Evaluation of the benefits, harms and cost-effectiveness of potential alternatives to iFOBT testing for colorectal cancer screening in Australia

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Novelty and Impact

This is the first comprehensive evaluation of the comparative health benefits, harms, and cost-effectiveness of this range of screening modalities in relation to iFOBT screening within a national organised bowel cancer screening program. The existing Australian program was found to be cost-effective and associated with a favourable benefits-to-harm balance when compared with the other strategies. The study findings support the currently ongoing rollout of iFOBT-based screening in Australia, which will be completed by 2020.

ABSTRACT

The Australian National Bowel Cancer Screening Program (NBCSP) will fully roll-out 2-yearly screening using immunochemical Faecal Occult Blood Test (iFOBT) in people aged 50-74 years by 2020. In this study, we aimed to estimate the comparative health benefits, harms, and cost-effectiveness of screening with iFOBT, versus other potential alternative or adjunctive technologies. A comprehensive validated microsimulation model, *Policy1-Bowel*, was used to simulate a total of 13 screening approaches involving use of iFOBT, colonoscopy, sigmoidoscopy, computed tomographic colonography (CTC), faecal DNA (fDNA) and plasma DNA (pDNA), in people aged 50-74 years. All strategies were evaluated in three scenarios: (i) perfect adherence, (ii) high (but imperfect) adherence, and (iii) low adherence. When assuming perfect adherence, the most effective strategies involved using iFOBT (annually, or biennially with/without adjunct sigmoidoscopy either at 50 or at 54, 64 and 74 years for individuals with negative iFOBT), or colonoscopy (10-yearly, or once-off at 50 years combined with biennial iFOBT). Colorectal cancer incidence (mortality) reductions for these strategies were 51-67(74-80)% in comparison to no screening; 2-yearly iFOBT screening (i.e. the NBCSP) would be associated with reductions of 51(74)%. Only 2-yearly iFOBT screening was found to be cost-effective in all scenarios in context of an indicative willingness-to-pay threshold of A$50,000/life-year saved (LYS); this strategy was associated with an incremental cost-effectiveness ratio of A$2,984/LYS- A$5,981/LYS (depending on adherence). The fully rolled-out NBCSP is highly cost-effective, and is also one of the most effective approaches for bowel cancer screening in Australia.

INTRODUCTION

Trials and observational studies have shown that colorectal cancer mortality can be reduced by screening with guaiac Faecal Occult Blood Testing (gFOBT) (by 13-33%),(1-3) flexible sigmoidoscopy (FS) (by 21-31%) (4-8) and colonoscopy (by 68-88%).(5;9;10) Potential alternative screening technologies, such as computed tomographic colonography (CTC), plasma DNA testing (pDNA) and multitarget faecal DNA testing (fDNA) have also been assessed for the detection of adenomas and cancer in the colorectum.(11-14) Therefore, a number of approaches to population screening could potentially be taken, but their population-level effects in Australia have not been assessed.

In Australia, the National Bowel Cancer Screening Program (NBCSP) will complete full roll-out by 2020, and will offer free 2-yearly immunochemical Faecal Occult Blood Testing (iFOBT) screening for people aged 50-74 years. (15) We have previously reported that with current levels of participation (~37% of individuals invited to participate in the NBCSP in 2013-2014),(16) the NBCSP is expected to prevent 92,200 cancer cases and 59,000 deaths over the 25-year period from 2015 to 2040, with an additional 24,300 and 37,300 cases and 16,800 and 24,800 deaths prevented if participation was increased to 50% and 60%, respectively. (17) We also found that the program is highly cost-effective due to the cancer treatment costs averted [cost-effectiveness ratio compared to no screening, ~A$2,000/ life-year saved (LYS)-A$3,000/LYS]. However, in previous work we did not compare the fully rolled-out NBCSP to other potential alternative screening approaches. A recent evaluation conducted by the US Preventive Services Task Force (USPSTF) compares eight different colorectal cancer screening approaches involving high-sensitivity gFOBT (HSgFOBT), iFOBT, fDNA, CTC, colonoscopy, sigmoidoscopy, or sigmoidoscopy combined with either HSgFOBT or iFOBT.(18) Under the assumption of 100% screening adherence, and using estimated life-years and the number of colonoscopies of each screening strategy, the USPSTF study found that screening with 10-yearly colonoscopy, 10-yearly sigmoidoscopy combined with annual iFOBT, 5-yearly CTC, and annual iFOBT

at ages 50-75 years would provide the best balance of benefits to harms in the US context. However, the study did not report on the impact of more realistic compliance assumptions (which could be expected to differ by screening modality and frequency) on either benefits or harms. Furthermore, cost-effectiveness was not considered because this is not part of the domain of issues considered by the USPSTF. The USPSTF provides information about the extent to what recommendation are supported by evidence, but with the understanding that policy-makers and clinician will need to consider other factors, including cost-effectiveness. (19)

The comparative benefits, harms and cost-effectiveness of the NBSCP compared to other potential alternative or adjunctive options for screening in Australia have not yet been evaluated. The aim of this study was therefore to evaluate the health benefits, harms, and cost-effectiveness of colorectal cancer screening with iFOBT, versus screening approaches using colonoscopy, sigmoidoscopy, CTC, fDNA and pDNA. This evaluation was performed to support the 2017 review of the *Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*, which was auspiced by Cancer Council Australia.

METHODS

Policy1-Bowel Model platform

A comprehensive microsimulation model, *Policy1-Bowel*, was used for the evaluation. The model simulates both the adenoma-carcinoma pathway and the serrated pathway in colorectal cancer development, assuming 15% of colorectal cancers are attributable to the serrated pathway. It was adapted from an existing colorectal cancer natural history model, the Adenoma and Serrated pathway to Colorectal CAncer (ASCCA) model (20) and was extensively re-calibrated jointly to the

original natural history data (21) and the Australian setting. (17) Detailed calibration and validation results for the Australian implementation have been described elsewhere.(17)

Briefly, the *Policy1-Bowel* model is constructed using Microsoft Visual Studio 2013 C++. The simulation begins from age 20 and continues on an annual time-step until the virtual individual dies or becomes 90 years old, whichever occurs first. The age- and sex- specific probability of dying from causes other than colorectal cancer was derived by subtracting the colorectal cancer mortality rate (22) from the all-cause mortality rate (23) in Australia in 2011. Although the model has undergone extensive calibration and validation, most of the observed data on adenoma used for calibration were available only up to age 74 years.(17) Routinely reported data in Australia groups all people aged 85 or older.(24) Furthermore, the age expectancy at the age of 90 years is less than 5 years for Australian men and women,(25) implying a high competing risk of death from causes other than bowel cancer. Therefore, in the base case analysis we terminated the simulation at the age of 90 years. In the analysis of screening, the oldest age of screening for the modelled screening strategies was 75 years; therefore, stopping the simulation at 90 years allows a further 15 years in which to capture the majorities of the remaining lifetime effects (health and costs) associated with screening. In the current analysis, lifetime outcomes for a single age cohort consisting of 10 million males and 10 million females were simulated for each strategy evaluated.

In addition to the probability of dying from other non-colorectal-cancer-related causes, colorectal cancer patients in the model were assumed to have a probability of dying from cancer for a period limited to five years from diagnosis. The modelled cancer survival probabilities vary by cancer stage, time since cancer diagnosis and whether the cancer was diagnosed due to symptomatic detection or via screening. The modelled five-year survival of symptomatically detected colorectal cancer patients was calibrated to data from Western Australia as previously described. (17;26) Screen-detected colorectal cancer patients were assumed to have improved survival compared with patients whose

cancer was symptomatically diagnosed at the same stage, consistent with data from international studies. (27-29) Colorectal patients who survived for five years after detection and treatment of cancer were considered cancer survivors in the model. These survivors are assumed to have no additional risk of dying from the colorectal cancer compared with the average population with no colorectal cancer. See Appendix for more information on the modelled cancer survival assumptions.

Screening and follow-up management strategies, test characteristics and cost assumptions

A total of 13 strategies using various test technologies for bowel screening, including iFOBT, colonoscopy, sigmoidoscopy, CTC, pDNA and fDNA, alone and in combination, and at different screening intervals were evaluated (Table 1). The screening strategies of interest were determined in a series of consultations with the population screening sub-committee of the Working Party for the review of the *Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer*. Test characteristics and costs were informed by a review of the literature and Australian reimbursement data. Analyses for fDNA, pDNA and CTC were considered exploratory since modelling was based on cross-sectional observational data on test characteristics, given no longitudinal data on longer term outcomes were available. A health services perspective was taken in this study. Overheads costs related to administration (other than the costs of sending test kits and invitation letter) and promotion of the screening program and individual's out-of-pocket cost were not included. For the home-based testing used in the current program, we accounted for iFOBT kit mailing (and return) costs, but not costs associated with sending invitation letters, or any other overhead costs of running the screening program. For the alternate strategies, we assumed that home-based sample collection would not be done, and therefore invitation letters asking participants to visit their general practitioner as a first step in the process would be required. As a result, the costs for modelled screening strategies using technology other than iFOBT all included the costs of sending an initial invitation letter. The assumed costs, test characteristics and data sources

for each of the screening approaches are summarised in Table 2. A detailed description of the modelled test characteristics are provided in the Appendix.

Table 1. Screening strategies evaluated

Strategy name	Screening strategy
No screening (comparator)	No screening
iFOBT2y	2-yearly iFOBT screening at 50-74 years (the fully rolled-out NBCSP from 2020 onwards)
iFOBT1y	Annual iFOBT screening at 50-74 years
plasmaDNA2y	2-yearly pDNA screening at 50-74 years [a]
fDNA5y	5-yearly fDNA screening at 50-74 years [b]
COL10y	10-yearly COL screening at 55,65 and 75 years
SIG10y	10-yearly SIG screening at 55,65 and 75 years
CTC10y	10-yearly CTC screening at 55,65 and 75 years
SIG@60	Once-off SIG screening at 60 years
SIG@55_iFOBT2y @60To74	Once-off SIG screening at 55 years combined with 2-yearly iFOBT at 60-74 years
COL@50_iFOBT2y @52To74	Once-off COL screening at 50 years combined with 2-yearly iFOBT at 52-74 years [c]
iFOBT2y+ SIG@50	2-yearly iFOBT screening at 50-74 years (the fully rolled-out NBCSP from 2020) combined with SIG at age 50 for negative iFOBT
iFOBT2y+SIG @54_64_74	2-yearly iFOBT screening at 50-74 years (the fully rolled-out NBCSP from 2020 combined with SIG at 54, 64 and 74 years for negative iFOBT
iFOBT2y+ plasmaDNA	2-yearly iFOBT screening at 50-74 years (the fully rolled-out NBCSP from 2020) combined with pDNA testing in under-screened individuals [a,d]

COL – colonoscopy; CTC - computed tomographic colonography; iFOBT – immunochemical faecal occult blood test; fDNA – faecal DNA test; pDNA-plasma DNA test; SIG –flexible sigmoidoscopy

[a] The modelled base case test characteristics of pDNA test was derived based on the test positive rate of the plasma DNA test for methylated Septin9 DNA reported in Church et al 2014.(12)

[b] The modelled base case test characteristics of fDNA test was derived based on the test positive rate of multitarget stool testing including FIT testing reported in Imperiale et al. 2014.(30)

[c] Individuals aged 50 years who do not participate in colonoscopy screening will be invited to have an iFOBT.

[d] Under-screened individuals are those who are not under colonoscopy surveillance and have not had an iFOBT test in the past 4 years (including those who are eligible for screening but have never had a screening test). Note – no leakage from main program is assumed after pDNA is offered (a favourable scenario).

Table 2. Selected key model parameters and assumptions

Key model parameter	Baseline		Sensitivity analysis range		
	Modelled value	Reference	Modelled value		Reference
			Lower end	Upper end	

Unit item cost					
iFOBT kit sent	A$10[a]	Assumption	N/A	N/A	Assumption
iFOBT kit received	A$22[b]	Assumption	$18	N/A	Assumption
Invitation letter (for non-iFOBT screening methods)	A$0.50	Assumption	N/A	N/A	Assumption
pDNA test	A$250	Assumption	A$125	N/A	Pilot study (31)
fDNA test[c]	A$877.50	Maximum out-of-pocket cost (USD 649) of Cologuard in US market (32)	A$400	N/A	Assumption
SIG	A$1,200	Assumption	A$1,000	A$1,800	Assumption
CTC	A$520	MBS item 56553 (33)	N/A	$720	Assumption
GP consultation for abnormal screening result or referral letter	A$37.05	MBS item 23 (33)	N/A	N/A	N/A
COL without complication[e]	A$1,800	Assumption	A$1,440	A$2,500	Assumption
COL with complication[e]	A$14,839	DRG-AG item G48A[f](34)	N/A	N/A	N/A
Stage 1 CRC treatment	A $36,914	Pignone et al 2011 (consistent with the findings of Ananda et al 2016) (35;36)	A$29,558	A$40,606	O'Leary et al 2004,(37)[g] assumption
Stage 2 CRC treatment	A$56,589		A$57,511	A$62,248	
Stage 3 CRC treatment	A$88,700		A$44,422	A$97,570	
Stage 4 CRC treatment	A$73,402		A$10,798	A$80,742	
Colonoscopy test detection rate (per lesion)					
Adenoma 1-5 mm	79.0%	Van Rijn et al 2006 (38)	71.0%	86.9%	Assumption
Adenoma 6-9 mm	85.0%		76.5%	93.5%	
Adenoma >10mm	92.0%		82.5%	100.0%	
SSA (any size)	78.0%		71.0%	86.9%	
CRC at any stage	95.0%	Pickhardt et al 2011 (39)	85.5%	100.0%	
Completeness	100% to the end of cecum	Assumption	N/A	N/A	N/A
Rate of non-fatal complication per procedure	0.0027	AIHW 2015(15)	0.0015	0.0035	N/A
Rate of fatal complication per procedure	0	AIHW 2015(15)	N/A	0.0001	Jentschura et al 1994(40)
iFOBT test characteristics (per person)[i]					
Specificity[h]	94.8%	Obtained via calibrating the	95.6%	94.1%	Assumption
Sensitivity for	15.2%		13.1%	17.4%	

adenoma of any size		modelled iFOBT positivity rate and COL outcome among positive iFOBT to data observed in the NBCSP (17)			
Sensitivity for adenoma > 5mm	30.2%		26.0%	34.3%	
Sensitivity for adenoma >10mm	41.5%		41.5%	47.1%	
Sensitivity for CRC	58.6%		50.7%	66.2%	
pDNA test characteristics (per person) [i]					
Specificity [h]	90.9%	Obtained via calibrating the modelled test positive rate to the findings of Church et al 2013 (12).	N/A	90.5%	Obtained via calibrating the modelled test positive rate to the findings of Jin et al 2015 (41)
Sensitivity for adenoma of any size	10.2%		N/A	24.0%	
Sensitivity for adenoma > 5mm	11.4%		N/A	28.4%	
Sensitivity for adenoma >10mm	12.4%		N/A	30.6%	
Sensitivity for CRC	49.9%		N/A	75.1%	
fDNA test characteristics (per person) [i]					
Specificity [h]	89.7%	Obtained via calibrating the modelled test positive rate the findings of Imperiale et al 2014 (13).	95.9%	N/A	Obtained via calibrating the modelled test positive rate the findings of Ahlquist et al 2008 **(42)**
Sensitivity for adenoma of any size	24.4%		8.3%	N/A	
Sensitivity for adenoma > 5mm	33.5%		13.2%	N/A	
Sensitivity for adenoma >10mm	39.4%		16.6%	N/A	
Sensitivity for CRC	92.4%		28.6%	N/A	
Sigmoidoscopy detection rate (per person)					
Adenoma 1-5 mm	79.0%	Assumed the same lesion-specific detection rate as per COL	71.0%	86.9%	Assumption
Adenoma 6-9 mm	85.0%		76.5%	93.5%	
Adenoma >10mm	92.0%		82.5%	100.0%	
SSA (any size)	78.0%		71.0%	86.9%	
CRC at any stage	95.0%		85.5%	100.0%	
Completeness	100% reach the recto-sigmoid junction, 80% reach the end of sigmoid, 0% beyond sigmoid	Assumption	N/A	N/A	N/A
CTC test characteristics (per person)					
Specificity [h]	90.0%	Johnson et al 2008(11)	91.8%	86.4%	Cotton et al 2004,(43) Johnson et al 2008,(11) and Pickhardt et al 2011 (39)
Sensitivity for adenoma of any size	40.1%		20.2%	42.3%	
Sensitivity for adenoma > 5mm	63.8%		39.9%	73.1%	
Sensitivity for	88.1%		54.2%	96.3%	

adenoma >10mm					
Sensitivity for CRC	88.7%		75.0%	96.5%	
Precancer natural history assumption	Baseline assumption	See Appendix Table A2	Least aggressive precancer natural history assumption	Most aggressive precancer natural history assumption	See Appendix Table A2

COL – colonoscopy; CTC - computed tomographic colonography; iFOBT – immunochemical faecal occult blood test; fDNA – faecal DNA test; GP – general practitioner; N/A- not applicable; pDNA-plasma DNA test; Sens – sensitivity; Spec – specificity; SIG – flexible sigmoidoscopy; SSA – sessile serrated adenoma

[a] *Includes estimated cost of one-way postage ($2) and an iFOBT test kit ($8)*

[b] *Includes estimated cost of one-way postage for the return of iFOBT test ($2) and cost of an iFOBT test being analysed in the lab ($20)*

[c] *Assume the fDNA cost US$649 in the base case (exchange rate used: US$1 USD = A$1.3521, 17 June 2016)*

[e] *With/without polypectomy*

[f] *Inflated cost of $12,881 based on CPI in Health in 2011-12 (100.0)(44) and in June 2014(115.2)(45)*[g] *These colorectal cancer treatment costs were assumed by a number of prior analysis that evaluated the cost-effectiveness of bowel cancer screening in Australia. (37;46)*

[h] *For any adenoma*

[i] *The present of sessile serrated adenoma was assumed to have no association with the positive outcome of iFOBT, plasma DNA and fecal DNA test (i.e. having sessile serrated adenoma would not increase the overall probability of the iFOBT, plasma DNA and fecal DNA test positive outcome being positive) in the model. See Appendix for more detailed test characteristics assumptions.*

Individuals who underwent iFOBT, pDNA or fDNA-based screening were assumed to be referred to colonoscopy for further diagnosis if the screening test outcome was positive; individuals who underwent CTC or sigmoidoscopy screening were referred to colonoscopy if any polyps were detected. Adenomas <5mm detected during sigmoidoscopy were assumed to be treated via immediate polypectomy; polyps >= 5mm were assumed not to be removed during sigmoidoscopy but to be treated in the follow-up colonoscopy. Polypectomy was assumed to be performed on all adenomas detected during colonoscopy. After referral colonoscopy, individuals were returned to the modelled routine screening strategy if no adenomatous polyps were detected (i.e. returned to 10-yearly colonoscopy screening for strategy COL10y, retuned to 2-yearly pDNA testing for strategy plasmaDNA2y etc); or further follow-up with surveillance colonoscopy in 1-5 years if any adenomatous polyps were detected (with further management depending on findings during serial colonoscopy follow-up). Detailed managements assumptions for screening, diagnosis and

surveillance assumed are provided in the Appendix. We assumed no screening occurred after the recommended screening stopping age specified by each strategy and that colonoscopy surveillance stopped at age 75 years, based on existing guidelines.(47)

Screening participation (adherence) assumptions

Participation assumptions, which took into account technology-specific issues and health services delivery issues for each option, were determined in a series of consultations with the population screening sub-committee of the Working Party. All strategies were evaluated under three screening adherence assumptions- perfect adherence (Scenario 1), high (but imperfect) adherence (Scenario 2), and low adherence (Scenario 3; current observed rate). Scenario 1 assumed a perfect adherence to screening invitation, follow-up colonoscopy referral after an abnormal screening outcome, and surveillance colonoscopy program referral after any conventional adenoma/sessile serrated adenoma was detected at colonoscopy. For Scenario 2, the screening initiation rate (i.e. screening participation rate among individuals who have never participated in screening) for the first invitation was assumed to be 57% for screening strategies using iFOBT, pDNA and fDNA, and 35% for screening strategies using colonoscopy, sigmoidoscopy and CTC; for Scenario 3 the corresponding participation rates were 29% and 15%. The screening initiation rate for the second invitation was assumed to be half of the strategy-specific rate modelled for first invitation based on the participation rate of Round 2 NBSCP invitation among individuals who did not participate in Round 1 screening.(15) The initiation rate in subsequent rounds were assumed to be half of the rate modelled for the second round invitation. Assuming a lower screening participation rate for strategies using colonoscopy, sigmoidoscopy and CTC as screening tests compared to strategies using iFOBT, pDNA and fDNA testing is consistent with the findings of a systematic review.(48) In both Scenario 2 and 3, the modelled rescreening probabilities (i.e. screening participation rate among individuals who have been screened at least once before) was 75% (current observed rate),(49) the modelled compliance to colonoscopy follow-up after an abnormal screening outcome was 71% (current observed rate),

(49) and the compliance to surveillance recommendations was assumed to be 80% (assumption). More information on the screening participation and follow-up compliance assumptions are provided in the Appendix.

Modelled analysis

We simulated the age-specific colorectal cancer incidence, colorectal cancer mortality, cost, life-years and the number of screening and diagnostic tests that occurred over the lifetime of a single cohort for each strategy. The age-standardised rates for colorectal cancer incidence and colorectal cancer mortality of all ages (i.e. 0-100 years, assuming no colorectal cancer in individual aged <20 years) were calculated assuming the 2001 Australian Standard Population. The health benefits associated with each of the strategies were estimated via the relative reduction in cancer incidence and mortality rates compared with no screening, over the lifetime of the cohort from birth. The total discounted lifetime costs and discounted life-years were calculated by accruing the predicted costs and life-years from age 20 to 89 years and discounting at a rate of 5% from age 40 years.(50) Cost-effectiveness ratios (CERs) were calculated for each strategy by dividing the incremental discounted cost by the incremental discounted life-years achieved compared to no screening. Incremental cost-effectiveness ratios (ICERs) were calculated for each dominating strategy (i.e. the strategy with the lowest cost compared to strategies with similar or lower effectiveness) in the cost-effectiveness analysis by dividing the incremental cost by the incremental life-years from the next most effective dominating strategy identified in the cost-effectiveness analysis, using standard methods. There is no direct source document on cost-effectiveness analysis guideline to inform the choice on the perspective for non-pharmaceutical interventions in Australia. In this study, we have used the same perspective, discount rate and willingness-to-pay (WTP) threshold ($50,000/LYS) as per a predicate Medical Services Advisory Committee (MSAC) evaluation of the National Cervical Screening Program.(51) Resource utilisation was estimated over the lifetime of 100,000 persons alive at 40 years. The number-needed-to-colonoscope (NNC) to prevent one cancer case and cancer death

(compared to no screening) was calculated by dividing the number of colonoscopies (including colonoscopies performed for the purpose of screening, follow-up of a positive screening test outcome and surveillance) by the number of cancer cases/deaths estimated over the lifetime of 100,000 persons alive at 40 years for each strategy. An incremental number-needed-to-colonoscope (INNC) was then calculated for each dominating strategy in the benefit-to-harm analysis by dividing the additional number of colonoscopies (ACs) by the additional number of colorectal cancer deaths prevented (CDP) from the next most beneficial dominating strategy in the benefit-to-harm analysis. All costs are presented in 2015 Australian dollars ($A1 = US$ 0.7706, 20 June 2015). One-way sensitivity analysis was performed for key parameters to characterise the impact of varying these parameters across a feasible range on the ranking of strategies in the cost-effectiveness analysis. Supplementary analysis was performed to assess the impact of the simulation stop age on the predicted health and cost-effectiveness outcomes by repeated the simulations for all screening strategies under three different participation scenarios with the simulation stopping at the age of 100.

RESULTS

Colorectal cancer incidence and mortality reductions

When assuming perfect adherence to screening, follow-up and surveillance recommendations (Scenario 1), and considering the range of results for all 13 strategies, colorectal cancer screening was predicted to reduce the overall age-standardised colorectal cancer incidence (all ages) by 35-67% and to reduce colorectal cancer mortality by 40-80% compared with no screening (Table 3). The corresponding reductions were 9-47% and 10-68%, respectively, when assuming high (but imperfect) adherence to screening, follow-up and surveillance recommendations (Scenario 2), and 4-38% and 4-56%, respectively, when assuming low adherence (Scenario 3). The 2-yearly iFOBT screening (i.e. the

fully rolled-out NBCSP) was predicted to reduce overall colorectal cancer incidence by 51% and mortality by 74% in Scenario 1, 32% and 51% respectively in Scenario 2, and 23% and 36% respectively in Scenario 3, compared with no screening.

