International Journal of Colorectal Disease (2019) 34:1953–1962
https://doi.org/10.1007/s00384-019-03419-7

ORIGINAL ARTICLE

Comparative effectiveness and cost-effectiveness analysis of a urine metabolomics test vs. alternative colorectal cancer screening strategies

Scott Barichello[1] · Lu Deng[2] · Kathleen P. Ismond[1,2] · Dustin E. Loomes[1] · Erin M. Kirwin[3] · Haili Wang[1,2] · David Chang[1,2] · Lawrence W. Svenson[1,3,4,5] · Nguyen Xuan Thanh[5]

Accepted: 25 September 2019 / Published online: 1 November 2019

Abstract

Purpose Despite the success of provincial screening programs, colorectal cancer (CRC) is still the third most common cancer in Canada and the second most common cause of cancer-related death. Fecal-based tests, such as fecal occult blood test (FOBT) and fecal immunochemical test (FIT), form the foundation of the provincial CRC screening programs in Canada. However, those tests have low sensitivity for CRC precursors, adenomatous polyps and have low adherence. This study evaluated the effectiveness and cost-effectiveness of a new urine metabolomic-based test (UMT) that detects adenomatous polyps and CRC.

Methods A Markov model was designed using data from the literature and provincial healthcare databases for Canadian at average risk for CRC; calibration was performed against statistics data. Screening strategies included the following: FOBT every year, FIT every year, colonoscopy every 10 years, and UMT every year. The costs, quality adjusted life years (QALY) gained, and incremental cost-effectiveness ratios (ICERs) for each strategy were estimated and compared.

Results Compared with no screening, a UMT strategy reduced CRC mortality by 49.9% and gained 0.15 life years per person at $42,325/life year gained in the base case analysis. FOBT reduced CRC mortality by 14.9% and gained 0.04 life years per person at $25,011/life year gained. FIT reduced CRC mortality by 35.8% and gained 0.11 life years per person at $25,500/life year while colonoscopy reduced CRC mortality by 24.7% and gained 0.08 life years per person at $50,875/life year.

Conclusions A UMT strategy might be a cost-effective strategy when used in programmatic CRC screening programs.

Keywords PolypDx · Markov model · Early detection of cancer · QALY · ICER

Scott Barichello and Lu Deng contributed equally to the work and are listed in alphabetical order by last name.

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00384-019-03419-7) contains supplementary material, which is available to authorized users.

✉ Lu Deng
lu.deng@metabolomictechnologies.ca

[1] Faculty of Medicine and Dentistry, University of Alberta, Edmonton, Alberta, Canada

[2] Metabolomic Technologies Inc., Suite 132, 9650 20 Avenue, Edmonton, AB T6R 3T2, Canada

[3] Government of Alberta, Edmonton, Alberta, Canada

[4] Cumming School of Medicine, University of Calgary, Calgary, Alberta, Canada

[5] School of Public Health, University of Alberta, Edmonton, Alberta, Canada

Introduction

Colorectal cancer (CRC) is the third most commonly diagnosed malignancy and the fourth leading cause of cancer-related deaths in the world and its burden is expected to increase by 60% to more than 2.2 million new cases and 1.1 million cancer deaths by 2030 [1]. CRC represents a significant and increasing health economic burden. In 2009, the estimated global CRC cost was $33.4 billion US dollars and was comprised of direct medical costs (56%), direct non-medical costs (22%), and productivity losses (22%) [2]. Patients with CRC have a significantly lower health-related quality of life negatively impacting their daily activities, mood, work productivity, and relationships [3].

CRC typically develops slowly, over the course of 10 to 20 years, with approximately 80–96% of tumors arising from adenomatous polyps (precancerous growths) [4, 5]. The 5-year survival rate of CRC increases from 14% for distant cancer to 90%

of localized cancer [6]. With early detection of CRC and removal of adenomatous polyps, the incidence and mortality of CRC can be reduced [7, 8]. Population-based screening programs aim to decrease the prevalence of CRC by detecting and treating earlier stages of cancer that respond well to conventional treatments relative to opportunistic screening practices [9]. In Canada, provincial screening programs are available in most provinces, except Northwest Territories, Nunavut, and Yukon [10]. Conventional fecal-based screening tests, such as fecal occult blood test (FOBT) and fecal immunochemical test (FIT), form the foundation of the provincial CRC screening programs in Canada. Conventional fecal-based screening tests (FOBT, FIT) detect hidden blood in stool which occurs mostly for later stage of cancer and have low sensitivity for adenomatous polyps [11]. New fecal DNA test detects DNA mutation in addition to hidden blood in stool with improved sensitivity [12], but is not currently available in Canada. With the nature of the stool sample, the effectiveness of the fecal-based screening tests (FOBT, FIT) is also hindered with low adherence [10, 13–19]. Colonoscopy has a superior sensitivity and specificity to non-invasive screening tests, but costs more than fecal-based tests, is with higher risk of procedural-related complications and has low rates of screening compliance [20]. More recently, a urine metabolomic-based test (UMT) has been reported to have a higher sensitivity for colonic adenomatous polyps than fecal-based tests [21–23] and an even higher sensitivity for CRC [24]. The UMT is based on the quantification of key metabolites (ascorbic acid, carnitine, succinic acid, kynurenine, and diacetylspermine) that were discovered through prospective trials to distinguish normal, adenomatous polyps, and CRC groups. The quantified metabolite concentration in urine was then analyzed by a multivariate algorithm to give a positive or negative result that indicates the presence or absence of adenomatous polyps or CRC. Like other non-invasive CRC screening tests, a positive UMT result would lead to the recommendation of follow-up diagnostic colonoscopy.

Extensive studies have been done to evaluate the effectiveness and cost-effectiveness of CRC screening tests, e.g., FOBT, FIT, and colonoscopy [11, 25–37], and have shown that screening is an effective way to reduce the incidence and mortality of CRC. The aim of the present study was to assess the effectiveness and cost-effectiveness of UMT, FOBT, FIT, and colonoscopy compared with no screening in Canadian population using a Markov economics analysis.

