Report prepared for the Ministry of Health

The cost effectiveness of bowel cancer screening in New Zealand: a cost-utility analysis based on pilot results

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sapere research group

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Executive summary

Sapere Research Group was contracted by the Ministry of Health to undertake cost effectiveness analysis of bowel screening in New Zealand, based upon the information generated from a pilot. We conducted microsimulation of a number of screening scenarios, both for the New Zealand population as a whole and for a Maori population. We found bowel screening to be highly cost effective, and in some scenarios actually to be cost saving from a health system perspective.

Sources of data and assumptions

The information for our analysis comes from the following sources:

- Existing burden of bowel cancer – Natural history model (MoDCONZ microsimulation, calibrated against the New Zealand cancer registry)
- Eligible population, e.g. what age group is invited to screening (Pilot and the MoH)
- Participation rates (Pilot)
- Performance of FIT in detecting adenomas and cancers
  - Sensitivity and specificity (International studies)
  - Different cut-off values (Pilot)
- Colonoscopy outcomes
  - Attendance (Pilot)
  - Adverse events (pilot)
  - Sensitivity (International studies)
- Treatment and follow up
  - Health outcomes (MoDCONZ microsimulation)
  - Cost impact (NZ cost data sets, analysed by BODE3 research team).

Methods

We used microsimulation to model the natural history of bowel cancer. The MoDCONZ (Modelling Disease and Cancer Outcomes in NZ) model was developed by a team of researchers from the University of Otago for the micro-simulation of life histories for a hypothetical sample of people. The sample is defined by age and sex parameters, and can be applied to the New Zealand population as a whole, or to a Maori population. The model has at its core a natural history of colorectal cancer, which captures the adenoma-carcinoma sequence, with assumptions based on the probabilities of initiation, progression and response to treatment of colorectal cancers (details are presented in Appendix 1).

We added a screening intervention model to MoDCONZ in order to estimate the benefits and costs of bowel cancer screening. The screening intervention estimates the:

- earlier detection of bowel cancer and the resulting changes in bowel cancer mortality;
- costs of screening (including surveillance); and
- cost offsets from reduces treatment of cancer.

We use the MODCONZ simulation tool to estimate the cost-effectiveness of bowel cancer screening as measured as the cost per quality adjusted life year (QALY), where the QALYs (quality adjusted life years) capture the increased life expectancy and improved quality of life from screening.

Summary of cost effectiveness results: whole population

If bowel cancer screening was rolled out nationally in New Zealand in the same way that it was undertaken in the pilot, it is estimated to dominate a scenario of no screening i.e. be cost saving with QALY gains. The comparison of the outcomes for screening and no screening are included in the table below.

Our best estimate of the cost per QALY for this scenario is -$1,344, i.e. cost saving with health benefits. There is some uncertainty in the result: we estimate the cost per QALY to fall in the range of -$5,786 to $4,850.

Cost effectiveness results for pilot screening parameters – whole population

Treatment	Costs	QALYs	Incremental		Cost per QALY (95%CI)
			Costs (95% CI)	QALYs (95%CI)	
No screening	$2,643	17.661	-$98 (-$627 - $219)	0.0730 (0.0451 - 0.1084)	Dominates* (-$5,786 - $4,850)
Screening	$2,544	17.734			

* The term dominates means screening is preferable in benefit to any other scenario, since there is no trade-off between cost and outcome

We have also modelled alternative scenarios, which are shown in the table below.

- The table is sorted in order of decreasing cost effectiveness, indicated by the average cost per average QALY column;
- The base scenario implemented in the pilot is indicated by the highlighted row.
- Alternative scenarios considered here vary the hypothetical implementation of screening with differing participation rates (varying from 50% to 100%), and differing cutoffs for the iFOBT test. The base case cutoff is 75ng. Alternative scenarios range up to a cutoff of 250ng. We explored scenarios for different age bands for the invited population.
- All of the scenarios resulted in similar cost-effectiveness results. The best estimate of each of scenarios falls within the estimated cost-effectiveness range of the scenario based on the pilot.

Cost effectiveness for different scenarios- whole New Zealand population

Screening age band	Participation rate	iFOBT cutoff (ng)	Avoided cancers	Avoided deaths	Incremental Cost	Incremental QALY	Incremental Cost per QALY - best estimate
50-74	100%	75	2,663	1,408	-$280	0.0827	**Dominates**
50-74	80%	75	2,284	1,237	-$219	0.0786	**Dominates**
60-74	56%	75	1,396	905	-$166	0.0690	**Dominates**
55-74	56%	75	1,636	974	-$158	0.0717	**Dominates**
50-69	56%	75	1,480	839	-$135	0.0701	**Dominates**
60-69	56%	75	859	605	-$122	0.0631	**Dominates**
65-74	56%	75	878	706	-$104	0.0626	**Dominates**
50-74	56%	75	1,738	980	-$98	0.0730	**Dominates**
50-74	56%	100	1,632	941	-$79	0.0719	**Dominates**
50-74	50%	75	1,578	905	-$64	0.0713	**Dominates**
50-59	56%	75	522	336	-$38	0.0607	**Dominates**
50-74	56%	150	1,412	849	-$29	0.0696	**Dominates**
50-74	56%	200	1,263	794	$11	0.0681	**$164**
50-74	56%	250	1,159	747	$34	0.0671	**$511**

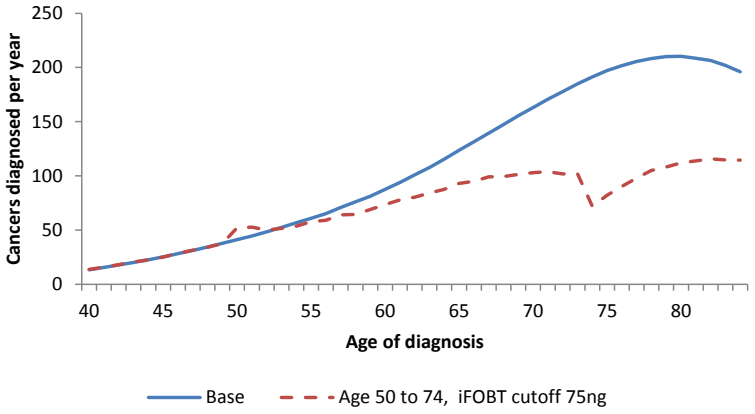
Key elements of these results are:

- In absolute terms, screening dominates for most scenarios. This means that bowel screening is cost saving in absolute terms, while still bringing health benefits. This result is driven by the savings from avoided costs of treating cancer being large enough to outweigh the costs of screening. This makes bowel screening an exceptionally cost effective health intervention, given that it both reduces health costs and produces benefits for the population. But even for those scenarios where there is a positive incremental cost per QALY, the cost is very low. Compared to average levels of cost per QALY funded by PHARMAC in the range of $16,000 to $45,000, a cost effectiveness result of less than $1,000 per QALY makes bowel screening highly cost effective compared to many other health interventions.
- Narrowing age bands for the eligible population improves the nominal cost effectiveness of the programme, although it decreases the absolute effectiveness across the population. This is because a narrower age band results in fewer screening episodes per person (reducing the cost of screening). Under this scenario the reduced cost of screening outweighs the reduced benefit of the programme, although in absolute terms fewer cancers and cancer deaths are avoided.
- The impact of age bands upon overall cost effectiveness dominates the other variables we have explored in these scenarios.
- Increasing the participation rate improves the cost-effectiveness. A higher participation rate results in increased net savings and increased QALY gains. Although the cost of screening increases with increased participation rates, the cost-offsets increase at a greater rate which leads to an increase in net savings.
- A lower FIT cutoff is more cost effective than a high cutoff. This is driven by the high avoided cost of cancers, where a higher cutoff leads to fewer avoided cancers and therefore smaller gains, which outweigh the decreased cost of colonoscopy as the cutoff rises.

The graph below shows the reduction in cancers by age of diagnosis under the screening parameters as implemented in the pilot. There is a bolus effect at the time that screening is

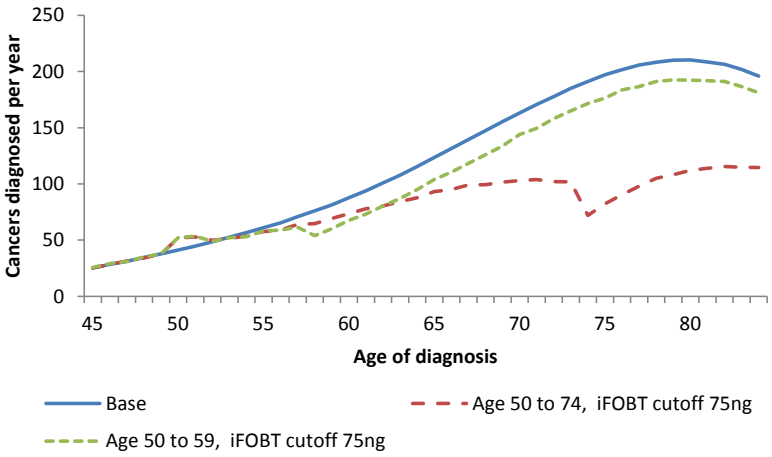
begun (age 50), with an increased number of cases diagnosed compared to a base scenario with no screening.

Diagnoses of cancers by age of diagnosis - cohort followed to age 84 – whole population



The next graph summarises the reduction in cancer achieved with different age groups invited to screening. While the *cost effectiveness* of using narrower age bands is generally improved, the absolute impact of using narrower bands is decreased, as fewer cancers are avoided across the population. The top line in the figure below represents the number of cancers diagnosed without screening, by age. The lower lines in the figure below represent the number of cancers with screening, with 50-74 represented by the lower line due to the greater reduction in cancers.

Diagnoses of cancers by age of diagnosis - cohort followed to age 84 – comparing different age bands – whole population



Summary of cost effectiveness results: Māori

Our microsimulation model was calibrated separately to the Māori population, so that we could undertake subgroup analysis of the effectiveness and cost effectiveness of screening for Māori; i.e. we estimate Maori specific rate of bowel cancer and bowel cancer mortality.

All other parameters are the same, i.e. same per event costs and same participation as for the whole population model..

The tables below summarise the cost effectiveness of the same range of scenarios analysed above, for the Māori population, and give further details for the base case as implemented in the pilot. While the broad patterns of cost effectiveness are the same for Māori as for the whole population, the level of cost effectiveness has decreased slightly, with fewer scenarios being cost saving. By the same token, the difference of $1,700 per QALY in cost effectiveness for Māori compared to the whole population in the base scenario implemented in the pilot is a small one, in the context of cost effectiveness results for health interventions more generally.

The table below presents the cost effectiveness result for Maori under the base case screening scenario as implemented in the pilot.

Cost effectiveness results for pilot screening parameters – Maori population

Treatment	Costs	QALYs	Incremental		Cost per QALY (95%CI)
			Costs (95% CI)	QALYs (95%CI)	
No screening	$2,233	16.901	$29	0.0759	$381
Screening	$2,262	16.977	(-$430 - $307)	(0.0463 - 0.1142)	(-$3,762- $6,288)

The table below presents the estimated cost effectiveness of screening for Maori under different scenarios.

Cost effectiveness for different scenarios- Maori population

Screening age band	Participation rate	iFOBT cutoff (ng)	Avoided cancers	Avoided deaths	Incremental Cost	Incremental QALY	Incremental Cost per QALY - best estimate
50-74	100%	75	263	183	-$83	0.0849	Dominates
60-74	56%	75	135	112	-$64	0.0708	Dominates
60-69	56%	75	83	75	-$53	0.0656	Dominates
50-74	80%	75	224	159	-$46	0.0810	Dominates
65-74	56%	75	83	84	-$38	0.0632	Dominates
55-74	56%	75	160	123	-$36	0.0746	Dominates
50-69	56%	75	145	107	-$12	0.0735	Dominates
50-59	56%	75	53	44	$11	0.0652	$164
50-74	56%	75	171	126	$29	0.0759	$381
50-74	56%	100	160	119	$38	0.0748	$514
50-74	50%	75	154	116	$53	0.0743	$718
50-74	56%	150	138	107	$79	0.0727	$1,086
50-74	56%	200	123	100	$108	0.0715	$1,511
50-74	56%	250	114	93	$124	0.0703	$1,760

Bowel screening remains a highly cost effective intervention for Māori. Given the width of confidence intervals, it cannot be concluded that screening is significantly less cost effective for Maori than for the New Zealand population as a whole.

Sensitivity of results to key parameters

We explored the impact of variation in key parameters within our model upon the overall result.

Only three variables appear to have any potential for material impact upon the overall cost effectiveness result:

- Natural history (prevalence of bowel cancer generated within MoDCONZ)
- Discount rate; and
- Cost of Cancer.

Even these results have a relatively small impact. The variable which has the greatest effect, Natural History, in the worst case still only increases the incremental cost per QALY to a value of $4,138, which we consider to be very cost-effective.

Conclusion: economically efficient

A national bowel cancer screening programme could be delivered in an economically efficient manner in New Zealand. We modelled different screening scenarios, all of which were highly cost-effective both for the whole population and for Māori, and in some cases were cost saving.

While bowel cancer screening results in cost-savings from reduced treatment of bowel cancer, there also are significant resource requirements, particularly in the capacity to provide colonoscopy for those with a positive iFOBT and for those referred for surveillance. These requirements may pose a constraint on how a national programme may be delivered. The policy and clinical decisions involved in planning an implementation of bowel screening will need to trade off cost effectiveness against the sensitivity and specificity which can reasonably be achieved and supported in a live screening programme on a national basis.

1. Introduction

Sapere Research Group have been commissioned to evaluate the cost-effectiveness of bowel cancer screening in the New Zealand context. We have worked in partnership with Litmus and Massey University on different aspects of an overall evaluation of a pilot implemented in Waitemata District Health Board. This cost effectiveness report is complementary to a cost of screening report also conducted by Sapere, and to epidemiological analysis and survey analysis of the pilot conducted by our research partners. The present report, presenting the results of a cost utility analysis, is intended to be able to be read either as a standalone piece, or in conjunction with the more detailed costing results in our companion report.

Bowel cancer is particularly common in New Zealand. Adenomas in the bowel can develop into cancer, and can then potentially spread beyond the bowel. The later bowel cancer is detected, the increased risk of serious harm or death. There are a number of treatment options, including surgery, radiotherapy and chemotherapy. The stage to which cancer has advanced is a key determinant of which treatments are used.

New Zealand ran a bowel screening pilot between 2011 and 2015. This provides us with New Zealand specific results on the short term outcomes of screening. Key outcomes include participation rates, and the numbers of adenomas and cancers detected. We use these short term New Zealand specific results in combination with longer term impacts of screening published in the medical literature to inform the long term estimated benefits of implementing a screening programme in New Zealand. The long term benefits of screening, such as reduced bowel cancer mortality, have been shown in international randomised control trials that evaluated outcomes over many years.

