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Cost Effectiveness of Age-Specific Screening Intervals for People With Family Histories of Colorectal Cancer

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Abstract

Background and Aims—The relative risk (RR) of colorectal cancer (CRC) decreases with increasing age among individuals with a family history of CRC. Currently, no screening recommendations specify less frequent screening with increasing age. The aim of this study is to determine whether such a refinement would be cost-effective.

Methods—The familial RR of developing CRC by an individual's age and number of affected first-degree relatives (FDRs) was determined from existing literature. For each number of affected FDRs, we used the Microsimulation Screening Analysis (MISCAN) model to estimate costs and effects of colonoscopy screening strategies varying in age range and interval. Screening was then optimized sequentially, starting with the youngest age group, and allowing the interval of screening to change at certain ages.

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Results—For people with one affected FDR (92% of those with a positive family history), screening every three years beginning at age 40 is most cost-effective. If no adenomas are found, the screening interval can gradually be extended to 5 and 7 years at ages 45 and 55, respectively. From a cost-effectiveness perspective, individuals with more affected FDRs preferably start screening earlier and at shorter intervals, but can also reduce frequency if no abnormalities are found.

Conclusions—After several subsequent negative colonoscopies, it is cost-effective to gradually increase the screening interval for individuals with a positive family history, provided that no new CRC cases have been found in FDRs.

Keywords

familial colorectal cancer risk; colonoscopy screening; screening ages; microsimulation modeling

Introduction

Colorectal cancer (CRC) is the third most common cancer in the U.S., with over 135,000 new diagnoses and about 50,000 deaths estimated in 2017.[1] Most cases are sporadic, with about 75% developing in average-risk individuals.[2] Familial adenomatous polyposis (FAP), polyposis syndromes and hereditary non-polyposis colorectal cancer (HNPCC, also known as Lynch syndrome) account for approximately 5% of all cases.[2, 3] The remaining 20% is found in individuals with a positive family history, but without a (diagnosed) inherited cancer syndrome.[2]

The more affected first-degree relatives (FDRs) an individual has, the higher his or her absolute and relative risk for developing CRC.[4] In a US-based study by Taylor et al.,[5] which objectively measured both family history and CRC diagnosis,[6] the relative risk of developing CRC compared with the general population, ranged from 0.89 (0.87–0.91) for individuals without affected FDRs, to 19.86 (7.29–43.24) in the rare subset of individuals with at least five affected FDRs (<0.001% of the study population). Of those with at least one affected FDR (i.e. 4.1% of the study population), 92% had one, 7% had two, and <1% had three or more affected FDRs.

Current recommendations state that individuals at average risk for CRC undergo colonoscopy every 10 years starting at age 50.[7, 8] People with a family history of CRC are recommended to start screening earlier and/or with a shorter interval.[8, 9] Even though CRC risk increases rapidly with the number of affected FDRs[5] and screening people with ≥3 FDRs more often than every 5 years was shown to be cost-effective[10], current guidelines do not distinguish between having 2 or 3, or even more affected FDRs.

Furthermore, the effectiveness of screening in individuals with a positive family history might be improved by allowing the screening intensity to vary with age. An evidence-based review has shown that the excess CRC risk that is associated with a given family history of CRC decreases with age.[6] For example, having a positive family history at young age (e.g. <45 years) is rare,[6] and is associated with a much higher age-specific RR for CRC than having a positive family history at older ages. In addition to distinguishing individuals with

2 affected FDRs from those with 3 or ≥4, the decrease in familial RR by age justifies an investigation of whether screening guidelines for people with a positive family history could be improved.

Methods

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model to quantify the effectiveness and costs of colonoscopy screening in individuals with a family history of CRC. We determined the optimal (i.e. most cost-effective) colonoscopy screening schedule based on age of the individual at risk (i.e., 30–44, 45–49, 50–54, 55–59, 60–64, 65–69, and 70+ years) and his/her number of affected FDRs (i.e., 1, 2, 3, and ≥4), where an FDR is defined as one's parent, sibling or offspring. For each level of family history, the most cost-effective ages to begin and end screening, and the age-group specific screening interval were determined assuming a willingness-to-pay threshold of $100,000 per quality-adjusted life year (QALY).

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC developed at the Department of Public Health of the Erasmus University Medical Center (Rotterdam, the Netherlands). The model's structure, underlying assumptions, and calibration are described in the Model Appendix. In brief, MISCAN-Colon simulates the life histories of a large population of persons from birth to death. As each simulated person ages, one or more adenomas may develop. These adenomas can progress from small (≤5 mm), to medium (6–9 mm), to large size (≥10 mm). Some adenomas can develop into preclinical cancer, which may progress through to cancer stages I to IV. During each stage CRC may be diagnosed because of symptoms. Survival after clinical diagnosis is determined by the stage at diagnosis, the localization of the cancer, and the person's age.[11]

Screening will alter some of the simulated life histories. Some cancers will be prevented by the detection and removal of adenomas; other cancers will be detected in an earlier stage with a more favorable survival. However, screening can also result in serious complications and over-diagnosis and over-treatment of CRC (i.e. the detection and treatment of cancers that would not have been diagnosed without screening). By comparing a simulation of life histories with screening to a simulation of the same life histories without screening, MISCAN-Colon quantifies the effectiveness of screening, as well as the associated costs.

