

# Cost-Effectiveness of Personalized Screening for Colorectal Cancer Based on Polygenic Risk and Family History



Dayna R. Cenin<sup>1,2,3</sup>, Steffie K. Naber<sup>1</sup>, Anne C. de Weerd<sup>1</sup>, Mark A. Jenkins<sup>4</sup>, David B. Preen<sup>2</sup>, Hooi C. Ee<sup>5</sup>, Peter C. O'Leary<sup>3,6,7</sup>, and Iris Lansdorp-Vogelaar<sup>1</sup>

## ABSTRACT

**Background:** There is growing evidence for personalizing colorectal cancer screening based on risk factors. We compared the cost-effectiveness of personalized colorectal cancer screening based on polygenic risk and family history to uniform screening.

**Methods:** Using the MISCAN-Colon model, we simulated a cohort of 100 million 40-year-olds, offering them uniform or personalized screening. Individuals were categorized based on polygenic risk and family history of colorectal cancer. We varied screening strategies by start age, interval and test and estimated costs, and quality-adjusted life years (QALY). In our analysis, we (i) assessed the cost-effectiveness of uniform screening; (ii) developed personalized screening scenarios based on optimal screening strategies by risk group; and (iii) compared the cost-effectiveness of both.

**Results:** At a willingness-to-pay threshold of \$50,000/QALY, the optimal uniform screening scenario was annual fecal immuno-

chemical testing (FIT) from ages 50 to 74 years, whereas for personalized screening the optimal screening scenario consisted of annual and biennial FIT screening except for those at highest risk who were offered 5-yearly colonoscopy from age 50 years. Although these scenarios gained the same number of QALYs (17,887), personalized screening was not cost-effective, costing an additional \$428,953 due to costs associated with determining risk (assumed to be \$240 per person). Personalized screening was cost-effective when these costs were less than ~\$48.

**Conclusions:** Uniform colorectal cancer screening currently appears more cost-effective than personalized screening based on polygenic risk and family history. However, cost-effectiveness is highly dependent on the cost of determining risk.

**Impact:** Personalized screening could become increasingly viable as costs for determining risk decrease.

## Introduction

Screening has been shown to be a cost-effective method to reduce the incidence and mortality of colorectal cancer (1–4). In countries with population screening programs, screening for colorectal cancer is based on age (5), with separate screening recommendations for those with a positive family history (6). However, genetic susceptibility also plays an important role in colorectal cancer risk and it has been suggested that, when combined with family history, this may improve risk prediction and diagnosis (7, 8).

Genome-wide association studies have shown that polygenic factors, such as common, low-risk genetic variants or single-nucleotide polymorphisms (SNP), play a significant role in defining colorectal cancer risk due to their relatively high prevalence in the population (9–12). In isolation, SNPs are only weakly associated with colorectal cancer risk; however, cumulatively they explain substantial variation in risk (9, 13). A polygenic test can be used to estimate someone's polygenic risk score based on the absence or presence of specific risk alleles. Such a risk score can be used to identify individuals at several times lower and greater (0.49–3.40) colorectal cancer risk than the average population (14).

Compared with age-based screening, personalized screening provides an opportunity to stratify the population allowing screening to be tailored to an individual's risk (15). This would allow for those at lower risk to start screening later and/or have longer screening intervals, whereas those at higher risk could start screening earlier, undergo more intensive screening or both (9, 15–17). Personalized screening also provides opportunities to detect cancers in younger at-risk individuals, who are currently excluded from age-based screening despite being at increased risk (18–20). In this way, personalized screening has the potential to reduce the harms of screening while maintaining, or even increasing, its benefits in addition to improving its cost-effectiveness.

Previous research has demonstrated the efficacy of stratifying the population for screening based on age and polygenic risk (21, 22), or in combination with other factors including family history (7, 23). However, no studies have evaluated the cost-effectiveness of such risk-stratified screening compared with uniform screening for colorectal cancer. To address this gap in knowledge, we investigated the impact of personalizing colorectal cancer screening, based on polygenic risk and family history and compared its cost-effectiveness to uniform screening.

<sup>1</sup>Erasmus MC, University Medical Center Rotterdam, Department of Public Health, Rotterdam, the Netherlands. <sup>2</sup>Centre for Health Services Research, School of Population and Global Health, The University of Western Australia, Perth, Western Australia, Australia. <sup>3</sup>Health Systems and Health Economics, School of Public Health, Faculty of Health Sciences, Curtin University, Perth, Western Australia, Australia. <sup>4</sup>Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Melbourne, Victoria, Australia. <sup>5</sup>Department of Gastroenterology, Sir Charles Gairdner Hospital, Perth, Western Australia, Australia. <sup>6</sup>Division of Obstetrics and Gynaecology, Faculty of Health and Medical Sciences, The University of Western Australia, Perth, Western Australia, Australia. <sup>7</sup>Clinical Biochemistry, PathWest Laboratory Medicine, QE2 Medical Centre, Nedlands, Western Australia, Australia.

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**Corresponding Author:** Dayna R. Cenin, Erasmus MC, University Medical Center Rotterdam, PO Box 2040, 3067 DK Rotterdam, the Netherlands. Phone: 31-6-57-62-72-54; E-mail: [d.cenin@erasmusmc.nl](mailto:d.cenin@erasmusmc.nl)

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## Methods and Materials

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon; ref. 24) model to estimate the costs, benefits and harms of different uniform screening strategies as well as personalized screening strategies that were based on polygenic risk and family history of colorectal cancer.

### MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for colorectal cancer developed at the Department of Public Health, Erasmus University Medical Center (24). The structure, underlying assumptions, and data sources used to calibrate the model are detailed in Supplementary Methods and Materials. In brief, the model simulates a large population of individuals from birth to death, first without and then with screening for colorectal cancer. As each simulated person ages, one or more adenomas may arise and some can progress in size from small (<5 mm) to medium (6–9 mm) to large (>10 mm). Some adenomas develop into preclinical cancer and subsequently progress through cancer stages I to IV. During each stage symptoms may present and colorectal cancer may be diagnosed. The introduction of screening may alter the simulated life histories through detection and removal of adenomas or through detection of colorectal cancer at an earlier stage with a more favorable survival. By comparing the life histories of a simulated population being screened to the corresponding life histories in a simulated population not screened, MISCAN-Colon quantifies the effectiveness and the costs of screening.

MISCAN-Colon was calibrated to match the age-specific incidence of colorectal cancer in Australia before the introduction of biennial fecal immunochemical test (FIT) screening for those ages 50 to 74 in 2006 (25). Stage distribution, localization of cancers in the colorectum, and five-year relative survival after clinical diagnosis of a cancer were based on Australian literature (26, 27). Additional assumptions of the MISCAN-Colon model are presented in **Table 1** and Supplementary Methods and Materials.

### Simulated population

For this analysis, we simulated a cohort of 100 million 40-year-olds, with life expectancy as observed in Australia in 2013 to 2015 (28). Individuals were followed for a lifetime, until a maximum age of 100 years, at which point they are all assumed to be dead.

