Long-term evaluation of benefits, harms, and cost-effectiveness of the National Bowel Cancer Screening Program in Australia: a modelling study

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Summary

Background No assessment of the National Bowel Screening Program (NBCSP) in Australia, which considers all downstream benefits, costs, and harms, has been done. We aimed to use a comprehensive natural history model and the most recent information about cancer treatment costs to estimate long-term benefits, costs, and harms of the NBCSP (2 yearly immunochemical faecal occult blood testing screening at age 50–74 years) and evaluate the incremental effect of improved screening participation under different scenarios.

Methods In this modelling study, a microsimulation model, Policy1-Bowel, which simulates the development of colorectal cancer via both the conventional adenoma-carcinoma and serrated pathways was used to simulate the NBCSP in 2006–40, taking into account the gradual rollout of NBCSP in 2006–20. The base-case scenario assumed 40% screening participation (currently observed behaviour) and two alternative scenarios assuming 50% and 60% participation by 2020 were modelled. Aggregate year-by-year screening, diagnosis, treatment and surveillance-related costs, resource utilisation (number of screening tests and colonoscopies), and health outcomes (incident colorectal cancer cases and colorectal cancer deaths) were estimated, as was the cost-effectiveness of the NBCSP.

Findings With current levels of participation (40%), the NBCSP is expected to prevent 92 200 cancer cases and 59 000 deaths over the period 2015–40; an additional 24 300 and 37 300 cases and 16 800 and 24 800 deaths would be prevented if participation was increased to 50% and 60%, respectively. In 2020, an estimated 101 000 programme-related colonoscopies will be done, associated with about 270 adverse events; an additional 32 500 and 49 800 colonoscopies and 88 and 134 adverse events would occur if participation was increased to 50% and 60%, respectively. The overall number needed to screen (NNS) is 647–788 per death prevented, with 52–59 colonoscopies per death prevented. The programme is cost-effective due to the cancer treatment costs averted (cost-effectiveness ratio compared with no screening at current participation, AUS$3014 [95% uncertainty interval 1807–5583] per life-year saved) in the cost-effectiveness analysis. In the budget impact analysis, reduced annual expenditure on colorectal cancer control is expected by 2030, with expenditure reduced by a cumulative AUS$1·7 billion, AUS$2·0 billion, and AUS$2·1 billion (2015 prices) between 2030 and 2040, at participation rates of 40%, 50%, and 60%, respectively.

Interpretation The NBCSP has potential to save 83 800 lives over the period 2015–40 if coverage rates can be increased to 60%. By contrast, the associated harms, although an important consideration, are at a smaller magnitude at the population level. The programme is highly cost-effective and within a decade of full roll-out, there will be reduced annual health systems expenditure on colorectal cancer control due to the impact of screening.

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Introduction

Colorectal cancer is the third most common cancer in Australia and the second most common cause of cancer death, with 14 962 new cases of bowel cancer diagnosed and 4149 bowel cancer deaths reported in 2013.[1] Most colorectal cancer cases (>90%) are diagnosed in individuals aged 50 years or older and the disease is more common in men than in women.[1] Due to the high burden of disease and the availability of new treatments for advanced cancer, the costs related to treatment are considerable, and have increased substantially over the past decade to an estimated AUS$1 billion annually in 2013.[2] Additionally, there are major costs associated with colonoscopy, sometimes used for ad-hoc screening, with an estimated 700 000 colonoscopies (for all purposes) done in 2012 in Australia.[3]

Screening with the faecal occult blood test (FOBT) has been shown to be effective in reducing bowel cancer incidence and mortality in long-term cohort follow up and in trials.[4] In Australia, the National Bowel Cancer Screening Program (NBCSP) was introduced in late 2006, offering free immunochemical faecal occult blood

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Research in context

Evidence before this study

Screening with the faecal occult blood test has been found to be effective in reducing bowel cancer incidence and mortality in long-term cohort follow-up and in trials. In Australia, the National Bowel Cancer Screening Program (NBCSP) was introduced in late 2006 and will be fully rolled out by 2020, at which stage it will offer biennial screening with free immunochemical faecal occult blood testing (iFOBT) to all people aged 50–74 years. The overall participation rate was 37% in 2013–14. Colorectal cancer treatment costs in Australia have increased rapidly in the past two decades. We searched PudMed and MEDLINE in March to April, 2016, to identify economic evaluations of biennial iFOBT screening in individuals aged 50–74 years in Australia. The literature review identified three modelling or health economics studies. However, no assessment that takes into account the effect of screening and surveillance on all downstream health and cost outcomes and the rapid increase in colorectal cancer treatment costs has been done.

Added value of this study

We did a comprehensive evaluation of the long-term benefits, costs, and harms of the NBCSP using a well calibrated and validated model, *Policy1-Bowel*. The model took into account both the conventional adenoma-carcinoma pathway and the serrated pathway in the natural history of colorectal cancer development, the phased implementation of NBCSP in the period 2006–20, the detailed management pathways for screening and colonoscopy surveillance, and the observed screening behaviour. The model also incorporated all the downstream benefits, costs, and harms of the NBCSP and the most recent information about cancer treatment costs, which have been rapidly increasing in Australia, in the cost-effectiveness evaluation. The study provided detailed predictions of the number of colorectal cancer cases, colorectal cancer deaths, the overall NBCSP programme cost, and resource use (including number of iFOBT test kits sent and returned to the programme, programme-related colonoscopies, and adverse events) that would occur in the period between 2006 and 2040.