In this section we further discuss:

- The purpose of evaluation;
- The burden of bowel cancer;
- The progression of bowel cancer and treatment options;
- The outcomes of the screening pilot;
- The long term benefits of screening.

1.1 Purpose of evaluation

This is part of a wider evaluation of the bowel cancer pilot in New Zealand. The purpose of this evaluation is to inform decisions regarding a national roll out of bowel cancer screening across New Zealand. As part of the wider evaluation, we have been commissioned to estimate the cost-effectiveness of bowel cancer screening. The two main questions are:

- What is the cost-effectiveness of screening as implemented in the pilot?
- What is the likely cost of a national roll out?

To estimate the cost-effectiveness of the pilot we apply the results of the pilot and estimate the long term outcomes for the New Zealand population. For the cost of national rollout

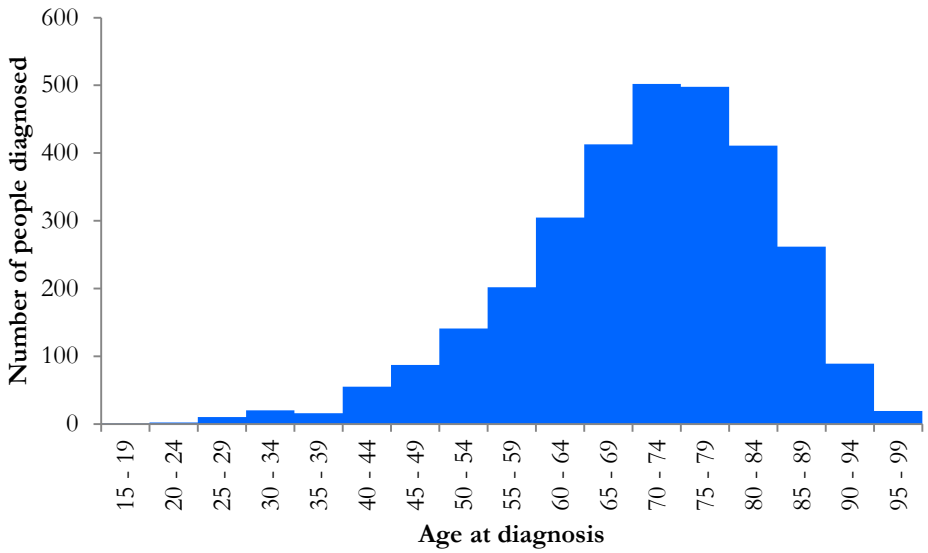
we evaluate possible scenarios for how a national rollout could be done (in a separate report). The scenarios build on the lessons from the pilot.

1.2 Bowel cancer is a very common cancer

Bowel cancer incidence and mortality is high in New Zealand in comparison with other countries. In 2009, 2837 people were diagnosed with bowel cancer and 1244 people died from the disease. It was the second most common cancer both in men and women, the second highest cause of cancer death for men (after lung cancer) and the third highest for women (after lung and breast cancers).

Rates of bowel cancer for Maori are lower than for the European patients, although mortality is similar across the two populations. The lower survival rate of bowel cancer among Maori may reflect later stage diagnosis, or poorer access to high quality health services.[1]

Figure 1 Distribution of age at diagnosis for bowel cancer in New Zealand – diagnoses made in 2011

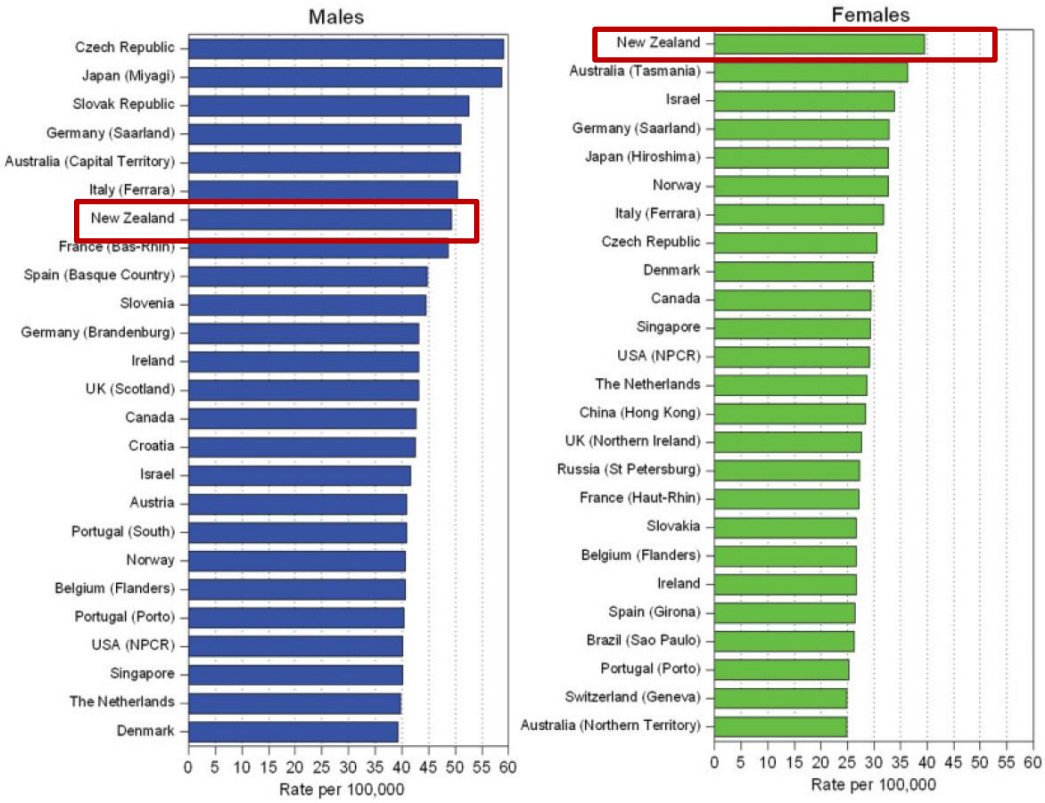


Source: Data source from the national cancer registry, graph by Sapere

1.2.2 New Zealand has the highest rate of bowel cancers for females

In developed countries, New Zealand has the highest rate of bowel cancers for females and the 7th highest for males, shown in Figure 2 below. In general, males have higher rates than female, with a difference of 20% in New Zealand. New Zealand, and a number of other countries with high rates, have had decreasing rates from 1986 to 2004[25].

Figure 2 Registries with the highest age standardised bowel cancer rates, by gender 1998 - 2002



Source: Center et al 2009[25]. Registries with the Highest Age-Standardized Colorectal Cancer Incidence Rates by Sex, 1998–2002.

1.3 Progression of bowel cancer and treatment options

1.3.1 Stages of bowel cancer

Once there has been progression beyond the pre-cancerous polyp, bowel cancer can be staged. There are various tools for staging cancers. Our analysis is based on the TNM tool.

TNM stands for Tumour, Node, Metastases. This staging system describes the size of a primary tumour (T), whether any lymph nodes contain cancer cells (N), and whether the cancer has spread to another part of the body (M). The four stage of bowel cancer can be described in simple terms as:

- Stage I: the cancer has not spread past the muscle wall of the bowel
- Stage II: the cancer has spread into or past the outer wall of the bowel
- Stage III: the cancer has spread to nearby lymph nodes
- Stage IV: the cancer has spread to other parts of the body

In New Zealand the PIPER project has found the following distribution of bowel cancer across stages, with bowel cancer split in to colon cancer and rectal caner:[2]

Stage at diagnosis Colon Cancer

- Stage I: 12%
- Stage II: 27%
- Stage III: 25%
- Stage IV: 24%
- Non-metastatic, unable to be further defined: 5%
- Unknown: 7%

Rectal Cancer

- Non-metastatic (stage I-III): 76%
- Stage IV: 19%
- Unknown: 5%

Currently in New Zealand nearly half of bowel cancers are diagnosed in the later stages i.e. stage 3 or 4. If the cancer is confined to the bowel (stage 3) around 4 in 10 will not survive 5 years post diagnosis. If the cancer is spread beyond the bowel more than 9 in 10 will not survive 5 years post diagnosis.

1.3.2 Treatment and followup for bowel cancer

Where polyps are detected in the bowel they can be removed at the time of detection by colonoscopy, preventing subsequent development into cancer. Where the situation has progressed to a cancer, the basic modes of treatment are surgery, chemotherapy and radiotherapy. Surgery may in some cases be a definitive treatment, particularly for early stage cancers, although adjuvant chemotherapy and in some cases radiation therapy can be used.

Where existing bowel conditions have been identified, regular followup with colonoscopy is recommended. In 2011 the New Zealand guideline group published the report "Guidance on Surveillance for People at Increased Risk of Colorectal Cancer"[3]. This work was developed by reviewing the NICE guidelines for the UK and seeking input from NZ specialists to make NZ specific estimates. The guideline covers:

- Personal history of adenomatous polyps;
- Personal history of inflammatory bowel disease;
- Personal history of colorectal cancer.

These recommendations are reported to be grade C, i.e. "The recommendation is supported by international expert opinion". This means there is a lack of "good" or "fair" evidence to support the recommendations.

A summary of the NZ guideline group recommendations are in Table 1 below. The risk is based on the most recent colonoscopy, since it can change with subsequent surveillance colonoscopies.

Table 1 New Zealand guidelines for surveillance

Risk	Definition	Surveillance
Low	• One or two adenomas smaller than 10 mm.	consider colonoscopy at 5 years
Intermediate	• Three or four adenomas smaller than 10 mm or • One or two adenomas if one is 10 mm or larger histological polyps with villous features • Polyps with high grade dysplasia.	offer colonoscopy at 3 years
High	• Five or more adenomas smaller than 10 mm or • Three or more adenomas if one is 10 mm or larger	offer colonoscopy at 1 year

Source: New Zealand Guidelines Group[3]

1.4 NZ pilot

The Bowel Screening Pilot (the 'BSP' or the 'pilot') has been running in Waitematā District Health Board (WDHB) since commencing with a 'soft launch' in October 2011, leading to the start of the first full screening round in January 2012.

The target population for the pilot is men and women aged from 50 to74 years at the time of invitation, who were both resident in the Waitematā DHB area and eligible for publicly funded healthcare. The screening test used is a single immunochemical faecal occult blood test (iFOBT). Eligible people were recalled for screening every two years. The specific details of the screening pathway are discussed further in section 2.3 below.

1.4.1 Preliminary results from the pilot

The results of the screening can be summarised for all of those screened, and for subgroups within the screened population. The subgroups include different age bands, with positivity rates at different cut-offs. Table 2 summarises the results of pilot and separates the first and second screening round. At the time of writing, results were available up to September 2015, with the last three months of the pilot remaining to be reported. The number of

colonoscopies and findings are based on colonoscopies performed in both public and private hospitals, with 8% of colonoscopies performed in the private sector.

Between January 2012 and September 2015:

- 237,669 people were sent FIT test kits. Just over half of these test kits were returned;
- 8,111 people had a positive test and were followed up with a colonoscopy;
- Of those with a positive test, approximately half had an adenoma, and 4 percent had a cancer.
- This resulted in 4,239 adenomas in 314 cancers detected.

There was some variation between Rounds One and Two of the screening pilot. As expected, the rate of participants detected with an adenoma or cancers was lower in Round Two. The participation rate was slightly lower in round 2, at 53 percent compared with 57 percent in Round One.

The four years of data from the pilot are insufficient to measure directly a reduction in cancers and cancer related mortality in the screened population, which will take place over a longer time period. However, the number of participants with adenomas and cancers detected suggest that the pilot would result in similar reductions to cancers and cancer related mortality found in international studies, discussed in further detail below in section 1.5.

Table 2 Summary results of the New Zealand pilot, based on data *from January 2012 to September 2015*

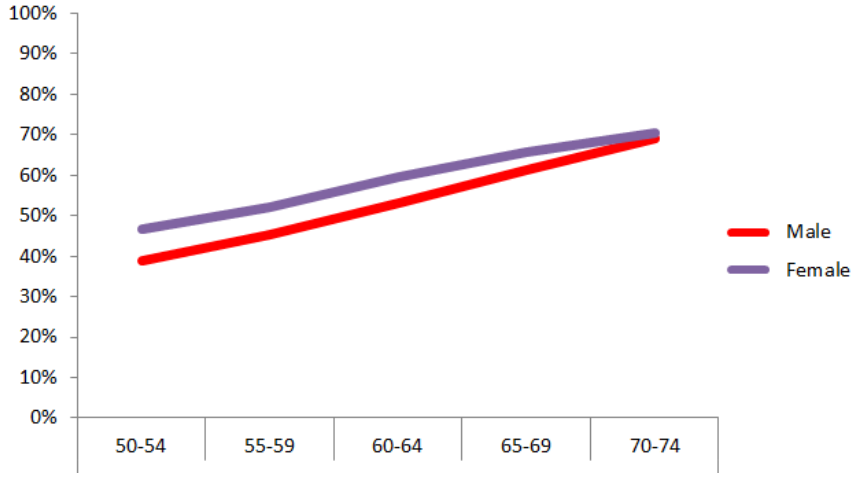
Outcome	Round 1	Round 2	Both rounds
Eligible participants – sent FIT	121,893	115,776	237,669
Definitive FIT returned (Participation rate)	69,179 (57%)	61,771 (53%)	130,950 (55%)
Positive FITs (Positivity)	5,218 (7.5%)	3,638 (5.9%)	8,856 (6.8%)
Participants for colonoscopy	4,840 (93%)	3,275 (90%)	8,115 (92%)
Adenomas • *Number* • *PPV*	*2,691* *55.6%*	*1,548* *47.3%*	*4,239* *52%*
Advanced adenomas • *Number* • *PPV*	*1,159* *23.9%*	*511* *15.6%*	*1670* *21%*
Cancer • *Number* • *PPV*	*218* *4.4%*	*96* *2.9%*	*314* *3.9%*

Source: Data provided by MoH, table by Sapere

Participation rate varies by age, ethnicity and previous participation

People aged between 50 and 74 years were eligible to take part in the pilot. Those in the younger age ranges are less likely to participate than those who are older, and men are less likely to take part than women, although the gap between sexes narrows with increasing age. Figure 3 below shows the participation rate by age group and sex, for people invited in the first fifteen months of Round Two. Data for those people invited in Round One showed similar trends[4].

