 1, we present $\pi_{22}(t)$ as a function of t, i.e., we present the cumulative probability of death caused by CRC for this strategy and similarly for the other strategies.

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