Methods

Markov model design

Using TreeAge Pro (TreeAge Software Inc., Williamston, MA), a Markov model was adapted from the previously published model by Ladabaum et al. [26, 27, 29–32] to include urine-based metabolomics technology test. The model structure is outlined in Figure S1 (Supplemental Information). In brief, the simulated population enters the model with different proportion of normal; small (< 10 mm) adenomatous polyp; large (> 10 mm) adenomatous polyp; localized CRC, regional CRC, and distant CRC, and each year, they have a certain probability to stay in the same state, to progress to the next state or to death. Diagnosed patients will get treatment, may die from the disease, or from other causes. People who have polyp removed or CRC treated will be under surveillance following Canadian guidelines [38]. Patients with low-risk polyps (< 10 mm) had a surveillance colonoscopy in 5 years, while those with high-risk polyps (> 10 mm) were recalled in 3 years, and then every 5 years. Patients with CRC had a surveillance colonoscopy within 1 year of diagnosis, 3 years later, and every 5 years subsequently. However, they are given a highly polyp/CRC recurrence rate to account for the fact that they are under higher risks of developing adenomas or cancers than the general population in the following years.

Natural history and model calibration

The base prevalence of small polyp, large polyp, and localized cancer at age 50 were set to be 14.25%, 0.75%, and 0.09%, respectively, based on previous publications [26, 27, 29–32]. Beginning at age 50 years, average-risk persons progress through the model for 50 1-year cycles, until age 100 years or death. Age-specific non-CRC mortality rates [39] were derived from age-specific mortality rates and age-specific sex ratio [40] reported by Statistics Canada. The model assumes 85% of CRC develops from adenomatous polyp. In the natural history model, CRCs are diagnosed with colonoscopy only once they lead to symptoms. The symptomatic presentation of localized cancer and regional cancer are taken from Ladabaum's model and is set to be 22%/year and 40%/year, respectively [31, 32, 34–37]. The symptomatic presentation of distant cancer is assumed to be 100%. Diagnosed CRCs are treated, resulting in stage-specific survival. To represent the Canadian population, model calibration was preformed to reproduce age-specific CRC incidence rate, the age-specific polyp prevalence for small polyp and large polyp. The annual transition rate to small polyp from normal, annual transition rate to large polyp from small polyp, annual transition rate to cancer from large polyp, and annual transition rate to cancer without polypoid precursors were derived from model calibration.

Screening strategies

We superimposed screening on the natural history model. Screening was performed from age 50 years up to age 74 years. The conventional screening strategies were analyzed including (1) FOBT every year, (2) FIT every year, and (3)

colonoscopy-based screening every 10 years. Both FIT and colonoscopy are recommended by Canadian Association of Gastroenterology and Canadian Task Force on Preventive Health Care [9, 39] as well as American College of Gastroenterology and the US Multi-Society Task Force [40]. Although it is not included in the US colorectal cancer screening guidelines [40], FOBT is recommended in Canadian screening guidelines and is still the primary test in colorectal screening programs in provinces like Ontario [41]. Screening interval of 1 year for the UMT was used for base case analysis. Screening interval of 2 years, 3 years, 4 years, and 5 years for the UMT strategy were also modeled for scenario analysis. In our model, if a non-colonoscopy-based screening test was positive but colonoscopy negative, the test was assumed to be a false positive and those individuals returned to their original screening strategy after a 10-year screening free period.

Markov model input parameters

Model inputs, including base prevalence, transition probabilities, characteristics of screening tests, health utilities, and costs, were collected/derived and summarized in Supplemental Table S1. In this study, we prioritized the use of local Alberta, Canada data. If the Alberta data were not available, we used data from published literature (applying a meta-analysis whenever necessary) with an order of prioritization being data from Canada, USA, and developed countries.

Characteristics of screening strategies

Individual screening test operating characteristics were extracted from the literature and outlined in Table 1. Removal of polyps with colonoscopy was modeled as complete. At a specificity of 91%, the sensitivity of UMT is 43% for adenomatous polyps [22] and 74% for CRC [24]. These values were used for base case analysis. Sensitivities of FIT test for small adenomatous polyp, large adenomatous polyp, and cancer were 10%, 24%, and 70%, respectively, with a specificity of 95% [30]. FOBT has a sensitivity of 5% for small polyps, 11% for large polyps, and 40% for cancer with a specificity of 97% [30]. The specificity of colonoscopy is assumed to be 100%, with a sensitivity of 85% for small polyp, 90% for large polyp, and 95% for cancer.

Programmatic uptake and adherence of FOBT [18, 19], FIT [10, 13–17], and colonoscopy [37, 38] have been assessed in several large studies. Uptake with the UMT was estimated using the available data on adherence of other widely used urine-based screening tests [42, 43]. For base case analysis,

Table 1 Clinical and economic outcomes in a cohort of 100,000 people

Screening strategy	No screening	FOBT, 1 year	FIT, 1 year	Colonoscopy, 10 years	UMT, 1 year
Cost per test	-	$22	$25	$1000	$95
Sensitivity for small polyp	-	5%	10%	85%	43%
Sensitivity for large polyp	-	11%	24%	90%	43%
Sensitivity for cancer	-	40%	70%	95%	74%
Specificity	-	97%	95%	100%	91%
Adherence	-	0.254	0.493	0.576	0.836
CRC deaths					
Total CRC deaths	3949	3363	2534	2975	1978
CRC deaths prevented (*n*)	0	587	1415	974	1971
CRC mortality reduction (%)		14.9%	35.8%	24.7%	49.9%
Total cost of strategy in cohort	0.55 billion	0.66 billion	0.82 billion	0.95 billion	1.20 billion
Quality adjusted life years					
Total QALY	2,421,296	2,425,587	2,431,955	2,429,138	2,436,609
Incremental QALY	-	4291	10,660	7842	15,314
QALY gained per person compared to no screening	-	0.04	0.11	0.08	0.15
ICER					
No screening	-	$25,011	$25,500	$50,875	$42,325
FOBT	-	-	$25,829	$82,130	$48,065
FIT	-	-	-	FIT dominates	$80,859
Colonoscopy	-	-	FIT dominates	-	$33,350
Total colonoscopies	3660	24,581	67,399	154,420	168,094
Colonoscopies per person	0.04	0.2	0.7	1.5	1.7

we performed a meta-analysis to pool the rate of each screening test and the results are outlined in both Table 1 and Table S1.

