Published in final edited form as:

Cancer Epidemiol Biomarkers Prev. 2020 January ; 29(1): 10–21. doi:10.1158/1055-9965.EPI-18-1123.

COST-EFFECTIVENESS OF PERSONALISED SCREENING FOR COLORECTAL CANCER BASED ON POLYGENIC RISK AND FAMILY HISTORY

Dayna R Cenin[1,2,3], **Steffie K Naber**[1], **Anne C de Weerdt**[1], **Mark A Jenkins**[4], **David B Preen**[2], **Hooi C Ee**[5], **Peter C O'Leary**[3,6,7], **Iris Lansdorp-Vogelaar**[1]

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

Abstract

Background: There is growing evidence for personalising colorectal cancer (CRC) screening based on risk factors. We compared the cost-effectiveness of personalised CRC 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 personalised screening. Individuals were categorised based on polygenic risk and family history of CRC. We varied screening strategies by start age, interval and test and estimated costs and quality-adjusted life years (QALYs). In our analysis we: 1) assessed the cost-effectiveness of uniform screening; 2) developed personalised screening scenarios based on optimal screening strategies by risk group; 3) compared the cost-effectiveness of both.

Results: At a willingness-to-pay threshold of $50,000/QALY, the optimal uniform screening scenario was annual faecal immunochemical testing (FIT) from 50-74 years, whereas for personalised 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. Although these scenarios gained the same number of QALYs (17,887), personalised screening was not cost effective, costing an additional $428,953 due to costs associated with determining risk

Corresponding author: Dayna R Cenin, Department of Public Health, Erasmus MC, University Medical Center, P.O. Box 2040, 3000 CA Rotterdam, The Netherlands, d.cenin@erasmusmc.nl, Telephone +31 10 704 30 05.

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

All authors have completed the ICMJE Conflict of Interest form (available on request from the corresponding author) and declare no direct conflict of interest.

(assumed to be $240 per person). Personalised screening was cost effective when these costs were less than ~$48.

Conclusion: Uniform CRC screening currently appears more cost effective than personalised screening based on polygenic risk and family history. However, cost-effectiveness is highly dependent on the cost of determining risk.

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

Keywords

colorectal cancer; screening; cost-effectiveness; risk; personalising; polygenic risk; family history

Introduction

Screening has been shown to be a cost-effective method to reduce the incidence and mortality of colorectal cancer (CRC).[1–4] In countries with population screening programs, screening for CRC 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 CRC 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 (SNPs), play a significant role in defining CRC risk due to their relatively high prevalence in the population.[9–12] In isolation, SNPs are only weakly associated with CRC 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) CRC risk than the average population.[14]

Compared with age-based screening, personalised 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, while those at higher risk could start screening earlier, undergo more intensive screening or both.[9, 15–17] Personalised 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, personalised 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 to uniform screening for CRC. To address this gap in knowledge, we investigated the impact of personalising CRC screening, based on polygenic risk and family history and compared its cost-effectiveness to uniform screening.

Methods and Materials

We used the Microsimulation Screening Analysis-Colon (MISCAN-Colon)[24] model to estimate the costs, benefits and harms of different uniform screening strategies as well as personalised screening strategies which were based on polygenic risk and family history of CRC.

MISCAN-Colon

MISCAN-Colon is a well-established microsimulation model for CRC 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 CRC. 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 CRC may be diagnosed. The introduction of screening may alter the simulated life histories through detection and removal of adenomas or through detection of CRC at an earlier stage with a more favourable 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 CRC in Australia before the introduction of biennial faecal immunochemical test (FIT) screening for those aged 50 to 74 in 2006.[25] Stage distribution, localisation 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 2013-2015.[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 CRC risk) and their first-degree family history of CRC (Table 2).[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 CRC.[29] The relative risk (RR) of developing CRC (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 0.5-0.9), “average” (RR between 0.9-1.2), “high” (RR between 1.2-1.8), and “very high” (RR >1.8). We assumed no other differences in life expectancy, CRC stage distribution, survival, or screening performance characteristics between the risk groups.