### Risk stratification

Using previous research, the population was stratified *a priori* into five risk groups based on their quintile of polygenic risk score (based on 45 SNPs shown to increase colorectal cancer risk) and their first-degree family history of colorectal cancer (**Table 2**; ref. 14). The expected prevalence of each of the five categories in the general population was based on a random assignment of 1,000 people given a 20% probability of being in any SNP quintile and a 10% probability of having at least one first-degree relative with colorectal cancer (29). The relative risk (RR) of developing colorectal cancer (compared with the average population risk) for each risk group was based on the combined RR of each quintile of polygenic risk score and family history based on observed virtual independence of the two factors (14). The five risk groups were defined as “very low” (RR < 0.5), “low” (RR between 0.5 and 0.9), “average” (RR between 0.9 and 1.2), “high” (RR between 1.2 and 1.8), and “very high” (RR > 1.8). We assumed no other differences in life expectancy, colorectal cancer stage distribution, survival, or screening performance characteristics between the risk groups.

### Screening and surveillance

In addition to a scenario without screening, we modeled 25 different screening strategies, varying screening start age (40, 46, 50, 54, or 60 years), test (FIT or colonoscopy), and interval (annual, biennial or triennial screening for FIT, and every 5 or 10 years for colonoscopy). For all FIT analyses, we assumed a positivity of 7.7% based on rates observed in the Queensland Bowel Cancer Screening Program between August 2006 and December 2010 (30, 31). Screening was always assumed to stop at age 74 years. Surveillance intervals and stop-age for all scenarios were based on the Australian National Health and Medical Research Council Clinical Practice Guidelines for Surveillance Colonoscopy (32).

### Participation

Screening programs can be assessed under the assumption of perfect adherence or observed adherence. In the first analyses, we assumed perfect adherence to all screening, diagnostic, and surveillance tests. Subsequently, we estimated the costs and effects of screening at adherence levels currently observed in Australia.

For the latter analysis, we simulated participation rates as reported by the Australian National Bowel Cancer Screening Program (NBCSP), a biennial FIT screening program, in 2017 (**Table 1**; ref. 33). Participation with annual and triennial FIT and with primary colonoscopy screening was set at the same screening participation rates. Age-specific participation rates were provided in 5-year age intervals between 50 and 74 years. As data were not available for screening participation for individuals ages 40 to 49 years, participation was assumed to be equal to those ages 50 to 54 years. We assumed that 76.0% of individuals who had previously attended screening would attend again in the next screening round, whereas 19.7% of individuals who had not attended in the previous round would now attend based on data from the NBCSP (33).

A positive FIT requires a consultation with a primary care provider, such as a general practitioner (GP), to discuss test results and obtain a referral for colonoscopy. For the observed adherence analyses, it was assumed that 90% of FIT-positive cases would attend this appointment (26). In addition, attendance at diagnostic colonoscopy was age specific ranging from 68.2% to 72.3% based on outcomes from the NBCSP (33). The participation rate for colonoscopy surveillance was assumed to be 80% (34).

### Assumptions for costs and utilities

The cost of screening with FIT was based on commercially available kits (35). This cost includes the test, postage, and test processing fees. The cost to analyze a FIT specimen was based on the Australian Medicare Benefits Schedule (MBS; ref. 36). The cost of attending a GP to obtain a referral for colonoscopy (standard consult) is set in the MBS (37). The cost for colonoscopy and complications from colonoscopy was obtained from the Independent Hospital Pricing Authority report on costs in Australian public hospitals (38). Costs for cancer care were based on costs of cancer treatment in the Australian setting (39). All costs are presented in Australian dollars (\$AUD), standardized to 2016 prices using the consumer price index where necessary (40).

To determine risk, we assumed all individuals underwent assessment for family history of colorectal cancer and polygenic testing prior to the commencement of colorectal cancer screening. We assumed assessment for family history of colorectal cancer would be undertaken by a GP and cost the same as a standard consult (**Table 1**; ref. 37). In addition, we assumed polygenic testing would cost \$200 based on a commercially available polygenic test for breast cancer (41).

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The assumed utility loss due to colorectal cancer screening was 0.00274 quality-adjusted life years (QALY) per colonoscopy (1.5 days at 0.5 utility) and 0.001918 QALYs per complication of colonoscopy (14 days at 0.5 utility; **Table 1**). We also assumed that life years (LY) with colorectal cancer care are of lower quality than those without colorectal cancer care (42). We assumed no disutility from determining or knowing polygenic risk score.

**Model outcomes**

For all scenarios, the model estimated health effects such as colorectal cancer incidence and colorectal cancer mortality, and required resources such as the number of screening and surveillance tests

performed between ages 40 and 74 years. From these outcomes, we calculated costs, life years, and QALYs lived with each strategy. Costs, life years and QALYs were discounted at an annual rate of 5%, as is recommended in Australia (43). Undiscounted results are presented in Supplementary Results (Supplementary Tables S6 and S7; Supplementary Fig. S8).

**Analyses**

Our analysis consisted of four parts. First, we determined costs, benefits, and harms of the aforementioned screening strategies applied to the population as a whole (uniform screening). We plotted the uniform screening scenarios in a cost-effectiveness plane and

**Table 1.** Model inputs: test characteristics, participation assumptions, utility losses, and costs associated with colorectal cancer screening and treatment.

<b>Test characteristics</b>				
Specificity and sensitivity of FIT <sup>a</sup>				
Specificity (per person)				95.0%
Sensitivity adenoma 1-5 mm				0.0%
Sensitivity adenoma 6-9 mm				9.0%
Sensitivity adenoma 10+ mm				32.0%
Sensitivity cancer long before clinical diagnosis <sup>b</sup>				36.5%
Sensitivity cancer shortly before clinical diagnosis <sup>b</sup>				72.8%
Specificity and sensitivity of colonoscopy <sup>c,d</sup>				
Specificity				86%
Sensitivity adenoma 1-5 mm				75%
Sensitivity adenoma 6-9 mm				85%
Sensitivity adenoma 10+ mm				95%
Sensitivity preclinical cancer				95%
Complication of colonoscopy <sup>e</sup>				
Fatal complication <sup>f</sup>				0.040%
General complication <sup>g</sup>				
50-54				0.096%
55-59				0.080%
60-64				0.054%
65-69				0.127%
70-74				0.073%
<b>Participation</b>				
Uptake of initial screening offer <sup>h</sup>				
50-54				28.5%
55-59				36.8%
60-64				43.2%
65-69				43.5%
70-74				52.5%
Uptake of rescreening <sup>h</sup>				
Previously attended				76.0%
Previously not attended				19.7%
Attendance at general practitioner <sup>i</sup>				
Attendance at general practitioner <sup>i</sup>				90.0%
Uptake of diagnostic test <sup>h</sup>				
50-54				72.3%
55-59				71.6%
60-64				71.4%
65-69				70.6%
70-74				68.2%
Adherence to surveillance <sup>j</sup>				
Adherence to surveillance <sup>j</sup>				80.0%
<b>Utility loss (QALYs)<sup>k</sup></b>				
Per FIT	0			
Per colonoscopy <sup>l</sup>	0.00274			
Per complication of colonoscopy <sup>m</sup>	0.01918			
Per LY with CRC care <sup>n,o</sup>	Initial care	Continuing care	Terminal care (death CRC)	Terminal care (death OC)
Stage I	0.12	0.05	0.70	0.05
Stage II	0.18	0.05	0.70	0.05
Stage III	0.24	0.24	0.70	0.24
Stage IV	0.70	0.70	0.70	0.70