Modeling familial risk

An increased risk for developing CRC can be modeled through an increased risk of developing adenomas, or by assuming that adenomas are more likely to progress to CRC. Whereas an increased adenoma prevalence has been observed in individuals with a positive family history, there is limited evidence for accelerated adenoma progression.[6] In the base-case analysis, we therefore modeled familial risk by assuming that individuals with affected FDRs develop more adenomas. Although the probability that a single adenoma progresses to CRC is not changed, an increased probability of developing adenomas does imply that, on average, CRC is diagnosed at a younger age.

Familial risk cohorts

We simulated a cohort of 10 million people for every combination of age group at risk (i.e., 30–44, 45–49, 50–54, 55–59, 60–64, 65–69 and 70+ years) and level of family history (i.e. having 0, 1, 2, 3, or 4 FDRs). These 35 cohorts differed in their estimated RR for developing CRC, which was based on two studies.[5, 12] Lifetime RRs for people having 1, 2, 3, or ≥4 affected FDRs were obtained from Taylor et al.[5] and the development of RR by age of the person at risk for CRC was obtained from Fuchs et al.[12] By assuming that the age distribution of RR does not depend on the level of family history, we transformed the lifetime RRs from Taylor et al.[5] into familial age-specific RR values. To this end, the RR of every age group in Fuchs et al.[12] was divided by the overall RR presented in Fuchs et al.[12], which was then multiplied with the lifetime RR from Taylor et al.[5] Using this calculation, we found the familial age-specific RRs given in Table 1. Although we recognize that having a single affected FDR is much more common than having 2, 3 or ≥4 affected FDRs (91.7% of those with at least one affected FDR versus 7.3%, 0.8% and 0.1%, respectively),[5] we simulated cohorts of equal size to ensure stability of model outcomes.

Data and assumptions for screening and surveillance

We let colonoscopy screening schedules differ in their start age (30, 35, 40, 45, and 50), interval (1, 2, 3, 5, 7, and 10 years) and end age (75, 80, 85, and 90).

Test characteristics and complication rates of colonoscopy are given in Table 2. The sensitivity increases from 75% for small adenomas (≤5 mm) to 85% for medium-sized adenomas (6–9 mm) and to 95% for large adenomas (≥10 mm) and colorectal cancer.[13] The specificity is assumed to be 86%.[14] The lack of specificity reflects the detection of non-adenomatous polyps, which involves unnecessary polypectomy or biopsy. Complications requiring a hospital admission or emergency department visit are assumed to increase exponentially with age.[15–17]

Individuals with adenomas detected and removed at screening were assumed to undergo colonoscopy surveillance according to current guidelines, and did not return to screening.[18] If the recommended surveillance interval is longer than either the current or any of the past screening intervals, then the surveillance interval is set equal to the minimum of those screening intervals. This ensures that individuals with adenomas detected (i.e. those in surveillance) have colonoscopies at a rate that is as at least as frequently as for those without adenomas detected. We assumed that surveillance continued until 5 years after the end age of screening. Because we wanted to obtain optimal recommendations for individuals following the guideline, adherence to screening and surveillance colonoscopies was assumed to be 100%.

Data and assumptions for costs and utilities

The assumed loss in quality of life due to CRC screening was equivalent to 1.5 day at 0.5 utility per colonoscopy (0.002 QALYs) and 2–4 days at 0.5 utility per complication (0.0027–0.0055 QALYs) (Table 2). We also assumed that life years (LYs) with CRC care have a lower quality than those without CRC care.[19]

The cost-effectiveness analyses were conducted from a modified societal perspective. We included both direct medical costs as well as patient time costs. However, direct non-health costs and costs of informal care givers were not included.[20] The costs of colonoscopies were based on 2014 Medicare payment rates and copayments (Table 2). For each type of complication, the average payment by Centers for Medicare and Medicaid Services (CMS) was calculated using frequency data on hospitalizations for colonoscopy complications from Craig Parzynski, MS, of Yale University (personal communication). Net costs of CRC care were obtained from an analysis of SEER-Medicare linked data[21] (personal communication, Robin Yabroff, PhD, and Martin Brown, PhD, both formerly of the National Cancer Institute). Patient time costs and copayments were added to all of these estimates, which were then updated to 2014 U.S. dollars using the Consumer Price Index.[22]

Outcomes

For each cohort we quantified the effectiveness (i.e., the number of CRC cases prevented, CRC deaths prevented, LYs gained, and QALYs gained) and resources (i.e. number of colonoscopies and costs) of all screening strategies considered, applying the conventional 3% annual discount rate for both.

Base-case analysis

For each of the 35 cohorts, we simulated the screening strategies described earlier and determined their costs and effects as compared to no (future) screening. We first compared the costs and effects of 10-yearly and 5-yearly colonoscopy screening for a 50-year old cohort without prior screening for different levels of family history. Then, the optimal screening strategy for each age group and level of family history was determined using the following approach.

Screening strategies were ranked by increasing costs. Strategies that were more costly and less effective than another strategy (i.e. strongly dominated strategies) were eliminated from consideration, as were those that provided an additional QALY at a higher incremental cost (i.e. weakly dominated strategies). For all non-dominated strategies, we calculated the incremental cost-effectiveness ratio (ICER), defined as the additional cost of a specific strategy, divided by its additional clinical benefit (in this case, QALYs gained), compared with the next less expensive strategy (i.e., the strategy with costs closest to, but lower than, the strategy of interest). The optimal screening strategy was then defined as the strategy with an ICER closest to the willingness-to-pay threshold of $100,000 per QALY gained.