Implication of all the available evidence

Our study findings suggest that the NBCSP in Australia will be very effective in reducing colorectal cancer mortality, and its effectiveness would be further increased with improved participation. The NBCSP was found to be highly cost-effective in the cost-effectiveness analysis, which involves discounting costs and effects over the lifetime of a single cohort. Findings from the (undiscounted) budget impact analysis for each year showed that the total annual cost to the health system to provide iFOBT screening, colonoscopy follow-up and surveillance, and colorectal cancer treatment would become less than the total cost without screening within a decade of full rollout of the programme in 2020, due mainly to avoidance of treatment costs for colorectal cancer.

testing (iFOBT) for Australians turning 55 years and 65 years in that year.[5] The programme has been expanding since then, via the addition of new age cohorts. The programme will be fully rolled out by 2020, at which stage it will offer biennial screening to all people aged 50–74 years. However, in the period between 2006 and 2019, some age cohorts will have been screened at a longer interval (for example, the birth cohort who received the first screening invitation at the age of 55 years in 2006 were eligible for the second screening invitation in 2016).[5] In 2013–14, about 2·3 million iFOBT test kits were sent by the NBCSP to eligible Australians (individuals aged 50 years, 55 years, 60 years, and 65 years) and 836 457 kits were completed and returned to the programme (yielding a participation rate of about 37·3%).[5] The reported overall positivity rate of the completed iFOBT tests was 7·0%.[5]

Three modelling or economic studies have been done to evaluate biennial iFOBT screening for people aged 50–74 years in Australia, but none of these have taken into account the effect of screening and surveillance on all downstream health and cost outcomes; and no analysis, to the best of our knowledge, to date has accounted for the rapid increase in colorectal cancer treatment costs in the past two decades.[2,6–8] A summary of the findings of these three studies is shown in the appendix.

See Online for appendix

The aims of this study were therefore to derive an accurate and updated estimate of the benefits, harms, resource use, annual expenditure, and cost-effectiveness of the fully implemented NBCSP in Australia over the period between 2015 and 2040, taking into account the effect of gradual rollout of the screening programme before 2020, the most current data for cancer treatment costs, and the effect of downstream management, including colonoscopy surveillance, on both the effects and costs of the programme; and to assess the effect of improved screening participation on these outcomes.

Methods

Model calibration and validation

We used the Policy1-Bowel microsimulation platform, which was developed by adapting and recalibrating an existing colorectal cancer natural history model, the Adenoma and Serrated Pathway to Colorectal CAncer model (ASCCA),[9] to natural history data and the Australian setting. The Policy1-Bowel model was constructed using Microsoft Visual Studio 2013 C++.

The model simulates 10 million men and 10 million women per single year age cohort, and incorporates sex-specific life table data. The simulation begins from age 20 years and continues on an annual time-step until the individual dies or becomes 90 years old, whichever occurs

first. The multiple cohort implementation simulates cohorts turning 20 years from 1911 to 2000, to obtain a full cross-sectional outcome in the population in the period between 2000 and 2059. As is the case for the ASCCA model,[9] Policy1-Bowel includes both the conventional adenoma-carcinoma pathway and serrated pathway in colorectal cancer development and is calibrated to the prevalence of lesions observed in the colonoscopy arm of the COCOS trial,[10] a Dutch trial of colorectal screening with colonoscopy and CT colonography, which was done in screening-naive individuals. For Policy1-Bowel, the precancer natural history assumptions were systematically recalibrated using the Nelder-Mead algorithm; target data included the age-specific, sex-specific, and size-specific prevalence of conventional adenoma, advanced conventional adenoma and serrated lesions, the relative proportions by degree of dysplasia and degree of villosity in conventional adenoma, and relative proportions of conventional adenoma multiplicity, advanced conventional adenoma multiplicity, and serrated lesion multiplicity among individuals detected with polyps observed in the COCOS trial. The model-predicted age-specific and age-standardised rates of colorectal cancer incidence and mortality in an unscreened population were calibrated to pre-NBCSP Australian data (appendix pp 40–43).[11] The least-squares method was used to examine the goodness of fit of the natural history solutions; the best fitting set of natural history assumptions was selected for base case analysis, and the top 200 best fitted natural history sets were selected for alternative natural history assumptions in uncertainty analysis (appendix pp 32–40).

The model was also calibrated to a number of aspects specific to colorectal cancer and to the NBCSP in Australia. In brief, the test characteristics of iFOBT were based on the literature and then calibrated to the observed iFOBT positivity rate and the colonoscopy outcomes among those with a positive iFOBT result, as observed each year in the NBCSP in 2006–14 (appendix pp 43–44).[12–16] The accuracy of colonoscopy for adenoma and cancer detection was based on the findings of two systematic reviews and calibrated to the proportion of the colonoscopy outcomes observed among positive iFOBT individuals in the NBCSP.[14,17,18] Detailed information about the modelled iFOBT and colonoscopy test characteristics are provided in the appendix (pp 19–23).