(Continued on the following page)

## Personalized Screening for Colorectal Cancer: Cost-Effectiveness Analysis

**Table 1.** Model inputs: test characteristics, participation assumptions, utility losses, and costs associated with colorectal cancer screening and treatment. (Cont'd)

<b>Costs (2016 \$AUD)<sup>p</sup></b>	
Per FIT invitation <sup>q</sup>	17.35
Per returned FIT <sup>r</sup>	22.60
Per GP visit <sup>s</sup>	37.05
Per colonoscopy (same day) <sup>t</sup>	1,627
Polygenic test <sup>u</sup>	200
Per complication of colonoscopy <sup>v</sup>	9,027
Treatment by stage and location <sup>w,x,y</sup>	
Stage I CC (without bevacizumab)	31,107
Stage I RC (without bevacizumab)	41,619
Stage II CC (without bevacizumab)	43,776
Stage III CC (without bevacizumab)	79,375
Stage II/III RC (without bevacizumab)	86,317
Stage IV CRC without bevacizumab	71,156
Stage IV CRC with bevacizumab	81,403

Abbreviations: CC, colon cancer; CRC, colorectal cancer; FIT, fecal immunochemical test; GP, general practitioner; OC, other cause; QALY, quality-adjusted life years; RC, rectal cancer; LY, life year.

<sup>a</sup>Specificity and sensitivity of FIT derived from results of the Queensland Health Report (31).

<sup>b</sup>We assume that FIT screening is more sensitive in cancers as they progress toward becoming symptomatic (visible bleeding) and clinically detectable. For preclinical cancers that will become symptomatic within the same stage, assumed test sensitivity is higher.

<sup>c</sup>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 or lead to (unnecessary) referral with sigmoidoscopy. The evidence synthesis reported no specificity for endoscopy for any adenoma. Specificity for colonoscopy is therefore based on Schroy and colleagues (62).

<sup>d</sup>Sensitivity of colonoscopy for the detection of adenomas and colorectal cancer within the reach of the endoscope was obtained from a systematic review on miss rates observed in tandem colonoscopy studies (63).

<sup>e</sup>Complications are conditional on polypectomy, and we assume that polypectomy is performed only if colonoscopy is positive.

<sup>f</sup>Fatal perforation taken from Viiala and colleagues (64) and includes only deaths from colonoscopies performed in outpatients within 30 days of, and attributed to, colonoscopy.

<sup>g</sup>Age-specific rate of complication taken from National Bowel Cancer Screening Monitoring report (33). A complication is considered as an unplanned hospital admission within 30 days of a diagnostic colonoscopy.

<sup>h</sup>Uptake of screening, rescreening, and participation in diagnostic follow-up taken from the National Bowel Cancer Screening Monitoring report (33).

<sup>i</sup>Attendance at general practitioner for referral to colonoscopy taken from Tran and colleagues (26).

<sup>j</sup>Attendance at surveillance colonoscopies assumed to be 80% based on Colquhoun and colleagues (34).

<sup>k</sup>The loss of quality of life associated with a particular event.

<sup>l</sup>Equal to 2 days per colonoscopy at a utility of 0.5.

<sup>m</sup>Complications associated with hospitalization with 30 days of colonoscopy were assumed to be equal to 14 days at a utility of 0.5.

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

<sup>o</sup>Utility losses for LYs with initial care were derived from a study by Ness and colleagues (42). For LYs with continuing care for stage I and II colorectal cancer, we assumed a utility loss of 0.05 QALYs; for LYs with continuing care for stage III and IV colorectal cancer, we assumed the corresponding utility losses for LYs with initial care. For LYs with terminal care for colorectal cancer, we assumed the utility loss for LYs with initial care for stage IV colorectal cancer. For LYs with terminal care for another cause, we assumed the corresponding utility losses for LYs with continuing care.

<sup>p</sup>Costs are from a health system's perspective and do not include patient time costs. All costs are presented in Australian dollars and are indexed to 2016 prices.

<sup>q</sup>FIT price based on the pricing of a commercially available alternative (35).

<sup>r</sup>The cost to analyze a specimen based in Australian Medicare Benefits Schedule (36).

<sup>s</sup>Cost to visit GP taken from Australian Medicare Benefits Schedule (37).

<sup>t</sup>Costs for colonoscopy are calculated based on information available from Independent Hospital Pricing Authority (38).

<sup>u</sup>Cost of polygenic test based on a commercially available polygenic test for breast cancer (41).

<sup>v</sup>Costs for complications of colonoscopy are calculated based on information available from Independent Hospital Pricing Authority (38).

<sup>w</sup>Cost of treatment taken from Ananda and colleagues (39).

<sup>x</sup>Proportion of rectal cancer assumed to be 30.81% (27).

<sup>y</sup>Proportion of stage IV cancers treated with bevacizumab assumed to be 50% (39).

performed an incremental cost-effectiveness analysis to see which scenarios were efficient.

Second, we followed the above steps for each risk group and used these results to determine the efficient screening strategies for each risk group. Then, we combined the efficient screening strategies for all risk groups and ordered them from least expensive to most expensive. Using this list, we developed a series of optimally personalized screening scenarios. As each personalized screening scenario can be a combination of different strategies for each risk subgroup, there will be many more personalized screening scenarios.

Third, we compared the outcomes of uniform and personalized screening to establish which method would yield better results. We did this by plotting all uniform and personalized screening scenarios in a single cost-effectiveness plane and by performing an incremental cost-effectiveness analysis to see whether personalized screening or uniform screening was most efficient.

Finally, we applied imperfect participation rates to uniform and personalized screening scenarios to determine their impact in a "real-world" scenario. The benefits and costs of screening were compared with the same population undergoing no screening.

**Table 2.** Stratification of individuals according to polygenic risk and family history of colorectal cancer<sup>a</sup>.

Risk group	Risk category	Description	RR	PP (%)
Very low	1	Lowest quintile for polygenic risk and no CRC in first-degree relatives	0.47	20
Low	2	Second lowest quintile for polygenic risk and no CRC in first-degree relatives	0.72	23
Average	3	Lowest quintile for polygenic risk and at least one CRC in first-degree relative OR middle quintile for polygenic risk and no CRC in first-degree relatives	0.93	18
High	4	Second highest quintile for polygenic risk and no CRC in first-degree relatives	1.14	14
	5	Second lowest quintile for polygenic risk and at least one CRC in first-degree relatives	1.45	3
	6	Middle quintile for polygenic risk and at least one CRC in first-degree relative OR highest quintile for polygenic risk and no CRC in first-degree relatives	1.70	18
Very high	7	Second highest quintile for polygenic risk and at least one CRC in first-degree relatives	2.31	2
	8	Highest quintile for polygenic risk and at least one CRC in first-degree relatives	3.40	2

Abbreviations: CRC, colorectal cancer; PP, population percentage; RR, relative risk, risk of colorectal cancer in category compared with the average risk of colorectal cancer.

<sup>a</sup>Stratification based on Jenkins and colleagues (14).