Figure 3 Participation in the Bowel Screening Pilot by age and sex: Round Two

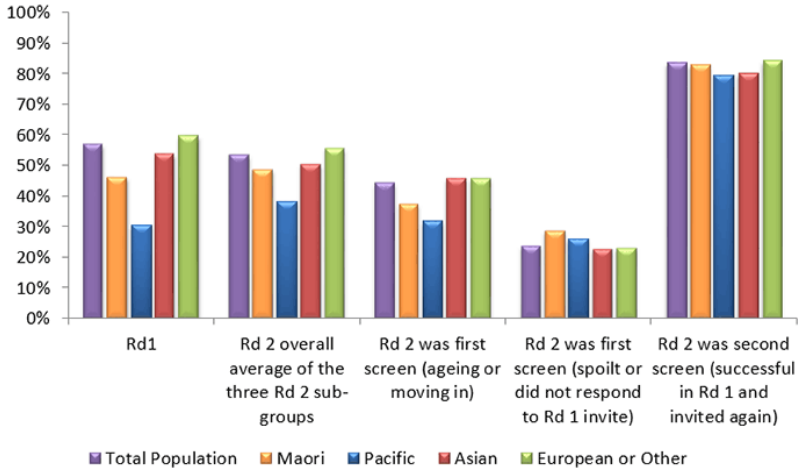


Source: MoH 2016[4]

Pacific people were less likely to participate than other population groups, particularly in round one of the pilot. Figure 4 shows the participation rates by ethnic group in each round, and in key subgroups for people in Round Two. The Round One participation rate for Pacific people was about half that of the "European and Other" group. Initiatives set in place in Round Two may be closing some of this gap[4].

Previous participation in screening is another indicator of likely response. People with a first invitation in Round Two had a lower participation rate than the average for Round One, at 44 percent compare with 57 percent. This lower rate can potentially be explained by a lower age group entering the screening population. Where people had not participated in the first round, there was only had a 24 percent participation rate in the second round. Where people had participated in the first round, there was an 83 percent participation rate in Round Two. These rates, split by ethnicity, are shown in Figure 4 below[4].

Figure 4 Participation in the Bowel Screening Pilot by ethnicity Showing those invited from 1 January 2012 to 30 September 2015

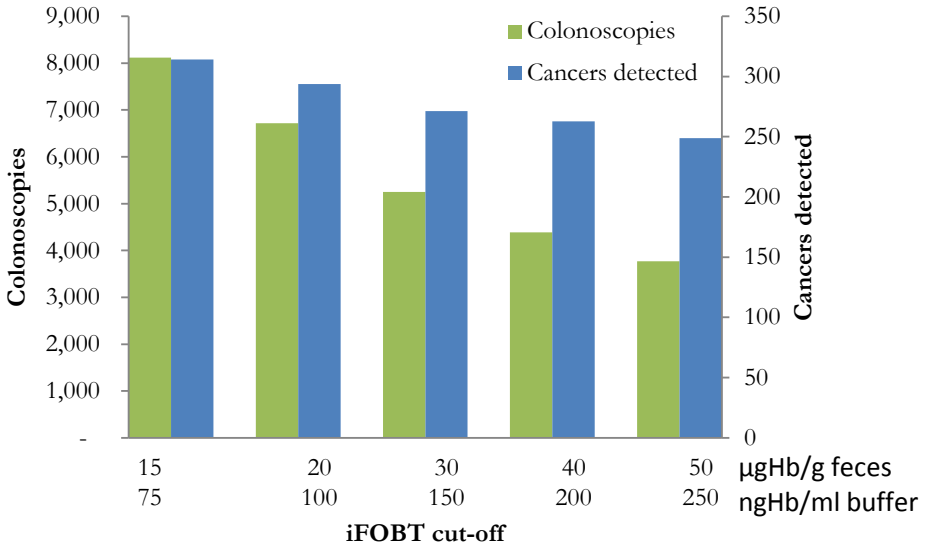


Source: MoH 2016[4]

Hypothetical pilot results based on higher iFOBT cut-offs

The results of the iFOBT are reported as a number. In the pilot a test was considered positive if the value was 75 ng (formally: 75 ngHb/ml buffer or 15 µgHb/g faeces). People with positive tests were referred for colonoscopy. We have estimated the number of colonoscopies and cancers if a higher cut-off had been used. With higher values fewer colonoscopies are performed, and fewer cancers are detected. However, the impact on the volume of colonoscopies is much greater than on the volume of cancers. For example, using a cut-off of 250ng would result in 55 percent fewer colonoscopies and 20 percent fewer cancers detected, compared with a cut-off of 75ng. With a higher cut-off patients are less likely to have a positive iFOBT result, but those with a positive iFOBT are more likely to have cancer or adenoma.

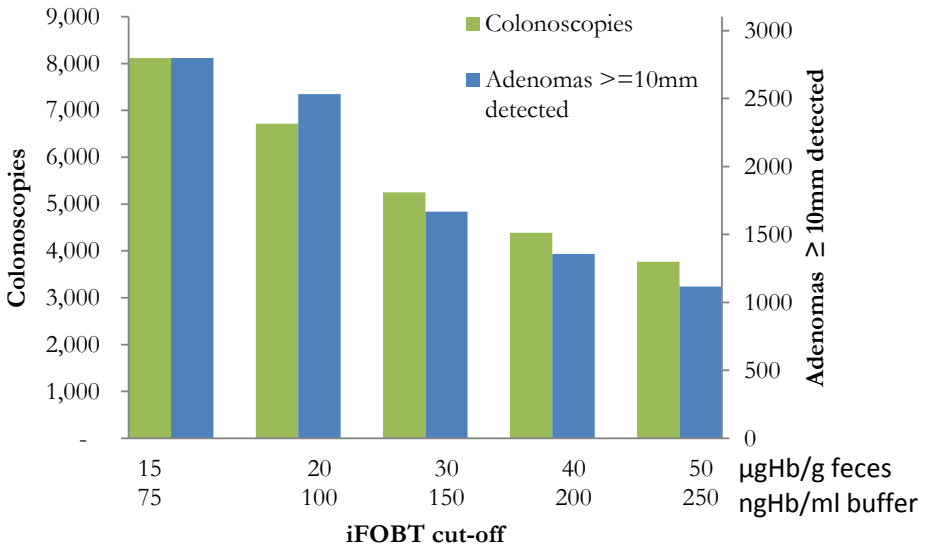
Figure 5 Hypothetical Pilot results based on higher FIT cut-offs – Cancers detected



Source: Data from MoH, graph by Sapere

When using a higher cut-off the reduction in the number of people with adenomas detected is much more pronounced that the reduction in cancers detected. As shown in Figure 6 below, using a higher cut-off reduces the rate of colonoscopies and people with adenomas ≥10mm detected at a similar rate.

Figure 6 Hypothetical Pilot results based on higher iFOBT cut-offs – Adenomas ≥10mm detected



Source: Data from MoH, graph by Sapere

Comparison with other bowel screening programmes

We have compared the results of the pilot with other screening programmes. In our comparison we use values reported in 2010 European guidelines,[13] which represent similar screening parameters to those used in the pilot. The age range was mostly between 50 and 74, and the iFOBT cut-off value was 100 ng.[5,6,7,8] We omitted the results of the Japanese screening programme as not comparable, since the age range is 40+, and there are patient charges associated with the initial screening[9].

There is large variation in the results of screening programmes internationally. The New Zealand pilot's participation rate of 52 percent is in the mid to upper end of the range of 7 – 67.7% percent, based on a recent review of 15 programmes across 12 countries[10].

The comparison of the Pilot to other screening programmes is included in Table 3 below. The New Zealand PPV for cancer is at the lower end of the range found internationally.

Table 3 Comparison of Pilot outcomes for 50 – 74 year olds with other screening programmes

Outcome	RCT	Range from other screening programs	New Zealand Pilot, both rounds all participants
Participation rate	61.5%	55.1% -91%	52%
Positive rate			
Round 1		4.4% - 11.1%	7.53%
Any Round	4.8%	7.1%	-
Round 2		3.9%	5.83%
Colonoscopy compliance rate	96%	75.1% - 93.1%	81%
PPV adenoma	59.8%	19.6% - 40.3%	59.9%
1st screen			
PPV cancer			
1st screen	10.2%	4.5% - 8.6%	4.4%
2nd screen		4.0%	3.9%

Source: Adapted from 2010 European guidelines for quality assurance in CRC screening and diagnosis[13]

1.5 Screening reduces cancer and cancer deaths

In this section we present the evidence regarding the benefits of bowel cancer screening as context for the detailed modelling and results we will present below.

There is high quality evidence that bowel cancer screening results in reduced bowel cancer related mortality. This is frequently shown in randomised controlled trials that compare the outcomes of tens of thousands of patients over periods of 12 to 18 years. Randomised controlled trials (RCTs) report that guaiac-based FOBT screening leads to a 16-22 percent reduction in bowel cancer related mortality. In New Zealand iFOBT is used instead of guaiac-based FOBT. The evidence relating to reductions in mortality is less robust for screening with iFOBT, although iFOBT is reported to perform either as well as or better than guaiac FOBT. For our purposes it is assumed that FIT screening will lead to the same or greater reductions in the incidence of cancer and cancer related mortality.

There is limited evidence that bowel cancer screening reduces the incidence of bowel cancer. Bowel cancer screening has been shown to result in earlier detection of bowel cancer in clinical trial settings.

There are a number of factors that influence the impact of bowel cancer screening. In the following chapter we explore these factors further and discuss how they may affect the results we will present. We compare the reported reduction in bowel cancer related mortality with our estimated reductions, while taking in to account the factors that may differ from the clinical trial settings.

1.5.1 Reviews are the primary source of information

We have used reviews as the primary source of information. Since there have been a number of recent reviews, including systematic reviews, there is little value in undertaking a further formal review ourselves. In instances where we needed more information than was reported in review papers, we used the original published reports of trials and studies.

Search strategy

Our main method for searching was using PubMed. Our search was undertaken in December 2015. Our PubMed search included the search term *"Early Detection of Cancer"[Mesh] and ("Intestinal Neoplasms"[Mesh]) and "fecal immunochemical test"* and was limited to reviews and clinical trials. We also searched the websites of a number of international agencies that are involved in bowel cancer screening.

1.5.2 Evidence for reduced mortality

Evidence

A number of reviews have reported that studies show bowel cancer screening reduces the incidence of bowel cancer and bowel cancer mortality.[11,12,13,14]

The European guidelines for quality assurance in CRC screening and diagnosis summarise the evidence for iFOBT (FIT) as: *"There is reasonable evidence from an RCT that FIT screening reduces rectal cancer mortality, and from case control studies that it reduces overall CRC mortality. There is additional evidence showing that FIT is superior to guaiac-based FOBT with respect to detection rate and positive predictive value"*[13]

Moderate quality evidence for iFOBT

The randomised control trial evidence for iFOBT is of limited value in determining the impact of how screening has been and would be implemented in New Zealand. European guidelines[13] identified one (RCT) for screening with iFOBT that evaluated bowel cancer related mortality. Other reviews imply that there are no RCTs for iFOBT evaluating bowel cancer related mortality[11,12,14].

This RCT found that one round of screening resulted in a reduction in rectal cancer. However, reduction in overall bowel cancer related mortality (i.e. rectal and other bowel cancers) was not statistically significant. [15] There are a number of reasons why these results may not be applicable to the New Zealand context, including:

- The population was Chinese aged 30 and above (a third under the age of 40);
- The iFOBT kit was developed by the authors, which differs from the test used in New Zealand;
- A quantitative individual risk-assessment questionnaire was also used to determine those at high risk;
- Positive iFOBT was followed up with flexible sigmoidoscope rather than colonoscopy;
- There was only one round of screening.

Three case controlled studies of iFOBT screening reported a significant reduction in bowel cancer mortality ranging from 23 to 81 percent. The range depended on the study and years since last iFOBT[13] These studies matched patients who either had a diagnosis of advanced bowel cancer[16] or death[17,18] from bowel cancer. The patients were from areas in Japan that offered screening with iFOBT to those aged 40 and over. In order to estimate the efficacy of screening they matched each person with a diagnosis of advanced bowel cancer or death from bowel cancer to area of residence, gender and age. This allowed a comparison of outcomes for those that participated in screening and those who did not. While these studies add confidence that bowel cancer screening with iFOBT will reduce bowel cancer mortality, they cannot (easily) be used as a comparison for our results.

High quality evidence for guaiac based FOBT

Randomized controlled trials have only been used to show reduced incidence of bowel cancer and/or bowel cancer mortality with screening programmes using either traditional guaiac-based FOBT or flexible sigmoidoscopy. Although RCTs have not shown that iFOBT decreases bowel cancer mortality, it is argued that they are unnecessary since iFOBT has demonstrated superior performance characteristics to guaiac-based FOBT[11,14]. In this section we summarise the findings from the RCT of guaiac-based tests in order to provide an estimate of the benefits from iFOBT screening.

There is some disagreement as to whether iFOBT is superior to guaiac-based FOBT. The American National Cancer Institute state that there is no clear evidence of superiority for either test[12]. However other reviews conclude that iFOBT is superior[11,13,14].

Three systematic reviews have evaluated the evidence for the efficacy of gFOBT screening. All three reviews found a significant reduction in bowel cancer mortality. The reviews did not find an effect on all-cause mortality.[13] The authors of one review noted that it was not

surprising that no effect on all-cause mortality was found, since bowel cancer accounted for only approximately 3.5 percent of deaths in the study groups[19].

The Cochrane systematic review considered four randomised control trials (RCTs) which indicated that screening had a 16 percent reduction (95% CI 10% -22%) in the relative risk of bowel cancer mortality. When adjusted for screening attendance in the individual studies, there was a 25 percent relative risk reduction (95% CI 16% - 0.34%) for those attending at least one round of screening. The studies included in the review included 320,000 participants and follow up ranged from 8 to 13 years[20]. Table 4 below includes a summary of the four RCTs included in the review.

One of the reviews,[19] reported that screening had a reduction in bowel cancer related mortality during 10 years, but decreased in screening periods beyond 10 years. In the Funen study the reduction in bowel cancer related mortality dropped to 11 percent after 17 years follow up, compared with 18 percent after 10 years[21].

Within each of the studies, those who entered were randomly allocated to receiving screening or not. The number of screening rounds in each of the trials ranged from two to nine. Follow was between 12 and 18 years. The rate of bowel cancer related mortality between those screened and those in the control arm was compared as the end of the follow up period.

Three of the four trials in the Cochrane review reported a reduction in the incidence of bowel cancer, with one study reporting an increase. The review did not attempt to quantify the pooled impact on the incidence of bowel cancer. All four of the trials reported an increase in early stage cancers (Dukes A) detected and a decrease in late stage cancers detected (Dukes C and D). The Authors noted that the proportion of cancers screen detected was fairly low, 23-46 percent of Dukes A in the two studies that reported.[20] A comparison of the proportion of cancers by stage (Dukes A to D) for screening and non-screening (control) for each of the four trials is shown in Figure 7 below.