The modelled invasive cancer natural history and cancer detection rates for iFOBT and colonoscopy were calibrated to predict cancer stage distributions among symptomatically detected cancers and screen-detected cancers that are consistent with the findings of a 2009 Australian study (appendix p 41).[19] The final cancer survival probabilities thus varied by stage at diagnosis, time since diagnosis, and whether cancer was diagnosed via screening or symptomatically detected. The modelled cancer stage-specific relative survival between screen-detected and symptomatically detected cancers were consistent with the findings of international studies.[20–22] These final calibrated survival assumptions assumed that within-stage survival is slightly worse for symptomatically detected cancers versus screen-detected cancers, which is clinically plausible.[20–22] Detailed information about natural history calibration methods and outcomes, model

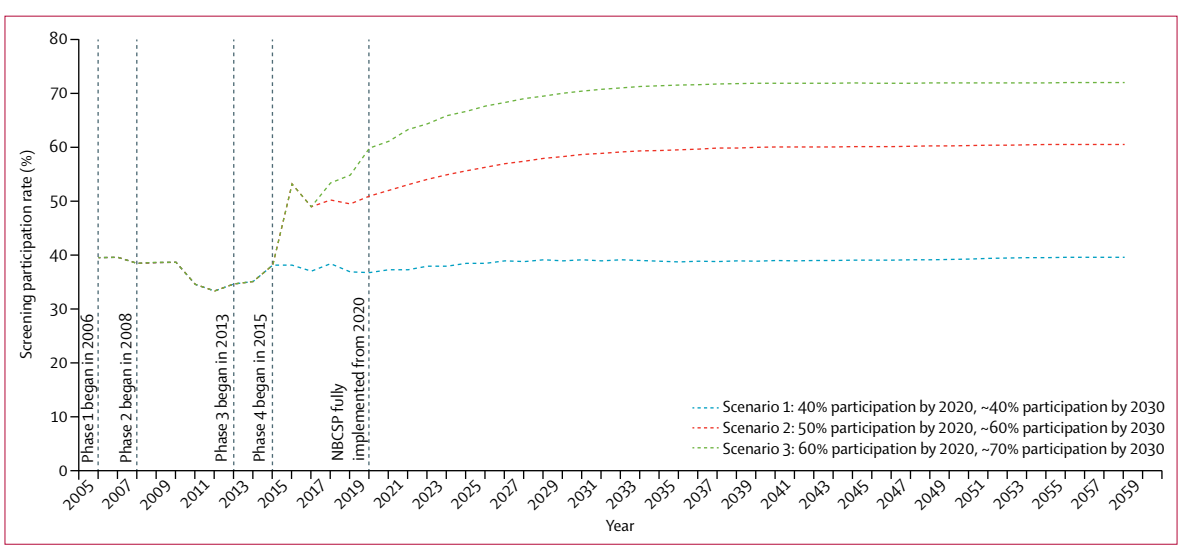

Figure 1: **Modelled screening participation in 2006–2059, all participation scenarios**
Individuals aged 55 years and 65 years were invited to participate in colorectal screening during NBCSP phase 1 in 2006–08; 50 years, 55 years, and 65 years were invited during phase 2 in 2008–13; 50 years, 55 years, 60 years, and 65 years were invited during phase 3 in 2013–14; 50 years, 55 years, 60 years, 65 years, 70 years, and 74 years were invited during NBCSP phase 4 in 2015; 50 years, 55 years, 60 years, 64 years, 65 years, 70 years, 72 years, and 74 years were invited during phase 4 in 2016; 50 years, 54 years, 55 years, 58 years, 60 years, 64 years, 68 years, 70 years, 72 years, and 74 years will be invited during phase 4 in 2017; 50 years, 54 years, 58 years, 60 years, 62 years, 64 years, 66 years, 68 years, 70 years, 72 years, and 74 years will be invited during phase 4 in 2018; 50 years, 52 years, 54 years, 56 years, 58 years, 60 years, 62 years, 64 years, 66 years, 68 years, 70 years, 72 years ,and 74 years will be invited for screening during phase 4 in 2019 and after the NBCSP programme is fully implemented in 2020. NBCSP=National Bowel Screening Programme.

validation outcomes, natural history assumptions, cancer survival assumptions, and other model parameters are provided in the appendix (pp 9–49).

Screening participation and colonoscopy compliance assumptions

The Policy1-Bowel model simulated the phased implementation of NBCSP in 2006–19 and the fully implemented biennial iFOBT screening programme for 50–74 years from 2020 onwards (see appendix pp 5–7 for the detailed programme rollout schedule).[12] Figure 1 shows the modelled participation rate for those invited, from the inception of the programme. For each calendar year from 2006 onward, the model assumed that all individuals who are eligible for screening will be sent an iFOBT kit. The number of individuals eligible for a NBCSP invitation each year is estimated to increase from 421735 in 2006 to about 3·6 million by 2020, and to 4·7 million by 2040 (see appendix p 5 for more detail on the estimated number of individuals eligible for an NBCSP invitation in each year).[23,24] We used NBCSP data to directly inform the modelled assumptions for the age-specific and sex-specific screening initiation rate among individuals who had never participated in the past (33–40%), taking into account the observed changes in these rates, which occurred as the programme rolled out between 2006 and 2014.[12] We also used NBCSP data to directly inform the modelled age-specific and sex-specific re-screening rate (about 74%) for those who had previously participated in the NBCSP at least once.[12]

From 2015, three alternative participation scenarios assuming different screening initiation rates were evaluated; screening re-attendance rates were assumed to remain at a similar level from 2015 onwards in all scenarios. Scenario 1 assumed that overall 2-yearly screening participation in the NBCSP, which includes a re-screening rate from the so-called ever-screened group and a screening initiation rate from the so-called never-screened group, remained at about 40% for 2020 onwards. Scenarios 2 and 3 modelled an increase in overall screening participation by assuming an increase in initiation rates from 2016 onwards. In scenario 2, the overall population participation rate assumed in the model was about 50% by 2020, increasing thereafter, becoming stable at around 60% by 2035, with the delay in realising the full effect being due to that associated with the delayed effect of the increase in screening initiation on subsequent overall re-screening rates (since 74% of people who had previously accepted an invitation to screen in the programme will re-screen).[5] For scenario 3, the modelled overall screening participation was increased to about 60% by 2020, leading to a fully realised increased coverage rate of about 70% by 2035. Detailed information about the screening initiation and ongoing participation assumptions and the data sources to inform these assumptions are provided in the appendix (pp 23–29).

