Original Article

How Much Colonoscopy Screening Should Be Recommended to Individuals With Various Degrees of Family History of Colorectal Cancer?

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BACKGROUND: Individuals with a family history of colorectal cancer (CRC) are at increased risk for CRC. Current screening recommendations for these individuals are based on expert opinion. The authors investigated optimal screening strategies for individuals with various degrees of family history of CRC based on a cost-effectiveness analysis. **METHODS:** The MISCAN-Colon microsimulation model was used to estimate costs and effects of CRC screening strategies, varying by the age at which screening was started and stopped and by screening interval. The authors defined 4 risk groups, characterized by the number of affected first-degree relatives and their age at CRC diagnosis. For all risk groups, the optimal screening strategy had an incremental cost-effectiveness ratio of approximately $50,000 per life-year gained. **RESULTS:** The optimal screening strategy for individuals with 1 first-degree relative diagnosed after age 50 years was 6 colonoscopies every 5 years starting at age 50 years, compared with 4 colonoscopies every 7 years starting at age 50 years for average risk individuals. The optimal strategy had 10 colonoscopies every 4 years for individuals with 1 first-degree relative diagnosed before age 50 years, 13 colonoscopies every 3 years for individuals with 2 or more first-degree relatives diagnosed after age 50 years, and 15 colonoscopies every 3 years for individuals with 2 or more first-degree relatives of whom at least 1 was diagnosed before age 50 years. **CONCLUSIONS:** The optimal screening strategy varies considerably with the number of affected first-degree relatives and their age of diagnosis. Shorter screening intervals than the currently recommended 5 years may be appropriate for the highest risk individuals. ***Cancer*** **2011;117:4166–74.** © *2011 American Cancer Society.*

KEYWORDS: early detection of cancer, colonoscopy, colorectal neoplasm, familial risk, cost-effectiveness analysis.

Individuals with a family history of sporadic colorectal cancer (CRC) are at increased risk for the disease.[1-3] Approximately 11% of the population aged 30 to 70 years has at least 1 first-degree relative diagnosed with CRC.[4,5] Of all CRC cases, 2% to 5% occur in individuals with known genetic disorders such as familial adenomatous polyposis (FAP) and hereditary nonpolyposis colorectal cancer (HNPCC).[6] Without treatment, the lifetime CRC risk is >95% in individuals with FAP, and 50% to 80% in individuals with HNPCC.[6] Our focus, however, is on individuals with at least 1 affected first-degree relative and no known genetic disorders, accounting for another 25% of all CRC cases. These individuals have approximately a 2-fold increased risk compared with the average risk population. The individual risk level increases with an increasing number of affected first-degree relatives and a younger age of diagnosis of the affected relatives.[2] We consider 4 risk groups of individuals with a CRC family history (excluding known genetic disorders), with a varying relative risk (RR): (1) 1.6 for individuals with 1 first-degree relative diagnosed after age 50 years, (2) 2.6 for individuals with 1 first-degree relative diagnosed before age 50 years, (3) 3.5 for individuals with 2 first-degree relatives both diagnosed after age 50 years, and (4) 5.6 for individuals with 2 first-degree relatives with at least 1 diagnosed before age 50 years.

Colonoscopy with removal of adenomas, the noninvasive precursor of CRC, decreases CRC incidence in both average risk individuals and in subjects with hereditary CRC syndromes.[7,8] Although it is generally advised that individuals with a family history of CRC have more intensive screening than the average risk individuals, the optimal strategy remains unclear. Expert opinion-based recommendations include a start of colonoscopy screening 10 years earlier in individuals

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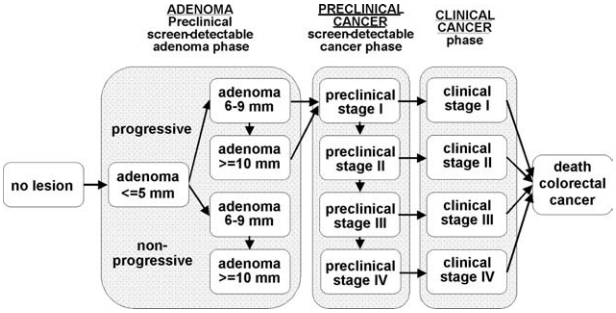

Figure 1. Adenoma and cancer stages in the MISCAN-Colon model are shown. Cancer stages correspond to the American Joint Committee on Cancer/International Union Against Cancer staging system for colorectal cancer. Adenomas are categorized by size.

with a family history than in the average risk population, or 10 years before the youngest age of diagnosis of the affected relatives.[9-11] Another recommendation is to use a 5-year interval for individuals with 1 first-degree relative diagnosed before age 60 years or 2 or more first-degree relatives diagnosed at any age, instead of the 10-year interval for the average risk population.[12-14] The differentiation in current guidelines for the 4 risk groups defined above is minor, whereas the risk levels increase considerably, suggesting that more differentiation is needed.

