Clinical Gastroenterology and Hepatology 2023;■:■–■

Risk-Stratified Screening for Colorectal Cancer Using Genetic and Environmental Risk Factors: A Cost-Effectiveness Analysis Based on Real-World Data

Rosita van den Puttelaar,[1] Reinier G. S. Meester,[1] Elisabeth F. P. Peterse,[1,2] Ann G. Zauber,[3] Jiayin Zheng,[2] Richard B. Hayes,[4] Yu-Ru Su,[2,5] Jeffrey K. Lee,[6,7] Minta Thomas,[2] Lori C. Sakoda,[2,6] Yi Li,[2] Douglas A. Corley,[6,7] Ulrike Peters,[2] Li Hsu,[2] and Iris Lansdorp-Vogelaar[1]

[1]Department of Public Health, Erasmus University Medical Center, Rotterdam, The Netherlands; [2]Public Health Sciences Division, Fred Hutchinson Cancer Research Center, Seattle, Washington; [3]Department of Epidemiology and Biostatistics, Memorial Sloan Kettering Cancer Center, New York, New York; [4]Division of Epidemiology, Department of Population Health, New York University School of Medicine, New York, New York; [5]Biostatistics Unit, Kaiser Permanente Washington Health Research Institute, Seattle, Washington; [6]Division of Research, Kaiser Permanente Northern California, Oakland, California; and [7]Department of Gastroenterology, Kaiser Permanente San Francisco, San Francisco, California

BACKGROUND & AIMS: **Previous studies on the cost-effectiveness of personalized colorectal cancer (CRC) screening were based on hypothetical performance of CRC risk prediction and did not consider the association with competing causes of death. In this study, we estimated the cost-effectiveness of risk-stratified screening using real-world data for CRC risk and competing causes of death.**

METHODS: **Risk predictions for CRC and competing causes of death from a large community-based cohort were used to stratify individuals into risk groups. A microsimulation model was used to optimize colonoscopy screening for each risk group by varying the start age (40–60 years), end age (70–85 years), and screening interval (5–15 years). The outcomes included personalized screening ages and intervals and cost-effectiveness compared with uniform colonoscopy screening (ages 45–75, every 10 years). Key assumptions were varied in sensitivity analyses.**

RESULTS: **Risk-stratified screening resulted in substantially different screening recommendations, ranging from a one-time colonoscopy at age 60 for low-risk individuals to a colonoscopy every 5 years from ages 40 to 85 for high-risk individuals. Nevertheless, on a population level, risk-stratified screening would increase net quality-adjusted life years gained (QALYG) by only 0.7% at equal costs to uniform screening or reduce average costs by 1.2% for equal QALYG. The benefit of risk-stratified screening improved when it was assumed to increase participation or costs less per genetic test.**

CONCLUSIONS: **Personalized screening for CRC, accounting for competing causes of death risk, could result in highly tailored individual screening programs. However, average improvements across the population in QALYG and cost-effectiveness compared with uniform screening are small.**

Keywords: Colorectal Cancer; Screening; Cost-Effectiveness; Genetic Risk; Environmental Risk.

Colorectal cancer (CRC) is the second leading cause of cancer deaths in the United States.[1] Screening can prevent 10%–68% of all CRC deaths,[2] depending on screening adherence and tests used. However, the extent to which screened individuals benefit from screening is highly variable, and some may be unnecessarily exposed to its burden and potential harms. If individuals who may benefit from screening could be more accurately identified, the intensity of screening could be increased in those at high risk, and the intensity could be reduced for those at lower risk, while maintaining comparable

Abbreviations used in this paper: **AUC, area under the receiver operating curve; CRC, colorectal cancer; E-score, environmental risk score; FIT, fecal immunochemical test; GERA, Genetic Epidemiology Research on Adult Health and Aging; ICER, incremental cost-effectiveness ratio; MISCAN-Colon, Microsimulation Screening Analysis-Colon; PRS, polygenic risk score; QALYG, quality-adjusted life years gained; WTP, willingness to pay.**

1542-3565
https://doi.org/10.1016/j.cgh.2023.03.003

benefits to uniform, non-personalized screening practices. Thus, personalized screening has the potential to improve patient-level experiences for the frequency of invasive procedures, optimize individual-level net benefit vs. harm, while simultaneously favorably influencing the net burden and costs of CRC screening.[3]

A prior CRC prediction model based on genetic and non-genetic risk factors estimated that the recommended start age of screening could differ by 12–14 years for individuals with the lowest vs. highest 10% of risk.[4] A prior simulation study suggested that personalized screening could potentially be cost-effective, depending on the discriminatory accuracy of prediction models.[5] However, the study was based on hypothetical performance of CRC risk prediction and did not account for the association between risk factors for CRC and competing causes of death.

In this study, we investigated the potential lifetime influence of uniform screening vs. personalized CRC screening on the basis of real-world data from Kaiser Permanente Northern California, while also accounting for how risk factors may influence competing causes of death.

What You Need to Know

Background

Personalized screening has the potential to improve screening experiences. However, the cost-effectiveness of risk-stratified screening based on real-world data has not been shown yet.

Findings

In this study, we investigated the potential lifetime influence of risk-stratified CRC screening based on real-world data. We showed that personalized screening plans changed for two-thirds of the population, giving individuals a more appropriate strategy that fits their risk level. Despite this, the population-level benefit was small.

Implications for patient care

Patient-level experiences for the frequency of invasive screening could be improved by increasing the intensity for individuals at high risk and reducing the intensity for those at low risk, while maintaining comparable benefits to uniform screening.

Methods

We first clustered individuals in predicted risk groups for CRC and competing causes of death. For each risk group, the Microsimulation Screening Analysis-Colon (MISCAN-Colon) model was used to simulate the lifetime benefits, harms, and costs of different screening strategies. Finally, cost-effectiveness analysis was used to determine optimal risk-stratified screening strategies and compare their costs and benefits with uniform screening.

Predicted Risk Distribution Based on Community-based Data

Risk predictions were based on the Genetic and Evolutionary Computation Conference's CRC risk prediction model, using an environmental risk score (E-score) based on common risk factors and polygenic risk score (PRS).[4] The Cox proportional hazard model was used to estimate hazard ratios of E-score and PRS for CRC and competing causes of death within the independent Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort from the community-based setting of Kaiser Permanente. The area under the receiver operating curve (AUC) in the GERA cohort was 65% for CRC and 64% for competing causes of death. A more detailed description of the data and distribution of the risk scores can be found in Supplementary File 1.

MISCAN-Colon Model

MISCAN-Colon is a microsimulation model that simulates a population that is similar to the U.S. population in terms of life expectancy and CRC risk from birth until death. It also simulates the development of CRC and the impact of screening within that population. The model structure and underlying assumptions can be found in more detail in other publications.[6,7]

Simulated Population

In MISCAN-Colon, each individual has an underlying "true" risk to develop CRC. This underlying risk distribution was previously calibrated on epidemiologic data on adenoma prevalence and multiplicity and cancer incidence. For risk-stratified screening, each individual in the model is assigned a predicted risk score based on their underlying risk and the AUC of the risk prediction model. Predicted and underlying risk will generally not be the same in an individual because of the imperfect prediction of the risk prediction model (Figure 1). Thus, high-risk individuals may be assigned a low risk score and vice versa. On average, however, the risk in a group of individuals with the same risk score will match the predicted risk for that group (see Supplementary File 2 for a more detailed description). Of note, the AUC averages prediction across the entire population, whereas we believe the risk prediction method is most clinically useful for modifying screening recommendations for approximately one-fifth of the population, those in the highest and lowest deciles.

Risk for competing causes of death was reflected in the life tables of MISCAN-Colon, which specifies the cumulative probability of death by age.

On the basis of the distribution of predicted risks in the GERA cohort, the simulated population was stratified into

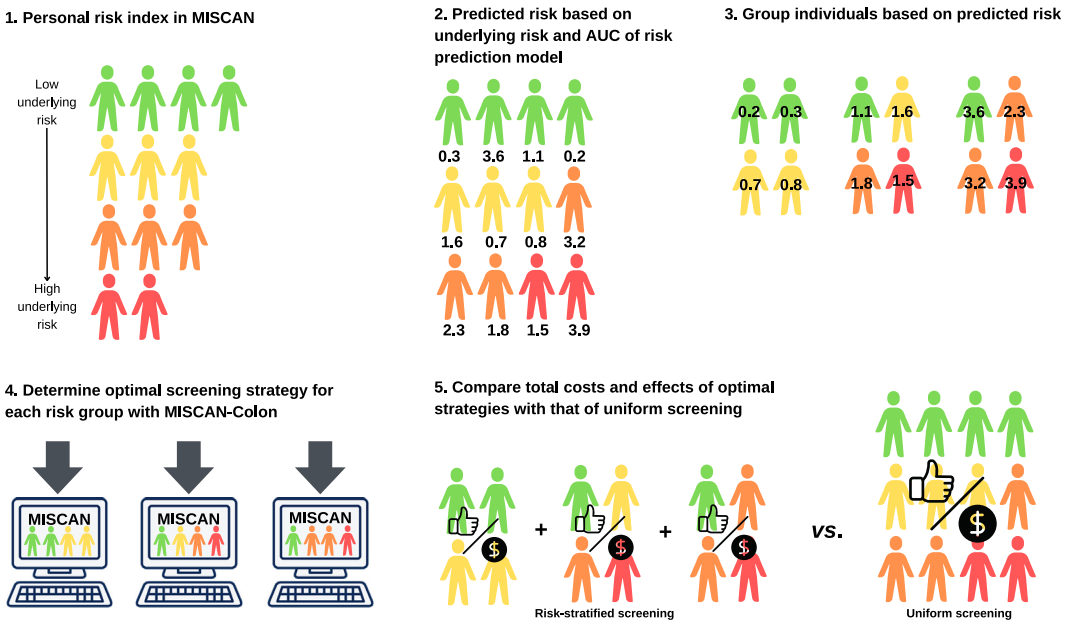

Figure 1. Overview of determining the cost-effectiveness of risk-stratified screening vs. uniform screening.

40 relative risk groups for CRC (ranging from 0.1 to >4.0 with increments of 0.1) and 20 for competing causes of death (ranging from 0.2 to >4.0 with increments of 0.2), resulting in 800 different cohorts. Relative risk was defined compared with the average population.

Screening Strategies

In risk-stratified screening, all individuals were assumed to undergo a baseline genetic screening. We simulated scenarios with and without colonoscopy screening, at selected start ages (40, 45, 50, 55, and 60 years), end ages (70, 75, 80, and 85 years), and screening intervals (5, 10, and 15 years). We also considered scenarios with a one-time colonoscopy at ages 50, 55, 60, 65, or 70 years. Similar scenarios for fecal immunochemical test (FIT) screening were considered, with screening intervals of 1, 2, and 3 years (Supplementary File 6). Risk-stratified screening was compared with a reference strategy of uniform screening, according to the U.S. Preventive Services Task Force recommendations.[8]

After detection and removal of adenomas, individuals were assumed to undergo colonoscopy surveillance based on current recommendations,[9] according to the shortest interval recommended.

Our analysis examined the benefits under full adherence to polygenic testing, screening, and surveillance. In sensitivity analysis we varied the adherence to screening. Test performance assumptions for each test can be found in Supplementary File 3.

Costs and Disutilities

In the base-case analysis, the cost for genetic testing was assumed to be $100 per individual.[10] Costs of screening, complications, and cancer treatment were computed from a healthcare-sector perspective (Supplementary File 3). For individuals aged 65 and older, costs from the Centers for Medicare and Medicaid Services were used, and for individuals younger than 65 commercial costs were used.[11] Costs were inflated to 2017 US dollars using the Personal Health Care Deflator Price Index. Cost assumptions were varied in sensitivity analysis.

We incorporated disutilities for undergoing a CRC screening test, for having a colonoscopy complication, and for having CRC, in line with previous analysis[12] (Supplementary File 3).

Analyses and Outcomes

For every 800 risk group combinations of predicted relative risk for CRC and competing causes of death, we calculated costs and effects of all screening strategies in the MISCAN-Colon model, applying a 3% annual discount rate.

The optimal strategy was derived for each of the 800 risk groups using incremental cost-effectiveness analysis. First, the efficient screening strategies were selected, that is, strategies (or combination strategies) that were less costly and more effective (ie, more quality-adjusted life years gained [QALYG]) than other strategies. Then for every efficient strategy, we determined the incremental cost-effectiveness ratio (ICER) compared with the next efficient strategy. Finally, the strategy with the highest QALYG and ICER below the assumed willingness-to-pay (WTP) threshold of $100,000 per QALYG was considered the optimal strategy.

Finally, the overall costs and effects of the uniform and risk-stratified screening were derived as the weighted average across the relative risk groups given

their smoothed respective sizes. Population weights were based on the community-based risk distribution in Kaiser Permanente. To enable a clean comparison of uniform vs risk-stratified screening, we also varied the WTP threshold to find acceptance thresholds for which the overall costs or QALYG of risk-stratified screening matched those of uniform screening. Primary outcomes were QALYG, number of colonoscopies, and costs per 1000 40-year-old individuals.

Sensitivity Analyses

In sensitivity analyses, we first varied costs for genetic testing by $0, $50, and $200 per test. Second, costs for CRC screening and treatment for individuals younger than 65 were set at the Centers for Medicare and Medicaid Services cost level. Furthermore, we repeated the analysis and did not take into account the impact of risk factors on competing causes of death.

Finally, when we evaluated participation, we compared uniform screening at the current 60% participation[13] with different participation scenarios for risk-based screening:

- 60% participation for all risk groups,
- 55%, 60%, and 65% for low-, medium-, and high-risk groups, respectively,
- 50%, 60%, and 70% for low-, medium-, and high-risk groups, respectively,
- 15% of high-risk and 41% of low-risk individuals would not follow their personal screening strategy and were screened according to the uniform strategy.[14]

In these scenarios, individuals with a relative risk of <0.5 were considered low risk, 0.5–2.0 were medium risk, and >2.0 were high risk. High- and low-risk cutoffs were based on risk of individuals with a family history[15] and its inverse.

In all sensitivity analyses, we kept the overall costs of risk-stratified screening equal to those of uniform screening.

Results

Optimal Risk-Stratified Screening Strategies

As expected, the simulated number of CRC cases and deaths varied with the predicted relative risk for CRC (Supplementary File 4). Consequently, the impact of screening was much larger in individuals with a high relative risk for CRC compared with those with a low risk. Therefore, optimal screening strategies ranged from a one-time colonoscopy at age 60 for the lowest risk groups to a colonoscopy every 5 years at ages 40–85 for the highest risk groups (Supplementary File 5). Of the 800 risk groups, 736 groups, which comprise 65.2% of the population, would have a different strategy recommended than the uniform screening strategy.

With these personalized screening plans, colonoscopy burden was reduced by 19%–71% for the lowest CRC risk groups, whereas the corresponding decrease in QALYG was modest (Figure 2). On the other hand, for high-risk individuals there is a more substantial increase in the number of QALYG compared with uniform screening. For individuals with a high relative risk for competing causes of death, colonoscopy burden was also decreased, resulting in a small increase in QALYG.

Population-Level Effect of Risk-Stratified Screening

Compared with no screening, uniform screening increased QALYG by 118, required 4076 colonoscopies, and cost $5.5 million. At a WTP level of $100,000, risk-stratified screening yielded 120 QALYG, required 4249 colonoscopies, and cost $5.7 million (Table 1, Figure 3).

When constraining the QALYG of risk-stratified screening to the uniform level (WTP threshold of $83,300/QALYG), risk-stratified screening required 3944 colonoscopies at a total cost of $5.5 million. This is a 1.2% cost decrease compared with uniform screening.

When constraining the overall costs of risk-stratified screening to the uniform level (WTP threshold of $88,100/QALYG), risk-stratified screening yielded 119 QALYG and required 4,029 colonoscopies. This is a 0.7% increase in QALYG compared with uniform screening.

Sensitivity Analysis

The results were sensitive to several assumptions. The impact of risk-stratified screening would be more substantial if it positively impacts participation for the highest risk groups (from 60% to 70%) or if costs for genetic testing go down to $50, with an increase in QALYG of 3.4% and 1.1%, respectively (Figure 4).

However, risk-stratified screening was no longer cost-effective if costs for genetic testing increase to $200, or if part of the population would not follow their personal screening strategy. The latter especially had a large impact on the cost-effectiveness, with a decrease of 1.7% in QALYG. Not considering the impact of risk factors on competing causes of death was still cost-effective, but the positive impact decreased substantially. The overall cost-effectiveness of risk-stratified screening was relatively insensitive to the source of assumed health-care costs.