Individuals with a positive iFOBT outcome were assumed to be referred to colonoscopy (and polypectomy if required). Colonoscopy surveillance was modelled based on the individual's colonoscopy outcome and surveillance guideline recommendations.[26,27] Screening and colonoscopy surveillance were assumed to cease at 75 years. The colonoscopy attendance rate for individuals with a positive iFOBT was assumed to be 71% in those aged 50–74 years, as reported for the NBCSP.[15] The attendance rate for further colonoscopy surveillance to follow up individuals with lesions originally detected by screening was assumed to be 80%. We assumed that colonoscopy was associated with a serious non-fatal adverse event rate of up to 0·27% (2·7 per 1000 procedures in the base case we assumed no fatal adverse events; for more detail on the justification of the assumed colonoscopy adverse event rate see the appendix [pp 22–23]).

Costs

Using a health services perspective, costs considered included those associated with iFOBT, follow-up of positive iFOBT results, colonoscopy (and polypectomy if required), and colorectal cancer treatment; overheads related to administration and promotion of the screening programme and individuals' out-of-pocket costs were not included. Detailed information and a summary of the aggregate cost assumptions is provided in the appendix (pp 17–18). Costs were obtained from the Australian Medical Benefits Schedule (MBS) and the Australian-refined Diagnostic Related Group (AR-DRG) categories, where applicable, and after consultation with experts (DJBSJ, PG), assumptions were made for the iFOBT kit and postage cost, as well as the cost of each kit received and analysed in the laboratory, and the cost of colonoscopy (without complications). The costs associated with cancer treatment were based on previous data and inflated to 2015 values;[7] these cost assumptions are consistent with the findings of a recent Australian study that found colorectal cancer treatment costs increased substantially over the past two decade.[2] All costs are presented in 2015 Australian dollars (AUS$1=US$ 0·7706, June 20, 2015). It should be noted that the model assumed iFOBT test kits were sent to all alive individuals of an eligible age (regardless of the individual's screening history) every year; hence this particular expenditure was independent of screening adherence assumptions. Cost-effectiveness ratios (CERs) were compared with no screening and referenced to the relevant indicative willingness-to-pay (WTP) threshold in Australia—AUS$50 000 per life-year saved (or quality-adjusted life-year saved).

Single and multiple cohort analyses

The health outcomes and costs of the NBCSP were evaluated using two approaches—single cohort analysis, which provides lifetime outcomes for a single birth cohort

of both sexes, and multiple cohort analysis, which provides cross-sectional outcomes over time. The single cohort analysis assessed the effect of the fully implemented biennial screening programme by comparing the lifetime cost and health outcomes of a birth cohort that is eligible to participate in the fully implemented biennial iFOBT programme from the age of 50 years (ie, screened cohort) with a birth cohort that has never been screened with iFOBT (ie, never-screened cohort). Three screened birth cohorts, each associated with different 2-yearly participation rates of 40% (scenario 1), 60% (scenario 2), and 70% (scenario 3), for ages 50–74 years, were evaluated (in the single cohort analysis, these rates were chosen to reflect the maximum cross-sectional participation expected to be achieved by 2035 as shown in figure 1).

A cost-effectiveness analysis was done using the overall life-time cost and life-years in a single cohort, which were accrued from 50 to 89 years and discounted at a rate of 5% starting at 50 years, the age when bowel cancer screening begins.[28] The CER was calculated by dividing the difference of the discounted lifetime cost by the difference of the discounted life-years between the screened and never-screened cohort. We used the same perspective, discount rate and WTP threshold as per a predicate Medical Services Advisory Committee (MSAC) evaluation of the National Cervical Screening Program.[29] The age-standardised rates of colorectal cancer incidence and mortality were estimated using the standard 2001 Australian population.[23] The base case analysis assumed the best fitted set for natural history assumptions; the 200 alternative fitted sets were used to quantify uncertainty due to the natural history assumptions and outcomes were presented as 95% uncertainty intervals (UI). To assess the robustness of the findings due to uncertainties in screening and management, univariate sensitivity analysis was also done on a number of key model assumptions for the findings for the CER of screening when compared with no screening in scenario 1 (appendix pp 9–11).

The multiple cohort analysis was used to estimate aggregate year-by-year screening, diagnosis, treatment, and surveillance-related costs, resource use (number of iFOBT tests sent, number returned, and number of colonoscopies), and health outcomes (incident colorectal cancer cases and colorectal cancer deaths) in the period 2000–59. Model-estimated age-specific rates for each year were applied to the 2000–13 Australian population and the projected 2013–60 populations.[23,24] The budget impact analysis was done using undiscounted cost outcomes from the multiple cohort analysis. The number-needed-to-screen (NNS) to prevent one colorectal cancer case/death was calculated by dividing the total number of iFOBT kits returned by the total number of colorectal cancer cases/deaths prevented in 2015–40. The number-needed-to-colonoscope (NNC) to prevent one colorectal cancer case/death was calculated by dividing the total number of colonoscopies by the total number of colorectal cancer cases/deaths prevented in 2015–40.