Screening and Surveillance

In addition to a scenario without screening, we modelled 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 programmes 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).[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 five-year age intervals between 50 and 74 years. As data was not available for screening participation for individuals aged 40-49 years, participation was assumed to be equal to those aged 50-54 years. We assumed that 76.0% of individuals who had previously attended screening would attend again in the next screening round while 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 analyse a FIT specimen was based on the Australian Medicare Benefits Schedule (MBS).[36] 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 were 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), standardised to 2016 prices using the consumer price index where necessary.[40]

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

The assumed utility loss due to CRC screening was 0.00274 quality-adjusted life years (QALYs) 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 (LYs) with CRC care are of lower quality than those without CRC 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 CRC incidence and CRC 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 (Table S6–7, Figure 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 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 optimal personalised screening scenarios. As each personalised screening scenario can be a combination of different strategies for each risk subgroup, there will be many more personalised screening scenarios.

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

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

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[44] (we applied age-adjusted health related quality of life so that quality of life deceased 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 personalised 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 personalised screening would be considered cost effective compared to 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 CRC incidence by 22-69% (18-58 fewer CRC cases per 1,000 individuals) and mortality by 35-79% (10-23 fewer CRC deaths). These scenarios yielded 0.11-0.32% more QALYs (20-58 additional QALYs) and costs increased by 0.5%-424% ($6,409-$5,277,930) per 1,000 individuals. These screening scenarios increased colonoscopy demand by 383-6,927 colonoscopies per 1,000 individuals (Table 3a). Several uniform screening scenarios were on the efficient frontier (Supplementary Results, Figure 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 Results Table S1, Figures S2a–e). 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), while 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).

Personalised screening

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

At a WTP threshold of $50,000 per QALY gained, the optimal personalised 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 personalised screening

When compared, personalised and uniform screening scenarios similarly reduced CRC incidence and mortality and yielded similar QALYs. Personalised 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 (Figure 1a), all of the personalised 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 scenarios. At this level of participation, none of the personalised screening scenarios were cost effective compared to uniform screening (Figure 1b).

Sensitivity analyses

Our results were not sensitive to changes in discounting, weighting of QALYs or adjustments to rates of participation (Supplementary Results Tables S2–5, Figures S3–6). However, excluding the costs of determining polygenic risk had a significant impact on our results with personalised screening dominating uniform screening scenarios at both perfect (Figure 1c) and realistic adherence (Supplementary Results Figure S7). The threshold analysis indicated that for personalised screening to be cost effective compared to uniform screening at the WTP of $50,000 per QALY gained, the cost for determining risk should not exceed $47.52 (Supplementary Results Table S8).

Discussion

We investigated the impact of personalising CRC 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 personalised screening. Although personalised and uniform screening showed similar reductions in CRC incidence and mortality and similar gains in QALYs, personalised screening incurred additional costs resulting from the whole population undergoing testing to determine their CRC risk.

The concept of personalised 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 effective compared to 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 personalised screening is highly dependent on these additional costs, we assessed the impact of excluding them. We found that when these costs were excluded, personalised 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 personalised screening will be impacted 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 unfavourable, the advantage of screening based on polygenic risk and family history remains limited largely because the current contribution of known SNPs to CRC 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 personalised 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 CRC screening.

In addition, although genetic testing for CRC 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 CRC,[33, 55] personalised screening presents an interesting proposition. On one hand, increasing the complexity of screening may reduce participation in screening, thereby diminishing the modest benefits. However, individuals at increased risk of CRC 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 CRC screening,[58] a simple risk assessment has the potential to positively impact screening participation.[59] When we applied realistic rates of participation we found that personalised screening remained suboptimal compared to uniform screening, even when participation in personalised screening was improved (Supplementary Results, Figure S6). This suggests that at present, increasing participation in uniform screening will likely yield better results.

Screening effectiveness will also be impacted by the choice of screening test and screening frequency. This will largely be determined by a health systems capacity to provide a given intervention to its population. Our analysis indicates that screening scenarios utilising colonoscopy are the most effective scenarios. However, as would be expected, these scenarios significantly increase colonoscopy utilisation. Although personalised screening more efficiently allocated colonoscopy utilisation compared to 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 personalised 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 CRC 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 favourable.[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 is little 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 personalised screening for CRC based on polygenic risk and family history. Our results suggest that although personalising screening based on CRC risk is slightly more effective than screening based on age alone, it is currently not necessarily cost effective. Cost-effectiveness of personalised screening will depend on the costs of determining risk and the magnitude of the benefits of personalisation. Our analysis suggests that the currently assumed cost of determining risk is too high compared to the gains and costs must be substantially lower for personalised 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 sub-optimal.