Table 3. Model estimated age-standardised rate of colorectal cancer incidence and colorectal cancer mortality per 100,000 persons at all ages

Strategy name	Scenario 1 (perfect adherence)				Scenario 2 ('high' adherence)				Scenario 3 ('low' adherence)			
	CRC incidence		CRC mortality		CRC incidence		CRC mortality		CRC incidence		CRC mortality	
	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]
No screening	62.7	-	23.0	-	62.7	-	23.0	-	62.7	-	23.0	-
iFOBT2y	30.6	51%	6.1	74%	42.5	32%	11.3	51%	48.3	23%	14.7	36%
iFOBT1y	24.0	62%	4.5	80%	33.1	47%	7.4	68%	38.8	38%	10.2	56%
plasmaDNA2y	39.5	37%	7.8	66%	50.6	19%	13.6	41%	54.4	13%	16.5	28%
fDNA5y	35.1	44%	7.6	67%	48.9	22%	14.8	36%	54.4	13%	18.1	21%
COL10y	20.6	67%	5.1	78%	44.5	29%	15.1	34%	54.5	13%	19.4	16%
SIG10y	30.0	52%	9.6	58%	51.4	18%	18.2	21%	57.6	8%	20.9	9%
CTC10y	34.0	46%	8.5	63%	54.0	14%	18.3	21%	58.7	6%	20.8	10%
SIG@60	40.7	35%	13.9	40%	57.2	9%	20.7	10%	60.4	4%	22.0	4%
SIG@55_iFOBT2y@60To74	29.5	53%	7.2	69%	49.7	21%	15.9	31%	55.4	12%	18.9	18%
COL@50_iFOBT2y@52To74	23.7	62%	5.0	78%	39.2	37%	10.4	55%	46.6	26%	14.0	39%
iFOBT2y+ SIG@50	25.9	59%	5.4	77%	41.4	34%	11.0	52%	48.2	23%	14.6	37%
iFOBT2y+SIG@54_64_74	21.9	65%	4.5	80%	38.8	38%	10.3	55%	47.2	25%	14.3	38%
iFOBT2y+plasmaDNA	n/a [c]	n/a [c]	n/a [c]	n/a [c]	42.2	33%	10.9	52%	47.7	24%	14.1	39%

ASR- age-standardised rate; Red- reduction;

[a] *Per 100,000 individuals, assuming 2001 Australian Standard Population all ages*

[b] *Compared with no screening*

[c] *This strategy is not applicable in Scenario 1 because there are no under-screened individuals given the assumption of perfect adherence to screening, follow-up and surveillance recommendations.*

When assuming perfect adherence to screening and follow-up recommendations (Scenario 1), six strategies predicted a reduction in colorectal cancer mortality (compared with no screening) greater than 74% - these were 10-yearly colonoscopy screening (78%), once-off colonoscopy at 50 years combined with 2-yearly iFOBT screening (78%), annual iFOBT screening (80%), 2-yearly iFOBT screening (74%), and 2-yearly iFOBT screening with adjunctive sigmoidoscopy either at 50 years or 54 ,64, and 74 years for individuals with negative iFOBT results (77-80%)(Table 3). After accounting for more realistic compliance to screening, follow-up and surveillance recommendations (Scenarios 2 and 3), the six most effective strategies predicted a >51% reduction in colorectal cancer mortality in Scenario 2 and >36% in Scenario 3: these were once-off colonoscopy screening at 50 years combined with 2-yearly iFOBT screening (Scenario 2: 55%; Scenario 3: 39%), annual iFOBT (Scenario 2: 68%; Scenario 3: 56%), 2-yearly iFOBT (Scenario 2: 51%; Scenario 3: 36%), 2-yearly iFOBT screening with adjunct sigmoidoscopy either at 50 years or 54 ,64, and 74 years screening for individuals with negative iFOBT (Scenario 2: 52-55%; Scenario 3: 37-38%), and 2-yearly iFOBT combined with pDNA testing for under-screened individuals, assuming that the offer of pDNA does not induce any 'leakage' (participation drop) in iFOBT screening (Scenario 2: 52%; Scenario 3: 39%)(Table 3). Screening with 10-yearly colonoscopy was predicted to be one of most effective strategies when assuming perfect adherence (Scenario 1) but not when more realistic compliance was assumed (Scenario 2 and 3) (Table 3). Screening with once-off sigmoidoscopy at 60 years was predicted to be the least effective strategy with the lowest reductions in colorectal cancer incidence (Scenario1: 35%, Scenario 2: 9%; Scenario 3: 4%) and mortality (Scenario1: 40%, Scenario 2: 10%; Scenario 3: 4%) compared to other strategies included in this evaluation.

Cost-effectiveness

The estimated life-years, lifetime cost and the cost-effectiveness ratio compared to no screening for each strategy are provided in the Appendix (Table A24-A26). When compared with no screening, all

strategies were estimated to be associated with a CER close to or lower than the indicative WTP threshold in Australia of A$50,000/LYS in all three scenarios.

Figure 1 shows the cost-effectiveness planes for Scenarios 1-3. The strategies identified on the cost-effectiveness frontier and the associated ICERs are marked. Given the indicative WTP threshold, only 2-yearly iFOBT (i.e. the fully rolled-out NBCSP) (ICER: A$2,984/LYS-A$5,981/LYS) would be cost-effective in all adherence scenarios. The strategy assuming annual screening with iFOBT was also found to be cost-effective in Scenarios 2 and 3 (ICER compared to 2-yearly iFOBT: A$14,162/LYS-A$18,798/LYS) but not in Scenario 1 (Figure 1). Overall, considering results for all adherence scenarios, the planned program (2-yearly iFOBT screening at 50-74 years) was the most effective strategy for which cost-effectiveness was consistently under the WTP threshold.

Resource utilisation

Table 4 shows the estimated number of iFOBTs, pDNA tests, fDNA tests, colonoscopies, sigmoidoscopies and CTCs in the lifetime of 100,000 persons alive at 40 years for each strategy. Strategies that assumed a more frequent screening interval were associated with a higher number of screening tests. In all adherence scenarios, the strategies which were predicted to lead to the highest number of colonoscopy procedures were screening with 10-yearly colonoscopy (35-172% increase in number of colonoscopy compared to 2-yearly iFOBT i.e. the fully rolled-out NBCSP), once-off colonoscopy at 50 years combined with 2-yearly iFOBT (38-86%) and annual iFOBT (48-93%). Once-lifetime or 10-yearly screening with sigmoidoscopy and 10-yearly CTC screening were estimated to lead to the lowest number of colonoscopies.

Table 4. Estimated lifetime resource utilisation of per 100,000 persons alive at 40 years

Strategy name	iFOBT [a,b]	pDNA [a]	fDNA [a,b]	COL [a]	SIG [a]	CTC [a]
Scenario 1 (perfect adherence)						
iFOBT2y	1,036,800	-	-	110,500	-	-
iFOBT1y	1,829,500	-	-	163,600	-	-

plasmaDNA2y	-	1,017,200	-	131,300	-	-
fDNA5y	-	-	437,600	92,800	-	-
COL10y	-	-	-	300,100	-	-
SIG10y	-	-	-	111,700	247,000	-
CTC10y	-	-	-	78,300	-	251,400
SIG@60	-	-	-	57,000	94,000	-
SIG@55_iFOBT2y@60To74	574,200	-	-	106,100	96,500	-
COL@50_iFOBT2y@52To74	810,400	-	-	205,800	-	-
iFOBT2y+ SIG@50	1,005,500	-	-	131,900	92,100	-
iFOBT2y+SIG@54_64_74	979,100	-	-	174,300	212,100	-
iFOBT2y+plasmaDNA	n/a [c]	n/a [c]	n/a [c]	n/a [c]	n/a [c]	n/a [c]
Scenario 2 ('high' adherence)						
iFOBT2y	725,500	-	-	57,500	-	-
iFOBT1y	1,423,800	-	-	97,200	-	-
plasmaDNA2y	-	722,300	-	63,400	-	-
fDNA5y	-	-	267,000	39,300	-	-
COL10y	-	-	-	117,000	-	-
SIG10y	-	-	-	31,100	100,000	-
CTC10y	-	-	-	21,200	-	100,600
SIG@60	-	-	-	12,200	32,900	-
SIG@55_iFOBT2y@60To74	252,600	-	-	32,800	33,800	-
COL@50_iFOBT2y@52To74	610,100	-	-	89,900	-	-
iFOBT2y+ SIG@50	723,300	-	-	60,500	18,400	-
iFOBT2y+SIG@54_64_74	717,700	-	-	73,500	66,000	-
iFOBT2y+plasmaDNA	723,700	30,000	-	59,800	-	-
Scenario 3 ('low' adherence)						
iFOBT2y	489,000	-	-	39,700	-	-
iFOBT1y	1,087,600	-	-	76,600	-	-
plasmaDNA2y	-	487,400	-	42,900	-	-
fDNA5y	-	-	156,100	23,400	-	-
COL10y	-	-	-	53,400	-	-
SIG10y	-	-	-	14,300	45,800	-
CTC10y	-	-	-	9,800	-	46,100
SIG@60	-	-	-	5,200	14,100	-
SIG@55_iFOBT2y@60To74	148,400	-	-	18,200	14,500	-
COL@50_iFOBT2y@52To74	452,100	-	-	54,800	-	-
iFOBT2y+ SIG@50	488,300	-	-	40,400	3,900	-
iFOBT2y+SIG@54_64_74	486,600	-	-	45,000	21,100	-
iFOBT2y+plasmaDNA	487,500	43,500	-	43,400	-	-

COL- colonoscopy; CTC – computed tomographic colonography; fDNA – faecal DNA test; iFOBT – Immunochemical faecal occult blood test; pDNA – plasma DNA test; SIG-flexible sigmoidoscopy

[a] Number rounded to the nearest 100

[b] Test performed not number of test kits sent

[c] This strategy is not applicable in Scenario 1 because there are no under-screened individuals given the assumption of perfect adherence to screening, follow-up and surveillance recommendations.

Benefit-to-harm ratio

Figure 2 shows the estimated NNC to prevent one colorectal cancer death for each strategy in comparison to no screening. The 'benefit-harms frontier' (i.e. strategies with the optimal balance between benefit and harm compared to strategies with similar effectiveness) and the INNC of the 'dominating' strategies are marked (Figure 2). Once-off sigmoidoscopy screening, 10-yearly CTC screening (INNC: 27-29 ACs/CDP), 2-yearly iFOBT screening (INNC: 39-117 ACs/CDP) and annual iFOBT screening (INNC: 61-263 ACs/CDP) were identified on the 'benefit-harms frontier' in all scenarios. Once-off sigmoidoscopy screening at 55 years combined with 2-yearly iFOBT screening at 60-74 years (INNC: 31-35 ACs/CDP) was also identified on the frontier in scenarios assuming realistic screening behaviour (Scenario 2 and 3). The planned program (2-yearly iFOBT screening) was found to be associated with a favourable benefits-to-harm balance, compared to the other strategies considered in this evaluation. Detailed model estimates of NNC to prevent one colorectal cancer case or one colorectal cancer death compared to 2-yearly iFOBT are provided in the Appendix (Table A27-A29).

Sensitivity analysis

Detailed outcomes for sensitivity analysis are provided in the Appendix Tables A30-A55. In the sensitivity analysis, which was conducted in the context of assuming 100% adherence, no impact was seen on the main cost-effectiveness findings when key parameters were varied across the feasible ranges specified (Table 2). As for the base case analysis, in all sensitivity analyses, strategies identified on the cost-effectiveness frontier were (in the order of increasing effectiveness) 2-yearly iFOBT screening (the fully rolled-out NBCSP), annual iFOBT screening, and once-off colonoscopy screening at 50 years combined with 2-yearly iFOBT screening. 2-yearly iFOBT screening were the only strategy found to be cost-effective in all one-way sensitivity analyses in context of an indicative WTP threshold of A$50,000/LYS in Australia. It was associated with ICER of: A$1,106/LYS-

A$7,546/LYS across all sensitivity analyses findings. No other strategies identified on the frontier were found to be cost-effective in the sensitivity analyses for any model runs.

Supplementary analysis

Detailed outcomes for supplementary analyses are provided in the Appendix (Table A56-A59 and Figure A19). The estimated colorectal cancer incidence and colorectal cancer mortality age-standardised rates in the supplementary analysis were predicted to be only slightly higher (<1 per 100,000 persons) in all screening strategies and participation scenarios when compared to the base case findings. The relative reduction in colorectal cancer incidence and mortality rates (versus no screening) and relative rankings of the strategies in terms of cost-effectiveness were very similar to the base case findings.

DISCUSSION

This is the first study that has performed a comprehensive evaluation of the health benefits, harms, and cost-effectiveness of the NBCSP Australia- 2-yearly iFOBT screening in people aged 50-74 years - in relation to other potential colorectal cancer screening strategies using alternative screening modalities, including pDNA, fDNA, sigmoidoscopy, CTC and colonoscopy. We found that a number of strategies could provide substantial reductions in both colorectal cancer incidence and mortality in a cohort of perfectly adherent people (>74% mortality reductions). Of the strategies considered, only biennial iFOBT screening (ICER: A$2,984/LYS-A$5,981/LYS) was consistently cost-effective at different levels of participation, given the indicative WTP threshold in Australia of A$50,000/LYS. A number of strategies were found to be associated with a favourable benefit-harm ratio; once-off sigmoidoscopy, 10-yearly CTC screening, and 2-yearly iFOBT screening were consistently found to have a favourable benefit-to-harm balance in all participation scenarios. We also found that the

existing NBCSP was one of the most effective, and also a cost-effective, option for bowel cancer screening in Australia. The NBCSP is associated with the one of the most favourable balance of benefits to-harms of all options considered, with 35-49 people needing to undergo colonoscopy for each cancer death prevented compared to no screening.

A strength of our study is that we used a comprehensive and calibrated model of colorectal cancer natural history that incorporated two biological pathways of colorectal cancer development – the adenoma-carcinoma pathway and the serrated pathway. Using this unique platform, we were able to perform a comprehensive evaluation of the health benefits, harms, and cost-effectiveness of various potentially feasible alternatives to the fully rolled-out NBCSP, and we were able to take into account varying levels of adherence. We incorporated colorectal cancer treatment costs that are consistent with the recent estimates in Australia, which has been rapidly increasing in the past 10 years.(36) A limitation of the study was that influential parameters including screening test costs, screening participation and screening test performance were based on assumptions, by necessity. The item costs assumed for potential alternative screening tests were based on the current item cost in Australia (e.g. for colonoscopy) or in other countries (e.g. for novel tests such as fDNA). These costs, however, have the potential to decrease if the test were to be used as a primary screening test within the NBCSP, and thus the cost-effectiveness of some of the strategies considered may improve in the future. There were great uncertainties associated with the screening participation rates that could potentially be achieved by using different screening modalities in Australia; however the impact of these uncertainties was assessed by evaluating the strategies in scenarios assuming different screening adherence. The modelled compliance rate to colonoscopy follow-up after positive iFOBT (~71%) was based on the current rate reported in Australia. It is likely to be an underestimate of the actual compliance rate due to underreporting of attendance in the context of non-mandatory reporting of colonoscopy to the NBCSP register.(52) Our assumptions for test characteristics for the different screening modalities were underpinned by different levels of

evidence, and in particular our findings for fDNA, pDNA and CTC should be considered exploratory since the test assumptions were based on data from cross-sectional studies only. Finally, the quality-adjusted-life-years (QALY) was not being considered in the cost-effectiveness analysis, the health-related quality of life between cancer survivors whose cancer was detected at an earlier stage due to screening were not represented in the effectiveness findings.

The recent evaluation conducted by the USPSTF compared the burden (i.e. number of colonoscopy) and effectiveness (i.e. life-years gained) of a large number of screening strategies involving HSgFOBT, iFOBT, fDNA, sigmoidoscopy with/without interval HSgFOBT or iFOBT, CTC and colonoscopy in the context of 100% screening adherence for all strategies.(18) Based on the findings, the USPSTF recommended 10-yearly colonoscopy screening, 10-yearly sigmoidoscopy screening combined with annual iFOBT, 5-yearly CTC screening or annual iFOBT screening for people 50-75 year based on the best balance of benefits to harms in the US context. (18) For strategies considered in both evaluations, our predictions of reduction in colorectal cancer incidence rate and mortality, and additional number of colonoscopies per life-years saved were broadly consistent with the findings of the USPSTF evaluation. However, we were able to extend the USPSTF work by relating findings to the operation of a centrally organised population screening program and examining the health outcomes and burden at realistic levels of screening participation. We also extended the work by considering cost-effectiveness. Because we considered this broader range of factors -benefits, harms and cost-effectiveness - in our evaluation, our final conclusions about the optimal screening strategies for colorectal cancer differ somewhat to the US evaluation.(18)

Once-off screening with sigmoidoscopy at 60 years was predicted to reduce the age-standardised colorectal cancer incidence and mortality rates over the lifetime of the (the theoretical situation of) perfectly adherent cohorts by 35% and 40% respectively. These reductions were estimated to be 48% and 52% respectively at 17 years after once-off sigmoidoscopy screening at 60 years , which are

broadly consistent with the long -term outcomes of the UK Flexible Sigmoidoscopy Screening Trial, which found a reduction of 35% (HR: 0·65 [95% CI 0·59-0·71]) in colorectal cancer incidence and a reduction of 41% (HR: 0·59 [0·49-0·70]) in colorectal cancer mortality in individuals who had an once-off screening with sigmoidoscopy at the age between 55 and 64 years, after 17 years of follow-up. (7)

We assumed that the cost of CTC would be similar to the current MBS item cost in Australia in the baseline analysis; however this cost estimate is unlikely to take into account the costs associated with developing the necessary infrastructure that would be required for CTC to be used more widely in screening. We have examined the impact of higher CTC cost (A$720) in the sensitivity analysis; 10-yearly CTC was not found to be cost-effective (dominated by 2-year iFOBT screening, i.e. the planned program) in both the base case analysis and the sensitivity analysis. It should also be noted that our evaluation did not take into account the health services challenges that would be required for the NBCSP to use technology other than iFOBT as primary screening test.

It should also be noted that all our findings for pDNA and fDNA screening should be considered exploratory, since the performance of these more novel tests, which underpins this modelled evaluation, has not yet been tested in terms of longitudinal outcomes or in randomised controlled trials. In this exploratory analysis, we found that screening with fDNA at 5-yearly intervals at a test cost of A$400-878 (based on current US costs) was not cost-effective, consistent with previous studies findings. (53;54) Screening with fDNA was also found to be associated with a less favourable benefit-to-harm balance compared to iFOBT screening, consistent with the recent USPSTF evaluation.(18)

Our finding that 2-yearly iFOBT screening would be less costly and more effective than 2-yearly plasma DNA screening is also consistent with previous findings.(55;56) Our results indicate that screening with the plasma DNA test is less effective than iFOBT in preventing colorectal cancer and

death due to the lower test sensitivity in detecting the precursors of colorectal cancer. By contrast, offering plasma DNA testing only for under-screened individuals could result in a modest improvement in colorectal incidence and mortality overall. However, this would need to be introduced with very careful controls to avoid potential 'leakage' in participation from the main iFOBT program; any leakage from the main program to the add-on program is expected to result in a detrimental effect in the overall effectiveness of the screening program. These aspects require further evaluation before the introduction of plasma DNA testing could be considered.

The *Policy1-Bowel* platform will in the future be harnessed to consider a range of important policy questions for the NBCSP in Australia, including the possible age-extension of the program (starting at 40 or 45 years, or ceasing screening at 79 or 84 years), the role of a number of alternative and/or new technologies of screening, and 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.

CONCLUSION

There are considerable uncertainties about the long-term program impact of pDNA and fDNA screening because longitudinal data on long-term mortality benefits are not yet available. We modelled the impact of these screening technologies in Australia based on the currently available data. We found that the fully rolled-out NBCSP is one of the most effective options for bowel cancer screening in Australia, and is also cost-effective. The cost-effectiveness of the program is high even in the context of the current lower participation rates, and the cost-effectiveness would be sustained if participation could be improved. The benefits of the program would scale with increasing participation. The balance of benefits to harms, represented by the number-needed-to-colonoscope for each colorectal cancer death prevented, also appears to be favourable for the current NBCSP. An

updated long-term impact analyses could be performed when more evidence on longitudinal cancer incidence and mortality outcomes become available for fDNA and pDNA.

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AUTHOR CONTRIBUTION

JBL led the *Policy1-Bowel* model development and calibration, participated in the study design, was responsible for the collation and integration of cost and epidemiological data into the model, performed all model analyses and result interpretations, and drafted the manuscript. DJBSJ, FAM, JDE, EH, MAJ, HCE, PG participated in the study design, development of screening and surveillance model, sourcing of cost and epidemiological data, and provide expert clinical advices throughout the project. MC, MJEG and VMHC participated in the development of *Policy1-Bowel* model and provided technical and modelling advices throughout the project. PG participated in the design of the project and sourcing of cost and epidemiological data. DS participated in the study design. KC oversaw the project, participated 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.

ETHICAL APPROVAL

This model-based study did not involve human participants, so ethics approval was not required.

FUNDING

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ROLE OF FUNDING SOURCE

The funder had no role in study design, data collection, or data analysis. The funder was an observer at meetings of advisory committees (i.e. meetings of the Cancer Council Australia Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer working party). JBL, MC and KC had access to raw data. The corresponding author had full access to all data in the study and had final responsibility for the decision to submit for publication.

COMPETING INTERESTS

The authors declare no direct conflict of interest.

DJBSJ, FAM, JDE, and MAJ are members of the Clinical Advisory Group for the National Bowel Cancer Screening Program and received sitting fees when it meets. HCE has been a clinical advisor to the

National Bowel Cancer Screening Program. PG is an employee of Cancer Council Australia, which has received fund from Department of Health Australia to develop the Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal Cancer. JBL, KC and EH are employees of Cancer Council NSW, which has been subcontracted by Cancer Council Australia to perform some work as part of the technical team to develop the Clinical Practice Guidelines for the Prevention, Early Detection and Management of Colorectal a cancer.

KC is 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 manufacturers assays for genetic testing for access to targeted therapies in colorectal cancer.

KC's group at Cancer Council NSW has performed modelling work to analyses the implications for resource use for the transition from cytology-based screening to HPV-based screening at longer intervals. This work was commissioned and funded by the Victorian Cytology Service (VCS Ltd.) to inform a response to the Australian Government Request for Tender for the National Cancer Screening Register (RFT Health/124/1415).

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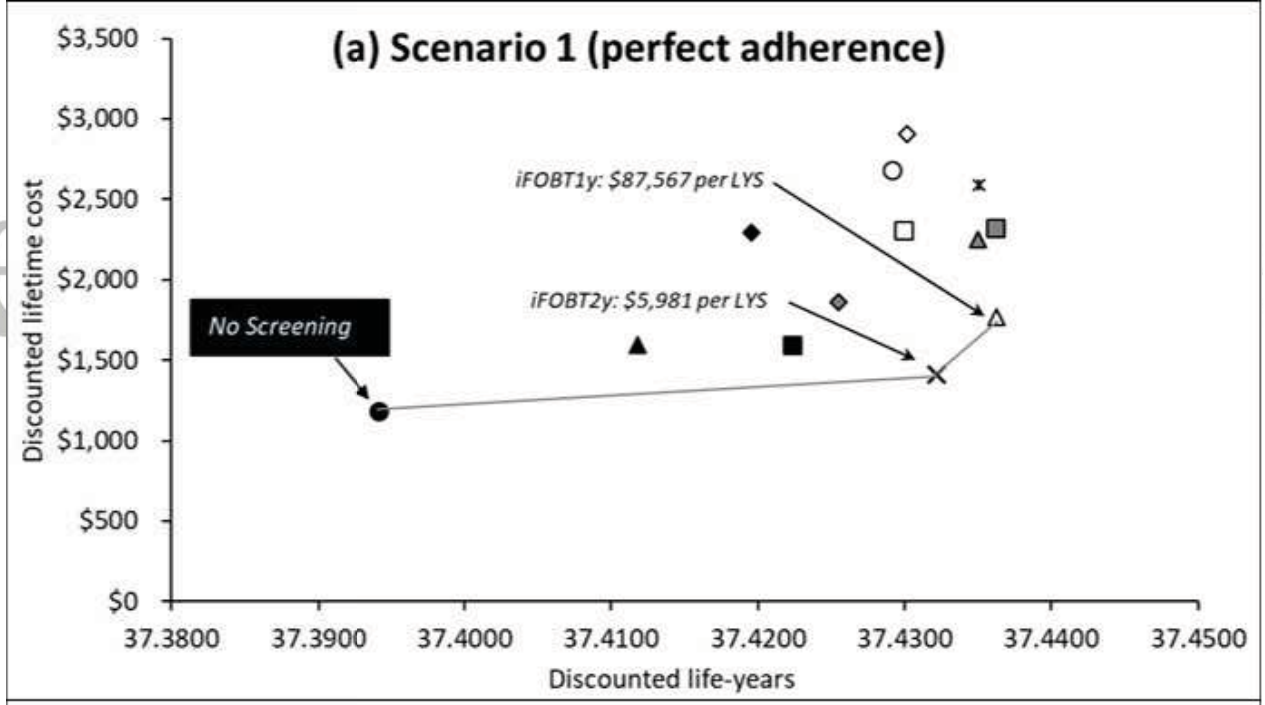
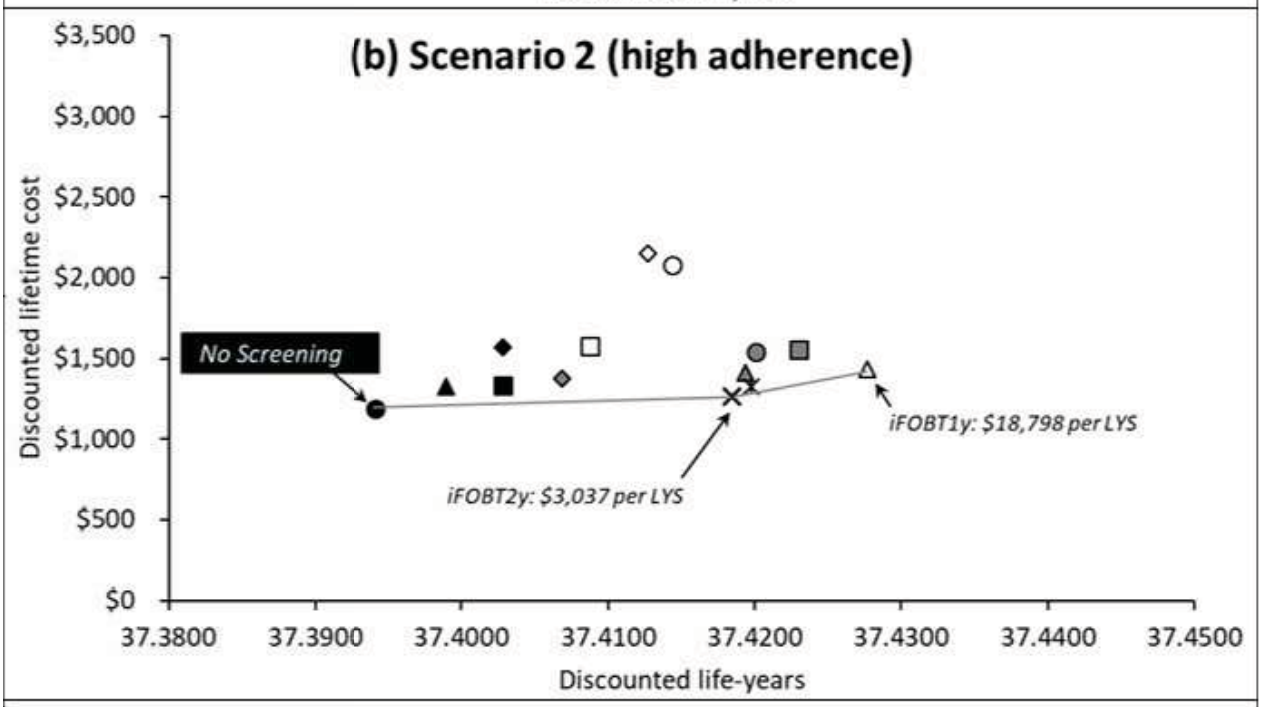
FIGURES

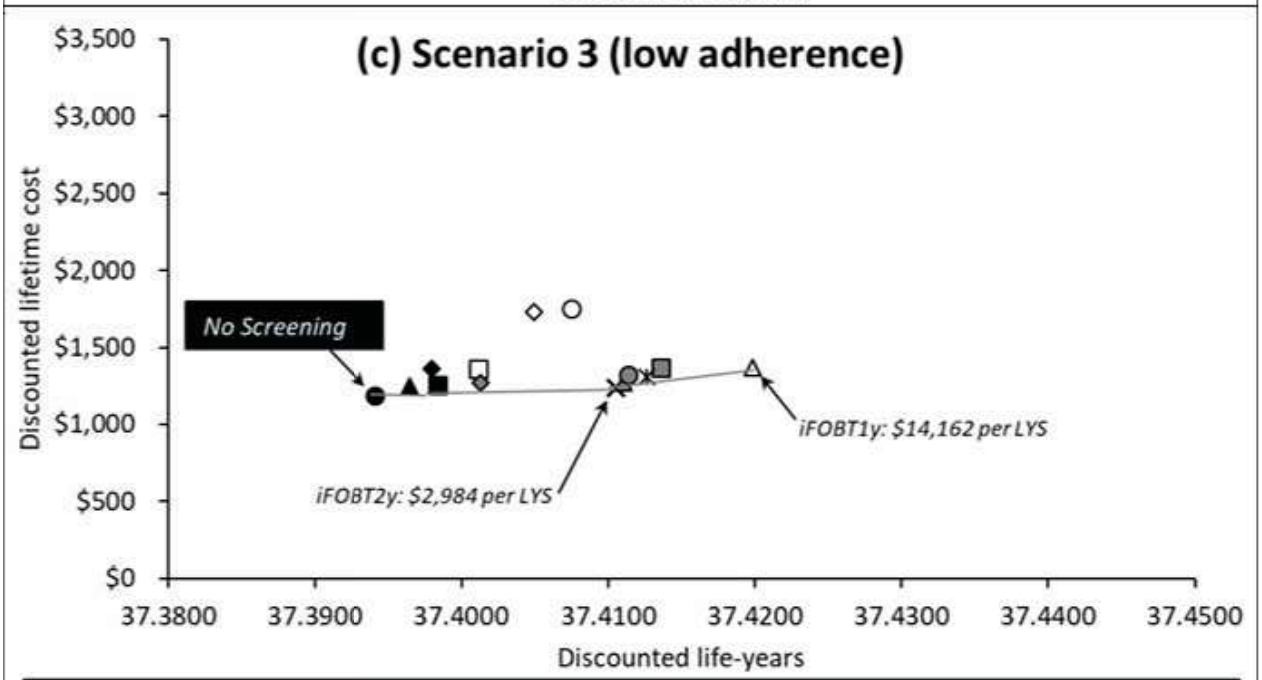
Figure 1. Cost-effectiveness planes for alternative adherence assumptions. Scenario 1 assumed perfect adherence; Scenario 2 assumes high (but more realistic) adherence; and Scenario 3 assumes low adherence. Text and numbers shown in the chart mark the strategies identified on the cost-effectiveness frontier and the incremental cost-effectiveness ratio (ICER) associated with that strategy.[See text for more detail on adherence assumptions in each Scenario].