At each step, scenarios with the highest incremental cost-effectiveness ratio (ICER) under a threshold of \$50,000 per QALY gained were identified as the optimally cost-effective strategy as this is a commonly used willingness-to-pay (WTP) threshold in Australia.

### Sensitivity analyses

In sensitivity analyses, we assessed the impact of weighting QALYs by age (ref. 44; we applied age-adjusted health-related quality of life so that quality of life decreased with increasing age) and discounting our results at 3% rather than 5% as this is a common international discounting rate (45). In addition, we explored the impact of changes in screening participation for personalized screening, holding the participation of uniform screening at current levels. To do this, we increased and decreased age-specific participation of the initial screening offer by 10 percentage points and adjusted the participation of rescreening.

Due to the uncertainty surrounding costs for determining risk profile, we also included a sensitivity analysis where these costs were excluded. Using this information, we conducted a threshold analysis to estimate the maximum cost for determining risk profile where personalized screening would be considered cost effective compared with uniform screening, at a WTP of \$50,000 per QALY gained.

## Results

### Uniform screening

Compared with no screening, the uniform screening scenarios (Table 3a) reduced colorectal cancer incidence by 22% to 69% (18–58 fewer colorectal cancer cases per 1,000 individuals) and mortality by 35% to 79% (10–23 fewer colorectal cancer deaths). These scenarios yielded 0.11% to 0.32% more QALYs (20–58 additional QALYs) and costs increased by 0.5% to 424% (\$6,409–\$5,277,930) per 1,000 individuals. These screening scenarios increased colonoscopy demand by 383 to 6,927 colonoscopies per 1,000 individuals (Table 3a). Several uniform screening scenarios were on the efficient frontier (Supplementary Fig. S1). Using a WTP threshold of \$50,000 per QALY gained, the optimal uniform screening scenario was annual FIT from 50 to 74 years (ICER \$43,174). Although close to the efficient frontier, biennial FIT screening from 50 to 74 years, the screening program currently implemented in Australia, was dominated. Colonoscopy screening scenarios were the most effective; however, they also had the highest ICERs.

### Optimal screening strategies per risk group

The efficient frontier included many of the same strategies for each risk group; however, the ICERs differed substantially (Supplementary

Table S1; Supplementary Fig. S2A–S2E). For example, annual screening with FIT from 54 to 74 years was on the efficient frontier for all risk groups; however, the ICERs ranged from \$86,929 for those at very low risk to \$3,687 for those at very high risk. Considering a WTP threshold of \$50,000 per QALY gained, the optimal screening strategy for those at very low risk was biennial FIT from 54 to 74 years (ICER \$33,639), whereas for those at highest risk, the optimal strategy was 5-yearly colonoscopy from 50 to 74 years (ICER \$39,568). Biennial FIT screening was only on the efficient frontier for the very low risk group (ICER \$63,911).

### Personalized screening

Using these efficient strategies, 39 personalized screening scenarios were created (Table 4). These scenarios (Table 5a) reduced colorectal cancer incidence by 4% to 68% (3–57 fewer colorectal cancer cases per 1,000 individuals) and mortality by 5% to 79% (2–23 fewer deaths). In addition, they yielded 0.02% to 0.32% more QALYs (3–58 additional QALYs) and increased costs by 19% to 432% (\$233,599–\$5,330,249). The personalized screening scenarios increased colonoscopy demand by 45 to 6,698 colonoscopies per 1,000 individuals (Table 5a).

At a WTP threshold of \$50,000 per QALY gained, the optimal personalized screening scenario consisted of the following: those at very low risk or low risk, screening should start at age 54 with biennial and annual FIT, respectively, those at average and high risk, screening should start at age 50 with annual FIT, and those at very high risk, screening should start at age 50 with 5-yearly colonoscopy (ICER \$45,682).

### Uniform screening versus personalized screening

When compared, personalized and uniform screening scenarios similarly reduced colorectal cancer incidence and mortality and yielded similar QALYs. Personalized screening more efficiently allocated colonoscopy demand; however, it cost more than uniform screening, due to the cost of determining risk. Although several scenarios from each type of screening were on the efficient frontier (Fig. 1A), all of the personalized screening scenarios had an ICER above \$100,000 and would therefore not be considered cost effective. At a WTP threshold of \$50,000 per QALY gained, the optimal screening scenario was annual FIT screening from 50 to 74 years.

### Realistic adherence

As might be expected, the application of realistic participation rates decreased the health benefits as well as the costs of all screening

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**Table 3.** Costs and effects (discounted at 5%) per 1,000 simulated 40-year-olds of all uniform screening scenarios assuming (a) perfect adherence and (b) realistic adherence.

<b>a. Effects of uniform screening scenarios assuming perfect adherence</b>											
<b>Screening strategy</b>											
Test	Start age	Interval	FITs	Colonoscopies	Complications	CRC incidence	CRC mortality	Life years <sup>a</sup>	Total QALYs <sup>a</sup>	Total costs <sup>a,b</sup>	ICER <sup>a,b</sup>
No screening			0	84	0.07	84	29	17,872	17,847	1,234,089	
FIT	60	3	3,981	467	0.24	66	19	17,889	17,867	1,240,498	317
FIT	60	2	5,935	576	0.27	62	16	17,892	17,871	1,256,805	4,314
FIT	54	3	5,571	561	0.28	64	18	17,894	17,873	1,304,332	Dominated
FIT	60	1	9,954	777	0.34	56	15	17,895	17,875	1,327,965	Dominated
FIT	54	2	8,101	695	0.32	59	16	17,898	17,878	1,343,651	11,768
FIT	50	3	6,990	625	0.30	63	17	17,897	17,877	1,371,842	Dominated
FIT	50	2	9,473	759	0.34	59	15	17,901	17,881	1,436,505	Dominated
FIT	46	3	7,789	660	0.29	63	17	17,898	17,878	1,462,077	Dominated
FIT	54	1	13,381	953	0.40	53	14	17,902	17,884	1,480,562	23,324
FIT	46	2	10,767	811	0.35	59	16	17,902	17,883	1,556,681	Dominated
FIT	50	1	15,397	1,042	0.43	53	14	17,905	17,887	1,634,262	43,174
FIT	40	3	9,187	707	0.30	64	18	17,899	17,879	1,635,282	Dominated
FIT	40	2	12,532	868	0.36	60	16	17,903	17,884	1,789,931	Dominated
COL	60	10	0	2,198	0.60	42	11	17,900	17,881	1,789,986	Dominated
FIT	46	1	17,171	1,109	0.44	54	14	17,906	17,889	1,830,442	122,612
COL	60	5	0	3,048	0.82	37	10	17,902	17,883	2,117,448	Dominated
FIT	40	1	19,338	1,165	0.44	57	16	17,906	17,888	2,201,540	Dominated
COL	54	10	0	2,928	0.86	39	10	17,907	17,889	2,294,199	Dominated
COL	50	10	0	3,245	0.91	37	9	17,911	17,893	2,706,770	Dominated
COL	54	5	0	4,540	1.16	31	7	17,911	17,894	3,016,912	Dominated
COL	46	10	0	3,341	1.01	39	10	17,912	17,895	3,181,465	Dominated
COL	50	5	0	5,012	1.24	29	7	17,916	17,899	3,664,480	184,883
COL	40	10	0	4,269	1.09	36	9	17,916	17,898	4,319,443	Dominated
COL	46	5	0	5,700	1.35	30	7	17,919	17,902	4,593,188	349,139
COL	40	5	0	7,011	1.57	26	6	17,924	17,904	6,462,019	648,900