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, personalising screening will become an increasingly cost-effective and attractive option. This consortium of researchers, and others, have previously called for the concept of personalised screening to be brought to the attention of key stakeholders.[15, 61] Our research seeks to highlight the possible implications of personalised 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 personalised screening in order to effectively plan for the future.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowldgements

DR Cenin, DB Preen, HC Ee, P O'Leary and I Lansdorp-Vogelaar received funding from the Cancer Council Western Australia Capacity and Collaboration Building Grant. This research also benefitted from our participation in the National Cancer Institute's Cancer Intervention and Surveillance Modeling Network (CISNET) (grant number: U01-CA199335). MA Jenkins is a Senior Research Fellow for the Australian National Health and Medical Research Council.

The funders of the study had no role in the study design, data collection, data analysis, data interpretation, or the writing of the report. DR Cenin and I Lansdorp-Vogelaar had full access to all the data and DR Cenin had final responsibility for the decision to submit for publication. The contents of the manuscript are solely the responsibility of the authors and do not necessarily represent the official views of the funding bodies.

References

1. Mandel JS, Bond JH, Church TR, Snover DC, Bradley GM, Schuman LM, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med. 1993;328(19):1365–71. [PubMed: 8474513]
2. Hardcastle JD, Chamberlain JO, Robinson MH, Moss SM, Amar SS, Balfour TW, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. The Lancet. 1996;348(9040):1472–7.
3. Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. The Lancet. 1996;348(9040):1467–71.

4. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. Epidemiol Rev. 2011;33:88–100. [PubMed: 21633092]
5. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJ, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. Gut. 2015;64(10):1637–49. [PubMed: 26041752]
6. Cancer Council Australia Colorectal Cancer Guidelines Working Party. Clinical practice guidelines for the prevention, early detection and management of colorectal cancer [Internet]. Sydney: Cancer Council Australia; 2018 [updated Version URL: https://wiki.cancer.org.au/australiawiki/index.php?oldid=191477. Available from: https://wiki.cancer.org.au/australia/Guidelines:Colorectal_cancer.
7. So HC, Kwan JS, Cherny SS, Sham PC. Risk prediction of complex diseases from family history and known susceptibility loci, with applications for cancer screening. Am J Hum Genet. 2011;88(5):548–65. [PubMed: 21529750]
8. Do CB, Hinds DA, Francke U, Eriksson N. Comparison of family history and SNPs for predicting risk of complex disease. PLoS Genet. 2012;8(10):e1002973. [PubMed: 23071447]
9. Dunlop MG, Tenesa A, Farrington SM, Ballereau S, Brewster DH, Koessler T, et al. Cumulative impact of common genetic variants and other risk factors on colorectal cancer risk in 42,103 individuals. Gut. 2013;62(6):871–81. [PubMed: 22490517]
10. Al-Tassan NA, Whiffin N, Hosking FJ, Palles C, Farrington SM, Dobbins SE, et al. A new GWAS and meta-analysis with 1000Genomes imputation identifies novel risk variants for colorectal cancer. Sci Rep. 2015;5:10442. [PubMed: 25990418]
11. Peters U, Bien S, Zubair N. Genetic architecture of colorectal cancer. Gut. 2015;64(10):1623–36. [PubMed: 26187503]
12. Huyghe JR, Bien SA, Harrison TA, Kang HM, Chen S, Schmit SL, et al. Discovery of common and rare genetic risk variants for colorectal cancer. Nat Genet. 2019;51(1):76–87. [PubMed: 30510241]
13. Chatterjee N, Shi J, Garcia-Closas M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. Nat Rev Genet. 2016;17(7):392–406. [PubMed: 27140283]
14. Jenkins MA, Makalic E, Dowty JG, Schmidt DF, Dite GS, MacInnis RJ, et al. Quantifying the utility of single nucleotide polymorphisms to guide colorectal cancer screening. Future Oncol. 2016;12(4):503–13. [PubMed: 26846999]
15. Chowdhury S, Dent T, Pashayan N, Hall A, Lyratzopoulos G, Hallowell N, et al. Incorporating genomics into breast and prostate cancer screening: assessing the implications. Genet Med. 2013;15(6):423–32. [PubMed: 23412607]
16. Hawken SJ, Greenwood CM, Hudson TJ, Kustra R, McLaughlin J, Yang Q, et al. The utility and predictive value of combinations of low penetrance genes for screening and risk prediction of colorectal cancer. Hum Genet. 2010;128(1):89–101. [PubMed: 20437058]
17. Khoury MJ, Janssens AC, Ransohoff DF. How can polygenic inheritance be used in population screening for common diseases? Genet Med. 2013;15(6):437–43. [PubMed: 23412608]
18. Siegel RL, Fedewa SA, Anderson WF, Miller KD, Ma J, Rosenberg PS, et al. Colorectal Cancer Incidence Patterns in the United States, 1974–2013. J Natl Cancer Inst. 2017;109(8).
19. Surveillance Epidemiology and End Results Program. Cancer stat facts: colon and rectum cancer: National Cancer Institute; 2017 [Available from: http://seer.cancer.gov/statfacts/html/colorect.html.
20. Troeung L, Sodhi-Berry N, Martini A, Malacova E, Ee H, O'Leary P, et al. Increasing Incidence of Colorectal Cancer in Adolescents and Young Adults Aged 15-39 Years in Western Australia 1982-2007: Examination of Colonoscopy History. Front Public Health. 2017;5:179. [PubMed: 28791283]
21. Pashayan N, Duffy SW, Chowdhury S, Dent T, Burton H, Neal DE, et al. Polygenic susceptibility to prostate and breast cancer: implications for personalised screening. Br J Cancer. 2011;104(10):1656–63. [PubMed: 21468051]
22. Frampton MJ, Law P, Litchfield K, Morris EJ, Kerr D, Turnbull C, et al. Implications of polygenic risk for personalised colorectal cancer screening. Ann Oncol. 2016;27(3):429–34. [PubMed: 26578737]