For each level of family history, the optimal screening strategy was determined in a sequential fashion, starting with the youngest age group, thereby allowing for appropriate screening histories in later age groups (see Figure 1). First, we optimized screening for individuals in the youngest age group (30–44 years), using the RR for this age group (Table 1). We considered different start ages and let screening continue until age 75, which is currently recommended for the general population.[7, 8] Second, we simulated screening at those ages within 30–44 years that were found to be cost-effective in step 1, and optimized screening for individuals aged 45–49 years, using the RR for this age group. In this case, the start age was only varied (45 or 50 years) if screening was not considered cost-effective at

ages 30–44 years. Different intervals were considered for screening from age 45 (or 50) until age 75. Third, we simulated screening at those ages within 30–44 and 45–49 years that were found to be cost-effective in step 1 and 2, and optimized the screening interval at ages 50–75, assuming the RR for age group 50–54 years. The same methodology was applied for age groups 55–59, 60–64, and 65–69. For those aged 70+, different end ages of screening were considered.

By using screening histories that were found to be optimal for the same level of family history, we implicitly assume that individuals do not acquire more affected FDRs over time. Therefore, these analyses specifically examine whether the screening interval can be lengthened for individuals whose family history remains constant.

Sensitivity analyses

In the sensitivity analyses, we adjusted our base-case assumptions in the following way.

1. *Screening history*. We considered all individuals underwent previous screening in line with guidelines for the general population (i.e. colonoscopy screening at ages 50, 60 and 70).
2. *Relative risk*. RRs were truncated at 10 to attenuate the effect of very high estimated RRs.
3. *Cost-effectiveness threshold*. We explored the effect of assuming a willingness-to-pay threshold of $50,000 per QALY.
4. *Familial risk*. We assessed the effect of a potential accelerated progression to cancer in those with a family history of CRC by dividing the average duration of progressive adenomas by the relative risks given in Table 1. The adenoma onset was then calibrated such that – in the absence of screening – CRC risk was similar to the base-case analysis.
5. *Sessile serrated adenomas*. To account for the fact that cancer may also develop from sessile serrated adenomas, which may be less easily detected by colonoscopy, we have expanded our model to include a separate pathway for sessile serrated adenomas, assuming lower colonoscopy sensitivity and longer adenoma dwelling times (see Appendix for technical details).

Results

For a cohort of 50-year-old previously unscreened individuals with no affected FDRs, no future screening results in 59 CRC cases and 24 CRC deaths per 1,000 simulated individuals. Colonoscopy at ages 50, 60 and 70 prevents 36 of these cases and 19 of these deaths at an expense of almost 3,400 colonoscopies (Table 3). Screening every 5 years instead of every 10 years requires 1,711 additional colonoscopies to prevent 4.4 additional CRC cases and 1.5 additional CRC deaths. This implies that over 1,000 additional colonoscopies are needed to prevent one additional CRC death. For individuals with 1, 2, 3 or ≥4 FDRs, this ‘number needed to screen’ was 304, 192, 135, and 75, respectively. In terms of cost-effectiveness, replacing 10-yearly screening by 5-yearly screening would cost

$186,000 per QALY gained in people without any affected FDRs, and $26,000, $9,000 and $1,000 per QALY gained in people with 1, 2 and 3 affected FDRs, respectively. It is potentially cost saving in people with 4 or more FDRs.

Cost-effective screening for individuals with one affected FDR

For individuals with a single affected FDR, optimization of screening for the youngest age group showed that screening every 3 years ideally starts at age 40 (Table 4). After two consecutive negative colonoscopies at ages 40 and 43, it is cost-effective to lengthen the screening interval to 5 years. From ages 55 to 70, the screening interval can be 7 years for those with a screening history of only negative colonoscopies. For illustrative purposes, the Supplementary Figure 1 shows the age-specific cost-efficiency frontiers in which the optimal strategies are marked.

Cost-effective screening for individuals with two or more affected FDRs

Individuals who already have 2 affected FDRs at young age should start screening every 3 years at age 35. After subsequent negative colonoscopies, this interval is preferably extended to 5 years at age 55, and to 7 years at age 70. For individuals with 3 or ≥4 affected FDRs, screening every 2 years is recommended from age 35 or 30, respectively. For individuals with 3 affected FDRs, the interval can be lengthened to 3, 5, and 7 years at age 45, 60, and 70 respectively. For those with ≥4 affected FDRs, intensive screening remains cost-effective at older ages, and the interval can only be extended to 3 years at age 70.

Sensitivity analyses

Results of the sensitivity analyses are shown in Table 5. When relative risks were truncated at 10, individuals with ≥3 affected FDRs preferably start off with screening every 3 years instead of every 2 years. However, it was cost-effective to switch to a 2-year interval at a later age. From age 55, optimal screening strategies were identical to the base-case analysis.

When we assumed that people had prior screening according to what is recommended for the general population instead of to their family history level, screening intervals did not tend to lengthen with age.

