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Cost-effectiveness of Active Identification and Subsequent Colonoscopy Surveillance of Lynch Syndrome Cases

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Abstract

Background & Aims: The province of Ontario, Canada, is considering immunohistochemical followed by cascade analyses of all patients who received a diagnosis of colorectal cancer (CRC) at an age younger than 70 years to identify individuals with Lynch syndrome. We evaluated the costs and benefits of testing for Lynch syndrome and determined the optimal surveillance interval for first-degree relatives (FDRs) found to have Lynch syndrome.

Methods: We developed a patient flow diagram to determine costs and yield of immunohistochemical testing for Lynch syndrome in CRC cases and, for those found to have Lynch syndrome, their FDRs, accounting for realistic uptake. Subsequently, we used the MISCAN-colon model to compare costs and benefits of annual, biennial, and triennial surveillance

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Author contributions

EFPP, SKN, ILV, NNB were involved in the concept and the design of the study. All authors were involved in data acquisition and data interpretation. EFPP performed the analysis; all analysis were verified by SKN. ILV and NNB supervised the study. EFPP wrote the manuscript. All authors critically reviewed the manuscript, and approved the final version.

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Conflict of Interest

The authors have nothing to disclose.

in FDRs identified with Lynch syndrome vs colonoscopy screening every 10 years (usual care for individuals without a diagnosis of Lynch syndrome).

Results: Testing 1000 CRC cases was estimated to identify 20 CRC index cases and 29 FDRs with Lynch syndrome at a cost of \$310,274. Despite the high cost of Lynch syndrome tests, offering the FDRs with Lynch syndrome biennial colonoscopy surveillance was cost effective at \$8785 per life-year gained compared with usual care, due to a substantial increase in life-years gained (+122%) and cost savings in CRC care. Triennial surveillance was more costly and less effective, and annual surveillance showed limited additional benefit compared with biennial surveillance.

Conclusions: Immunohistochemical testing for Lynch syndrome in persons younger than 70 years who received a diagnosis of colorectal cancer, and then testing first-degree relatives of those found to have Lynch syndrome, provides a good balance between costs and long-term benefits. Colonoscopy surveillance every 2 years is the optimal surveillance interval for patients with Lynch syndrome.

Keywords

colon; polyp; risk; family

Introduction

Lynch Syndrome (LS) is an autosomal dominant genetic disorder, caused by a germline mutation in one of the DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6* or *PMS2*) or by last exomes deletions of *EPCAM*. LS is the most common cause of hereditary colorectal cancer (CRC), and accounts for approximately 3% of all CRC cases.¹ Individuals with LS have a 15-66% probability of developing CRC before the age of 70 years, depending on sex and type of mutation.²⁻⁷ The average age of CRC diagnosis in LS cases is 45 years,³ which is substantially younger than the general population in which the majority of CRC cases is diagnosed in individuals aged 65 or older.⁸ Intensive colonoscopy surveillance in LS cases that have not developed CRC yet has been shown to lead to a substantial reduction in CRC incidence and mortality.⁹ However, in order to qualify for such intensive surveillance, individuals first need to be identified with LS. Historically, identification of individuals with LS has been based on the Amsterdam or revised Bethesda criteria.¹⁰ However, sensitivity and specificity of these criteria are limited, and because both sets of criteria rely on accurate family history, their implementation in routine clinical practice has been poor.¹⁰

More recently, laboratory-based testing of CRC cases through immunohistochemistry (IHC) has been suggested as a more effective pathway for identifying individuals with LS.¹⁰ First-degree relatives (FDRs) of LS-positive cases can undergo cascade testing: genetic counseling and testing for a known germline mutation in a mismatch repair gene. Those with LS can then be offered intensified colonoscopy surveillance to enable timely detection of CRC. Compared to currently used criteria, programmatic IHC testing is likely to increase the number of LS identifications. Therefore, the province of Ontario, Canada, is currently considering introducing reflex testing of all CRC cases under age 70 years.¹¹ In this study, we 1) evaluated the costs and life-years gained (LYG) of IHC testing for LS followed by

cascade testing in CRC cases below age 70 and 2) determined the optimal colonoscopy surveillance interval in LS identified FDRs.

Methods

A pathway from CRC diagnosis to the identification of FDRs with LS, including the associated probabilities and costs, was developed based on experience at the Familial Gastrointestinal Cancer Registry, Mount Sinai Hospital, Toronto, Ontario, supplemented with literature. Subsequently, we used the Microsimulation Screening Analysis (MISCAN)-Colon decision model to estimate costs and LYG of triennial, biennial and annual colonoscopy in identified FDRs with LS. We compared results with that of colonoscopy screening every 10 years, the recommended strategy for individuals without an increased risk of CRC. Costs and LYG in both steps were combined to determine overall cost-effectiveness of universal LS testing and subsequent intensive colonoscopy surveillance.

Development of patient flow diagram

Figure 1 and Appendix Table 1 describe the flow of CRC patients and their FDRs through IHC testing for LS. The patient flow diagram does not reflect cases that are missed due to a lack of test sensitivity. First, all CRC diagnosed under age 70 years are tested for expression deficiencies of MLH1, MSH2/6 and PMS2. Cases with MSH2/6 or PMS2 deficiencies are directly referred to a patient navigator, who informs them about the possibility of undergoing germline testing. The genomic DNA of tumors that lack MLH1 expression is first tested for the *BRAF*V600E mutation. If the tumor is *BRAF*wildtype, methylation of the *MLH1* promoter is determined. Patients with MLH1 negative tumors are only referred to a patient navigator if they are *BRAF*wildtype and do not have hypermethylation of the *MLH1* promoter (Figure 1). CRC cases that have a germline mutation receive post-test genetic counselling in which FDRs are traced. We assumed an average of 5.96 FDRs per CRC case diagnosed with LS.¹² These FDRs are offered genetic counseling, subsequent germline testing and, if positive for LS, post-test genetic counseling (Figure 1).

MISCAN-Colon microsimulation model

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus MC, University Medical Center (Rotterdam, the Netherlands). The model's structure, underlying assumptions and calibration for the Canadian setting have been described elsewhere.¹³ In brief, MISCAN-Colon simulates the life histories of a large population of persons from birth to death, with adenoma prevalence and CRC incidence as observed in the Canadian population. By comparing all life histories with and without screening and surveillance, MISCAN-Colon quantifies the effectiveness of screening and surveillance as well as the associated costs.

Model adjustments for the Lynch syndrome population

We adjusted the MISCAN-Colon model built for the general Canadian population to reflect the LS population by assuming that, on average, adenomas progress 10 times faster (Appendix Table 2). Adenoma onset was then calibrated to the age-specific cumulative CRC risk described by Bonadona et al.,³ assuming an average CRC risk of 42% at age 80 for both

sexes. We assumed the same difference in relative risk between men and women as modeled for the general population (Appendix Figure 1). As LS cases have a better overall colorectal cancer survival, we adjusted survival in the MISCAN-colon model using an hazard ratio of overall survival of 0.65 compared to the general population.¹⁴ We assumed no differences in CRC stage distribution or other-cause mortality between LS patients and the average-risk population.