<b>b. Effects of uniform screening scenarios assuming realistic adherence</b>											
No screening			0	84	0.07	84	29	17,872	17,847	1,234,089	Dominated
FIT	60	3	1,952	228	0.14	77	24	17,879	17,855	1,249,846	1,936
FIT	60	2	3,022	285	0.16	74	23	17,881	17,857	1,259,357	3,446
FIT	54	3	2,488	255	0.15	76	24	17,880	17,857	1,278,301	Dominated
FIT	60	1	5,427	398	0.21	69	20	17,885	17,863	1,292,600	6,544
FIT	54	2	3,931	328	0.18	73	22	17,884	17,860	1,300,838	Dominated
FIT	50	3	3,253	288	0.17	75	23	17,882	17,859	1,310,216	Dominated
FIT	50	2	4,721	361	0.19	72	22	17,885	17,863	1,346,432	Dominated
FIT	46	3	3,691	305	0.16	75	23	17,883	17,860	1,351,925	Dominated
FIT	54	1	7,355	478	0.24	67	19	17,890	17,868	1,373,779	15,702
FIT	46	2	5,504	390	0.20	72	22	17,887	17,864	1,407,164	Dominated
FIT	40	3	4,500	332	0.17	75	23	17,884	17,861	1,435,530	Dominated
FIT	50	1	8,779	529	0.26	66	19	17,892	17,871	1,459,998	29,326
COL	60	10	0	987	0.30	65	21	17,884	17,862	1,460,994	Dominated
FIT	40	2	6,651	425	0.21	72	22	17,888	17,866	1,528,067	Dominated
COL	54	10	0	1,048	0.35	67	21	17,884	17,862	1,550,987	Dominated
FIT	46	1	10,156	573	0.27	66	19	17,894	17,873	1,572,125	56,064
COL	60	5	0	1,413	0.45	60	18	17,887	17,865	1,592,938	Dominated
COL	50	10	0	1,176	0.37	65	21	17,886	17,864	1,679,843	Dominated
FIT	40	1	12,108	626	0.28	67	19	17,895	17,874	1,792,630	151,031
COL	54	5	0	1,825	0.55	57	17	17,890	17,869	1,821,556	Dominated
COL	46	10	0	1,215	0.43	66	21	17,887	17,865	1,831,735	Dominated
COL	50	5	0	2,040	0.60	55	17	17,893	17,873	2,050,622	Dominated
COL	40	10	0	1,622	0.47	62	19	17,890	17,868	2,218,841	Dominated
COL	46	5	0	2,377	0.67	53	16	17,896	17,876	2,395,405	Dominated
COL	40	5	0	2,986	0.79	50	15	17,901	17,880	3,102,085	221,941

Note: Gray shading highlights uniform screening scenarios on the efficient frontier prior to considering personalized screening.

Abbreviations: COL, colonoscopy; CRC, colorectal cancer; FIT, fecal immunochemical test; ICER, incremental cost-effectiveness ratio; QALY, quality-adjusted life years.

<sup>a</sup>Results are discounted at an annual rate of 5%.

<sup>b</sup>Costs are presented in Australian dollars.

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**Table 4.** Specifics of the personalized screening scenarios, when costs and QALYs are discounted at 5%<sup>a</sup>.

Screening strategy	Risk groups				
	Very low	Low	Average	High	Very high
PS1	NoScr	NoScr	NoScr	NoScr	FIT_60_1
PS2	NoScr	NoScr	NoScr	NoScr	FIT_54_1
PS3	NoScr	NoScr	NoScr	FIT_60_2	FIT_54_1
PS4	NoScr	NoScr	NoScr	FIT_60_1	FIT_54_1
PS5	NoScr	NoScr	NoScr	FIT_54_2	FIT_54_1
PS6	NoScr	NoScr	NoScr	FIT_54_1	FIT_54_1
PS7	NoScr	NoScr	FIT_60_2	FIT_54_1	FIT_54_1
PS8	NoScr	NoScr	FIT_54_2	FIT_54_1	FIT_54_1
PS9	NoScr	NoScr	FIT_54_2	FIT_54_1	FIT_50_1
PS10	NoScr	FIT_60_2	FIT_54_2	FIT_54_1	FIT_50_1
PS11	NoScr	FIT_54_2	FIT_54_2	FIT_54_1	FIT_50_1
PS12	NoScr	FIT_54_2	FIT_54_1	FIT_54_1	FIT_50_1
PS13	NoScr	FIT_54_2	FIT_54_1	FIT_50_1	FIT_50_1
PS14	FIT_54_3	FIT_54_2	FIT_54_1	FIT_50_1	FIT_50_1
PS15	FIT_54_2	FIT_54_2	FIT_54_1	FIT_50_1	FIT_50_1
PS16	FIT_54_2	FIT_54_2	FIT_54_1	FIT_50_1	COL_54_5
PS17	FIT_54_2	FIT_54_2	FIT_54_1	FIT_50_1	COL_50_5
PS18	FIT_54_2	FIT_54_1	FIT_54_1	FIT_50_1	COL_50_5
PS19	FIT_54_2	FIT_54_1	FIT_50_1	FIT_50_1	COL_50_5
PS20	FIT_54_2	FIT_50_1	FIT_50_1	FIT_50_1	COL_50_5
PS21	FIT_50_2	FIT_50_1	FIT_50_1	FIT_50_1	COL_50_5
PS22	FIT_50_2	FIT_50_1	FIT_50_1	COL_50_5	COL_50_5
PS23	FIT_50_2	FIT_50_1	FIT_50_1	COL_50_5	COL_46_5
PS24	FIT_54_1	FIT_50_1	FIT_50_1	COL_50_5	COL_46_5
PS25	FIT_50_1	FIT_50_1	FIT_50_1	COL_50_5	COL_46_5
PS26	FIT_50_1	FIT_50_1	FIT_46_1	COL_50_5	COL_46_5
PS27	FIT_50_1	FIT_50_1	FIT_46_1	COL_50_5	COL_40_5
PS28	FIT_50_1	FIT_50_1	FIT_46_1	COL_46_5	COL_40_5
PS29	FIT_50_1	FIT_50_1	COL_50_5	COL_46_5	COL_40_5
PS30	FIT_50_1	FIT_46_1	COL_50_5	COL_46_5	COL_40_5
PS31	FIT_46_1	FIT_46_1	COL_50_5	COL_46_5	COL_40_5
PS32	FIT_46_1	FIT_46_1	COL_50_5	COL_40_5	COL_40_5
PS33	FIT_46_1	FIT_46_1	COL_46_5	COL_40_5	COL_40_5
PS34	FIT_46_1	COL_50_5	COL_46_5	COL_40_5	COL_40_5
PS35	FIT_46_1	COL_46_5	COL_46_5	COL_40_5	COL_40_5
PS36	FIT_46_1	COL_46_5	COL_40_5	COL_40_5	COL_40_5
PS37	COL_50_5	COL_46_5	COL_40_5	COL_40_5	COL_40_5
PS38	COL_50_5	COL_40_5	COL_40_5	COL_40_5	COL_40_5
PS39	COL_46_5	COL_40_5	COL_40_5	COL_40_5	COL_40_5

Note: Screening strategies: screening test, screening start age, screening interval.