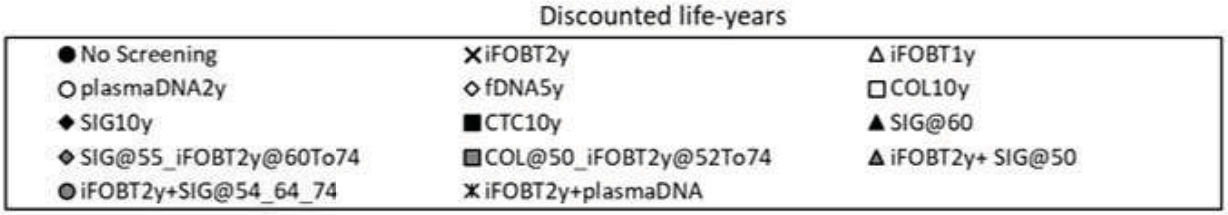
Figure 2. Comparison of lifetime number of colorectal cancer deaths versus lifetime number of colonoscopies per 100,000 persons alive at 40 years for each strategy. Scenario 1 assumed perfect adherence; Scenario 2 assumes high (but more realistic) adherence; and Scenario 3 assumes lower adherence. The number-needed–to-colonoscope (NNC) required per death prevented compared to no screening is presented beside each strategy. The text and numbers in the box shown in the chart mark the strategies identified on the 'benefit-harms frontier' and the incremental number-needed–to-colonoscope (INNC) compared to the next less effective strategy on the 'frontier'. [See text for more detail on adherence assumptions in each Scenario].

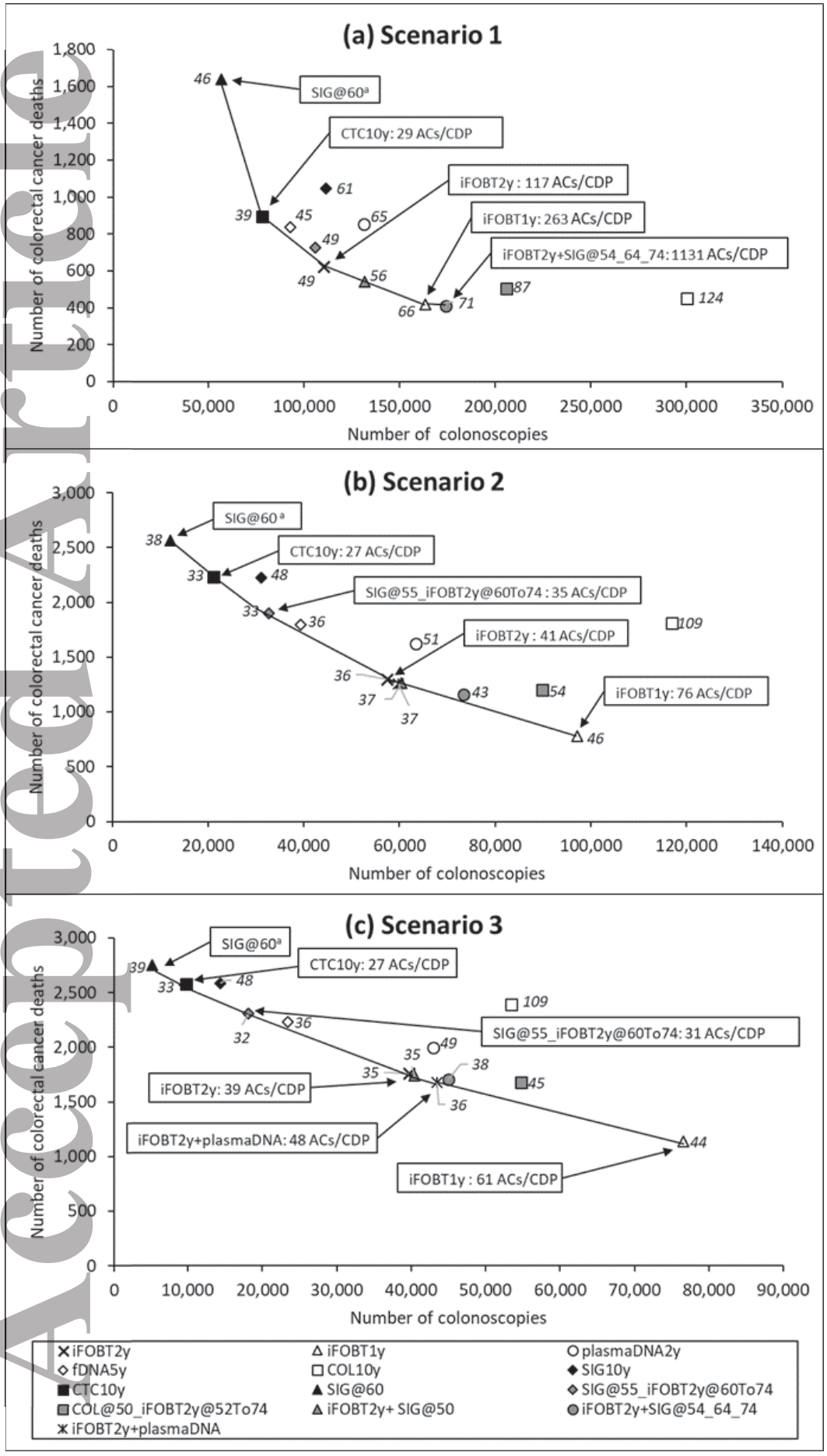
AC – additional number of colonoscopies; CDP – cancer death prevented;
[a] Compared to no screening











Supplementary material accompanying the article:

Evaluation of the benefits, harms and cost-effectiveness of potential alternatives to iFOBT testing for colorectal cancer screening in Australia

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Policy1-Bowel Model platform overview

The *Policy1-Bowel* model was developed by adapting an existing colorectal cancer natural history model, the Adenoma and Serrated Pathway to Colorectal CAncer model (ASCCA), to the Australian setting. (1;2) The model was constructed using Microsoft Visual Studio 2013 C++. It is a micro-simulation model, which simulates 10 million men and 10 million women per single age cohort, incorporating sex-specific life table data. The simulation begins from age 20 and continues on an annual time-step until the individual dies or becomes 90 years old, whichever happens first. The modelled natural history of colorectal cancer development and colorectal cancer screening are described in the sections below.

Model of colorectal cancer development natural history

Precancer natural history

Similar to the *ASCCA* model, the *Policy1* model simulates the development of colorectal cancer via both conventional adenoma-carcinoma pathway and serrated pathway in individuals in the general average-risk population. Although most individual in the general population may develop at most one adenoma, the model is capable to simulate up to ten adenomas and ten serrated lesions per individual simultaneously.

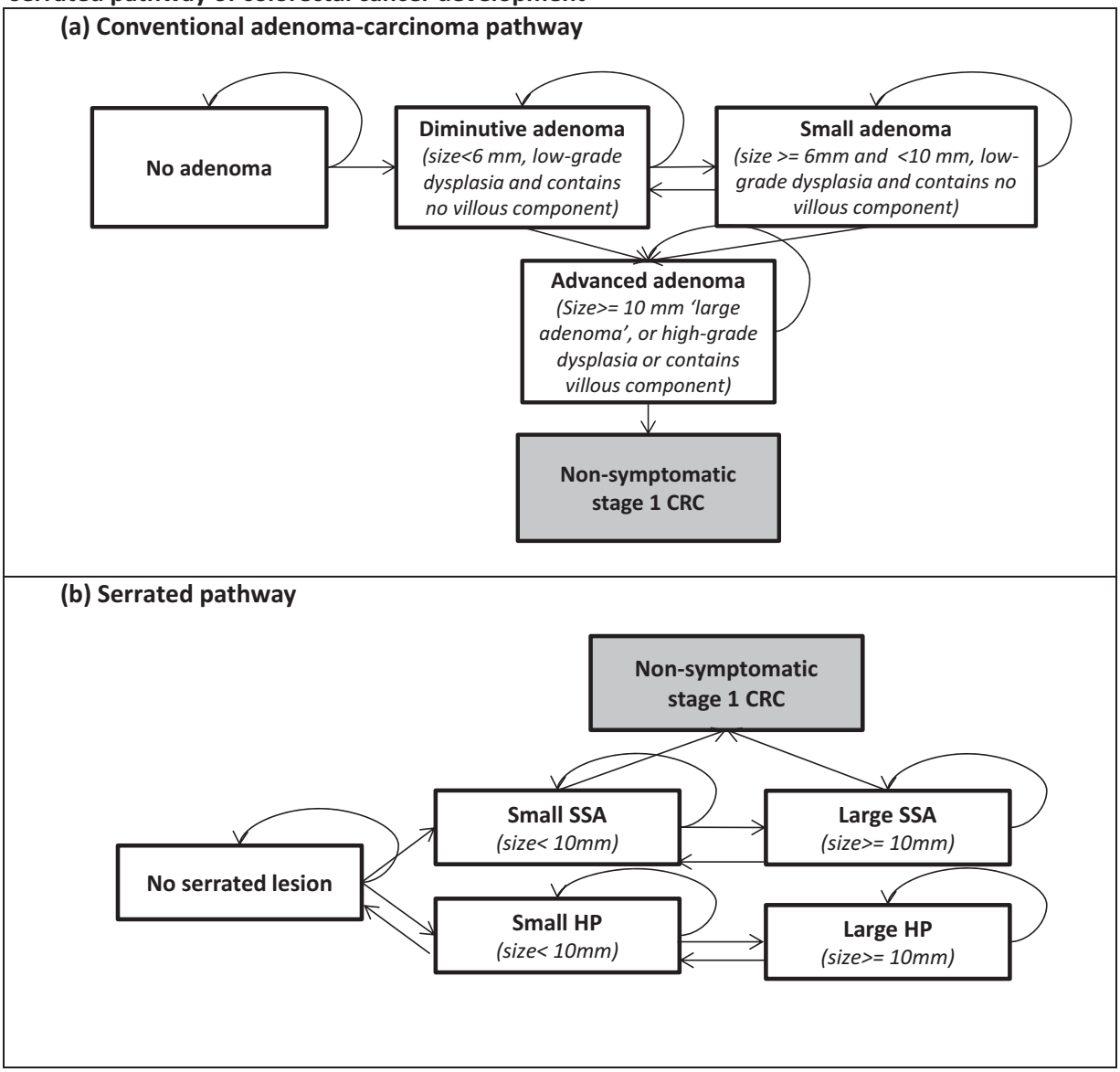
The modelled conventional adenoma-carcinoma pathway simulates the development of colorectal cancer from a conventional adenoma in human bowel. The location, shape, size, degree of dysplasia, and architecture of adenoma are modelled (Table A1). A conventional adenoma is assumed to first appear as diminutive in size (<6mm) and is associated with low-grade dysplasia and tubular architecture. Over time, an adenoma may progress into a more advances stage by increased in size or developed high-grade dysplasia and/or villous architecture. The model assumed a small or large size adenomas could regress into smaller size (but could but not regress completely) if it does not have high-grade dysplasia or villous histology. A conventional adenoma that is large in size, or with high-grade dysplasia, or with villous histology is defined as advanced adenoma, which could further progress into invasive cancer. Figure A1 shows the model's natural history pathways.

Table A1 Summary of the modelled characteristics of adenoma, hyperplastic polyps and sessile serrated adenoma

Characteristics	Category
Adenoma	
Location	Caecum, ascending, transverse, descending, sigmoid, rectum
Shape	Sessile, pedunculated, flat

Size	Diminutive (<6mm), small (>=6mm and<10 mm) , large (>=10mm)
Degree of dysplasia	Low-grade or high-grade
Architecture	Tubular or villous
Hyperplastic polyps (HP)	
Location	Caecum, ascending, transverse, descending, sigmoid, rectum
Size	Small (<10mm), large (>=10mm)
Sessile Serrated Adenoma (SSA)	
Location	Caecum, ascending, transverse, descending, sigmoid, rectum
Size	Small (<10mm), large (>=10mm)

Figure A1 Flow chart of the modelled (a) conventional adenoma-carcinoma pathway and (b) serrated pathway of colorectal cancer development



The modelled serrated pathway simulates the progression of two types of serrated lesions – hyperplastic polyps (HP) and sessile serrated adenoma (SSA) into colorectal cancer. The model assumes HP and SSA will first appear as a small size lesion. Over time, a HP can completely regress or progress into a larger size but could not progress into colorectal cancer. A SSA can progress/regress in size and progress into cancer regardless of the lesion size. However, it cannot completely regress. The risk of developing serrated polyps was assumed to be independent from the risk of developing adenoma lesion.

The modelled precancer natural history assumptions were systematically recalibrated using the Nelder-Mead algorithm to the data observed in COCOS trial (a Dutch trial of colorectal screening with colonoscopy and CT colonography).[3] The calibration targets data including age- , sex- and size-specific prevalence of adenoma, advanced adenoma, and serrated lesions, proportion of adenoma by degree of dysplasia proportion of adenoma by degree of villosity, the distribution of adenoma multiplicity, advanced adenoma multiplicity and serrated lesion multiplicity among individuals detected with bowel polyps. About 200,000 scenarios with different natural history assumptions were assessed. The least-squares method was used to examine the goodness-of-fit of the natural history solutions. Detailed model calibration outcomes have been reported elsewhere.(2)

The set of natural history assumption which best fitted to the COCOS data was selected for base case analysis; the natural history sets that predicted the highest and the lowest colorectal cancer incidence/mortality rate among the top 200 best fitted natural history sets were selected for alternative natural history assumptions for uncertainty analysis (Table A2). Figure A2 compares the modelled age-specific colorectal cancer incidence rate associated with the base case and the alternative precancer natural history assumptions evaluated in the sensitivity analysis.

Table A2 Summary of modelled natural history parameters of the conventional adenoma pathway and serrated adenoma pathway of colorectal cancer development

Parameters	Baseline	Sensitivity analysis	
		Least aggressive precancer natural history assumption	Most aggressive precancer natural history assumption
Conventional adenoma-carcinoma Pathways			
Adenoma incidence rate [a]			
Male, 20-39 years	0.01%	0.003%	0.03%
Male, 40-49 years	0.07%	0.07%	0.05%
Male, 50-54 years	0.10%	0.14%	0.13%
Male, 55-59 years	0.20%	0.14%	0.20%
Male, 60-64 years	0.25%	0.17%	0.25%
Male, 65-69 years	0.28%	0.18%	0.28%

Parameters	Baseline	Sensitivity analysis	
		Least aggressive precancer natural history assumption	Most aggressive precancer natural history assumption
Male, 70-94 years	0.31%	0.19%	0.31%
Male, 75+ years	0.34%	0.22%	0.33%
Female, 20-39 years	0.00%	0.002%	0.02%
Female, 40-49 years	0.05%	0.05%	0.04%
Female, 50-54 years	0.07%	0.10%	0.08%
Female, 55-59 years	0.14%	0.10%	0.13%
Female, 60-64 years	0.18%	0.12%	0.16%
Female, 65-69 years	0.20%	0.13%	0.18%
Female, 70-94 years	0.22%	0.14%	0.20%
Female, 75+ years	0.24%	0.15%	0.21%
Adenoma size progression and regression rate [a]			
Progress from diminutive (<6 mm) to small (6-9 mm) size	10%	17%	11%
Progress from small (6-9 mm) to large (>=10 mm) size	20%	11%	13%
Regress from small (6-9 mm) to diminutive (<6 mm) size	48%	69%	43%
Regress from large(>=10 mm) to small (6-9 mm) size	17%	26%	20%
Probability of developing high-grade dysplasia by adenoma size [a]			
Diminutive adenoma	0.4%	0.6%	0.5%
Small adenoma	0.7%	0.3%	0.6%
Large adenoma	0.8%	0.8%	0.8%
Probability of developed villous component [a]			
Diminutive adenoma	0.4%	0.6%	0.6%
Small adenoma	3.5%	1.9%	2.0%
Large adenoma	5.4%	6.1%	5.6%
Probability of adenoma with sessile shape by section of bowel [b]			
Cecum	87.3%	N/A	N/A
Ascending colon	86.5%	N/A	N/A
Transverse colon	86.2%	N/A	N/A
Descending colon	85.7%	N/A	N/A
Sigmoid	66.5%	N/A	N/A
Rectum	66.2%	N/A	N/A
Probability of adenoma with pedunculated shape by section of bowel [b]			
Cecum	1.3%	N/A	N/A
Ascending colon	8.2%	N/A	N/A
Transverse colon	5.2%	N/A	N/A
Descending colon	13.1%	N/A	N/A
Sigmoid	30.3%	N/A	N/A
Rectum	32.3%	N/A	N/A

Parameters	Baseline	Sensitivity analysis	
		Least aggressive precancer natural history assumption	Most aggressive precancer natural history assumption
Probability of adenoma with flat shape by section of bowel [b]			
Cecum	11.4%	N/A	N/A
Ascending colon	5.3%	N/A	N/A
Transverse colon	8.6%	N/A	N/A
Descending colon	1.2%	N/A	N/A
Sigmoid	3.2%	N/A	N/A
Rectum	1.5%	N/A	N/A
Distribution of adenoma by section of bowel, 20-64 years [b]			
Cecum	10.9%	N/A	N/A
Ascending colon	22.1%	N/A	N/A
Transverse colon	13.7%	N/A	N/A
Descending colon	10.9%	N/A	N/A
Sigmoid	22.9%	N/A	N/A
Rectum	19.5%	N/A	N/A
Distribution of adenoma by section of bowel, 65+ years [b]			
Cecum	11.1%	N/A	N/A
Ascending colon	26.3%	N/A	N/A
Transverse colon	19.8%	N/A	N/A
Descending colon	11.5%	N/A	N/A
Sigmoid	15.7%	N/A	N/A
Rectum	15.6%	N/A	N/A
Probability of advanced adenoma progress into stage 1 non-symptomatic cancer [a]			
Male, colon cancer	2.1%	N/A	N/A
Male, rectum cancer	5.1%	N/A	N/A
Female, colon cancer	2.0%	N/A	N/A
Female, rectum cancer	3.5%	N/A	N/A
Serrated pathway			
Hyperplastic polyp incidence rate [a]			
Male, 20-39 years	0.05%	0.05%	0.10%
Male, 40-49 years	0.15%	0.13%	0.11%
Male, 50-54 years	0.13%	0.12%	0.09%
Male, 55-59 years	0.24%	0.25%	0.26%
Male, 60-64 years	0.24%	0.25%	0.26%
Male, 65-69 years	0.24%	0.25%	0.26%
Male, 70-74 years	0.24%	0.25%	0.26%
Male, 75+ years	0.24%	0.25%	0.26%
Female, 20-39 years	0.03%	0.03%	0.06%
Female, 40-49 years	0.09%	0.09%	0.07%
Female, 50-54 years	0.08%	0.08%	0.05%
Female, 55-59 years	0.14%	0.17%	0.15%

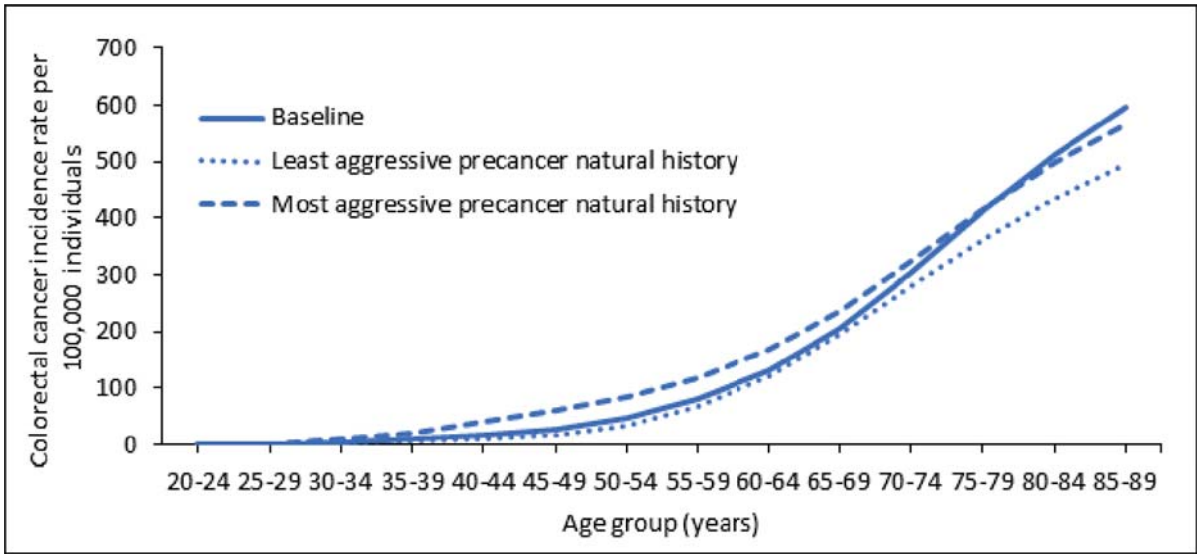
Parameters	Baseline	Sensitivity analysis	
		Least aggressive precancer natural history assumption	Most aggressive precancer natural history assumption
Female, 60-64 years	0.14%	0.17%	0.15%
Female, 65-69 years	0.14%	0.17%	0.15%
Female, 70-74 years	0.51%	0.38%	0.59%
Female, 75+ years	0.51%	0.38%	0.59%
Sessile serrate adenoma incidence rate [a]			
Male, 20-39 years	0.092%	0.063%	0.073%
Male, 40-49 years	0.032%	0.024%	0.024%
Male, 50-54 years	0.009%	0.018%	0.012%
Male, 55-59 years	0.009%	0.016%	0.009%
Male, 60-64 years	0.009%	0.016%	0.009%
Male, 65-69 years	0.009%	0.016%	0.009%
Male, 70-74 years	0.009%	0.016%	0.009%
Male, 75+ years	0.009%	0.016%	0.009%
Female, 20-39 years	0.067%	0.050%	0.070%
Female, 40-49 years	0.023%	0.019%	0.023%
Female, 50-54 years	0.007%	0.014%	0.012%
Female, 55-59 years	0.006%	0.012%	0.008%
Female, 60-64 years	0.006%	0.012%	0.008%
Female, 65-69 years	0.007%	0.012%	0.008%
Female, 70-74 years	0.007%	0.012%	0.008%
Female, 75+ years	0.007%	0.012%	0.008%
Hyperplastic polyps size progression and regression rate [a]			
Progress from small (<10 mm) to large (>=10 mm) size	2%	2%	2%
Regress from small (<10 mm) size to none	7%	9%	8%
Regress from large (>= 10 mm) to small (<10 mm) size	29%	26%	22%
Sessile serrate adenoma size progression and regression rate [a]			
Progress from small (<10 mm) to large (>=10 mm) size	3%	2%	3%
Regress from large (>= 10mm) to small (<10 mm) size	33%	10%	11%
Distribution of hyperplastics polyps by section of bowel [b]			
Cecum	4%	N/A	N/A
Ascending colon	12%	N/A	N/A
Transverse colon	9%	N/A	N/A
Descending colon	7%	N/A	N/A
Sigmoid	26%	N/A	N/A
Rectum	42%	N/A	N/A
Distribution of sessile serrated adenoma by section of bowel [b]			

Parameters	Baseline	Sensitivity analysis	
		Least aggressive precancer natural history assumption	Most aggressive precancer natural history assumption
Cecum	12%	N/A	N/A
Ascending colon	28%	N/A	N/A
Transverse colon	20%	N/A	N/A
Descending colon	7%	N/A	N/A
Sigmoid	13%	N/A	N/A
Rectum	21%	N/A	N/A
Probability of sessile serrated adenoma (any size) progress into stage 1 non-symptomatic cancer[a]			
Male, colon cancer	0.17%	N/A	N/A
Male, rectum cancer	0.43%	N/A	N/A
Female, colon cancer	0.16%	N/A	N/A
Female, rectum cancer	0.29%	N/A	N/A

[a] *Annual rate*

[b] *Input parameters not outcome of calibration*

Figure A2 Modelled age-specific colorectal cancer incidence associated with base case, least aggressive, and most aggressive precancer natural history assumptions when screening was no available

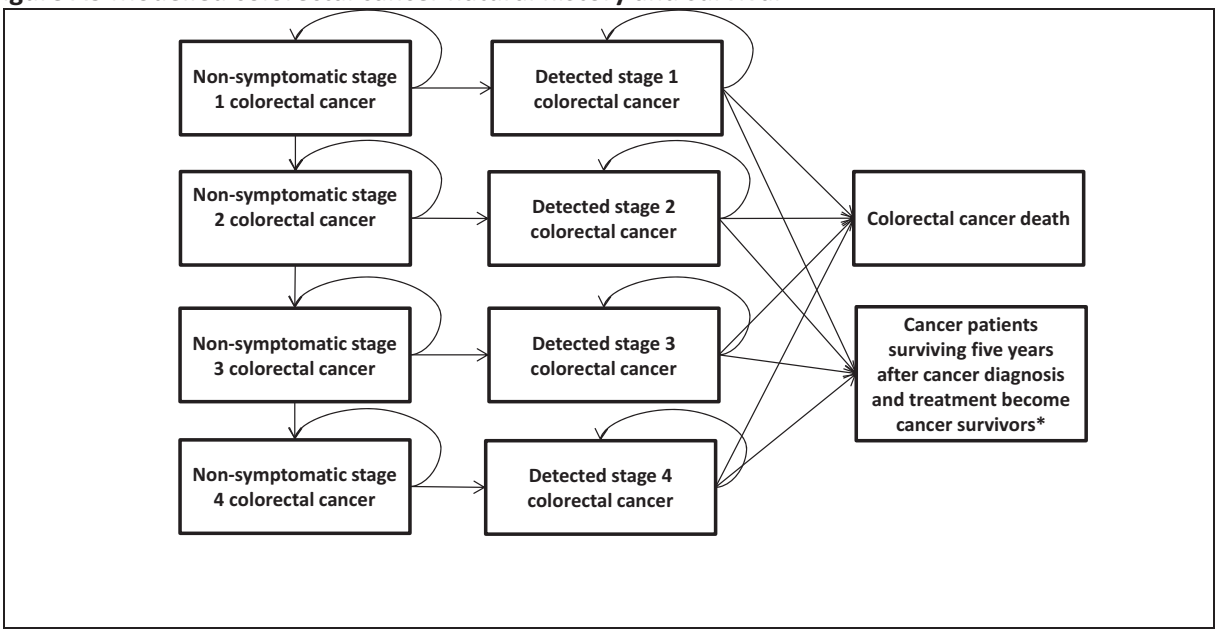


Colorectal cancer natural history and survival

Colorectal cancer was modelled by The American joint Committee on cancer (AJCC) staging 1, 2, 3 and 4. In the model, colorectal cancer will first appear as Stage 1 cancer without any symptom. Each year, a non-symptomatic cancer may be diagnosed because of the onset of symptoms or remain undiagnosed and likely to progress into a more advanced stage (Figure A3). In the scenarios assuming bowel cancer screening, an underlying non-symptomatic cancer may also be diagnosed by

screening test and colonoscopy (depends on the modelled screening test characteristics and the modelled colonoscopy detection rate). The symptomatically-detected cancers in this study refer to colorectal cancers that are diagnosed due to the presence of symptoms. It includes cancers diagnosed in individuals who have never participated in in screening, cancers diagnosed in individuals who have previously participated in screening but cancer was missed by the screening and/or diagnosis test due to imperfect test accuracy and/or imperfect colonoscopy compliance, and interval cancers that arise between two screening rounds. Cancers diagnosed via colonoscopy after referral of an iFOBT-positive or during subsequent colonoscopy surveillance are referred as screen-detected cancers here.