Simulated population

For each screening and surveillance strategy, we simulated a cohort of 10 million individuals identified with LS in year 2015 to generate stable model results. Their median age was 42 years, with an interquartile range of 31-55 years in accordance with the age distribution of LS-identified FDRs in a Dutch study.¹² Distribution by sex was based on the percentage of women in the 2015 Ontario population, accounting for the age distribution of the FDRs.¹⁵

LS testing and colonoscopy surveillance strategies

We simulated five LS testing and colonoscopy strategies for LS positive FDRs:

1. No LS testing and no colonoscopy screening.
2. No LS testing. FDRs are offered colonoscopy screening every 10 years at ages 50-80 years (i.e. usual care).
3. LS testing. FDRs with LS are offered triennial colonoscopy surveillance at ages 25-59 years, extending the surveillance interval to 5 years at ages 60-80 if no adenomas are detected.¹⁶
4. LS testing. Similar to strategy 3, except that LS positive FDRs are offered biennial surveillance rather than triennial surveillance.
5. LS testing. Similar to strategy 3, except that LS positive FDRs are offered annual surveillance rather than triennial surveillance.

We assumed a 60% screening participation for the usual care strategy (strategy 2).¹⁷ For strategies 3-5, we assumed an 80% surveillance adherence for LS positive FDRs,^{10, 18-20} irrespective of the surveillance interval.

The analysis was conducted from a third party health-care payer perspective. All costs were expressed in 2018 Canadian dollars (Figure 1, Appendix Table 3). Colonoscopy test characteristics have been published previously (Appendix Table 4).¹³ For 10-yearly colonoscopy screening, individuals with adenomas detected and removed at screening at any age enter a surveillance regimen, for which we assumed 100% adherence. This entails a subsequent colonoscopy in 3 years in case of high-risk findings (i.e. one adenoma $\geq$ 10mm or 3 adenomas $<$ 10mm) and in 5 years in case of low-risk findings (i.e. 2 adenomas $<$ 10mm). For any of the simulated strategies, individuals with adenomas detected at their last scheduled colonoscopy will undergo such surveillance beyond age 80 until no adenomas are detected.

Outcomes

For all strategies, we evaluated the number of CRC cases and deaths, the costs of diagnosing CRC cases through symptoms and the costs of CRC treatment. For strategy 2 (usual care), the LYG and associated costs from colonoscopy screening compared to strategy 1 (no screening) were also evaluated. For strategies 3–5 with intensified colonoscopy surveillance for LS positive FDRs, we estimated costs for LS testing of the index cases and their FDRs, if applicable, and downstream LYG and costs of CRC surveillance of LS positive FDRs. We used this to calculate the average cost-effectiveness ratio (ACER; compared to usual care) of LS testing followed by intensified colonoscopy surveillance for LS positive FDRs, assuming a willingness-to-pay threshold of \$100,000 per LYG. Furthermore, the incremental cost-effectiveness ratios (ICERs) of the different strategies were evaluated. Costs and LYG were discounted at an annual rate of 3% to the year in which the index case was diagnosed with CRC. The results section starts with costs of LS testing per 1,000 CRC cases, but they are then converted to costs per 1,000 FDRs identified with LS, and all subsequent outcomes of colonoscopy screening and surveillance are presented per 1,000 FDRs with identified LS.

Sensitivity analyses

To evaluate the robustness of our results, we varied all parameters in one-way sensitivity analyses (Appendix Table 1–3), in addition to evaluating a scenario in which 5-yearly colonoscopy instead of 10-yearly colonoscopy is the usual care and a scenario in which the surveillance interval between ages 60 to 80 is not extended when no adenomas are detected. As the progression rate of CRC in LS is uncertain, we evaluated 0x, 2x, 5x, 10x and 20x faster adenoma progression than the general population. For these five progression rates, adenoma onset was recalibrated to obtain a uniform age-specific CRC incidence.³ Furthermore, a probabilistic sensitivity analysis was performed to evaluate the uncertainty of our estimates (Appendix Table 1–3). Each of the progression assumption was used in 20% of the runs. For the probability parameters, 1000 values were drawn from beta distributions; gamma distribution were used for all other parameters.

Results

LS testing in index CRC cases and first-degree relatives

Testing 1,000 index CRC cases for LS through IHC and subsequent germline testing identified twenty LS cases (Figure 1), with an associated cost of \$278,558 (Appendix Table 5). The costs of cascade testing of the 119 family members of those twenty LS cases were estimated at an additional \$31,716, and resulted in the identification of 29 FDRs with LS. Overall tumor testing of 1,000 index CRC cases for LS would thus cost \$310,274 to identify 29 FDRs with LS, which corresponds to \$10.462 million per 1,000 LS positive FDRs (Table 1).

CRC surveillance in first-degree relatives with LS

In the absence of CRC screening, MISCAN-Colon predicted 359 CRC cases and 165 CRC deaths per 1,000 LS positive FDRs of CRC patients diagnosed below the age of 70, from their LS diagnosis until death (Table 1). Associated costs of CRC diagnosis and care were

estimated at \$67.465 million. In the strategy without LS testing but with 10-yearly colonoscopy screening at 60% participation (usual care), the number of CRC cases and deaths was reduced to 308 (−14%) and 112 (−33%) per 1,000 LS positive FDRs, respectively. This strategy gained 334 life-years per 1,000 LS positive FDRs compared to no screening. Total costs of usual care were \$63.992 million per 1,000 FDRs, and therefore usual care was cost-saving compared to no CRC screening.

LS testing was very cost-effective compared to no LS testing. The benefits of LS testing depend on the subsequent colonoscopy surveillance that is offered to the FDRs that are identified with LS. Compared to the care these FDRs would receive had they not been diagnosed with LS, universal LS testing through IHC and subsequent intensified colonoscopy surveillance resulted in 722 (+116%), 741 (+122%), and 753 (+126%) LYG per 1,000 FDRs with LS, and increased CRC screening and surveillance costs to \$4.237 million (+291%), \$5.669 million (+423%), and \$9.932 million (+816%) for triennial, biennial and annual surveillance from age 25 (Table 1), respectively. The shorter the surveillance interval, the more CRC cases are averted, and therefore CRC care costs are lower. Strikingly, the total costs of LS testing, CRC surveillance and CRC care of offering biennial surveillance to LS cases were lower than those of triennial surveillance. The number of LYG per 1,000 LS positive FDRs was 741 for biennial surveillance, resulting in an ICER of \$8,785 compared to usual care. Offering LS cases annual colonoscopy surveillance minimally increased the number of LYG (753, +1.6%) and increased total costs by approx. \$2.565 million (+3.8%) per 1000 LS positive FDRs, resulting in an unfavorable ICER of \$218,647 per LYG compared to biennial colonoscopy surveillance (Table 1).