Discussion

In this study, we show that personalized screening changed screening plans for 65.2% of the population, giving individuals a more appropriate screening strategy that fits their risk level. Despite this more risk-tailored screening, it would increase QALYG by only 0.7% on a

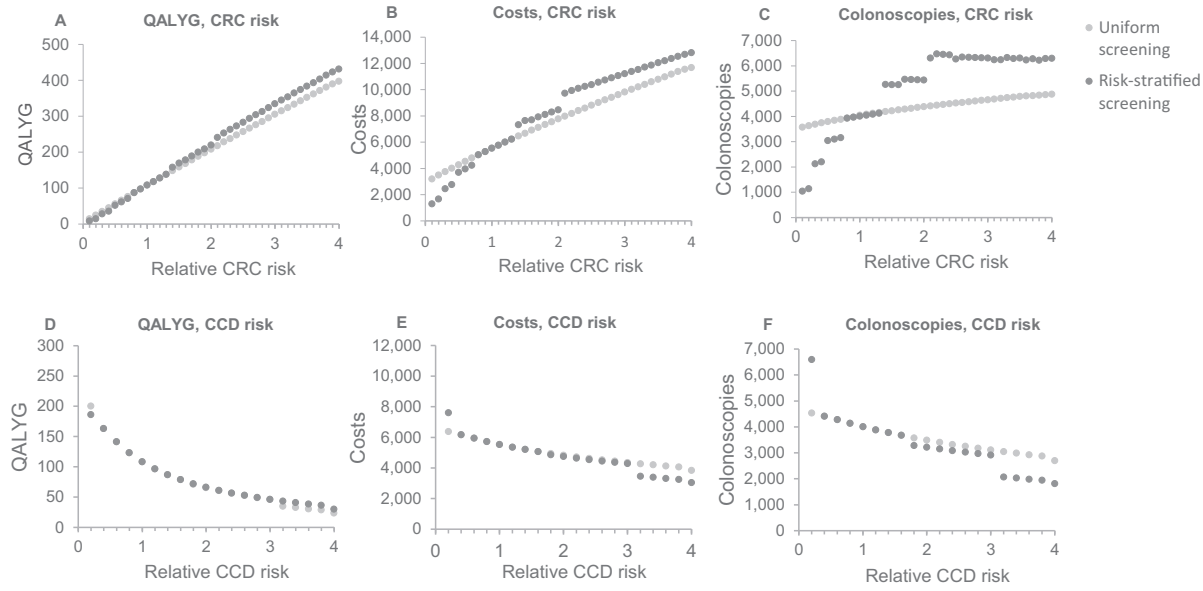

Figure 2. Costs ($, *1000), QALYG, and number of colonoscopies per 1000 individuals for uniform and risk-stratified screening for different relative risks for CRC (*A–C*) and competing causes of death (CCD) (*D–F*). For example, individuals with a relative risk of 2.0 for CRC were screened more often under risk-stratified screening compared with uniform screening (*C*). As a result, more cancers were prevented, and QALYG increased (*A*). However, costs also increased (*B*) as a result of increased screening costs. Willingness-to-pay threshold equals $90,100, at which the overall costs of risk-stratified screening are equal to those of uniform screening.

population level at equal costs to uniform screening or reduce costs by 1.2% for equal QALYG.

There are several factors influencing the limited population-level benefit of personalized screening. First, a better discriminatory accuracy for risk prediction models would likely translate into improved outcomes. Genome-wide modeling of PRS and newly identified CRC-associated single nucleotide polymorphisms will continue to improve prediction model performance[16] and thereby the expected benefit from risk-stratified screening.[5] Another factor is the additional cost of polygenic testing. We showed that if these costs could be lowered, for example by sharing them across other candidate diseases for risk-stratified screening (such as breast, prostate, or lung cancer), QALYG could be increased up to 1.6%. Sensitivity analyses also showed that the benefit of personalized screening increased if it positively impacts participation. Conversely, risk-stratified screening was not cost-effective if part of the population was not willing to follow their personal screening strategy.

One could argue on the basis of these results that the impact of risk-stratified screening may not yet be good enough on the population level for practical implementation. The impact of risk-stratified screening primarily impacts individuals in the highest and lowest deciles of risk. Because this is only a small proportion of the population, this results in a minimal detectable population-level effect. However, this effect is similar to the effects of tailoring screening to other subpopulations such as those with a strong family history alone, who are currently recommended by guidelines to have more intense screening with colonoscopy every 5 years.

Our findings are consistent with previous studies. A similar study to ours showed that with a cost of polygenic testing of $200 per test, risk-stratified screening could be cost-effective from an AUC value of 0.65 onward.[5] However, that study did not take the risk for competing causes of death into account and hence may have overestimated the net benefit of personalized screening. In another study with a lower AUC value of 0.6, personalized screening was on average cost-effective (based on World Health Organization criteria), but there was a large variability in life years saved.[17] A higher discriminatory accuracy was more likely to result in an increase of life years. In that study, risk-stratification remained highly cost-effective for a total cost for risk testing of $160 and $400 for a discriminatory accuracy of 0.6 and 0.9, respectively.

It is a critical next step for the field of precision medicine to evaluate the potential benefits using detailed modeling. An important strength of this study is that it uses risk prediction modeling including both genetic and lifestyle/environment information that has been externally estimated in a community-based cohort. Moreover, the impact of these risk factors on competing causes of death has been incorporated. However, this study also has some limitations. First, it is a complex analysis based on a relatively weak risk prediction tool, making risk stratification not highly impactful or economically attractive on a population level. Second, we assumed fixed risk scores by age and over lifetime, whereas some

Table 1. Lifetime Effects and Costs per 1000 40-Year-Old Individuals for No Screening, Uniform Screening, and Risk-Stratified Screening at a WTP Threshold of $100,000/QALYG, and Risk-Stratified Screening With Constrained QALYG and Costs at the Uniform Screening Level[a]

						Costs, USD ([a]1000)[b,c]		
Strategy	Colonoscopies	CRC cases	CRC deaths	Life years[b]	QALYG[b]	Estimating relative risk	CRC screening and treatment costs	Total
No screening	86[g]	86	35	23,274	0	0	4570	4570
Uniform screening[d]	4076	35	9	23,391	118	0	5534	5534
Risk-stratified screening								
- WTP $100,000	4249	34	9	23,414	120	100	5601	5701
- Constrained QALYG[a]	3944	35	9	23,412	119	100	5368	5468
- Constrained costs[a]	4029	35	9	23,413	118	100	5431	5531
Alternative costs of polygenic testing[e]								
- $0 per individual	4164	34	9	23,414	120	0	5534	5534
- $50 per individual	4099	35	9	23,413	119	50	5475	5528
- $200 per individual	3892	35	9	23,412	117	200	5330	5530
CMS costs[e,f]								
- Uniform screening	4076	35	9	23,391	118	0	4454	4454
- Risk-stratified screening	3971	35	9	23,413	119	100	4353	4453
Participation[e]								
- Uniform screening	2480	56	20	23,373	71	0	5148	5148
- 60%	2401	55	20	23,366	71	100	5049	5149
- 55%-60%-65%	2421	55	20	23,370	72	100	5047	5147
- 50%-60%-70%	2446	55	19	23,375	73	100	5048	5148
Excluding competing causes of death-risk[e]	3973	35	9	23,392	118	100	5428	5528
Willingness to follow personal strategy[e]	4199	32	8	21,307	116	100	5433	5533

NOTE. For all sensitivity analysis, we considered a WTP threshold at which the overall costs were equal to that of uniform screening.
[a]Willingness-to-pay threshold (WTP) equals $83,300 and $88,100 for constrained QALYG and costs, respectively.
[b](Quality-adjusted) life years (gained) and costs were discounted at an annual rate of 3%.
[c]Costs are in 2017 US dollars (USD).
[d]Uniform colonoscopy screening was defined as colonoscopy screening from ages 45 to 75 with a screening interval of 10 years.
[e]At a WTP at which overall costs are equal to that of uniform colonoscopy screening.
[f]Compared to uniform screening with CMS costs.
[g]Only colonoscopies for CRC diagnosis were considered.

literature suggests the effect of the genetic risk on CRC may be higher at younger ages.[18] Therefore, we may have overestimated or underestimated the benefit of risk-stratified screening in some age groups. Information on the long-term performance of risk prediction models is currently lacking. However, for lifetime risk predictions the age-dependent PRS makes little difference, because the risk for developing CRC is low in early ages and age is a major risk factor for cancer.[19] Furthermore, we assumed that the true underlying risk distribution in the population is equal to the risk distribution used in MISCAN-Colon, although the true risk distribution is unobservable. The assumed "true" risk distribution in the model was previously calibrated to clinical and epidemiologic data targets and is our best approximation of reality consistent with those targets. Finally, the hazard ratios were derived from a non-Hispanic white population, possibly limiting the generalizability to the whole population. Further data and research are needed to obtain risk prediction models applicable to racial and ethnic minorities.

Notwithstanding these limitations, our analyses may have important implications for clinical practice, because they result in very different screening recommendations for different risk groups. For some risk groups with a very low predicted risk for CRC and high risk for competing causes of death, no screening was even recommended. Estimated risks in these individuals were comparable with the risk of breast cancer in men. Nevertheless, some of these individuals may be wrongly classified as low risk and will develop CRC. Consequently, they are now worse off with risk-stratified screening. This is unfortunately inherent to population screening where there is always a tradeoff between benefits and harms. Therefore, it is important to validate risk-stratified CRC screening in

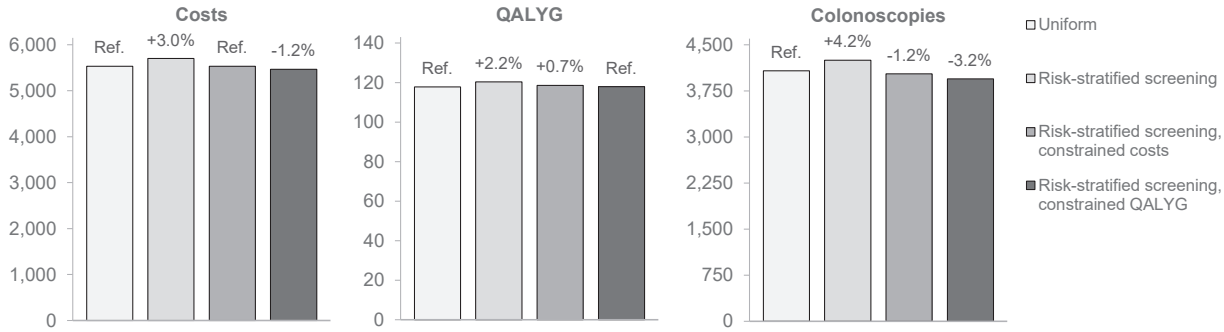

Figure 3. Costs (*1,000, $), QALYG, and colonoscopies for uniform vs risk-stratified screening per 1000 individuals. Three different thresholds were considered for risk-stratified screening: $100,000/QALYG and thresholds resulting in the overall QALYG or costs constrained at the uniform screening level ($83,300 and $88,100, respectively).

clinical studies and also to evaluate whether risk-stratified recommendations will be followed by the population.

In the base-case analysis, we focused on individuals willing to undergo genetic testing and adhere to subsequent screening recommendations. Previous studies have shown that approximately 75% of the population is interested in single nucleotide polymorphism testing for increased CRC risk.[20,21] Uptake of genetic testing will depend on the implementation and information provided to the public. Nevertheless, the cost-effectiveness of risk-stratified screening should not be affected by the actual uptake of genetic testing; individuals who are not genetically tested will simply be offered the uniform screening recommendations as in a situation with and without genetic testing.

However, our sensitivity analysis shows that it is essential for cost-effectiveness that individuals are willing to follow their personalized screening strategies after genetic testing. Knowledge of having an increased genetic risk is known to improve health behavior and screening participation.[22,23] It is less clear to what extent people accept different screening regimes based on genetic and lifestyle/environmental factors. Previous studies have shown that whereas 85% of women were willing to participate in more frequent screening, only 49%–59% were willing to undergo less frequent screening based on their genetic profile.[14,24] It is therefore important to counsel and inform individuals before and after genetic testing to avoid potential decrease in adherence.

On considering future implementation, thought should be given to more complex logistics of personalized screening recommendations. We distinguished 800 different risk groups, and risk prediction required detailed patient information. The actual number of different screening recommendations was substantially smaller than 800, namely 22. Nevertheless, this is still a substantial number of risk groups for tailored recommendations. Limiting the number of risk groups could decrease the complexity but also the potential benefit of risk-stratified screening.[5]

In conclusion, risk-stratified screening based on CRC risk and competing causes of death had a substantial effect on individual-level screening programs. However, the overall population-level estimated health benefits were modest. Further research is needed to improve the accuracy of risk prediction and to assess

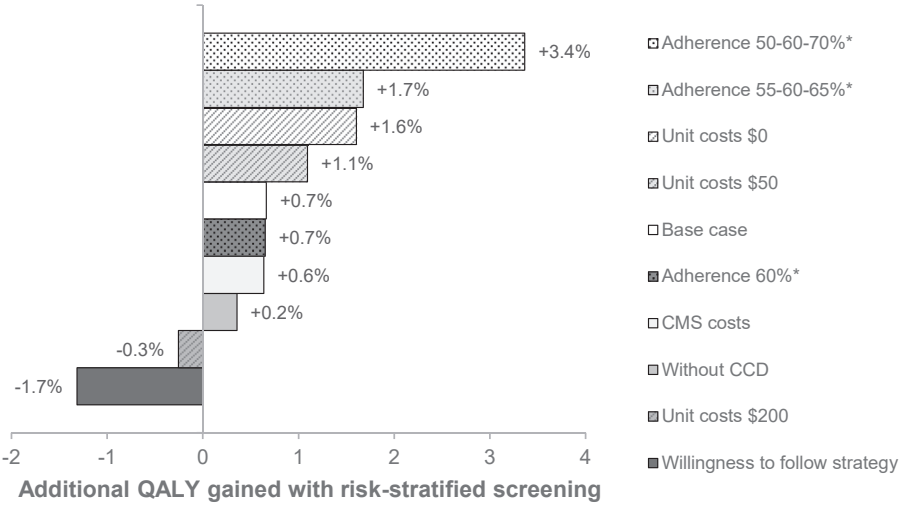

Figure 4. Additional QALY gained/lost when uniform screening is replaced by risk-stratified screening at a willingness-to-pay threshold that ensures that the costs of risk-stratified screening were equal to those of uniform screening. CMS, Centers for Medicare and Medicaid Services. *Compared uniform with screening with 60% participation. CCD, competing causes of death.

the willingness to follow risk-stratified screening recommendations.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at https://doi.org/10.1016/j.cgh.2023.03.003.

References

1. Siegel RL, Miller KD, Goding Sauer A, et al. Colorectal cancer statistics. CA Cancer J Clin 2020;70:145–164.
2. Lauby-Secretan B, Vilahur N, Bianchini F, et al. The IARC perspective on colorectal cancer screening. N Engl J Med 2018; 378:1734–1740.
3. Kuipers EJ, Spaander MC. Personalized screening for colorectal cancer. Nature Reviews Gastroenterology & Hepatology 2018; 15:391–392.
4. Jeon J, Du M, Schoen RE, et al. Determining risk of colorectal cancer and starting age of screening based on lifestyle, environmental, and genetic factors. Gastroenterology 2018; 154:2152–2164.
5. Naber SK, Kundu S, Kuntz KM, et al. Cost-effectiveness of risk-stratified colorectal cancer screening based on polygenic risk: current status and future potential. JNCI Cancer Spectrum 2020;4:pkz086.
6. van Hees F, Habbema JDF, Meester RG, et al. Should colorectal cancer screening be considered in elderly persons without previous screening? a cost-effectiveness analysis. Ann Intern Med 2014;160:750–759.
7. Loeve F, Boer R, Oortmarssen G, et al. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Computers and Biomedical Research 1999; 32:13–33.
8. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325:1965–1977.
9. Gupta S, Lieberman D, Anderson JD, et al. Recommendations for follow-up after colonoscopy and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastrointest Endosc 2020;91:463–485.
10. 23andMe. 2022 Available from: https://www.23andme.com/. Accessed July 28, 2022.
11. Ladabaum U, Mannalithara A, Brill JV, et al. Contrasting effectiveness and cost-effectiveness of colorectal cancer screening under commercial insurance vs Medicare. Am J Gastroenterol 2018;113:1836.
12. Peterse EFP, Meester RGS, de Jonge L, et al. Comparing the cost-effectiveness of innovative colorectal cancer screening tests. JNCI 2021;113:154–161.
13. Smith RA, Andrews K, Brooks D, et al. Cancer screening in the United States, 2016: a review of current American Cancer Society guidelines and current issues in cancer screening. CA Cancer J Clin 2016;66:95–114.
14. Meisel SF, Pashayan N, Rahman B, et al. Adjusting the frequency of mammography screening on the basis of genetic risk: attitudes among women in the UK. The Breast 2015;24:237–241.
15. Butterworth AS, Higgins JPT, Pharoah P. Relative and absolute risk of colorectal cancer for individuals with a family history: a meta-analysis. Eur J Cancer 2006;42:216–227.
16. Thomas M, Sakoda LC, Hoffmeister M, et al. Genome-wide modeling of polygenic risk score in colorectal cancer risk. Am J Hum Genet 2020;107:432–444.
17. Subramanian S, Bobashev G, Morris RJ, et al. Personalized medicine for prevention: can risk stratified screening decrease colorectal cancer mortality at an acceptable cost? Cancer Causes Control 2017;28:299–308.
18. Thomas M, Sakoda LC, Hoffmeister M, et al. Response to Li and Hopper. Am J Hum Genet 2021;108:527–529.
19. Schaid DJ, Sinnwell JP, Batzler A, et al. Polygenic risk for prostate cancer: decreasing relative risk with age but little impact on absolute risk. Am J Hum Genet 2022; 109:900–908.
20. Leventhal K-G, Tuong W, Peshkin BN, et al. "Is it really worth it to get tested?": primary care patients' impressions of predictive SNP testing for colon cancer. Journal of Genetic Counseling 2013;22:138–151.
21. Anderson AE, Flores KG, Boonyasiriwat W, et al. Interest and informational preferences regarding genomic testing for modest increases in colorectal cancer risk. Public Health Genomics 2014;17:48–60.
22. Graves KD, Leventhal K-G, Nusbaum R, et al. Behavioral and psychosocial responses to genomic testing for colorectal cancer risk. Genomics 2013;102:123–130.
23. Ramsey S, Blough D, McDermott C, et al. Will knowledge of gene-based colorectal cancer disease risk influence quality of life and screening behavior? Public Health Genomics 2010;13:1–12.
24. Mbuya Bienge C, Pashayan N, Brooks JD, et al. Women's views on multifactorial breast cancer risk assessment and risk-stratified screening: a population-based survey from four provinces in Canada. Journal of Personalized Medicine 2021;11:95.