Figure A3 Modelled colorectal cancer natural history and survival



** Cancer patients surviving five years after diagnosis and treatment become cancer survivors. Cancer survivors in the model were assumed to have no additional risk of death due to colorectal cancer compared with the average population with no colorectal cancer.*

Patients diagnosed with colorectal cancer were associated with an increased risk of dying due to colorectal cancer and the risk varied by cancer stage at diagnosis. The modelled cancer survival probabilities vary by cancer stage, time since cancer diagnosis and whether the cancer was diagnosed due to symptoms present or colorectal screening (i.e. symptomatically-detected cancer or screened-detected cancer). Table A3 shows the modelled 5-year survival for symptomatically detected-cancer and screened-detected cancer. The modelled survival rate of symptomatically-detected colorectal cancer patients was obtained by calibrating the predicted age-specific colorectal cancer mortality rate to data observed in Australia in 2000-2003 before NBCSP was introduced (see Lew et al 2017 (2) model calibration outcomes) and was consistent with the observed 5-year survival

rate among colorectal cancer patients in public hospitals in Western Australia . (4;5) The screened-detected colorectal cancer patients were assumed to have a relative 5-year survival of 1.15 for Stage 1, 1.20 for Stage 2, 1.35 for Stage 3 cancer and 2.33 for Stage 4 cancer compared with symptomatically-detected cancer patients, broadly consistent with the three international studies data (Table A3) .(6-8)

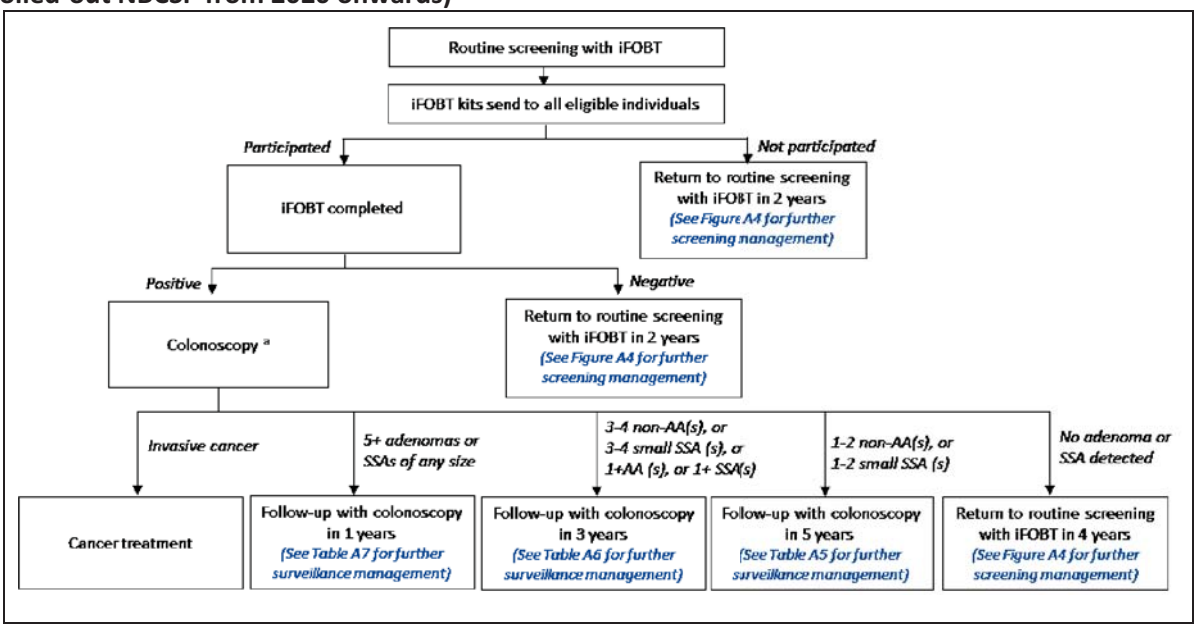
Table A3 Modelled overall 5-year survival rate in patient detected with colorectal cancer

Cancer stage	Modelled 5-year survival rate		Relative survival (screened-detected cancer versus symptomatically-detected cancer)
	Symptomatically detected cancer	Screen-detected cancer	
1	86.9%	99.9%	1.15
2	73.0%	87.3%	1.20
3	42.4%	57.3%	1.35
4	9.5%	22.1%	2.33

The model assumed that patients who survived for five years after detection and treatment of cancer were became cancer survivors. These survivors are assumed to have no additional risk of dying from the disease compared with the average population with no colorectal cancer.

Managements for routine screening of different screening strategies

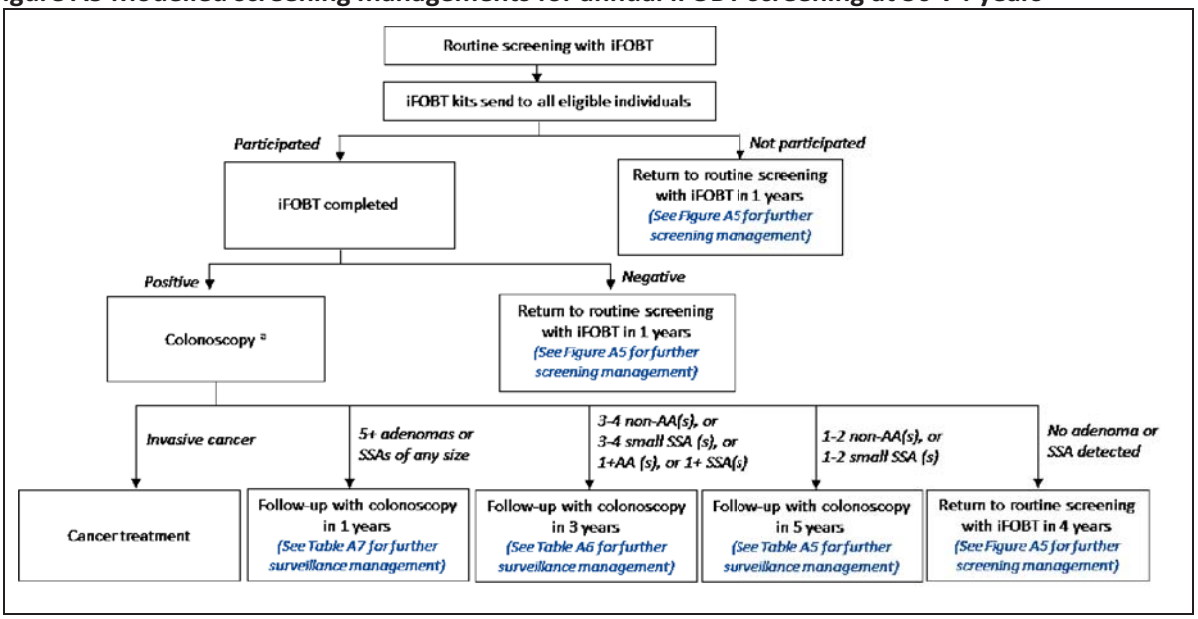
Figure A4 Modelled screening managements for 2-yearly iFOBT screening at 50-74 years (the fully rolled-out NBCSP from 2020 onwards)



[a] The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had a positive

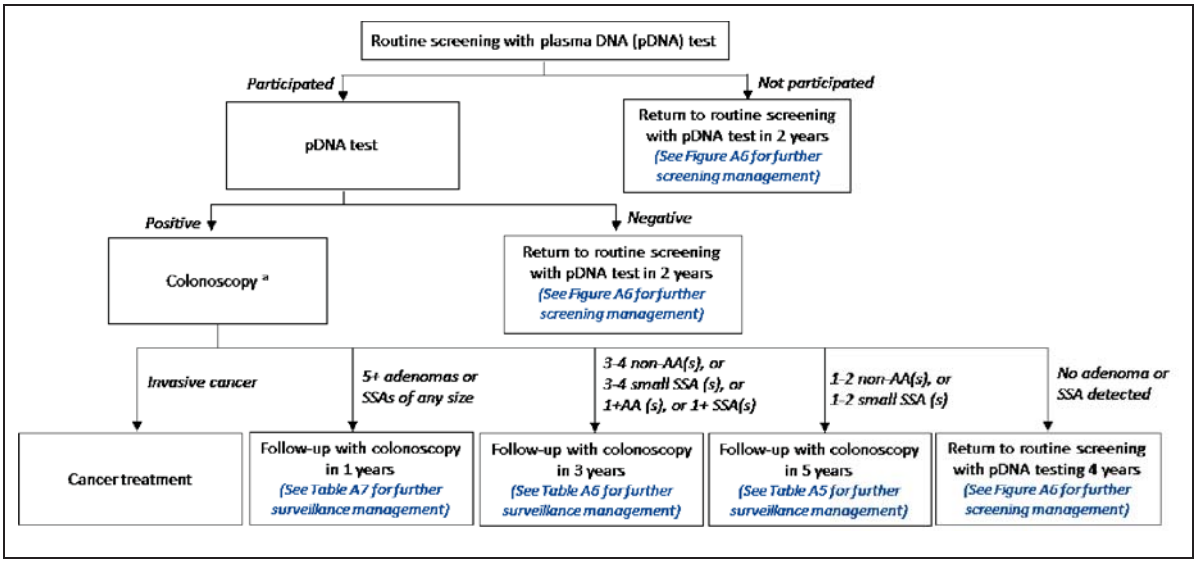
screening test result but did not attend colonoscopy were invited to participate in the next iFOBT screening event in 2 years in the model.

Figure A5 Modelled screening managements for annual iFOBT screening at 50-74 years



[a] *The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had a positive screening test result but did not attend colonoscopy were invited to participate in the next iFOBT screening event in the model.*

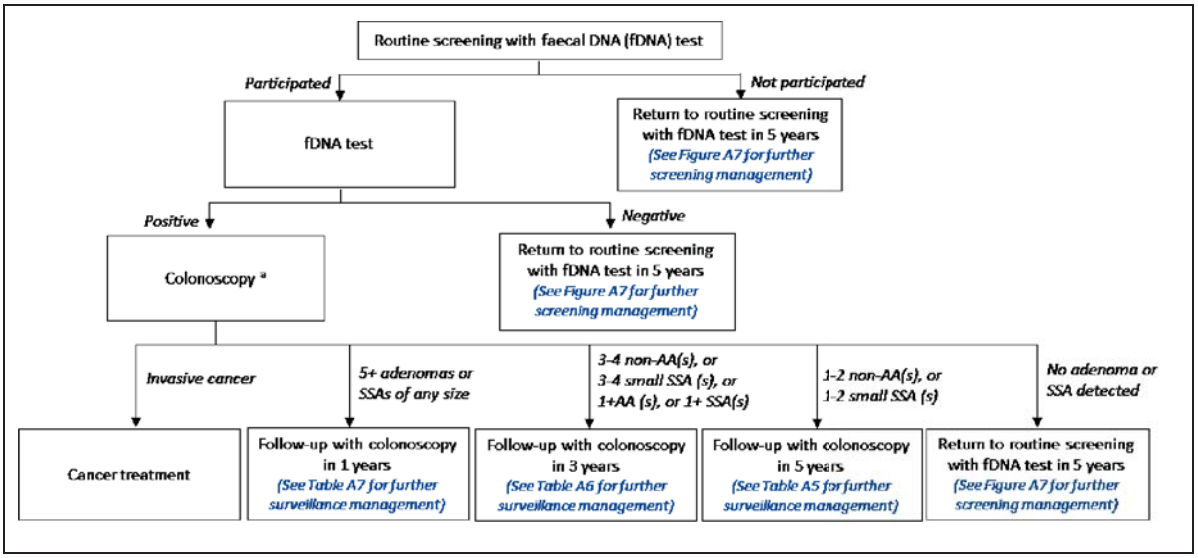
Figure A6 Modelled screening managements for 2-yearly screening using plasma DNA test at 50-74 years



[a] *The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had a positive*

screening test result but did not attend colonoscopy were invited to participate in the next pDNA screening event in 2 years in the model.

Figure A7 Modelled screening managements for 5-yearly screening using faecal DNA test at 50-74 years



[a] *The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had a positive screening test result but did not attend colonoscopy were invited to participate in the next fDNA screening event in 2 years in the model.*

Figure A8 Modelled screening managements for 10-yearly screening using colonoscopy at 55, 65 and 75 years

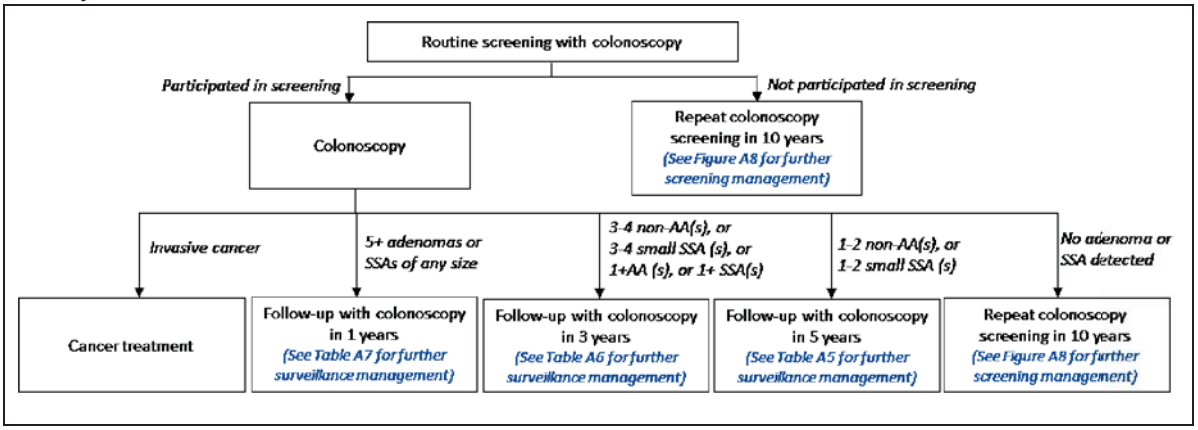
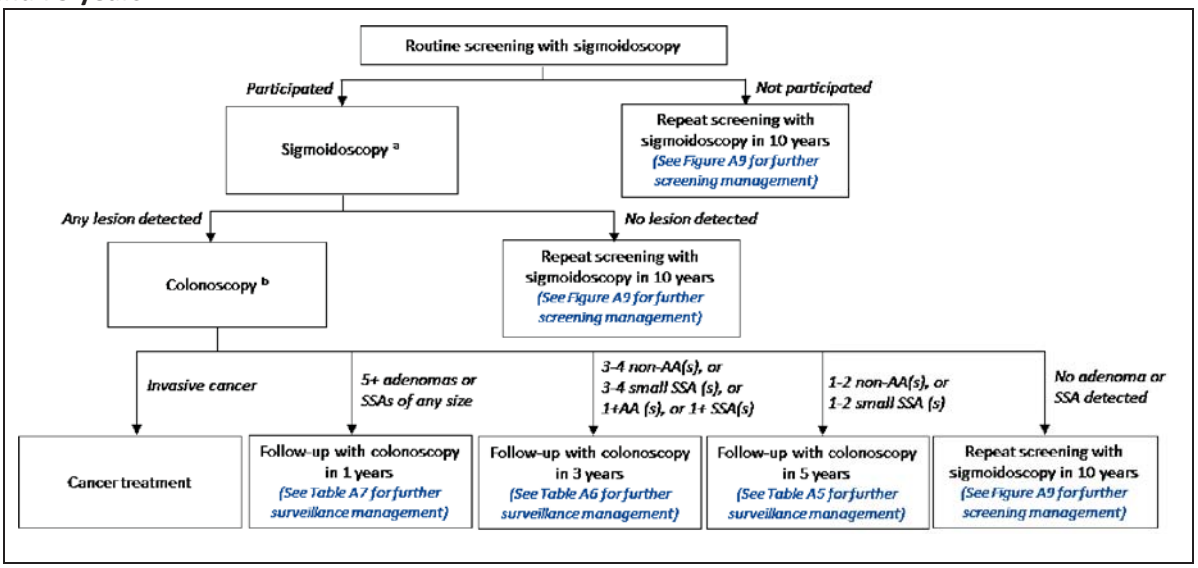


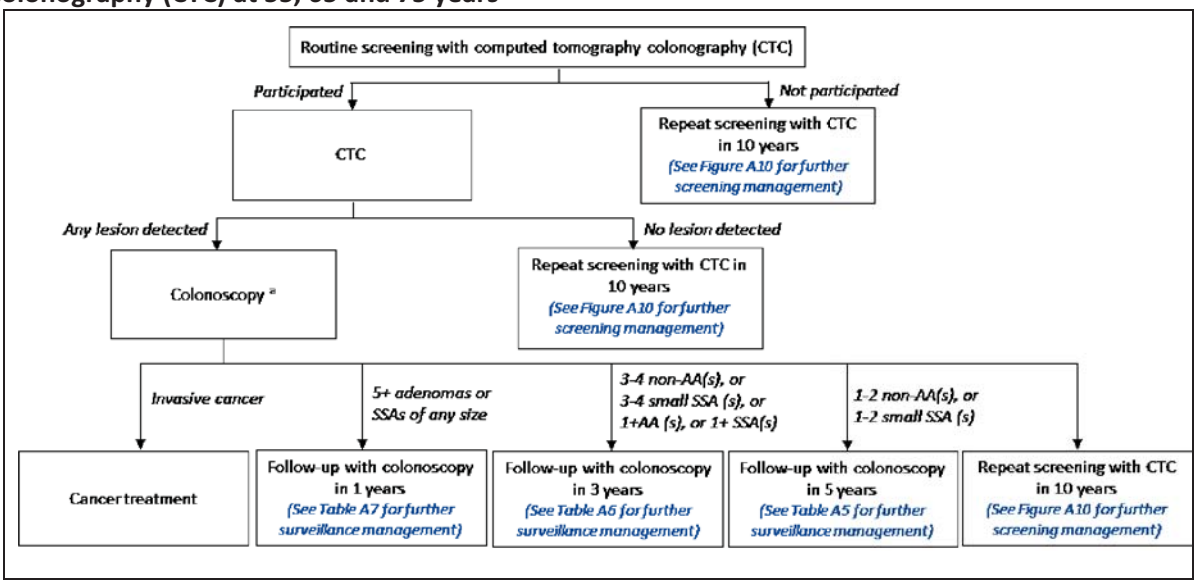
Figure A9 Modelled screening managements for 10-yearly screening using sigmoidoscopy at 55, 65 and 75 years



[a] Adenomas <5mm detected during sigmoidoscopy were assumed to be treated via immediate polypectomy; polyps >= 5mm were assumed not to be removed during sigmoidoscopy but to be treated in the follow-up colonoscopy.

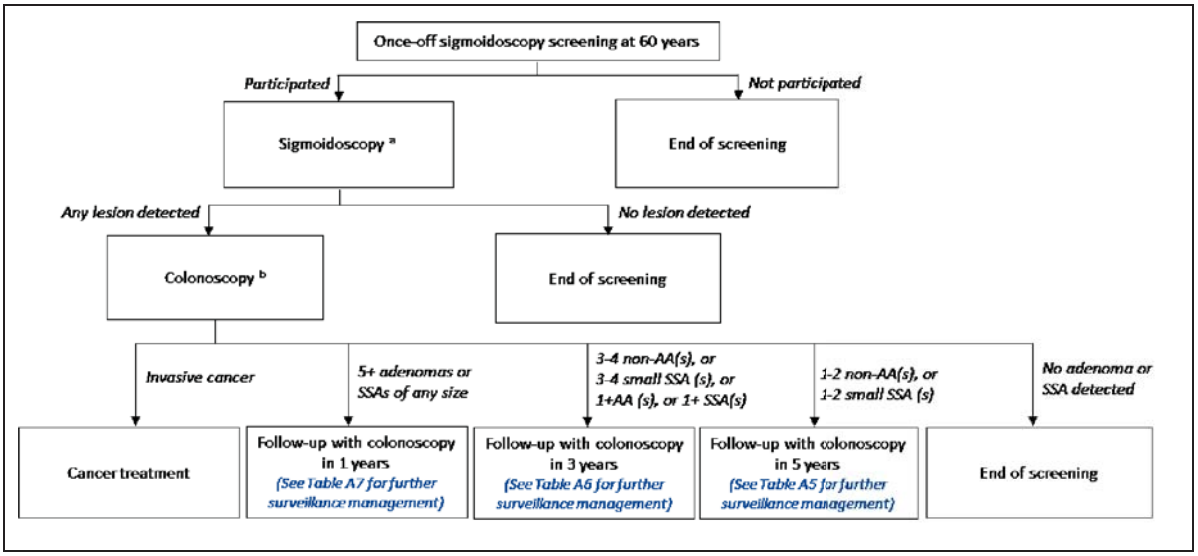
[b] The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had lesion detected at sigmoidoscopy but did not attend colonoscopy were invited to participate in the next sigmoidoscopy screening event in 10 years in the model.

Figure A10 Modelled screening managements for 10-yearly screening using computed tomography colonography (CTC) at 55, 65 and 75 years



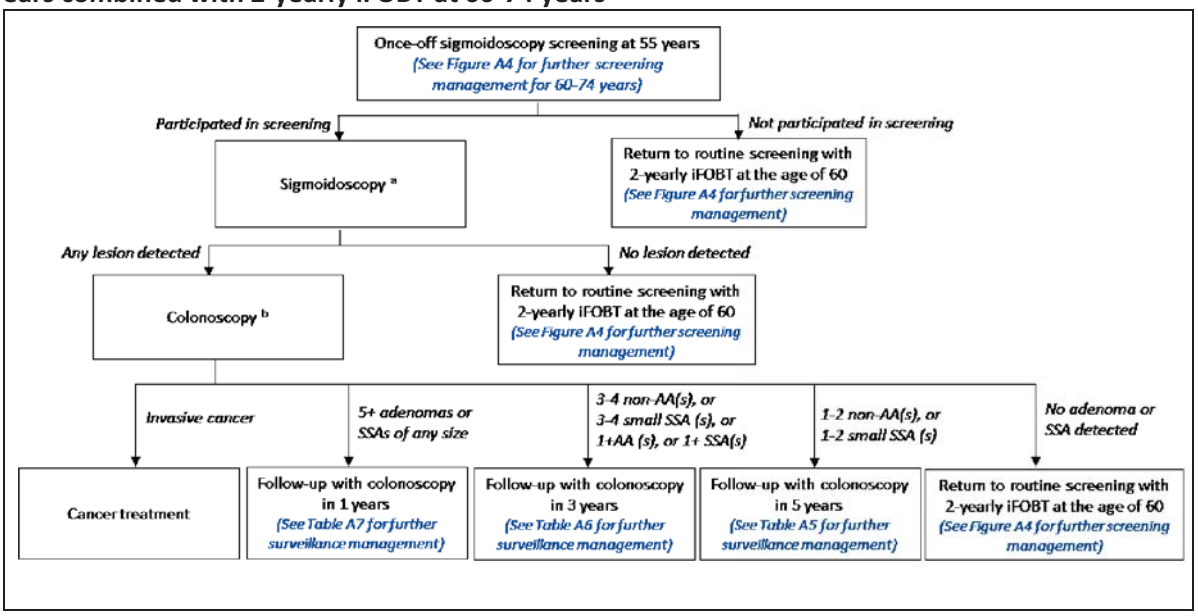
[a] The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had any lesion detected at CTC but did not attend colonoscopy were invited to participate in the next CTC screening event in 10 years in the model.