Role of the funding source

The study sponsors took no part in designing the study question or in the analysis or interpretation of results. They also did not take part in the writing of the Article or in the decision to submit for publication. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

Over the lifetime of a cohort, biennial iFOBT screening between 50 years and 74 years was estimated to reduce colorectal cancer incidence by 23% (95% UI 20–24) and colorectal cancer mortality by 36% (32–38), respectively, when assuming the current 40% participation rate (scenario 1; table 1). A greater reduction in both cancer incidence (33% and 38%, respectively) and mortality (52% and 59%, respectively) were estimated if the participation was increased to 60% (scenario 2) or 70% (scenario 3). Scenarios assuming higher screening participation rates were associated with a higher overall proportion of early stage, screen-detected cancers. After screening and surveillance cease at 75 years, screened cohorts are predicted to experience an ongoing further

	Colorectal cancer incidence rate per 100 000 individuals*		Colorectal cancer mortality rate per 100 000 individuals*		Discounted cost per person,† base case‡ (AUS$; 95% UI)§¶	Discounted life-years per person,† base case‡ (95% UI)§¶
	Base case ASR‡	% reduction, base case‡ (95% UI)§¶	Base case ASR‡	% reduction, base case‡ (95% UI)§¶		
No screening	62·6	..	22·9	..	$1653 (1468–1881)	15·571 (15·552–15·590)
Scenario 1, 40% participation	48·4	23% (20–24)	14·6	36% (32–38)	$1732 (1682–1937)	15·597 (15·579–15·614)
Scenario 2, 60% participation	41·9	33% (29–35)	11·0	52% (47–55)	$1761 (1727–1958)	15·610 (15·594–15·626)
Scenario 3, 70% participation	39·0	38% (33–39)	9·5	59% (53–61)	$1798 (1769–1989)	15·617 (15·602–15·632)

UI=uncertainty interval. ASR=age-standardised rate. *Assuming 2001 Australian population, all ages. †Discounted at 5% per annum starting at 50 years (the age when bowel cancer screening begins), accrued from 50 years to 89 years. ‡Used best-fitting set of natural history assumptions. §Compared with no screening. ¶95% UI generated via 200 runs with alternative sets of calibrated natural history assumptions.

Table 1: **Single cohort analysis findings of health outcomes and costs over the lifetime of a cohort**

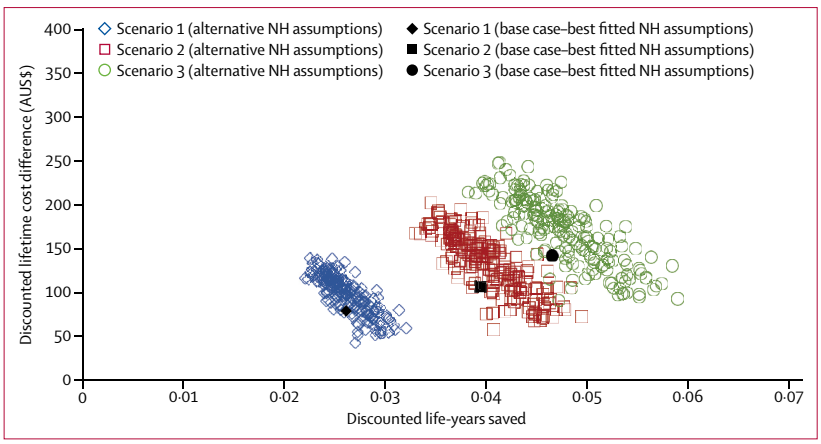

Figure 2: **Probabilistic sensitivity analysis for cost-effectiveness for all scenarios**
Scenario 1=40% participation; Scenario 2=60% participation; Scenario 3=70% participation. The CER of screening was estimated to be AUS$3014 (95% UI 1807–5583) per life-year saved in Scenario 1, AUS$2693 (1543–5195) per life-year saved in Scenario 2, and AUS$3048 (1830–5611) per life-year saved in Scenario 3, compared with no screening. NH=natural history.

decrease in cancer incidence and mortality over the next 5 years (appendix pp 50–51).

Compared with the indicative WTP threshold of AUS$50 000 per life-years saved, all base case scenarios found that biennial iFOBT screening is cost-effective compared with no screening in the cost-effectiveness analysis. The predicted CER was AUS$3014 per life-years saved in scenario 1, AUS$2693 per life-years saved in scenario 2, and AUS$3048 per life-years saved in scenario 3 when compared with no screening (figure 2). In the natural history uncertainty analysis, biennial iFOBT screening was predicted to be cost-effective in all runs of the three scenarios; the 95% UIs of the CERs of screening were estimated to be AUS$1807–5583 per life-years saved in scenario 1, AUS$1543–5195 per life-years saved in scenario 2, and AUS$1830–5611 per life-years saved in scenario 3 when compared with no screening (figure 2).

The estimated age-standardised colorectal incidence and mortality rates and cancer stage distributions for each year in the period between 2005 and 2050 are provided in the appendix (pp 52–53). Taking into account the age-structure of the Australian population over time, about 12 600 incident colorectal cancer cases and 4600 colorectal cancer deaths were predicted in 2005. Under the no screening assumption, by 2040, the numbers would increase to 29 900 incident cases and 11 200 deaths (figure 3). A lesser magnitude for the increase in the number of incident colorectal cancer cases and colorectal cancer deaths over time was predicted in the screening scenarios. Over a short-term period from 2015 to 2019, the NBCSP was predicted to detect an additional 4800–7900 colorectal cancer cases and to prevent 1900–2000 colorectal cancer deaths depending on the assumed screening participation rate (table 2). An additional 97 000–137 400 colorectal cancers and 57 100–81 800 colorectal cancer deaths are predicted to be prevented in the two decades after the biennial iFOBT screening is fully implemented in 2020 (depending on participation). This is equivalent to an average 3500–5000 colorectal cancer cases and 2300–3200 colorectal cancer deaths prevented per year in the period 2015–40.