Correspondence
Address correspondence to: Rosita van den Puttelaar, MSc, Department of Public Health, Erasmus Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands. e-mail: r.vandenputtelaar@erasmusmc.nl.

Acknowledgments
Our experiments were implemented as a high-performance computing (HPC) workflow using the EMEWS framework. They were run on Bebop, an HPC cluster managed by the Laboratory Computing Resource Center at Argonne National Laboratory. Bebop has 1024 nodes composed of 672 Intel Broadwell processors with 36 cores per node and 128 GB of RAM and 372 Intel Knights Landing processors with 64 cores per node and 96 GB of RAM.

CRediT Authorship Contributions
Rosita van den Puttelaar, MSc (Formal analysis: Lead; Methodology: Lead; Writing – original draft: Lead)
Reinier G. S. Meester, PhD (Formal analysis: Supporting; Supervision: Lead; Visualization: Supporting; Writing – original draft: Supporting)
Elisabeth E. P. Peterse, PhD (Conceptualization: Equal; Investigation: Lead; Methodology: Supporting)
Ann G. Zauber, PhD (Writing – review & editing: Supporting)
Jiayin Zheng, PhD (Formal analysis: Equal; Investigation: Equal; Methodology: Equal; Writing – review & editing: Supporting)
Richard B. Hayes, PhD (Writing – review & editing: Supporting)
Yu-Ru Su, PhD (Writing – review & editing: Supporting)
Jeffrey K. Lee, PhD (Writing – review & editing: Supporting)
Minta Thomas, PhD (Formal analysis: Equal; Writing – review & editing: Supporting)
Lori C. Sakoda, PhD (Formal analysis: Supporting; Writing – review & editing: Supporting)

Yi Li, PhD (Formal analysis: Supporting)

Douglas A. Corley, PhD (Visualization: Supporting; Writing – review & editing: Supporting)

Ulrike Peters, PhD, MPH (Funding acquisition: Lead; Project administration: Lead; Writing – review & editing: Supporting)

Li Hsu, PhD (Conceptualization: Supporting; Formal analysis: Equal; Investigation: Equal; Writing – review & editing: Supporting)

Iris Lansdorp-Vogelaar, PhD (Funding acquisition: Supporting; Supervision: Equal; Writing – original draft: Supporting)

Conflicts of interest

The authors disclose no conflicts.

Funding

Supported by grants U01-CA199335 and U01-CA253913 from the National Cancer Institute (NCI) as part of the Cancer Intervention and Surveillance Modeling Network (CISNET). The content is solely the responsibility of the authors and does not necessarily represent the official views of the National Institutes of Health.

Supplementary File 1. Risk Distribution in the Population

Risk predictions were based on GECCO's CRC risk prediction model, which used the E-score[1] and PRS based on known genome-wide association studies loci,[2] besides sex, family history, and endoscopy history as confounders. To account for the impact of screening on natural history, this study included endoscopy history at study entry (ie, at the time a risk ascertainment would be applied, along with other risk factor ascertainment) as a risk factor and censored the time-to-event outcome at 6 months after the first endoscopy during the follow-up. The risk scores are thus adjusted for endoscopy history and can be seen as the actual CRC risk distribution in the population without modification by screening. We used the Cox proportional hazard model to estimate the distribution of hazard ratios of E-score and PRS for CRC and competing causes of death using an independent cohort, the Genetic Epidemiology Research on Adult Health and Aging (GERA) cohort (detailed description of this cohort composed of KPNC health plan members can be found in dbGaP, Study Accession: phs000674.v3.p3). The Cox proportional hazard model for competing causes of death included sex and variables in the E-score as predictors. The E-score is the same as used in the CRC risk prediction model. Risk estimates were based on GERA non-Hispanic white people because the scores were developed for this population. A total of 70,049 participants were included. The average baseline age was 61.9 years (range, 20–90; Q1, 53.9; Q3, 70.9; interquartile range [IQR], 17.9), and the average follow-up was 6.3 years (range, 0.0–15.6; Q1, 2.9; Q3, 10.2; IQR, 7.3).

These Cox proportional hazard prediction models had an AUC of 65% for CRC and 64% for competing causes of death.[3] Both competing events, ie, CRC and other-cause death, were left-truncated at survey age and right-censored at age of loss of follow-up.

As input for the cost-effectiveness analysis, we next estimated the distribution of relative risk for CRC and other-cause death within the GERA cohort. For this analysis, we only considered individuals without family history for CRC, because separate screening guidelines already exist to screen people with a family history. For each participant, the relative risk score for CRC was calculated by taking the ratio of the participant's absolute risk estimate without endoscopy and the average of absolute risk estimates for developing CRC. The relative risk score for competing causes of death was similarly calculated for each participant. The median of the relative CRC risk scores was 0.89 with IQR of 0.52. For the competing causes of death-risk, the median of the relative risk was 0.86 with IQR of 0.58. The correlation between 2 relative risk scores was 0.13. The distributions of the relative risk scores are shown in Figure 1, and the joint distributions are provided in Table 1. These risk distributions constituted input for the simulations with the MISCAN-Colon model. Because of the limited sample size (especially at the tail), there were unusual patterns for some risk groups. As solution, we smoothed the data using two-dimensional Kernel Density estimation, which smooths the distributions of CRC risk and other-cause mortality simultaneously.

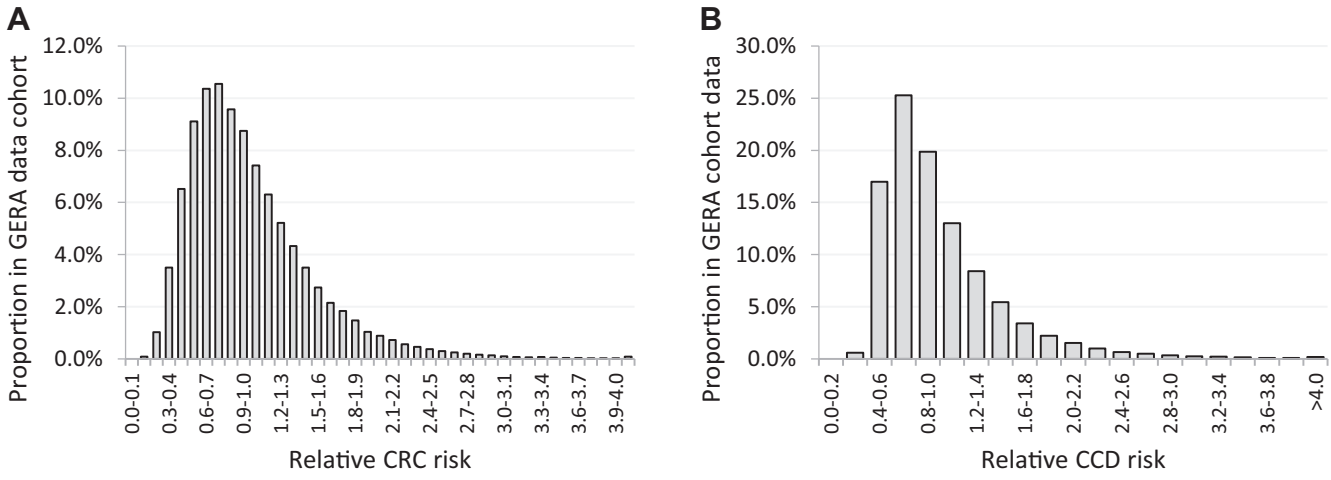

Figure 1. Distribution of relative CRC (*A*) and CCD (*B*) risks in the GERA cohort. Relative risk was defined compared with the average population. CCD, competing causes of death.

Table 1. Smoothed Distribution of Individuals Over Relative CRC and Competing Causes of Death Risk Groups (Multiplied by100)

		Relative competing causes of death-risk																				
		0.0–0.2	0.2–0.4	0.4–0.6	0.6–0.8	0.8–1.0	1.0–1.2	1.2–1.4	1.4–1.6	1.6–1.8	1.8–2.0	2.0–2.2	2.2–2.4	2.4–2.6	2.6–2.8	2.8–3.0	3.0–3.2	3.2–3.4	3.4–3.6	3.6–3.8	3.8–4.0	>4.0
Relative CRC risk	0.0–0.1	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000	0.0000
	0.1–0.2	0.0000	0.0519	0.1641	0.2061	0.1490	0.0871	0.0486	0.0271	0.0158	0.0093	0.0055	0.0033	0.0022	0.0016	0.0010	0.0008	0.0006	0.0004	0.0003	0.0003	0.0002
	0.2–0.3	0.0000	0.1252	0.3940	0.5019	0.3727	0.2213	0.1263	0.0725	0.0425	0.0251	0.0151	0.0092	0.0060	0.0044	0.0029	0.0022	0.0017	0.0013	0.0009	0.0008	0.0006
	0.3–0.4	0.0000	0.2374	0.7452	0.9593	0.7283	0.4405	0.2573	0.1511	0.0890	0.0529	0.0325	0.0203	0.0131	0.0098	0.0066	0.0048	0.0036	0.0027	0.0020	0.0019	0.0013
	0.4–0.5	0.0000	0.3667	1.1517	1.4926	1.1533	0.7117	0.4246	0.2545	0.1503	0.0907	0.0572	0.0362	0.0235	0.0175	0.0120	0.0083	0.0060	0.0043	0.0033	0.0034	0.0022
	0.5–0.6	0.0000	0.4776	1.5051	1.9606	1.5362	0.9667	0.5884	0.3588	0.2126	0.1311	0.0845	0.0541	0.0352	0.0258	0.0181	0.0120	0.0083	0.0058	0.0046	0.0052	0.0035
	0.6–0.7	0.0000	0.5414	1.7149	2.2483	1.7828	1.1423	0.7080	0.4384	0.2619	0.1652	0.1078	0.0693	0.0454	0.0324	0.0230	0.0151	0.0105	0.0074	0.0059	0.0070	0.0048
	0.7–0.8	0.0000	0.5500	1.7517	2.3190	1.8620	1.2126	0.7626	0.4779	0.2909	0.1872	0.1220	0.0786	0.0516	0.0360	0.0256	0.0170	0.0124	0.0089	0.0069	0.0082	0.0058
	0.8–0.9	0.0000	0.5146	1.6474	2.2085	1.8004	1.1903	0.7572	0.4786	0.2987	0.1952	0.1263	0.0815	0.0536	0.0368	0.0258	0.0177	0.0138	0.0100	0.0072	0.0087	0.0063
	0.9–1.0	0.0000	0.4540	1.4616	1.9840	1.6466	1.1062	0.7118	0.4531	0.2887	0.1899	0.1223	0.0795	0.0525	0.0355	0.0244	0.0176	0.0147	0.0106	0.0071	0.0084	0.0063
	1.0–1.1	0.0000	0.3838	1.2458	1.7100	1.4464	0.9896	0.6447	0.4129	0.2650	0.1741	0.1125	0.0739	0.0491	0.0330	0.0224	0.0172	0.0153	0.0106	0.0067	0.0081	0.0062
	1.1–1.2	0.0000	0.3145	1.0341	1.4360	1.2354	0.8605	0.5663	0.3643	0.2334	0.1529	0.0996	0.0657	0.0442	0.0302	0.0207	0.0165	0.0151	0.0099	0.0063	0.0076	0.0059
	1.2–1.3	0.0000	0.2538	0.8456	1.1896	1.0348	0.7300	0.4827	0.3114	0.2003	0.1317	0.0864	0.0566	0.0393	0.0282	0.0196	0.0154	0.0134	0.0082	0.0054	0.0067	0.0053
	1.3–1.4	0.0000	0.2041	0.6846	0.9738	0.8523	0.6059	0.4015	0.2596	0.1693	0.1123	0.0741	0.0482	0.0352	0.0263	0.0184	0.0137	0.0107	0.0060	0.0041	0.0055	0.0043
	1.4–1.5	0.0000	0.1635	0.5475	0.7842	0.6910	0.4944	0.3298	0.2135	0.1407	0.0942	0.0625	0.0411	0.0312	0.0233	0.0159	0.0114	0.0079	0.0041	0.0030	0.0044	0.0034
	1.5–1.6	0.0000	0.1300	0.4334	0.6220	0.5535	0.3986	0.2695	0.1749	0.1153	0.0776	0.0518	0.0347	0.0266	0.0191	0.0125	0.0090	0.0058	0.0031	0.0024	0.0038	0.0029
	1.6–1.7	0.0000	0.1033	0.3421	0.4896	0.4404	0.3187	0.2189	0.1430	0.0940	0.0636	0.0431	0.0292	0.0216	0.0149	0.0097	0.0070	0.0045	0.0028	0.0023	0.0035	0.0026
	1.7–1.8	0.0000	0.0819	0.2694	0.3839	0.3489	0.2534	0.1757	0.1161	0.0768	0.0531	0.0367	0.0246	0.0170	0.0118	0.0081	0.0056	0.0038	0.0027	0.0025	0.0033	0.0024
	1.8–1.9	0.0000	0.0643	0.2097	0.2983	0.2741	0.2005	0.1398	0.0937	0.0630	0.0449	0.0319	0.0209	0.0135	0.0096	0.0068	0.0044	0.0032	0.0024	0.0025	0.0030	0.0020
	1.9–2.0	0.0000	0.0497	0.1611	0.2301	0.2142	0.1586	0.1115	0.0759	0.0517	0.0377	0.0271	0.0176	0.0111	0.0079	0.0054	0.0032	0.0026	0.0020	0.0021	0.0025	0.0016
	2.0–2.1	0.0000	0.0378	0.1236	0.1795	0.1690	0.1262	0.0898	0.0620	0.0425	0.0306	0.0221	0.0147	0.0094	0.0064	0.0039	0.0024	0.0019	0.0015	0.0017	0.0020	0.0014
	2.1–2.2	0.0000	0.0282	0.0956	0.1431	0.1353	0.1013	0.0727	0.0511	0.0344	0.0241	0.0172	0.0120	0.0078	0.0049	0.0029	0.0019	0.0014	0.0012	0.0014	0.0016	0.0013
	2.2–2.3	0.0000	0.0213	0.0751	0.1149	0.1082	0.0815	0.0590	0.0418	0.0274	0.0186	0.0132	0.0094	0.0061	0.0036	0.0023	0.0018	0.0012	0.0010	0.0012	0.0013	0.0011
	2.3–2.4	0.0000	0.0167	0.0598	0.0911	0.0852	0.0653	0.0483	0.0340	0.0216	0.0147	0.0106	0.0074	0.0048	0.0028	0.0019	0.0017	0.0013	0.0010	0.0011	0.0010	0.0009
	2.4–2.5	0.0000	0.0134	0.0473	0.0713	0.0667	0.0524	0.0400	0.0278	0.0176	0.0123	0.0090	0.0063	0.0042	0.0024	0.0017	0.0016	0.0014	0.0011	0.0009	0.0010	0.0008
	2.5–2.6	0.0000	0.0105	0.0370	0.0558	0.0530	0.0424	0.0331	0.0228	0.0150	0.0106	0.0078	0.0057	0.0040	0.0022	0.0014	0.0014	0.0013	0.0011	0.0008	0.0009	0.0008
	2.6–2.7	0.0000	0.0081	0.0292	0.0447	0.0426	0.0341	0.0267	0.0186	0.0129	0.0091	0.0067	0.0049	0.0036	0.0020	0.0011	0.0011	0.0011	0.0011	0.0007	0.0007	0.0006
	2.7–2.8	0.0000	0.0062	0.0234	0.0364	0.0344	0.0272	0.0211	0.0150	0.0109	0.0077	0.0058	0.0041	0.0028	0.0015	0.0009	0.0007	0.0007	0.0011	0.0007	0.0005	0.0004
	2.8–2.9	0.0000	0.0047	0.0187	0.0296	0.0276	0.0217	0.0168	0.0121	0.0088	0.0064	0.0049	0.0032	0.0020	0.0011	0.0007	0.0004	0.0005	0.0009	0.0006	0.0004	0.0003
	2.9–3.0	0.0000	0.0036	0.0146	0.0232	0.0219	0.0173	0.0136	0.0097	0.0067	0.0053	0.0040	0.0026	0.0017	0.0009	0.0007	0.0003	0.0003	0.0006	0.0006	0.0005	0.0004
	3.0–3.1	0.0000	0.0027	0.0110	0.0175	0.0168	0.0137	0.0112	0.0075	0.0049	0.0042	0.0031	0.0023	0.0016	0.0010	0.0006	0.0003	0.0003	0.0004	0.0006	0.0006	0.0004
	3.1–3.2	0.0000	0.0021	0.0081	0.0131	0.0128	0.0107	0.0092	0.0060	0.0038	0.0034	0.0026	0.0021	0.0016	0.0010	0.0006	0.0003	0.0003	0.0003	0.0006	0.0006	0.0003
	3.2–3.3	0.0000	0.0016	0.0062	0.0104	0.0102	0.0083	0.0073	0.0051	0.0035	0.0029	0.0023	0.0020	0.0014	0.0009	0.0006	0.0003	0.0002	0.0002	0.0006	0.0006	0.0002
	3.3–3.4	0.0000	0.0014	0.0049	0.0085	0.0086	0.0066	0.0059	0.0046	0.0033	0.0026	0.0022	0.0019	0.0012	0.0007	0.0004	0.0002	0.0002	0.0002	0.0005	0.0006	0.0001
	3.4–3.5	0.0000	0.0011	0.0038	0.0066	0.0070	0.0055	0.0049	0.0040	0.0030	0.0023	0.0022	0.0018	0.0009	0.0005	0.0004	0.0002	0.0001	0.0002	0.0004	0.0004	0.0001
	3.5–3.6	0.0000	0.0009	0.0028	0.0048	0.0056	0.0047	0.0040	0.0032	0.0025	0.0020	0.0020	0.0016	0.0006	0.0003	0.0004	0.0003	0.0002	0.0002	0.0003	0.0002	0.0000
	3.6–3.7	0.0000	0.0007	0.0022	0.0037	0.0045	0.0039	0.0031	0.0023	0.0020	0.0018	0.0017	0.0013	0.0004	0.0003	0.0005	0.0004	0.0002	0.0002	0.0002	0.0001	0.0000
	3.7–3.8	0.0000	0.0006	0.0021	0.0035	0.0041	0.0033	0.0023	0.0018	0.0019	0.0016	0.0012	0.0009	0.0003	0.0002	0.0004	0.0004	0.0003	0.0002	0.0002	0.0001	0.0000
	3.8–3.9	0.0000	0.0006	0.0025	0.0042	0.0046	0.0033	0.0021	0.0016	0.0019	0.0015	0.0010	0.0008	0.0003	0.0001	0.0003	0.0003	0.0004	0.0003	0.0002	0.0001	0.0000
	3.9–4.0	0.0000	0.0007	0.0028	0.0049	0.0054	0.0036	0.0024	0.0016	0.0017	0.0013	0.0010	0.0009	0.0004	0.0001	0.0002	0.0003	0.0005	0.0005	0.0003	0.0001	0.0000
	>4.0	0.0000	0.0006	0.0024	0.0045	0.0050	0.0033	0.0022	0.0014	0.0013	0.0010	0.0009	0.0008	0.0004	0.0001	0.0001	0.0002	0.0005	0.0005	0.0003	0.0002	0.0000