23. Hsu L, Jeon J, Brenner H, Gruber SB, Schoen RE, Berndt SI, et al. A model to determine colorectal cancer risk using common genetic susceptibility loci. Gastroenterology. 2015;148(7):1330–9 e14. [PubMed: 25683114]
24. Loeve F, Boer R, van Oortmarssen GJ, van Ballegooijen M, Habbema JD. The MISCAN-COLON simulation model for the evaluation of colorectal cancer screening. Comput Biomed Res. 1999;32(1):13–33. [PubMed: 10066353]
25. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program monitoring report: phase 2, July 2008- June 2011 Canberra: Australian Institute of Health and Welfare; 2012 [Available from: https://www.aihw.gov.au/reports/cancer-screening/bowel-cancer-screening-2008-2011/contents/table-of-contents.
26. Tran B, Keating CL, Ananda SS, Kosmider S, Jones I, Croxford M, et al. Preliminary analysis of the cost-effectiveness of the National Bowel Cancer Screening Program: demonstrating the potential value of comprehensive real world data. Intern Med J. 2011;42(7):794–800.
27. Ananda SS, McLaughlin SJ, Chen F, Hayes IP, Hunter AA, Skinner IJ, et al. Initial impact of Australia's National Bowel Cancer Screening Program. Med J Aust. 2009;191(7):378–81. [PubMed: 19807627]
28. Australian Bureau of Statistics 3302.0.55.001 - Life Tables, States, Territories and Australia, 2013-2015 [Internet]. Canberra: Australian Bureau of Statistics; 2017 [updated 2016 Oct 27 Available from: http://www.abs.gov.au/AUSSTATS/abs@.nsf/allprimarymainfeatures/97E435FA3B82A89DCA2570A6000573D3?opendocument.
29. Fuchs CS, Giovannucci EL, Colditz GA, Hunter DJ, Speizer FE, Willett WC. A prospective study of family history and the risk of colorectal cancer. N Engl J Med. 1994;331(25):1669–74. [PubMed: 7969357]
30. Appleyard M, Grimpen F, Spucches C, Si D, A T. Participation in the national bowel cancer screening program and screening outcomes in Queensland. J Gastroenterol Hepatol. 2011;26(Suppl 4):29.
31. Queensland Health. Queensland Bowel Cancer Screening Program: Statistical Report August 2006 – December 2010. Internet. Brisbane: Queensland Health, 2011.
32. Cancer Council Australia Colonoscopy Surveillance Working Party. Clinical Practice Guidelines for Surveillance Colonoscopy – in adenoma follow-up; following curative resection of colorectal cancer; and for cancer surveillance in inflammatory bowel disease Sydney: Cancer Council Australia; 2011 [
33. Australian Institute of Health and Welfare. National Bowel Cancer Screening Program: monitoring report 2017. Cancer series no. 104. Cat. no. CAN 103 Canberra: AIHW; 2017 [Available from: https://www.aihw.gov.au/reports/cancer-screening/bowel-cancer-screening-program-monitoring-2017/contents/table-of-contents.
34. Colquhoun P, Chen HC, Kim JI, Efron J, Weiss EG, Nogueras JJ, et al. High compliance rates observed for follow up colonoscopy post polypectomy are achievable outside of clinical trials: efficacy of polypectomy is not reduced by low compliance for follow up. Colorectal Dis. 2004;6(3):158–61. [PubMed: 15109378]
35. Clinical Genomics. ColoVantage Home Test Kit: Clinical Genomics; 2016 [Available from: http://www.colovantage.com.au/Store/ProdID/1/ColoVantage_Home.
36. MBS Online. Medicare Benefits Schedule - Item 73934: Australian Government Department of Health; 2016 [Available from: http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=73934&qt=item&criteria=73934%20.
37. MBS Online. Medicare Benefits Schedule - Item 23: Australian Government Department of Health; 2016 [updated 5 November 2013 Available from: http://www9.health.gov.au/mbs/fullDisplay.cfm?type=item&q=23&qt=item&criteria=23.
38. Independent Hospital Pricing Authority. Australian Public Hospitals Cost Report 2013-2014 Round 18 [Internet]. Sydney: Independent Hospital Pricing Authority; 2016 [updated 11 February 2016 Available from: https://www.ihpa.gov.au/publications/australian-public-hospitals-cost-report-2013-2014-round-18.