As expected, a lower cost-effectiveness threshold resulted in less intensive screening.

When, in addition to an increased adenoma onset, familial risk was modeled by assuming a faster progression of adenomas, optimal strategies were somewhat more intensive.

Finally, using a model with a separate pathway for sessile serrated polyps did not (significantly) alter our results.

Discussion

This study confirms that it is effective and cost-effective to screen people with affected FDRs more often than people in the general population. The more affected FDRs an individual has, the earlier the start age of screening and the shorter the optimal screening interval. For individuals with a single affected FDR (approximately 92% of people with at

least one affected FDR)[5], the optimal screening interval gradually increased from 3 years at age 40 to 7 years at age 55. This increase suggests that the benefits of age-specific CRC screening guidelines for people with a positive family history, but with persistent negative screening results, may be substantial. As the optimal screening interval did not (significantly) lengthen with age in individuals who had prior screening as recommended for the general population, it is crucial that intensified screening is offered as soon as an FDR is diagnosed with CRC. An increase of the screening interval can then be considered at a later stage, when an individual has had several negative colonoscopies.

We modeled an increased risk of developing CRC as an increased risk of developing adenomas. Although the duration distribution of a single adenoma to progress to CRC was assumed to be independent of family history, we found that it is cost-effective to screen individuals at increased risk at shorter intervals than the general population. There are two reasons for this finding. The first one is that at every screening, a random percentage of adenomas is missed due to a lack of sensitivity, and this percentage translates to a larger absolute number of missed adenomas in higher-risk populations. Most of these missed adenomas will be picked up by subsequent screenings, but some may progress to cancer before being detected. The second reason is that, although in every risk group, the same (small) percentage of adenomas is fast-growing, the absolute number of fast-growing adenomas is higher in those at increased risk. Both mechanisms underscore the need for screening with shorter intervals in those at higher risk, which has been explained more extensively elsewhere.[23] Results of one of our sensitivity analyses have shown that if adenomas in individuals at familial risk would be characterized by shorter dwelling times, then optimal screening intervals could be even shorter.

Offering individuals with one affected FDR colonoscopy screening at a 3-year interval may seem aggressive, and is more intensive than existing guidelines.[8, 9] However, individuals who already have an affected FDR at young age are more likely to have multiple affected FDRs at a later age. This is reflected in the familial RR for CRC being much higher for younger individuals than for older individuals.[12] Intensified screening at young age, with a subsequent lengthening of the screening interval after consecutive negative findings, could therefore be considered a very reasonable option for those with affected FDRs.

As the optimal screening interval varied both with age and number of affected FDRs, guidelines could be improved by a more detailed grouping of family history. An earlier study already showed that intervals of less than 5 years may be appropriate for those with multiple affected FDRs.[10] The fact that this has not been incorporated in guidelines yet, may be because it is considered too complex by policy makers. However, it only involves a small group of individuals and does not affect the general population. The age-dependency could even be simplified, by e.g. lengthening the interval only at age 55, and only for individuals with 1–3 affected FDRs (Table 6).

Although we presented results for different levels of family history and age groups in a similar way, it should be noted that having 3 or more affected FDRs is rare (i.e., less than 1% of all people with a family history), especially at young age.[5] It cannot be ruled out that these people have an undiagnosed syndrome that increases their CRC risk significantly.

However, as long as such a syndrome has not been diagnosed yet, screening these people more often based on their number of affected FDRs is probably beneficial.

In general, U.S. guidelines recommend that screening begins at age 40 for individuals with one FDR diagnosed with CRC below age 60 or two or more FDRs diagnosed at any age.[8, 9] In contrast with an earlier study, we found that for individuals with ≥2 affected FDRs, the optimal start age of screening is below age 40.[10] One U.S. guideline states that for individuals with one FDR diagnosed with CRC at age ≥60, multiple negative colonoscopies may support lengthening the colonoscopy interval.[24] We showed that such lengthening is cost-effective, and that it may also be recommended for individuals with a more pronounced family history of CRC.

In this study, we only considered the number of FDRs diagnosed with CRC to estimate familial CRC risk. Although to a smaller extent, combinations of affected second- and third-degree relatives can also increase colorectal cancer risk significantly.[5] The same is true for FDRs with adenomas detected instead of cancer.[25] The inclusion of such alternatives would, from a computational perspective, only imply considering slightly lower relative risks. The optimal screening intervals may then be longer, but the finding that age-specific screening guidelines are likely to result in large benefits would still apply.

Despite current screening recommendations, we did not take into account the age at which the relative's proband is diagnosed with CRC because of conflicting evidence regarding its impact. Based on data from the Utah Population Database, Taylor et al. concluded that the proband's age at diagnosis does significantly impact CRC risk in relatives,[5] but Schoen et al. recently concluded the opposite based on results from the Prostate, Lung, Colorectal and Ovarian (PLCO) Screening trial.[26] However, even if the proband's age at diagnosis would impact the relative risk in family members, our conclusions may still be useful. If having an FDR diagnosed at young age would imply an equal increase in familial RR across all age groups, then this may shorten optimal screening intervals but lengthening the screening interval would still be cost-effective. If a CRC diagnosis at young age would increase familial RR especially at young ages, then a more rapid lengthening of the interval might even be cost-effective.