Relative risk scores were calculated by taking the ratio of the participant's absolute risk estimate and the average of absolute risk estimates.

Supplementary File 2. Risk Indices in MISCAN

The performance of risk prediction is represented in the distribution of risk scores in the population. The AUC value of the CRC risk prediction model described in Supplementary File 1 is equal to 0.65 and is referred to as estimated risk distribution.

The risk indices in MISCAN-Colon were used as starting point of our analysis. In MISCAN-Colon, each simulated individual has an underlying "true" risk index that represents an individual's predisposition to develop adenomas and cancer. This underlying distribution of risk is unobservable, was calibrated on real-world data, and is assumed to come from a Gamma distribution with mean 1 and variance 1.98628. Next, we have the distribution of predicted relative CRC risk obtained by the risk prediction model. We thus have 2 marginal distributions in the same population. The level of AUC of the risk prediction model determines the match between predicted and underlying risk. For this analysis, we split the simulated population into 40 different predicted relative risk (RR) groups, with RR ranging from 0.1 to >4 with increments of 0.1.

We used an elliptical copula approach[5] to generate a joint distribution of underlying and predicted risk ensuring that both marginal distributions are maintained. The copula assigns a distribution of underlying risk value from the model to each of the RR groups. A more detailed description of this copula approach can be found in another publication.[4] In this way we "mapped" the predicted risk distribution into true underlying risk in MISCAN-Colon, respecting each of the following:

(1) The prediction model's discriminatory accuracy, ie, the distribution of predicted hazard ratios or RR in the population (Figure 1).

(2) The prediction model's calibration, by making sure that for each RR group, the average underlying risk assigned in MISCAN matched up to the predicted risk.

(3) MISCAN-Colon's calibration to clinical and epidemiologic data targets, by making sure the overall underlying risk distribution was as previously calibrated (Figure 2).

With these distributions we also model heterogeneity within risk groups, such that we take into account that risk prediction is not perfect, for example, the underlying risk scores for CRC relative risk group [1.5, 1.6] in Figure 3. Taken together, these underlying distributions for all risk groups add up to the overall distribution of risk indices as shown in Figure 2.

A graphical representation of the elliptical copula is presented in Figure 4. This figure shows the concordance between the underlying risk distribution in MISCAN-Colon and the predicted RR distribution in the GERA cohort for 10,000 simulated individuals. For the analysis, we determined the concordance of the 2 distributions for 50 million simulated individuals, but plotting this many symbols in one figure did not visualize the elliptical copula very well.

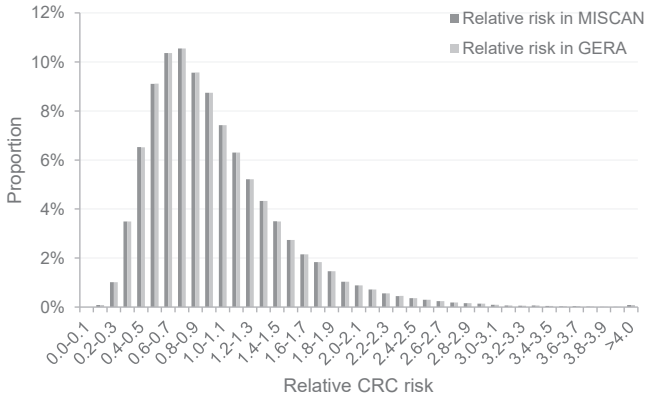

Figure 1. Distribution of relative risks in the GERA cohort and "mapped" relative risk used in MISCAN-Colon obtained with the copula.

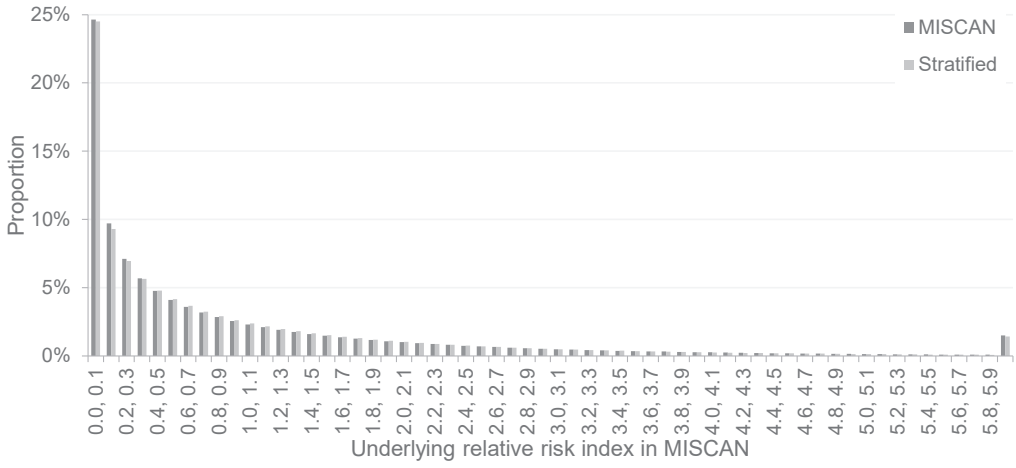

Figure 2. Overall distribution of personal risk indices in the original MISCAN-Colon model vs using a stratified approach.

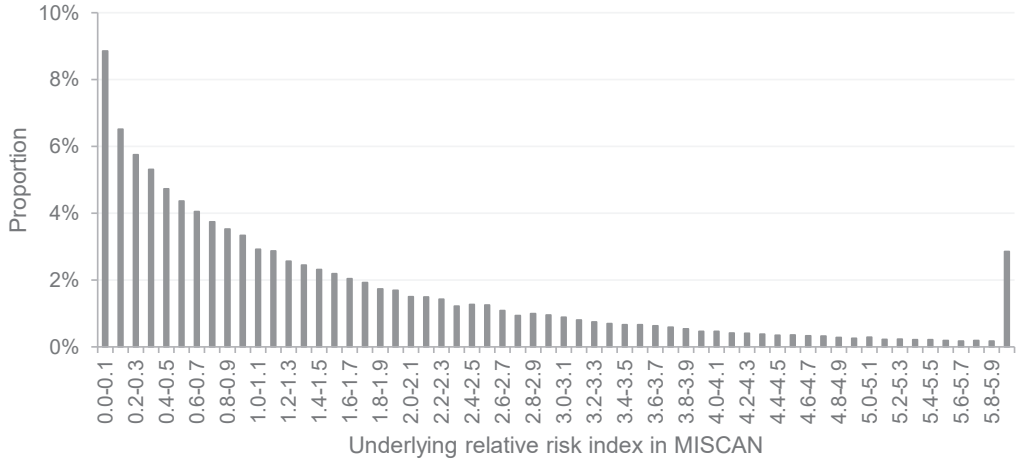

Figure 3. Distribution of personal risk indices in the original MISCAN-Colon model for CRC relative risk group [1.5, 1.6].

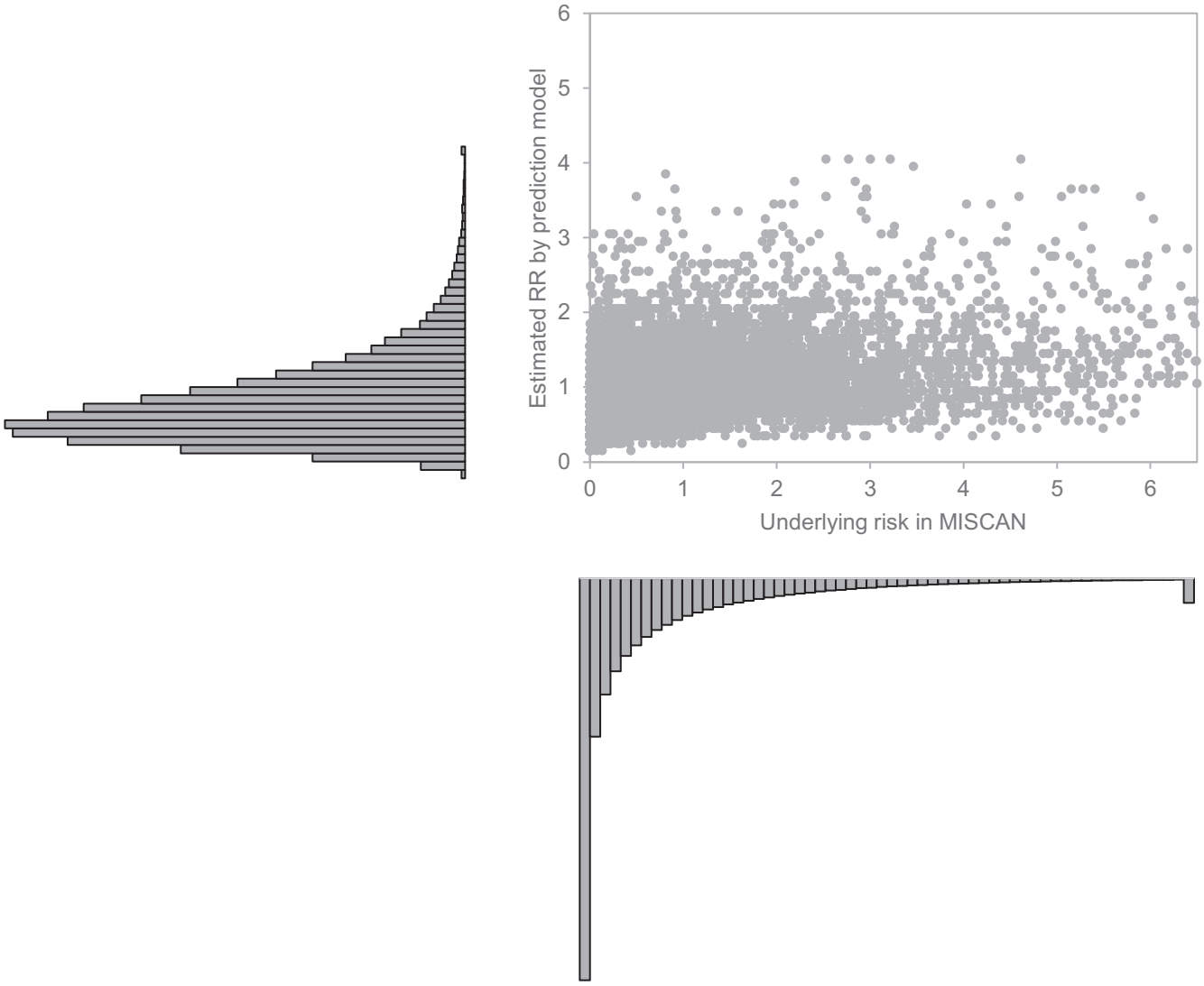

Figure 4. Graphical representation of the elliptical copula. The scatter plot shows the concordance between the underlying risk distribution in MISCAN (x-axis) and the estimated relative risk distribution in the GERA cohort (y-axis) for 10,000 simulated individuals.