In the (undiscounted) budget impact analysis, the overall expenditure on treatment for colorectal cancer was estimated to be AUS$858 million in 2006, increasing to about AUS$1 billion by 2010 and about AUS$2 billion by 2040 in the no screening scenario (2015 prices). This increase in expenditure occurs even in the absence of additional treatment advances or other changes in average treatment costs and is due to growth and ageing of the population (figure 3). The commencement of the NBCSP is predicted to result in a transient increase in overall expenditure in 2006–28, but a reduced annual expenditure on colorectal cancer control from 2029 onwards is expected in all screening participation scenarios. The total expenditure was estimated to be reduced by a cumulative AUS$1·7 billion, AUS$2·0 billion, and AUS$2·1 billion (2015 prices) between 2030 and 2040, at participation rates of 40%, 50%, and 60%, respectively (predicted from data in figure 3C). Notably, although the NBCSP is predicted to be associated with a lower annual expenditure than no screening in long term, it is predicted to be highly cost-effective (but not cost-saving) in the single cohort analysis when discounted costs and discounted life-years were used to estimate the cost-effectiveness ratio (table 1).

Over the period 2015–40, we estimate about 99 million iFOBT test kits will be sent out to eligible individuals (figure 3E). Depending on screening participation, 38–66 million test kits will be returned for further analysis and 3·1–5·0 million individuals will undergo colonoscopy (figure 3; table 2). This is equivalent to an average of 1·5–2·5 million individuals being screened by iFOBT and 118 300–191 300 individuals undergoing colonoscopy each year in that period (table 2). The estimated average number of colonoscopies per year increased to 134 500 in scenario 1, 193 900 in scenario 2, and 223 800 in scenario 3 over a 40-year period between 2015 and 2054. The number of non-fatal colonoscopy-related adverse events was estimated to increase over time as the number of colonoscopies increased. An average of 320–520 adverse events a year was estimated in 2015–40 (table 2).

Over the period 2015–40, an NNS of 414, 480, and 510, respectively, and an NNC of 33, 37, and 38, respectively, was estimated in scenarios 1, 2, and 3 to prevent one colorectal cancer case; the associated NNS was 647, 737, and 788, respectively, and the associated NNC was 52, 57, and 59, respectively, to prevent one colorectal cancer death.

In sensitivity analysis, the CER of screening (compared with no screening) was found to be most sensitive to the potential range of cancer treatment costs