We will identify the optimal screening strategies per risk group based on a cost-effectiveness analysis. We hereto used the MISCAN-Colon simulation model and the results from a recent meta-analysis.[2]

MATERIALS AND METHODS

MISCAN-Colon

The MISCAN-Colon microsimulation model was developed at the Department of Public Health at ErasmusMC, the Netherlands, in collaboration with the US National Cancer Institute to assess the effect of different interventions on the occurrence of CRC in a population. A detailed description of the model and the data sources that informed the quantification of the model can be found in previous publications[15,16] and also in a standardized model profiler.[17] In brief, the model simulates individuals from birth to death, first without screening and subsequently with the changes that would occur under the implementation of a screening program. In every individual, adenomas can arise, and some of them will develop into cancer. A schematic representation of the natural history as used in the model is given in Figure 1. Adenomas are initially small (1-5 mm) and progress to medium (6-9 mm) and large (10+ mm) adenomas. The majority of adenomas are assumed to be nonprogressive and will never develop into cancer. The progressive adenomas have the ability to become cancer, but not all of them will make it to cancer in an individual's lifetime. The adenomas that do become malignant transform into stage I cancers and will progress into stages II, III, and IV, unless diagnosed earlier. The survival after clinical diagnosis depends on age and the cancer stage at diagnosis. Screening can result in a gain in life-years when cancers are detected and treated at earlier stages or when adenomas are detected and consequently removed before they become cancer.

The validity of the model has been tested on the results of large (randomized) screening and surveillance studies. In particular, we were able to simulate the same number of screen-detected and interval cancers as observed in the Minnesota Colon Cancer Control Study, the Funen trial and the Nottingham trial,[18] the CoCap sigmoidoscopy study,[19] and the National Polyp Study.[20] The model was able to explain observed incidence and mortality trends in the United States when accounting for risk factor trends, screening practice, and chemotherapy treatment.[21]

For the average risk population of this analysis, disease parameters were adjusted to reproduce adenoma prevalence data from autopsy studies[22-31] and Surveillance, Epidemiology, and End Results (SEER) incidence data from 1975 to 1979,[32] when they were not yet influenced by screening. Survival after CRC diagnosis by stage was based on SEER 1996 to 1999 data.[32]

Population and Risk Levels

We modeled a cohort of 30-year-olds in the United States in 2005. We categorized the individuals with a family history into 4 risk groups, depending on the number of first-degree relatives or age at diagnosis. The RR estimates per group were based on a recent meta-analysis.[2] The groups consisted of (1) individuals with 1 first-degree relative diagnosed after age 50 years, with a RR of 1.6; (2) 1 first-degree relative diagnosed at or before age 50 years (RR, 2.6); (3) 2 or more first-degree relatives diagnosed after age 50 years (RR, 3.5); and (4) 2 or more first-degree relatives with at least 1 of them diagnosed at or before age 50 years (RR, 5.6). These 4 groups are shortly referred to as "1 first-degree relative >50 years," "1 first-degree relative $\leq$50 years," "2+ first-degree relatives >50 years," and "2+ first-degree relatives $\leq$50 years." Individuals with a family history were simulated by adjusting the RR for CRC compared with the average risk population. We

Table 1. Assumptions for Costs (2007 Dollars) and Complications Associated With Colonoscopy and Colorectal Cancer Treatment[43]

Polypectomy	Colonoscopy Costs
Without	$662
With	$846

Colonoscopy Complications[a] (With and Without Polypectomy)	Rate per 1000 Colonoscopies	Costs
Perforations	0.7	$12,446
Serosal burn	0.3	$5,208
Bleed with transfusion	0.4	$5,208
Bleed without transfusion	1.0	$320

Stage at Diagnosis	Treatment Costs per Phase of Care[b]			
	Initial	Continuous (Per Year)	Terminal Care (Death From CRC)	Terminal Care (Death From Other Cause)
Stage I	$28,668	$2,395	$51,935	$12,703
Stage II	$39,700	$2,237	$51,712	$11,035
Stage III	$48,951	$3,249	$54,776	$14,708
Stage IV	$64,801	$10,419	$73,522	$39,679

CRC indicates colorectal cancer.