Supplementary File 3. Test Characteristics, Costs, and Disutilities in This Study

Test characteristics		
	Colonoscopy	FIT
Specificity	86%[a]	96.4%
Sensitivity[b]		
Adenoma 1–5 mm	75%	0.00%[c]
Adenoma 6–9 mm	85%	11.4%
Adenoma 10+ mm	95%	15.9%
Cancer	95%	62.565%/88.6%[d]
Reach	95% reaches the cecum	

Screening tests				
	Commercial costs ($)	CMS costs ($)	Disutility when positive	Disutility when negative
Colonoscopy				
Screening without lesion removal	1330.14	898.10	NA	0.000496
Diagnostic without lesion removal[e]	1330.14	847.07	NA	0.000496
Surveillance without lesion removal	1330.14	845.53	NA	0.000496
Any colonoscopy with lesion removal	1760.68	1222.71	0.001401	NA
FIT	23.79	21.82	0.001330	0.000063
Polygenic test	100	100	NA	NA

Colorectal cancer care				
2007–2013 Commercial costs per LY CRC care (2017 US$)[f]	Initial care	Continuing care	Terminal care Death CRC	Terminal care Death OC
Stage I CRC	51,774	5328	104,483	27,440
Stage II CRC	73,418	6196	117,777	29,528
Stage III CRC	106,670	9586	123,305	40,367
Stage IV CRC	158,511	45,444	155,054	97,101
2007–2013 CMS costs per LY CRC care (2017 US$)[f]				
Stage I CRC	38,351	3946	77,395	20,326
Stage II CRC	54,384	4590	87,242	21,872
Stage III CRC	79,015	7101	91,337	29,901
Stage IV CRC	117,416	33,662	114,855	71,926
Utility loss per LY with CRC care[f,g]				
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

Colonoscopy complications			
	Commercial costs (2017 US$)	CMS costs (2017 US$)	Utility loss
Serious gastrointestinal event[h]	10,914	8085	0.0055
Other gastrointestinal event[i]	8256	6116	0.0027
Cardiovascular event[j]	8889	6584	0.0048

CMS, Centers for Medicare and Medicaid Services; FIT, fecal immunochemical test.
[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 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.[6]
[c]We assumed that they are small adenomas and therefore cannot cause a positive stool test.
[d]"Long" before clinical diagnosis/"Short" before clinical diagnosis.
[e]Used for colonoscopies performed as a diagnostic follow-up after a positive non-colonoscopy test and for colonoscopies performed for diagnosis of symptom-detected CRC cases.
[f]Care for CRC was divided into 3 clinically relevant phases: initial, continuing, and terminal care. 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; and the continuing care phase was defined as all months in between. In the terminal care phase, we distinguished between CRC patients dying of CRC and CRC patients dying of another cause (OC). 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.
[g]Utility losses for LYs with initial care were derived from a study by Ness et al.[7] 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.
[h]Serious gastrointestinal events are perforations, gastrointestinal bleeding, or transfusions. The rate depends on age, formula: $1/[\exp(9.27953 - 0.06105 \times \text{Age}) + 1] - 1/[\exp(10.78719 - 0.06105 \times \text{Age}) + 1$.
[i]Other gastrointestinal events are paralytic ileus, nausea and vomiting, dehydration, or abdominal pain. The rate depends on age, formula: $1/[\exp(8.81404 - 0.05903 \times \text{Age}) + 1] - 1/[\exp(9.61197 - 0.05903 \times \text{Age}) + 1]$.
[j]Cardiovascular events are myocardial infarction or angina, arrhythmias, congestive heart failure, cardiac or respiratory arrest, syncope, hypotension, or shock. The rate depends on age, formula: $1/[\exp(9.09053 - 0.07056 \times \text{Age}) + 1] - 1/[\exp(9.38297 - 0.07056 \times \text{Age}) + 1]$.

Supplementary File 4. Impact of Relative Risk on Screening Resources, Benefits, and Costs

We calculated results for 3 selected relative CRC (RR = 0.5, 1.5, and 3.5) and competing causes of death risk (RR = 0.5, 1.5, and 3.5) groups to illustrate the impact of these factors on the effects (quality-adjusted life years gained, QALYG) and costs of screening. Results were presented for the following:

- the reference strategy of uniform colonoscopy screening every 10 years from ages 45 to 75, following the recent U.S. guideline recommendations[8,9];
- colonoscopy screening at ages 60 and 70;
- colonoscopy screening every 10 years from ages 45 to 75;
- colonoscopy screening every 5 years from ages 45 to 80.

As expected, the simulated number of CRC cases and deaths varied substantially with the relative risk for CRC (Table 1). Consequently, the impact of screening was much larger in individuals with a high relative risk (3.5) for CRC, compared with those with a low RR (0.5). For example, colonoscopy screening at ages 60 to 70, compared with no screening, yielded 38 QALYG per 1000 individuals among individuals who carried a relative risk for CRC of 0.5; for those carrying a relative risk of 1.5 and 3.5, the respective QALYG were 105 and 228. More intensive screening strategies (eg, colonoscopy screening at ages 45–75, every 10 years) resulted in fewer CRC cases and deaths, and as a result, QALYG was increased for all 3 risk groups. However, the incremental benefits of intensifying screening decreased. For example, screening every 5 years at ages 45–80 prevented only 4 additional CRC cases, compared with screening every 10 years at ages 45–75, for individuals with a relative risk for CRC of 3.5.

Total costs also increased with CRC risk because of increased CRC care costs. Compared with no screening, screening increased costs for individuals with a low relative risk (0.5) for CRC. However, for individuals with a relative risk of 1.5 and 3.5, total costs with colonoscopy screening at ages 60 to 70 decreased as a result of cost savings on CRC treatment.

The pattern for competing causes of death-risk was similar, but now the low-risk individuals had a higher

benefit of screening because of increased life expectancy (Table 1). Colonoscopy screening at ages 60 and 70 for individuals who carry a relative risk for competing causes of death of 0.5 yielded 119 QALYG, whereas the QALYG for individuals with relative risk of 3.5 was only 20. For more intensive screening however, the difference is relatively small compared with the impact of CRC risk. The decrease in costs for higher competing causes of death-risk groups was also relatively small.

Table 1. Lifetime Effects and Costs per 1000 40-year-old Individuals for Different Relative CRC and Competing Causes of Death Risks and Different Strategies

	Strategy	Colonoscopies		CRC cases		CRC deaths		QALYG[a]		Costs (1000)[a,b]	
CRC risk											
RR 0.5	No screening	45		45		18		0		2385	
	COL, 60, 70 y	2053	(+2008)	23	(–21)	7	(–11)	38	(+38)	2901	(+516)
	COL, 45–75 y, 10 y	3793	(+3748)	19	(–26)	5	(–13)	56	(+56)	4277	(+1892)
	COL, 45-80y, 5y	6170	(+6126)	16	(-29)	4	(-14)	62	(+62)	5895	(+3510)
RR 1.5	No screening	117		117		47		0		6442	
	COL, 60, 70 y	2510	(+2393)	60	(–57)	17	(–30)	105	(+105)	5926	(–516)
	COL, 45–75 y, 10 y	4191	(+4074)	50	(–67)	12	(–35)	158	(+158)	6680	(+238)
	COL, 45–80 y, 5y	5675	(+5558)	45	(–72)	11	(–37)	169	(+169)	7612	(+1170)
RR 3.5	No screening	237		237		98		0		13,736	
	COL, 60, 70 y	3048	(+2811)	123	(–115)	35	(–63)	228	(+228)	11,303	(–2433)
	COL, 45–75 y, 10 y	4763	(+4525)	101	(–136)	24	(–73)	352	(+352)	10,797	(–2938)
	COL, 45–80 y, 5 y	5460	(+5223)	97	(–140)	23	(–75)	364	(+364)	11,154	(–2582)
CCD risk											
RR 0.5	No screening	114		114		49		0		5761	
	COL, 60, 70 y	2629	(+2515)	53	(–61)	17	(–32)	119	(+119)	5157	(–604)
	COL, 45–75 y, 10 y	4414	(+4300)	44	(–70)	12	(–36)	163	(+163)	6165	(+404)
	COL, 45–80 y, 5 y	6425	(+6311)	38	(–76)	10	(–39)	176	(+176)	7384	(+1623)
RR 1.5	No screening	83		83		33		0		4470	
	COL, 60, 70 y	2308	(+2194)	43	(–2)	12	(–6)	72	(+72)	4466	(+2080)
	COL, 45–75 y, 10 y	4010	(+3896)	35	(–10)	9	(–9)	108	(+108)	5531	(+3146)
	COL, 45–80 y, 5 y	5859	(+5745)	31	(–14)	7	(–11)	118	(+118)	6739	(+4354)
RR 3.5	No screening	38		38		14		0		2439	
	COL, 60, 70 y	1480	(+1442)	26	(–19)	7	(–11)	20	(+20)	3025	(+639)
	COL, 45–75 y, 10 y	2990	(+2952)	20	(–25)	4	(–14)	41	(+41)	4204	(+1818)
	COL, 45–80 y, 5 y	4386	(+4348)	18	(–27)	3	(–14)	45	(+45)	5272	(+2887)

NOTE. Risk groups had the same competing causes of death and CRC risk of 1.0 in the 2 analyses. For every strategy, the start age, end age, and screening interval are given. Changes compared with no screening were also reported.
CCD, competing causes of death; COL, colonoscopy; QALYG, quality-adjusted life years gained; RR, relative risk.
[a](Quality-adjusted) life years (gained) and costs were discounted at an annual rate of 3%.
[b]Costs are in 2017 US dollars (USD).

Supplementary File 5. Optimal Screening Strategies Under Risk-Stratified Screening

Table 1. Optimal Screening Strategies for Each Risk Group in Risk-Stratified Screening, Using a Willingness-To-Pay Threshold of $90,100 per Quality-Adjusted Life Year Gained, at Which the Costs of Risk-Stratified Screening Are Equal to Those of Uniform Screening

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
0.1–0.2	0.2–0.4	60	70	10	2	16.0
0.1–0.2	0.4–0.6	60	70	10	2	0.0
0.1–0.2	0.6–0.8	60	70	10	2	0.0
0.1–0.2	0.8–1.0	60	70	10	2	0.0
0.1–0.2	1.0–1.2	60	70	10	2	0.0
0.1–0.2	1.2–1.4	60	70	10	2	0.0
0.1–0.2	1.4–1.6	No screening	—	—	0	0.0
0.1–0.2	1.6–1.8	No screening	—	—	0	0.0
0.1–0.2	1.8–2.0	No screening	—	—	0	0.0
0.1–0.2	2.0–2.2	No screening	—	—	0	0.0
0.1–0.2	2.2–2.4	No screening	—	—	0	0.0
0.1–0.2	2.4–2.6	No screening	—	—	0	0.0
0.1–0.2	2.6–2.8	No screening	—	—	0	0.0
0.1–0.2	2.8–3.0	No screening	—	—	0	0.0
0.1–0.2	3.0–3.2	No screening	—	—	0	0.0
0.1–0.2	3.2–3.4	No screening	—	—	0	0.0
0.1–0.2	3.4–3.6	No screening	—	—	0	0.0
0.1–0.2	3.6–3.8	No screening	—	—	0	0.0
0.1–0.2	3.8–4.0	No screening	—	—	0	0.0
0.1–0.2	>4.0	No screening	—	—	0	0.0
0.2–0.3	0.2–0.4	55	70	15	2	27.0
0.2–0.3	0.4–0.6	55	70	15	2	23.2
0.2–0.3	0.6–0.8	55	70	10	2	19.9
0.2–0.3	0.8–1.0	55	70	10	2	16.7
0.2–0.3	1.0–1.2	60	70	10	2	14.4
0.2–0.3	1.2–1.4	60	70	10	2	0.0
0.2–0.3	1.4–1.6	60	70	10	2	0.0
0.2–0.3	1.6–1.8	60	70	10	2	0.0
0.2–0.3	1.8–2.0	60	70	10	2	0.0
0.2–0.3	2.0–2.2	60	70	10	2	0.0
0.2–0.3	2.2–2.4	60	70	10	2	0.0
0.2–0.3	2.4–2.6	No screening	—	—	0	0.0
0.2–0.3	2.6–2.8	No screening	—	—	0	0.0
0.2–0.3	2.8–3.0	No screening	—	—	0	0.0
0.2–0.3	3.0–3.2	No screening	—	—	0	0.0

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
0.2–0.3	3.2–3.4	No screening	—	—	0	0.0
0.2–0.3	3.4–3.6	No screening	—	—	0	0.0
0.2–0.3	3.6–3.8	No screening	—	—	0	0.0
0.2–0.3	3.8–4.0	No screening	—	—	0	0.0
0.2–0.3	>4.0	No screening	—	—	0	0.0
0.3–0.4	0.2–0.4	55	75	10	3	45.7
0.3–0.4	0.4–0.6	55	75	10	3	38.9
0.3–0.4	0.6–0.8	55	70	10	2	28.0
0.3–0.4	0.8–1.0	55	70	10	2	23.8
0.3–0.4	1.0–1.2	55	70	10	2	20.5
0.3–0.4	1.2–1.4	55	70	10	2	17.8
0.3–0.4	1.4–1.6	55	70	10	2	15.6
0.3–0.4	1.6–1.8	55	70	10	2	0.0
0.3–0.4	1.8–2.0	55	—	—	1	0.0
0.3–0.4	2.0–2.2	60	70	10	2	0.0
0.3–0.4	2.2–2.4	55	—	—	1	0.0
0.3–0.4	2.4–2.6	60	70	10	2	0.0
0.3–0.4	2.6–2.8	60	70	10	2	0.0
0.3–0.4	2.8–3.0	60	70	10	2	0.0
0.3–0.4	3.0–3.2	60	70	10	2	0.0
0.3–0.4	3.2–3.4	No screening	—	—	0	0.0
0.3–0.4	3.4–3.6	No screening	—	—	0	0.0
0.3–0.4	3.6–3.8	No screening	—	—	0	0.0
0.3–0.4	3.8–4.0	No screening	—	—	0	0.0
0.3–0.4	>4.0	No screening	—	—	0	0.0
0.4–0.5	0.2–0.4	50	80	10	4	63.3
0.4–0.5	0.4–0.6	50	70	10	3	55.8
0.4–0.5	0.6–0.8	55	75	10	3	47.8
0.4–0.5	0.8–1.0	55	70	10	2	40.9
0.4–0.5	1.0–1.2	55	70	10	2	26.4
0.4–0.5	1.2–1.4	55	70	10	2	22.9
0.4–0.5	1.4–1.6	55	70	10	2	20.1
0.4–0.5	1.6–1.8	55	70	10	2	17.8
0.4–0.5	1.8–2.0	55	70	10	2	15.9
0.4–0.5	2.0–2.2	55	70	10	2	14.2
0.4–0.5	2.2–2.4	55	70	10	2	0.0
0.4–0.5	2.4–2.6	55	70	10	2	0.0
0.4–0.5	2.6–2.8	55	—	—	1	0.0
0.4–0.5	2.8–3.0	55	—	—	1	0.0
0.4–0.5	3.0–3.2	55	—	—	1	0.0

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
0.4–0.5	3.2–3.4	55	—	—	1	0.0
0.4–0.5	3.4–3.6	55	—	—	1	0.0
0.4–0.5	3.6–3.8	55	—	—	1	0.0
0.4–0.5	3.8–4.0	55	—	—	1	0.0
0.4–0.5	>4.0	No screening	—	—	0	0.0
0.5–0.6	0.2–0.4	50	80	10	4	83.9
0.5–0.6	0.4–0.6	50	80	10	4	68.7
0.5–0.6	0.6–0.8	50	70	10	3	58.9
0.5–0.6	0.8–1.0	50	70	10	3	50.5
0.5–0.6	1.0–1.2	50	70	10	3	43.7
0.5–0.6	1.2–1.4	50	70	15	2	38.3
0.5–0.6	1.4–1.6	50	70	15	2	24.8
0.5–0.6	1.6–1.8	50	70	15	2	22.0
0.5–0.6	1.8–2.0	50	70	15	2	19.7
0.5–0.6	2.0–2.2	50	70	15	2	17.7
0.5–0.6	2.2–2.4	50	70	15	2	15.9
0.5–0.6	2.4–2.6	50	70	15	2	14.4
0.5–0.6	2.6–2.8	50	70	15	2	0.0
0.5–0.6	2.8–3.0	50	70	15	2	0.0
0.5–0.6	3.0–3.2	55	—	—	1	0.0
0.5–0.6	3.2–3.4	55	—	—	1	0.0
0.5–0.6	3.4–3.6	55	—	—	1	0.0
0.5–0.6	3.6–3.8	55	—	—	1	0.0
0.5–0.6	3.8–4.0	55	—	—	1	0.0
0.5–0.6	>4.0	55	—	—	1	0.0
0.6–0.7	0.2–0.4	50	80	10	4	99.2
0.6–0.7	0.4–0.6	50	80	10	4	85.7
0.6–0.7	0.6–0.8	50	80	10	4	70.0
0.6–0.7	0.8–1.0	50	70	10	3	59.9
0.6–0.7	1.0–1.2	50	70	10	3	51.9
0.6–0.7	1.2–1.4	50	70	10	3	45.5
0.6–0.7	1.4–1.6	50	70	10	3	40.4
0.6–0.7	1.6–1.8	50	70	15	2	36.2
0.6–0.7	1.8–2.0	50	70	15	2	23.6
0.6–0.7	2.0–2.2	50	70	15	2	21.1
0.6–0.7	2.2–2.4	50	70	15	2	19.0
0.6–0.7	2.4–2.6	50	70	15	2	17.2
0.6–0.7	2.6–2.8	50	70	15	2	15.7
0.6–0.7	2.8–3.0	50	70	15	2	14.3
0.6–0.7	3.0–3.2	50	70	15	2	0.0