This study was performed from a societal perspective, because it aims to inform societal rather than individual decisions. If we would have adopted a healthcare provider or patient perspective, several indirect costs would have been excluded. This is noteworthy as patient time costs make up 40–48% of colonoscopy costs, but only 3–28% of cancer care costs. This means that if we would perform the same analysis from a healthcare provider perspective, screening would be relatively cheaper compared to CRC treatment. Although more intensive strategies might then be considered optimal, lengthening screening intervals after several negative colonoscopies is likely to remain cost-effective.

This study also has its limitations. First, using the number of affected FDRs gives an indication of an individual's family history, but is dependent on his or her family size. For an individual with a small family, one affected FDR is more telling than for an individual with a large family. For individuals without siblings and offspring, it would not be possible to have

3 or more affected FDRs, regardless of the level of familial CRC risk. Second, in the absence of true age-specific estimates of RRs for all levels of affected FDRs, we estimated these RRs ourselves. As in some cases our approach ended up in relatively high values, we also truncated the RRs in a sensitivity analysis. Third, the MISCAN model has been calibrated to SEER incidence data from 1975–1979, i.e. before the onset of screening. Since then, CRC incidence has risen by 15% in individuals below age 50, who are not eligible for mass screening.[27] This suggests that, if screening would not have been available, CRC incidence might have increased in those above age 50 as well. If we would have incorporated this possible increase in our model, strategies might have become slightly more intensive. However, it is unlikely that it would have altered the conclusion that lengthening the screening interval after several subsequent negative colonoscopies may be cost-effective. Finally, we assumed that an individual's level of family history remains constant over time, although in real life, it is likely to increase as an individual ages. Although exploring all possible life histories was not feasible, we did consider a scenario with prior screening according to what is recommended for the general population. The results of this analysis provide the age-specific screening intervals that should be offered to someone whose family history has just been revealed. After some years of more intensive screening, optimal intervals would probably lengthen towards those found in the base-case analysis.

In summary, our model results indicate that it is cost-effective to offer individuals with a positive family history of CRC more intensive colonoscopy screening than people in the general population, especially at younger ages. Furthermore, for individuals with a constant level of family history over time, it is cost-effective to gradually increase the screening interval after several subsequent negative colonoscopies. If no adenomas develop, it is unlikely that these individuals are affected by genetic predisposition; therefore, continuing intensive colonoscopy screening would provide little or no additional health benefit and is clearly not cost-effective.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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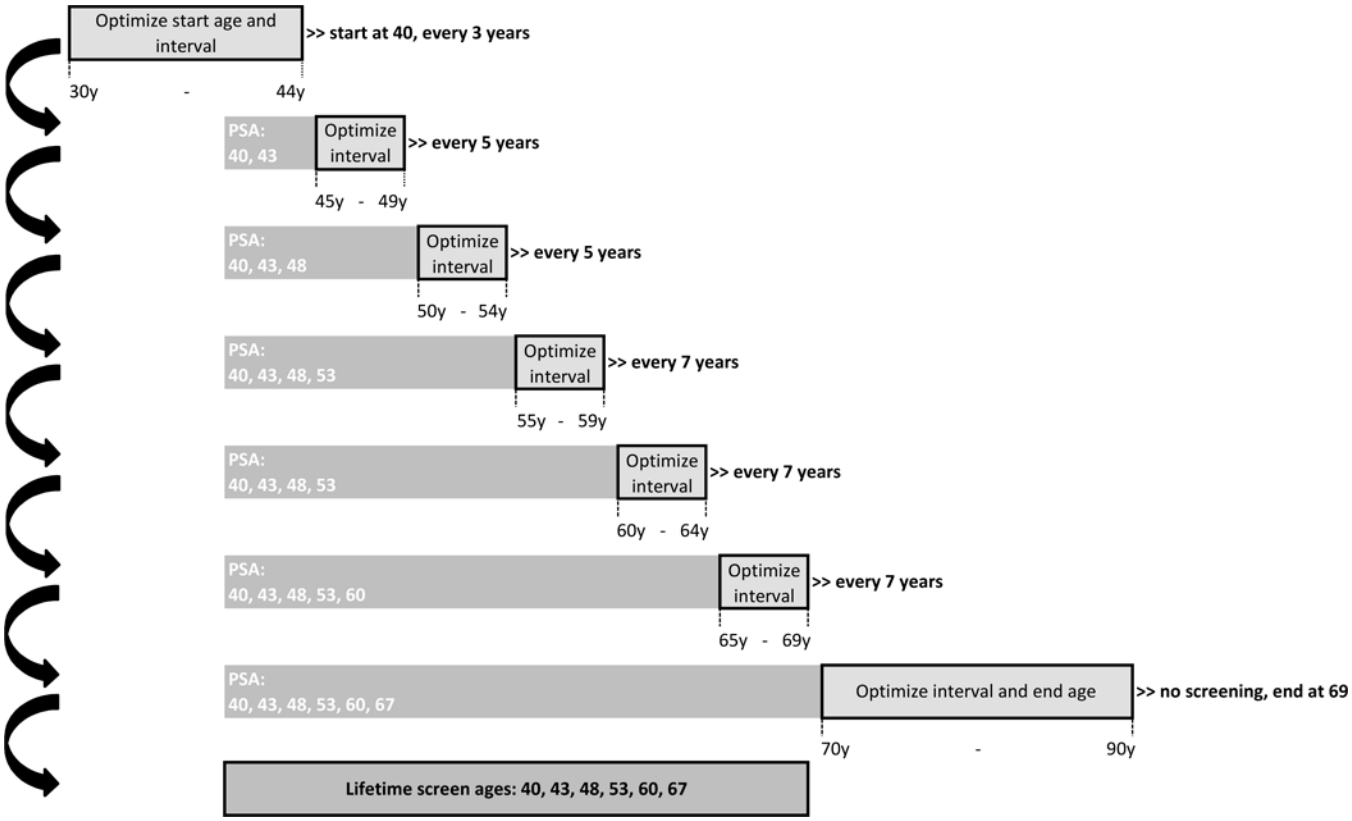