[a] Once in every 10,000 colonoscopies with polypectomy the complication is assumed to be fatal.

[b] Costs for cancer care were divided into 3 clinically relevant phases of care—initial, continuing, and terminal care. The initial phase was defined as the first 12 months after diagnosis, the terminal phase was defined as the final 12 months of life, and the continuing phase was defined as all months between the initial and terminal phases. For patients surviving <24 months, the final 12 months were allocated to the terminal phase. The remaining months of observation were allocated to the initial phase.

modeled the increased risk for CRC by multiplying the age-specific adenoma onset rate for both progressive and nonprogressive adenomas by the same RR for all ages.

Screening Strategies

For every risk group we simulated colonoscopy screening strategies, which differed with respect to:

- The age at which screening was started, which varied between 30 and 60 years;
- The screening interval that varied between 2 and 10 years;
- The age at which screening was stopped, which was never after the age of 90 years; and
- The number of colonoscopies followed from the previous 3 parameters, which had to be at least 2.

Individuals with adenomas were referred to surveillance following the guidelines of the US Multi-Society Task Force on Colorectal Cancer.[33] If the screening interval was shorter than the recommended surveillance interval, the latter was shortened to the screening interval.

Per polyp sensitivity was assumed to be the same for screening and surveillance colonoscopy: 80% for small adenomas, 85% for medium adenomas, and 95% for large adenomas and cancers.[34-36] We assumed complications like perforations and bleedings to occur at a rate of 2.4 per 1000 colonoscopies.[37-40] Colonoscopy with polypectomy resulted in mortality once in every 10,000 colonoscopies.[41] We assumed a 100% compliance for both screening and surveillance colonoscopies. In this way, our analyses focus on optimal strategies for individuals who comply with the guidelines.

Costs

Costs included costs for colonoscopy, complications of colonoscopy, and treatment of CRC (Table 1). The costs of colonoscopy screening and surveillance were assumed to be equal, but to depend on whether polypectomy was

performed. The costs associated with colonoscopy were based on 2007 Medicare average payments.[42] Costs for complications of colonoscopy were based on the relevant diagnosis-related group codes.[42] Treatment costs were derived from a comparison of costs for CRC cases relative to matched controls in the SEER-Medicare files.[43] All costs were updated to 2007 dollars using the medical care component of the Consumer Price Index. The final cost inputs used in the model are summarized in Table 1.

Analysis

We used the MISCAN-Colon model to estimate costs and number of life-years gained compared with the situation without screening for all screening strategies. For each risk group, we identified the efficient screening strategies, that is, strategies that did not have an alternative or combination of alternatives that would result in more life-years at the same or less costs. This resulted in a set of efficient strategies for each risk group. For every efficient strategy, we determined the incremental cost-effectiveness ratio (ICER), which is calculated as the incremental costs per incremental life-year gained compared with the next less cost-efficient strategy. For all risk groups, the optimal strategy was considered the strategy with an ICER value closest to a threshold of $50,000 per life-year gained.[44] Costs and life-years gained were discounted at 3% per year.

Sensitivity Analysis

There is uncertainty on the dwell time of adenomas. Recent data from a randomized controlled sigmoidoscopy study have indicated a probably longer dwell time than the 20 years we assumed, at least for distal lesions.[45] Therefore, we repeated the analysis with an increased mean dwell time of 30 years for the average population. The adenoma incidence by age was concurrently adjusted to keep the CRC incidence unchanged. To account for the influence of screening and CRC treatment on quality of life, we used quality-adjusted life-years as a sensitivity analysis. We assumed 1 day loss per colonoscopy, and a loss of 0.26, 0.3, 0.4, or 0.75 per year in stage I, II, III, or IV initial care, a 0.15 loss per year in continuous care, a 0.75 loss per year in terminal care before dying of CRC, and a 0.35 loss per year in terminal care in the case of dying of another cause.[46,47] We assessed the influence of discounting by repeating the analysis with a discount percentage of 0% and 5%.