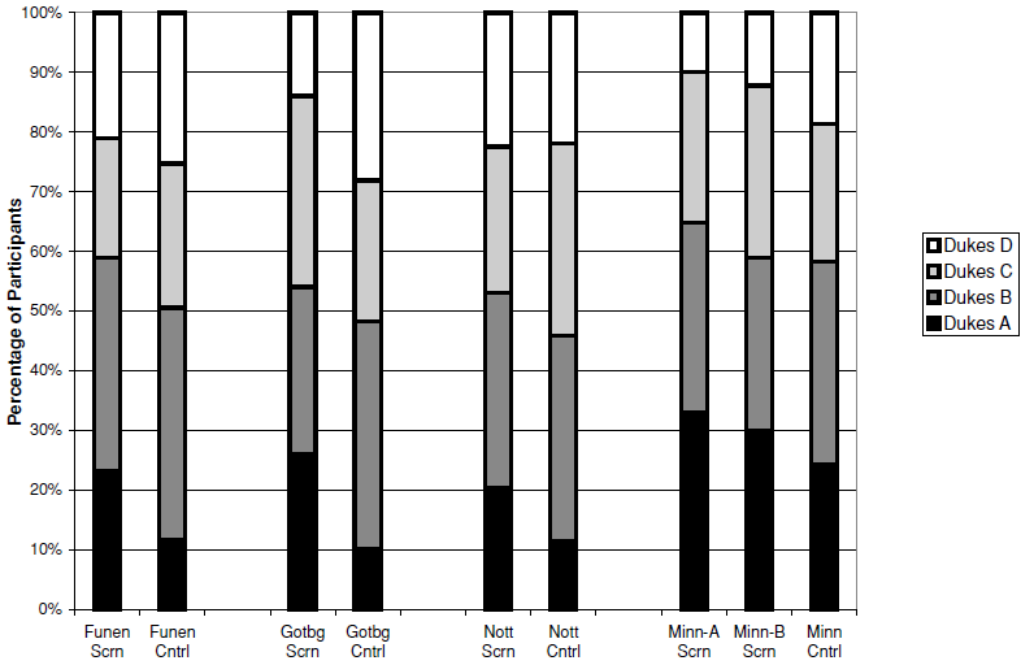
Two of the studies (Goteborg and Minnesota) used re-hydrated slides in testing; this resulted in higher positivity rates but lower positive predictive values (PPV) for detecting cancers. The overall impact of using re-hydrated slides was that a similar number of cancers were detected, but an increased number of adenomas[20].

Table 4 Summary of randomised controlled trials evaluating the impact guaiac-based FOBT screening on bowel cancer mortality

Study	Funen	Goteborg	Minnesota	Nottingham
Country	Denmark	Sweden	U.S.	U.K
Lead Author	Kronberg[21]	Lindholm[22]	Mandel[23]	Hardcastle[24]
Number invited to Screening	30,967	34,411	31,157	76,466
Age range	45-75	60-64	50-80	45-74
Length of follow up (years)	17	15.5	18	11.7
First year of study	1985	1982	1975	1981
No. of screening rounds	9	2	6 (Biannual)	6
Participation rate? First screening At least one round	 66.8% -	 63.3% 70.0%	 - 75% -78%	 53.4% 59.6%
Rehydration	No	Mostly‡	Mostly‡	No
Positivity 1st round Re-screening	1.0% 0.8-3.8%	3.8% 4.2 – 4.4%	9.8‡ (All rounds)	2.1%* 1.2*
PPV Adenoma (≥10mm) 1st round Re-screening	32% 15-38%	14.2% 13.3-14.2%	NR	33%* 25%*
PPV cancer 1st round Re-screening	17% 5-19%	5.9% 4.1%	1.9-2.7% (All rounds)	9.9%* 11.9%*
Risk reduction in bowel cancer mortality	11%	16%	21-33%	15%

‡ Rehydration was started during the Goteborg and Minnesota studies. Rehydration was adopted early in the follow up period. In the Minnesota the positivity increased from 2.4% t0 9.8% once rehydration was started
* Results from Nottingham: first screening are based on respondents to first invitation, Re-screening is based on those rescreened within 27 months
NR: Not reported, reporting for Minnesota was limited to polyps detected and no information on size was provided.
Source: Reproduced from Hewitson et al 2008[20]. Positivity and PPV taken from original publications

Figure 7 Comparison of the stage of cancers detected in the randomised controlled trials evaluating the impact guaiac-based FOBT screening



Source: Hewitson et al 2008[20]

Evidence does not yet support any one screening test over another

The American College of Physicians, the National Colorectal Cancer Roundtable, the American Cancer Society, and the Journal of the American Medical Association have all issued statements that evidence does not yet support any one screening test over another and that the currently available CRC screening, the available test include stool based tests (iFOBT and guaiac-based FOBT), flexible sigmoidoscopy and colonoscopy[11].

In terms of stool based tests the iFOBT has now largely replaced guaiac-based FOBT. Guaiac-based FOBT is no longer recommended by any of the U.S. screening for CRC guidelines[14].

2. Methods

2.1 General methods

A cost-effectiveness analysis (CEA) compares the incremental costs and outcomes (effects) of different courses of action. In this case, we are comparing the screening programme with the status quo, essentially opportunistic diagnosis of colorectal cancer. Typically the results of the CEA are expressed in terms of a ratio where the denominator is a gain in health from a specified measure (such as years of life gained or premature births) and the numerator is the cost associated with the health gain.

We have undertaken a cost utility analysis (CUA) – a specific form of CEA. The CUA approach measures the effects of interventions in quality-adjusted life years (QALYs) rather than trying to value the consequences of interventions in monetary terms (as would be the approach in a standard Cost Benefit Analysis). The QALY measures the number of years of healthy life gained as a result of the intervention.

We completed three key work-streams of activity to produce the following outputs:

- **A: Effectiveness -** identifying the impact of screening on health outcomes to produce the following primary outputs:
  - cancer incidence (counts and rates) by cancer stage and site, and cancer related mortality that would eventuate in the absence of the screening programme;
  - life-years gained due to screening;
  - utility scores for defined health states along the screening and treatment pathway; and
  - quality adjusted life-years gained (QALYs) due to screening.
- **Costs -** determining the cost of providing screening and the incremental cost impact to produce the following outputs:
  - current costs of diagnosis and treatment of bowel cancer;
  - key resources (and their costs) for designing and implementing the BSP; and
  - the impact on diagnostic and treatment services as a result of the screening and the net change in cost;
- **Putting the results into context -** determining cost effectiveness and undertaking comparative analysis to produce the following primary outputs:
  - the incremental cost per QALY for screening if done the same way as the pilot (in comparison with the status quo);
  - the estimated incremental cost per QALY for national implementation of a bowel screening programme under various scenarios (in comparison with the status quo);
  - sensitivity analysis to assess reliability and validity of results of the CUA;
  - comparative analysis to assess the relative potential value of bowel screening in New Zealand, with similar programmes evaluated overseas and with other interventions; and

- Comparative analysis with published cost effectiveness analysis to assess the reliability of the CUA.

We used the perspective of health funder for this study. This means that we have focussed on the costs incurred by the state health sector along each stage of the screening and treatment pathways. This approach is narrower than a broader societal perspective incorporating indirect costs to other government sectors and society, (such as lost productivity), but enables better comparison with other CEA studies of bowel screening programmes.

2.1.1 A wide range of factors influence the impact of screening

The efficacy of screening depends on a number of parameters, including:

- Existing burden of bowel cancer: the prevalence of adenomas and cancers in the population. Key determinants are:
  - age of the population and when they develop bowel cancer;
  - trend in incidence of bowel cancer;
  - stage at which cancers are diagnosed;
  - existing methods for detection.
- Eligible population, i.e. who is invited to screening;
- Participation rate, i.e. how many people participate in screening and return a sample;
- Performance of iFOBT in detecting adenomas and cancers, with the performance dependent upon the cut-off used;
- Attendance for follow up colonoscopy;
- Treatment of cancers, and follow up for those at higher risk of development of cancer.

The New Zealand cancer registry provides us with the burden of bowel cancer. The cancer registry provides information on the number of bowel cancers diagnosed and how many people die from bowel cancer, with information on the stage of the cancer at diagnosis and about the person (such as age, gender and ethnicity). The cancer registry data has been used to calibrate the natural history model we are using to simulate the incidence of cancer in the absence of a screening programme. We then apply a screening scenario to estimate the impact screening has on the bowel cancer for a given population against this baseline.

The experience of the pilot provides us with information on many of the necessary parameters. During the period of the pilot for which data are available (3.5 years) 237,699 patients were invited, 130,950 FIT kits returned, and 8,115 people who had colonoscopies. Further sub group analyses provide information on the performance of iFOBT in different age groups targeted and at different cut-off values.

We will use additional studies and reports of screening experience to supplement the information from the pilot. For example we use studies on the sensitivity and specificity to determine the rate of false negatives, i.e. the number of people with a negative iFOBT test that had an adenoma or cancer. Further, we use international experience to estimate the impact of running a screening programme beyond four years.

2.1.2 Focus on single iFOBT at a range of cut-off values and a range of age bands

When assessing the safety and efficacy of bowel cancer screening we have focused on how screening was implemented during the pilot. We also assess the cost-effectiveness of screening if a national roll-out was implemented differently from the pilot.

The pilot used a single sample iFOBT (also referred to as 'fecal immunochemical test' or FIT). The particular iFOBT used in the pilot is known as OC-Sensor. The sensitivity cut off for test positivity in the pilot was 75 ng HB/mL. The population offered screening were those aged 50 – 74 at average risk of cancer (i.e. excluding people at high risk of bowel cancer, such as those with a family history of bowel cancer).

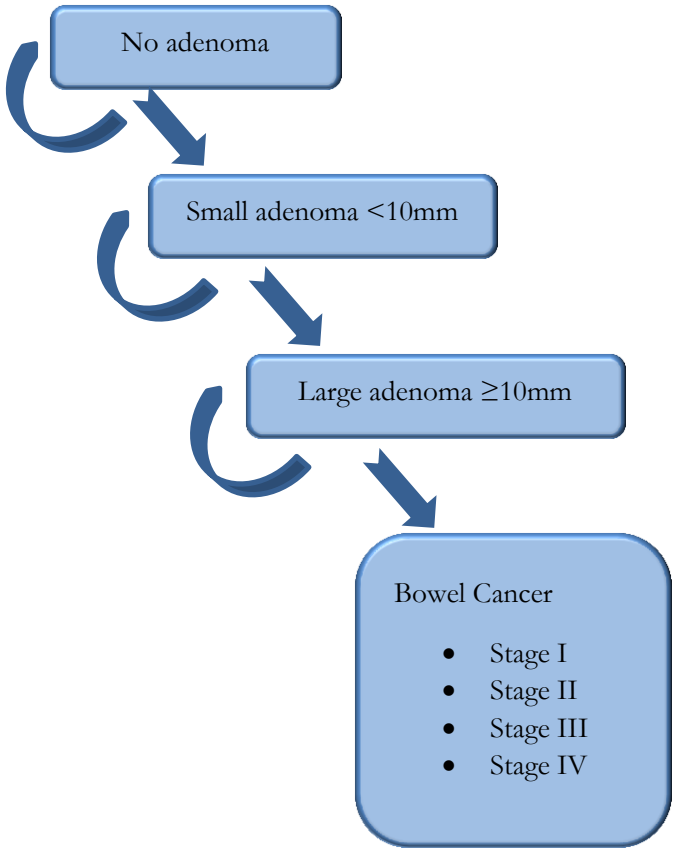
We have modelled screening using one iFOBT test per screening round. Evidence suggests there is little or no benefit of performing more than one iFOBT test per screening round.[63,32] However other parameters may vary in any future implementation of screening. Specifically, we considered varying iFOBT cut-offs, and different age bands of invited people.

2.2 Modelling the natural history of bowel cancer

We used microsimulation to model the natural history of bowel cancer. The MoDCONZ (Modelling Disease and Cancer Outcomes in NZ) microsimulation model was developed by a team of researchers from the University of Otago. We were granted permission to use the model by the research team, and contributed to the final development, refinement and implementation of the model.

The MoDCONZ model is a micro-simulation of life histories for a hypothetical sample of people. The sample is defined by age and sex parameters. The model has at its core a natural history of colorectal cancer, which captures the adenoma-carcinoma sequence, with assumptions (developed from extensive review of the clinical literature) based on the probabilities of initiation, progression and response to treatment of colorectal cancers – see Appendix 1 for details. Essentially, the model simulates the progression of individuals through the clinical sequence, as shown in Figure 8 below. Adenoma risk and growth are modelled as a random process with systematic variation across age, gender, ethnicity and other risk factors measured at the individual level.

Figure 8 Natural history of adenoma to bowel cancer



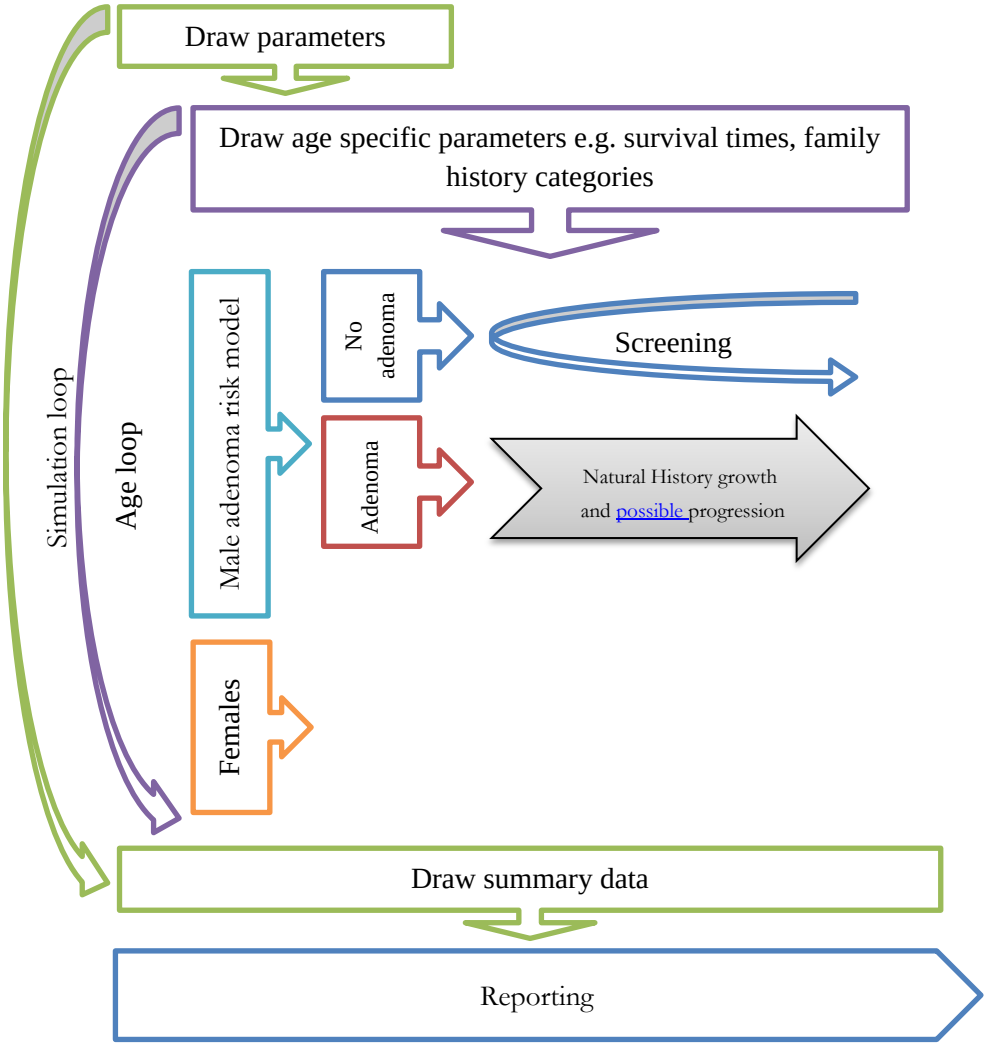
In order to understand the current pattern of health outcomes we ran the MoDCONZ model with a hypothetical sample of people. The model forecast the cancer incidence (counts and rates) by cancer stage and cancer related mortality, that would eventuate in the absence of the screening programme.