Sensitivity analyses

The ICER of reflex tumor testing for all patients with CRC below age 70 followed by biennial colonoscopy compared to 10-yearly colonoscopy for FDRs identified with LS varied between being Cost-Saving and \$34,230 in our one-way sensitivity analyses (Appendix Figure 2, Appendix Table 6). The ICER of universal tumor testing followed by annual colonoscopy of FDRs with LS exceeded the threshold of \$100,000 per LYG in all sensitivity and scenario analyses, except in the scenario where a cumulative CRC risk of 60% at age 80 was assumed for LS cases (Appendix Table 6) and the scenario in which it assumed that the adenoma progression of LS cases is 20x faster than the general population, which resulted in ICERs of \$95,197 and \$93,835. Finally, at a willingness-to-pay threshold of \$100,000, LS testing with subsequent biennial colonoscopy surveillance was the optimal strategy in 77.2% of our probabilistic sensitivity analyses (Figure 2).

Discussion

The results of this study suggest that programmatic testing for LS with IHC in patients with CRC diagnosed under age 70 years followed by cascade testing is very cost-effective, and that biennial colonoscopy surveillance of identified FDRs with LS is optimal. Testing tumors of 1,000 CRC patients for LS was estimated to result in the identification of 29 FDRs with LS, at a cost of \$310,274. Despite the high cost of LS testing, offering these FDRs with LS biennial versus 10-yearly colonoscopy screening resulted in a favorable ICER of \$8,785 due

to a substantial increase in LYG (+122%) and cost savings in CRC care. Strikingly, due to cost savings in CRC care, the total costs of biennial surveillance were lower than those of triennial surveillance. Annual colonoscopy surveillance provided little benefit compared to biennial surveillance at a much higher cost, resulting in an ICER of \$218,647. LS testing with biennial colonoscopy surveillance was the optimal strategy in 77.2% of our probabilistic sensitivity analyses (willingness-to-pay threshold of \$100,000), demonstrating the robustness of our conclusion.

With LS testing costs of more than \$10,000 per LS positive FDR identified, investigating the presence of LS in all CRC index cases <70 years and their FDRs is expensive. To identify one FDR with LS, 35 tumor samples of CRC index cases have to be analyzed by IHC, and 3 germline tests have to be performed. This emphasizes the costs of IHC testing being an important driver for the cost-effectiveness of LS testing and subsequent colonoscopy surveillance, which we also observed in our sensitivity analyses. The additional costs of offering a LS case biennial CRC surveillance were \$4,585 compared to 10-yearly-colonoscopy. As LS cases are at very high risk of developing CRC, substantial downstream cost savings in CRC treatment (\$11,467) occur by preventing CRC cases and by diagnosing CRC cases in an earlier stage. Overall, LS testing in CRC patients below age 70 and subsequent biennial colonoscopy surveillance requires an upfront investment, that is largely offset by future savings in CRC treatment.

A recent study compared CRC incidence in LS cases between three countries with different colonoscopy surveillance policies (1-, 2- and 3-year intervals), and found no difference in cumulative CRC incidence among countries.²¹ As we found only minor differences in the number of CRC cases (244–228 CRC cases per 1,000 LS cases), those results are consistent with our findings. Nevertheless, as the additional costs are also small, our results demonstrate that surveillance every two years rather than every three years is worthwhile, while surveillance every year is not.

Our study has some limitations. First, we did not include any strategies in which we evaluated other methods for LS testing. Other studies have compared different strategies for LS testing and determined that screening with IHC is the most cost-effective strategy.^{12, 22–25} Second, not all steps in the patient flow diagram could be based on Canadian data. We varied all estimates in our sensitivity analyses and demonstrated that they did not influence our recommendation of offering biennial colonoscopy surveillance to LS cases. Third, the CRC risk for LS cases is uncertain; estimates vary greatly among studies.^{2–7} We calibrated our model to the largest study that accounted for ascertainment bias.^{3, 26} Fourth, we did not evaluate gene-specific colonoscopy surveillance due to its high uncertainty in CRC risk and natural history. To address limitation three and four, we performed sensitivity analyses with a 30% and 60% CRC risk at age 80, which revealed that more intense colonoscopy surveillance might be optimal for LS cases with high-risk mutations, which should therefore be further explored in future studies. Fifth, the natural history of CRC in LS is uncertain. We covered this uncertainty by evaluating five different progression assumptions. Only if we assumed that the progression of adenomas in LS is 20x faster than the progression in the general population, the ICER of annual surveillance was below the willingness-to-pay threshold, being \$93,835 per LYG compared to biennial surveillance.

Sixth, the assumptions regarding the costs for LS testing used in our study are not reflective for settings where genetic testing is performed using multiple-gene panels. Furthermore, we did not take into account that patients with Stage II CRC with adverse features may undergo IHC testing to guide chemotherapy. Lower costs for LS testing would make programmatic testing for LS even more cost-effective, and it would not influence the optimal surveillance interval. Seventh, we used LY G rather than quality-adjusted life years gained. An important determinant of the quality-of-life of LS cases is the distress LS patients experience from knowing they have LS. To our knowledge, no data is available that quantifies this disutility, which is why we could not incorporate it in our analyses. Lastly, we did not consider other LS-related cancers, such as the increased risk for endometrial cancer and ovarian cancer; we assumed that apart from an increased CRC risk, LS cases have a normal life-expectancy. This potentially resulted in an overestimation of life-years gained per CRC death prevented. However, an asymptomatic individual identified with LS has the additional benefit of potential earlier detection or prevention of other cancer types and this additional benefit is also not captured in the current analysis.

Despite these limitations, our study may be of great value to policy makers and fellow researchers. To our knowledge, it is the first cost-effectiveness analysis that evaluates different colonoscopy surveillance intervals in LS cases identified by IHC testing. The optimal colonoscopy surveillance interval for LS cases is a topic of intense debate,²¹ and therefore this study provides insights that can be used to inform surveillance guidelines internationally. In line with previous studies, LS testing with more intensive colonoscopy surveillance was very cost-effective compared to usual care.^{22–25} However, we revealed that biennial colonoscopy surveillance was cost-saving compared to triennial surveillance, and that annual colonoscopy was not cost-effective compared to biennial colonoscopy. Another major strength of our study is that both the costs to identify LS in CRC cases and the subsequent costs of cascade testing and colonoscopy surveillance of at-risk relatives were included in our analyses. Furthermore, we used a well-established microsimulation model that has been used to inform CRC screening guidelines in several countries, among which the United States.^{27, 28} This is also the first study to evaluate universal LS testing in CRC index cases (in this case limited to patients <70) and subsequent cascade screening and colonoscopy surveillance in at-risk relatives for the Canadian setting. Important barriers that have been identified for implementation of a population-based program for Lynch syndrome screening in Canada are the education of stakeholders and concerns regarding sustaining various resources.¹¹ The results of this study provide data that is essential to overcome these barriers. For other countries with universal LS screening, the results of this study can be used to optimize existing programs, as it provides insight in which elements of the patient flow diagram are important drivers for the (cost-)effectiveness LS screening.