Screening and treatment costs

Screening and treatment costs are outlined in Table S1. Cost inputs were estimated using Alberta-based data and inflated to 2018 Canadian dollars.

Cost of FIT and FOBT were provided by Alberta Health Services. A $95 cost per UMT was used based on consultation with the UMT vendor (Metabolomic Technologies Inc.). To estimate the costs of colonoscopy and polypectomy, a cohort of 19,059 individuals who underwent colonoscopy in 2010 who did not develop colorectal cancer within a year was analyzed. The total inpatient, ambulatory, and physician care costs for the day of the procedure were compared with total costs the day prior and following the colonoscopy. The average colonoscopy cost and cost of colonoscopy with a small or large polypectomy were estimated from the Alberta cost data. Costs of colorectal cancer screening program administration, variable across regions, were not included in the treatment cost analysis.

To estimate costs for patients diagnosed with a colorectal cancer (colon, rectosigmoid junction, or rectum), a retrospective cohort of 42,416 patients (local confined cancer $n = 6722$, regional cancer spread $n = 4768$, distant cancer spread $n = 3608$) diagnosed between January 1, 2004 and December 31, 2006, were identified through the Alberta Cancer Registry. These individuals were matched to 5 controls each, by age, location, and gender. The incremental surgical, inpatient, ambulatory, and physician costs were calculated as the difference in total costs between those with cancer and the controls. The Alberta Health Services Cancer Pharmacy provided chemotherapy costs. The total ongoing chemotherapy costs, including biologics, were tabulated for a sample of patients from the cancer cohort group. The average difference total cost, for 1 year to 5 years following diagnosis, were tabulated by cancer stage at diagnosis; local, regional, or distant. Indirect cost such as lost productivity was not considered in the cost analysis.

Analyses

The cost-effectiveness in terms of costs, quality adjusted life years (QALY), and the incremental cost-effectiveness ratio (ICER) for each strategy were determined and compared with each other as well as to no screening or natural history. Clinical outcomes such as CRC mortality and the number of colonoscopies were also included. Future QALYs and costs were discounted by an annually discounted rate to account for the effect of time on those values due to opportunity cost, catastrophic risk, and pure time preference. According to the Canadian Agency for Drugs and Technologies in Health (CADTH) guidelines, an annual discount rate of 1.5% was used for base case analysis and a range of 0–3% was used in sensitivity analysis [44]. Tornado diagrams on each screening strategies pair were generated on input parameters including test characteristics, health utilities, and cost. We used lower and upper values of the confidence interval as listed in Table S1 or ± 20% if a confidence interval was not available. One-way sensitivity analysis on adherence for each screening strategy was also performed. To see how resampling parameter values affect the base case calculation, probabilistic sensitivity analysis was conducted with Monte Carlo simulation with the number of samples sets to be 1000 and the incremental cost-effectiveness (ICE) scatterplot was generated for each screening strategy compared with no screening.

Results

Model development and calibration

Our model was adapted from the previously published Markov model by Ladabaum et al. [26, 27, 29–32] to include a UMT screening strategy. The Markov model developed by Ladabaum's group has been calibrated to US numbers [29] and has been validated through multiple trials. In this study, we aimed to evaluate the screening strategies in Canadian population with prioritized use of local Alberta, Canada data. We calibrated our model for natural history to reproduce Alberta age-specific CRC incidence published by Alberta Health Service (Fig. 1a) and the age-specific prevalence of small polyp and large polyp derived from the autopsy data. (Fig. 1b–c) [29, 45].

Model output: clinical and economic outcomes and cost-effectiveness

The clinical and economic outcomes of the base case analysis are summarized in Table 1. For a cohort of persons at an average risk for colorectal cancer, all screening strategies beginning at age 50 were associated with CRC mortality reduction, an increase in both QALYs and associated cost as compared with no screening strategy.

With no screening, the expected number of deaths from CRC in the 100,000 person cohort was 3949. A UMT screening strategy with base case operating characteristics resulted in the greatest reduction in CRC-related mortality with a 49.9% reduction in CRC-associated mortality compared with no screening or non-adherence. This significant reduction in mortality was followed by FIT with 35.8% reduction, colonoscopy with 24.7% reduction, and FOBT with 14.9% reduction (Table 1). The urine screening strategy is also the most effective strategy for QALY. Compared with no screening, a UMT