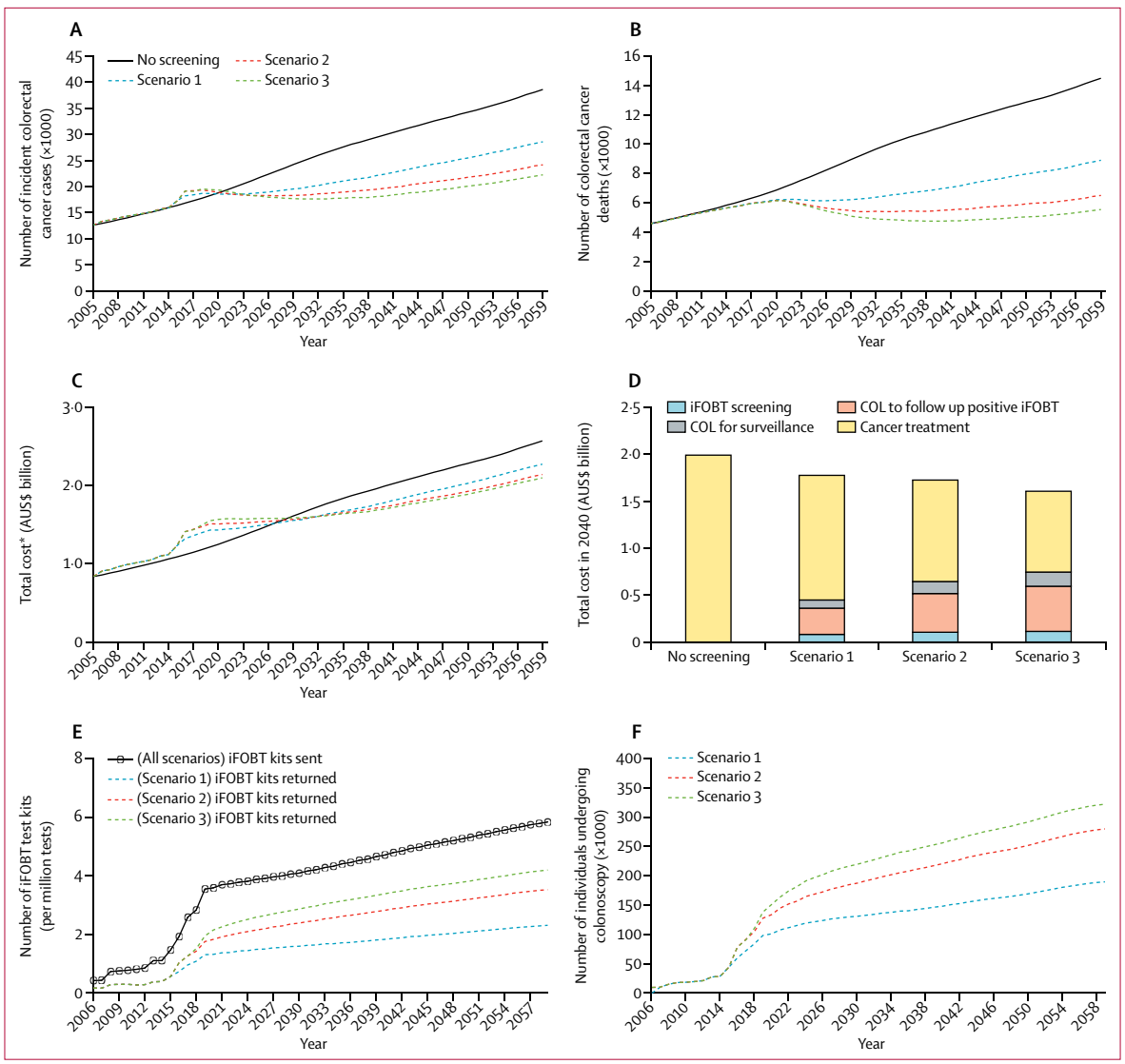

Figure 3: **Predicted health outcomes, costs, and resource use over the period 2005–59**
(A) Number of incident colorectal cancer cases, (B) number of colorectal cancer deaths, (C) total cost, (D), breakdown of total costs in 2040, (E) number of iFOBT kits sent/returned, and (F) number of individuals undergoing colonoscopy. iFOBT=immunochemical faecal occult blood test. COL=colonoscopy. *Cost associated with iFOBT screening includes cost of iFOBT test kits sent to eligible individuals, laboratory procedures to analyse returned iFOBT test kits from participants; return postage; cost associated with follow-up of individuals with a positive iFOBT result with colonoscopy (and polypectomy if required), including cost of general practitioner visit after positive iFOBT result, specialist visit for colonoscopy procedure, polypectomy, and the relevant histopathology tests; cost associated with colonoscopy surveillance for individuals who previously had adenomas detected and removed by polypectomy includes cost of specialist visit for colonoscopy procedure, polypectomy and the relevant histopathology tests.

(CER range: AUS$1439–11 463 per life-years saved) and colonoscopy costs (the base case colonoscopy assumption, including specialist visit for colonoscopy procedure, polypectomy and the relevant histopathology tests, was AUS$1800; screening was predicted to become cost-saving when colonoscopy was assumed to cost AUS$1440; CER of screening was AUS$6380 per life-years saved when colonoscopy was assumed to cost AUS$2500). The CER was found to be moderately sensitive to alternative assumptions about colonoscopy lesion detection rates, colonoscopy-related deaths, relative survival for screen-detected versus symptomatically detected cancer, and iFOBT test kit costs, but not to the other parameters examined in the sensitivity analysis. The detailed findings of the sensitivity analysis are provided in the appendix (pp 59–60).

Discussion

Our results indicate that the NBCSP is highly cost-effective. In the multiple cohort analysis, even at the current relatively low levels of participation, the NBCSP is

	2015–19		2020–40		2015–54	
	Model estimates	Compared with no screening	Model estimates	Compared with no screening	Model estimates	Compared with no screening
Total number of incident colorectal cancer cases*						
No screening	86 400	..	516 400	..	1 067 000	..
Scenario 1	91 200	4800 additional cases detected	419 400	97 000 cases prevented	856 900	210 100 cases prevented
Scenario 2	93 900	7500 additional cases detected	392 400	124 000 cases prevented	783 200	283 800 cases prevented
Scenario 3	94 400	7900 additional cases detected	379 000	137 400 cases prevented	747 300	319 700 cases prevented
Total number of colorectal cancer deaths*						
No screening	31 600	..	191 800	..	397 800	..
Scenario 1	29 700	1900 deaths prevented	134 700	57 100 deaths prevented	272 400	125 300 deaths prevented
Scenario 2	29 700	1900 deaths prevented	117 900	73 900 deaths prevented	228 900	168 800 deaths prevented
Scenario 3	29 600	2000 deaths prevented	110 000	81 800 deaths prevented	209 200	188 500 deaths prevented
Total screening, diagnosis, treatment, and surveillance related costs						
No screening	$5·7 billion	..	$34·4 billion	..	$71·1 billion	..
Scenario 1	$6·7 billion	$1·0 billion additional cost	$33·3 billion	$1·1 billion less	$67·6 billion	$3·5 billion less
Scenario 2	$7·1 billion	$1·3 billion additional cost	$33·5 billion	$884 million less	$66·9 billion	$4·2 billion less
Scenario 3	$7·1 billion	$1·4 billion additional cost	$33·8 billion	$589 million less	$66·8 billion	$4·4 billion less
Total number of iFOBT tests returned						
Scenario 1	4·7 million	NA	33·5 million	NA	66·5 million	NA
Scenario 2	6·0 million	NA	49·8 million	NA	99·5 million	NA
Scenario 3	6·3 million	NA	59·7 million	NA	118·1 million	NA
Total number of individuals undergoing colonoscopy*						
Scenario 1	358 300	NA	2·7 million	NA	5·4 million	NA
Scenario 2	446 700	NA	3·9 million	NA	7·8 million	NA
Scenario 3	462 200	NA	4·5 million	NA	9·0 million	NA
Total number of colonoscopy-related non-fatal adverse events						
Scenario 1	967	NA	7335	NA	14 524	NA
Scenario 2	1206	NA	10 485	NA	20 945	NA
Scenario 3	1248	NA	12 201	NA	24 169	NA

Currency is AUS$. iFOBT=immunochemical faecal occult blood testing. NA=not applicable. *Numbers are rounded to the nearest hundred.

Table 2: **Estimated total health outcomes, overall costs, resource use, and adverse events over the periods 2015–19, 2020–40, and 2015–54**

expected to prevent at least 92 200 colorectal cancer cases and 59 000 deaths over the next 25 years. If participation rates of 60% or more were achieved for the target population, which is consistent with what has been achieved in the organised cervical and breast cancer screening programmes in Australia, the number of cases prevented and lives saved from this highly cost-effective programme would increase even further. In the budget impact analysis, the annual expenditure on colorectal cancer control is predicted to become less than in the absence of screening within a decade of full roll-out; this will occur when the very substantial savings in cancer treatment costs start to be realised.