In conclusion, we estimated that programmatic IHC testing for LS in patients with CRC diagnosed < 70 years followed by cascade testing and subsequent biennial colonoscopy surveillance of identified FDRs is very cost-effective in Canada. These findings should urge policy makers to further explore the possibilities of implementing universal LS testing.

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Appendix

Appendix Figure 1.

Cumulative CRC risk assumed by MISCAN-Colon was calibrated to Bonadona et al.¹

CRC = Colorectal cancer

Appendix Figure 2.

Results of the one-way sensitivity analyses: Incremental cost-effectiveness ratios (\$) of LS testing and subsequent biennial colonoscopy surveillance in FDRs with LS under alternative model assumptions. Ratios plotted are compared to the previous efficient strategy. LS= Lynch syndrome, FDR= First-degree relative, CRC = Colorectal cancer

Appendix Table 1.

Assumptions regarding the participation of CRC Index cases and their FDRs in every step of the patient flow diagram, and the positivity rates of the genetic tests.

Parameter	Value (Range ^a)	Source
<i>LS Testing of Index CRC Cases</i>		
Combined proportion of possible LS cases	4.5% (2.25–6.75%)	Ontario ^b Estimate
Proportion of index CRC cases with an MLH1 deficiency, subsequently tested for <i>BRAF</i> V600E	13.3%	
Proportion of MLH1 deficient <i>BRAF</i> wildtype tumors without <i>MLH1</i> promoter hypermethylation	64%	
Proportion of MLH1 deficient <i>BRAF</i> wildtype tumors without <i>MLH1</i> promoter hypermethylation, referred to genetic counseling	33%	
Proportion of index CRC cases with an MSH2/6 or PMS2 deficiency, subsequently referred to genetic counseling	1.7%	
<i>Index Case Genetic Pathway</i>		

Parameter	Value (Range ^a)	Source
Proportion of patients accepting genetic counseling	84% (42-100%)	2
Proportion of patients that once seen by genetic counselor will undergo genetic testing	80% (40-100%)	3,4
Proportion of patients undergoing genetic testing that are positive for LS	67% (33-100%)	5-8
<i>FDRs LS cases</i>		
Average number of FDRs of identified LS case	5.96 (2.98-8.94)	9
Proportion of FDRs that accept genetic counseling	52% (26-78%)	10
Proportion of FDRs that once seen by genetic counselor will undergo genetic testing	95% (47.5-100%)	10
Proportion of FDRs testing positive on a germline test	50% (25-75%)	11
<i>Colonoscopy participation^c</i>		
Colonoscopy screening participation not diagnosed with LS	60% (40-80%) ^d	12
Colonoscopy surveillance participation diagnosed with LS	80% (70-90%) ^d	10,13-15

CRC=Colorectal cancer, FDR=first-degree relative, LS= Lynch Syndrome

^a. Alternative values evaluated in sensitivity analyses. Ranges evaluated were mean*0.5 –mean*1.5.

^b. Estimates were based on experience at the Familial Gastrointestinal Cancer Registry, Mount Sinai Hospital, Toronto, Ontario

^c. In the Probabilistic Sensitivity Analysis, the participation when not being diagnosed with LS was never lower than the participation when being diagnosed with LS, using preference ordering.¹⁶

^d. As we are more certain of these estimated, smaller ranges were evaluated.

Appendix Table 2.

Natural History adjustments for the Lynch Syndrome population.

Parameter	Value (Range ^a)	Source
Probability of having developed colorectal cancer before age 80	42% (30-60%)	1
Dwelling times, faster progression compared to the general population	10x (0x/2x/5x/20x) ^b	Assumption
Hazard Ratio overall survival of CRC in LS cases versus CRC in the general population	0.65 (0.59-0.71)	17

CRC= Colorectal cancer, LS= Lynch Syndrome

^a. Alternative values evaluated in sensitivity analyses.

^b. In the Probabilistic Sensitivity Analysis, 0x, 2x, 5x, 10x and 20x faster dwelling times were evenly incorporated.

Appendix Table 3.

Assumptions regarding costs. All costs are in 2018 Canadian Dollars.

Procedure	Costs (Range ^a)	Source ^b
Related to genetic testing		
Combined costs of lab testing in index CRC case	224 (112-336)	Ontario Estimate
IHC MLH1, MSH2/6, PMS2	150	
<i>BRAF</i> V600E mutation	300	
Methylation of <i>MLH1</i> promoter	400	
Cost of patient navigator per individual referred to genetic counseling	108 (54-162)	Ontario Estimate ^c
Costs of pre-test genetic counseling in CRC index case	255 (128-383)	Ontario Estimate ^d
Avg. cost of germline test in index CRC case	1,099 (549-1,648)	Ontario Estimate ^e

Procedure	Costs (Range ^a)		Source ^b	
<i>MSH2/6, PMS2</i>	1,200			
<i>MLH1</i>	1,040			
Post-test genetic counseling and tracing FDRs for LS positive cases & Costs of pre-test genetic counseling of FDRs (per index CRC case with LS) & Post-test genetic counseling FDR	90 (45-135)	Ontario Estimate ^f		
Somatic testing for LS negative cases	500 (250-750)	Ontario Estimate		
Costs of germline testing for LS in a FDR with a known mutation	400 (200-600)	Ontario Estimate		
<i>Related to colonoscopies^g</i>				
Colonoscopy without polypectomy	947 (474-1,421)	18		
Colonoscopy with polypectomy & Colonoscopy for diagnosis of CRC by symptoms	1,192 (596-1,788)	18		
CRC care^h				
<i>Females (50.7%)ⁱ</i>	Stage I	Stage II	Stage III	Stage IV
Initial	29,240 (14,620-58,481)	42,537 (21,269-85,074)	63,432 (31,746-126,865)	80,855 (40,427-161,709)
Continuing	7,664 (3,832-15,328)	10,155 (5,077-20,310)	13,269 (6,635-26,539)	40,423 (20,212-80,846)
Terminal, death CRC	324,973 (162,487-649,947)	236,714 (118,357-473,429)	144,521 (72,260-289,041)	131,414 (65,707-262,828)
Terminal, death OC	31,064 (15,532-62,129)	29,295 (14,647-58,590)	30,743 (15,371-61,486)	28,703 (14,351-57,405)
<i>Males (49.3%)ⁱ</i>	Stage I	Stage II	Stage III	Stage IV
Initial	33,131 (16,565-66,261)	50,829 (25,414-101,658)	70,868 (35,434-141,736)	90,642 (45,321-181,285)
Continuing	8,386 (4,193-16,773)	12,292 (6,146-16,773)	15,442 (7,721-30,884)	50,015 (25,008-100,030)
Terminal, death CRC	329,770 (164,885-659,539)	207,153 (103,577-414,307)	147,150 (73,575-294,299)	124,025 (62,013-248,050)
Terminal, death OC	33,210 (16,605-66,420)	49,954 (24,977-99,909)	36,949 (18,747-73,898)	34,412 (17,206-68,825)

CRC= Colorectal cancer, LS= Lynch syndrome, FDR=first-degree relative, OC= other causes.