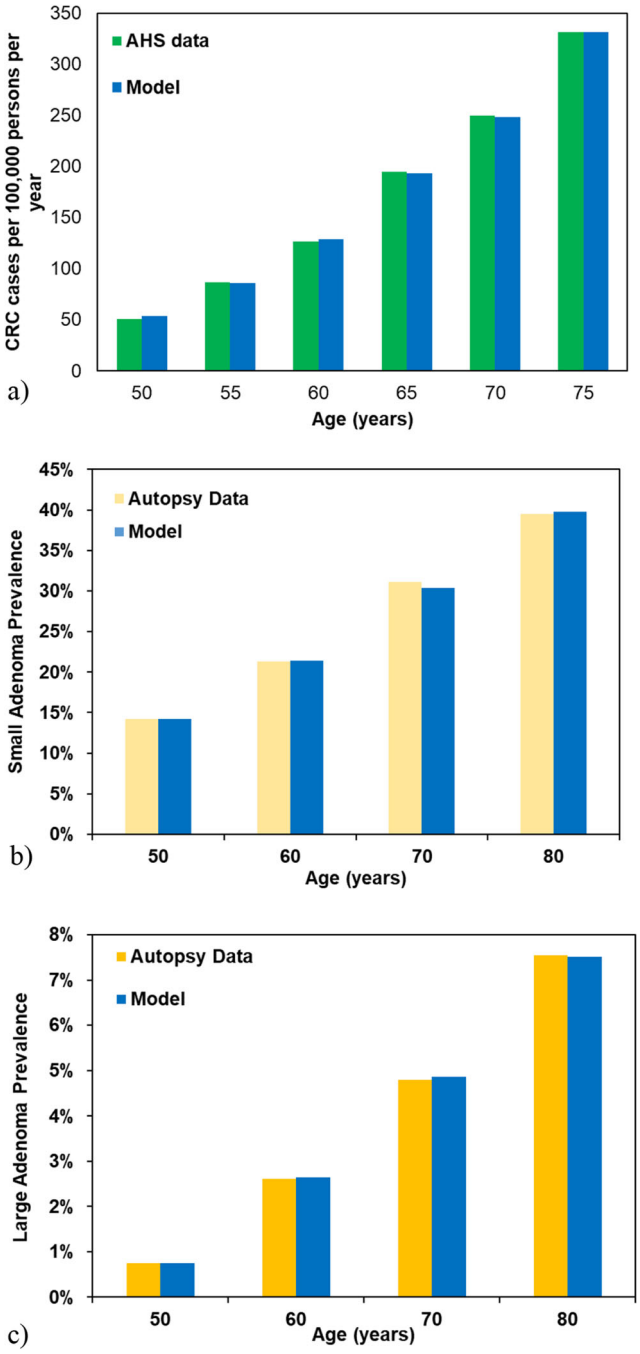


Fig. 1 **a** The natural history model reproduced the age-specific CRC incidence rate from AHS Cancer Statistic Report. The natural history model reproduced the age-specific prevalence of **b** small and **c** large adenomatous poly from autopsy data

screening strategy was associated with the largest QALY gain averaged per person at 0.15 years followed by FIT with 0.11 years, colonoscopy with 0.08 years, and FOBT with 0.04 years, respectively.

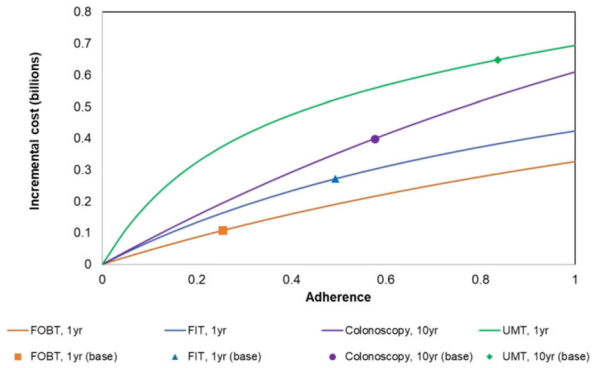
There is a total cost of 0.55 billion for no screening strategy for a cohort of 100,000. This consists of the cost for colonoscopy and cancer treatment cost of systematic patients. Among four screening strategies, FOBT has the lowest total cost due to its low adherence rate and low cost per test. Colonoscopy has the second lowest total cost as a 10-year adherence rate of 0.576 [37, 38] was used in the model to represent the real screening uptake. Notably, FIT screening strategy was found to be less costly and associated with a greater gain in QALY when compared with the colonoscopy screening strategy. As such, a FIT screening strategy dominated the colonoscopy screening strategy in this model. A UMT strategy required the highest cost, but still considered to be cost-effective with ICER at $42,325 at the $50,000-per-QALY threshold [46]. Interestingly, the ICER of the UMT strategy is lower than the ICER of the colonoscopy strategy at $50,875, despite the higher cost. This is because the UMT strategy is selecting and directing the people who have polyp or CRC for the follow up colonoscopies which makes it more effective. Colonoscopies required for each strategy were also outlined in Table 1. A no screening strategy was associated with 0.04 colonoscopies/person as these patients underwent colonoscopy only as symptoms manifested. The colonoscopy-based screening strategy required the second most colonoscopies (1.5/person). A UMT screening strategy resulted in the most colonoscopies (1.7/person). FIT screening resulted in 0.7 colonoscopies/person, and FOBT with 0.2 colonoscopies/person.

Sensitivity analysis

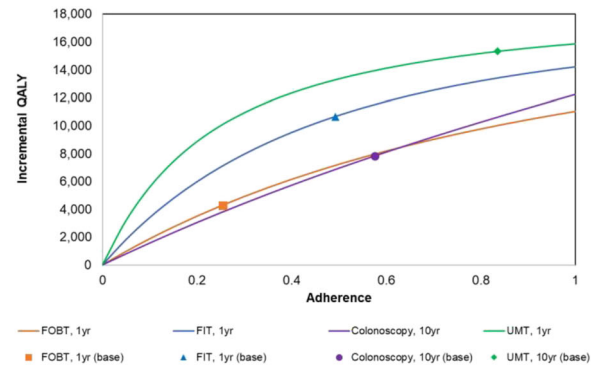
From tornado diagrams for each screening strategies pair, the most influential variables for ICERs were discount rate, sensitivity of the tests, and adherence of tests (Table 2). From one-way sensitivity analysis on adherence in the range of no adherence to 100% adherence, titration plots were generated to show the influence of adherence on incremental cost (Fig. 2a), incremental effectiveness (Fig. 2b), and ICERs (Fig. 2c) for each screening strategy compared with no screening. The base case adherence values were also shown on the plots. In general, screening strategy becomes more effective and costs more as the adherence increases. At the same adherence rate, a UMT strategy is the most effective one with the highest cost. At 100% adherence rate, a UMT is more effective than colonoscopy that is because the screening colonoscopy was at 10 years interval. A colonoscopy strategy has the highest ICER, followed by UMT, FOBT, and FIT, when they are at the same adherence rate. Interestingly, the ICERs for FOBT, FIT, and UMT increase with higher adherence rate, while the ICER for colonoscopy reaches a maximum of $51,064 at an adherence rate of 0.25. The model result for UMT is quite sensitive to the adherence number. The ICER for UMT is dropped from $42,325 per QALY at adherence rate of 0.836 to $41,574 per QALY at adherence rate of 0.75, or $40,705 per QALY at adherence rate of 0.65.