For the highest risk group, we performed a sensitivity analysis on the way the disease develops by modeling the increased risk with a shorter adenoma dwell time of 10 instead of 20 years.

We decided not to perform a probabilistic sensitivity analysis after having weighed the computational effort required against the limited added value because of the lack of data on the probability distributions of most of the parameter values.

RESULTS

The efficient strategies per risk group are shown in Figure 2. The higher the risk among those screened, the more life-years were gained at the same costs. Because of the greater health gain in higher risk groups, more intensive strategies, with shorter screening intervals and wider age ranges, met the criteria of an ICER close to $50,000 per life-year gained (Table 2). For individuals with 1 first-degree relative >50 years, the optimal strategy had an interval of 5 years. The optimal age to start screening in this group was 50 years, and the optimal age to stop screening was 75 years. For individuals with 1 first-degree relative ≤50 years, the optimal screening interval was 4 years, and the optimal ages to start and stop screening were 45 and 81 years. The optimal screening interval for individuals with 2+ first-degree relatives >50 years was 3 years, with the same age range (45-81 years). For individuals with 2+ first-degree relatives ≤50 years, the optimal screening interval was also 3 years, with a further widened age range of 42 to 84 years. The mortality reduction that resulted from the optimal strategies varied between 72% and 84%, and increased with risk level. The number needed to scope to prevent 1 death decreased from 220 for individuals with 1 first-degree relative >50 years to 130 for individuals with 2+ first-degree relatives ≤50 years.

For the average risk population, the optimal screening strategy had an interval of 7 years, starting at age 50 years and stopping at age 71 years (4 colonoscopies). Therefore, according to our model, if one has the resources to screen the general population 4×, it would be more cost-effective to screen those aged from 50 to 71 years every 7 years than to screen, for example, those aged from 50 to 80 years every 10 years. Only if one has no more resources than needed to provide 2 colonoscopies in a lifetime would one screen every 10 years.

Sensitivity Analysis

With an adenoma dwell time of 30 instead of 20 years, the strategy with 3 instead of 4 colonoscopies every 7 years

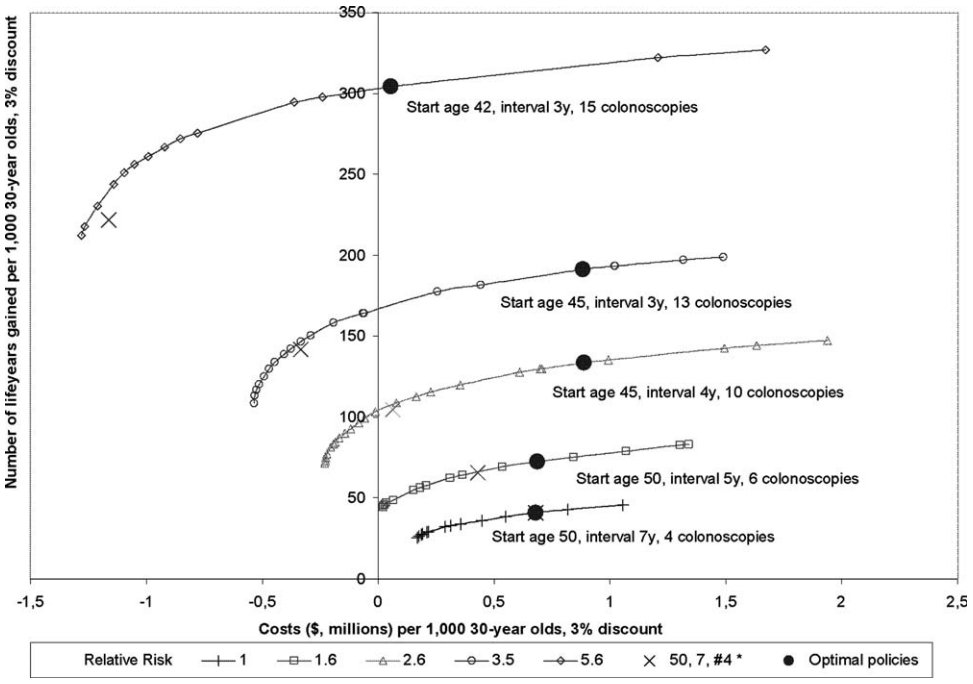

Figure 2. Discounted costs (millions of dollars) and life-years gained per 1000 30-year-olds of the efficient strategies are shown, with relative risk levels corresponding to the category of family history.