The strength of this analysis is that it uses a comprehensive and extensively calibrated model of colorectal cancer natural history that incorporates two biological pathways of colorectal cancer—the conventional adenoma-carcinoma pathway and the serrated pathway. We comprehensively assessed the effect of uncertainty and the main findings were found to be robust under a range of assumptions. Furthermore, the model takes into account the phased implementation of NBCSP in the period 2006–20, detailed colonoscopy follow-up and surveillance management pathways, and the observed screening behaviour in Australia, and incorporates colorectal cancer treatment costs that are consistent with the latest estimates,[2,7] which have rapidly increased in the past two decades.

A limitation, by necessity, was that a number of influential parameters related to future screening practice were based on assumptions. However, we explored a range of potential future participation scenarios and the assumptions were conservative with respect to follow-up colonoscopy compliance rates. The modelled compliance rate to colonoscopy follow-up after positive iFOBT (about 71%) was derived from the current rate reported in Australia. This number is likely to be an underestimate of the actual compliance rate due to under-reporting of attendance in the context of non-mandatory reporting of colonoscopy to the NBCSP register.[12] As for previous modelled analyses in other settings, the screening participation was assumed to be

independent of an individual's underlying risk of cancer development in the model.[25] Although we incorporated the latest available data for treatment costs, this might further increase in future due to new innovations in the use of therapeutic agents or investigation methods.[2] Furthermore, we did not consider the longer term cost savings due to a potential decrease in iFOBT kit and postage costs. We also did not consider the programme administrative costs (other than the costs of sending test kits) in the analysis. The estimated CER associated with screening would be likely to increase with addition of programme administrative costs, although these costs are likely to scale linearly with participation rates. However, although we note these limitations about future assumptions, the modelled outcomes show a good correspondence with programme outcomes to date (a detailed discussion of the comparison between modelled data and the observed outcomes of the NBCSP in terms of the iFOBT test positivity rate, estimated programme sensitivity and colonoscopy outcomes can be found in the appendix [pp 43–44]). As further data become available about future screening behaviour and health services and cancer treatment costs, such data can be incorporated into updated analyses.

Our finding that biennial iFOBT screening is highly cost-effective when compared with no screening is consistent with other international cost-effectiveness evaluations,[30,31] some of which have even found iFOBT screening to be cost-saving[32–34] (see appendix [pp 62–63] for a detailed comparison with the findings of other key modelled evaluations internationally). To the best of our knowledge, our analysis, however, is the first in Australia to take into account all costs and benefits of the NBCSP, although a number of previous Australian evaluations have been done.[6,7,35–37] These generally found that biennial FOBT screening was cost-effective, but estimated much higher values for the cost-effectiveness ratio, from AUS$25 000–54 000 per life-years saved[6,7] compared with our estimate of AUS$3014 (95% UI 1807–5583) per life-years saved (given current participation). The differences are probably due to a range of factors, but most prominently among these is our incorporation of the greatly increased bowel cancer treatment costs, particularly for advanced cancer (consistent with the recent estimates[2]). Compared with previous research,[8] our findings predict more lives will be saved by the NBCSP; a previous study estimated that 70 038 deaths would be prevented between 2015 and 2055 when assuming 40% screening participation. Modelling over the same period and with similar participation assumptions, we estimate that 125 300 deaths will be prevented. We extensively calibrated and validated our model against the NBCSP outcomes to 2014. Differences in the results between studies are probably due to a range of factors, including different underlying natural history assumptions in the microsimulation models used, and we also accounted for improved stage-specific cancer survival for screen-detected versus symptomatically detected cancers, which is consistent with international findings.[20–22]

The Policy1-Bowel platform is now able to be harnessed to consider a range of important policy questions for the NBCSP in Australia, including the use of alternative iFOBT test thresholds, technologies, and alternate screening age ranges, and in the future can be used to assess the possible role of a risk-based approach to screening, wherein individuals are screened according to their a-priori risk of developing colorectal cancer in their lifetime (see appendix pp 64–65 for further discussion). However, in terms of the current programme, we show that a relatively modest increase in participation in the programme will have an enormous effect on the cumulative burden of disease over the next 25 years; with 83 800 deaths preventable in that period. These findings underpin the need to continue efforts to increase participation in the programme and show that the NBCSP is one of the most cost-effective and life-saving public health programmes in Australia.

Contributions

J-BL led the development of the Policy1-Bowel model, natural history calibration, and was responsible for the collation and integration of cost and epidemiological data into the model, performed model analysis, and drafted the manuscript. X-MX, MC, MJEG, VMHC, and KC participated in model development and natural history calibration. DJBSJ, DRC, MS, and PG assisted in sourcing of data and assumptions. DJBSJ, DRC, and EH participated in the sourcing of cost and epidemiological data. KC oversaw the project, participating in model development, sourcing of epidemiological data, and all aspects of the analysis, and drafted the manuscript. All authors reviewed the study's findings, and read and approved the final manuscript.

Declaration of interests

We declare no competing interests. KC and MS are co-PIs of an unrelated trial of cervical screening, which is funded by the Victorian Cytology Service (VCS). The trial has received equipment and a funding contribution from Roche Molecular Systems, which also manufactures assays for genetic testing for access to targeted therapies in colorectal cancer. DJBSJ is a member of the Clinical Advisory Group for the NBCSP and therefore receives a sitting fee when it meets.

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