Table 2 Sensitivity of incremental cost effectiveness ratio (ICER) in a population of 100,000 individuals at average risk for colorectal cancer undergoing various cancer prevention screening strategies beginning at age 50 years

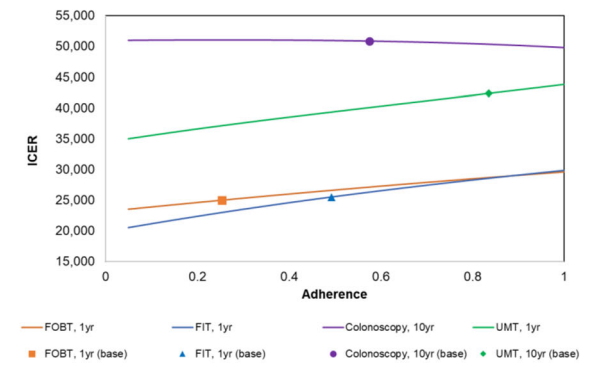
Screening strategy	Most sensitive variable	ICER	
		Low	High
UMT vs. no screening	Discount rate	$34,296	$52,546
UMT vs. FOBT	Discount rate	$39,677	$60,994
UMT vs. FIT	Sensitivity of FIT for large polyp	$69,500	$116,323
UMT vs. colonoscopy	Discount rate	$27,070	$41,101
Colonoscopy vs. no screening	Discount rate	$41,206	$63,394
Colonoscopy vs. FOBT	Sensitivity of FOBT for large polyp	$77,286	$147,562
Colonoscopy vs. FIT	Adherence of FIT	$1,624,237	$19,252
FIT vs. no screening	Discount rate	$21,190	$30,922
FIT vs. FOBT	Sensitivity of FIT for small polyp	$22,855	$37,254
FOBT vs. no screening	Discount rate	$20,640	$30,526



a)



b)



c)

Fig. 2 Titration plots of **a** incremental cost vs. adherence, **b** incremental effectiveness vs. adherence, and **c** ICERs vs. adherence with base case adherence values shown on the plot

To see how resampling parameter values affects the base case calculation, the ICE scatterplot was generated from probabilistic sensitivity analysis for each screening strategy compared with no screening and shown in Fig. 3. The probabilistic sensitivity analysis did not change the ranking of the strategies when compared with the base case results. The willingness-to-pay (WTP) line at $50,000 per incremental QALY was also shown in Fig. 3. The region below and to the right of the line includes points where the screening strategy is cost-effective. At WTP = 50,000, the percentage of cost-effective simulation iterations for a FOBT or FIT strategy is 100%, followed by 95% for a UMT strategy and 44% for a colonoscopy strategy.

Scenario analysis

For FOBT, FIT, and colonoscopy, the screening intervals have been previously evaluated extensively with recommendation of annual screening for FOBT or FIT and 10-year screening interval for colonoscopy in guidelines [9, 39, 40]. Since the UMT is relatively a new test, we evaluated the screening interval at 1 to 5 years. The effectiveness and cost of the test decreased as the interval of UMT screening increased (Fig. 4). When compared with no screening, the ICERs for a UMT strategy at screening interval of 1 to 5 years are $42,325 to $34,980 per QALY gained that are all below $50,000 per QALY gained. Thus, a UMT strategy with screening intervals at 1 to 5 years is cost-effective when compared with no screening (Fig. 4). The incremental cost per QALY gained for UMT increased as the screening frequency increased, for example, $40,774 per QALY gained for screening every 4 years vs. 5 years, $41,145 per QALY gained for screening every 3 vs. 4 years, $49,612 per QALY gained for screening every 2 vs. 3 years, and $73,789 per QALY gained for screening every 1 vs. 2 years. FIT every 1 year dominated UMT every 4 or 5 years. UMT every 1, 2, or 3 years were more effective compared with other screening strategies.

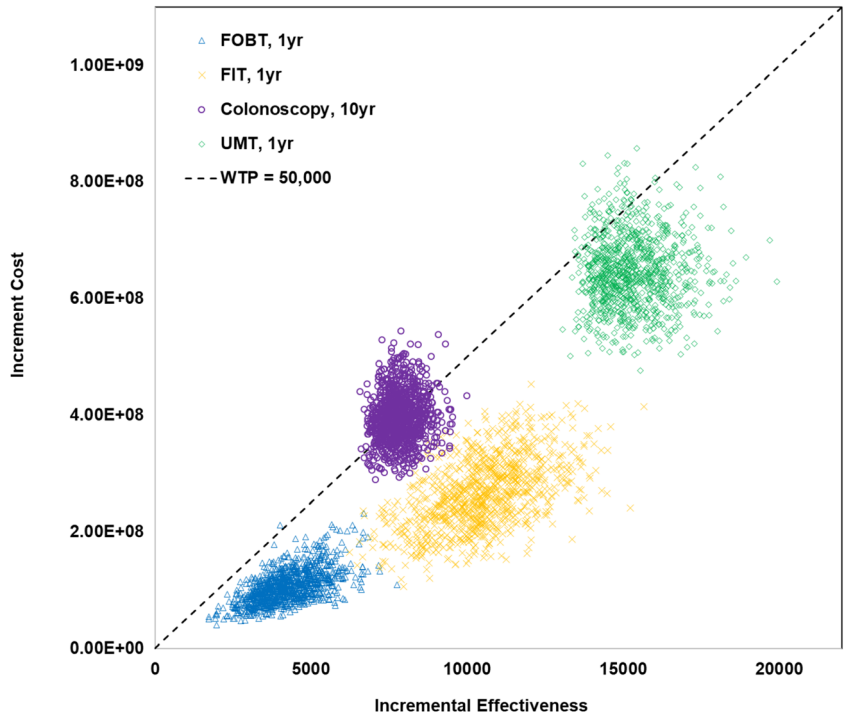


Fig. 3 Cost-effectiveness plane with willingness to pay set at $50,000 per QALY gained in a population of 100,000 individuals at average risk for colorectal cancer undergoing various cancer prevention screening strategies beginning at age 50