Figure A11 Modelled screening managements for once-off screening using sigmoidoscopy at 60 years



[a] Adenomas <5mm detected during sigmoidoscopy were assumed to be treated via immediate polypectomy; polyps >= 5mm were assumed not to be removed during sigmoidoscopy but to be treated in the follow-up colonoscopy.
[b] The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1.

Figure A12 Modelled screening managements for once-off screening using sigmoidoscopy at 55 years combined with 2-yearly iFOBT at 60-74 years



[a] Adenomas <5mm detected during sigmoidoscopy were assumed to be treated via immediate polypectomy; polyps >= 5mm were assumed not to be removed during sigmoidoscopy but to be treated in the follow-up colonoscopy.

[b] *The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had any lesion detected at sigmoidoscopy but did not attend colonoscopy were invited to participate in the next iFOBT screening event at the age of 60 in the model.*

Figure A13 Modelled screening managements for once-off screening using colonoscopy at 50 years combined with 2-yearly iFOBT at 52-74 years

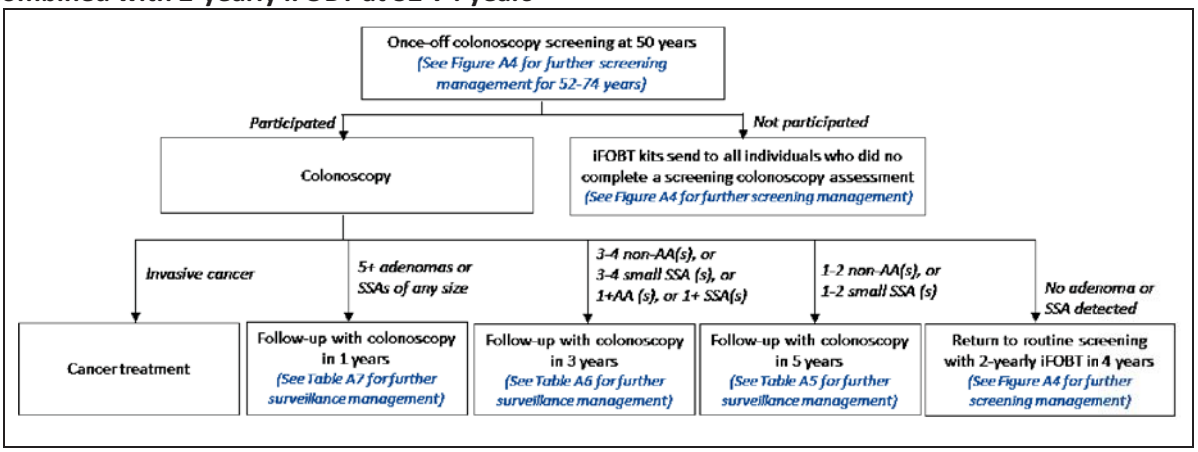
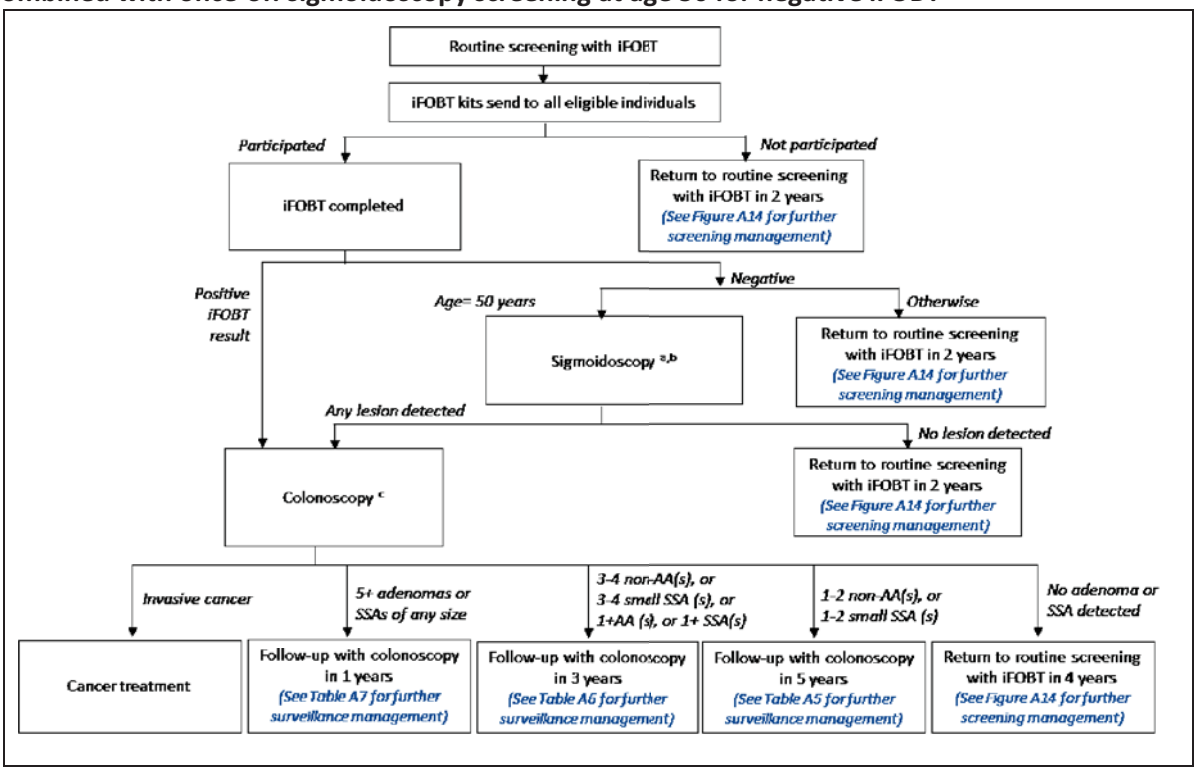


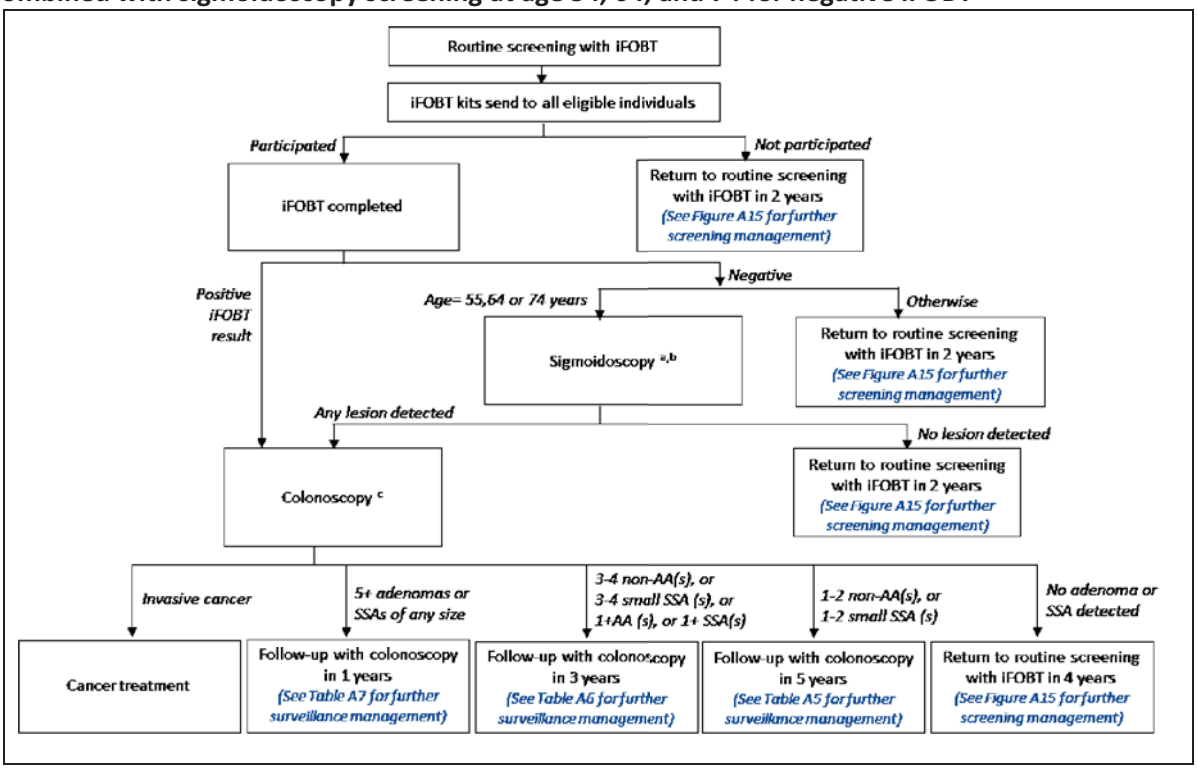
Figure A14 Modelled screening managements for 2-yearly iFOBT screening at 50-74 years combined with once-off sigmoidoscopy screening at age 50 for negative iFOBT



[a] *Adenomas <5mm detected during sigmoidoscopy were assumed to be treated via immediate polypectomy; polyps >= 5mm were assumed not to be removed during sigmoidoscopy but to be treated in the follow-up colonoscopy.*
[b] *Individuals who did not attend sigmoidoscopy were invited to participate in the next iFOBT screening event in 2 years in the model.*

[c] *The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had positive iFOBT result or lesion detected at sigmoidoscopy but did not attend colonoscopy were invited to participate in the next iFOBT screening event in 2 years in the model.*

Figure A15 Modelled screening managements for 2-yearly iFOBT screening at 50-74 years combined with sigmoidoscopy screening at age 54, 64, and 74 for negative iFOBT

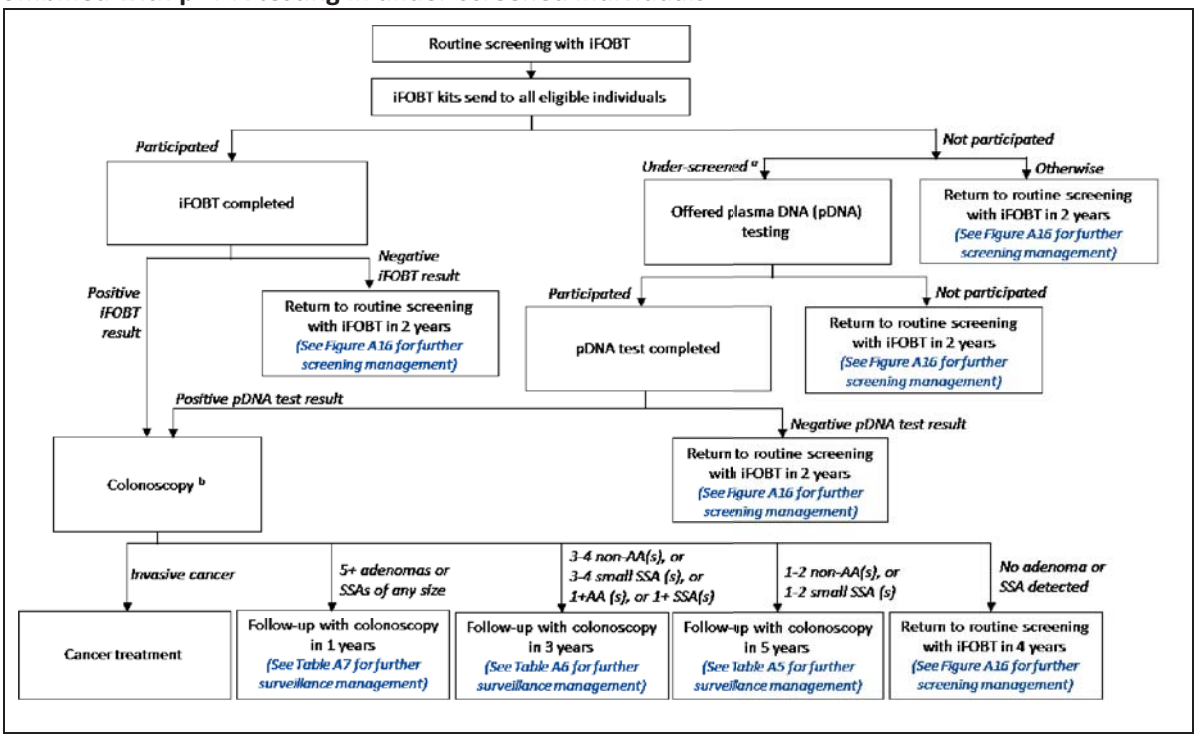


[a] *Adenomas <5mm detected during sigmoidoscopy were assumed to be treated via immediate polypectomy; polyps >= 5mm were assumed not to be removed during sigmoidoscopy but to be treated in the follow-up colonoscopy.*

[b] *Individuals who did not attend sigmoidoscopy were invited to participate in the next iFOBT screening event in 2 years in the model.*

[c] *The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had a positive iFOBT result or lesion detected at sigmoidoscopy but did not attend colonoscopy were invited to participate in the next iFOBT screening event in 2 years in the model.*

Figure A16 Modelled screening managements for 2-yearly iFOBT screening at 50-74 years combined with pDNA testing in under-screened individuals



[a] Under-screened individuals are those who are not under colonoscopy surveillance and have not had an iFOBT test in the past 4 years (including those who are eligible for screening but have never had a screening test). Note – no leakage from main program is assumed after pDNA is offered (a favourable assumption).

[b] The compliance rates to colonoscopy referral after a positive screening result (~70%) modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on the average rates in the NBCSP in the period between 2010 and 2014 (Figure A18); perfect compliance to colonoscopy referral was assumed for Scenario 1. Individuals who had a positive screening test result but did not attend colonoscopy were invited to participate in the next iFOBT screening event in the model.

Managements for follow-up colonoscopy after a positive screening result and surveillance colonoscopy

The further management for patients who attend colonoscopy because of a positive screening result was modelled based on guideline recommendations and expert consultation (Table A4).

Table A4 Colonoscopy management for individuals referred to colonoscopy due to positive FOBT result

Outcome of colonoscopy	Follow-up management*
No adenomatous polyps	Return to the modelled screening strategy
1-2 non-advanced adenoma(s)/small SSA(s)	Follow-up with colonoscopy in 5 years
3-4 non-advanced adenomas/small SSAs or 1 or more advanced adenoma(s)/large SSA(s)	Follow-up with colonoscopy in 3 years
5 or more adenomas/SSAs at any size	Follow-up with colonoscopy in 12 months
Invasive cancer	Cancer treatment

** Management was modelled based on the recommendation of Cancer Council Australia Surveillance Colonoscopy Guidelines Working Party. Colonoscopic Surveillance Intervals – Adenomas [4]*

Individuals with previous abnormal findings (detection of at least one adenoma) at colonoscopy were managed by colonoscopic surveillance. All conventional adenomas and sessile serrated lesions detected during surveillance colonoscopy were assumed to be completely removed by polypectomy. The National Bowel Cancer Screening Program (NBCSP) recommended that further management be based on national clinical practice guidelines.[3;4] The further surveillance managements for individuals detected with no polyps or with one or two non-advanced adenoma(s)/small SSA(s) varied by individuals' previous colonoscopy outcome; individuals detected with three or four non-advanced adenomas/small SSAs or with one or more advanced adenoma(s)/large SSA(s) were followed-up with another colonoscopy in three years; patients detected with five or more adenomas/SSAs at any size were followed-up with another colonoscopy in 12 months; patients detected with colorectal cancer were referred to cancer treatment (see Table A5, Table A6 and Table A7).

Table A5 Colonoscopy management for individuals referred to colonoscopy due to previously detected with one or two non-advanced adenoma(s)/small SSA(s)

Outcome of colonoscopy	**Follow-up management***
No adenomatous polyps or 1-2 non-advanced adenoma(s)/small SSA(s)	50% return to routine screening and 50% follow-up with colonoscopy in 10 years #
3-4 non-advanced adenomas/small SSAs or 1 or more advanced adenoma(s)/large SSA(s)	Follow-up with colonoscopy in 3 years
5 or more adenomas/SSAs at any size	Follow-up with colonoscopy in 12 months
Invasive cancer	Cancer treatment

** Based on the recommendation of Cancer Council Australia Surveillance Colonoscopy Guidelines Working Party. Colonoscopic Surveillance Intervals – Adenomas [4]*
 # Personal communication with Professor. D James B St John

Table A6 Colonoscopy management for individuals referred to colonoscopy due to previously detected with three or four non-advanced adenomas/small SSAs or at least one advanced adenoma(s)/large SSA(s)

Outcome of colonoscopy	**Follow-up management***
No adenomatous polyps or 1-2 non-advanced adenoma(s)/small SSA(s)	50% follow-up with colonoscopy in 3 years 50% follow-up with colonoscopy in 5 years#
3-4 non-advanced adenomas/small SSAs or 1 or more advanced adenoma(s)/large SSA(s)	Follow-up with colonoscopy in 3 years
5 or more adenomas/SSAs at any size	Follow-up with colonoscopy in 12 months
Invasive cancer	Cancer treatment

** Based on the recommendation of Cancer Council Australia Surveillance Colonoscopy Guidelines Working Party. Colonoscopic Surveillance Intervals – Adenomas [4]*
 # Personal communication with Professor. D James B St John

Table A7 Colonoscopy management for individuals referred to colonoscopy due to previously detected with five or more conventional adenomas/ SSAs

Outcome of colonoscopy	Follow-up management*
No adenomatous polyps or 1-2 non-advanced adenoma(s)/small SSA(s)	Follow-up with colonoscopy in 3 years
3-4 non-advanced adenomas/small SSAs or 1 or more advanced adenoma(s)/large SSA(s)	Follow-up with colonoscopy in 3 years
5 or more adenomas/SSAs at any size	Follow-up with colonoscopy in 12 months
Invasive cancer	Cancer treatment

* *Based on the recommendation of Cancer Council Australia Surveillance Colonoscopy Guidelines Working Party. Colonoscopic Surveillance Intervals – Adenomas* [4]

Test characteristics assumptions

Immunochemical fecal occult blood test (iFOBT)

The model assumed 1.6% of all iFOBT tests returned were incorrectly completed based on data observed in the National Bowel Cancer Screening Program (NBCSP) in 2013-14.(9) All individuals who have incorrectly completed test were assumed to have completed a second test kit sent to them correctly.

The modelled test characteristics of a correctly completed iFOBT were obtained via calibrating to the iFOBT positive rate (the proportion of participants with a positive result out of all participants who returned a valid FOBT kit) observed among the men and women invited to participate in NBCSP and the colonoscopy outcomes among those with a positive iFOBT result the period between 2006 and 2014.(9-13) The relevant model calibration outcomes were reported elsewhere.(2) Table A8 shows the modelled lesion-specific iFOBT test positive rate for baseline. Two alternative iFOBT test characteristics assumptions, one assumed a relative 15% increase and another one assumed relative 15% decrease in the iFOBT test positive rates were assessed in the sensitivity analysis.

Table A8 Modelled lesion-specific test positive rate of iFOBT

Category	Modelled iFOBT positive rate		
	Baseline	Sensitivity analysis	
		Lower end	Upper end
Background rate in all individuals (per individual) [a]	5.0%	4.3%	5.8%
Additional positive rate per adenoma 1-5 mm [b]	0.7%	0.6%	0.8%
Additional positive rate per adenoma 6-9 mm [b]	11.0%	9.4%	12.7%
Additional positive rate per adenoma >10 mm [b]	35.0%	29.8%	40.3%
Additional positive rate per HP	0%	0.0%	0.0%
Additional positive rate per SSA	0%	0.0%	0.0%
Additional positive rate for stage 1 CRC	40.0%	34.0%	46.0%
Additional positive rate for stage 2 CRC	65.0%	55.3%	74.8%
Additional positive rate for stage 3 CRC	75.0%	63.8%	86.3%
Additional positive rate for stage 4 CRC	75.0%	63.8%	86.3%

CRC- colorectal cancer; HP- hyperplastic polyp; SSA – sessile serrate adenoma

[a] A background positive rate was assumed for all individuals (including perfectly healthy individuals who have no polyps or cancer)

[b] Same positive rate was assumed for adenoma within the same size category regardless of the histopathology characteristic of the adenoma (i.e. with or without high-grade dysplasia, and with/without villous architecture)

Table A9 provides a summary of the modelled per-person iFOBT test sensitivity and specificity that were estimated from a group of never-screened individuals aged 50-74 years in the model. These virtual individuals underwent one round of screening using both iFOBT test (assuming lesion-specific iFOBT positive rate provided in Table A8) and colonoscopy (assuming colonoscopy detection rate provided in Table A16) in the model. The following definitions were used when estimating the test sensitivity and test specificity of the modelled iFOBT in Table A9:

- Individuals who had a positive iFOBT result were counted as true positive if their colonoscopy findings met the criteria defined for each category of colonoscopy outcome specified in Table A9, i.e. any adenoma, adenoma >5mm, >10mm, respectively; otherwise, the individuals were counted as false positive.
- Individuals who had a negative iFOBT result were counted as false negative if their colonoscopy outcome met the criteria defined for each category of colonoscopy outcome specified in Table A9; otherwise, the individuals were counted as true negative.
- Test sensitivity was calculated by dividing true positive by the sum of true positive and false negative.
- Test specificity was calculated by dividing the true negative by the sum of true negative and false positive.

Table A9 Modelled test sensitivity and specificity of iFOBT (per person)

Colonoscopy outcome	Baseline		Sensitivity analysis (lower end)		Sensitivity analysis (upper end)	
	Sens	Spec	Sens	Spec	Sens	Spec
Any adenoma	15.2%	94.8%	13.1%	95.6%	17.4%	94.1%
Adenoma > 5mm	30.2%	94.6%	26.0%	95.4%	34.3%	93.8%
Adenoma >=10mm	41.5%	94.1%	35.7%	95.0%	47.1%	93.2%
CRC	58.6%	-	50.7%	-	66.2%	-

CRC- colorectal cancer; Sens- sensitivity; Spec-specificity

In a recent publication of Australian Institute of Health and Welfare (AIHW), the sensitivity of iFOBT was reported to be 83% for colorectal cancer (ant stage) detection within the NBCSP.(14) This 'program sensitivity' was measured using the following definitions for the true positive (i.e. screen-detected cancers) and false negative (i.e. interval cancers) of the iFOBT:

- True positive (i.e. screen-detected cancer): Colorectal cancers diagnosed in individuals who participated in the NBCSP and had a positive iFOBT result. Any colorectal cancer diagnosis after a positive screening result, regardless of the time between screening and diagnosis were included in the true positive counts. (14)

- False negative (i.e. interval cancers): Colorectal cancer diagnosed within 2-years in individual who participated in the NBCSP and had a negative iFOBT result. (14)

The differences between the modelled iFOBT's sensitivity in detecting colorectal cancer reported in Table A9 (58.6%) and the data reported by AIHW (83%)(14) is due to different methods (or definition) were used to measure the true positive and false negative of the test by the current study and AIHW. It should be noted that this reported 'program sensitivity' can only be an imperfect estimate of the true cross-sectional sensitivity (defined as ratio of the true positive rate to the sum of the true positive and the false negative rate at the time of screening). Using interval cancers to estimate the false negative rate is expected to inflate sensitivity because interval cancers over the subsequent 2 years are not a perfect surrogate for the actual false negative rate at the time of testing; there may also be slow-growing cancers present at the time of screening that would only become symptomatically apparent after a longer period if missed by the screening test. In order to directly compare the modelled iFOBT test characteristics with the AIHW data, we estimated program sensitivity as an output from the model using the same criteria for false negative outcomes as in the recent AIHW report (i.e. interval colorectal cancer diagnosed within 2-years after a negative iFOBT result); the modelled program sensitivity estimate was 82.5%, very close to the AIHW findings. (14)

Plasma DNA test

The modelled baseline lesion-specific test positive rate of plasma DNA test (Table A10) was obtained by calibrating the individual health state-specific test positive rate to the findings of a multicentre US and German study by Church et al 2014 (Table A11).(15) This study conducted by Church and colleagues recruited 7,920 asymptomatic average-risk individuals who were 50 year-old or older; all study participants had a plasma DNA test (Epi proColon Assay) for SEPT9 biomarker and underwent colonoscopy.(15) The per-person test positive rate, test sensitivity, and test specificity of the modelled plasma DNA test (Table A11 and Table A12) were estimated from the screening (using plasma DNA test) and colonoscopy outcomes of a group of never-screened individuals aged 50-74 years in the model who underwent one round of bowel screening using both plasma DNA test (assuming lesion-specific plasma DNA test provided in Table A10) and colonoscopy (assuming colonoscopy detection rate provided in Table A16). The following definitions were used when estimating the test sensitivity and test specificity of the modelled plasma DNA test in Table A12:

- Individuals who had a positive plasma DNA test result were counted as true positive if their colonoscopy findings met the criteria defined for each category of colonoscopy outcome specified in Table A12, i.e. any adenoma, adenoma >5mm, >10mm, respectively; otherwise, the individuals were counted as false positive.
- Individuals who had a negative plasma DNA test result were counted as false negative if their colonoscopy outcome met the criteria defined for each category of colonoscopy outcome specified in Table A12; otherwise, the individuals were counted as true negative.
- Test sensitivity was calculated by dividing true positive by the sum of true positive and false negative.
- Test specificity was calculated by dividing the true negative by the sum of true negative and false positive.

An alternative set of test assumptions was derived by calibrating the individual health state-specific test positive rate to the findings of a study conducted in a Chinese population by Jin et al 2015 for sensitivity analysis (Table A10 and Table A11).(16) Jin and colleagues reported the test outcomes of 476 participants aged 20-84 years (135 patients with colorectal cancer, 169 patients with adenomatous polyps, 81 with hyperplastic polyps and 91 healthy controls); EPi proColon 2.0 test for SEPT9 testing was used for screening test. (16) Due to the fact that patients with colorectal cancer were over-sampled in this study, (16) the reported combined test sensitivities of adenoma and colorectal cancer were not included as calibration target while deriving the second set of test assumptions for sensitivity analysis.