^a. Alternative values evaluated in sensitivity analyses. Ranges evaluated were mean*0.5 –mean*1.5.

^b. Ontario Estimate: costs are based on experience at the Familial Gastrointestinal Cancer Registry, Mount Sinai Hospital, Toronto, Ontario

^c. Annual salary of a navigator (\$70,000) was divided by the estimated number of cases per year (650).

^d. Includes 1 hour Salary for Genetic Counselor (\$90) and Ontario Health Insurance Plan (OHIP) Fee Schedule code A225 (\$165).

^e. 62% of individuals were tested for MLH1.

^f. Includes 1 hour Salary for Genetic Counselor (\$90).

^g. Costs of colonoscopy were obtained from the 2013 Ontario Health Insurance Plan (OHIP) Schedule of Benefits and Fees, 18 and updated to 2018 Canadian dollars using the consumer price index (CPI; All-items).¹⁹ These were varied together in the one-way sensitivity analysis.

^h. CRC care was divided in three clinically relevant phases. The initial care phase was defined as the first 12 months after diagnosis, the terminal care phase as the final 12 months of life, and the continuing care phase as all months in between. For patients surviving less than 24 months, the last 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.

The costs attributable to CRC care by sex, CRC stage, and phase of care (initial, continuing, and terminal care) included outpatient visits, hospitalizations, treatment, home care, long-term care, and rehabilitation. The costs were estimated using

health care administrative data in a matched cohort study, which compared the health care costs of CRC patients with their age- and sex-matched controls,³⁸ and updated to 2018 Canadian dollars using the CPI.¹⁹

ⁱ. Based on the 2015 Ontario Population, accounting for the age distribution of the FDRs.

Appendix Table 4.

Colonoscopy test characteristics

Sensitivity	
Adenoma 1-5 mm	75%
Adenoma 6-9 mm	85%
Adenoma 10+ mm	95%
Colorectal Cancer	95%
Specificity	86% ^a
Reach (until cecum)	95%
Fatal complication risk ^b	1/14,000

^a.The lack of specificity with endoscopy reflects the detection of non-adenomatous lesions, where the non-adenomatous lesions are removed and therefore induce polypectomy and biopsy.

^b.The fatal complication risk was only included for colonoscopies with polypectomy, and was based on Rabeneck et al.²⁰

Appendix Table 5.

Number of individuals and associated costs per 1000 CRC index cases in every step of the patient flow diagram.

Step in patient flow diagram	No. of individuals	Costs (\$) ^a
<i>LS testing of index CRC cases</i>		
Immunohistochemistry MLH1, MSH2/6, PMS2	1000	150,000
<i>BRAF</i> V600E mutation	133	39,900
Methylation <i>MLH1</i> promoter	85	34,000
Total		223,900
<i>Index Case Genetic Pathway</i>		
Patient navigator	45	4,848
Pre-germline testing counseling	38	9,639
Germline testing	30	33,234
Positive cases: post-germline testing counseling	20	1,796
Negative cases: somatic testing	10	5,141
Total		54,658
<i>First-Degree Relatives Pathway</i>		
FDRs of LS positive CRC index cases	119	
Pre-germline testing counseling	62	5,567
Germline testing	59	23,505
Post-germline testing counseling	29	2,644
Total		31,716
Total		310,274

CRC=Colorectal cancer, FDR= First-degree relatives, LS= Lynch syndrome

^a.Costs are in 2018 Canadian Dollars.

Appendix Table 6.

Results of one-way sensitivity analyses per 1,000 LS positive first-degree relatives of CRC index cases.

<i>Usual Care is 5-yearly Colonoscopy</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{d,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
5-yearly colonoscopy	293	105		1.514	61.690	63.204	362	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.462	4.237	53.048	67.747	722	12,617	D
2-yearly colonoscopy	235	66	10.462	5.669	51.441	67.573	741	11,516	11,516
1-yearly colonoscopy	228	66	10.462	9.932	49.743	70.138	753	17,728	218,647
<i>No interval extensions for ages 60-80</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{d,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	229	63	10.462	4.798	51.845	67.105	739	7,672	D
2-yearly colonoscopy	207	59	10.462	6.970	49.078	66.510	772	5,741	5,741
1-yearly colonoscopy	176	55	10.462	13.557	45.493	69.513	802	11,785	100,826
<i>No decreased dwelling time</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{d,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)

No LS Testing or CRC Screening	354	157		0.221	64.196	64.417	-	-	-
No LS testing									
10-yearly colonoscopy	245	93		1.380	55.624	57.005	363	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	150	50	10.462	4.613	43.341	58.417	727	3,880	3,880
2-yearly colonoscopy	140	49	10.462	6.131	41.932	58.525	742	4,010	7,111
1-yearly colonoscopy	131	48	10.462	10.483	40.627	61.572	753	11,716	284,648
<i>Halved dwelling time</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	363	166		0.229	67.431	67.66	-	-	-
No LS testing									
10-yearly colonoscopy	271	102		1.275	59.987	61.262	371	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	179	57	10.462	4.500	47.678	62.639	766	3,486	D
2-yearly colonoscopy	167	55	10.462	5.995	45.926	62.383	785	2,705	2,705
1-yearly colonoscopy	155	54	10.462	10.306	44.151	64.919	800	8,529	176,255
<i>5x faster dwelling time</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	362	166		0.228	67.227	67.455	-	-	-
No LS testing									
10-yearly colonoscopy	293	108		1.155	61.431	62.586	353	-	Cost-Saving
LS Testing									

3-yearly colonoscopy	215	63	10.462	4.349	50.331	65.143	747	6,491	D
2-yearly colonoscopy	205	61	10.462	5.809	48.627	64.898	766	5,599	5,599
1-yearly colonoscopy	196	61	10.462	10.098	46.972	67.532	778	11,621	208,305

20x faster dwelling time

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS testing									
10-yearly colonoscopy	335	118		1.047	65.172	66.219	305	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	287	74	10.462	4.157	56.789	71.408	694	13,348	D
2-yearly colonoscopy	279	73	10.462	5.572	54.881	70.915	719	11,345	11,345
1-yearly colonoscopy	268	73	10.462	9.809	52.444	72.716	739	15,000	93,835

Lower Cumulative Incidence (30% at age 80)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS testing									
10-yearly colonoscopy	218	79		1.046	44.488	45.534	233	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	172	48	10.462	4.284	37.525	52.271	509	24,387	D
2-yearly colonoscopy	166	47	10.462	5.718	36.380	52.560	523	24,227	24,227
1-yearly colonoscopy	161	47	10.462	10.010	35.183	55.655	531	33,911	366,988