starting at age 50 years had an ICER closest to $50,000 per life-year gained for the average risk population, because of an increased ICER value of both strategies. Adjusting for quality of life resulted in more quality-adjusted life-years than nonadjusted life-years because of the prevention of CRC by colonoscopy screening and a consequently lower number of life-years in treatment. The incremental effectiveness conversely decreased with an increasing number of colonoscopies because of the 1-day loss per colonoscopy. At a threshold of $50,000 per quality-adjusted life-year, the optimal strategy for individuals with 1 first-degree relative >50 years changed to screening every 4 instead of every 5 years between the ages of 50 and 74 years. The strategies for the higher risk groups remained the same. Discounting had a more substantial impact on the effects of screening and savings from treatment than on colonoscopy costs, because the latter occur earlier in time. As a consequence, not discounting was favorable for screening, with shorter intervals and more colonoscopies as a result (Table 3). With a 5% discount, in contrast, we found longer screening intervals and fewer colonoscopies. With a shorter adenoma dwell time for individuals in the highest risk group, the optimal screening interval was 2 instead of 3 years, with screening ages between 44 and 88 years.

DISCUSSION

The optimal colonoscopy screening strategy for individuals with a CRC family history had a screening interval of 3 to 5 years, depending on the number of affected relatives and their age at diagnosis. The age ranges of the optimal strategies varied from 50-75 to 42-84.

Sometimes higher thresholds than $50,000 per life-year gained are considered acceptable,[44] allowing more frequent colonoscopy screening. Increasing the threshold up to $75,000 resulted in screening intervals of 2 to 4 years and age ranges that varied from 46-78 to 43-89 (results not shown). Further increasing the threshold to $100,000 did not shorten the intervals further, but only resulted in 1 or 2 additional colonoscopies in the 2 highest risk groups.

Screening becomes somewhat less cost-effective in individuals without affected relatives, because they have a lower risk than the total population (RR, 0.9). To adjust to the threshold ICER used, theoretically screening intensity needs to be decreased slightly.

There are several US guidelines for CRC screening in individuals with a family history.[11,12,14] In some guidelines, screening starts at age 40 years if someone has at least 1 affected first-degree relative. In the case of 1 first-degree relative diagnosed after age 60 years, the recommended

Table 2. Optimal Screening Strategies at Various Relative Risk Levels Associated With a Family History of Colorectal Cancer, and Their Associated Costs (in Dollars) and Life-Years Gained per 1000 30-Year-Olds

Category of Family History	Relative Risk	Optimal Strategy			Compared to No Screening, per 1,000 30-Year-Olds				Compared to Next Less Expensive Efficient Strategy
		No. of Screens	Screening Interval, y	Age Range, y	Mortality Reduction, %	No. Needed to Scope to Prevent 1 Death	Total Costs	No. of Life-Years Gained	ICER
1 FDR diagnosed after age 50 years	1.6	6	5	50-75	72	220	$690,000	72	$48,000
1 FDR diagnosed before age 50 years	2.6	10	4	45-81	79	190	$890,000	134	$50,000
2 or more FDRs diagnosed after age 50 years	3.5	13	3	45-81	84	180	$880,000	191	$47,000
2 or more FDRs, at least 1 diagnosed before age 50 years	5.6	15	3	42-84	84	130	$50,000	304	$46,000

ICER indicates incremental cost-effectiveness ratio; FDR, first-degree relative.
Discount of costs and effects is 3% yearly.

Table 3. Optimal Strategies per Relative Risk Level for the Sensitivity Analysis on Discounting, 0% and 5%[2]

Category of Family History	Relative Risk	Optimal Strategy, 0% Discount			Optimal Strategy, 5% Discount		
		No. of Screens	Screening Interval, y	Age Range, y	No. of Screens	Screening Interval, y	Age Range, y
1 FDR diagnosed after age 50 years	1.6	9	4	45-77	6	6	49-79
1 FDR diagnosed before age 50 years	2.6	14	3	42-81	10	4	47-83
2 or more FDRs diagnosed after age 50 years	3.5	15	3	41-83	11	4	44-84
2 or more FDRs, at least 1 diagnosed before age 50 years	5.6	23	2	41-85	15	3	43-85

FDR indicates first-degree relative.