Table A10 Modelled lesion-specific test positive rate of plasma DNA test

Category	Modelled plasma DNA test positive rate	
	Base case	Sensitivity analysis [a]
Background rate in all individuals [b]	9.1%	9.1%
Additional positive rate per non-AA (any size)	0.0%	9.0%
Additional positive rate per adenoma (any size) with HGD but no villous architecture	4.0%	16.0%
Additional positive rate per adenoma (any size) with villous architecture but no HGD	6.0%	21.0%
Additional positive rate per adenoma (any size) with both HGD and villous architecture	6.0%	21.0%
Additional positive rate per SSA or HP	0%	0%
Additional positive rate for stage 1 CRC	35.0%	60.0%
Additional positive rate for stage 2 CRC	63.0%	80.0%
Additional positive rate for stage 3 CRC	46.0%	80.0%
Additional positive rate for stage 4 CRC	77.0%	100.0%

AA-Advanced adenoma; CRC- colorectal cancer; HGD –high-grade dysplasia; HP- hyperplastic polyp; SSA- sessile serrated adenoma

[a] *Only one alternative set of assumption was assessed in the sensitivity analysis*

[b] *A background positive rate was assumed for all individuals (including perfectly healthy individuals who have no polyps or cancer)*

Table A11 Modelled plasma DNA test positive rate (per person) compared with observed data

Colonoscopy outcome	Base case		Sensitivity analysis [a]	
	Modelled	Church et al 2014(15) (95% CI)	Modelled	Jin et al 2015(16) (95% CI)
No polyps	9.1%	9.1% (7.0-11.3%)	9.5%	N/A
Any adenoma	10.2%	N/A	24.0%	20.7% (15.1-27.3%)
Non-AA	9.2%	6.9% (3.8- 10.5%)	21.3%	N/A
AA	12.8%	11.2% (7.2-15.7%)	31.2%	27.4% (18.7-37.6%)
AA with HGD	13.9%	12.1% (2.5-24.3%)	33.2%	N/A
AA with villous	15.1%	14.3% (6.0-24.3%)	35.8%	N/A
AA > 10 mm	12.4%	9.4% (4.8-14.7%)	30.6%	N/A
Stage I CRC	41.7%	35.0% (13.3-59.6%)	67.7%	66.7% (95% CI not available)
Stage II CRC	66.8%	63.0% (32.5-87.7%)	83.7%	82.6% (95% CI not available)
Stage III CRC	51.7%	46.0% (16.5-85.4%)	83.9%	84.1% (95% CI not available)
Stage IV CRC	78.9%	77.4% (23.7-100.0%)	100%	100.0% (95% CI not available)
CRC overall	49.9%	48.2% (32.4-63.6%)	75.1%	74.8% (67.0-81.6%)

AA-Advanced adenoma; CRC-colorectal cancer; HGD –high-grade dysplasia

[a] *Only one alternative set of assumption was assessed in the sensitivity analysis*

Table A12 Modelled test sensitivity and specificity of plasma DNA test by lesion size (per person)

Colonoscopy outcome	Baseline		Sensitivity analysis [a]	
	Sens	Spec	Sens	Spec
Any adenoma	10.2%	90.9%	24.0%	90.5%
Adenoma > 5mm	11.4%	90.8%	28.4%	88.6%
Adenoma >=10mm	12.4%	90.8%	30.6%	88.0%
CRC	49.9%	-	75.1%	

CRC- colorectal cancer; Sens- sensitivity; Spec-specificity

[a] *Only one alternative set of assumption was assessed in the sensitivity analysis*

Faecal DNA test (fDNA)

The modelled baseline lesion-specific test positive rate of fDNA test (Table A13) was derived by calibrating the individual health state-specific test positive rate to the findings of Imperiale et al 2014 (Table A14).(17) This multicentre US and Canada study conducted by Imperiale and colleagues recruited asymptomatic average-risk individuals aged

between 50 and 84 years; all participants provided a stool specimen for FIT (OC FIT-CHEK, Polymedco) and multitarget stool DNA test (consists of molecular assays for aberrantly methylated *BMP3* and *NDRG4* promoter regions, mutant *KRAS*, and β-actin, as well as immunochemical assay for human hemoglobin) and screening colonoscopy. (17) The study findings were based on the screening outcomes of 9,989 participants.(17) The modelled per-person test positive rate (Table A14) and test sensitivity and specificity (Table A15) were estimated from the screening and colonoscopy outcomes of a group of never-screened individuals aged 50-74 years in the model who underwent one round of screening using both faecal DNA test (assuming lesion-specific faecal DNA test positive rate provided in Table A13) and colonoscopy (assuming colonoscopy detected rate provided in Table A16). The following definitions were used when estimating the test sensitivity and test specificity of the modelled plasma DNA test in Table A15:

- Individuals who had a positive faecal DNA test result were counted as true positive if their colonoscopy findings met the criteria defined for each category of colonoscopy outcome specified in Table A12, i.e. any adenoma, adenoma >5mm, >10mm, respectively; otherwise, the individuals were counted as false positive.
- Individuals who had a negative faecal DNA test result were counted as false negative if their colonoscopy outcome met the criteria defined for each category of colonoscopy outcome specified in Table A12; otherwise, the individuals were counted as true negative.
- Test sensitivity was calculated by dividing true positive by the sum of true positive and false negative.
- Test specificity was calculated by dividing the true negative by the sum of true negative and false positive.

An alternative set of fecal DNA test positive rate, which represents the worst case assumption was derived for sensitivity analysis based on the findings of stool DNA test 1 of Ahlquist et al 2008 (Table A13, Table A14 and Table A15).(18) The study was conducted in US. It recruited asymptomatic average-risk individuals aged between 50 and 80 years; all participants provided stool samples for stool DNA testing and occult blood testing (using Hemoccult and Hemoccult Sensa cards), and underwent colonoscopy.(18) Two different stool DNA testing assays were

examined in the study. The positive rate of stool DNA test 1 assays (based on the test outcomes of 2,497 participants) was found to be significantly lower than the positive rate of stool DNA test 2 assay (based on the test outcomes of 217 participants). (18) The outcome of stool DNA test 1 assays was used for sensitivity analysis.

Table A13 Modelled lesion-specific test positive rate of faecal DNA test

Category	Modelled faecal DNA test positive rate	
	Base case	Sensitivity analysis [a]
Background rate in all individuals [b]	10.0%	4.0%
Additional positive rate per non-AA (any size)	5.0%	0.0%
Additional positive rate per AA (any size) with HGD but no villous architecture	61.0%	26.0%
Additional positive rate per AA (any size) with villous architecture but no HGD	40.0%	20.0%
Additional positive rate per AA (any size) with both HGD and villous architecture	61.0%	26.0%
Additional positive rate per SSA or HP	0%	0%
Additional positive rate for stage 1 CRC	88.0%	23.0%
Additional positive rate for stage 2 CRC	92.0%	23.0%
Additional positive rate for stage 3 CRC	95.0%	23.0%
Additional positive rate for stage 4 CRC	100.0%	23.0%

AA-Advanced adenoma; CRC- colorectal cancer; HGD –high-grade dysplasia; HP- hyperplastic polyp; SSA- sessile serrated adenoma

[a] Only one alternative set of assumption was assessed in the sensitivity analysis

[a] A background positive rate was assumed for all individuals (including perfectly healthy individuals who have no polyps or cancer)

Table A14 Modelled faecal DNA test positive rates (per person) compared with observed data

Colonoscopy outcome	Baseline		Sensitivity analysis [a]	
	Modelled	Imperiale et al 2014(17) (Cologuard)	Modelled	Ahlquist et al 2008(18) (SDT-1)
No polyps	10.3%	10.2% (95% CI: 9.3-11.1%)	4.1%	4% (95%CI: 2-6%)
Non-AA	17.3%	17.2% (95%CI: 15.9-18.6%)	4.3%	4% (95%CI: 3-5%)
AA	43.9%	42.4% (95%CI: 38.9-46.0%)	19.2%	17% (95%CI: 11-23%)
AA with HGD	68.5%	69.2% (95% CI: 52.4-83.0%)	31.0%	N/A
CRC overall	92.4%	92.3% (95%CI: 83.0-97.5%)	28.6%	25% (95%CI: 5-57%)

AA-Advanced adenoma; CI- confidence interval; CRC-colorectal cancer; HGD –high-grade dysplasia

[a] Only one alternative set of assumption was assessed in the sensitivity analysis

Table A15 Modelled test sensitivity and specificity of faecal DNA test by lesion size (per person)

Colonoscopy outcome	Baseline		Sensitivity analysis [a]	
	Sens	Spec	Sens	Spec
Any adenoma	24.4%	89.7%	8.3%	95.9%
Adenoma > 5mm	33.5%	88.3%	13.2%	95.7%
Adenoma >=10mm	39.4%	87.6%	16.6%	95.5%
CRC	92.4%	-	28.6%	-

CRC- colorectal cancer; Sens- sensitivity; Spec-specificity

[a] Only one alternative set of assumption was assessed in the sensitivity analysis

Colonoscopy

The modelled lesion-specific positive rates of colonoscopy are summarised in Table A16. The modelled positive rate of colonoscopy for conventional adenomas, hyperplastic polyps and sessile serrated adenomas were based on the findings of a 2006 systematic review by van Rijn and colleagues.(19) The study found the colonoscopy miss rate for large adenoma (>= 10mm) was 2.1% (95%CI: 0.3-7.3%), for small adenoma (5 -10mm) was 13% (95% CI: 8.0-18.0%), and for diminutive adenoma (< 5 mm) was 26% (95%CI: 27-35%).(19) The miss rate of sessile serrated polpys of any size was assumed to be similar to the miss rate of diminutive adenoma in the model (Table A16). The modelled detection rate of colorectal cancer (any stage) was based on the findings of a 2011 systematic review and meta-analysis conducted by Pickhardt and colleagues, which reported a sensitivity of 94.7% (95% CI: 90.4-97.2%) for colorectal cancer detection.(20) The model assumed the end of caecum was reached in all colonoscopy procedures and the test specificity for detecting polyps and colorectal cancer of colonoscopy was 100% i.e. individuals who have no polyps or cancer in the bowel were assumed to always have a negative colonoscopy outcome. Polypectomy was assumed to be performed on all polyps detected by colonoscopy, except hyperplastic polyps, with 100% completeness. Based on data observed in 2013-2014 in NBCSP, 0.27% individuals undergoing colonoscopy in the model was assumed to experience colonoscopy-related-non-fatal adverse event.(9)

Table A16 Modelled lesion-specific positive rate of colonoscopy

Polyp/cancer	Modelled colonoscopy detection rate		
	Base case	Sensitivity analysis	
		Lower end	Upper end
Diminutive adenoma (<5mm)	79.0%	71.1%	86.9%
Small adenoma (6-9mm)	85.0%	76.5%	93.5%
Large adenoma (>= 10mm)	92.0%	82.8%	100.0%
Sessile serrated polyp (any size)	78.0%	70.2%	85.8%
Hyperplastic polyp (<10 mm)[a]	78.0%	70.2%	85.8%

Hyperplastic polyp (>=10 mm)[a]	92.0%	82.8%	100.0%
Colorectal cancer (any stage)	95.0%	85.5%	100.0%

Taking both the test characteristics of iFOBT and colonoscopy into account, the modelled colonoscopy outcomes among individuals with positive iFOBT were validated to data observed in NBCSP in the period between 2006 and 2014. (9-13) The model validation outcomes were reported elsewhere.18(2) Two alternative colonoscopy test characteristics assuming colonoscopy detection rate increased/decreased by 10% were assessed in sensitivity analysis.

Sigmoidoscopy

The model assumed the end of sigmoid was reached in 80% of the sigmoidoscopy procedures and recto-sigmoid junction was reached in all of the sigmoidoscopy procedures. The lesion-specific detection rate of sigmoidoscopy was assumed to be similar the rated modelled for colonoscopy for polyps in rectum and sigmoid (Table A16). In the strategies assuming sigmoidoscopy screening with, polypectomy was assumed performed on adenoma with size < 5mm detected by sigmoidoscopy; all detection polyps with a size >= 5mm were assumed not to be removed during the follow-up colonoscopy. The modelled per-person test sensitivity and specificity (Table A17) were estimated from the screening and colonoscopy outcomes of a group of never-screened individuals aged 50-74 years in the model who underwent one round of screening using both sigmoidoscopy test (assuming lesion-specific detection rate as per Table A16 for adenoma within the reach of sigmoidocsopy in sigmoid and rectum) and colonoscopy (assuming lesion-specific detection rate as per Table A16). The following definitions were used when estimating the test sensitivity and test specificity of the modelled sigmoidoscopy in Table A15 (note: colonoscopy was assumed to be able to detect polyps in colon and rectum depends on the modelled lesion-specific positive rate; sigmoidosocpy could only detect polyps in rectum or sigmoid within the reach of sigmoidoscopy):

- Individuals who had a lesion detected by sigmoidoscopy were counted as true positive if their colonoscopy findings met the criteria defined for each category of colonoscopy outcome specified in Table A12, i.e. any adenoma, adenoma >5mm, >10mm, respectively; otherwise, the individuals were counted as false positive .
- Individuals who had no lesion detected by sigmoidoscopy were counted as false negative if their colonoscopy outcome met the criteria defined for each category of colonoscopy outcome specified in Table A12; otherwise, the individuals were counted as true negative.

- Test sensitivity was calculated by dividing true positive by the sum of true positive and false negative.
- Test specificity was calculated by dividing the true negative by the sum of true negative and false positive.

Two alternative sets of sigmoidoscopy test characteristics assuming polyp detection rate increased/ decreased by 10% were assessed in sensitivity analysis.

Table A17 Modelled test characteristics of sigmoidoscopy

Test characteristics	Modelled sigmoidoscopy test characteristics		
	Base case	Sensitivity analysis	
		Lower end	Upper end
Specificity [a]	93.2%	93.7%	92.5%
Sensitivity for adenoma of any size [b]	40.9%	37.8%	44.2%
Sensitivity for adenoma >5mm [b]	46.2%	42.8%	49.5%
Sensitivity for adenoma >10mm [b]	47.6%	44.2%	50.9%
Sensitivity for CRC [b]	47.9%	44.7%	50.5%
Completeness	100% reach the recto-sigmoid junction, 80% reach the end of sigmoid, 0% beyond sigmoid	Same as baseline assumption	Same as baseline assumption

[a] *For detecting any adenoma in colon or rectum*
[b] *For all adenomas and CRCs at colon or rectum*

Computed tomography colonography (CTC)

The modelled baseline per-lesion positive rate of CTC test was derived by calibrating the model predictions to the test sensitivity and specificity reported by Johnson et al 2008 (Table A18 and Table A19).(21) The same assumption was used by the modelling evaluation performed for US Service Preventative Task Force when simulating the test accuracy of CTC.(22) The modelled per-person test sensitivity and specificity (Table A19) were estimated from the screening and colonoscopy outcomes of a group of never-screened individuals aged 50-74 years in the model who underwent one round of screening using both CTC (assuming lesion-specific CTC positive rate provided in Table A18) and colonoscopy (assuming colonoscopy detected rate provided in Table A16). The following definitions were used when estimating the test sensitivity and test specificity of the modelled CTC in Table A19:

- Individuals who had a positive CTC were counted as true positive if their colonoscopy findings met the criteria defined for each category of colonoscopy outcome specified in

Table A12, i.e. any adenoma, adenoma >5mm, >10mm, respectively; otherwise, the individuals were counted as false positive.

- Individuals who had a negative CTC result were counted as false negative if their colonoscopy outcome met the criteria defined for each category of colonoscopy outcome specified in Table A12; otherwise, the individuals were counted as true negative.
- Test sensitivity was calculated by dividing true positive by the sum of true positive and false negative.
- Test specificity was calculated by dividing the true negative by the sum of true negative and false positive.

Two alternative test assumptions, representing a 'worst case' and a 'best case' assumption of CTC were derived for sensitivity analyses (Table A18 and Table A19). The 'worst case' assumption was obtained by calibrating the model predicted test sensitivity and specificity to the findings of Cotton et al 2004 (Table A18 and Table A19).(23) The 'best case' assumption was obtained by (i) calibrating the predicted test sensitivity and specificity for detecting adenomas to the upper end of the CI range of the findings of Johnson et al 2008(21), and (ii) calibrating the test sensitivity for colorectal cancer detection to the findings of Pickhardt et al 2011.(20)

Table A18 Modelled per-lesion test positive rate of CTC

Category	Modelled CTC positive rate		
	Baseline	Sensitivity analysis	
		Lower end	Upper end
Background false positive rate in all individuals (per individual) [a]	8%	8%	4%
Positive rate per adenoma 1-5 mm	13%	0%	14%
Positive rate per adenoma 6-9 mm	20%	15%	35%
Positive rate per adenoma >10 mm	84%	47%	95%
Positive rate per small HP	2%	0%	2%
Positive rate per large HP	10%	0%	10%
Positive rate per small SSA	2%	0%	2%
Positive rate per large SSA	10%	0%	10%
Positive rate for CRC (any stage)	84%	70%	95%

[a] A background positive rate was assumed for all individuals (including perfectly healthy individuals who have no polyps or cancer)

Table A19 Modelled per-person test sensitivity and specificity of CTC compared with observed data

Colonoscopy outcome	Baseline		Sensitivity analysis			
			Lower end		Upper end	
	Modelled	Johnson et al 2008(21) (95% CI)	Modelled	Cotton et al 2004(23) (95% CI)	Modelled	Johnson et al 2008(21) & Pickhardt et al 2011(20)
Sensitivity						
Any adenoma	40.1%	N/A	20.2%	N/A	42.3%	N/A
Adenoma > 5 mm	63.8%	65.0% (58.0-73.0%)	39.9%	39.0% (29.6-48.4%)	73.1%	65.0% (58.0-73.0%)
Adenoma >= 10 mm	88.1%	90% (84.0-96.0%)	54.2%	55.0% (39.9-70.0%)	96.3%	90% (84.0-96.0%)
CRC	88.7%	90% (84.0-96.0%) [a]	75.0%	75%	96.5%	96.1% (93.8-97.7%)
Specificity						
Any adenoma	90.0%	N/A	91.8%	N/A	93.8%	N/A
Adenoma > 5 mm	87.4%	89.0% (85.1-92.3%)	91.7%	90.5% (87.9-93.1%)	90.9%	89.0% (85.1-92.3%)
Adenoma >= 10 mm	86.4%	86.0% (81.3-90.0%)	91.9%	96.0% (94.3-97.6%)	89.3%	86.0% (81.3-90.0%)

CRC- colorectal cancer; Sens- sensitivity; Spec-specificity

[a] *Assumed the same test sensitivity as per adenoma >= 10 mm*

Screening participation, compliance to follow-up colonoscopy and compliance to surveillance colonoscopy assumptions

Screening participation rates

A literature review was conducted to review the screening participations of Australian towards screening using iFOBT, pDNA, fDNA, colonoscopy, flexible sigmoidoscopy and CTC in studies published from 2000. Five studies were identified in the literature search (Table A20). The observed screening participations for screening using iFOBT was 27.1% (1 study) (24), for colonoscopy was 16.3-40.1% (3 studies) (24-26), for flexible sigmoidoscopy was 22% (1 study), and for CTC was 16.3-28.4% (3 studies) (24;25;27). No study on the participation of screening using pDNA or fDNA was found in the literature search. Participation for screening using colonoscopy was found to be similar to the rate observed for CTC in two studies that compared the two screening tests. (24;25) One study that compared the participation for iFOBT, colonoscopy and CTC found a lower participation rate in the study arm that offered colonoscopy or CTC for screening (13.6-17.8%) than the study arm that offered iFOBT (27.4%), consistent with the findings of a systematic review of international literature. (24;28)

Table A20 Summary of the screening participations towards screening using iFOBT, pDNA, fDNA, colonoscopy, flexible sigmoidoscopy and CTC observed in five Australian studies

Study	Settings	iFOBT	pDNA	fDNA	COL	FS	CTC
Collett et al 2000 (29), (Australia)	6,446 asymptomatic individuals aged 55-64 years randomly selected from the electoral roll or volunteered to participated in the study after hearing about the program. All study participants were invited for screening with FS	N/A	N/A	N/A	N/A	22%	N/A
Scott et al 2004(25), (Australia)	1,344 study participants (aged 50-54 years and 65-69 years) randomly selected from the parliamentary	N/A	N/A	N/A	16.3%	N/A	18.1%

	electoral roll. The study participants were randomly allocated to one of the three screening strategies: colonoscopy, CTC or the choice of colonoscopy or CTC						
Edward et al 2004 (27), Australia	1,452 study participants (aged 50-54 years and 65-69 years) randomly selected from the Western Australia Electoral Commission database. The study participants were offered screening with CTC	N/A	N/A	N/A	N/A	N/A	28.4%
Corbett et al 2004, (26)(Australia)	A total of 881 individuals aged between 55 and 74 years were invited to screen using colonoscopy: 520 individuals were selection from the electoral roll (ER) and 361 individuals were recruited from the general practice (GP)	N/A	N/A	N/A	35.1% (ER arm) - 40.1% (GP arm)	N/A	N/A
Multicentre Australian Colorectal-neoplasia Screening (MACS) Group 2006(24), Australia	1,679 participants (aged 50-54 years and 65-69 years) who lived within a reasonable proximity to the participating study centers in suburbs of Perth, Adelaide and Melbourne and representing a broad mixture of socioeconomics regions were selected from the	27.4%	N/A	N/A	17.8%	N/A	16.3%

	Commonwealth Electoral Office. Study participants were randomly allocated to one of six strategies: FOBT, FOBT and FS, CTC, colonoscopy, or one of two groups offered a choice of these four screening tests.						

COL- colonoscopy; CTC-computed tomography colonography; fDNA – faecal DNA test; iFOBT -immunochemical faecal occult blood test; FS- flexible sigmoidoscopy; pDNA – plasma DNA test

Three screening participation rates were modelled in the study:

- Scenario 1 (i.e. a perfect scenario) assumed a perfect adherence to screening recommendations and colonoscopy referral for all strategies.
- Scenario 2 assumed an overall ~ 60% screening adherence rate for strategies assumed screening strategies used iFOBT based on a stretched goal of the NBCSP screening participation. Strategies that assumed screening using pDNA or fDNA were assumed to have a similar participation rate as iFOBT screening strategies. Screening participation rate modelled for strategies assuming screening using colonoscopy, sigmoidoscopy, or CTC were ~35% overall, informed by the on the upper end of range observed in of the three tests in the studies summarised in Table A20.
- Scenario 3 assumed an overall ~ 40% screening adherence rate for strategies assumed screening strategies used iFOBT based on the currently observed NBCSP screening participation rate.(9) Strategies that modelled screening using pDNA or fDNA were assumed to have a similar participation rate as iFOBT screening strategies. Screening participation rate modelled for colonoscopy, sigmoidoscopy, or CTC screening strategies were ~15% overall, informed by the lower end of range observed in of the three tests in the studies summarised in Table A20.

The overall screening participation rates mentioned above for each scenario incorporated two different screening participation assumptions – the screening initiation rates and screening re-attendance rates. The modelled screening initiation rates refer to the screening participation among individuals who have never participated in NBCSP in the past. Screening re-attendance or re-screening rates refer to the screening participation rates among individuals who have participated in

NBCSP at least once in the past. More details of screening initiation rates and screening re-attendance rates are provided in the sections below.

Screening initiation rates

The screening initiation assumptions are summarised in Table A21. Screening invitation rate in this study is referring to the screening participation rate among individuals who have never participated in screening previously. We assumed the screening initiation rate of the second invitation round was half of the rate modelled for first invitation round for each strategy and the uptake rate in the subsequent rounds was half of the rate modelled for second invitation round. This assumption was made based on the screening participation rate of Round 2 NBSCP invitation observed among the individuals who did not participate in Round 1 screening compared to the update rate of Round 1 NBCSP invitation. (14)

Table A21. Screening initiation assumptions

Screening uptake rate	Scenario 1 (perfect adherence)	Scenario 2 (high adherence)	Scenario 3 (low adherence)
First invitation	100%	57.0% for strategies use iFOBT, pDNA test or fDNA test; 35.0% for strategies use COL, SIG or CTC	29% for strategies use iFOBT, pDNA test or fDNA test;(30) 15% for strategies use COL, SIG or CTC
Second invitation	100%	28.5% for strategies use iFOBT, pDNA test or fDNA test; 17.5% for strategies use COL, SIG or CTC	14.5% for strategies use iFOBT, pDNA test or fDNA test; 7.5% for strategies use COL, SIG or CTC
Third invitation	100%	14.3% for strategies use iFOBT, pDNA test or fDNA test; 8,8 % for strategies use COL, SIG or CTC	7.3% for strategies use iFOBT, pDNA test or fDNA test; 3.8% for strategies use COL, SIG or CTC

COL – colonoscopy; CTC - computed tomographic colonography; iFOBT – immunochemical faecal occult blood test; fDNA – faecal DNA test; pDNA – plasma DNA test; SIG – sigmoidoscopy

Table A22 shows the modelled proportion of a birth cohort being screened at least once in the lifetime of varies among strategies modelled in each scenario (except Scenario 1). These differences among the proportion estimated for the strategies were due to (i) the variation in maximum lifetime number of screening round associated with the screening strategies due to different screening interval was modelled, and (ii) imperfect screening initiation rate.