39. Ananda S, Kosmider S, Tran B, Field K, Jones I, Skinner I, et al. The rapidly escalating cost of treating colorectal cancer in Australia. Asia Pac J Clin Oncol. 2016;12(1):33–40. [PubMed: 25866889]
40. Australian Bureau of Statistics. Consumer Price Index Inflation Calculator [Internet]. Canberra: Australian Bureau of Statistics; 2016 [updated 26 July 2016 Available from: http://www.abs.gov.au/websitedbs/d3310114.nsf/home/Consumer+Price+Index+Inflation+Calculator.
41. BREVAGenplus. Pay for your test: Genetic Technologies Limited; 2018 [updated 2018 Available from: http://www.brevagenplus.com/payment/.
42. Ness R, Holmes A, Klein R, Dittus R. Utility valuations for outcome states of colorectal cancer. Am J Gastroenterol. 1999;94(6):1650–7. [PubMed: 10364039]
43. Australian Government Department of Health. The Pharmaceutical Benefits Advisory Committee (PBAC) Guidelines: Australian Government Department of Health; 2016 [updated 2016 Sep. Available from: https://pbac.pbs.gov.au/section-d/section-d-cea/d4-variables-in-the-economic-evaluation.html.
44. Hanmer J, Lawrence WF, Anderson JP, Kaplan RM, Fryback DG. Report of nationally representative values for the noninstitutionalized US adult population for 7 health-related quality-of-life scores. Med Decis Making. 2006;26(4):391–400. [PubMed: 16855127]
45. Sanders GD, Neumann PJ, Basu A, Brock DW, Feeny D, Krahn M, et al. Recommendations for Conduct, Methodological Practices, and Reporting of Cost-effectiveness Analyses: Second Panel on Cost-Effectiveness in Health and Medicine. JAMA. 2016;316(10):1093–103. [PubMed: 27623463]
46. Pashayan N, Morris S, Gilbert FJ, Pharoah PDP. Cost-effectiveness and Benefit-to-Harm Ratio of Risk-Stratified Screening for Breast Cancer: A Life-Table Model. JAMA Oncol. 2018;4(11):1504–10. [PubMed: 29978189]
47. NIH: US National Library of Medicine. What is the cost of genetic testing, and how long does it take to get the results? 2017 [updated 26 September 2017 Available from: https://ghr.nlm.nih.gov/primer/testing/costresults.
48. Jiao S, Peters U, Berndt S, Brenner H, Butterbach K, Caan BJ, et al. Estimating the heritability of colorectal cancer. Hum Mol Genet. 2014;23(14):3898–905. [PubMed: 24562164]
49. Win AK, Macinnis RJ, Hopper JL, Jenkins MA. Risk prediction models for colorectal cancer: a review. Cancer Epidemiol Biomarkers Prev. 2012;21(3):398–410. [PubMed: 22169185]
50. Jeon J, Du M, Schoen RE, Hoffmeister M, Newcomb PA, Berndt SI, et al. Determining Risk of Colorectal Cancer and Starting Age of Screening Based on Lifestyle, Environmental, and Genetic Factors. Gastroenterology. 2018;154(8):2152–64 e19. [PubMed: 29458155]
51. Nicholls SG, Etchegary H, Carroll JC, Castle D, Lemyre L, Potter BK, et al. Attitudes to incorporating genomic risk assessments into population screening programs: the importance of purpose, context and deliberation. BMC Med Genomics. 2016;9(1):25. [PubMed: 27215612]
52. Nicholls SG, Wilson BJ, Craigie SM, Etchegary H, Castle D, Carroll JC, et al. Public attitudes towards genomic risk profiling as a component of routine population screening. Genome. 2013;56(10):626–33. [PubMed: 24237344]
53. Taylor S A population-based survey in Australia of men's and women's perceptions of genetic risk and predictive genetic testing and implications for primary care. Public Health Genomics. 2011;14(6):325–36. [PubMed: 21494016]
54. Hall AE, Chowdhury S, Hallowell N, Pashayan N, Dent T, Pharoah P, et al. Implementing risk-stratified screening for common cancers: a review of potential ethical, legal and social issues. J Public Health (Oxf). 2014;36(2):285–91. [PubMed: 23986542]
55. Altobelli E, Lattanzi A, Paduano R, Varassi G, di Orio F. Colorectal cancer prevention in Europe: burden of disease and status of screening programs. Prev Med. 2014;62:132–41. [PubMed: 24530610]
56. Rees G, Martin PR, Macrae FA. Screening participation in individuals with a family history of colorectal cancer: a review. Eur J Cancer Care (Engl). 2008;17(3):221–32. [PubMed: 18419625]
57. Edwards AG, Naik G, Ahmed H, Elwyn GJ, Pickles T, Hood K, et al. Personalised risk communication for informed decision making about taking screening tests. Cochrane Database Syst Rev. 2013(2):CD001865. [PubMed: 23450534]