The MoDCONZ model allows the user to lay a screening programme over the base forecast in order to assess the impact of screening on bowel cancer related health outcomes. Essentially, any individuals who are screened and receive a positive diagnosis of cancer have their survival pattern altered, adjusted relative to demographic parameters. Further, if adenomas are detected, the adenomas are removed and the risk of them developing further is reduced.

Figure 9 below shows the high level architecture of the MoDCONZ algorithm. A set of parameters are drawn for each simulation loop and used for the modelling of each individual in the population. For each age the population is processed in four groups: for each gender the adenoma risk model (see Appendix 1) is applied to divide the cohort into those with and without a lifetime risk of developing adenomas. For those with no adenomas there is no base case, but the cohort is run through screening to determine the number of people eligible, the returned iFOBTs and the consequences, including false positives and colonoscopies. For those with adenomas, their natural history simulation models adenoma growth and potential progression into cancers and cancer deaths, and the base case for those with detected cancers

is collected in the same manner as for the cohort participating in screening. Data is collected for each simulation and processed for reporting.

Figure 9 MoDCONZ algorithm architecture



Outputs from the MoDCONZ model

MoDCONZ allows for extensive reporting on a number of outcomes which can be broken down into distinct categories. Outputs can be separated out according to groups of screening/no screening, sex and age. The key outputs from MoDCONZ include:

- Incidence of bowel cancers by stage;
- Incidence of bowel cancer related deaths;
- Life years;
- Quality adjusted life years (QALYs);
- Number of FITs completed;
- Number of colonoscopies;
- Cost of screening;
- Cost offsets from screening.

2.2.2 Model calibration and validation

The base microsimulation model addresses the sensitivity of the natural history parameters through a Bayesian calibration with incidence and death data.

Bayesian calibration

The set of parameter vectors for the simulation are the output of a Bayesian calibration process. The natural history model has many parameters that are not known constants. The multiple sets of parameter vectors collectively represent the uncertainty of their values. By looping the natural history model through a large number of parameter vectors, an estimation of the credible intervals of the outcome of interest (e.g. number of cancers) can be obtained by statistical measures of the resulting sample of values obtained for that outcome.

Approximately, the Bayesian calibration involves finding the parameter sets that lead the model outputs to match our observed calibration targets from the New Zealand cancer register as well as possible. The resulting posterior set contains 100 parameter vectors. We use a normal approximation based on the mean and variance to derive the uncertainty of outcomes.

For a larger parameter set of 1000, the 95% approximate credible intervals are obtained by locating the 2.5th and 97.5th percentiles of the outcome of interest.

2.2.3 Falling rates of bowel cancer mortality

In New Zealand, and a number of other countries, the rates of bowel cancer mortality and incidence have been falling for the last 30 years. Over the 20 years prior to 2005 the NZ bowel cancer mortality rate for men decreased by 35 percent[25]. The MoDCONZ model accounts for this decreasing trend in bowel cancer mortality and incidence through a quadratic fit to underlying incidence. While this fits the observed data, this approach limits the degree to which future extrapolation of incidence (and therefore screening impact) can robustly be conducted.

2.3 Screening intervention model

We added a screening intervention model to MoDCONZ in order to estimate the benefits and costs of bowel cancer screening. The screening intervention estimates the:

- earlier detection of bowel cancer and the resulting changes in bowel cancer mortality;
- costs of screening (including surveillance); and
- cost offsets from reduces treatment of cancer.

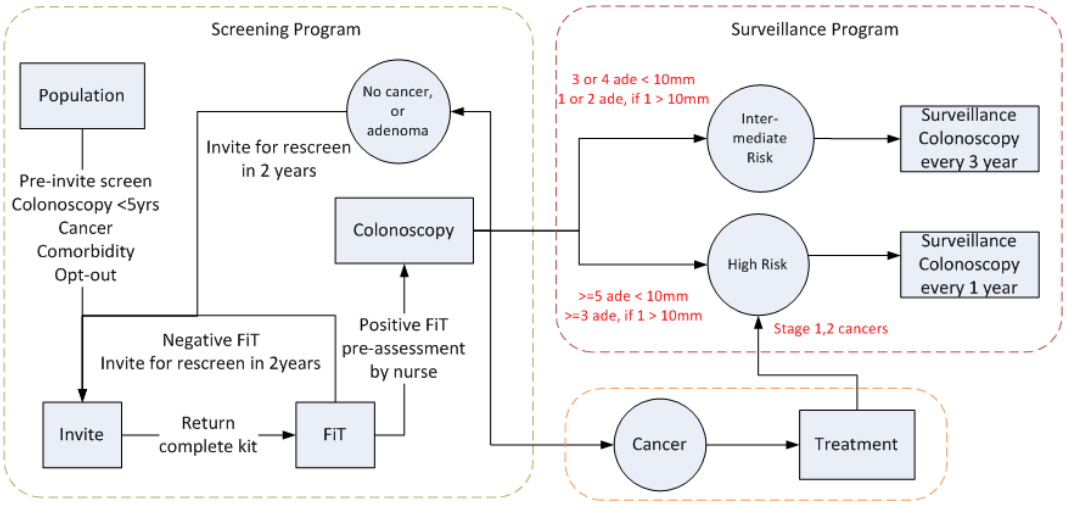
The screening intervention model is summarised in Figure 10 below. A number of steps are modelled, from the proportion of the population invited through to the outcomes from colonoscopies. The values used, and the underlying evidence base, for each step of the intervention model is detailed in the following sections.

The screening steps in the model are as follows:

- Population for screening identified, based on invitation criteria, i.e. age;
- Most people who meet the criteria are invited and sent an iFOBT kit;
- Some patients return iFOBT that can be analysed;
- People notified of iFOBT result:
  - Positive tests are followed up with a call from the person's general practitioner, and the person is referred for colonoscopy;
  - Negative results are notified via mail to the participant and their GP, the person is invited to screening in the next round (as long as they still meet the invitation criteria).
- Invitation to colonoscopy for those with a positive iFOBT:
  - If cancer found, treatment is offered and the person leaves screening for treatment. Early (Stage 1 or 2) cancers enter the colonoscopy surveillance program;
  - Adenomas are removed (in our model we assume all adenomas ≥3mm are removed);
  - Intermediate and high risk patients, defined by the number and size of adenomas, leave screening and enter colonoscopy surveillance;
  - Histology is performed on all adenomas and cancer found;
  - Low risk patients and those without adenomas[i] are invited to screening in the next round.

[i] In the pilot, when those who had a colonoscopy and no adenomas were found, they were invited back to screening in five years. In MoDCONZ we model the participants being invited back in two years. The difference is unlikely to have a significant effect on the result.

Figure 10 Screening and surveillance intervention model schematic



2.4 Modelling specifications

2.4.1 Cohort

We have modelled a cohort of patients from age 40 through to death, assuming a maximum age of 111. Our cohort is notionally based on those born in 1957, a cohort of 56,552 people (based on the number alive at age 44) made up of 27,832 males and 28,720 females. This approach allows us to track a population through the entire duration of screening, i.e. from first to last year of eligibility. This approach represents the steady state cost-effectiveness, which may differ from the cost-effectiveness in the short term (since in the short term screening is offered for the first time to those who are towards the end of the age band). Cost and QALYs are calculated from the age of 50, i.e. the first year screening is offered.

2.4.2 Discounting

As with all economic analyses, we discount future benefits back to today's dollars. A discount rate of 3.5 percent p.a. is applied to benefits and costs. 3.5 percent is the standard discount rate applied by New Zealand's pharmaceutical purchasing agency PHARMAC[26] in economic analysis, and facilitates comparability of results for this analysis with analyses for other health interventions. The discount rate is a 'real' rate of return, i.e. inflation is accounted for within the discount rate.

2.4.3 Proportion invited

Nearly all of the population aged 50 – 74 in the Waitemata district were invited to take part in screening and sent a iFOBT kit; however 4 percent were not invited. The reasons for not being invited include:

- People opted out;
- Registered as already having bowel cancer and/or in surveillance;

In our model, we assume that 96 percent of people in the eligible age range would be sent an iFOBT kit.

2.4.4 iFOBT participation rate

The New Zealand pilot provides information for two rounds of screening. In the base case we assume the participation rate by age band will be the same for future rounds. We explore scenarios using a range of participation rates, which will inform the value of programmes to sustain or improve the participation rates.

We define iFOBT participation rate as the proportion of people sent an iFOBT kit that return a kit that produces a result. Those who return a kit which cannot be analysed are counted as not participating.

We have included three parameters in our model for iFOBT participation:

- New to screening, i.e. the first round;
- Participated in previous round;
- Did not participate in previous round.

We have assumed that in the steady state iFOBT participation for Maori will be the same as for the whole population. While the participation rate for Maori was lower than the overall population in the pilot, in the 2nd round of the pilot Maori had the highest rate of participation among those who did not participate in the 1st round. If this trend of increased participation for Maori continued then the participation rate for Maori will ultimately converge with the overall population.

Participation based on the pilot

The preliminary results of the pilot provide participation rates split by age group and previous participation. For those new to screening, we use the rates reported by age groups (reported as 'new to screening' Table 5 below). For those who have previously been invited to screening, the participation rates are dependent on whether the individual participated in the previous round.

In order to estimate the participation rate given participation in previous rounds, we applied the observed ratio of increased participation. For example, for all age groups the participation rate is 1.51 higher (83 percent compared with 55 percent) for those who have previously participated compared with those participating in the first round. Applying this to those aged 50 – 54 results in an estimated participation rate of 62 percent for those who previously participated. For the age group 70 – 74 the participation rate in the pilot was 70 percent, applying a multiplier of 1.51 to estimate the participation rate for those who previously participated would results in an estimate exceeding 100%; therefore in this case we have assumed a participation rate of 95 percent.

Table 5 Participation rates used in our model

Age group	50-54	55-59	60-64	65-69	70-74
New to screening	43%	49%	56%	64%	70%
Participated in previous round	65%	73%	85%	95%	95%
Did not participate in previous round	18%	21%	24%	27%	30%

Comparison with published analyses

In the four cost-utility analyses we reviewed in detail, three included participation rates in the base case. The rates were ~37 percent[27] and 60 percent[28,29]. One analysis assumed 100 percent participation and varied the rate in the sensitivity analysis[30]. The published analyses we reviewed used the same participation rates regardless of age or previous participation of the individual (although one study assumed all invited would participate at least once[29]). It is not surprising that the participation rates varied, since international experience shows a wide range of participation.

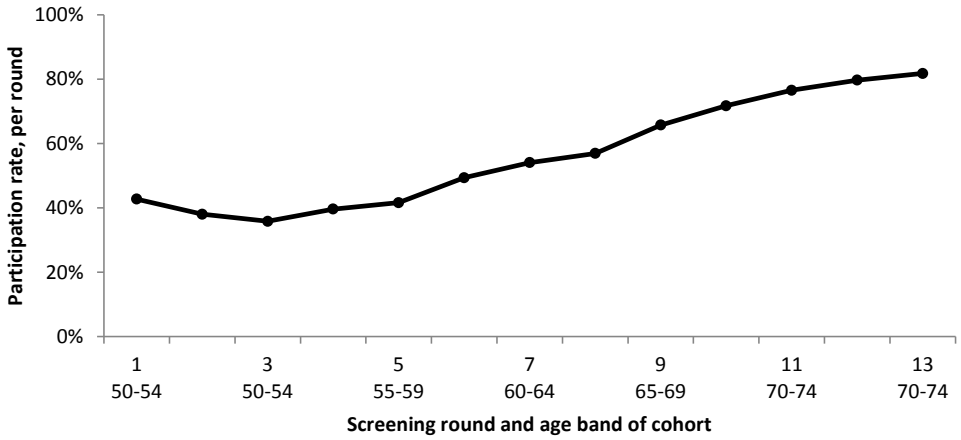
Examples of participation rates changing over time with varying starting age for cohorts

We have included our projected participation rates in order to illustrate the impact of using our estimated participation rates. We include two scenarios to show the impact of starting screening at different ages.

Example: starting with a cohort of age 50

Figure 11 below shows how the participation rate changes over time for a cohort with a starting age of 50 (i.e. the base case for our analysis). The participation rate is 43 percent in the first round and drops to the lowest participation rate of 36 percent in the 3rd round. The participation rate rises steady to a maximum of 82 percent in the 13th round. The average participation rate is 56 percent.

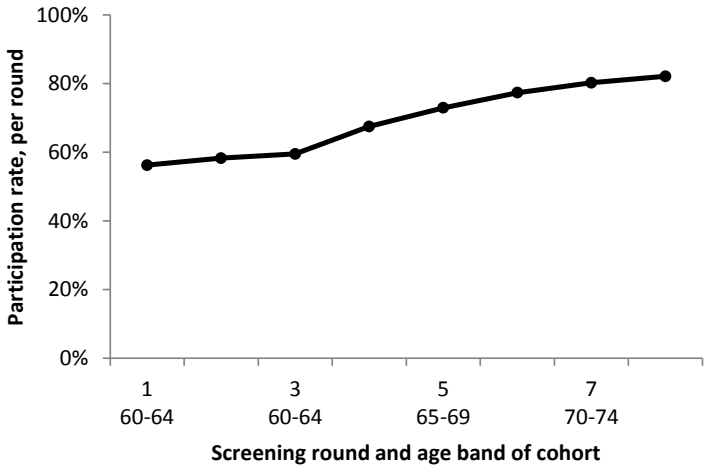
Figure 11 Example of participation rates changing over time: starting with a cohort of age 50



Example: starting with a cohort of age 60

Figure 12 below shows how the participation rate changes over time for a cohort with a starting age of 60. The participation rate is 56 percent in the first round. The participation rate rises steady to a maximum of 82 percent in the 9th round. The average participation rate is 69 percent.

Figure 12 Example of participation rates changing over time: starting with a cohort of age 60



2.5 Performance of iFOBT

The performance of iFOBT, as with any test, is measured as sensitivity and specificity. Sensitivity is the ability to correctly detect those with adenomas or cancers. Specificity is the

ability to correctly identify those without either adenomas or cancers. The sensitivity and specificity, along with the prevalence, determine the positive predictive values, i.e. the likely hood that someone with a positive FIT has an adenoma or cancer.