Table A22. Modelled proportion of a birth cohort being screened at least once in the lifetime of each strategy in scenario 1, 2 and 3

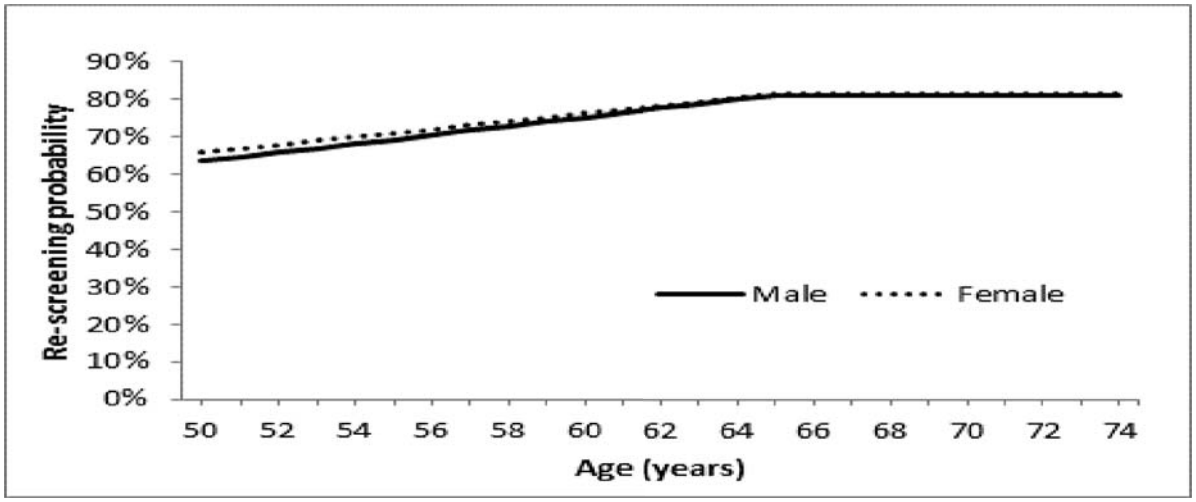
	Maximum lifetime number of screening round [a]	Scenario 1 (perfect adherence)	Scenario 2 ('high adherence)	Scenario 3 ('low' adherence)
iFOBT2y	13	100%	>94%	>71%
iFOBT1y	25	100%	>99%	90%
plasmaDNA2y	13	100%	>94%	>71%
fDNA2y	13	100%	>94%	>71%
fDNA5y	5	100%	59%	49%
COL10y	3	100%	51%	24%
SIG10y	3	100%	51%	24%
CTC10y	3	100%	51%	24%
SIG@60	1	100%	35%	15%
SIG@55_iFOBT2y @60To74	9	100%	81%	52%
COL@50_iFOBT2y @52To74	13	100%	>94%	>71%
iFOBT2y+ SIG@50	13	100%	>94%	>71%
iFOBT2y+SIG @54_64_74	13	100%	>94%	>71%
iFOBT2y+ plasmaDNA	13	100%	>99%	96%

[a] *Assumed perfect adherence to screening invitation*

Screening re-attendance rate (re-screening probabilities)

Of those who have previously participated in the screening program, the re-attendance rate of the subsequent screening invitations (re-screening probability) modelled for Scenario 2 (low adherence) and 3 (high adherence) was derived based on the screening participations rates observed among 55 and 60 years individuals in 2013 who had attended screening in the first invitation round (Figure A17).(9) Detailed method used to derive the re-screening probabilities has been described elsewhere. (2) The sex- and age-standardised re-screening probabilities in 50-74 years was 75% in the model.

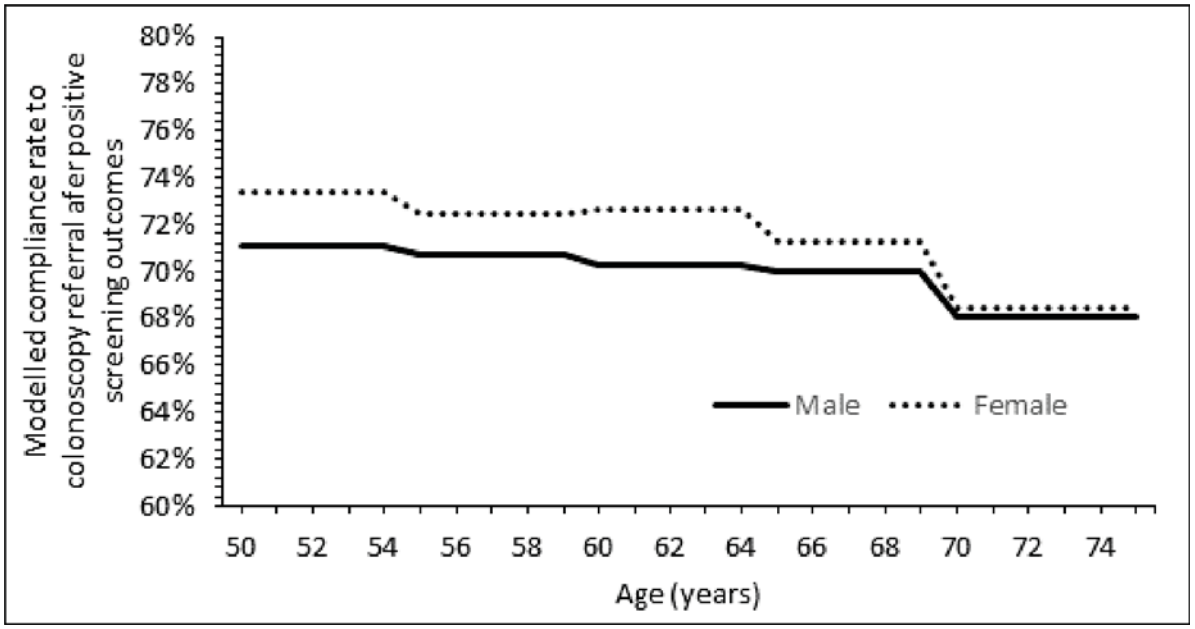
Figure A17 Modelled re-screening probabilities in men and women who have previously participated in NBCSP



Colonoscopy compliance rates

The compliance rates to colonoscopy referral after a positive screening result modelled for Scenario 2 (low adherence) and 3 (high adherence) was based on rates observed in the NBCSP in 2015 (Figure A18). (30) The sex- and age-standardised (in 50-74 years) compliance rate was 71% in the model.

Figure A18 Modelled compliance rate to colonoscopy referral after a positive screening result in men and women



As there is currently no data available to inform the compliance rate of surveillance colonoscopy in Australia, the compliance rate for surveillance was assumed to be 80% for Scenario 2 and 3 in this study. This assumption is consistent with a previous study that estimated the effectiveness of bowel cancer screening in Australia.(31)

Cost assumptions

The modelled unit item cost assumptions are summarised in Table A23.

Table A23. Summary of modelled unit item cost assumptions

Unit item cost	Modelled value	Reference
iFOBT kit sent	A$10[a]	Assumption
iFOBT kit received	A$22[b]	Assumption
Invitation letter (for non-iFOBT screening methods)	A$0.50	Assumption
pDNA test	A$250	Assumption
fDNA test [c]	A$877.50	Maximum out-of-pocket cost (USD 649) of Cologuard in US market (32)
SIG	A$1,200	Assumption
CTC	A$520	MBS item 56553 (33)
GP consultation for abnormal screening result	A$37.05	MBS item 23 (33)
COL without complication [e]	A$1,800	Assumption
COL with complication [e]	A$14,838.91	DRG-AG item G48A [f](34)
Stage 1 CRC treatment	A $36,914	Pignone et al 2011 (consistent with the findings of Ananda et al 2016) (35;36)
Stage 2 CRC treatment	A$56,589	
Stage 3 CRC treatment	A$88,700	
Stage 4 CRC treatment	A$73,402	

COL – colonoscopy; CTC - computed tomographic colonography; iFOBT – immunochemical faecal occult blood test; fDNA – faecal DNA test; GP – general practitioner

[a] Includes estimated cost of one-way postage ($2) and an iFOBT test kit ($8)

[b] Includes estimated cost of one-way postage for the return of iFOBT test ($2) and cost of an iFOBT test being analysed in the lab ($20)

[c] Assume the fDNA cost US$649 in the base case (exchange rate used: US$1 USD = A$1.3521, 17 June 2016)

[e] With/without polypectomy

Costs associated with iFOBT screening

A home-based testing was assumed for the iFOBT screening. The model assumed a cost of $10.00 ($2.00 for postage and $8.00 for an iFOBT kit) for each iFOBT kit sent out to the eligible screening participants (all alive individuals in the eligible age in the model regardless of the screening history). Each iFOBT kit returned was assumed to be associated with a cost of $22.00 ($2.00 for postage and $20.00 for the test kit being analysed in the laboratory).

Costs associated with pDNA screening

The model assumed a cost of $0.50 for each invitation letter sent out to the eligible screening participants (all alive individuals in the eligible age in the model regardless of the screening history).

In this study, pDNA screening was assumed to be conducted at the General Practitioner (GP) clinic (i.e. individuals would need to visit GP to take a pDNA test). Therefore, a cost of GP visit ($37.05) and a cost of pDNA test ($250) were assumed for each individual who participated in pDNA screening.

Costs associated with fDNA screening

The model assumed a cost of $0.50 for each invitation letter sent out to the eligible screening participants (all alive individuals in the eligible age in the model regardless of the screening history). In this study, fDNA screening was assumed to be conducted at the GP clinic (i.e. individuals would need to visit GP to take a fDNA test). Therefore, a cost of GP visit ($37.05) and a cost of fDNA test ($877.50) were assumed for each individual who participated in fDNA screening.

Costs associated with sigmoidoscopy screening

The model assumed a cost of $0.50 for each invitation letter sent out to the eligible screening participants (all alive individuals in the eligible age in the model regardless of the screening history). In this study, we assumed that individuals would need to visit GP to obtain a referral for sigmoidoscopy screening before attending a sigmoidoscopy assessment. Therefore, a cost of GP visit ($37.05) and a cost of screening sigmoidoscopy ($1,200.00) were assumed for each individual who participated in sigmoidoscopy screening.

Costs associated with CTC screening

The model assumed a cost of $0.50 for each invitation letter sent out to the eligible screening participants (all alive individuals in the eligible age in the model regardless of the screening history). In this study, we assumed individuals would need to visit GP to obtain a referral for CTC screening before attending a CTC assessment. Therefore, a cost of GP visit ($37.05) and a cost of screening CTC ($520.00) were assumed for each individual who participated in CTC screening.

Costs associated with colonoscopy screening

The model assumed a cost of $0.50 for each invitation letter sent out to the eligible screening participants (all alive individuals in the eligible age in the model regardless of the screening history). In this study, we assumed individuals would need to visit GP to obtain a referral for colonoscopy

screening before attending a colonoscopy assessment. Therefore, a cost of GP visit ($37.05) and a cost of screening colonoscopy ($1,800 if no complication; $14,838,91 with complication) were assumed for each individual who participated in colonoscopy screening.

Costs associated with colonoscopy assessment to follow-up abnormal screening outcome or for surveillance

Individuals under surveillance or with abnormal screening (including iFOBT, pDNA, fDNA, sigmoidoscopy, and CTC) result would need to visit GP to discuss the result of the screening and to obtain a referral for colonoscopy. Therefore, a cost of GP visit ($37.05) and a cost of screening colonoscopy ($1,800 if no complication; $14,838,91 with complication) were assumed for each individual who had a colonoscopy assessment to follow-up abnormal screening outcome or for the purpose of surveillance in the model.

Costs associated with colorectal cancer treatment

The stage-specific cost of colorectal cancer treatment (Table A23) was obtained from Pignone et al 2011 and inflated to 2014 value, which is consistent with the finding of a recent published Australian study.(35;36) The cost was applied during the first year when cancer was diagnosed in the model.

Additional model base case outcomes

Cost-effectiveness

Model-estimated discounted costs, discounted life-years and the cost-effectiveness ratio compared to no screening of each strategy are shown in Table A24, Table A25 and Table A26.

Table A24. Model-estimated discounted costs, discounted life-years, and cost-effectiveness ratio compared to no screening for each strategy in Scenario 1 (perfect adherence)

Strategy name	Discounted lifetime cost [a]	Discounted life-years [a]	*CER ($ per life-year saved)* [b]
No Screening	$1,187	37.3941	-
iFOBT2y	$1,415	37.4322	$5,981
iFOBT1y	$1,772	37.4362	$13,879
plasmaDNA2y	$2,681	37.4291	$42,684
fDNA5y	$2,909	37.4302	$47,733
COL10y	$2,307	37.4299	$31,323
SIG10y	$2,295	37.4196	$43,530
CTC10y	$1,592	37.4223	$14,358
SIG@60	$1,597	37.4118	$23,239
SIG@55_iFOBT2y@60To74	$1,861	37.4255	$21,478
COL@50_iFOBT2y@52To74	$2,323	37.4362	$26,990
iFOBT2y+ SIG@50	$2,250	37.4350	$26,011
iFOBT2y+SIG@54_64_74	$2,590	37.4350	$34,279
iFOBT2y+plasmaDNA	n/a [c]	n/a [c]	n/a [c]

CER- cost-effectiveness ratio; COL- colonoscopy; CTC – computed tomographic colonography; fDNA – faecal DNA test; iFOBT – Immunochemical faecal occult blood test; SIG-sigmoidoscopy

[a] Average number estimated in the lifetime of an individual, discounted by 5% from 40 years.

[b] Compared with no screening.

[c] This strategy is not applicable in Scenario 1 because there are no under-screened individuals given the assumption of perfect adherence to screening, follow-up and surveillance recommendations.

Table A25. Model-estimated discounted costs, discounted life-years, and cost-effectiveness ratio compared to no screening for each strategy in Scenario 2 ('high' adherence)

Strategy name	Discounted lifetime cost [a]	Discounted life-years [a]	*CER ($ per life-year saved)* [b]
No Screening	$1,187	37.3941	-
iFOBT2y	$1,261	37.4185	$3,037
iFOBT1y	$1,434	37.4277	$7,357
plasmaDNA2y	$2,075	37.4144	$43,826
fDNA5y	$2,149	37.4127	$51,748
COL10y	$1,579	37.4088	$26,719
SIG10y	$1,571	37.4029	$43,907
CTC10y	$1,333	37.4028	$16,700

SIG@60	$1,322	37.3989	$28,108
SIG@55_iFOBT2y@60To74	$1,376	37.4068	$14,831
COL@50_iFOBT2y@52To74	$1,557	37.4230	$12,818
iFOBT2y+ SIG@50	$1,410	37.4194	$8,815
iFOBT2y+SIG@54_64_74	$1,541	37.4201	$13,639
iFOBT2y+plasmaDNA	$1,324	37.4198	$5,339

CER- cost-effectiveness ratio; COL- colonoscopy; CTC – computed tomographic colonography; fDNA – faecal DNA test; iFOBT – Immunochemical faecal occult blood test; SIG-sigmoidoscopy
[a] Average number estimated in the lifetime of an individual, discounted by 5% from 40 years.
[b] Compared with no screening.

Table A26. Model-estimated discounted costs, discounted life-years, and cost-effectiveness ratio compared to no screening for each strategy in Scenario 3 ('low' adherence)

Strategy name	Discounted lifetime cost [a]	Discounted life-years [a]	*CER ($ per life-year saved)* [b]
No Screening	$1,187	37.3941	-
iFOBT2y	$1,236	37.4105	$2,984
iFOBT1y	$1,367	37.4198	$7,023
plasmaDNA2y	$1,755	37.4074	$42,663
fDNA5y	$1,732	37.4049	$50,356
COL10y	$1,362	37.4012	$24,791
SIG10y	$1,361	37.3980	$45,421
CTC10y	$1,252	37.3983	$15,326
SIG@60	$1,245	37.3964	$25,244
SIG@55_iFOBT2y@60To74	$1,271	37.4013	$11,694
COL@50_iFOBT2y@52To74	$1,366	37.4136	$9,221
iFOBT2y+ SIG@50	$1,270	37.4111	$4,914
iFOBT2y+SIG@54_64_74	$1,324	37.4113	$7,943
iFOBT2y+plasmaDNA	$1,311	37.4126	$6,702

CER- cost-effectiveness ratio; COL- colonoscopy; CTC – computed tomographic colonography; fDNA – faecal DNA test; iFOBT – Immunochemical faecal occult blood test; SIG-sigmoidoscopy
[a] Average number estimated in the lifetime of an individual, discounted by 5% from 40 years.
[b] Compared with no screening.

Number-needed-to-colonoscope (NNC)

The model estimated number-needed-to-scope (NNC) to prevent one colorectal cancer case or colorectal cancer death, compared to 2-yearly iFOBT screening are shown in Table A27, Table A28 and Table A29.

Table A27. Model-estimated number-needed-to-scope (NNC) to prevent one colorectal cancer case or colorectal cancer death, compared to 2-yearly iFOBT screening (current program from 2020) in Scenario 1 (perfect adherence)

Strategy name	CRC cases	CRC deaths	NNC to prevent one CRC case	NNC to prevent one CRC death
iFOBT2y	3,214	621	-	-
iFOBT1y	2,391	420	65	263
plasmaDNA2y	4,341	854	More cancers	More deaths
fDNA5y	3,944	839	More cancers	More deaths
COL10y	1,966	453	152	1,127
SIG10y	3,237	1,050	More cancers	More deaths
CTC10y	3,752	896	More cancers	More deaths
SIG@60	4,689	1,639	More cancers	More deaths
SIG@55_iFOBT2y@60To74	3,119	728	-47 [b]	More deaths
COL@50_iFOBT2y@52To74	2,519	505	137	817
iFOBT2y+ SIG@50	2,746	543	46	273
iFOBT2y+SIG@54_64_74	2,075	410	56	302
iFOBT2y+plasmaDNA	n/a	n/a	n/a	n/a

COL- colonoscopy; CTC - computed tomographic colonography; fDNA- faecal DNA test; iFOBT-Immunochemical faecal occult blood test; pDNA- plasma DNA test; prev – prevented; SIG-sigmoidoscopy.

[a] Number of colonoscopies, colorectal cancer cases and colorectal cancer deaths per 100,000 persons alive at 40 years were used for the NNC calculations.

[b] This strategy was predicted to be associated with lower number of incident colorectal cancer cases and lower number of colonoscopies when compared to 2-yearly iFOBT screening

Table A28. Model-estimated number-needed-to-scope (NNC) to prevent one colorectal cancer case or colorectal cancer death, compared to 2-yearly iFOBT screening (current program from 2020) in Scenario 2 ('high' adherence)

Strategy name	CRC cases	CRC deaths	NNC to prevent one CRC case	NNC to prevent one CRC death
iFOBT2y (current program)	4,810	1,296	-	-
iFOBT1y	3,548	776	31	76
plasmaDNA2y	5,899	1,627	More cancers	More deaths
fDNA5y	5,824	1,797	More cancers	More deaths
COL10y	5,219	1,810	More cancers	More deaths
SIG10y	6,142	2,229	More cancers	More deaths
CTC10y	6,486	2,233	More cancers	More deaths
SIG@60	6,922	2,563	More cancers	More deaths
SIG@55_iFOBT2y@60To74	5,844	1,900	More cancers	More deaths
COL@50_iFOBT2y@52To74	4,480	1,204	98	353
iFOBT2y+ SIG@50	4,692	1,267	26	105
iFOBT2y+SIG@54_64_74	4,305	1,159	32	117
iFOBT2y+plasmaDNA	4,771	1,260	61	67

COL- colonoscopy; CTC - computed tomographic colonography; fDNA- faecal DNA test; iFOBT-Immunochemical faecal occult blood test; pDNA- plasma DNA test; prev – prevented; SIG-sigmoidoscopy.

[a] Number of colonoscopies, colorectal cancer cases and colorectal cancer deaths per 100,000 persons alive at 40 years were used for the NNC calculations.

Table A29. Model-estimated number-needed-to-scope (NNC) to prevent one colorectal cancer case or colorectal cancer death, compared to 2-yearly iFOBT screening (current program from 2020) in Scenario 3 ('low' adherence)

Strategy name	CRC cases	CRC deaths	NNC to prevent one CRC case	NNC to prevent one CRC death
iFOBT2y	5,644	1,755	-	-
iFOBT1y	4,317	1,137	28	60
plasmaDNA2y	6,451	1,999	More cancers	More deaths
fDNA5y	6,566	2,229	More cancers	More deaths
COL10y	6,566	2,392	More cancers	More deaths
SIG10y	6,970	2,584	More cancers	More deaths
CTC10y	7,123	2,579	More cancers	More deaths
SIG@60	7,359	2,748	More cancers	More deaths
SIG@55_iFOBT2y@60To74	6,637	2,309	More cancers	More deaths
COL@50_iFOBT2y@52To74	5,447	1,675	76	188
iFOBT2y+ SIG@50	5,627	1,738	37	38
iFOBT2y+SIG@54_64_74	5,482	1,702	32	99
iFOBT2y+plasmaDNA	5,546	1,678	38	48

COL- colonoscopy; CTC - computed tomographic colonography; fDNA- faecal DNA test; iFOBT-Immunochemical faecal occult blood test; pDNA- plasma DNA test; prev – prevented; SIG-sigmoidoscopy.

[a] Number of colonoscopies, colorectal cancer cases and colorectal cancer deaths per 100,000 persons alive at 40 years were used for the NNC calculations.

Sensitivity analyses outcomes

Table A30 summarises the strategies identified on the cost-effectiveness frontier (i.e. dominating strategies) in each category explored in the one-way sensitivity analysis. The strategies identified on the cost-effectiveness frontier in all sensitivity analyses were (in the order of increasing effectiveness) iFOBT2y and iFOBT1y, similar to the baseline findings. COL@50_iFOBT2y@52To74 was identified as the third (last) strategy on the frontier in some cases (Table A30). iFOBT2y (i.e. current program) was the only strategy found to be cost-effective in sensitivity analyses in the context of an indicative willingness-to-pay (WTP) threshold of A$50,000/life-year saved in Australia, associated with ICER of A$1,106-7,546/life-year saved. No other strategies identified on the frontier were considered cost-effective given the WTP threshold.

Table A30 Strategies identified on the cost-effectiveness frontier in the one-way sensitivity analysis

Category	Strategy/ICER	Strategies on cost-effectiveness frontier		
		1st	2nd	3rd
Baseline	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) iFOBT $18	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$5,381	$98,583	$1,674,850
(Alt) pDNA cost $125	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) fDNA cost $400	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) SIG cost $1,000	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) SIG cost $1,800	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) CTC cost $720	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) COL cost $1,440	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$2,344	$72,922	$1,782,001
(Alt) COL cost $2,500	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$12,640	$138,404	$1,296,423
(Alt) Lower cancer treatment cost	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$13,562	$101,685	$10,974,031
(Alt) Higher cancer treatment cost	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$4,420	$82,727	$2,188,450
(Alt) Lower COL test positive rate	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$7,031	$80,279	$2,344,442
(Alt) Higher COL test positive rate	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$5,138	$90,549	$1,662,330

(Alt) Lower non-fatal COL adverse event rate	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$5,748	$82,207	$21,453,439
(Alt) Higher non-fatal COL adverse event rate	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,933	$89,895	N/A
(Alt) Higher fatal COL adverse event rate	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,982	$88,698	N/A
(Alt) Lower iFOBT test positive rate	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$5,381	$56,745	$772,787
(Alt) Higher iFOBT test positive rate	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$6,483	$131,182	N/A
(Alt) pDNA test characteristics	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) fDNA test	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$25,195	$87,567	N/A
(Alt) Lower SIGpositive rate	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) Higher SIG positive rate	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) Lower CTC positive rate	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) Higher CTC positive rate	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$5,938	$87,524	N/A
(Alt) Less aggressive NH	Strategy name	iFOBT2y	iFOBT1y	N/A
	ICER	$8,983	$81,124	N/A
(Alt) More aggressive NH	Strategy name	iFOBT2y	iFOBT1y	COL@50_iFOBT2y@52To74
	ICER	$3,858	$58,319	$317,546

Alt- althernative assumption; COL – colonoscopy; CTC - computed tomographic colonography; iFOBT – immunochemical faecal occult blood test; fDNA – faecal DNA test; N/A- not applicable; pDNA-plasma DNA test; SIG – sigmoidoscopy

[a] *Compared to no screening*

Detailed estimated discounted lifetime cost, discounted life-years and incremental cost-effectiveness ratio (ICER) for each strategy in the one-way sensitivity analysis are provided in Table A31 - Table A55 below. Strategies presented in Table A31 to Table A55 are sorted in the ascending order according to life-years value. Strategies that predicted a higher lifetime cost than any of the more effective strategies (i.e. strategy estimated with more life-years) were considered 'dominated' in the analysis. The 'dominated' strategies were strategies that are more costly and less effective than other strategies included in the evaluation and therefore considered not cost-effective. ICER was calculated for each dominating strategy by dividing the incremental cost by the incremental life-years from the next less effective dominating strategy identified in the analysis. Of these strategies, strategies that associated with a higher ICER than the next most effective strategy were considered

as ‘extended dominated’. If ‘extended dominated’ strategy was found in the analysis, ICERs were re-calculated among the remaining dominating strategies after the ‘extended dominated’ strategy was excluded.

Alternative iFOBT test cost

Table A31 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming each iFOBT test kit received cost $18

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
SIG10y	$2,295	37.41958	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,897	37.42571	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y	$1,393	37.43243	$5,381
iFOBT2y+ SIG@50	$2,272	37.43509	Dominated
iFOBT2y+SIG@54_64_74	$2,667	37.43527	Dominated
iFOBT1y	$1,748	37.43603	$98,583
COL@50_iFOBT2y@52To74	$2,313	37.43636	$1,674,850

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative pDNA test cost

Table A32 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming each pDNA test cost $125

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
SIG10y	$2,295	37.41958	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,861	37.42550	Dominated
plasmaDNA2y	$2,199	37.42896	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,250	37.43497	Dominated
iFOBT2y+SIG@54_64_74	$2,590	37.43504	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio

[a] *Strategies sorted by life-years*
[b] *Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.*

Alternative fDNA test cost

Table A33 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming each fDNA test cost $400

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
SIG10y	$2,295	37.41958	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,861	37.42550	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,055	37.43024	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,250	37.43497	Dominated
iFOBT2y+SIG@54_64_74	$2,590	37.43504	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio
[a] *Strategies sorted by life-years*
[b] *Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.*

Alternative sigmoidoscopy test cost

Table A34 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming each sigmoidoscopy cost $1,000

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,527	37.41157	Dominated
SIG10y	$2,158	37.41970	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,811	37.42562	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,176	37.43511	Dominated
iFOBT2y+SIG@54_64_74	$2,529	37.43532	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio

[a] *Strategies sorted by life-years*
[b] *Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.*

Table A35 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming each sigmoidoscopy cost $1,800

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,807	37.41159	Dominated
SIG10y	$2,816	37.41979	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$2,177	37.42564	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,622	37.43507	Dominated
iFOBT2y+SIG@54_64_74	$3,138	37.43523	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio
[a] *Strategies sorted by life-years*
[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 year

Alternative CTC test cost

Table A36 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming each CTC cost $720

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
SIG10y	$2,295	37.41958	Dominated
CTC10y	$1,759	37.42247	Dominated
SIG@55_iFOBT2y@60To74	$1,861	37.42550	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,250	37.43497	Dominated
iFOBT2y+SIG@54_64_74	$2,590	37.43504	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio
[a] *Strategies sorted by life-years*
[b] *Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.*

Alternative colonoscopy cost

Table A37 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming each colonoscopy cost $1,440

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,533	37.41157	Dominated
SIG10y	$2,197	37.41954	Dominated
CTC10y	$1,523	37.42250	Dominated
SIG@55_iFOBT2y@60To74	$1,772	37.42569	Dominated
plasmaDNA2y	$2,518	37.42808	Dominated
COL10y	$1,953	37.43059	Dominated
fDNA5y	$2,785	37.43061	Dominated
iFOBT2y (current program)	$1,277	37.43233	$2,344
iFOBT2y+ SIG@50	$2,102	37.43492	Dominated
iFOBT2y+SIG@54_64_74	$2,456	37.43534	Dominated
iFOBT1y	$1,565	37.43629	$72,922
COL@50_iFOBT2y@52To74	$1,982	37.43652	$1,782,001

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A38 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming each colonoscopy cost $2,500

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,725	37.41164	Dominated
SIG10y	$2,569	37.41965	Dominated
CTC10y	$1,783	37.42231	Dominated
SIG@55_iFOBT2y@60To74	$2,156	37.42569	Dominated
plasmaDNA2y	$3,009	37.42826	Dominated
COL10y	$2,995	37.42999	Dominated
fDNA5y	$3,138	37.43054	Dominated
iFOBT2y (current program)	$1,670	37.43231	$12,640
iFOBT2y+SIG@54_64_74	$3,118	37.43512	Dominated
iFOBT2y+ SIG@50	$2,649	37.43515	Dominated
iFOBT1y	$2,169	37.43592	$138,404
COL@50_iFOBT2y@52To74	$2,983	37.43654	$1,296,423

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative cancer treatment cost

The 'lower' colorectal cancer treatment cost assessed in the sensitivity assumed A$29,558 for stage 1 colorectal cancer, A$57,511 for stage 2 colorectal cancer, A$44,422 for stage 3 colorectal cancer, and A$10,798 for stage 4 colorectal cancer, based on the findings of O'Leary et al 2004.(37) This colorectal cancer treatment cost were assumed by a number of prior analysis that evaluated the cost-effectiveness of bowel cancer screening in Australia. (37;38)

The 'higher' colorectal cancer treatment cost assessed in the sensitivity assumed A$40,606 for stage 1 colorectal cancer, A$62,248 for stage 2 colorectal cancer , A$97,570 for stage 3 colorectal cancer, and A$80,74 for stage 4 colorectal cancer i.e. a 10% increased from baseline assumption.