Figure 1.

Sequential optimization method, for an example of individuals with one affected FDR (corresponds with the first row in Table 4). First, the optimal start age and interval for the youngest cohort (30-year-olds) is determined. The resulting screening ages between ages 30 and 44 are assumed as prior screening for the 45-year-olds, for whom the screening interval from age 45 is optimized. The screening ages until age 49 are then incorporated in the prior screening for 50-year-olds, and so on. For 70-year-olds, the optimal end age of screening is determined. In the figure, the derivation of an optimal screening strategy is given in these subsequent steps (indicated by the black arrows).

Table 1.

Model inputs: Estimated relative risk of developing colorectal cancer for people with a positive family history by age, as compared to the average-risk population of the same age (grey section). Values were computed by multiplying the lifetime RR (right column) with the age-specific RR for individuals with ≥1 affected FDR (bottom row).

		AGE GROUP OF PERSON TO BE SCREENED							
		30–44	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70+**	**Lifetime RR[a]**
LEVEL OF FAMILY HISTORY	**1 affected FDR**	5.49	4.12	3.00	2.00	1.60	1.36	1.08	2.04
	2 affected FDRs	8.66	6.49	4.73	3.16	2.52	2.15	1.70	3.22
	3 affected FDRs	12.74[b]	9.55	6.96	4.65	3.71	3.16	2.50	4.73
	≥4 affected FDRs	28.99[b]	21.72[b]	15.84[b]	10.58[b]	8.45	7.20	5.70	10.77[c]
	Age-specific RR for individuals with ≥1 affected FDR[d]	2.69	2.02	1.47	0.98	0.78	0.67	0.53	

FDR = first-degree relative; RR = relative risk.

[a] Lifetime RRs are based on data reported in Table 1 from Taylor et al.[5] In that study, the weighted average of the lifetime RRs presented equals ~0.936. To ensure that the population has an average RR of 1, we divided the reported RRs by ~0.936.

[b] In a sensitivity analysis, relative risks were truncated at 10.

[c] For ≥4 affected FDR, we computed a weighted average of the relative risk associated with having 4 and ≥5 affected FDRs (7.74 and 19.86 respectively). We merged these family history categories because having ≥5 affected FDRs is very rare (less than 1 per 100,000 people).

[d] The presented age-specific RR values were calculated by dividing the age-specific RRs for people with ≥1 affected FDR from Table 3 in Fuchs et al.[12] (RRs of 4.63, 3.47, 2.53, 1.69, 1.35, 1.15, and 0.91 for age groups 30–44, 45–49, 50–54, 55–59, 60–64, 65–69, and ≥70 years, respectively) by the overall RR for people with ≥1 affected FDR presented in the same study (RR of 1.72).

Table 2.

Model inputs: Test characteristics, utility loss and costs of colonoscopy screening and treatment.

COLONOSCOPY TEST CHARACTERISTICS				
Sensitivity				
Small adenomas (≤5 mm)	75%[a,b]			
Medium-sized adenomas (6–9 mm)	85%[a,b]			
Large adenomas (≥10 mm)	95%[a,b]			
Colorectal cancer	95%[a]			
Specificity	86%[c]			
Reach	95% reaches the cecum; the reach of the remaining 5% is distributed uniformly over colon and rectum			
Complication rate for positive test				
Serious gastrointestinal event[d]	Age-specific[e]			
Other gastrointestinal event[f]	Age-specific[g]			
Cardiovascular event[h]	Age-specific[i]			
Mortality rate				
Positive test	0.0191 per 1,000[j]			
Negative test	0			
UTILITY LOSS (QALYs)[k]				
Per colonoscopy	0.0020			
Per complication of colonoscopy				
Serious gastrointestinal event[d]	0.0055			
Other gastrointestinal event[f]	0.0027			
Cardiovascular event[h]	0.0048			
Per LY with CRC care[l,m]	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*
Stage I CRC	0.12	0.05	0.70	0.05
Stage II CRC	0.18	0.05	0.70	0.05
Stage III CRC	0.24	0.24	0.70	0.24
Stage IV CRC	0.70	0.70	0.70	0.70
COSTS (2014 US$)[n]				
Per colonoscopy				
without polypectomy/biopsy	1,422			
with polypectomy/biopsy	1,699			
Per complication of colonoscopy				
Serious gastrointestinal event[d]	11,142			
Other gastrointestinal event[f]	7,587			
Cardiovascular event[h]	8,453			
Per LY with CRC care[l]	Initial care	Continuing care	Terminal care *Death CRC*	Terminal care *Death other cause*

COLONOSCOPY TEST CHARACTERISTICS				
Stage I CRC			64,110	
Stage II CRC	49,475	2,918	63,856	17,429
Stage III CRC	60,033	4,068	67,353	21,620
Stage IV CRC	78,124	12,274	88,749	50,122

QALY = quality-adjusted life year; LY = life year; CRC = colorectal cancer.