Abbreviations: COL, colonoscopy; FIT, fecal immunochemical test; NoScr, no screening.

<sup>a</sup>All screening ends at or before the age of 74 years.

scenarios. At this level of participation, none of the personalized screening scenarios were cost effective compared with uniform screening (Fig. 1B).

### Sensitivity analyses

Our results were not sensitive to changes in discounting, weighting of QALYs or adjustments to rates of participation (Supplementary Tables S2–S5; Supplementary Figs. S3–S6). However, excluding the costs of determining polygenic risk had a significant impact on our results with personalized screening dominating uniform screening scenarios at both perfect (Fig. 1C) and realistic adherence (Supplementary Fig. S7). The threshold analysis indicated that for personalized screening to be cost effective compared with uniform screening at the WTP of \$50,000 per QALY gained, the cost for determining risk should not exceed \$47.52 (Supplementary Table S8).

## Discussion

We investigated the impact of personalizing colorectal cancer screening based on polygenic risk and family history. We found that uniform screening was equally effective (cancers and deaths prevented) but more cost effective than personalized screening. Although personalized and uniform screening showed similar reductions in colorectal cancer incidence and mortality and similar gains in QALYs, personalized screening incurred additional costs resulting from the whole population undergoing testing to determine their colorectal cancer risk.

The concept of personalized screening is promising and has previously been shown to be more effective than a strategy based on age alone (7, 21–23). Our results add support to these findings. However, our results do not align with recent findings that risk-stratified screening based on polygenic risk profile for breast cancer is cost

## Personalized Screening for Colorectal Cancer: Cost-Effectiveness Analysis

**Table 5.** Costs and effects (discounted at 5%) of per 1,000 simulated 40-year-olds of all personalized screening scenarios assuming (a) perfect adherence and (b) realistic adherence.

<b>a. Effects of personalized screening scenarios assuming perfect adherence</b>									
Screening strategy	FITs	Colonoscopies	Complications	CRC incidence	CRC mortality	Life years <sup>a</sup>	Total QALYs <sup>a</sup>	Total costs <sup>a,b</sup>	ICER <sup>a,b</sup>
No screening	0	84	0.07	84	29	17,872	17,847	1,234,089	
PS01	360	130	0.09	81	27	17,874	17,850	1,467,668	Dominated
PS02	515	141	0.10	81	27	17,875	17,851	1,471,312	Dominated
PS03	1,722	276	0.16	73	23	17,882	17,859	1,505,808	Dominated
PS04	2,554	324	0.18	71	22	17,883	17,860	1,513,829	Dominated
PS05	2,190	305	0.18	72	23	17,884	17,861	1,520,843	Dominated
PS06	3,322	368	0.20	70	22	17,885	17,863	1,542,584	Dominated
PS07	5,226	525	0.27	63	18	17,891	17,871	1,628,434	Dominated
PS08	5,920	562	0.28	63	18	17,893	17,873	1,656,571	Dominated
PS09	6,017	568	0.28	63	18	17,894	17,873	1,662,780	15,998
PS10	7,406	663	0.32	59	16	17,897	17,877	1,734,789	19,167
PS11	7,898	687	0.33	59	16	17,898	17,878	1,756,804	19,251
PS12	9,596	770	0.35	57	15	17,899	17,880	1,801,421	24,261
PS13	10,057	792	0.36	57	15	17,900	17,881	1,834,425	28,076
PS14	11,189	859	0.38	55	14	17,902	17,884	1,911,354	32,041
PS15	11,700	881	0.39	55	14	17,902	17,884	1,924,610	33,605
PS16	11,089	991	0.43	52	14	17,903	17,885	1,952,870	38,059
PS17	11,089	1,023	0.44	52	13	17,903	17,885	1,978,086	39,563
PS18	12,293	1,078	0.45	51	13	17,904	17,886	2,013,777	39,692
PS19	12,939	1,106	0.46	51	13	17,905	17,887	2,063,215	45,682
PS20	13,382	1,125	0.47	51	13	17,905	17,888	2,098,112	63,213
PS21	13,646	1,136	0.47	51	13	17,906	17,888	2,116,904	64,062
PS22	10,378	1,951	0.68	43	11	17,909	17,893	2,487,033	81,839
PS23	10,378	1,969	0.69	43	11	17,910	17,893	2,519,388	82,386
PS24	11,148	2,001	0.69	43	11	17,910	17,893	2,534,168	86,970
PS25	11,518	2,017	0.70	43	11	17,910	17,894	2,564,321	95,845
PS26	12,085	2,037	0.70	43	11	17,911	17,894	2,627,025	127,618
PS27	12,085	2,100	0.71	43	11	17,911	17,895	2,699,821	135,361
PS28	12,085	2,209	0.74	43	11	17,912	17,896	2,880,990	172,640
PS29	6,575	3,465	0.99	35	9	17,915	17,899	3,469,210	180,219
PS30	6,964	3,480	0.99	35	9	17,915	17,899	3,512,866	181,642
PS31	7,289	3,492	1.00	35	9	17,916	17,899	3,549,627	226,549
PS32	7,289	3,804	1.05	34	8	17,917	17,901	3,943,469	282,951
PS33	7,289	4,017	1.09	34	8	17,918	17,902	4,238,838	349,821
PS34	3,372	4,929	1.25	30	7	17,920	17,903	4,694,318	370,115
PS35	3,372	5,105	1.28	30	7	17,920	17,903	4,915,213	696,391
PS36	3,372	5,531	1.35	29	7	17,922	17,904	5,515,822	707,094
PS37	0	6,328	1.47	27	6	17,922	17,904	5,935,615	1,808,159
PS38	0	6,612	1.51	27	6	17,923	17,904	6,365,416	2,057,076
PS39	0	6,782	1.54	27	6	17,923	17,905	6,564,338	3,860,049

<b>b. Effects of personalized screening scenarios assuming realistic adherence</b>									
Screening strategy	FITs	Colonoscopies	Complications	CRC incidence	CRC mortality	Life years <sup>a</sup>	Total QALYs <sup>a</sup>	Total costs <sup>a,b</sup>	ICER <sup>a,b</sup>
No screening	0	84	0.07	84	29	17,872	17,847	1,234,089	
PS01	203	107	0.08	82	28	17,873	17,848	1,473,736	Dominated
PS02	283	112	0.08	82	28	17,874	17,849	1,475,367	Dominated
PS03	908	168	0.11	79	26	17,877	17,853	1,521,883	Dominated
PS04	1,402	198	0.13	77	25	17,878	17,854	1,523,703	Dominated
PS05	1,101	180	0.12	78	25	17,878	17,854	1,529,310	Dominated
PS06	1,814	218	0.14	76	25	17,880	17,856	1,538,207	Dominated
PS07	2,783	282	0.17	73	23	17,882	17,859	1,623,617	Dominated
PS08	3,074	296	0.17	73	22	17,883	17,860	1,637,150	Dominated
PS09	3,134	299	0.18	73	22	17,883	17,861	1,640,166	Dominated
PS10	3,834	337	0.19	71	21	17,885	17,862	1,705,874	Dominated
PS11	4,042	345	0.19	71	21	17,885	17,863	1,716,293	Dominated
PS12	5,140	393	0.21	69	20	17,887	17,865	1,740,403	Dominated
PS13	5,447	405	0.22	69	20	17,888	17,866	1,757,876	26,955
PS14	5,946	428	0.23	68	20	17,889	17,867	1,820,048	Dominated
PS15	6,239	439	0.23	68	20	17,889	17,867	1,827,488	Dominated