58. Hewitson P, Ward AM, Heneghan C, Halloran SP, Mant D. Primary care endorsement letter and a patient leaflet to improve participation in colorectal cancer screening: results of a factorial randomised trial. Br J Cancer. 2011;105(4):475–80. [PubMed: 21829202]

59. Church T Colorectal cancer screening: will non-invasive procedures triumph? Genome Med. 2014;6(6):125. [PubMed: 25031625]

60. Peterse EFP, Meester RGS, Siegel RL, Chen JC, Dwyer A, Ahnen DJ, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: Microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. Cancer. 2018.

61. Cenin D, O'Leary P, Lansdorp-Vogelaar I, Preen D, Jenkins M, Moses E. Integrating personalised genomics into risk stratification models of population screening for colorectal cancer. Aust N Z J Public Health. 2017;41(1):3–4. [PubMed: 27774701]

62. Schroy PC 3rd, Coe A, Chen CA, O'Brien MJ, Heeren TC. Prevalence of advanced colorectal neoplasia in white and black patients undergoing screening colonoscopy in a safety-net hospital. Ann Intern Med. 2013;159(1):13–20. [PubMed: 23817700]

63. van Rijn JC, Reitsma JB, Stoker J, Bossuyt PM, van Deventer SJ, Dekker E. Polyp miss rate determined by tandem colonoscopy: a systematic review. Am J Gastroenterol. 2006;101(2):343–50. [PubMed: 16454841]

64. Viiala CH, Zimmerman M, Cullen DJ, Hoffman NE. Complication rates of colonoscopy in an Australian teaching hospital environment. Intern Med J. 2003;33(8):355–9. [PubMed: 12895166]