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
0.6–0.7	3.2–3.4	50	70	15	2	0.0
0.6–0.7	3.4–3.6	50	70	15	2	0.0
0.6–0.7	3.6–3.8	55	—	—	1	0.0
0.6–0.7	3.8–4.0	55	—	—	1	0.0
0.6–0.7	>4.0	55	—	—	1	0.0
0.7–0.8	0.2–0.4	50	80	10	4	114.1
0.7–0.8	0.4–0.6	50	80	10	4	98.3
0.7–0.8	0.6–0.8	50	80	10	4	83.8
0.7–0.8	0.8–1.0	50	70	10	3	69.1
0.7–0.8	1.0–1.2	50	70	10	3	59.9
0.7–0.8	1.2–1.4	50	70	10	3	52.5
0.7–0.8	1.4–1.6	50	70	10	3	46.6
0.7–0.8	1.6–1.8	50	70	10	3	41.6
0.7–0.8	1.8–2.0	50	70	10	3	37.5
0.7–0.8	2.0–2.2	50	70	15	2	34.0
0.7–0.8	2.2–2.4	50	70	15	2	26.6
0.7–0.8	2.4–2.6	50	70	15	2	24.5
0.7–0.8	2.6–2.8	50	70	15	2	22.6
0.7–0.8	2.8–3.0	50	70	15	2	16.6
0.7–0.8	3.0–3.2	50	70	15	2	15.2
0.7–0.8	3.2–3.4	50	70	15	2	13.9
0.7–0.8	3.4–3.6	50	70	15	2	0.0
0.7–0.8	3.6–3.8	50	70	15	2	0.0
0.7–0.8	3.8–4.0	50	70	15	2	0.0
0.7–0.8	>4.0	55	—	—	1	0.0
0.8–0.9	0.2–0.4	45	75	10	4	142.8
0.8–0.9	0.4–0.6	45	75	10	4	124.3
0.8–0.9	0.6–0.8	45	75	10	4	105.5
0.8–0.9	0.8–1.0	45	75	10	4	83.0
0.8–0.9	1.0–1.2	45	75	10	4	72.6
0.8–0.9	1.2–1.4	45	75	10	4	59.9
0.8–0.9	1.4–1.6	50	70	10	3	53.2
0.8–0.9	1.6–1.8	50	70	10	3	47.6
0.8–0.9	1.8–2.0	50	70	10	3	42.9
0.8–0.9	2.0–2.2	50	70	10	3	38.8
0.8–0.9	2.2–2.4	50	70	15	2	35.4
0.8–0.9	2.4–2.6	50	70	15	2	28.1
0.8–0.9	2.6–2.8	50	70	15	2	26.0
0.8–0.9	2.8–3.0	50	70	15	2	24.0
0.8–0.9	3.0–3.2	50	70	15	2	22.2

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
0.8–0.9	3.2–3.4	50	70	15	2	20.6
0.8–0.9	3.4–3.6	50	70	15	2	19.3
0.8–0.9	3.6–3.8	50	70	15	2	0.0
0.8–0.9	3.8–4.0	50	70	15	2	0.0
0.8–0.9	>4.0	50	70	15	2	0.0
0.9–1.0	0.2–0.4	45	75	10	4	159.8
0.9–1.0	0.4–0.6	45	75	10	4	139.0
0.9–1.0	0.6–0.8	45	75	10	4	118.1
0.9–1.0	0.8–1.0	45	75	10	4	102.1
0.9–1.0	1.0–1.2	45	75	10	4	81.6
0.9–1.0	1.2–1.4	45	75	10	4	72.2
0.9–1.0	1.4–1.6	45	75	10	4	64.7
0.9–1.0	1.6–1.8	45	70	10	3	58.2
0.9–1.0	1.8–2.0	50	70	10	3	53.0
0.9–1.0	2.0–2.2	45	70	10	3	48.2
0.9–1.0	2.2–2.4	45	70	10	3	39.7
0.9–1.0	2.4–2.6	45	70	10	3	36.3
0.9–1.0	2.6–2.8	50	70	10	3	29.3
0.9–1.0	2.8–3.0	50	70	15	2	27.2
0.9–1.0	3.0–3.2	50	70	15	2	25.1
0.9–1.0	3.2–3.4	50	70	15	2	23.3
0.9–1.0	3.4–3.6	50	70	15	2	21.8
0.9–1.0	3.6–3.8	50	70	15	2	20.3
0.9–1.0	3.8–4.0	50	70	15	2	19.2
0.9–1.0	>4.0	50	70	15	2	0.0
1.0–1.1	0.2–0.4	45	80	5	8	176.7
1.0–1.1	0.4–0.6	45	75	10	4	153.7
1.0–1.1	0.6–0.8	45	75	10	4	131.0
1.0–1.1	0.8–1.0	45	75	10	4	113.3
1.0–1.1	1.0–1.2	45	75	10	4	98.8
1.0–1.1	1.2–1.4	45	75	10	4	80.3
1.0–1.1	1.4–1.6	45	75	10	4	71.9
1.0–1.1	1.6–1.8	45	75	10	4	64.9
1.0–1.1	1.8–2.0	45	70	10	3	58.9
1.0–1.1	2.0–2.2	45	70	10	3	53.7
1.0–1.1	2.2–2.4	45	70	10	3	49.5
1.0–1.1	2.4–2.6	45	70	10	3	45.6
1.0–1.1	2.6–2.8	45	70	10	3	42.2
1.0–1.1	2.8–3.0	45	70	10	3	30.4
1.0–1.1	3.0–3.2	45	70	10	3	28.0

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
1.0–1.1	3.2–3.4	50	70	15	2	26.1
1.0–1.1	3.4–3.6	50	70	15	2	24.5
1.0–1.1	3.6–3.8	50	70	15	2	22.7
1.0–1.1	3.8–4.0	50	70	15	2	21.3
1.0–1.1	>4.0	50	70	15	2	0.0
1.1–1.2	0.2–0.4	45	80	5	8	191.7
1.1–1.2	0.4–0.6	45	80	5	8	167.4
1.1–1.2	0.6–0.8	45	75	10	4	144.1
1.1–1.2	0.8–1.0	45	75	10	4	123.2
1.1–1.2	1.0–1.2	45	75	10	4	108.0
1.1–1.2	1.2–1.4	45	75	10	4	95.5
1.1–1.2	1.4–1.6	45	75	10	4	79.0
1.1–1.2	1.6–1.8	45	75	10	4	71.2
1.1–1.2	1.8–2.0	45	70	10	3	64.9
1.1–1.2	2.0–2.2	45	70	10	3	59.0
1.1–1.2	2.2–2.4	45	70	10	3	54.5
1.1–1.2	2.4–2.6	45	70	10	3	50.1
1.1–1.2	2.6–2.8	45	70	10	3	46.4
1.1–1.2	2.8–3.0	45	70	10	3	43.0
1.1–1.2	3.0–3.2	45	70	10	3	40.1
1.1–1.2	3.2–3.4	45	70	10	3	28.8
1.1–1.2	3.4–3.6	45	70	10	3	26.9
1.1–1.2	3.6–3.8	50	70	15	2	25.1
1.1–1.2	3.8–4.0	50	70	15	2	23.5
1.1–1.2	>4.0	50	70	15	2	18.8
1.2–1.3	0.2–0.4	45	80	5	8	208.6
1.2–1.3	0.4–0.6	45	80	5	8	181.8
1.2–1.3	0.6–0.8	45	75	5	7	155.2
1.2–1.3	0.8–1.0	45	75	10	4	134.1
1.2–1.3	1.0–1.2	45	75	10	4	117.6
1.2–1.3	1.2–1.4	45	75	10	4	104.1
1.2–1.3	1.4–1.6	45	75	10	4	86.2
1.2–1.3	1.6–1.8	45	70	10	3	77.8
1.2–1.3	1.8–2.0	45	70	10	3	70.6
1.2–1.3	2.0–2.2	45	70	10	3	64.5
1.2–1.3	2.2–2.4	45	70	10	3	59.4
1.2–1.3	2.4–2.6	45	70	10	3	54.9
1.2–1.3	2.6–2.8	45	70	10	3	50.8
1.2–1.3	2.8–3.0	45	70	10	3	47.2
1.2–1.3	3.0–3.2	45	70	10	3	43.8

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
1.2–1.3	3.2–3.4	45	70	10	3	40.8
1.2–1.3	3.4–3.6	45	70	10	3	29.6
1.2–1.3	3.6–3.8	45	70	10	3	27.7
1.2–1.3	3.8–4.0	45	70	10	3	25.9
1.2–1.3	>4.0	50	70	15	2	20.7
1.3–1.4	0.2–0.4	45	80	5	8	224.7
1.3–1.4	0.4–0.6	45	75	5	7	195.6
1.3–1.4	0.6–0.8	45	80	5	8	168.8
1.3–1.4	0.8–1.0	45	75	10	4	144.7
1.3–1.4	1.0–1.2	45	75	10	4	126.6
1.3–1.4	1.2–1.4	45	75	10	4	112.2
1.3–1.4	1.4–1.6	45	75	10	4	100.3
1.3–1.4	1.6–1.8	45	75	10	4	84.2
1.3–1.4	1.8–2.0	45	70	10	3	76.6
1.3–1.4	2.0–2.2	45	75	10	4	69.8
1.3–1.4	2.2–2.4	45	75	10	4	64.2
1.3–1.4	2.4–2.6	45	70	10	3	59.3
1.3–1.4	2.6–2.8	45	70	10	3	54.9
1.3–1.4	2.8–3.0	45	70	10	3	50.9
1.3–1.4	3.0–3.2	45	70	10	3	47.5
1.3–1.4	3.2–3.4	45	70	10	3	44.3
1.3–1.4	3.4–3.6	45	70	10	3	41.5
1.3–1.4	3.6–3.8	45	70	10	3	38.7
1.3–1.4	3.8–4.0	45	70	10	3	27.9
1.3–1.4	>4.0	45	70	10	3	22.3
1.4–1.5	0.2–0.4	45	80	5	8	251.9
1.4–1.5	0.4–0.6	45	80	5	8	220.9
1.4–1.5	0.6–0.8	45	75	5	7	191.9
1.4–1.5	0.8–1.0	45	80	5	8	155.6
1.4–1.5	1.0–1.2	45	75	10	4	136.3
1.4–1.5	1.2–1.4	45	75	10	4	120.9
1.4–1.5	1.4–1.6	45	75	10	4	108.1
1.4–1.5	1.6–1.8	45	75	10	4	97.7
1.4–1.5	1.8–2.0	45	75	10	4	82.8
1.4–1.5	2.0–2.2	45	75	10	4	75.6
1.4–1.5	2.2–2.4	45	70	10	3	69.6
1.4–1.5	2.4–2.6	45	70	10	3	64.3
1.4–1.5	2.6–2.8	45	70	10	3	59.6
1.4–1.5	2.8–3.0	45	70	10	3	55.5
1.4–1.5	3.0–3.2	45	70	10	3	51.5

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
1.4–1.5	3.2–3.4	45	70	10	3	48.0
1.4–1.5	3.4–3.6	45	70	10	3	45.2
1.4–1.5	3.6–3.8	45	70	10	3	42.3
1.4–1.5	3.8–4.0	45	70	10	3	40.0
1.4–1.5	>4.0	45	70	10	3	29.5
1.5–1.6	0.2–0.4	45	80	5	8	267.8
1.5–1.6	0.4–0.6	45	80	5	8	235.2
1.5–1.6	0.6–0.8	45	80	5	8	203.9
1.5–1.6	0.8–1.0	45	75	5	7	178.0
1.5–1.6	1.0–1.2	45	85	5	9	145.2
1.5–1.6	1.2–1.4	45	75	10	4	128.8
1.5–1.6	1.4–1.6	45	75	10	4	115.6
1.5–1.6	1.6–1.8	45	75	10	4	104.4
1.5–1.6	1.8–2.0	45	85	10	5	94.9
1.5–1.6	2.0–2.2	45	70	10	3	80.8
1.5–1.6	2.2–2.4	45	70	10	3	74.5
1.5–1.6	2.4–2.6	45	75	10	4	68.6
1.5–1.6	2.6–2.8	45	70	10	3	63.8
1.5–1.6	2.8–3.0	45	70	10	3	59.2
1.5–1.6	3.0–3.2	45	70	10	3	55.2
1.5–1.6	3.2–3.4	45	70	10	3	51.4
1.5–1.6	3.4–3.6	45	70	10	3	48.4
1.5–1.6	3.6–3.8	45	70	10	3	45.3
1.5–1.6	3.8–4.0	45	70	10	3	42.7
1.5–1.6	>4.0	45	70	10	3	31.6
1.6–1.7	0.2–0.4	45	80	5	8	284.8
1.6–1.7	0.4–0.6	45	80	5	8	249.8
1.6–1.7	0.6–0.8	45	80	5	8	217.3
1.6–1.7	0.8–1.0	45	80	5	8	189.5
1.6–1.7	1.0–1.2	45	70	5	6	166.8
1.6–1.7	1.2–1.4	45	70	5	6	147.2
1.6–1.7	1.4–1.6	45	75	10	4	132.9
1.6–1.7	1.6–1.8	45	75	10	4	110.8
1.6–1.7	1.8–2.0	45	75	10	4	100.7
1.6–1.7	2.0–2.2	45	75	10	4	92.2
1.6–1.7	2.2–2.4	45	70	10	3	79.5
1.6–1.7	2.4–2.6	45	70	10	3	73.3
1.6–1.7	2.6–2.8	45	70	10	3	67.9
1.6–1.7	2.8–3.0	45	70	10	3	63.1
1.6–1.7	3.0–3.2	45	70	10	3	58.8

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
1.6–1.7	3.2–3.4	45	70	10	3	54.9
1.6–1.7	3.4–3.6	45	70	10	3	51.6
1.6–1.7	3.6–3.8	45	70	10	3	48.2
1.6–1.7	3.8–4.0	45	70	10	3	45.5
1.6–1.7	>4.0	45	70	10	3	34.0
1.7–1.8	0.2–0.4	45	80	5	8	301.1
1.7–1.8	0.4–0.6	45	85	5	9	264.5
1.7–1.8	0.6–0.8	45	80	5	8	230.0
1.7–1.8	0.8–1.0	45	80	5	8	200.4
1.7–1.8	1.0–1.2	45	75	5	7	176.8
1.7–1.8	1.2–1.4	45	70	5	6	157.6
1.7–1.8	1.4–1.6	45	70	5	6	142.1
1.7–1.8	1.6–1.8	45	75	10	4	128.1
1.7–1.8	1.8–2.0	45	85	10	5	117.5
1.7–1.8	2.0–2.2	45	75	10	4	98.0
1.7–1.8	2.2–2.4	45	75	10	4	84.8
1.7–1.8	2.4–2.6	45	70	10	3	78.2
1.7–1.8	2.6–2.8	45	75	10	4	72.5
1.7–1.8	2.8–3.0	45	70	10	3	67.5
1.7–1.8	3.0–3.2	45	70	10	3	62.9
1.7–1.8	3.2–3.4	45	70	10	3	58.7
1.7–1.8	3.4–3.6	45	70	10	3	55.2
1.7–1.8	3.6–3.8	45	70	10	3	51.8
1.7–1.8	3.8–4.0	45	70	10	3	48.8
1.7–1.8	>4.0	45	70	10	3	36.3
1.8–1.9	0.2–0.4	45	80	5	8	319.0
1.8–1.9	0.4–0.6	45	80	5	8	279.3
1.8–1.9	0.6–0.8	45	75	5	7	243.3
1.8–1.9	0.8–1.0	45	80	5	8	212.1
1.8–1.9	1.0–1.2	45	75	5	7	187.0
1.8–1.9	1.2–1.4	45	75	5	7	166.8
1.8–1.9	1.4–1.6	45	70	5	6	149.2
1.8–1.9	1.6–1.8	45	70	5	6	135.7
1.8–1.9	1.8–2.0	45	70	5	6	124.5
1.8–1.9	2.0–2.2	45	75	10	4	114.4
1.8–1.9	2.2–2.4	45	70	10	3	95.5
1.8–1.9	2.4–2.6	45	70	10	3	88.3
1.8–1.9	2.6–2.8	45	70	10	3	76.9
1.8–1.9	2.8–3.0	45	85	10	5	71.6
1.8–1.9	3.0–3.2	45	70	10	3	66.7

