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 modelled iFOBT positivity rate and COL outcome among positive iFOBT to data observed in the NBCSP (17)	95.6%	94.1%	Assumption
Sensitivity for adenoma of any size	15.2%		13.1%	17.4%	
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	N/A	90.5%	Obtained via

Sensitivity for adenoma of any size	10.2%	calibrating the modelled test positive rate to the findings of Church et al 2013 (12).	N/A	24.0%	calibrating the modelled test positive rate to the findings of Jin et al 2015 (41)
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 adenoma >10mm	88.1%		54.2%	96.3%	
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

Department of Health, Australia

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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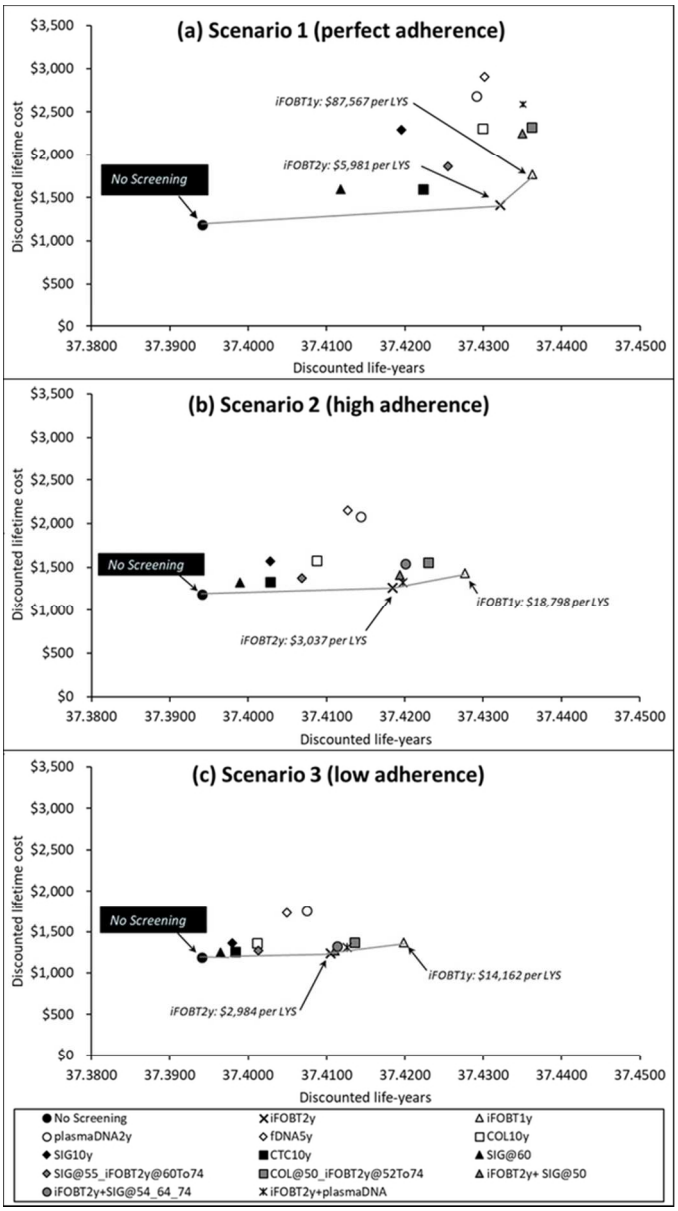
FIGURES

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



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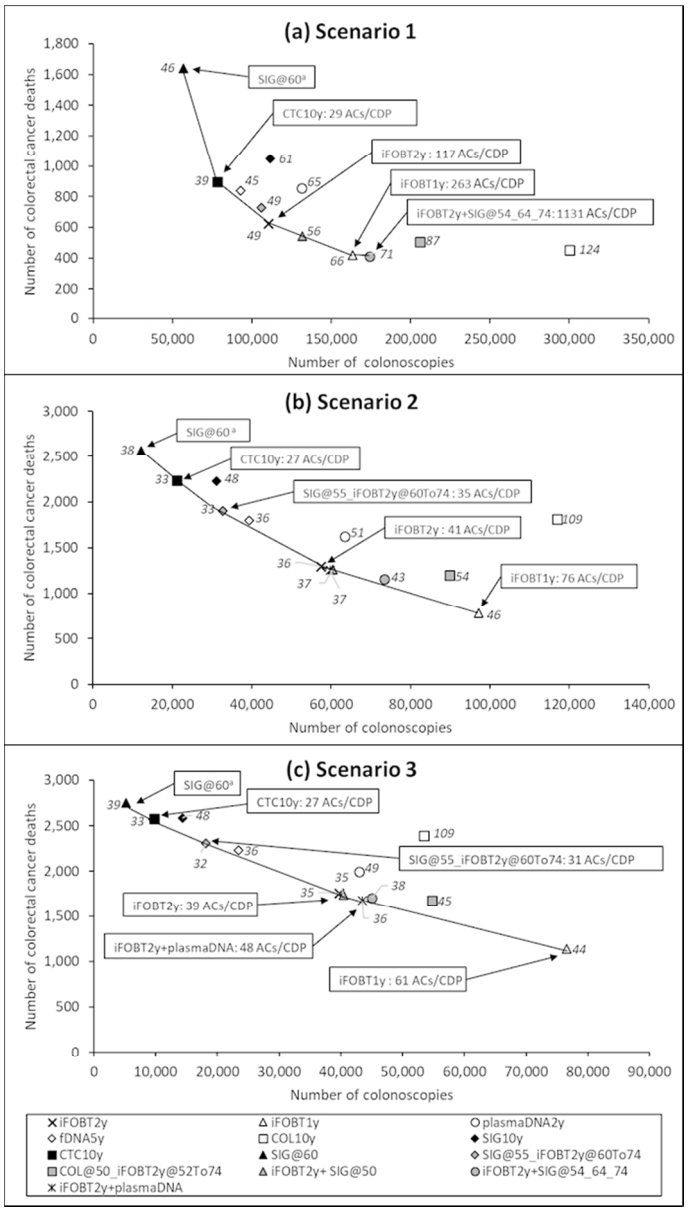

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243x431mm (72 x 72 DPI)