Table A39 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming lower cancer treatment cost

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$723	37.39459	-
SIG@60	$1,282	37.41169	Dominated
SIG10y	$2,081	37.41970	Dominated
CTC10y	$1,389	37.42246	Dominated
SIG@55_iFOBT2y@60To74	$1,705	37.42551	Dominated
plasmaDNA2y	$2,481	37.42781	Dominated
COL10y	$2,154	37.43013	Dominated
fDNA5y	$2,707	37.43038	Dominated
iFOBT2y (current program)	$1,241	37.43275	$13,562
iFOBT2y+ SIG@50	$2,138	37.43513	Dominated
iFOBT2y+SIG@54_64_74	$2,547	37.43544	Dominated
iFOBT1y	$1,634	37.43661	$101,685
COL@50_iFOBT2y@52To74	$2,184	37.43666	$10,974,031

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A40 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming higher cancer treatment cost

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,306	37.39443	-
SIG@60	$1,680	37.41169	Dominated
SIG10y	$2,388	37.41965	Dominated
CTC10y	$1,682	37.42250	Dominated
SIG@55_iFOBT2y@60To74	$1,963	37.42557	Dominated
plasmaDNA2y	$2,755	37.42869	Dominated
COL10y	$2,357	37.42969	Dominated
fDNA5y	$2,974	37.43044	Dominated
iFOBT2y (current program)	$1,474	37.43251	$4,420

iFOBT2y+ SIG@50	$2,338	37.43505	Dominated
iFOBT2y+SIG@54_64_74	$2,726	37.43533	Dominated
iFOBT1y	$1,818	37.43666	$82,727
COL@50_iFOBT2y@52To74	$2,368	37.43692	$2,188,450

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative colonoscopy test characteristics

See Table A16 for more information on the 'lower' and 'higher' colonoscopy test positive rate assessed in the sensitivity analysis.

Table A41 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming lower colonoscopy test positive rate

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,604	37.41107	Dominated
SIG10y	$2,334	37.41906	Dominated
CTC10y	$1,638	37.42071	Dominated
SIG@55_iFOBT2y@60To74	$1,920	37.42457	Dominated
plasmaDNA2y	$2,713	37.42619	Dominated
fDNA5y	$2,936	37.42800	Dominated
COL10y	$2,334	37.42834	Dominated
iFOBT2y (current program)	$1,440	37.43011	$7,031
iFOBT2y+ SIG@50	$2,310	37.43358	Dominated
iFOBT2y+SIG@54_64_74	$2,703	37.43390	Dominated
iFOBT1y	$1,802	37.43461	$80,279
COL@50_iFOBT2y@52To74	$2,351	37.43484	$2,344,442

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A42 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming higher colonoscopy test positive rate

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,591	37.41195	Dominated
SIG10y	$2,315	37.42009	Dominated
CTC10y	$1,591	37.42355	Dominated
SIG@55_iFOBT2y@60To74	$1,890	37.42635	Dominated
plasmaDNA2y	$2,667	37.42949	Dominated
fDNA5y	$2,888	37.43116	Dominated
COL10y	$2,279	37.43177	Dominated

iFOBT2y (current program)	$1,390	37.43364	$5,138
iFOBT2y+ SIG@50	$2,270	37.43604	Dominated
iFOBT2y+SIG@54_64_74	$2,665	37.43615	Dominated
iFOBT1y	$1,748	37.43758	$90,549
COL@50_iFOBT2y@52To74	$2,299	37.43792	$1,662,330

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A43 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming a 0.15% of non-fatal adverse event rate was associated with each colonoscopy

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,595	37.41162	Dominated
SIG10y	$2,317	37.41970	Dominated
CTC10y	$1,609	37.42241	Dominated
SIG@55_iFOBT2y@60To74	$1,897	37.42563	Dominated
plasmaDNA2y	$2,678	37.42809	Dominated
fDNA5y	$2,905	37.43022	Dominated
COL10y	$2,290	37.43048	Dominated
iFOBT2y (current program)	$1,405	37.43199	$5,748
iFOBT2y+ SIG@50	$2,280	37.43510	Dominated
iFOBT2y+SIG@54_64_74	$2,673	37.43531	Dominated
iFOBT1y	$1,761	37.43633	$82,207
COL@50_iFOBT2y@52To74	$2,311	37.43635	$21,453,439

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A44 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming a 0.35% of non-fatal adverse event rate was associated with each colonoscopy

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,601	37.41143	Dominated
SIG10y	$2,326	37.41982	Dominated
CTC10y	$1,615	37.42236	Dominated
SIG@55_iFOBT2y@60To74	$1,905	37.42560	Dominated
plasmaDNA2y	$2,691	37.42801	Dominated
fDNA5y	$2,914	37.42997	Dominated
COL10y	$2,315	37.43046	Dominated
iFOBT2y (current program)	$1,415	37.43249	$5,933
iFOBT2y+ SIG@50	$2,291	37.43522	Dominated

iFOBT2y+SIG@54_64_74	$2,687	37.43539	Dominated
COL@50_iFOBT2y@52To74	$2,336	37.43640	Dominated
iFOBT1y	$1,778	37.43653	$89,895

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A45 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming a 0.01% of fatal adverse event rate was associated with each colonoscopy

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,598	37.41141	Dominated
SIG10y	$2,323	37.41946	Dominated
CTC10y	$1,612	37.42229	Dominated
SIG@55_iFOBT2y@60To74	$1,902	37.42515	Dominated
plasmaDNA2y	$2,682	37.42829	Dominated
COL10y	$2,302	37.42924	Dominated
fDNA5y	$2,907	37.43006	Dominated
iFOBT2y (current program)	$1,413	37.43193	$5,982
iFOBT2y+ SIG@50	$2,288	37.43429	Dominated
iFOBT2y+SIG@54_64_74	$2,683	37.43448	Dominated
COL@50_iFOBT2y@52To74	$2,320	37.43580	Dominated
iFOBT1y	$1,768	37.43594	$88,698

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative iFOBT test characteristics

See Table A16 for more information on the 'lower' and 'higher' iFOBT test positive rate assessed in the sensitivity analysis.

Table A46 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming lower iFOBT test positive rate

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
SIG10y	$2,295	37.41958	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,885	37.42489	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
iFOBT2y (current program)	$1,379	37.42987	$5,381

COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y+ SIG@50	$2,252	37.43394	Dominated
iFOBT2y+SIG@54_64_74	$2,658	37.43439	Dominated
iFOBT1y	$1,695	37.43543	$56,745
COL@50_iFOBT2y@52To74	$2,293	37.43620	$772,787

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A47 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming higher iFOBT test positive rate

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
SIG10y	$2,295	37.41958	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,920	37.42628	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,448	37.43432	$6,483
iFOBT2y+ SIG@50	$2,323	37.43599	Dominated
iFOBT2y+SIG@54_64_74	$2,705	37.43622	Dominated
COL@50_iFOBT2y@52To74	$2,349	37.43727	Dominated
iFOBT1y	$1,844	37.43734	$131,182

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative pDNA test characteristics

See Table A10 for more information on the alternative pDNA test characteristics assessed in the sensitivity analysis.

Table A48 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming alternative pDNA test characteristics

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
SIG10y	$2,295	37.41958	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,861	37.42550	Dominated
COL10y	$2,307	37.42988	Dominated

fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,250	37.43497	Dominated
iFOBT2y+SIG@54_64_74	$2,590	37.43504	Dominated
plasmaDNA2y	$2,632	37.43530	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative fDNA test characteristics

See Table A13 for more information on the alternative fDNA test characteristics assessed in the sensitivity analysis.

Table A49 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming alternative fDNA test characteristics

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	Dominated
SIG@60	$1,596	37.40696	Dominated
fDNA5y	$2,855	37.41122	Dominated
SIG10y	$2,229	37.41297	Dominated
CTC10y	$1,164	37.42219	-
SIG@55_iFOBT2y@60To74	$1,809	37.42355	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
iFOBT2y (current program)	$1,415	37.43215	$25,195
iFOBT2y+ SIG@50	$2,178	37.43364	Dominated
iFOBT2y+SIG@54_64_74	$2,477	37.43396	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,567

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative sigmoidoscopy test characteristics

See Table A13 for more information on the 'lower' and 'higher' sigmpodscopy test positive rate assessed in the sensitivity analysis.

Table A50 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming lower sigmoidoscopy test positive rate

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41064	Dominated
SIG10y	$2,312	37.41858	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,895	37.42511	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,277	37.43475	Dominated
iFOBT2y+SIG@54_64_74	$2,665	37.43512	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A51 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming higher sigmoidoscopy test positive rate

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,599	37.41253	Dominated
SIG10y	$2,332	37.42075	Dominated
CTC10y	$1,592	37.42233	Dominated
SIG@55_iFOBT2y@60To74	$1,910	37.42610	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,299	37.43523	Dominated
iFOBT2y+SIG@54_64_74	$2,697	37.43548	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative CTC test characteristics

See Table A18 for more information on the 'lower' and 'higher' CTC test positive rate assessed in the sensitivity analysis.

Table A52 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming lower CTC test positive rate

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
CTC10y	$1,625	37.41557	Dominated
SIG10y	$2,295	37.41958	Dominated
SIG@55_iFOBT2y@60To74	$1,861	37.42550	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,250	37.43497	Dominated
iFOBT2y+SIG@54_64_74	$2,590	37.43504	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A53 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming higher CTC test positive rate

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,187	37.39412	-
SIG@60	$1,597	37.41177	Dominated
SIG10y	$2,295	37.41958	Dominated
CTC10y	$1,552	37.42415	Dominated
SIG@55_iFOBT2y@60To74	$1,861	37.42550	Dominated
plasmaDNA2y	$2,681	37.42913	Dominated
COL10y	$2,307	37.42988	Dominated
fDNA5y	$2,909	37.43019	Dominated
iFOBT2y (current program)	$1,413	37.43213	$5,938
iFOBT2y+ SIG@50	$2,250	37.43497	Dominated
iFOBT2y+SIG@54_64_74	$2,590	37.43504	Dominated
COL@50_iFOBT2y@52To74	$2,323	37.43620	Dominated
iFOBT1y	$1,772	37.43623	$87,524

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Alternative pre-cancer natural history assumptions

Detailed description of the 'less aggressive' and 'more aggressive' natural history assumptions are provided elsewhere. (2)

Table A54 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming less aggressive natural history assumption

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$981	37.40961	-
SIG@60	$1,414	37.42608	Dominated
SIG10y	$2,162	37.43284	Dominated
CTC10y	$1,461	37.43391	Dominated
SIG@55_iFOBT2y@60To74	$1,742	37.43814	Dominated
plasmaDNA2y	$2,513	37.43961	Dominated
COL10y	$2,160	37.44195	Dominated
fDNA5y	$2,726	37.44196	Dominated
iFOBT2y (current program)	$1,272	37.44205	$8,983
iFOBT2y+ SIG@50	$2,142	37.44484	Dominated
iFOBT2y+SIG@54_64_74	$2,547	37.44548	Dominated
COL@50_iFOBT2y@52To74	$2,181	37.44594	Dominated
iFOBT1y	$1,636	37.44654	$81,124

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Table A55 Model-estimated discounted lifetime costs, discounted life-years and incremental cost-effectiveness ratio when assuming more aggressive natural history assumption

Strategy name [a]	Discounted lifetime cost [b]	Discounted life-years [b]	ICER ($cost/life-years saved)
No Screening	$1,566	37.35991	-
SIG@60	$1,957	37.38087	Dominated
SIG10y	$2,673	37.39095	Dominated
CTC10y	$1,968	37.39442	Dominated
SIG@55_iFOBT2y@60To74	$2,251	37.39732	Dominated
COL10y	$2,633	37.40293	Dominated
plasmaDNA2y	$2,998	37.40412	Dominated
fDNA5y	$3,196	37.40772	Dominated
iFOBT2y (current program)	$1,752	37.40820	$3,858
iFOBT2y+SIG@54_64_74	$3,005	37.41198	Dominated
iFOBT2y+ SIG@50	$2,612	37.41282	Dominated
iFOBT1y	$2,099	37.41414	$58,319
COL@50_iFOBT2y@52To74	$2,610	37.41575	$317,546

ICER- incremental cost-effectiveness ratio

[a] Strategies sorted by life-years

[b] Value accrued from age 20 to 89 years, discounting at a rate of 5% from age 40 years.

Supplementary analysis

A supplementary analysis that extended the model simulation stop age from 90 year-old (base case setting) to 100 year-old was performed. All strategies in three participation scenarios (perfect adherence, high adherence, and low adherence) were evaluated with the simulation for each virtual individual in the model began from the age of 20 and stop at the age of 100.

The predicted age-standardised rate (ASR) of colorectal cancer incidence and colorectal cancer mortality of each screening strategy in the supplementary analyses are summarised in Table A56. When compared to the base case findings (i.e. simulation stop at the age of 90), the estimated colorectal cancer incidence and colorectal cancer mortality ASRs in the supplementary analysis were predicted to be modestly higher (<1 per 100,000 persons) in all cases. The relative reduction in colorectal cancer incidence and mortality rates of each screening strategy versus no screening were also found to be similar to the base case findings.

The cost-effectiveness findings of the supplementary analysis are provided in Figure A19, Table A57, Table A58,and Table A59. The overall cost-effectiveness findings are similar to the base case findings, 2-yearly iFOBT screening and annual iFOBT screening were the only two strategies identified on the cost-effectiveness frontier in all participation scenarios; the ICER associated with these strategies in the three participation scenarios were also found to be similar to the base case findings.

Table A56. (Supplementary analysis) Estimated age-standardised rate of colorectal cancer incidence and colorectal cancer mortality per 100,000 persons, simulation for each virtual individual began from the age of 20 and stop at the age of 100.

Strategy name	Scenario 1 (perfect adherence)				Scenario 2 ('high' adherence)				Scenario 3 ('low' adherence)			
	CRC incidence		CRC mortality		CRC incidence		CRC mortality		CRC incidence		CRC mortality	
	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]	ASR[a]	*% Red* [b]
No screening	63.0	-	23.2	-	63.0	-	23.2	-	63.0	-	23.2	-
iFOBT2y	31.2	50%	6.4	72%	42.9	32%	11.5	51%	48.9	22%	14.9	36%
iFOBT1y	24.7	61%	4.8	79%	33.8	46%	7.7	67%	39.4	38%	10.5	55%
plasmaDNA2y	40.1	36%	8.1	65%	51.1	19%	13.9	40%	54.8	13%	16.8	28%
fDNA5y	35.7	43%	7.9	66%	49.4	22%	15.1	35%	54.9	13%	18.3	21%
COL10y	21.2	66%	5.4	77%	45.0	29%	15.4	34%	54.9	13%	19.6	16%
SIG10y	30.6	51%	9.9	58%	51.9	18%	18.5	21%	57.9	8%	21.1	9%
CTC10y	34.6	45%	8.8	62%	54.4	14%	18.5	20%	59.0	6%	21.0	10%
SIG@60	41.3	35%	14.2	39%	57.5	9%	20.9	10%	60.7	4%	22.3	4%
SIG@55_iFOBT2y@60To74	30.2	52%	7.5	68%	50.2	20%	16.2	30%	55.9	11%	19.1	18%
COL@50_iFOBT2y@52To74	24.3	61%	5.4	77%	39.8	37%	10.7	54%	47.0	25%	14.3	39%
iFOBT2y+ SIG@50	26.6	58%	5.7	75%	41.9	33%	11.3	51%	48.7	23%	14.9	36%
iFOBT2y+SIG@54_64_74	22.6	64%	4.8	79%	39.4	37%	10.6	54%	47.8	24%	14.6	37%
iFOBT2y+plasmaDNA	n/a [c]	n/a [c]	n/a [c]	n/a [c]	42.7	32%	11.2	52%	48.2	23%	14.4	38%

ASR- age-standardised rate; Red- reduction;

[a] *Per 100,000 individuals, assuming 2001 Australian Standard Population 0-89 years*

[b] *Compared with no screening*

[c] *This strategy is not applicable in Scenario 1 because there are no under-screened individuals given the assumption of perfect adherence to screening, follow-up and surveillance recommendations.*

Figure A19. (Supplementary analysis) Cost-effectiveness planes for alternative adherence assumptions, simulation for each virtual individual began from the age of 20 and stop at the age of 100. Text and numbers shown in the chart mark the strategies identified on the cost-effectiveness frontier and the incremental cost-effectiveness ratio (ICER) associated with that strategy.[See text for more detail on adherence assumptions in each Scenario].

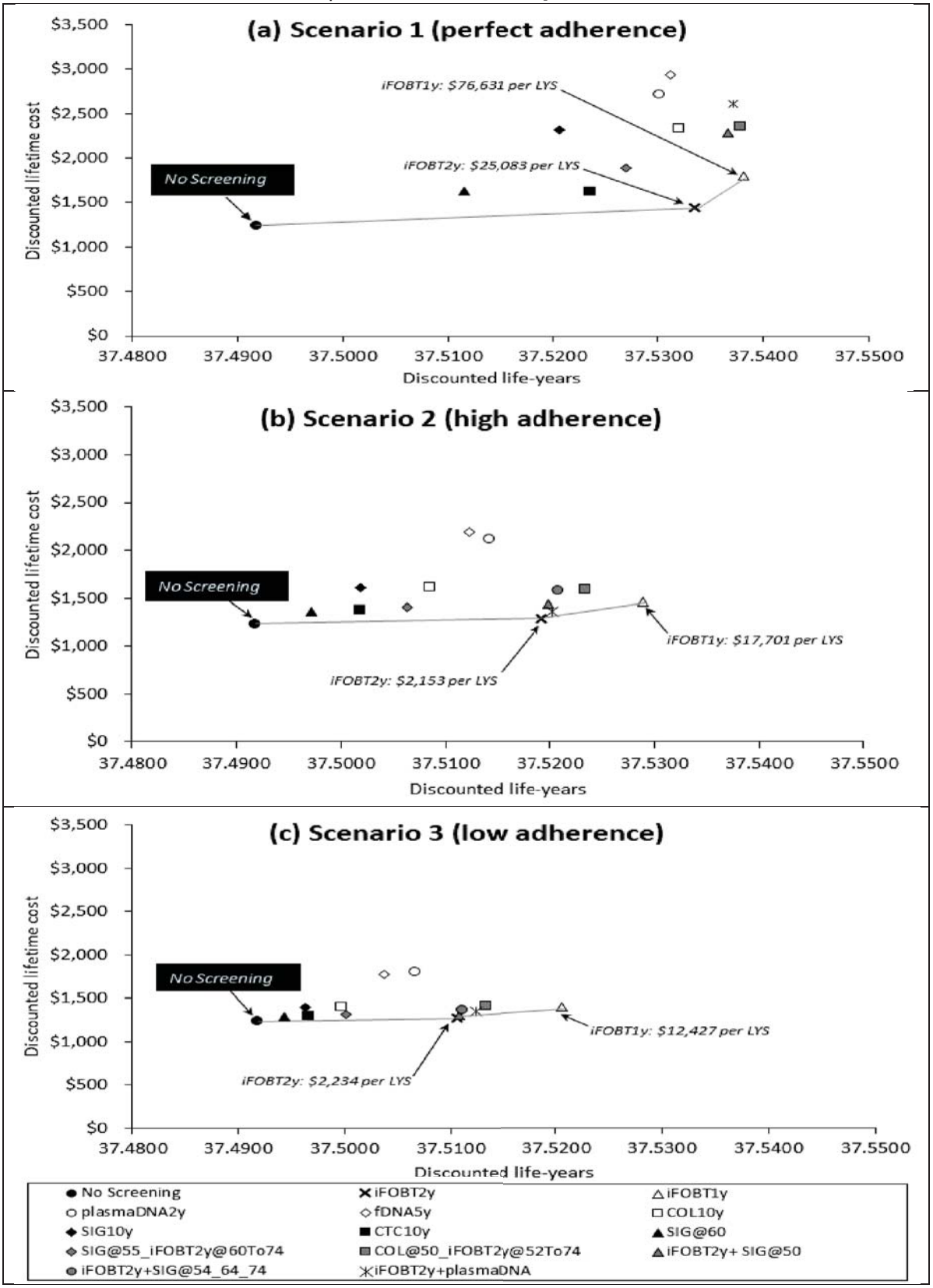


Table A57. (Supplementary analysis) Model-estimated discounted costs, discounted life-years, and cost-effectiveness ratio compared to no screening for each strategy in Scenario 1 (perfect adherence), simulation for each virtual individual began from the age of 20 and stop at the age of 100

Strategy name	Discounted lifetime cost [a]	Discounted life-years [a]	*CER ($ per life-year saved)* [b]
No Screening	$1,232	37.4919	-
iFOBT2y (current program)	$1,442	37.5335	$5,058
iFOBT1y	$1,797	37.5381	$12,229
plasmaDNA2y	$2,712	37.5302	$38,677
fDNA5y	$2,941	37.5312	$43,491
COL10y	$2,325	37.5321	$27,201
SIG10y	$2,320	37.5207	$37,806
CTC10y	$1,618	37.5237	$12,147
SIG@60	$1,634	37.5115	$20,516
SIG@55_iFOBT2y@60To74	$1,889	37.5269	$18,762
COL@50_iFOBT2y@52To74	$2,351	37.5378	$24,346
iFOBT2y+ SIG@50	$2,278	37.5366	$23,406
iFOBT2y+SIG@54_64_74	$2,612	37.5371	$30,543
iFOBT2y+plasmaDNA	n/a [c]	n/a [c]	n/a [c]

CER- cost-effectiveness ratio; COL- colonoscopy; CTC – computed tomographic colonography; fDNA – faecal DNA test; iFOBT – Immunochemical faecal occult blood test; SIG-sigmoidoscopy

[a] Average number estimated in the lifetime of an individual, discounted by 5% from 40 years.

[b] Compared with no screening.

[c] This strategy is not applicable in Scenario 1 because there are no under-screened individuals given the assumption of perfect adherence to screening, follow-up and surveillance recommendations.

Table A58. (Supplementary analysis) Model-estimated discounted costs, discounted life-years, and cost-effectiveness ratio compared to no screening for each strategy in Scenario 2 ('high' adherence), simulation for each virtual individual began from the age of 20 and stop at the age of 100

Strategy name	Discounted lifetime cost [a]	Discounted life-years [a]	*CER ($ per life-year saved)* [b]
No Screening	$1,232	37.4919	-
iFOBT2y	$1,290	37.5192	$2,153
iFOBT1y	$1,464	37.5290	$6,256
plasmaDNA2y	$2,111	37.5141	$39,487
fDNA5y	$2,187	37.5123	$46,870
COL10y	$1,610	37.5086	$22,687
SIG10y	$1,607	37.5018	$37,799
CTC10y	$1,371	37.5018	$14,054
SIG@60	$1,365	37.4971	$25,281
SIG@55_iFOBT2y@60To74	$1,412	37.5063	$12,468
COL@50_iFOBT2y@52To74	$1,591	37.5235	$11,375
iFOBT2y+ SIG@50	$1,443	37.5198	$7,562
iFOBT2y+SIG@54_64_74	$1,572	37.5209	$11,726
iFOBT2y+plasmaDNA	$1,357	37.5203	$4,427

CER- cost-effectiveness ratio; COL- colonoscopy; CTC – computed tomographic colonography; fDNA – faecal DNA test; iFOBT – Immunochemical faecal occult blood test; SIG-sigmoidoscopy

[a] Average number estimated in the lifetime of an individual, discounted by 5% from 40 years.

[b] *Compared with no screening.*

Table A59. (Supplementary analysis) Model-estimated discounted costs, discounted life-years, and cost-effectiveness ratio compared to no screening for each strategy in Scenario 3 ('low' adherence), simulation for each virtual individual began from the age of 20 and stop at the age of 100

Strategy name	Discounted lifetime cost [a]	Discounted life-years [a]	*CER ($ per life-year saved)* [b]
No Screening	$1,232	37.4919	-
iFOBT2y	$1,273	37.5106	$2,234
iFOBT1y	$1,399	37.5206	$5,804
plasmaDNA2y	$1,794	37.5067	$37,939
fDNA5y	$1,773	37.5038	$45,566
COL10y	$1,401	37.4998	$21,304
SIG10y	$1,402	37.4962	$38,949
CTC10y	$1,293	37.4967	$12,890
SIG@60	$1,289	37.4943	$23,239
SIG@55_iFOBT2y@60To74	$1,311	37.5001	$9,579
COL@50_iFOBT2y@52To74	$1,402	37.5134	$7,937
iFOBT2y+ SIG@50	$1,306	37.5108	$3,952
iFOBT2y+SIG@54_64_74	$1,359	37.5112	$6,584
iFOBT2y+plasmaDNA	$1,347	37.5125	$5,622

CER- cost-effectiveness ratio; COL- colonoscopy; CTC – computed tomographic colonography; fDNA – faecal DNA test; iFOBT – Immunochemical faecal occult blood test; SIG-sigmoidoscopy

[a] *Average number estimated in the lifetime of an individual, discounted by 5% from 40 years.*

[b] *Compared with no screening.*

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