[a]The sensitivity of colonoscopy for the detection of adenomas and CRC within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies.[13]

[b]Colonoscopy sensitivity for sessile serrated adenomas (used in one of the sensitivity analyses) was assumed to be 10 percentage points lower.

[c]The lack of specificity reflects the detection of non-adenomatous polyps, which leads to unnecessary polypectomy or biopsy.

[d]Serious gastrointestinal events are perforations, gastrointestinal bleeding, or transfusions.

[e]Formula: 1/[exp(9.27953 − 0.06105 × Age) + 1] − 1/[exp(10.78719 − 0.06105 × Age) + 1]

[f]Other gastrointestinal events are paralytic ileus, nausea and vomiting, dehydration, or abdominal pain.

[g]Formula: 1/[exp(8.81404 − 0.05903 × Age) + 1] − 1/[exp(9.61197 − 0.05903 × Age) + 1]

[h]Cardiovascular events are myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock.

[i]Formula: 1/[exp(9.09053 − 0.07056 × Age) + 1] − 1/[exp(9.38297 − 0.07056 × Age) + 1]

[j]Risk of dying from a colonoscopy at age 65 (Warren et al.[15], Gatto et al.[17] and Van Hees et al.[16]).

[k]The loss of quality of life associated with a particular event.

[l]Care for CRC was divided in three clinically relevant phases: the initial, continuing, and terminal care phase. The initial care phase was defined as the first 12 months after diagnosis; the terminal care phase was defined as the final 12 months of life; the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between CRC patients dying from CRC and CRC patients dying from another cause. For patients surviving less than 24 months, the final 12 months were allocated to the terminal care phase and the remaining months were allocated to the initial care phase.

[m]Utility losses for LYs with initial care were derived from a study by Ness and colleagues.[19] For LYs with continuing care for stage I and II CRC, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV CRC, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for CRC, we assumed the utility loss for LYs with initial care for stage IV CRC. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.

[n]Costs include copayments and patient time costs (i.e. the opportunity costs of spending time on screening or being treated for a complication or CRC), but do not include travel costs, costs of lost productivity, and unrelated health care and non-health care costs in added years of life. We assumed that the value of patient time was equal to the median wage rate in 2014: $17.09 per hour.[28] We assumed that colonoscopies used up 36 hours, serious gastrointestinal complications 192 hours, other gastrointestinal complications 96 hours and cardiovascular complications 120 hours of patient time. Patient time costs associated with CRC care were provided by Yabroff (personal communication), and were calculated using the methodology described in a study by Yabroff and colleagues.[29]

Table 3.

Costs and effects of screening a previously unscreened 50-year-old cohort with colonoscopy until age 70 for different levels of familial risk at age 50, using either a 10-year or a 5-year screening interval, as compared to no screening (effectiveness and costs per 1,000 simulated persons).

No. of affected FDRs at age 50	Screening interval	EFFECTS COMPARED TO NO SCREENING				COSTS COMPARED TO NO SCREENING[c] (* $1,000)				INCREMENTAL EFFECTS AND COSTS WHEN 10-YEAR INTERVAL IS REPLACED BY 5-YEAR INTERVAL[c]		
		Colonoscopies[a]	CRC cases prevented	CRC deaths prevented	QALYs gained[b,c]	Screening and surveillance	Complications	CRC diagnosis and care[d]	Total costs	QALYs gained	Total costs (*$1,000)	Costs per QALY gained (*$1,000)
0	10	3,381	36	19	104	3,860	60	−1,488	2,433	+9 (+8%)	+1,621 (+67%)	185
	5	5,092	40	20	113	5,689	77	−1,712	4,054			
1	10	4,613	113	60	343	5,297	144	−4,778	663	+26 (+7%)	+659 (+99%)	26
	5	5,701	123	64	369	6,452	162	−5,292	1,322			
2	10	5,201	171	92	544	6,086	196	−7,393	−1,111	+25 (+5%)[e]	+216 (+24%)	9
	5	5,803	179	95	568	6,759	209	−7,863	−895			
3	10	5,589	229	128	785	6,721	242	−10,340	−3,378	+18 (+2%)[e]	+11 (+0%)	1
	5	5,857	235	130	803	7,042	249	−10,657	−3,367			
≥4	10	6,104	348	226	1,557	7,768	326	−17,955	−9,860	+2 (+0%)[e]	−12 (−0%)	Potentially cost-saving
	5	6,117	348	226	1,559	7,785	327	−17,985	−9,873			

FDR = first-degree relative; CRC = colorectal cancer; QALY = quality-adjusted life year.

[a] Number of colonoscopies performed for screening, surveillance and diagnosis of CRC, minus the number of clinical CRC diagnoses in case of no screening.

[b] The impact of screening on quantity and quality of life incorporated in one measure, i.e. the net health benefit of screening.

[c] Costs and QALYs were discounted with 3%.