Higher Cumulative Incidence (60% at age 80)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{a,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	510	240		0.327	99.024	99.352	-	-	-
No LS testing									
10-yearly colonoscopy	444	163		1.121	93.110	94.231	494	-	D
LS Testing									
3-yearly colonoscopy	356	99	10.462	4.135	78.906	93.503	1072	Cost-Saving	D
2-yearly colonoscopy	344	97	10.462	5.562	76.476	92.501	1100	Cost-Saving	Cost-Saving
1-yearly colonoscopy	333	98	10.462	9.768	73.953	94.183	1118	Cost-Saving	95,197
Lower Hazard Ratio Overall Survival (0.59)									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{a,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	158		0.227	69.302	69.529	-	-	-
No LS testing									
10-yearly colonoscopy	308	106		1.082	64.677	65.758	321	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	243	64	10.462	4.228	54.406	69.096	692	9,009	D
2-yearly colonoscopy	235	63	10.462	5.657	52.778	68.898	710	8,080	8,080
1-yearly colonoscopy	228	63	10.462	9.910	51.071	71.443	721	14,236	235,800
Higher Hazard Ratio Overall Survival (0.71)									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{a,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	360	173		0.228	65.423	65.65	-	-	-
No LS testing									

10-yearly colonoscopy	309	117		1.086	61.341	62.427	344	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	71	10.462	4.246	51.848	66.556	749	10,203	D
2-yearly colonoscopy	236	70	10.462	5.681	50.259	66.402	770	9,345	9,345
1-yearly colonoscopy	228	70	10.462	9.952	48.566	68.980	782	14,958	203,055

LS Testing of Index CRC Cases: Combined proportion of possible LS cases –50%(2.25%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	18.007	4.237	53.048	75.292	722	29,097	D
2-yearly colonoscopy	235	66	18.007	5.669	51.441	75.117	741	27,292	27,292
1-yearly colonoscopy	228	66	18.007	9.932	49.743	77.682	753	32,645	218,647

LS Testing of Index CRC Cases: Combined proportion of possible LS cases +50%(6.75%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	7.948	4.237	53.048	65.233	722	3,194	D
2-yearly colonoscopy	235	66	7.948	5.669	51.441	65.058	741	2,615	2,615
1-yearly colonoscopy	228	66	7.948	9.932	49.743	67.623	753	8,658	218,647

Index Case Genetic Pathway: Proportion of patients accepting genetic counseling –50% (42%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	18.17	4.237	53.048	75.455	722	29,518	D
2-yearly colonoscopy	235	66	18.17	5.669	51.441	75.281	741	27,693	27,693
1-yearly colonoscopy	228	66	18.17	9.932	49.743	77.845	753	33,034	218,647
<i>Index Case Genetic Pathway: Proportion of patients accepting genetic counseling +50% (100%)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	9.229	4.237	53.048	66.514	722	6,494	D
2-yearly colonoscopy	235	66	9.229	5.669	51.441	66.340	741	5,759	5,759
1-yearly colonoscopy	228	66	9.229	9.932	49.743	68.905	753	11,714	218,647
<i>Index Case Genetic Pathway: Proportion of patients that once seen by genetic counselor will undergo genetic testing -50% (40%)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-

No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	18.495	4.237	53.048	75.780	722	30,354	D
2-yearly colonoscopy	235	66	18.495	5.669	51.441	75.606	741	28,490	28,490
1-yearly colonoscopy	228	66	18.495	9.932	49.743	78.170	753	33,809	218,647

Index Case Genetic Pathway: Proportion of patients that once seen by genetic counselor will undergo genetic testing +50% (100%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	8.856	4.237	53.048	66.141	722	5,533	D
2-yearly colonoscopy	235	66	8.856	5.669	51.441	65.967	741	4,844	4,844
1-yearly colonoscopy	228	66	8.856	9.932	49.743	68.531	753	10,824	218,647

Index Case Genetic Pathway: Proportion of patients undergoing genetic testing that are positive for LS -50% (33%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	20.124	4.237	53.048	77.409	722	34,549	D
2-yearly colonoscopy	235	66	20.124	5.669	51.441	77.234	741	32,486	32,486

1-yearly colonoscopy	228	66	20.124	9.932	49.743	79.799	753	37,693	218,647
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Index Case Genetic Pathway: Proportion of patients undergoing genetic testing that are positive for LS +50% (100%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	7.242	4.237	53.048	64.527	722	1,377	D
2-yearly colonoscopy	235	66	7.242	5.669	51.441	64.353	741	884	884
1-yearly colonoscopy	228	66	7.242	9.932	49.743	66.917	753	6,975	218,647

FDRs LS cases: Average number of FDRs of identified LS case -50%(2.98)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	19.845	4.237	53.048	77.130	722	33,831	D
2-yearly colonoscopy	235	66	19.845	5.669	51.441	76.956	741	31,803	31,803
1-yearly colonoscopy	228	66	19.845	9.932	49.743	79.521	753	37,029	218,647

FDRs LS cases: Average number of FDRs of identified LS case +50%(8.94)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or	359	165		0.227	67.237	67.465	-	-	-

CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	7.335	4.237	53.048	64.620	722	1,616	D
2-yearly colonoscopy	235	66	7.335	5.669	51.441	64.445	741	1,112	1,112
1-yearly colonoscopy	228	66	7.335	9.932	49.743	67.010	753	7,197	218,647
FDRs LS cases: Proportion of FDRs that accept genetic counseling -50%(26%)									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	19.845	4.237	53.048	77.130	722	33,831	D
2-yearly colonoscopy	235	66	19.845	5.669	51.441	76.956	741	31,803	31,803
1-yearly colonoscopy	228	66	19.845	9.932	49.743	79.521	753	37,029	218,647
FDRs LS cases: Proportion of FDRs that accept genetic counseling +50%(78%)									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	7.335	4.237	53.048	64.620	722	1,616	D
2-yearly colonoscopy	235	66	7.335	5.669	51.441	64.445	741	1,112	1,112

1-yearly colonoscopy	228	66	7.335	9.932	49.743	67.010	753	7,197	218,647
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FDRs LS cases: Proportion of FDRs that once seen by genetic counselor will undergo genetic testing –50%(47.5%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	20.035	4.237	53.048	77.320	722	34,319	D
2-yearly colonoscopy	235	66	20.035	5.669	51.441	77.145	741	32,268	32,268
1-yearly colonoscopy	228	66	20.035	9.932	49.743	79.710	753	37,481	218,647

FDRs LS cases: Proportion of FDRs that once seen by genetic counselor will undergo genetic testing +50%(100%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	9.984	4.237	53.048	67.269	722	8,437	D
2-yearly colonoscopy	235	66	9.984	5.669	51.441	67.094	741	7,610	7,610
1-yearly colonoscopy	228	66	9.984	9.932	49.743	69.659	753	13,513	218,647