Discussion

This study examines the effectiveness and cost-effectiveness of using a UMT screening strategy for CRC in the Canadian healthcare system and makes comparisons to currently existing CRC screening strategies. A Markov model was adapted from the previously published model by Ladabaum et al. [26, 27, 29–32] and recalibrated to reproduce the prevalence of adenomatous polyps and the incidence of CRC reported in Canada. Screening strategies examined in this study resulted in a reduction in CRC related mortality (14.9–49.9%) and an increase in QALY (4291–15,314) consistent with outcomes presented in other studies [11, 25–34, 36]. In our model, the CRC mortality reduction from screening colonoscopy is 24.7% which is much less than 49% reported by Chen et al. [37] when assuming 100% adherence to one single screening colonoscopy performed between 50 and 65 years of age, but is very close to their finding on CRC mortality reduction by 24% to 30% when assuming 50% adherence to one single screening colonoscopy performed between 50 and 65 years of age.

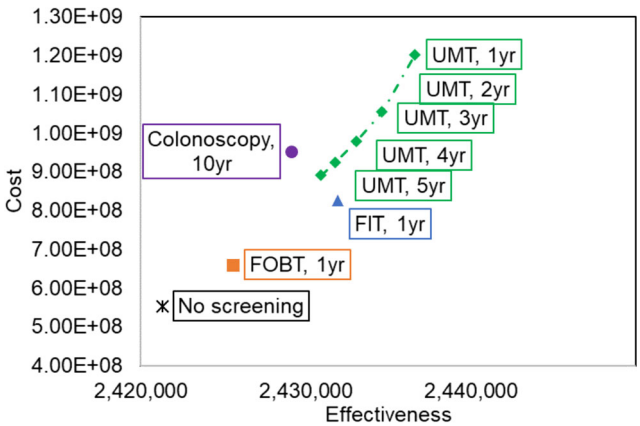


Fig. 4 Cost and effectiveness with no screening, FOBT every year, FIT every year, colonoscopy every 10 years, and UMT at screening intervals of 1 to 5 years

Colonoscopy remains integral to CRC prevention due to the therapeutic aspect of adenomatous polyp removal. Notably, the compliance to colonoscopy as a confirmative and treatment tool after a positive non-invasive screening result increased significantly to 0.840 [47–49], compared with the low adherence of colonoscopy as an initial screening test at 0.576 [37, 38]. This underlies the importance of non-invasive screening tests' ability to increase CRC screening effectiveness by screening a larger segment of the population through higher adherence, and later driving those patients with positive test results to undergo a colonoscopy. UMT is expected to have a much higher adherence rate compared with fecal-based tests (FIT and FOBT) at 0.836 vs. 0.254 and 0.493, respectively. Additionally, UMT has a much higher sensitivity compared with FIT and FOBT for small adenomatous polyps (43% vs. 5% and 10%, respectively), large adenomatous polyps (43% vs. 11% and 24%, respectively), and comparable sensitivity for cancer (74% vs. 40% and 70%, respectively). With the high adherence rate and high sensitivity, the UMT screening strategy drives more needed people for colonoscopy and treatment which leads it to be the most effective, but also costliest strategy. Based on the scenario analysis, one might consider a UMT strategy at 2 years or 3 years to be less costly, but still effective screening modality. As the urine

metabolomics technology continues to evolve, it is reasonable to expect that analyses of test results may become cheaper, and test specificity may increase, both of which would independently drive down the overall cost of the strategy.

There are several limitations to this study. First, the results are modeling estimates from a Markov simulation with several assumptions. The principal health states in the model are normal; small (< 10 mm) adenomatous polyp; large (> 10 mm) adenomatous polyp; localized, regional, or distant CRC; and dead. The size or the location of polyp is not considered. The model assumes 85% CRC develops from adenomas polyp and does not account for the detection of patients with sessile serrated adenoma (SSP), the likely precursor of a significant percentage. Even among well-validated, published models, there are significant differences in predicted costs and effectiveness of CRC strategies within the same health care system. Absolute values for costs, QALYs gained, and ICERs of the various strategies may not be as important as the relative ranking of the strategies. Secondly, although most of the Markov model inputs were derived from real world data, input such as the adherence of a UMT is unknown and collected from literatures on other urine-based tests. Currently, there are a 3000-size utility trial going on in Alberta that will collect real world adherence data on UMT [50]. The cost inputs for the model exclude indirect costs as well as the overhead cost of developing and implementing a screening program. Lastly, based on available publications, UMT does not distinguish small polyp and large polyp, or different stages of CRC. Thus, one sensitivity number of 43% was used for both small and large polyp, 74% was used for all cancer stages. With continuous clinical trials, we expect to see more publications in these areas with extended sample size.

In summary, a Markov model was developed and calibrated to reproduce the prevalence of adenomatous polyps and the incidence of CRC reported in Canada. For the base case analysis, the model predicts that a UMT every year strategy to be the costliest and most effective compared with other three strategies evaluated: FOBT every year, FIT every year, and colonoscopy every 10 years. The UMT every year screening strategy had the second highest ICER at $42,325 per QALY gained and was a cost-effective strategy.

Acknowledgments We would like to thank Richard N. Fedorak, Carole Chambers, and Grace Wong (Pharmacy Cancer Services, Alberta Health Services) for their contribution to this manuscript.

Author contributions SB, LD, and DEL were responsible for the study conceptualization and design; SB, LD, KPI, DEL, EMK, HW, and LSW acquired and analyzed the data; statistical analyses of economic data were done by EMK and LSW; TXN and LD built the model and conducted formal analysis. All authors contributed to data interpretation and validation at each project stage. SB and LD led the preparation of the manuscript and all authors participated in its critical review and revision for important intellectual content. All authors approved the manuscript version for publishing and agreed to be accountable for all aspects of the work presented therein. Lastly, DC, LSW, and TXN acquired resources and provided supervision.