(Continued on the following page)



**Table 5.** Costs and effects (discounted at 5%) of per 1,000 simulated 40-year-olds of all personalized screening scenarios assuming (a) perfect adherence and (b) realistic adherence. (Cont'd)

<b>b. Effects of personalized screening scenarios assuming realistic adherence</b>									
PS16	5,897	479	0.25	67	20	17,889	17,867	1,832,472	Dominated
PS17	5,897	494	0.25	67	20	17,889	17,867	1,840,654	Dominated
PS18	6,688	525	0.26	66	19	17,890	17,869	1,861,200	Dominated
PS19	7,144	541	0.27	66	19	17,891	17,869	1,888,754	37,121
PS20	7,468	552	0.27	66	19	17,891	17,870	1,909,081	43,619
PS21	7,625	557	0.27	66	19	17,891	17,870	1,918,670	50,380
PS22	5,787	873	0.37	62	18	17,892	17,871	2,021,485	Dominated
PS23	5,787	885	0.37	62	18	17,892	17,872	2,032,352	Dominated
PS24	6,320	903	0.37	61	18	17,893	17,872	2,043,097	Dominated
PS25	6,598	911	0.38	61	18	17,893	17,872	2,060,946	Dominated
PS26	7,039	925	0.38	61	18	17,893	17,873	2,096,862	Dominated
PS27	7,039	955	0.39	61	18	17,894	17,873	2,123,266	Dominated
PS28	7,039	1,016	0.41	60	17	17,895	17,875	2,188,845	61,316
PS29	3,785	1,489	0.51	56	17	17,895	17,875	2,342,739	Dominated
PS30	4,097	1,499	0.52	56	17	17,895	17,875	2,368,540	Dominated
PS31	4,366	1,507	0.52	56	17	17,895	17,875	2,390,967	Dominated
PS32	4,366	1,654	0.55	55	16	17,897	17,877	2,539,024	Dominated
PS33	4,366	1,759	0.58	55	16	17,898	17,878	2,648,884	148,949
PS34	2,029	2,100	0.64	53	16	17,898	17,878	2,770,951	Dominated
PS35	2,029	2,182	0.66	53	16	17,898	17,878	2,854,071	Dominated
PS36	2,029	2,380	0.69	52	15	17,899	17,879	3,081,587	268,852
PS37	0	2,675	0.74	51	15	17,899	17,879	3,196,125	Dominated
PS38	0	2,805	0.76	50	15	17,900	17,880	3,359,342	Dominated
PS39	0	2,883	0.78	50	15	17,900	17,880	3,434,699	677,027

Note: Gray shading highlights screening scenarios on the efficient frontier prior to considering uniform screening.

Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test; PS, personalized screening; QALY, quality-adjusted life years.

<sup>a</sup>Results are discounted at an annual rate of 5%.

<sup>b</sup>Costs are presented in Australian dollars.

<sup>c</sup>The personalized screening scenarios are described in **Table 4**.

effective compared with the standard age-based screening program (46). This discrepancy may be due to differences in the discriminatory performance of risk-stratification algorithms or differences in the cost for determining risk, which was substantially lower in this analysis (£50 or ~\$90) than in ours (~\$240). However, it is difficult to accurately determine how much of the cost for establishing risk should be allocated to a screening program. The cost of polygenic testing varies widely (47), and there is potential to combine testing for other cancers. Given this difficulty and because cost-effectiveness of personalized screening is highly dependent on these additional costs, we assessed the impact of excluding them. We found that when these costs were excluded, personalized screening was cost effective. The threshold analysis suggested that at a WTP of \$50,000 per QALY gained, the cost to determine risk should not exceed ~\$48, which is significantly lower than the cost assumed in this analysis.

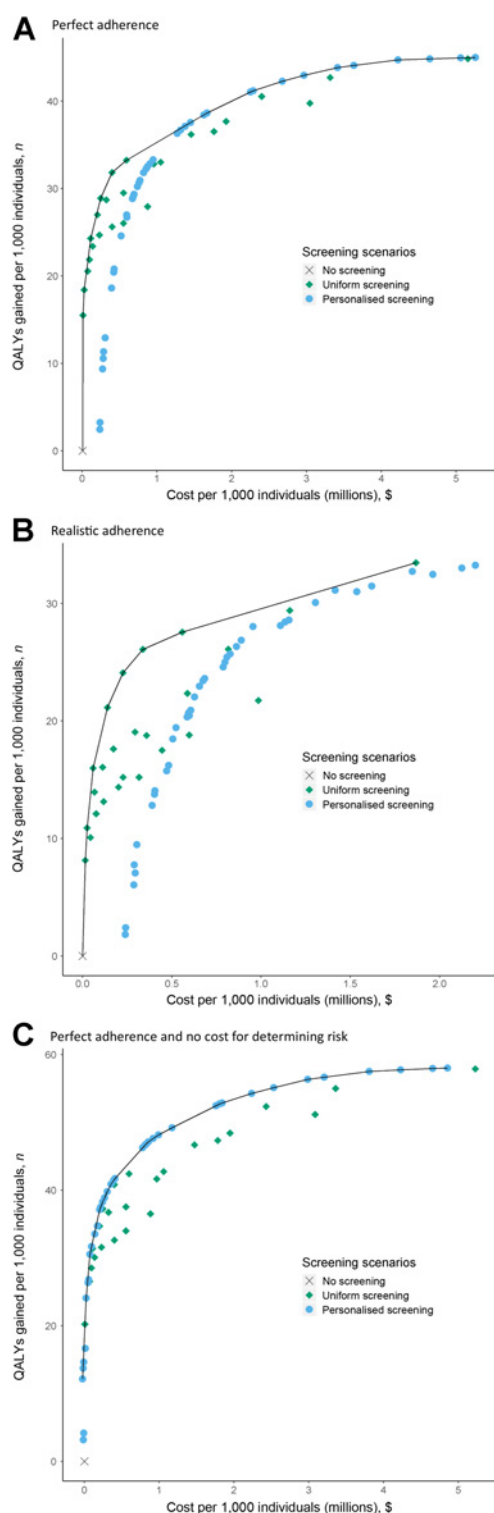
The effectiveness of personalized screening will be affected by the precision with which the population is stratified (15). This will be affected by both the accuracy of the metric used to stratify the population and the proportion of the population willing to undertake polygenic testing. Although our results appear unfavorable, the advantage of screening based on polygenic risk and family history remains limited largely because the current contribution of known SNPs to colorectal cancer risk is modest (9, 10, 48). As new SNPs are identified, the discriminatory utility of polygenic testing will increase and the performance of risk assessment based on this metric could improve (15). The inclusion of other factors in risk assessment, such as obesity and smoking status, may also enhance the discriminatory performance of personalized screening (13, 49, 50). It may also be

pertinent to consider results from an individual's screening history. As these factors will vary over an individual's lifespan, assessment of risk may need to become more dynamic in nature, and although such inclusions will present challenges, they will likely improve the harm-benefit ratio of colorectal cancer screening.