FDRs LS cases: Proportion of FDRs testing positive on a germline test –50%(25%)

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or	359	165		0.227	67.237	67.465	-	-	-

CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	20.835	4.237	53.048	78.120	722	36,379	D
2-yearly colonoscopy	235	66	20.835	5.669	51.441	77.945	741	34,230	34,230
1-yearly colonoscopy	228	66	20.835	9.932	49.743	80.510	753	39,389	218,647
FDRs LS cases: Proportion of FDRs testing positive on a germline test +50%(75%)									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	7.005	4.237	53.048	64.290	722	767	D
2-yearly colonoscopy	235	66	7.005	5.669	51.441	64.116	741	303	303
1-yearly colonoscopy	228	66	7.005	9.932	49.743	66.680	753	6,410	218,647
Colonoscopy screening participation not diagnosed with LS = 40%									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS testing									
10-yearly colonoscopy	325	130		0.799	64.351	65.150	222	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.462	4.237	53.048	67.747	722	5,200	D
2-yearly colonoscopy	235	66	10.462	5.669	51.441	67.573	741	4,671	4,671

1-yearly colonoscopy	228	66	10.462	9.932	49.743	70.138	753	9,401	218,647
<i>Colonoscopy screening participation not diagnosed with LS = 80%</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	291	94		1.370	61.465	62.835	445	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.462	4.237	53.048	67.747	722	17,727	D
2-yearly colonoscopy	235	66	10.462	5.669	51.441	67.573	741	15,985	15,985
1-yearly colonoscopy	228	66	10.462	9.932	49.743	70.138	753	23,700	218,647
<i>Colonoscopy surveillance participation diagnosed with LS = 70%</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	258	80	10.462	3.736	54.822	69.020	632	16,866	D
2-yearly colonoscopy	251	79	10.462	4.989	53.416	68.867	649	15,478	15,478
1-yearly colonoscopy	244	79	10.462	8.719	51.930	71.111	659	21,890	218,647
<i>Colonoscopy surveillance participation diagnosed with LS = 90%</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or	359	165		0.227	67.237	67.465	-	-	-

CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	229	55	10.462	4.738	51.274	66.475	812	5,188	D
2-yearly colonoscopy	220	54	10.462	6.350	49.467	66.279	834	4,571	4,571
1-yearly colonoscopy	212	54	10.462	11.145	47.557	69.164	847	10,072	218,647
Related to genetic testing: Combined costs of lab testing in index CRC case –50%(\$112)									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	D
LS Testing									
3-yearly colonoscopy	244	67	6.69	4.237	53.048	63.975	722	Cost-Saving	D
2-yearly colonoscopy	235	66	6.69	5.669	51.441	63.801	741	Cost-Saving	Cost-Saving
1-yearly colonoscopy	228	66	6.69	9.932	49.743	66.366	753	5,660	218,647
Related to genetic testing: Combined costs of lab testing in index CRC case +50%(\$336)									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	14.235	4.237	53.048	71.520	722	19,383	D
2-yearly colonoscopy	235	66	14.235	5.669	51.441	71.345	741	18,039	18,039

1-yearly colonoscopy	228	66	14.235	9.932	49.743	73.910	753	23,650	218,647
<i>Related to genetic testing: Cost of patient navigator per individual referred to genetic counseling –50%(\$54)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.381	4.237	53.048	67.666	722	9,459	D
2-yearly colonoscopy	235	66	10.381	5.669	51.441	67.491	741	8,584	8,584
1-yearly colonoscopy	228	66	10.381	9.932	49.743	70.056	753	14,460	218,647
<i>Related to genetic testing: Cost of patient navigator per individual referred to genetic counseling +50%(\$162)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.544	4.237	53.048	67.829	722	9,880	D
2-yearly colonoscopy	235	66	10.544	5.669	51.441	67.655	741	8,985	8,985
1-yearly colonoscopy	228	66	10.544	9.932	49.743	70.219	753	14,849	218,647
<i>Related to genetic testing: Costs of pre-test genetic counseling in CRC index case –50%(\$128)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or	359	165		0.227	67.237	67.465	-	-	-

CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.3	4.237	53.048	67.585	722	9,252	D
2-yearly colonoscopy	235	66	10.3	5.669	51.441	67.411	741	8,386	8,386
1-yearly colonoscopy	228	66	10.3	9.932	49.743	69.975	753	14,267	218,647
<i>Related to genetic testing: Costs of pre-test genetic counseling in CRC index case +50%(\$383)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.625	4.237	53.048	67.910	722	10,088	D
2-yearly colonoscopy	235	66	10.625	5.669	51.441	67.735	741	9,183	9,183
1-yearly colonoscopy	228	66	10.625	9.932	49.743	70.300	753	15,042	218,647
<i>Related to genetic testing: Avg. cost of germline test in index CRC case -50%(\$550)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	9.903	4.237	53.048	67.188	722	8,228	D
2-yearly colonoscopy	235	66	9.903	5.669	51.441	67.013	741	7,411	7,411

1-yearly colonoscopy	228	66	9.903	9.932	49.743	69.578	753	13,320	218,647
<i>Related to genetic testing: Avg. cost of germline test in index CRC case +50%(\$1,649)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million\$)	Total costs ^{b,b} (million\$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	11.022	4.237	53.048	68.307	722	11,111	D
2-yearly colonoscopy	235	66	11.022	5.669	51.441	68.133	741	10,158	10,158
1-yearly colonoscopy	228	66	11.022	9.932	49.743	70.698	753	15,989	218,647
<i>Related to genetic testing: Post-test genetic counseling and tracing FDRs for LS positive cases -50%(\$45)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million\$)	Total costs ^{b,b} (million\$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.292	4.237	53.048	67.577	722	9,231	D
2-yearly colonoscopy	235	66	10.292	5.669	51.441	67.403	741	8,367	8,367
1-yearly colonoscopy	228	66	10.292	9.932	49.743	69.968	753	14,249	218,647
<i>Related to genetic testing: Post-test genetic counseling and tracing FDRs for LS positive cases +50%(\$135)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million\$)	Total costs ^{b,b} (million\$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or	359	165		0.227	67.237	67.465	-	-	-

CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.633	4.237	53.048	67.918	722	10,108	D
2-yearly colonoscopy	235	66	10.633	5.669	51.441	67.743	741	9,202	9,202
1-yearly colonoscopy	228	66	10.633	9.932	49.743	70.308	753	15,061	218,647
<i>Related to genetic testing: Somatic testing for LS negative cases -50%(\$250)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.377	4.237	53.048	67.662	722	9,451	D
2-yearly colonoscopy	235	66	10.377	5.669	51.441	67.488	741	8,576	8,576
1-yearly colonoscopy	228	66	10.377	9.932	49.743	70.053	753	14,452	218,647
<i>Related to genetic testing: Somatic testing for LS negative cases +50%(\$750)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.547	4.237	53.048	67.832	722	9,888	D
2-yearly colonoscopy	235	66	10.547	5.669	51.441	67.658	741	8,993	8,993