2.5.1 Data source for iFOBT performance

Our approach to determining the performance of iFOBT had two elements. Firstly we used studies where all participants received a colonoscopy (as a gold standard investigation) to determine the sensitivity and specificity of iFOBT at a given cut-off. Secondly we used the results of the pilot to infer how the sensitivity and specificity change for different cut-off levels.

Evidence for sensitivity and specificity

Our search revealed four studies that reported on the sensitivity and specificity of iFOBT where all subjects were given a colonoscopy to confirm whether they had adenomas or cancer.

We used the results of a large Japanese study, reported by Morikawa et al,[31] to form the basis of the estimates in our analysis. We used this study as the basis for our estimates for sensitivity and specificity because of the large sample size and detailed reporting. The large sample makes for more robust estimates for the less common finding of cancers. Even in this large study only 81 cancers were detected. The second largest study we reviewed[33] only detected 8 cancers. None of the other three studies we reviewed included estimates of sensitivity and specificity for non-advanced adenoma or the difference stages of cancers.

Comparison of Morikawa et al with other studies.

We compared the sensitivity and specificity values reported by Morikawa et al with results from three other studies. The results are similar in all four cases, although the sensitivity and specificity reported by Morikawa tend to be a little lower than the other studies.

The comparison has a number of limitations, which include the different countries, age bands, brand of iFOBT test used and the definition of advanced adenoma. Despite these limitations, the comparison gives us confidence that the sensitivity and specificity values reported by Morikawa et al provide the best available basis for our model.

Table 6 summarises the comparison of the sensitivity and specificity values. Where a range of results are reported we have taken those that are most comparable with Morikawa and the pilot; e.g. a single iFOBT test and using a cut-off of 100 ngHb/ml buffer.

Further details of the Japanese study are included in the following section. Details of the other studies are detailed in Appendix 2 (details of iFOBT performance).

Table 6 Comparison of sensitivity and specificity of a single iFOBT test in asymptomatic population

Country, lead Author	Detecting advanced Adenoma*		Detecting cancer		Brand	Positivity	Population
	Sensitivity	Specificity	Sensitivity	Specificity			
Japan Morikawa[31]	22.8 (19.4 – 26.2)†	95.1† (94.8 – 95.1) †	65.8 (55.4 – 76.3)	94.6 (94.3 – 94.9)	Magstream 1000	5.6%	21,805 patients Average age of 48.2 years 1983 and 2002
Korea Park[32]	23.7 (13.6 – 36.6)	94.0 (91.9 – 95.6)	69.2 (38.6 – 90.9)	93.7 (91.7 – 95.3)	OC sensor	NR	770 patients Aged 50 – 74 2007 to 2008
Amsterdam de Wijkerslooth[33]	29 (21- 39)	97 (95 - 98)	75 (36-96)	95 (93 - 96)	OC sensor	6%	1,256 patients Aged 50 – 74 2009 to 2010
Germany Brenner[34]	NR	NR	73.3 (NR)	95.5 (NR)	OC sensor	NR	2,235 patients Aged 50 –79 2005 - 2009

† Morikawa: The 95% CI for Advanced adenoma were not reported, we assumed the same range as for adenoma ≥ 10 mm excluding high-grade dysplasia as reported in Morikawa 2005. The specificity was not reported, the values in the table in below refer to the specificity for advanced neoplasia (i.e. includes cancers)

*Advanced adenoma defined different for each of the studies,

Morikawa - adenomas with diameters of ≥ 10 mm (Reported in the follow up 2007 publication)

Park - tubular adenomas with diameters of ≥ 10 mm, or to tubulovillous or villous adenomas, or those with high-grade dysplasia regardless of size.

de Wijkerslooth - adenoma ≥ 10 mm, an adenoma with villous histology (≥ 25 % villous), and / or an adenoma with high-grade dysplasia

Details of the large Japanese study used to base our estimates of sensitivity and specificity

Morikawa et al provide details regarding the sensitivity and specificity of the iFOBT, based on 21,805 patients who were undergoing colonoscopy who also undertook iFOBT.

We used two publications from the study. The first publication[35] is the main report, which provides information on overall specificity and sensitivity by stage of cancer. The second publication[35] was used to determine the sensitivity of detection for adenomas <10mm and ≥10mm. A key limitation of this study is the relatively low age of the participants, where the average age of 48.2 years is below the age bands commonly recommended for screening. However, despite the low age, the positivity of the iFOBT test was 5.6 percent, which is not much lower than the positivity in the first round New Zealand pilot of 7.5 percent.

The study used a single iFOBT test with 100ng HB/mL cut-off (reported as *20* µg/g). The test used was a Magstream 1000/Hem SP automated system (Fujirebio). The study was undertaken in Japan between 1983 and 2002. The Magstream 1000 used in this study is reported not to perform as well as the OCsensor test used in the New Zealand pilot, on the basis of a direct comparison of the two iFOBT tests. At the same cut-off level, the Magstream was reported to have greater sensitivity but lower sensitivity than OC sensor[36]. Another study found that neither the OC sensor or Magstream appeared to be better than the other[37].

Table 7 Sensitivity and specificity reported by Morikawa et al, based on 1 FIT with 100ng cut-off

Disease	Sensitivity (95% CI) %	Specificity (95% CI) %	Positivity* %	Positive predictive value (PPV)* %
Non-advanced adenoma	10.4 (9.5 – 11.3)	95.5 (95.2 – 95.8)	5.6%	2.4%
Cancer	65.8 (55.4 – 76.3)	94.6 (94.3 – 94.9)	5.6%	4.2%
Advanced adenoma or Cancer	27.1 (23.9 – 30.3)	95.1 (94.8 – 95.4)	5.6%	16%

Source: Morikawa et al 2005[31]

2.5.2 Performance of iFOBT at different cut-off levels

In order to estimate the sensitivity and specificity of iFOBT at different cut-off levels, we started with the results reported by Morikawa et al based on a cut-off of 100ng Hb/mL (reported as *20* µg/g). and applied the relative changes in adenomas or cancers detected at different cut-off levels as observed in the New Zealand pilot.

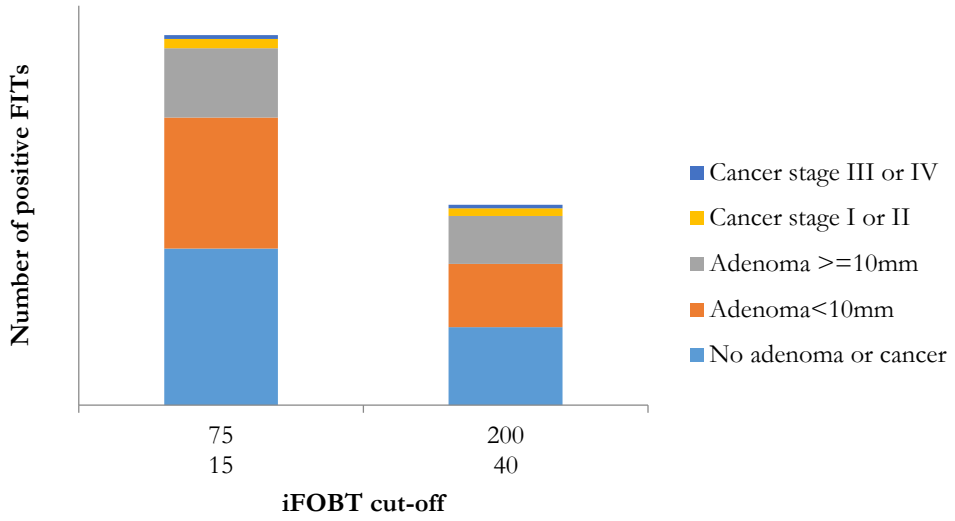
We were provided with the results of 8,336 colonoscopies performed as part of the New Zealand bowel screening pilot. All colonoscopies were undertaken for people with an iFOBT result of 75 ng Hb/mL and above. The dataset reported the most advanced finding

(i.e. most advanced cancer or largest adenoma) and the ng HB/mL level of the FIT. This allows us to estimate how many adenomas or cancer may have been detected at different cut-off levels.

Using a cut-off of 200 instead of 75 ng Hb/mL would result in 46% fewer positive iFOBT results; i.e. a fall in positivity from 6.8 percent to 3.7 percent. There would be a reduction in all findings, from no adenomas to advanced cancers, shown in Figure 13 below.

PPV for cancers increases at higher cut-off, i.e. although fewer cancers are found, a positive FIT is more likely to mean the person has a cancer. The proportion of people with positive FIT that have bowel cancer is estimated to be 3.5 percent and 5.5 percent at 75 and 200 ng Hb/mL cut-off respectively. This is below the high level recommended in European guidelines.

Figure 13 Comparison of the number of positive iFOBTs (FITs) at different cut-offs



2.5.3 Sensitivity and specificity values used in our analysis

The sensitivity of the iFOBT is greater for cancers than for adenomas. Further, the sensitivity is greater for those with advanced cancer than early cancer. The estimated sensitivity for early stage cancer (stage I or II) is 59.7 percent, compared with late stage cancer (stage III or IV) with a sensitivity of 85.9 percent. The sensitivity for adenomas is relatively low with a 7.7 percent and 25.2 percent sensitivity for small (< 10mm) and large (>=10mm) adenomas respectively. The specificity is estimated to be 94.7%, that is a person without an adenoma or cancer has a 5.3 percent chance of a positive iFOBT (i.e. false positive).

In order to model the cost-effectiveness of screening using different iFOBT cut-off values, we estimated the sensitivity and specificity at different cut-off values, which were then used in our scenario analyses. Increasing the cut-off increases the specificity and decreases the sensitivity, reducing both true and false positive results. The sensitivity and specificity values

at different cut-off levels are reported in Table 8 below. The estimates are separated for size of adenoma and stage of cancer.

Table 8 Estimated sensitivity of a single iFOBT at different cut-off levels

Cut-off (ng HB/mL)	Specificity	Sensitivity, base value (95% CI)			
	Adenoma or cancer	Adenoma <10mm	Adenoma >= 10mm	Cancer – Stage 1 or 2	Cancer – Stage 3 or 4
75	94.7% (94.4% - 95%)	7.7% (7.1% - 8.4%)	25.2% (22.2% - 28.2%)	59.7% (27% - 92.5%)	85.9% (67.4% - 100%)
100	95.5% (95.2% - 95.8%)	7% (6.4% - 7.6%)	22.8% (20.1% - 25.5%)	56.5% (25.6% - 87.5%)	78.3% (61.4% - 95.1%)
150	96.4% (96.1% - 96.7%)	4.6% (4.2% - 5%)	19.8% (17.4% - 22.1%)	51.8% (23.5% - 23.5%)	73.5% (57.7% - 89.3%)
200	97% (96.7% - 97.3%)	3.7% (3.4% - 4.1%)	17.4% (15.4% - 19.5%)	50.4% (22.8% - 78%)	70.6% (55.4% - 85.8%)
250	97.4% (97.1% - 97.7%)	3.1% (2.8% - 3.4%)	15.8% (13.9% - 17.6%)	47.7% (21.6% - 73.9%)	66.8% (52.4% - 81.2%)

2.5.4 Comparison with published analysis

Of the four analyses we reviewed in detail, only one assessed iFOBT using a cut-off of 75ng Hb/ml[28]. Two of the analyses assessed FOBT rather than iFOBT[27,29], while the other analysis did not specify the cut-off used for iFOBT[30]. The values used in the published analysis for an iFOBT with a cut-off of 75ng Hb/ml are comparable to the values we use[28]. The points of distinction are that our specificity is lower but our sensitivity values for adenomas are higher.

Table 9 Sensitivity and specificity values used for an iFOBT with cut-off of 75ng – comparing our estimated with a published study

	Goede et al[28]	Our analysis
Specificity	97.05 %	94.7%
Sensitivity		
Adenoma ≤ 5mm	0%	7.7%
Adenoma 6-9mm	5.7%	7.7%
Adenoma ≥10mm	14.4%	22.5%
Early cancer	58.5%	59.7%
Late cancer	87.0%	85.9%

2.6 Colonoscopy

In this section we report the values and rationale for the following colonoscopy related inputs:

- Rate of successful colonoscopy;
- Accuracy of colonoscopy (sensitivity and specificity);
- Complications from colonoscopy.

2.6.1 Rate of successful colonoscopy

People with a positive iFOBT test are invited to have a colonoscopy. The rate of colonoscopy is lower than 100%, since some people may not respond, while in some cases a colonoscopy cannot successfully be performed.

In the pilot, 92 percent of people with a positive iFOBT had a successful colonoscopy. In the first round of the pilot, the rate was slightly higher with 93% of those with a positive iFOBT having a colonoscopy, compared with 90 percent in the second round.

In our model we have assumed the rate of successful colonoscopies to be the same as the pilot, i.e. 92 percent. For the purposes of probabilistic sensitivity analysis, we estimate the plausible 95% CI to be 90 to 95 percent.

The rate of successful colonoscopies is similar to those in other published cost-utility analyses. Of the four published cost-utility analyses we reviewed in detail, three studies included base case adherence rates of 80[29], 85%[28] and 92%[27]. One study assumed perfect adherence in the base case and varied the adherence rates in the sensitivity analysis[30].

2.6.2 Accuracy of colonoscopy

Colonoscopy is the gold standard for detecting adenomas and cancers. However, sometimes adenomas and cancers are missed during colonoscopy. For the purpose of our model we have assumed specificity to be 100%, i.e. there are no cases of false positives, where an adenoma or cancer is falsely thought to be present. However, sensitivity is less than 100 percent, since some adenomas and cancers may not be detected. As with FIT, the sensitivity is better with more advanced/larger adenomas and more advanced cancers.

The sensitivity/performance of colonoscopy is better for distal rather than proximal adenomas/cancers. The further the adenoma/cancer lies from the anus, the increased risk of not being detected.

Of the four published cost-utility analyses we reviewed in detail,[27,28,29,30] the sensitivities for adenomas range from 75 to 95 percent, and the sensitivities for cancer ranged from 94 to 97 percent. Only one study[29] differentiated the sensitivity between proximal and distal cancers. The most commonly cited source of sensitivity for values was a systematic review of missed rate of polyps by van Rijn et al[38].

The systematic review by van Rijn[38] aimed to identify studies in which patients had undergone two same-day colonoscopies with polypectomy. They also aimed to determine the miss rate of optical colonoscopy independent of other diagnostic tests. When they searched for studies between 1984 and 2005, they identified six cohorts including 465 patients that met the criteria. The sensitivity was 97.9% for polyps ≥ 10mm (95% CI 92% - 99%) and 76.2% for polyps < 10mm (95% CI 72% - 81%)[ii].