screening interval is 10 years, as in the general population. For individuals with 1 first-degree relative diagnosed before age 60 years and for individuals with 2 or more first-degree relatives, 5-yearly colonoscopy is recommended. Others have suggested, based on prospective observational studies, that screening should start at age 45 to 50 years, and that colonoscopy every 5 years would be sufficient.[48,49] Controlled studies to analyze the effect of these strategies on incidence or mortality are not available. Our results are in line with a recommended starting age of 45 years, but with shorter intervals. However, note that the shorter intervals for individuals with 1 first-degree relative $\leq$50 years or 2+ first-degree relatives were approximately half the interval for the average risk population (3-4 vs 7 years according to our results), which corresponds with the 50% difference in interval as recommended in the guidelines (5 vs 10 years). The 10-yearly recommendation for the average risk population was based on expert opinion, and chosen for simplicity. This strategy was suboptimal in our analysis, because it was as effective as 3 colonoscopies every 7 years starting at age 54 years, but more expensive ($0.50 instead of $0.45 million). This strategy with a 7-year interval had an ICER of $43.000 per life-year gained, which is close to the threshold of $50,000 per life-year gained.

Lengthening the model assumption of the average dwell time for an adenoma to become cancer from 20 to 30 years did not lengthen our optimal screening interval for the average risk population. However, as expected, the incremental cost-effectiveness of 4 colonoscopies relative to 3 colonoscopies became worse because of the lower incremental effectiveness of the last colonoscopy. By lengthening the dwell time further, the ICER of 3 colonoscopies every 7 years would eventually increase to >$50,000 per life-year gained as well, and longer intervals would become optimal in combination with fewer screening rounds. Besides a longer adenoma dwell time, higher colonoscopy costs relative to the treatment costs would also challenge our conclusion that shorter screening intervals may be appropriate than currently recommended. However, this is unlikely in view of the increasing costs of chemotherapy drugs involved in CRC treatment. We looked at the influence of trends in survival and treatment costs in an earlier analysis, where more recent survival data, taking the effects of greater use of adjuvant treatment into account, had a minimal effect on the number of life-years gained.[50] This will therefore have a small impact on our results. Another important assumption is that increased cancer risk is caused by an equally increased adenoma incidence across all ages. We assessed this assumption in an earlier analysis based on several colonoscopy studies.[51] Alternatively, a faster progressive development of adenomas could cause higher risk in these individuals. We found a shorter interval of 2 instead of 3 years for the highest risk group when we assumed the increased risk to be caused by a combination of a higher adenoma incidence and faster progression of the adenomas. Therefore, this would suggest even more diversification in screening intensity between risk groups.

A limitation of this study is that we did not account for the number of first-degree relatives an individual has, which affects the risk for CRC. For example, an individual with 2 first-degree relatives both diagnosed with CRC is at higher risk than someone with 10 first-degree relatives, 2 of whom are diagnosed with CRC. Also family history, and thus the estimated risk of an individual, changes over time, because relatives are or are not being diagnosed with CRC. Ideally, the screening strategy is adjusted accordingly.

Our results show that individualizing screening guidelines based on family history could improve the effectiveness substantially. Individualized guidelines are more complex than the current guidelines and could confuse both physicians and screenees, resulting in lower adherence rates. Individuals could also hesitate to adhere to more frequent invasive colonoscopies, especially if their insurance company does not cover earlier or more frequent colonoscopies. Adherence generally does not influence the cost-effectiveness of screening, because it influences both costs and effects, and was therefore assumed to be 100% in our analysis. However, lower adherence rates would obviously decrease the effectiveness of screening. Conversely, individualized guidelines could also increase the adherence because of a better awareness of the individuals risk for CRC. Besides, it fits with the trend toward more personalized medical care, and individuals might appreciate that the recommendation is based on their personal risk profile. Implementation studies should look into these issues.

Risk for CRC also depends on lifestyle. Recently, a risk prediction tool has become available that estimates an individual's CRC risk based on a self-administered questionnaire.[52,53] Both family history and lifestyle factors are included. Results of cost-effectiveness analyses, such as those presented in this article, can be used to translate the risk estimates resulting from this prediction model to screening recommendations.

In conclusion, the optimal colonoscopy screening strategy varies considerably with the number of affected relatives and their age of diagnosis. For the higher risk individuals, shorter intervals than the currently recommended 5 years may be appropriate.

CONFLICT OF INTEREST DISCLOSURES

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