[d] Screening prevents costs by preventing LYs with CRC care and induces costs by adding LYs with CRC care. The net effect can be a reduction in costs (negative values) or an increase in costs (positive values).

[e] For people with 2 or more affected FDRs, the number of QALYs gained by replacing 10-yearly by 5-yearly colonoscopy is lower than for people with 1 affected FDR. This is because the adenoma risk for people with 2 or more FDRs is very high, and a large share of the simulated cohort will therefore go into surveillance. The screening interval is only applied to people without a history of adenomas, and not for those in surveillance.

Table 4.

Optimal colonoscopy screening intervals under base-case assumptions (threshold = $100,000 per QALY gained) by age group and number of affected FDRs.[a]

		AGE GROUP OF PERSON TO BE SCREENED									
		30–34	**35–39**	**40–44**	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**75+**
FAMILY HISTORY	**1 affected FDR**	-	-	3	5	5	7	7	7	-[c]	-
	2 affected FDRs	-	3	3	3	3[b]	5	5	5[b]	7	-
	3 affected FDRs	-	2[b]	2[b]	3	3	3	5	5	7[b]	-
	≥4 affected FDRs	2	2	2	2	2	2	2	2	3	-

FDR = first-degree relative.

[a] The effects, costs and ICER of all efficient strategies for individuals with 1, 2, 3 and ≥4 affected FDRs are given in Appendix Tables 1, 2, 3 and 4, respectively.

[b] The ICER is just below the willingness-to-pay threshold of $100,000 per QALY gained (i.e., between $90,000 and $100,000).

[c] The next ICER is just above the willingness-to-pay threshold of $100,000 per QALY gained (i.e., between $100,000 and $110,000).

Table 5.

Optimal colonoscopy screening intervals in sensitivity analyses (threshold = $100,000 per QALY gained, unless stated otherwise) by age group and number of affected FDRs.

		AGE GROUP OF PERSON TO BE SCREENED									
		30–34	35–39	40–44	45–49	50–54	55–59	60–64	65–69	70–74	75+
FAMILY HISTORY	RRs truncated at 10[a]										
	3 affected FDRs	-	3	3	3[d]	2	3	5[d]	5	7[c]	-
	≥4 affected FDRs	-	3	3	2[c]	3	2[c]	2	2	3[d]	-
	Threshold of $50,000 per QALY gained										
	1 affected FDR	-	-	5	7[d]	7	7[c]	10	10[d]	-	-
	2 affected FDRs	-	-	3	5	5	7[d]	7	10[d]	7[c]	-
	3 affected FDRs	-	3[c]	3[c]	5[d]	3[c]	5	5	5[c]	-[d]	-
	≥4 affected FDRs	-	2[d]	2[d]	3	2	3	3	3[c]	-	-
	Prior screening as in general population[b]										
	1 affected FDR	-	-	3	3	3[c]	5	7[d]	7	3	-
	2 affected FDRs	-	3	3	3	3	3	3	3	3	-
	3 affected FDRs	-	2[c]	2[c]	2	3[d]	3	3	2[c]	3	-
	≥4 affected FDRs	2	2	2	2	2	2	2	2	2	-
	Increased risk modeled as increased adenoma onset and faster progression										
	1 affected FDR	-	3	3	5	5	7	7	10	7	-
	2 affected FDRs	-	2	2	3	3	5	5	5[c]	7[c]	-
	3 affected FDRs	2	2	2	2	3	3	3[c]	5	7	-
	≥4 affected FDRs	1	1	1	1	2[d]	2	2	2[c]	3	-
	Serrated pathway modeled separately										
	1 affected FDR	-	-	3	5	5	7	7	7	10	-
	2 affected FDRs	-	3	3	3	2	5	5	7[d]	7	-

	AGE GROUP OF PERSON TO BE SCREENED									
	30–34	**35–39**	**40–44**	**45–49**	**50–54**	**55–59**	**60–64**	**65–69**	**70–74**	**75+**
3 affected FDRs	-	2	2	2	2	3[d]	3	3	7	-
≥4 affected FDRs	2	2	2	2	2	2	2	2	2	-

FDR = first-degree relative; RR = relative risk (as compared to the general population); QALY = quality-adjusted life year.

[a] For none of the age groups, having less than 3 FDRs is associated with a RR above 10.

[b] Prior screening was assumed to be colonoscopy screening at ages 50, 60 and 70 instead of what is optimal for that family history category.

[c] The ICER is just below the willingness-to-pay threshold (i.e., between $90,000 and $100,000 when the willingness to pay was $100,000 per QALY, and between $40,000 and $50,000 when the willingness to pay was $50,000 per QALY).

[d] The next ICER is just above the willingness-to-pay threshold (i.e., between $100,000 and $110,000 when the willingness to pay was $100,000 per QALY, and between $50,000 and $60,000 when the willingness to pay was $50,000 per QALY).

Table 6.

Simplified colonoscopy strategies for individuals with 1, 2–3, or ≥4 affected FDRs.

		START AGE	INTERVAL UNDER AGE 55	INTERVAL FROM AGE 55	END AGE
FAMILY HISTORY	**1 affected FDR**	40	5	7	70
	2–3 affected FDRs	35	3	5	75
	≥4 affected FDRs	30	2	2	75

FDR = first-degree relative.