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
1.8–1.9	3.2–3.4	45	70	10	3	62.3
1.8–1.9	3.4–3.6	45	70	10	3	58.6
1.8–1.9	3.6–3.8	45	70	10	3	54.8
1.8–1.9	3.8–4.0	45	70	10	3	51.8
1.8–1.9	>4.0	45	70	10	3	38.9
1.9–2.0	0.2–0.4	40	80	5	9	333.8
1.9–2.0	0.4–0.6	40	80	5	9	293.1
1.9–2.0	0.6–0.8	45	75	5	7	255.1
1.9–2.0	0.8–1.0	45	80	5	8	222.6
1.9–2.0	1.0–1.2	45	75	5	7	196.3
1.9–2.0	1.2–1.4	45	70	5	6	175.3
1.9–2.0	1.4–1.6	45	75	5	7	156.5
1.9–2.0	1.6–1.8	45	70	5	6	142.5
1.9–2.0	1.8–2.0	45	70	5	6	130.7
1.9–2.0	2.0–2.2	45	75	10	4	120.2
1.9–2.0	2.2–2.4	45	75	10	4	111.4
1.9–2.0	2.4–2.6	45	75	10	4	103.5
1.9–2.0	2.6–2.8	45	70	10	3	81.2
1.9–2.0	2.8–3.0	45	70	10	3	75.4
1.9–2.0	3.0–3.2	45	70	10	3	70.1
1.9–2.0	3.2–3.4	45	70	10	3	65.5
1.9–2.0	3.4–3.6	45	70	10	3	61.8
1.9–2.0	3.6–3.8	45	70	10	3	57.8
1.9–2.0	3.8–4.0	45	70	10	3	54.5
1.9–2.0	>4.0	45	70	10	3	44.5
2.0–2.1	0.2–0.4	40	80	5	9	350.8
2.0–2.1	0.4–0.6	40	80	5	9	307.8
2.0–2.1	0.6–0.8	40	85	5	10	268.0
2.0–2.1	0.8–1.0	45	80	5	8	234.2
2.0–2.1	1.0–1.2	45	75	5	7	206.3
2.0–2.1	1.2–1.4	45	75	5	7	184.4
2.0–2.1	1.4–1.6	45	70	5	6	164.9
2.0–2.1	1.6–1.8	45	70	5	6	151.2
2.0–2.1	1.8–2.0	45	75	5	7	137.5
2.0–2.1	2.0–2.2	45	70	5	6	126.4
2.0–2.1	2.2–2.4	45	75	10	4	117.3
2.0–2.1	2.4–2.6	45	70	10	3	109.0
2.0–2.1	2.6–2.8	45	75	10	4	101.6
2.0–2.1	2.8–3.0	45	70	10	3	95.1
2.0–2.1	3.0–3.2	45	70	10	3	73.9

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
2.0–2.1	3.2–3.4	45	70	10	3	69.1
2.0–2.1	3.4–3.6	45	70	10	3	65.0
2.0–2.1	3.6–3.8	45	70	10	3	60.8
2.0–2.1	3.8–4.0	45	70	10	3	57.5
2.0–2.1	>4.0	45	70	10	3	47.0
2.1–2.2	0.2–0.4	40	80	5	9	365.8
2.1–2.2	0.4–0.6	40	80	5	9	321.7
2.1–2.2	0.6–0.8	40	80	5	9	280.0
2.1–2.2	0.8–1.0	40	80	5	9	244.4
2.1–2.2	1.0–1.2	40	75	5	8	215.8
2.1–2.2	1.2–1.4	45	75	5	7	192.4
2.1–2.2	1.4–1.6	45	70	5	6	173.9
2.1–2.2	1.6–1.8	45	70	5	6	158.3
2.1–2.2	1.8–2.0	45	70	5	6	143.9
2.1–2.2	2.0–2.2	45	70	5	6	132.6
2.1–2.2	2.2–2.4	45	70	5	6	122.8
2.1–2.2	2.4–2.6	45	70	10	3	114.4
2.1–2.2	2.6–2.8	45	70	10	3	106.6
2.1–2.2	2.8–3.0	45	70	10	3	99.7
2.1–2.2	3.0–3.2	45	70	10	3	93.4
2.1–2.2	3.2–3.4	45	70	10	3	72.7
2.1–2.2	3.4–3.6	45	70	10	3	68.5
2.1–2.2	3.6–3.8	45	70	10	3	64.1
2.1–2.2	3.8–4.0	45	70	10	3	60.5
2.1–2.2	>4.0	45	70	10	3	49.6
2.2–2.3	0.2–0.4	40	80	5	9	399.2
2.2–2.3	0.4–0.6	40	80	5	9	336.6
2.2–2.3	0.6–0.8	40	80	5	9	293.3
2.2–2.3	0.8–1.0	40	75	5	8	256.5
2.2–2.3	1.0–1.2	40	85	5	10	226.6
2.2–2.3	1.2–1.4	40	70	5	7	202.3
2.2–2.3	1.4–1.6	40	75	5	8	182.5
2.2–2.3	1.6–1.8	45	70	5	6	165.5
2.2–2.3	1.8–2.0	45	75	5	7	151.4
2.2–2.3	2.0–2.2	45	70	5	6	140.2
2.2–2.3	2.2–2.4	45	75	5	7	129.1
2.2–2.3	2.4–2.6	45	70	5	6	120.2
2.2–2.3	2.6–2.8	40	70	10	4	112.2
2.2–2.3	2.8–3.0	45	70	10	3	105.1
2.2–2.3	3.0–3.2	45	75	10	4	98.4

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
2.2–2.3	3.2–3.4	45	70	10	3	92.3
2.2–2.3	3.4–3.6	45	70	10	3	87.4
2.2–2.3	3.6–3.8	45	70	10	3	67.6
2.2–2.3	3.8–4.0	45	70	10	3	63.7
2.2–2.3	>4.0	45	70	10	3	52.1
2.3–2.4	0.2–0.4	40	80	5	9	414.8
2.3–2.4	0.4–0.6	40	85	5	10	350.4
2.3–2.4	0.6–0.8	40	80	5	9	305.4
2.3–2.4	0.8–1.0	40	80	5	9	266.7
2.3–2.4	1.0–1.2	40	85	5	10	235.5
2.3–2.4	1.2–1.4	40	80	5	9	210.4
2.3–2.4	1.4–1.6	40	70	5	7	190.0
2.3–2.4	1.6–1.8	40	75	5	8	171.9
2.3–2.4	1.8–2.0	40	70	5	7	157.8
2.3–2.4	2.0–2.2	40	70	10	4	145.2
2.3–2.4	2.2–2.4	40	80	10	5	134.6
2.3–2.4	2.4–2.6	40	70	10	4	125.2
2.3–2.4	2.6–2.8	40	70	10	4	116.8
2.3–2.4	2.8–3.0	40	80	10	5	109.3
2.3–2.4	3.0–3.2	40	70	10	4	102.4
2.3–2.4	3.2–3.4	40	70	10	4	96.1
2.3–2.4	3.4–3.6	40	70	10	4	91.0
2.3–2.4	3.6–3.8	45	70	10	3	85.6
2.3–2.4	3.8–4.0	45	75	10	4	66.5
2.3–2.4	>4.0	45	75	10	4	54.5
2.4–2.5	0.2–0.4	40	80	5	9	430.2
2.4–2.5	0.4–0.6	40	80	5	9	364.0
2.4–2.5	0.6–0.8	40	75	5	8	317.4
2.4–2.5	0.8–1.0	40	75	5	8	277.2
2.4–2.5	1.0–1.2	40	85	5	10	245.4
2.4–2.5	1.2–1.4	40	75	5	8	219.0
2.4–2.5	1.4–1.6	40	75	5	8	196.6
2.4–2.5	1.6–1.8	40	75	5	8	179.1
2.4–2.5	1.8–2.0	40	70	5	7	165.0
2.4–2.5	2.0–2.2	45	70	5	6	151.1
2.4–2.5	2.2–2.4	45	70	5	6	140.2
2.4–2.5	2.4–2.6	40	80	10	5	130.3
2.4–2.5	2.6–2.8	40	70	10	4	121.6
2.4–2.5	2.8–3.0	40	70	10	4	113.9
2.4–2.5	3.0–3.2	40	80	10	5	106.6

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
2.4–2.5	3.2–3.4	40	80	10	5	100.1
2.4–2.5	3.4–3.6	40	80	10	5	94.8
2.4–2.5	3.6–3.8	45	70	10	3	89.2
2.4–2.5	3.8–4.0	45	70	10	3	84.6
2.4–2.5	>4.0	45	70	10	3	56.9
2.5–2.6	0.2–0.4	40	85	5	10	445.6
2.5–2.6	0.4–0.6	40	80	5	9	393.7
2.5–2.6	0.6–0.8	40	80	5	9	329.9
2.5–2.6	0.8–1.0	40	80	5	9	288.7
2.5–2.6	1.0–1.2	40	75	5	8	254.9
2.5–2.6	1.2–1.4	40	75	5	8	228.5
2.5–2.6	1.4–1.6	40	70	5	7	206.0
2.5–2.6	1.6–1.8	40	70	5	7	186.8
2.5–2.6	1.8–2.0	40	70	5	7	171.3
2.5–2.6	2.0–2.2	40	70	5	7	157.8
2.5–2.6	2.2–2.4	40	70	10	4	146.2
2.5–2.6	2.4–2.6	40	80	10	5	135.9
2.5–2.6	2.6–2.8	40	80	10	5	126.8
2.5–2.6	2.8–3.0	40	70	10	4	119.1
2.5–2.6	3.0–3.2	40	70	10	4	111.4
2.5–2.6	3.2–3.4	40	70	10	4	104.7
2.5–2.6	3.4–3.6	40	70	10	4	99.1
2.5–2.6	3.6–3.8	40	80	10	5	93.4
2.5–2.6	3.8–4.0	40	70	10	4	88.5
2.5–2.6	>4.0	45	70	10	3	59.4
2.6–2.7	0.2–0.4	40	80	5	9	461.9
2.6–2.7	0.4–0.6	40	75	5	8	406.7
2.6–2.7	0.6–0.8	40	80	5	9	342.4
2.6–2.7	0.8–1.0	40	80	5	9	299.3
2.6–2.7	1.0–1.2	40	80	5	9	264.7
2.6–2.7	1.2–1.4	40	80	5	9	236.5
2.6–2.7	1.4–1.6	40	85	5	10	213.9
2.6–2.7	1.6–1.8	40	70	5	7	194.8
2.6–2.7	1.8–2.0	40	80	5	9	178.5
2.6–2.7	2.0–2.2	40	70	5	7	163.7
2.6–2.7	2.2–2.4	40	70	5	7	151.7
2.6–2.7	2.4–2.6	40	70	10	4	141.2
2.6–2.7	2.6–2.8	40	70	10	4	131.9
2.6–2.7	2.8–3.0	40	70	10	4	123.6
2.6–2.7	3.0–3.2	40	70	10	4	115.9

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
2.6–2.7	3.2–3.4	40	70	10	4	108.8
2.6–2.7	3.4–3.6	40	70	10	4	103.0
2.6–2.7	3.6–3.8	40	70	10	4	96.9
2.6–2.7	3.8–4.0	40	70	10	4	92.1
2.6–2.7	>4.0	45	70	10	3	76.7
2.7–2.8	0.2–0.4	40	80	5	9	477.6
2.7–2.8	0.4–0.6	40	80	5	9	421.8
2.7–2.8	0.6–0.8	40	80	5	9	367.9
2.7–2.8	0.8–1.0	40	80	5	9	310.2
2.7–2.8	1.0–1.2	40	80	5	9	274.2
2.7–2.8	1.2–1.4	40	80	5	9	245.6
2.7–2.8	1.4–1.6	40	80	5	9	221.8
2.7–2.8	1.6–1.8	40	70	5	7	202.5
2.7–2.8	1.8–2.0	40	70	5	7	185.8
2.7–2.8	2.0–2.2	40	75	5	8	170.1
2.7–2.8	2.2–2.4	40	85	5	10	157.9
2.7–2.8	2.4–2.6	40	70	5	7	146.8
2.7–2.8	2.6–2.8	40	70	5	7	137.4
2.7–2.8	2.8–3.0	40	70	10	4	128.6
2.7–2.8	3.0–3.2	40	70	10	4	120.6
2.7–2.8	3.2–3.4	40	70	10	4	113.0
2.7–2.8	3.4–3.6	40	70	10	4	107.0
2.7–2.8	3.6–3.8	40	70	10	4	100.9
2.7–2.8	3.8–4.0	40	70	10	4	95.7
2.7–2.8	>4.0	40	70	10	4	79.9
2.8–2.9	0.2–0.4	40	80	5	9	491.6
2.8–2.9	0.4–0.6	40	80	5	9	434.3
2.8–2.9	0.6–0.8	40	80	5	9	379.9
2.8–2.9	0.8–1.0	40	80	5	9	320.3
2.8–2.9	1.0–1.2	40	80	5	9	283.1
2.8–2.9	1.2–1.4	40	80	5	9	253.6
2.8–2.9	1.4–1.6	40	70	5	7	228.9
2.8–2.9	1.6–1.8	40	70	5	7	208.0
2.8–2.9	1.8–2.0	40	70	5	7	190.9
2.8–2.9	2.0–2.2	40	70	5	7	175.5
2.8–2.9	2.2–2.4	40	70	5	7	162.9
2.8–2.9	2.4–2.6	40	75	5	8	152.1
2.8–2.9	2.6–2.8	40	70	5	7	141.6
2.8–2.9	2.8–3.0	40	70	5	7	132.5
2.8–2.9	3.0–3.2	40	80	10	5	124.1

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
2.8–2.9	3.2–3.4	40	70	10	4	116.7
2.8–2.9	3.4–3.6	40	70	10	4	110.4
2.8–2.9	3.6–3.8	40	70	10	4	104.0
2.8–2.9	3.8–4.0	40	70	10	4	98.8
2.8–2.9	>4.0	40	70	10	4	82.2
2.9–3.0	0.2–0.4	40	85	5	10	507.5
2.9–3.0	0.4–0.6	40	85	5	10	447.9
2.9–3.0	0.6–0.8	40	85	5	10	391.4
2.9–3.0	0.8–1.0	40	85	5	10	331.7
2.9–3.0	1.0–1.2	40	80	5	9	293.4
2.9–3.0	1.2–1.4	40	75	5	8	262.5
2.9–3.0	1.4–1.6	40	80	5	9	237.5
2.9–3.0	1.6–1.8	40	75	5	8	216.4
2.9–3.0	1.8–2.0	40	85	5	10	198.5
2.9–3.0	2.0–2.2	40	70	5	7	182.3
2.9–3.0	2.2–2.4	40	70	5	7	169.2
2.9–3.0	2.4–2.6	40	85	5	10	157.5
2.9–3.0	2.6–2.8	40	70	5	7	147.1
2.9–3.0	2.8–3.0	40	75	5	8	137.6
2.9–3.0	3.0–3.2	40	70	10	4	129.2
2.9–3.0	3.2–3.4	40	70	10	4	121.3
2.9–3.0	3.4–3.6	40	70	10	4	115.0
2.9–3.0	3.6–3.8	40	70	10	4	108.4
2.9–3.0	3.8–4.0	40	70	10	4	102.9
2.9–3.0	>4.0	40	80	10	5	85.9
3.0–3.1	0.2–0.4	40	80	5	9	523.9
3.0–3.1	0.4–0.6	40	80	5	9	462.6
3.0–3.1	0.6–0.8	40	80	5	9	404.6
3.0–3.1	0.8–1.0	40	80	5	9	355.0
3.0–3.1	1.0–1.2	40	80	5	9	315.0
3.0–3.1	1.2–1.4	40	75	5	8	271.7
3.0–3.1	1.4–1.6	40	85	5	10	245.4
3.0–3.1	1.6–1.8	40	75	5	8	223.9
3.0–3.1	1.8–2.0	40	80	5	9	205.3
3.0–3.1	2.0–2.2	40	70	5	7	188.5
3.0–3.1	2.2–2.4	40	75	5	8	175.0
3.0–3.1	2.4–2.6	40	75	5	8	162.9
3.0–3.1	2.6–2.8	40	70	5	7	152.4
3.0–3.1	2.8–3.0	40	70	5	7	142.5
3.0–3.1	3.0–3.2	40	70	5	7	133.7