Funding information This study was funded by research grants from the Centre of Excellence for Gastrointestinal Inflammation and Immunity Research (CEGIIR), University of Alberta, Canada and the National Institute of Biomedical Imaging and Bioengineering (NIBIB) at the National Institutes of Health (NIH), USA (grant number 1UG3EB024965-01).

Compliance with ethical standards

Conflict of interest HW is cofounder and shareholder in Metabolomics Technologies Inc., while LD, KPI, and DC are employees of Metabolomics Technologies Inc.

References

1. Arnold M, Sierra MS, Laversanne M, Soerjomataram I, Jemal A, Bray F (2017) Global patterns and trends in colorectal cancer incidence and mortality. Gut 66(4):683
2. Ó Céilleachair AJ, Hanly P, Skally M, O'Neill C, Fitzpatrick P, Kapur K et al (2013) Cost comparisons and methodological heterogeneity in cost-of-illness studies. Med Care 51(4):339–350
3. Sanford SD, Zhao F, Salsman JM, Chang VT, Wagner LI, Fisch MJ (2014) Symptom burden among young adults with breast or colorectal cancer. Cancer 120(15):2255–2263
4. Stewart SL, Wike JM, Kato I, Lewis DR, Michaud F (2006) A population-based study of colorectal cancer histology in the United States, 1998–2001. Cancer 107(S5):1128–1141
5. Rashtak S, Rego R, Sweetser SR, Sinicrope FA (2017) Sessile serrated polyps and colon cancer prevention. Cancer Prev Res 10(5):270–278
6. Siegel RL, Miller KD, Jemal A (2018) Cancer statistics, 2018. CA Cancer J Clin 68(1):7–30
7. Edwards BK, Ward E, Kohler BA, Eheman C, Zauber AG, Anderson RN, Jemal A, Schymura MJ, Lansdorp-Vogelaar I, Seeff LC, van Ballegooijen M, Goede SL, Ries LA (2010) Annual report to the nation on the status of cancer, 1975–2006, featuring colorectal cancer trends and impact of interventions (risk factors, screening, and treatment) to reduce future rates. Cancer 116(3):544–573
8. Zauber AG, Winawer SJ, O'Brien MJ, Lansdorp-Vogelaar I, van Ballegooijen M, Hankey BF et al (2012) Colonoscopic polypectomy and long-term prevention of colorectal-cancer deaths. N Engl J Med 366(8):687–696
9. Leddin DJ, Enns R, Hilsden R, Plourde V, Rabeneck L, Sadowski DC, Signh H (2010) Canadian Association of Gastroenterology position statement on screening individuals at average risk for developing colorectal cancer: 2010. Can J Gastroenterol 24(12):705–714
10. Zubero MB, Arana-Arri E, Pijoan JI, Portillo I, Idigoras I, Lopez-Urrutia A et al (2014) Population-based colorectal cancer screening: comparison of two fecal occult blood test. Front Pharmacol 4:175
11. Barzi A, Lenz HJ, Quinn DI, Sadeghi S (2017) Comparative effectiveness of screening strategies for colorectal cancer. Cancer 123(9):1516–1527
12. Imperiale TF, Ransohoff DF, Itzkowitz SH, Levin TR, Lavin P, Lidgard GP, Ahlquist DA, Berger BM (2014) Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 370(14):1287–1297
13. van Roon AH, Wilschut JA, Hol L, van Ballegooijen M, Reijerink JC, 't Mannetje H et al (2011) Diagnostic yield improves with collection of 2 samples in fecal immunochemical test screening without affecting attendance. Clin Gastroenterol Hepatol 9(4):333–339

14. Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanas A, Andreu M, Carballo F, Morillas JD, Hernández C, Jover R, Montalvo I, Arenas J, Laredo E, Hernández V, Iglesias F, Cid E, Zubizarreta R, Sala T, Ponce M, Andrés M, Teruel G, Peris A, Roncales MP, Polo-Tomás M, Bessa X, Ferrer-Armengou O, Grau J, Serradesanferm A, Ono A, Cruzado J, Pérez-Riquelme F, Alonso-Abreu I, de la Vega-Prieto M, Reyes-Melian JM, Cacho G, Díaz-Tasende J, Herreros-de-Tejada A, Poves C, Santander C, González-Navarro A, COLONPREV Study Investigators (2012) Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. N Engl J Med 366(8):697–706
15. van Roon AH, Goede SL, van Ballegooijen M, van Vuuren AJ, Looman CW, Biermann K, Reijerink JC, Mannetje H', van der Togt A, Habbema JD, van Leerdam M, Kuipers EJ (2013) Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. Gut 62(3):409–415
16. Singh H, Bernstein CN, Samadder JN, Ahmed R (2015) Screening rates for colorectal cancer in Canada: a cross-sectional study. CMAJ open 3(2):E149–E157
17. Singal AG, Corley DA, Kamineni A, Garcia M, Zheng Y, Doria-Rose PV, Quinn VP, Jensen CD, Chubak J, Tiro J, Doubeni CA, Ghai NR, Skinner CS, Wernli K, Halm EA (2018) Patterns and predictors of repeat fecal immunochemical and occult blood test screening in four large health care systems in the United States. Am J Gastroenterol 113(5): 746–754
18. Major D, Bryant H, Delaney M, Fekete S, Gentile L, Harrison M, Mai V, Nicholson E, Taylor Y (2013) Colorectal cancer screening in Canada: results from the first round of screening for five provincial programs. Curr Oncol 20(5):252–257
19. Solbak NM, Xu JY, Vena JE, Al Rajabi A, Vaseghi S, Whelan HK et al (2018) Patterns and predictors of adherence to colorectal cancer screening recommendations in Alberta's Tomorrow Project participants stratified by risk. BMC Public Health 18(1):177
20. Church J (2013) Complications of colonoscopy. Gastroenterol Clin N Am 42(3):639–657
21. Wang H, Tso V, Wong C, Sadowski D, Fedorak RN (2014) Development and validation of a highly sensitive urine-based test to identify patients with colonic adenomatous polyps. Clin Transl Gastroenterol 5(3):e54-e
22. Deng L, Chang D, Foshaug RR, Eisner R, Tso VK, Wishart DS, et al. (2017) Development and validation of a high-throughput mass spectrometry based urine metabolomic test for the detection of colonic adenomatous polyps. Metabolites 7(3)
23. Deng L, Fang H, Tso VK, Sun Y, Foshaug RR, Krahn SC, Zhang F, Yan Y, Xu H, Chang D, Zhang Y, Fedorak RN (2017) Clinical validation of a novel urine-based metabolomic test for the detection of colonic polyps on Chinese population. Int J Color Dis 32(5): 741–743
24. Deng L, Ismond KP, Liu Z, Constable J., Wang H, Kingham PT, Chang D, Fedorak RN (2018) Urinary metabolomics to identify a unique biomarker panel for detecting colorectal cancer: a multicentre study. Cancer Epidemiol Biomarkers Prev
25. Pignone M, Saha S, Hoerger T, Mandelblatt J (2002) Cost-effectiveness analyses of colorectal cancer screening. Ann Intern Med 137(2):96
26. Ladabaum U, Chopra CL, Huang G, Scheiman JM, Chernew ME, Fendrick AM (2001) Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer. A cost-effectiveness analysis. Ann Intern Med 135(9):769–781
27. Song K, Fendrick AM, Ladabaum U (2004) Fecal DNA testing compared with conventional colorectal cancer screening methods: a decision analysis. Gastroenterology 126(5):1270–1279
28. Telford JJ, Levy AR, Sambrook JC, Zou D, Enns RA (2010) The cost-effectiveness of screening for colorectal cancer. CMAJ 182(12):1307–1313
29. Ladabaum U, Song K (2005) Projected national impact of colorectal cancer screening on clinical and economic outcomes and health services demand. Gastroenterology 129(4):1151–1162
30. Sharaf RN, Ladabaum U (2013) Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. Am J Gastroenterol 108(1):120–132
31. Ladabaum U, Allen J, Wandell M, Ramsey S (2013) Colorectal cancer screening with blood-based biomarkers: cost-effectiveness of methylated septin 9 DNA versus current strategies. Cancer Epidemiol Biomark Prev 22(9):1567–1576
32. Ladabaum U, Mannalithara A (2016) Comparative effectiveness and cost effectiveness of a multitarget stool DNA test to screen for colorectal neoplasia. Gastroenterology 151(3):427–39 e6
33. Ouakrim DA, Boussioutas A, Lockett T, Hopper JL, Jenkins MA. (2014) Cost-effectiveness of family history-based colorectal cancer screening in Australia. BMC Cancer 14(1)
34. Knudsen AB, Zauber AG, Rutter CM, Naber SK, Doria-Rose VP, Pabiniak C et al (2016) Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US Preventive Services Task Force. Jama 315(23):2595–2609
35. Brenner H, Kretschmann J, Stock C, Hoffmeister M (2016) Expected long-term impact of screening endoscopy on colorectal cancer incidence: a modelling study. Oncotarget 7(30): 48168–48179
36. Prakash MK, Lang B, Heinrich H, Valli PV, Bauerfeind P, Sonnenberg A et al (2017) CMOST: an open-source framework for the microsimulation of colorectal cancer screening strategies. BMC Med inform Decis Making 17(1):80
37. Chen C, Stock C, Hoffmeister M, Brenner H (2018) Public health impact of colonoscopy use on colorectal cancer mortality in Germany and the United States. Gastrointest Endosc 87(1):213–21.e2
38. Siegel RL, Miller KD, Fedewa SA, Ahnen DJ, Meester RGS, Barzi A et al (2017) Colorectal cancer statistics, 2017. CA Cancer J Clin 67(3):177–193
39. (2016) Recommendations on screening for colorectal cancer in primary care. Can Med Assoc J 188(5):340–8
40. Rex DK, Boland CR, Dominitz JA, Giardiello FM, Johnson DA, Kaltenbach T et al (2017) Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on colorectal cancer. Am J Gastroenterol 112:1016
41. Tinmouth J, Vella ET, Baxter NN, Dubé C et al (2016) Colorectal cancer screening in average risk populations: evidence summary. Can J Gastroenterol Hepatol 2016:18
42. Oboler SK, Prochazka AV, Gonzales R, Xu S, Anderson RJ (2002) Public expectations and attitudes for annual physical examinations and testing. Ann Intern Med 136(9):652–659
43. Anabtawi A, Mathew LM (2013) Improving compliance with screening of diabetic patients for microalbuminuria in primary care practice. ISRN Endocrinol 2013:893913
44. (2017) Guidelines for the economic evaluation of health technologies: Canada. CADTH, Ottawa
45. (2017) Surveillance & Reporting: The 2017 report on Cancer Statistics in Alberta. Edmonton

46. Neumann PJ, Cohen JT, Weinstein MC (2014) Updating cost-effectiveness—the curious resilience of the $50,000-per-QALY threshold. N Engl J Med 371(9):796–797
47. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, Ederer F (1993) Reducing mortality from colorectal cancer by screening for fecal occult blood. N Engl J Med 328(19): 1365–1371
48. Selby JV, Friedman GD, Quesenberry CP, Weiss NS (1992) A case–control study of screening sigmoidoscopy and mortality from colorectal cancer. N Engl J Med 326(10):653–657
49. Jorgensen OD (2002) A randomised study of screening for colorectal cancer using faecal occult blood testing: results after 13 years and seven biennial screening rounds. Gut 50(1):29–32
50. Oct 22. GlobeNewswire http://www.globenewswire.com/news-release/2018/10/22/1624637/0/en/Alberta-to-begin-assessing-a-new-colorectal-cancer-screening-strategy-using-Metabolomic-Technologies-PolypDx.html. Accessed 22 Oct 2018