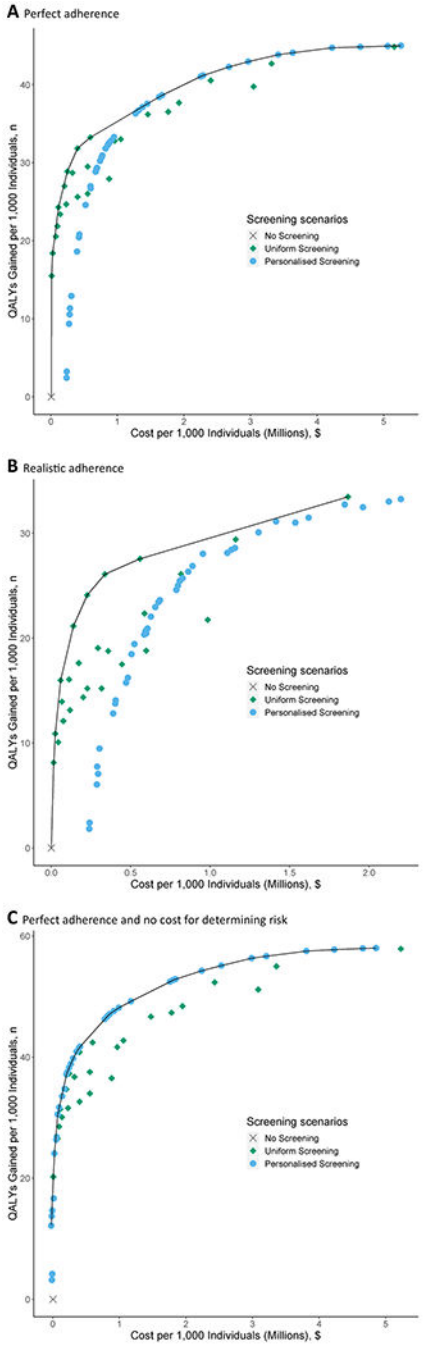

Figure 1:

Costs and quality-adjusted life years (discounted at 5%) per 1,000 40-year-olds for all uniform and personalised colorectal cancer screening scenarios and a scenario without screening, with the efficient frontier connecting the economically efficient strategies[a] assuming: a) perfect adherence; b) realistic adherence and c) perfect adherence and no costs associated with determining risk.

Abbreviations: QALYs = quality-adjusted life years

Note: A description of the personalised screening scenarios can be found in Table 4.

a. 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. Quality-adjusted life years 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.

Table 1:

Model Inputs: Test characteristics, participation assumptions, utility losses and costs associated with colorectal cancer screening and treatment

TEST CHARACTERISTICS	
Specificity and sensitivity of FIT [a]	
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 [b]	36.5%
Sensitivity cancer shortly before clinical diagnosis [b]	72.8%
Specificity and sensitivity of colonoscopy [c, d]	
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 [e]	
Fatal complication [f]	0.040%
General complication [g]	
50–54	0.096%
55–59	0.080%
60–64	0.054%
65–69	0.127%
70–74	0.073%
PARTICIPATION	
Uptake of initial screening offer [h]	
50–54	28.5%
55–59	36.8%
60–64	43.2%
65–69	43.5%
70–74	52.5%
Uptake of rescreening [h]	
Previously attended	76.0%
Previously not attended	19.7%
Attendance at General Practitioner [i]	90.0%
Uptake of diagnostic test [h]	
50–54	72.3%

TEST CHARACTERISTICS				
55–59				71.6%
60–64				71.4%
65–69				70.6%
70–74				68.2%
Adherence to surveillance [j]				80.0%
UTILITY LOSS (QALYs) [k]				
Per FIT	0			
Per colonoscopy [l]	0.00274			
Per complication of colonoscopy [m]	0.01918			
Per LY with CRC Care [n, o]	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
COSTS (2016 $AUD) [p]				
Per FIT invitation [q]				17.35
Per returned FIT [r]				22.60
Per GP visit [s]				37.05
Per colonoscopy (same day) [t]				1,627
Polygenic test [u]				200
Per complication of colonoscopy [v]				9,027
Treatment by stage and location [w, x, y]				
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; Abbreviations: FIT = faecal immunochemical test; GP = General Practitioner; OC = Other Cause; QALY = Quality-Adjusted Life Year; RC = Rectal Cancer; LY = Life Year

[a.] Specificity and sensitivity of FIT derived from results of Queensland Health report[31]

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

[c.] 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 et al, 2013[62]

[d] 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[63]

[e] Complications are conditional on polypectomy, and we assume that polypectomy is only performed if colonoscopy is positive