1-yearly colonoscopy	228	66	10,547	9,932	49,743	70,223	753	14,857	218,647
<i>Related to genetic testing: Costs of germline testing for LS in a FDR with a known mutation –50%(\$200)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.062	4.237	53.048	67.347	722	8,640	D
2-yearly colonoscopy	235	66	10.062	5.669	51.441	67.173	741	7,803	7,803
1-yearly colonoscopy	228	66	10.062	9.932	49.743	69.738	753	13,701	218,647
<i>Related to genetic testing: Costs of germline testing for LS in a FDR with a known mutation +50%(\$600)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	67.237	67.465	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.862	4.237	53.048	68.147	722	10,700	D
2-yearly colonoscopy	235	66	10.862	5.669	51.441	67.973	741	9,766	9,766
1-yearly colonoscopy	228	66	10.862	9.932	49.743	70.538	753	15,609	218,647
<i>Related to Colonoscopies: Costs of colonoscopies –50%(\$474/\$596^f)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{b,b} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or	359	165		0.114	67.237	67.351	-	-	-

CRC Screening									
No LS testing									
10-yearly colonoscopy	308	112		0.542	62.908	63.450	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.462	2.119	53.048	65.629	722	5,610	D
2-yearly colonoscopy	235	66	10.462	2.835	51.441	64.738	741	3,160	3,160
1-yearly colonoscopy	228	66	10.462	4.966	49.743	65.172	753	4,105	36,951
<i>Related to Colonoscopies: Costs of colonoscopies +50%(\$1,472/\$1,788^f)</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS testing									
10-yearly colonoscopy	359	165		0.341	67.237	67.578	-	-	-
LS Testing									
3-yearly colonoscopy	244	67	10.462	6.356	53.048	69.866	722	13,729	D
2-yearly colonoscopy	235	66	10.462	8.504	51.441	70.408	741	14,409	28,093
1-yearly colonoscopy	228	66	10.462	14.898	49.743	75.104	753	25,204	400,343
<i>Colorectal cancer care costs -50%</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million \$)	Total costs ^{ab} (million \$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS testing									
10-yearly colonoscopy	359	165		0.227	33.619	33.846	-	-	-
LS Testing									
3-yearly colonoscopy	244	67	10.462	4.237	26.524	41.223	722	22,365	D
2-yearly colonoscopy	235	66	10.462	5.669	25.721	41.852	741	22,850	32,610

1-yearly colonoscopy	228	66	10.462	9.932	24.872	45.266	753	30,351	291,020
<i>Colorectal cancer care costs +50%</i>									
Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million\$)	Costs CRC Care ^b (million\$)	Total costs ^{b,f} (million\$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening	359	165		0.227	100.856	101.083	-	-	-
No LS testing									
10-yearly colonoscopy	308	112		1.084	94.362	95.446	334	-	D
LS Testing									
3-yearly colonoscopy	244	67	10.462	4.237	79.572	94.271	722	Cost-Saving	D
2-yearly colonoscopy	235	66	10.462	5.669	77.162	93.294	741	Cost-Saving	Cost-Saving
1-yearly colonoscopy	228	66	10.462	9.932	74.615	95.010	753	Cost-Saving	146,275

CRC= Colorectal Cancer, LS= Lynch Syndrome, LYG= Life-Years Gained, ACER= Average Cost-Effectiveness Ratio, ICER= Incremental Cost-Effectiveness Ratio, D= Dominated.

^aCRC cases and deaths include those from LS diagnosis until death.

^bCosts and life-years gained were discounted at an annual rate of 3%.

^cInclude total costs of screening CRC index cases and their FDRs, including LS negative and non-participants.

^dInclude costs of CRC screening, diagnosis and surveillance.

^eCompared to no LS screening.

^fCosts used for colonoscopies without polypectomy/with polypectomy.

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Abbreviations

CRC	Colorectal Cancer
FDR	First-degree Relative
ICER	incremental cost-effectiveness ratio
IHC	Immunohistochemistry
LS	Lynch Syndrome
LYG	Life-years Gained

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Need to Know

Background:

We evaluated the costs and benefits of testing for Lynch syndrome in patients younger than 70 years with colorectal cancer (CRC), and first-degree relatives of those found to have Lynch syndrome. We then investigated the optimal surveillance interval for these patients with Lynch syndrome.

Findings:

Immunohistochemical testing for Lynch syndrome in persons younger than 70 years who have received a diagnosis of CRC, followed by testing of first-degree relatives of those found to have Lynch syndrome, with surveillance colonoscopy every 2 years, reduces risk of cancer at a reasonable cost.

Implications for patient care:

Patients who receive a diagnosis of colorectal cancer at an age of 70 years or younger should be tested for Lynch syndrome; first-degree relatives of those found to have Lynch syndrome who are also found to have Lynch syndrome should undergo colonoscopy examination every 2 years.

Figure 1.

Patient flow diagram of CRC index cases and cascade testing.

CRC = Colorectal cancer, IHC= Immunohistochemistry, LS= Lynch syndrome, FDR= First-degree relative

Figure 2. Cost-effectiveness acceptability curve of the probabilistic sensitivity analyses. CRC = Colorectal cancer, LS= Lynch syndrome,

Table 1.

Base case results per 1,000 first-degree relatives with Lynch Syndrome.

Strategy	CRC Cases ^a	CRC Deaths ^a	Costs LS Testing ^{b,c} (million\$)	Costs CRC screening ^{b,d} (million \$)	Costs CRC Care ^b (million \$)	Total costs ^{a,b} (million\$)	LYG ^b (y)	ACER ^{b,e} (\$)	ICER ^b (\$)
No LS Testing or CRC Screening									
No LS Testing	359	165		0.227	67.237	67.465	-	-	-
10-yearly colonoscopy	308	112			62.908	63.992	334	-	Cost-Saving
LS Testing									
3-yearly colonoscopy	244	67	10.462	4.237	53.048	67.747	722	9,670	D
2-yearly colonoscopy	235	66	10.462	5.669	51.441	67.573	741	8,785	8,785
1-yearly colonoscopy	228	66	10.462	9.932	49.743	70.138	753	14,655	218,647

CRC= Colorectal Cancer, LS= Lynch Syndrome, LYG= Life-Years Gained, ACER= Average Cost-Effectiveness Ratio, ICER= Incremental Cost-Effectiveness Ratio, D= Dominated.

^a CRC cases and deaths include those from LS diagnosis until death.

^b Results were discounted at an annual rate of 3%.

^c Include total costs of screening CRC index cases and their FDRs, including LS negative and non-participants.

^d Include costs of CRC screening, diagnosis and surveillance.

^e Compared to no LS screening.