We identified a study of 12,487 patients in who had a new diagnosis of bowel cancer, who had a colonoscopy in the previous three years[39]. This allowed the authors to determine the rate of new or missed cancers. The study was based on patients in Ontario Canada with a diagnosis of bowel cancer between April 1997 and March 2002. The rates of new or missed cancers varied by location of bowel cancer, ranging from 5.9% for right sided cancer to 2.3 percent for rectal or sigmoid cancers. The overall rate of new or missed bowel cancers was 3.4% (430 of 12,487). This means the sensitivity is at least 96.6%, since it is only the number of missed cancers which affects the sensitivity.

The specificity and sensitivity values for colonoscopy values used in our analysis are reported in Table 10 below. The specificity value of 100 percent is based on common practice, as reflected in the cost-utility analyses we reviewed. The sensitivity values by adenoma size are based on the findings of the systematic review discussed above[38]. We have assumed the sensitivity for cancer is the same as for adenoma's ≥ 10mm; this assumption is based on the close values reported for adenomas[38] and cancers[39]. These values we use are similar to the values used in the cost-utility analyses we reviewed.

Table 10 Performance of colonoscopy - values used in our analysis

Measure	Value (95% CI)
Specificity	100%
Sensitivity: Adenoma <10mm	76% (72% - 81%)
Sensitivity: Adenoma ≥ 10mm	98% (92% - 99%)
Sensitivity: Cancer	98% (92% - 99%)

Source: Sapere; based on values reported by van Rijn et al[38]

2.6.3 Complications from colonoscopies

In the pilot about 1 percent of colonoscopies resulted in readmission. The most common reasons for readmission were bleeding and perforation, representing approximately 60 percent and 11 percent of readmissions respectively. We have assumed 1 percent of colonoscopies result in a readmission.

[ii] van Rijn et al reported the miss rate for adenomas 1-5mm and 5-9mm. We combined the number of missed polps for all adenomas <10mm in order to get one value for miss rate.

Comparison with published analyses

Each of the analyses we reviewed in detail specified complications differently. It is therefore difficult to make meaningful comparisons. Tappenden et al[29] assumed a bleeding rate of 4.4 per 1,000 and perforation rates between 0.8 and 1.7 per 1,000. The lower perforation rate is for colonoscopy without polypectomy. Goede et al[28] assumed a complication rate of 2.4 per 1,000. Complications included were perforation, serosal burn, bleed with transfusion and bleed without transfusion. Ladabaum et al[30] assumed a major haemorrhage rate of 1.6 per 1,000 and a perforation rate of 0.85 per 1,000. Tran et al[27] did not state the colonoscopy complication rates used in their model, although they did reference the source.

2.7 Using QALYs to quantify health benefits

Since the underlying principle of screening is to detect adenomas before they become cancers, and to detect cancers before they progress to more severe disease, health related quality of life (HRQoL) is inevitably an important consideration. We have quantified the changes in health outcomes using quality adjusted life years (QALYs). QALYs account for the time people spend in each health state and how the HRQoL differs for each health state.

Since New Zealand based quality of life data for bowel cancer patients is not currently available, we have used published QALY values for our model. Our model includes different QoL scores for the three phases of cancer, initial, continuing care and terminal phase. The QoL in the initial phase was dependent on the stage at diagnosis, with more advanced cancer being associated with a lower QoL score.

It was assumed that those without bowel cancer would have the QoL of the general population. We based our estimate on study with 1,327 respondents from the general population in New Zealand surveyed using the EQ-5D tool with the visual analogue score technique[40]. The QoL was reported for seven different age bands. Given we are estimating the QALYs in participants aged 50 and above, we estimated the average QoL for those aged 50 and above. We weighted the different scores by the proportion of the New Zealand population in each age band as recorded in the latest census (2013). The QoL value for those without bowel cancer is estimated to be 0.792.

Table 11 QoL for those without bowel cancer: population weights and QoL scores used

Age band	Proportion of over 50 population*	QoL score
50 -54	21%	0.822
55-64	35%	0.816
65-74	25%	0.796
75+	19%	0.708
Total	**100%**	**0.792**

* Proportion of population taken from the 2013 censes as reported by Stats New Zealand

The QoL scores for the initial phase of cancer were taken from the analyses reported by Tappenden et al, based in turn on the results the survey reported by Ness et al. This study surveyed 90 patients regarding 7 different bowel cancers health states. The QoL scores ranged from 0.74 for *'stage I rectal or stage I/II colon cancer'* and 0.25 for 'stage IV rectal or colon cancer'. These values are used for the stage I and stage IV respectively. We followed the approach of Tappenden, estimating the QoL values for the in between cancer stages, Stage II and Stage III as having QoL scores of 0.70 and 0.50 respectively.

While the QoL values derived by Ness should reflect the whole time spent in each health state, i.e. each stage of bowel cancer, other studies suggest that over time patients QoL improves (Ramsey et al)[42] and that the QoL is close to the general population[42,45, 46, 47]. Therefore we assume that in the continuing care phase, after the initial phase, patients QoL improves to the level observed in the general population, i.e. 0.792.

In the terminal phase, the last year of life, the QoL score is assumed to be 0.25. This is based on the assumption that the last year will be similar to being in stage IV of cancer.

If a patient lives for 1 year or less, the QoL score for the terminal phase is applied (0.25). If a patient lives between 1 and 2 years, the QoL for the terminal phase is applied for the last year of life, and the QoL from the initial phase is applied to the remainder of the life. If a patient lives more than 2 years, Initial and terminal phase QoL scores are used for the first and last year respectively, with the QoL score for continuing care applied to the time in between.

The QoL scores for cancer are only applied to diagnosed cancer.

Table 12 QoL scores used in our model

Health State: stage of bowel cancer	QoL score (95% CI)
No diagnoses bowel cancer	0.792 (0.713 - 0.870)
Initial phase (first year following diagnosis)	
Stage I	0.74 (0.69 – 0.78)
Stage II	0.70 (0.65 – 0.75)
Stage III	0.50 (0.44 – 0.56)
Stage IV	0.25 (0.20-0.31)
Continuing care phase	0.792 (0.713 - 0.870)
Terminal phase – cancer (last year of life)	0.25 (0.20-0.31)

2.7.1 Comparison with values used in published analyses

There is a very limited range of QoL scores used in published analyses of bowel screening. However, the application of those QoL scores is highly varied, which leads to varied QALY estimates from a given reduction in bowel cancer. QoL scores used in the literature vary from 0.25 to 0.90 for the different cancer stages, and from 0.91 to 1.0 for those without cancer. Table 13 below provides a brief summary of how three published studies applied QoL scores, further details are below.

The QoL scores are based on two key studies. One study asks cancer patients to compare different health states, which requires patients to imagine what it would be like to be in each of the health state. While the second study asks patients how they feel given their current bowel cancer health state, although this study focused on the continuing care phase and is therefore limited to those who have a had diagnosis for at least a year.

Table 13 QoL scores used in published assessments

First author , year, country	Health state	QoL (Utility score)	Comment
Tappenden 2004[29] UK	No known adenomas	0.91	Undiagnosed cancers assumed to have same QoL as no cancer. No cancer assumed to have some QoL decrement.
	Cancer Dukes A*	0.74	
	Cancer Dukes B*	0.70	
	Cancer Dukes C*	0.50	
	Cancer Dukes D*	0.25	
Goede 2013[28] Dutch	No known adenomas	1	QoL varies overtime within each health state
	Cancer Dukes A*	0.74, 0.85, 0.25	
	Cancer Dukes B*	0.70, 0.85, 0.25	
	Cancer Dukes C*	0.50, 0.85, 0.25	
	Cancer Dukes D*	0.25	
Ladabaum 2013[30]	No known adenomas	1 (Assumed)	Limited details provided. QoL between 37 – 60 months applied to entire time in health state
	Localized colorectal cancer	0.90	
	Regional colorectal cancer	0.80	
	Distant colorectal cancer	0.76	

**TNM staging is used in our analysis. Dukes A, B, C, and D have similar definitions as TNM stages I, II, III, and IV respectively*

Tappenden et al[29] noted that 'evidence on the quality of life associated with colorectal cancer in scant and conflicting' pg 60. Three studies were identified which attempted to measure quality of life associated with bowel cancer. Only one of these studies, Ness 1999[41], provided relevant information that could be used in their analysis.

Ness et al surveyed 90 patients regarding 7 different bowel cancers health states. The QoL scores ranged from 0.74 for *'stage I rectal or stage I/II colon cancer'* and 0.25 for 'stage IV rectal or colon cancer'. These values where used by Tappenden et al for the Dukes A and Dukes D respectively, Tappenden estimated the QoL values for the in between cancer stages, Duke B and Dukes C as having QoL scores of 0.70 and 0.50 respectively. Tappenden at al assumed a

QoL score of 0.91 for those without cancer (or with a cancer that isn't diagnosed). 0.91 was based on separate study and determined by assuming the same QoL as for middle-aged individuals with one chronic health problem. QoL scores where applied for the duration of time spent in each health state.

Ness et al[41] derived their QoL scores using a standard gamble method. Each participant ended up producing QoL scores for five of the seven bowel cancer health states (only five per participant was used to shorten the interview time). Therefore, participants had to imagine the impact of being in a health state. Some of the patients would have experienced some of the health states as the participants were those we had colonoscopy with removal of adenomas.

Goede et al 2013[28] used the MISCAN-colon model, which also use the QoL a values reported by Ness et al. However, they apply them differently. Goede et al modelled:

- QoL loss from bowel cancer is only included in the sensitivity analysis and not in the base case.
- Values from Ness only applied during the first year of person being in each of stage of cancer
- QoL in the year prior to death from bowel cancer is 0.25 (i.e. same as stage IV)
- QoL after 1 year of being in each stage, but prior to last year of life is 0.85 regardless of stage of cancer *[separate study reported]*
- Quality of life score for being cancer free is 1, i.e. no decrement

It is debatable whether to use the approach of varying quality of life during the time spent in each stage of cancer (as per MISCAN-colon), or using constant values (as per Tappenden). The former approach is likely to be more reflective of how QoL changes over time, but the later aligns with the source of the QoL scores as estimated by Ness et al.

The increase in Quality of life after one year (but not in the year prior to death and not in stage IV) as modelled by MISCANZ is based on the findings of Ramsey et al[42]. Ramsey et al reported *'After 3 years, respondents in all TNM stages of disease except Stage IV reported a relatively uniform and high quality of life.'* These findings are based on 173 respondents in the US who had a diagnosis of bowel cancer for at least 1 year, the stage of cancer at diagnosis varied across the respondents. The Health Utilities Index (HUI) Mark III was one of the tools used to measure QoL scores; individual dimensions are weighted according to values derived from the general Canadian population and summed to produce QoL score ranging from 0–1. The average quality of life score for all respondents was 0.85, this is the value used by Goede et al after 1 year of being in each stage, but prior to last year of life.

Ladabaum et al[30] provide limited details on how QoL scores are used in their model. However, they reference the Ramsey study as the source of the QoL scores. It appears Ladabaum have taken the QoL scores as reported for respondents with 37 – 60 months since diagnosis, based on the results of the HUI tool. For example, a QoL score of 0.76 was applied to those with distant bowel cancer (i.e. stage IV), this not likely to represent most patients with distant bowel cancer as the majority of patients diagnosed with distant bowel cancer live for less than 1 year, with the QoL at the end of life being very poor. This method may underestimate the impact of bowel cancer on patient's quality of life, and overestimate the QALY gains from bowel cancer screening.

2.7.2 Quality of life scores in the literature

Disability weights for the Global Burden of Disease 2013 study[43]

The Global Burden of Disease (GBD) study assesses health losses from diseases, injuries, and risk factors using disability-adjusted life-years, which need a set of disability weights to quantify health levels associated with nonfatal outcomes. The objective of this study was to estimate disability weights for the GBD 2013 study.

Given the number and variety of health states included, there are limitations on the detail on the health states. While the study does not look at the stage of bowel cancer, or even bowel cancer itself, it does report on cancer in general. The QoL scores for cancer range from 0.431 for those in terminal phase without medication and 0.712 for diagnosis and primary treatment. Further results are in Table 14 below.

Table 14 Disability weights for the Global Burden of Disease 2013 study - Cancer health states

Health state	Disability weight	QoL score (implied)
Cancer: Diagnosis and primary treatment	0.288	0.712
Cancer: Metastatic	0.451	0.549
Mastectomy	0.036	0.964
Stoma	0.095	0.905
Terminal phase: With medication (for cancers and end-stage kidney or liver disease)	0.540	0.460
Terminal phase: Without medication (for cancers and end-stage kidney or liver disease)	0.569	0.431

Source: Salomon et al 2011: Table 2

Färkkilä et al 2013 Health-related quality of life in colorectal cancer[44]

519 patients with bowel cancer responded to the survey. Patients were separated into 5 different health states. Three tools were used to measure QoL, include the EQ-5D (3 level). In order to estimate QoL values for the general population, a UK tariff was applied to the EQ-5d results. The QoL scores ranged from 0.850 for those in remission and 0.643 for those receiving palliative care; further results are in Table 15 below. The QoL values for

advanced bowel cancer are relatively high compared to the findings of Ness, this could be due to relatively high time from metastases (16.1 for metastatic and 15.9 for palliative care health states)

Table 15 QoL scores from Farkkila et al - EQ-5D 3L

Disease severity	Health state	QoL score
Local disease	primary treatment group	0.760
	in rehabilitation	0.835
	in remission	0.850
Advanced disease	in metastatic disease	0.820
	palliative care	0.643

2.7.3 Other quality of life studies

There are a number of studies that assess the impact of bowel cancer on quality of life. However, many of these studies do not report QoL scores that can be used to inform QALYs. We have summarised some of these studies below, since they provide insights into the impact of bowel cancer on QoL. These studies suggest that those who survive bowel cancer tend to have similar QoL values to the general population.

21,802 patients surviving 12 to 36 months after a diagnosis of CRC and treated in the National Health Service in England[45] were included in this study. While the study uses the EQ-5D tool it does not report the resulting QoL scores; this severely limits the usability of the findings to inform our analysis. The results were *"One or more generic health problems were reported by 65% of respondents, with 10% of patients reporting problems in all five domains. The reporting of problems was higher than in the general population and was most marked in those age less than 55 years. Certain subgroups reported a higher number of problems, notably those with one or more other LTCs, those with active or recurrent disease, those with a stoma, and those at the extremes of the age range (<55 and > 85 years)."*

A study of 726 woman who had bowel cancer for an average of 7 years appear to report health-related quality of life comparable with that of similarly aged women in the general population[46].

In a study of 309 bowel cancer patients that had survived one year from diagnosis, they scored their physical, role, cognitive, and global health functioning only slightly worse than the general population[47].

2.8 Cost of treating cancer

There are significant costs to the health sector for treating bowel cancer and caring for those with bowel cancer. Bowel cancer is estimated to cost the health sector an additional $46,000[iii] per person diagnosed with bowel cancer. We base our estimates on work done by the Department of Public Health, University of Otago, Wellington[48]. This research team used an excess difference approach to estimate the additional cost incurred by those with bowel cancer, compared with the general population.