[f] Fatal perforation taken from Viiala et al, 2003[64] and includes only deaths from colonoscopies performed in outpatients within 30 days of, and attributed to, colonoscopy

[g] 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

[h] Uptake of screening, rescreening and participation in diagnostic follow up taken from National Bowel Cancer Screening Monitoring report[33]

[i] Attendance at general practitioner for referral to colonoscopy taken from Tran et al, 2011[26]

[j] Attendance at surveillance colonoscopies assumed to be 80% based on Colquhoun et al, 2003[34]

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

[l] Equal to 2 days per colonoscopy at a utility of 0.5

[m] Complications associated with hospitalisation with 30 days of colonoscopy were assumed to be equal to 14 days at a utility of 0.5

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

[o] 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 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

[p] Costs are from a health systems perspective and do not include patient time costs. All costs are presented in Australian dollars ($AUD) and are indexed to 2016 prices

[q] FIT price based on the pricing of a commercially available alternative[35]

[r] The cost to analyse a specimen based in Australian Medicare Benefits Schedule[36]

[s] Cost to visit GP taken from Australian Medicare Benefits Schedule[37]

[t] Costs for colonoscopy are calculated based on information available from Independent Hospital Pricing Authority[38]

[u] Cost of polygenic test based on a commercially available polygenic test for breast cancer[41]

[v] Costs for complications of colonoscopy are calculated based on information available from Independent Hospital Pricing Authority[38]

[w] Cost of treatment taken from Ananda et al, 2016[39]

[x] Proportion of rectal cancer assumed to be 30.81%[27]

[y] Proportion of Stage IV cancers treated with bevacizumab assumed to be 50%[39]

Table 2:

Stratification of individuals according to polygenic risk and family history of colorectal cancer [a]

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
	4	Second highest quintile for polygenic risk and no CRC in first degree relatives	1.14	14
High	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

[a] Stratification based on Jenkins et al[14]

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

a. Effects of uniform screening scenarios assuming perfect adherence

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
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

a. Effects of uniform screening scenarios assuming perfect adherence

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
COL	40	5	0	7,011	1.57	26	6	17,924	17,904	6,462,019	648,900

b. Effects of uniform screening scenarios assuming realistic adherence

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
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

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2020 July 01.

a. Effects of uniform screening scenarios assuming perfect adherence

Screening Strategy			FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
Test	Start Age	Interval									
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

Abbreviations: COL = colonoscopy; CRC = colorectal cancer, FIT = faecal immunological test; ICER = incremental cost-effectiveness ratio; QALYs = quality-adjusted life years

Grey shading highlights uniform screening scenarios on the efficient frontier prior to considering personalised screening.

a. Results are discounted at an annual rate of 5%

b. Costs are presented in Australian Dollars ($AUD)

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2020 July 01.

Table 4:

Specifics of the personalised screening scenarios, when costs and QALYs are discounted at 5%[a]

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

Screening Strategy	Risk Groups				
	Very Low	Low	Average	High	Very High
PS39	COL_46_5	COL_40_5	COL_40_5	COL_40_5	COL_40_5

Abbreviations: COL = colonoscopy; FIT = faecal immunochemical test, NoScr = no screening

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

[a] All screening ends at or before the age of 74 years

Table 5:

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

a. Effects of personalised screening scenarios assuming perfect adherence

Screening Strategy	FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
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

a. Effects of personalised screening scenarios assuming perfect adherence

Screening Strategy	FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
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. Effects of personalised screening scenarios assuming realistic adherence

Screening Strategy	FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
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

a. Effects of personalised screening scenarios assuming perfect adherence

Screening Strategy	FITs	Colonoscopies	Complications	CRC Incidence	CRC Mortality	Life Years[a]	Total QALYs[a]	Total Costs[ab]	ICER[ab]
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
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

Abbreviations: CRC = colorectal cancer; FIT = faecal immunochemical test; PS = personalised screening; QALYs = quality-adjusted life years

Grey shading highlights screening scenarios on the efficient frontier prior to considering uniform screening.

[a.] Results are discounted at an annual rate of 5%.

Cancer Epidemiol Biomarkers Prev. Author manuscript; available in PMC 2020 July 01.

[b] Costs are presented in Australian Dollars ($AUD)

[c] The personalised screening scenarios are described in Table 4