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
3.0–3.1	3.2–3.4	40	70	5	7	125.5
3.0–3.1	3.4–3.6	40	70	10	4	119.4
3.0–3.1	3.6–3.8	40	70	10	4	112.2
3.0–3.1	3.8–4.0	40	70	10	4	106.4
3.0–3.1	>4.0	40	70	10	4	88.9
3.1–3.2	0.2–0.4	40	80	5	9	538.9
3.1–3.2	0.4–0.6	40	85	5	10	476.0
3.1–3.2	0.6–0.8	40	80	5	9	416.4
3.1–3.2	0.8–1.0	40	80	5	9	365.3
3.1–3.2	1.0–1.2	40	75	5	8	323.6
3.1–3.2	1.2–1.4	40	75	5	8	280.2
3.1–3.2	1.4–1.6	40	80	5	9	253.4
3.1–3.2	1.6–1.8	40	85	5	10	231.2
3.1–3.2	1.8–2.0	40	75	5	8	212.0
3.1–3.2	2.0–2.2	40	70	5	7	195.4
3.1–3.2	2.2–2.4	40	70	5	7	180.9
3.1–3.2	2.4–2.6	40	70	5	7	168.3
3.1–3.2	2.6–2.8	40	70	5	7	157.1
3.1–3.2	2.8–3.0	40	70	5	7	147.3
3.1–3.2	3.0–3.2	40	75	5	8	138.0
3.1–3.2	3.2–3.4	40	75	5	8	130.1
3.1–3.2	3.4–3.6	40	70	10	4	123.0
3.1–3.2	3.6–3.8	40	80	10	5	116.0
3.1–3.2	3.8–4.0	40	70	10	4	110.1
3.1–3.2	>4.0	40	80	10	5	92.0
3.2–3.3	0.2–0.4	40	80	5	9	553.1
3.2–3.3	0.4–0.6	40	80	5	9	489.1
3.2–3.3	0.6–0.8	40	85	5	10	428.1
3.2–3.3	0.8–1.0	40	80	5	9	375.3
3.2–3.3	1.0–1.2	40	75	5	8	333.1
3.2–3.3	1.2–1.4	40	85	5	10	288.3
3.2–3.3	1.4–1.6	40	75	5	8	259.6
3.2–3.3	1.6–1.8	40	75	5	8	237.5
3.2–3.3	1.8–2.0	40	80	5	9	218.0
3.2–3.3	2.0–2.2	40	75	5	8	200.4
3.2–3.3	2.2–2.4	40	70	5	7	186.1
3.2–3.3	2.4–2.6	40	70	5	7	173.6
3.2–3.3	2.6–2.8	40	70	5	7	161.7
3.2–3.3	2.8–3.0	40	70	5	7	151.5
3.2–3.3	3.0–3.2	40	70	5	7	142.3

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
3.2–3.3	3.2–3.4	40	70	5	7	133.5
3.2–3.3	3.4–3.6	40	70	5	7	126.5
3.2–3.3	3.6–3.8	40	70	5	7	119.2
3.2–3.3	3.8–4.0	40	70	5	7	113.2
3.2–3.3	>4.0	40	70	10	4	94.7
3.3–3.4	0.2–0.4	40	85	5	10	568.6
3.3–3.4	0.4–0.6	40	80	5	9	502.5
3.3–3.4	0.6–0.8	40	80	5	9	440.2
3.3–3.4	0.8–1.0	40	80	5	9	386.2
3.3–3.4	1.0–1.2	40	85	5	10	342.7
3.3–3.4	1.2–1.4	40	80	5	9	307.4
3.3–3.4	1.4–1.6	40	80	5	9	268.9
3.3–3.4	1.6–1.8	40	70	5	7	245.2
3.3–3.4	1.8–2.0	40	85	5	10	224.9
3.3–3.4	2.0–2.2	40	80	5	9	207.6
3.3–3.4	2.2–2.4	40	80	5	9	192.1
3.3–3.4	2.4–2.6	40	70	5	7	178.9
3.3–3.4	2.6–2.8	40	70	5	7	167.0
3.3–3.4	2.8–3.0	40	70	5	7	156.4
3.3–3.4	3.0–3.2	40	70	5	7	147.0
3.3–3.4	3.2–3.4	40	75	5	8	138.1
3.3–3.4	3.4–3.6	40	80	5	9	130.7
3.3–3.4	3.6–3.8	40	75	5	8	123.2
3.3–3.4	3.8–4.0	40	75	5	8	117.2
3.3–3.4	>4.0	40	80	10	5	97.8
3.4–3.5	0.2–0.4	40	80	5	9	583.6
3.4–3.5	0.4–0.6	40	85	5	10	515.4
3.4–3.5	0.6–0.8	40	85	5	10	451.8
3.4–3.5	0.8–1.0	40	85	5	10	397.0
3.4–3.5	1.0–1.2	40	80	5	9	351.6
3.4–3.5	1.2–1.4	40	75	5	8	315.9
3.4–3.5	1.4–1.6	40	80	5	9	276.2
3.4–3.5	1.6–1.8	40	80	5	9	252.1
3.4–3.5	1.8–2.0	40	70	5	7	230.9
3.4–3.5	2.0–2.2	40	75	5	8	213.3
3.4–3.5	2.2–2.4	40	80	5	9	197.7
3.4–3.5	2.4–2.6	40	80	5	9	184.5
3.4–3.5	2.6–2.8	40	70	5	7	171.8
3.4–3.5	2.8–3.0	40	80	5	9	161.1
3.4–3.5	3.0–3.2	40	85	5	10	151.0

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
3.4–3.5	3.2–3.4	40	70	5	7	142.4
3.4–3.5	3.4–3.6	40	70	5	7	134.4
3.4–3.5	3.6–3.8	40	70	5	7	126.7
3.4–3.5	3.8–4.0	40	70	5	7	120.5
3.4–3.5	>4.0	40	70	10	4	100.7
3.5–3.6	0.2–0.4	40	85	5	10	621.3
3.5–3.6	0.4–0.6	40	85	5	10	551.1
3.5–3.6	0.6–0.8	40	85	5	10	463.6
3.5–3.6	0.8–1.0	40	80	5	9	406.9
3.5–3.6	1.0–1.2	40	85	5	10	360.6
3.5–3.6	1.2–1.4	40	75	5	8	324.2
3.5–3.6	1.4–1.6	40	85	5	10	283.9
3.5–3.6	1.6–1.8	40	80	5	9	259.0
3.5–3.6	1.8–2.0	40	80	5	9	237.7
3.5–3.6	2.0–2.2	40	75	5	8	219.2
3.5–3.6	2.2–2.4	40	70	5	7	203.6
3.5–3.6	2.4–2.6	40	75	5	8	189.1
3.5–3.6	2.6–2.8	40	70	5	7	176.8
3.5–3.6	2.8–3.0	40	70	5	7	165.6
3.5–3.6	3.0–3.2	40	85	5	10	155.8
3.5–3.6	3.2–3.4	40	70	5	7	146.2
3.5–3.6	3.4–3.6	40	80	5	9	138.7
3.5–3.6	3.6–3.8	40	70	5	7	130.5
3.5–3.6	3.8–4.0	40	70	5	7	123.8
3.5–3.6	>4.0	40	70	10	4	103.5
3.6–3.7	0.2–0.4	40	80	5	9	635.9
3.6–3.7	0.4–0.6	40	85	5	10	564.2
3.6–3.7	0.6–0.8	40	85	5	10	475.1
3.6–3.7	0.8–1.0	40	80	5	9	417.2
3.6–3.7	1.0–1.2	40	75	5	8	370.1
3.6–3.7	1.2–1.4	40	80	5	9	332.2
3.6–3.7	1.4–1.6	40	75	5	8	291.6
3.6–3.7	1.6–1.8	40	85	5	10	266.0
3.6–3.7	1.8–2.0	40	75	5	8	243.6
3.6–3.7	2.0–2.2	40	85	5	10	225.0
3.6–3.7	2.2–2.4	40	75	5	8	208.5
3.6–3.7	2.4–2.6	40	70	5	7	194.2
3.6–3.7	2.6–2.8	40	70	5	7	181.7
3.6–3.7	2.8–3.0	40	70	5	7	170.2
3.6–3.7	3.0–3.2	40	70	5	7	159.8

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
3.6–3.7	3.2–3.4	40	70	5	7	150.2
3.6–3.7	3.4–3.6	40	85	5	10	142.2
3.6–3.7	3.6–3.8	40	85	5	10	133.9
3.6–3.7	3.8–4.0	40	70	5	7	127.2
3.6–3.7	>4.0	40	80	10	5	106.3
3.7–3.8	0.2–0.4	40	80	5	9	651.5
3.7–3.8	0.4–0.6	40	85	5	10	577.9
3.7–3.8	0.6–0.8	40	80	5	9	487.2
3.7–3.8	0.8–1.0	40	80	5	9	427.9
3.7–3.8	1.0–1.2	40	80	5	9	380.1
3.7–3.8	1.2–1.4	40	85	5	10	341.2
3.7–3.8	1.4–1.6	40	80	5	9	308.8
3.7–3.8	1.6–1.8	40	75	5	8	282.1
3.7–3.8	1.8–2.0	40	80	5	9	251.1
3.7–3.8	2.0–2.2	40	85	5	10	231.0
3.7–3.8	2.2–2.4	40	85	5	10	215.0
3.7–3.8	2.4–2.6	40	75	5	8	199.8
3.7–3.8	2.6–2.8	40	85	5	10	187.2
3.7–3.8	2.8–3.0	40	70	5	7	175.2
3.7–3.8	3.0–3.2	40	70	5	7	164.5
3.7–3.8	3.2–3.4	40	70	5	7	154.7
3.7–3.8	3.4–3.6	40	85	5	10	146.4
3.7–3.8	3.6–3.8	40	80	5	9	138.0
3.7–3.8	3.8–4.0	40	75	5	8	131.0
3.7–3.8	>4.0	40	70	5	7	109.8
3.8–3.9	0.2–0.4	40	85	5	10	668.5
3.8–3.9	0.4–0.6	40	80	5	9	593.3
3.8–3.9	0.6–0.8	40	85	5	10	522.4
3.8–3.9	0.8–1.0	40	75	5	8	460.8
3.8–3.9	1.0–1.2	40	75	5	8	396.1
3.8–3.9	1.2–1.4	40	75	5	8	356.5
3.8–3.9	1.4–1.6	40	80	5	9	317.4
3.8–3.9	1.6–1.8	40	85	5	10	296.3
3.8–3.9	1.8–2.0	40	80	5	9	266.3
3.8–3.9	2.0–2.2	40	85	5	10	237.5
3.8–3.9	2.2–2.4	40	80	5	9	220.5
3.8–3.9	2.4–2.6	40	70	5	7	205.6
3.8–3.9	2.6–2.8	40	80	5	9	192.1
3.8–3.9	2.8–3.0	40	70	5	7	180.1
3.8–3.9	3.0–3.2	40	70	5	7	168.8

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
3.8–3.9	3.2–3.4	40	80	5	9	158.8
3.8–3.9	3.4–3.6	40	75	5	8	150.6
3.8–3.9	3.6–3.8	40	70	5	7	141.9
3.8–3.9	3.8–4.0	40	80	5	9	135.1
3.8–3.9	>4.0	40	75	5	8	112.9
3.9–4.0	0.2–0.4	40	80	5	9	682.1
3.9–4.0	0.4–0.6	40	85	5	10	606.0
3.9–4.0	0.6–0.8	40	80	5	9	533.4
3.9–4.0	0.8–1.0	40	80	5	9	471.0
3.9–4.0	1.0–1.2	40	85	5	10	398.0
3.9–4.0	1.2–1.4	40	85	5	10	364.3
3.9–4.0	1.4–1.6	40	75	5	8	331.5
3.9–4.0	1.6–1.8	40	80	5	9	303.7
3.9–4.0	1.8–2.0	40	75	5	8	279.5
3.9–4.0	2.0–2.2	40	85	5	10	258.8
3.9–4.0	2.2–2.4	40	70	5	7	226.1
3.9–4.0	2.4–2.6	40	70	5	7	210.3
3.9–4.0	2.6–2.8	40	80	5	9	196.9
3.9–4.0	2.8–3.0	40	85	5	10	184.1
3.9–4.0	3.0–3.2	40	70	5	7	173.1
3.9–4.0	3.2–3.4	40	75	5	8	162.9
3.9–4.0	3.4–3.6	40	70	5	7	154.1
3.9–4.0	3.6–3.8	40	75	5	8	145.7
3.9–4.0	3.8–4.0	40	70	5	7	138.5
3.9–4.0	>4.0	40	70	5	7	115.8
>4.0	0.2–0.4	40	80	5	9	692.9
>4.0	0.4–0.6	40	85	5	10	615.7
>4.0	0.6–0.8	40	80	5	9	543.1
>4.0	0.8–1.0	40	85	5	10	479.4
>4.0	1.0–1.2	40	80	5	9	413.6
>4.0	1.2–1.4	40	80	5	9	372.5
>4.0	1.4–1.6	40	75	5	8	338.3
>4.0	1.6–1.8	40	80	5	9	309.9
>4.0	1.8–2.0	40	80	5	9	286.1
>4.0	2.0–2.2	40	70	5	7	264.3
>4.0	2.2–2.4	40	70	5	7	246.8
>4.0	2.4–2.6	40	75	5	8	214.7
>4.0	2.6–2.8	40	75	5	8	200.7
>4.0	2.8–3.0	40	70	5	7	188.3
>4.0	3.0–3.2	40	75	5	8	176.9

Table 1. Continued

Relative CRC risk	Relative CCD risk	Start age	End age	Interval	No. of colonoscopies	QALYG
>4.0	3.2–3.4	40	80	5	9	166.3
>4.0	3.4–3.6	40	70	5	7	157.4
>4.0	3.6–3.8	40	85	5	10	148.6
>4.0	3.8–4.0	40	70	5	7	141.2
>4.0	>4.0	40	70	5	7	118.2

CCD, competing causes of death.

Supplementary File 6. Risk-Stratified Screening Including FIT and Colonoscopy Strategies

Because FIT screening may be appropriate and cost-effective for low-risk individuals, we did an additional analysis in which we considered both FIT and colonoscopy screening. In this additional analysis, we considered FIT screening with the same start (40, 45, 50, 55, and 60 years) and end ages (70, 75, 80, and 85 years) as for the colonoscopy screening scenarios and 1-, 2-, or 3-year intervals. After a positive FIT, a follow-up colonoscopy was performed. Yearly uniform FIT screening at ages 45–75 was used as reference case in this analysis.

With FIT, uniform screening yielded 110 quality-adjusted life years gained, required 1674 colonoscopies, and cost $3.5 million per 1000 40-year-old individuals. At a WTP threshold of $100,000 per QALY, optimal risk-stratified screening strategies ranged from a FIT every 2 years at ages 45–70 for the lowest risk groups to a yearly FIT at ages 40–85 for the highest risk groups. Risk-stratified screening yielded 119 QALYG, required 2011 colonoscopies, and cost $3.6 million per 1000 40-year old individuals (Table 1).

At a WTP threshold of $0 per QALYG, both costs and QALYG of risk-stratified screening were higher than for uniform screening, which makes it difficult to compare the cost-effectiveness of risk-stratified screening vs uniform screening. With a unit cost of $47 for risk testing, costs of risk-stratified screening at a WTP threshold of $0 per QALYG were equal to that of uniform screening. Uniform FIT screening is therefore dominated if unit costs for risk testing are lower than $47.

Table 1. Effects and Costs per 1000 40-Year-Old Individuals for Uniform FIT Screening and Risk-Stratified Screening at a WTP Threshold of $0 and $100,000 per QALYG

						Costs, USD (1000)[a,b]		
	Colonoscopies	CRC cases	CRC deaths	Life years[a]	QALYG[a]	Polygenic test	CRC screening & treatment costs	Total
Uniform FIT screening[c]	1690	47	11	23,409	110	0	3486	3486
Risk-stratified screening								
- WTP = 0	1795	44	10	23,412	114	100	3439	3539
- WTP = $100,00	2011	43	9	23,417	119	100	3476	3576

[a](Quality-adjusted) life years (gained) and costs were discounted at an annual rate of 3%.
[b]Costs are in 2017 US dollars (USD).
[c]Uniform FIT screening was defined as yearly FIT screening from ages 45 to 75.

References

1. Jeon J, Du M, Schoen RE, et al. Determining risk of colorectal cancer and starting age of screening based on lifestyle, environmental, and genetic factors. Gastroenterology 2018; 154:2152–2164.
2. Thomas M, Sakoda LC, Hoffmeister M, et al. Genome-wide modeling of polygenic risk score in colorectal cancer risk. Am J Hum Genet 2020;107:432–444.
3. Heagerty PJ, Lumley T, Pepe MS. Time-dependent ROC curves for censored survival data and a diagnostic marker. Biometrics 2000;56:337–344.
4. Naber SK, Kundu S, Kuntz KM, et al. Cost-effectiveness of risk-stratified colorectal cancer screening based on polygenic risk: current status and future potential. JNCI Cancer Spectrum 2020;4:pkz086.
5. Mai J-F, Scherer M. Simulating copulas: stochastic models, sampling algorithms, and applications. # N/A, 2017.
6. Van Rijn JC, Reitsma JB, Stoker J, et al. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol 2006;101:343–350.
7. Ness RM, Holmes AM, Klein R, et al. Utility valuations for outcome states of colorectal cancer. Am J Gastroenterol 1999; 94:1650–1657.
8. Wolf AMD, Fontham ETH, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society. CA Cancer J Clin 2018; 68:250–281.
9. Davidson KW, Barry MJ, Mangione CM, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. JAMA 2021;325:1965–1977.