In addition, although genetic testing for colorectal cancer has been shown to be acceptable to the community (51), individuals may not always be willing to undergo testing, for a variety of reasons, including concerns over privacy, possible misuse of data, and potential negative psychological impacts of findings (52–54). For this analysis, we assumed all individuals would undergo testing to determine their risk profile; however, due consideration of how to manage this issue is required.

The benefits of population screening are largely dependent on participation. With many countries already experiencing suboptimal levels of participation in routine age-based screening for colorectal cancer (33, 55), personalized screening presents an interesting proposition. On the one hand, increasing the complexity of screening may reduce participation in screening, thereby diminishing the modest benefits. However, individuals at increased risk of colorectal cancer have been shown to be more compliant to screening guidelines than those at average risk (56), suggesting that the provision of risk information may assist in screening uptake (16, 57). Coupled with evidence that involvement of GPs improves participation in colorectal cancer screening (58), a simple risk assessment has the potential to positively affect screening participation (59). When we applied realistic rates of participation, we found that personalized screening remained suboptimal compared with uniform screening, even when participation in personalized screening was improved (Supplementary Fig. S6).

## Personalized Screening for Colorectal Cancer: Cost-Effectiveness Analysis



**Figure 1.**

Costs and quality-adjusted life years (discounted at 5%) per 1,000 40-year-olds for all uniform and personalized colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies<sup>a</sup> assuming perfect adherence (**A**), realistic adherence (**B**), and perfect adherence and no costs associated with determining risk (**C**). A description of the personalized screening scenarios can be found in **Table 4**.

This suggests that at present, increasing participation in uniform screening will likely yield better results.

Screening effectiveness will also be affected by the choice of screening test and screening frequency. This will largely be determined by a health system's capacity to provide a given intervention to its population. Our analysis indicates that screening scenarios utilizing colonoscopy are the most effective scenarios. However, as would be expected, these scenarios significantly increase colonoscopy utilization. Although personalized screening more efficiently allocated colonoscopy utilization compared with uniform screening, such increases in demand will likely be infeasible, especially in countries with limited colonoscopy capacity.

Moving from an age-based screening program will result in a redistribution of the harms and benefits. This raises ethical issues as although personalized screening may be optimal at a population level, individuals may experience increased harms or reduced benefits as a result of their screening protocol. As would be expected, our analysis indicates that when individuals undergo less frequent screening (either by starting screening later or by having a longer screening interval), they experience higher colorectal cancer incidence and mortality. However, this will be partly offset by a reduction in other harms such as invasive tests, false-positive test results, adverse events, anxiety, and inconvenience. These concerns hold for the inclusion of younger individuals, although recent evidence suggests that their inclusion is favorable (60).

Limitations exist with our research. First, we only considered a limited number of risk categories. Effectiveness and cost-effectiveness could be further improved as the discriminatory performance of risk stratification improves. Second, we only included a limited number of low-intensity screening strategies. It is possible that other low-intensity screening strategies, such as one-off colonoscopy or less frequent FIT screening would be more efficient. Third, we did not compare the (cost-)effectiveness of stratifying the population based on family history alone. However, as the aim of this research was to explore the possible implications of combining SNPs and family history in a risk assessment, and, as determining polygenic risk is assumed to be quite expensive, such a comparison would potentially make this analysis look even less cost effective. Finally, there is some uncertainty regarding the assumptions for participation in screening. We assumed that participation in screening of any form would be equal to participation in uniform biennial FIT screening. However, this is unlikely as participation in screening varies widely (5). Unfortunately, to date, there are few data examining multiple screening modalities within one population to adequately address this concern.

In summary, this research presents an exploration of the possible impact of personalized screening for colorectal cancer based on polygenic risk and family history. Our results suggest that although personalizing screening based on colorectal cancer risk is slightly more effective than screening based on age alone, it is currently not necessarily cost effective. Cost-effectiveness of personalized screening will depend on the costs of determining risk and the magnitude of the

<sup>a</sup>Discounted costs and life years gained reflect total costs and life years gained of a screening program, accounting for time preference for present over future outcomes. QALYs gained are plotted on the y-axis, and total costs are plotted on the x-axis. Each possible screening strategy is represented by a point. Strategies that form the solid line connecting the points lying left and upward are the economically rational subset of choices. This line is called the efficient frontier. The inverse slope of the line represents the incremental cost-effectiveness ratio of the connected strategies. Points lying to the right and beneath the line represent the dominated strategies.

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benefits of personalization. Our analysis suggests that the currently assumed cost of determining risk is too high compared with the gains and costs must be substantially lower for personalized screening to become cost effective. The balance of cost and benefits will be contingent on the discriminatory performance of risk-stratification algorithms on polygenic risk and family history, which remains suboptimal.

However, we cannot ignore the changing landscape that advances in technology provide and, as improvements in risk stratification occur and costs for polygenic testing decrease, personalizing screening will become an increasingly cost-effective and attractive option. This consortium of researchers, and others, have previously called for the concept of personalized screening to be brought to the attention of key stakeholders (15, 61). Our research seeks to highlight the possible implications of personalized screening based on risk assessment, which we believe can and will play a significant role in improving our screening programs. As such, we reiterate our call that key stakeholders carefully consider the evidence for personalized screening in order to effectively plan for the future.

### Disclosure of Potential Conflicts of Interest

M.A. Jenkins reports receiving other commercial research support from and has ownership interest (including patents) in Genetype Pty Ltd. No potential conflicts of interest were disclosed by the other authors.

### Disclaimer

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. D.R. Cenin and I. Lansdorp-Vogelaar had full access to all the data, and D.R. Cenin had final responsibility for the decision to submit for publication. The contents of the

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### Authors' Contributions

**Conception and design:** D.R. Cenin, M.A. Jenkins, D.B. Preen, P.C. O'Leary, I. Lansdorp-Vogelaar

**Development of methodology:** D.R. Cenin, S.K. Naber, A.C. de Weerd, P.C. O'Leary, I. Lansdorp-Vogelaar

**Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.):** D.R. Cenin, M.A. Jenkins

**Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis):** D.R. Cenin, S.K. Naber, A.C. de Weerd, M.A. Jenkins, H.C. Ee, P.C. O'Leary, I. Lansdorp-Vogelaar

**Writing, review, and/or revision of the manuscript:** D.R. Cenin, S.K. Naber, M.A. Jenkins, D.B. Preen, H.C. Ee, P.C. O'Leary, I. Lansdorp-Vogelaar

**Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases):** D.R. Cenin, S.K. Naber

**Study supervision:** D.B. Preen, P.C. O'Leary, I. Lansdorp-Vogelaar

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# Cancer Epidemiology, Biomarkers & Prevention

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Dayna R. Cenin, Steffie K. Naber, Anne C. de Weerd, et al.

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