2.8.1 Method for estimating costs

The objective of the study was to determine health system expenditure on cancers by time since diagnosis using data for an entire country. Patients included in the analyses were all Usually Resident New Zealand cancer patients, with a prevalent cancer at any point in the July 2006 to June 2011 period. The costs were taken from the following data sources:

- hospitalisations and inpatient procedures
- community laboratory tests;
- non-admitted patient events (e.g., outpatients);
- community pharmaceuticals dispensed (including patient contribution);
- general practice consultations

The established "excess" or "net" cost approach was used, whereby the expected health system cost of a New Zealand citizens by sex and age group without the cancer diagnosis was calculated, and then subtracted from the observed total health care costs of those with bowel cancer. This approach avoids the need to classify in advance what counts as a specific cancer-related cost.

Bowel cancer was defined as cancer recorded as colon, rectosigmoid, rectum, and anus and anal canal. These cancers were identified using the ICD 10 codes C18 - C21.

The costs were broken into three time periods:

- 1st year following diagnosis
- Remission (time between 1 year and last 6 months)
- 6 months prior to death

The costs in the 1st year and remission differ by stage of cancer at diagnosis. Dukes staging was used, and we have assumed that Dukes A, B, C, D have the same costs as TMN stages I, II, III, and IV respectively. The costs in the 6 months prior to death are assumed to be the same for all stages of cancer.

The costs were estimated by age bands for males and females. Cost were inflation adjusted and reported in 2011 New Zealand dollars. We further inflation adjusted the study's reported figures to 2017 dollars. Figures were inflated up to 2015 based on the actual general inflation

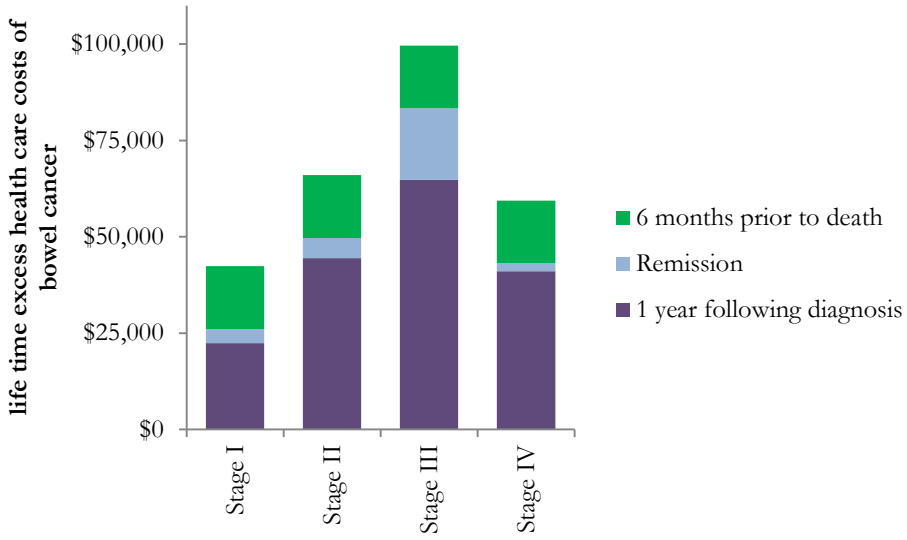
[iii] Reported as $43,000 in 2011 dollars. Inflation adjusted to 2016 dollars.

rate using the Reserve bank of New Zealand's inflation calculator; to inflate to 2016 the historical inflation rate of 2.5% p.a. was used.

2.8.2 Costs of treating bowel cancer

The pattern of costs found by the Otago team is the same for male and females, although the costs for males are approximately 15% higher. The majority of the costs are experienced in the first 6 months following diagnosis, and the cost in the first 6 months varies significantly by stage of bowel cancer at diagnosis; this can be seen in Figure 14 below. The cost of treating bowel cancer is highest for those diagnosed with stage III cancer, with the cost 50% higher than stage II and IV and over twice the cost of stage I.

Figure 14 Lifetime excess health care costs from bowel cancer, by stage of cancer and time since diagnosis – females aged 60 - 69



The life time costs tend to be higher for those with a younger age of diagnosis. This trend is shown in Figure 15 below. The trend of decreasing excess costs is seen in each of the three time periods following diagnosis.

The reduction in initial costs with increasing age could be due to older patients being less likely to receive treatments, if not being healthy enough for treatment and having less potential benefit from treatment. The reduction in remission costs with increasing age is likely due to the shorter life expectancy to accumulate costs. The reduction in end of life costs (last 6 months) with increasing age is likely to be due to increased costs for older people without bowel cancer.

Figure 15 Lifetime excess health care costs from bowel cancer, by age and stage of cancer – females

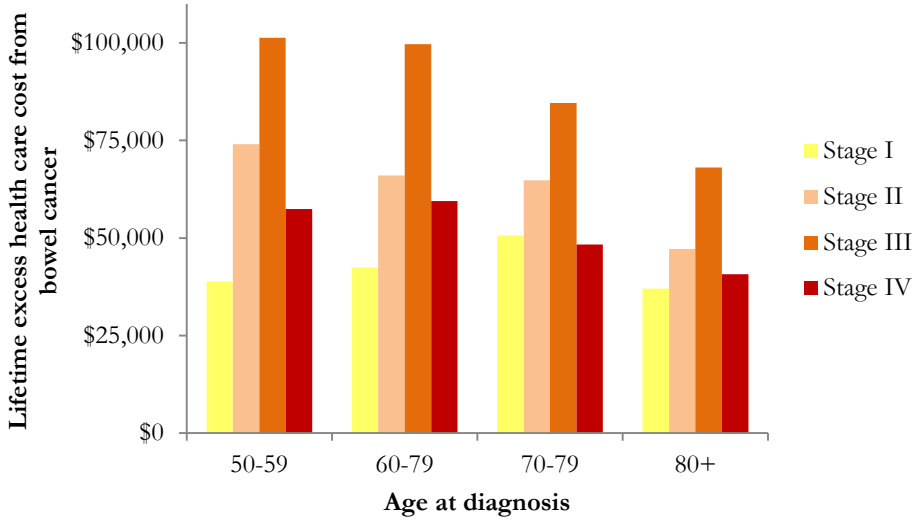


Table 16 and Table 17 below include the costs of treating cancer included in our model, for females and males respectively. The costs differ by gender, age band, stage of cancer and time since diagnosis.

Table 16 Lifetime excess health care costs from bowel cancer - females

Age	Stage	1 year following diagnosis	Remission	6 months prior to death
50-59	Stage I	$17,472	$1,185	$19,244
	Stage II	$46,922	$6,047	$19,244
	Stage III	$67,285	$12,304	$19,244
	Stage IV	$32,303	$4,440	$19,244
60-79	Stage I	$21,866	$3,604	$15,906
	Stage II	$43,431	$5,055	$15,906
	Stage III	$63,224	$18,074	$15,906
	Stage IV	$40,092	$1,986	$15,906
70-79	Stage I	$32,840	$2,343	$14,200
	Stage II	$45,458	$3,548	$14,200
	Stage III	$60,332	$7,997	$14,200
	Stage IV	$30,502	$2,430	$14,200
80+	Stage I	$22,598	$2,847	$10,691
	Stage II	$32,665	$2,697	$10,691
	Stage III	$49,052	$6,626	$10,691
	Stage IV	$26,202	$2,806	$10,691

Table 17 Lifetime excess health care costs from bowel cancer - males

Age	Stage	1 year following diagnosis	Remission	6 months prior to death
50-59	Stage I	$25,097	$3,597	$19,244
	Stage II	$63,811	$8,158	$19,244
	Stage III	$71,676	$16,067	$19,244
	Stage IV	$42,267	$3,415	$19,244
60-79	Stage I	$25,754	$2,443	$15,906
	Stage II	$53,956	$7,227	$15,906
	Stage III	$58,748	$14,823	$15,906
	Stage IV	$40,157	$4,630	$15,906
70-79	Stage I	$33,651	$3,467	$14,200
	Stage II	$55,016	$6,134	$14,200
	Stage III	$59,439	$14,948	$14,200
	Stage IV	$36,584	$4,772	$14,200
80+	Stage I	$34,660	$5,284	$10,691
	Stage II	$48,613	$2,514	$10,691
	Stage III	$44,713	$8,680	$10,691
	Stage IV	$35,657	$4,107	$10,691

2.8.3 Comparison with other estimates

The most relevant comparisons are estimates based on New Zealand specific information, since health system organisation and costs vary considerably across different countries. Compared to the one other New Zealand study we identified, our costs are relatively high. This is not surprising, since the other New Zealand study used a relatively conservative approach.

Our estimates for cost of treating cancer are similar or lower than those reported internationally and used in published cost-utility analyses. It is expected that some countries will have higher costs for treating cancer, particularly where there are higher health care costs in general. The pattern of costs for each of the stages of cancer is similar to what we have used; except in stage IV cancer where there is significant variation in prices used. These findings are further detailed in the sections below.

Cost of cancer studies

The Ministry of Health (MoH) has estimated the cost of bowel cancer to be NZ $28,000[iv] per person, as reported in their Price of Cancer report[49]. This estimated cost is approximately 40% lower than the estimate we are using. There are a number differences in the methods used to derive these estimates. The likely reason why the MoH's estimate is lower is because it includes only costs that were specifically coded as being due to cancer. Therefore this result should be treated as a lower bound estimate[48]. The Price of Cancer report did not include estimates by stage of cancer, so we cannot compare the relative costs by stage.

A study based in Ireland[50] estimated the cost of treating bowel cancer by modelling the likely costs experienced by those with bowel cancer. The estimated costs by stage in Ireland are very similar to the cost we are using in our model, the only substantive difference being that the cost of stage IV is estimated to be higher than in NZ. The authors concluded *'The findings illustrate the impact of biological agents on costs of cancer care*. Therefore, this difference in stage IV is likely to be due costs and usage of expensive biologic chemotherapy agents used in stage IV. The average cost of bowel cancer, regardless of stage, is estimated to be much higher in Ireland; this is likely to be due to more patients being diagnosed with later stage cancer and the higher costs in Stage IV cancer.

A study based on Medicare data in the US[51], reported the estimated cost of treating bowel cancer to be $54,000[v]. This study used an excess cost approach (i.e. the same approach as the costs used in the Otago analysis). The main difference in methods is that costs were extrapolated out to 25 years and costs were discounted at a rate of 3.5%. While the overall cost is similar to the NZ estimate, the cost by stage of cancer is very different. These US estimates find that stage I has the highest cost, and stage IV has the lowest cost. This pattern of cost by stage differs from all the other studies we identified. The cost of stage IV, is estimated to be negative due to the short life expectancy associated with stage IV. We expect the cost of treating Stage IV bowel cancer would currently higher, than in the patients observed between 1996 and 2002, this increased cost is due to high cost biologic chemotherapy treatments.

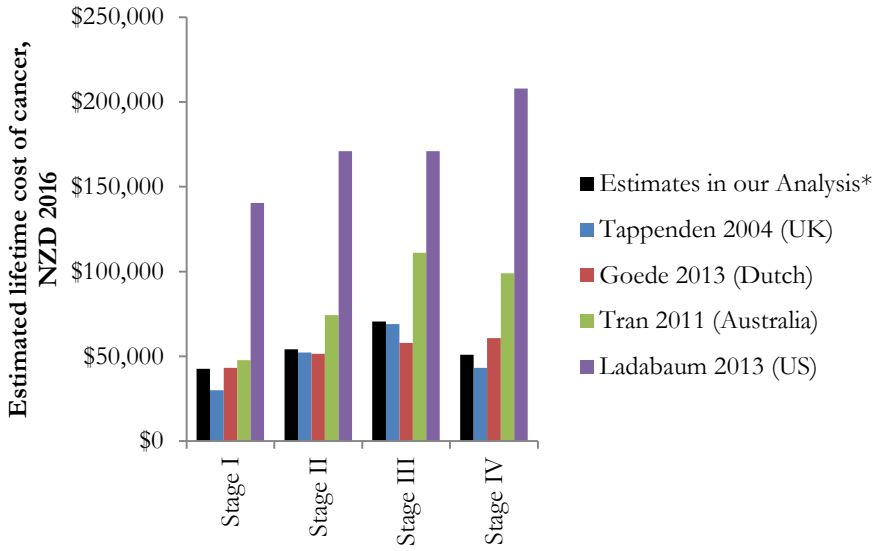
Cost used in other cost-utility analyses

We have taken the estimates by stage of cancer from published cost-effectiveness studies (converting them to 2016 NZ dollars) and compared them with our estimates. Two of the four studies have values that are similar to the costs in our analysis. One study has similar costs for early cancer and higher costs for late cancer. One study has much higher costs for all stages, which may be attributable to being based on the US treatment regimens and US costs (where US medical expenditure per person is among the highest in the world). This comparison is shown in Figure 16 below.

[iv] Reported as $24,824 in 2008/09, we have inflation adjusted to 2016 cost

[v] Cost of treating bowel cancer reported to be $28,626 in 2006 USD, We converted to 2016 NZD

Figure 16 Comparison of costs for treatment, by stage of bowel cancer



*The estimates for our analysis are based on the average for female and males, for those aged 60 – 79.

All four studies had stage I with the lowest cost, with increasing costs for Stage and II and III. Two of the studies had stage IV costs that were lower than stage III costs. The studies that have higher costs for stage IV likely include significant use of expensive biologic chemotherapy agents.

The estimated costs by stage of bowel cancer reported in each of the studies are summarised in Table 18 below. In order to convert the reported costs into comparable costs, we used the exchange rate based on the year the costs were incurred in order to get New Zealand costs, then we adjusted for inflation to get 2016 costs.

Table 18 Cost of treating cancers used in published cost-effectiveness analyses

First author , year	Stage of cancer	Cost as reported	Cost adjusted to 2016 NZD
Tappenden 2004[29] (UK)	Dukes A	£8,299	$30,054
	Dukes B	£14,442	$52,299
	Dukes C	£19,076	$69,080
	Dukes D	£11,945	$43,257
Goede 2013[28] (Dutch)	I	€25,540	$43,214
	II	€30,440	$51,505
	III	€34,240	$57,935
	IV	€35,940	$60,811
Tran 2011[27] (Australian)	I	$34,337	$47,754
	II	$53,487	$74,386
	III	$79,924	$111,153
	IV	$71,156	$98,959
Ladabaum 2013[30]* (US)	Local	$90,672	$140,407
	Regional	$110,389	$170,938
	Distal	$134,286	$207,943

*Ladabaum included cost per year of continuing care for local and regional cancers. For the purposes of this comparison, we assumed 5 and 3 years of continuing care for local and regional cancers respectively

2.9 Cost of screening

Data on the cost of screening for the purpose of cost effectiveness analysis were derived as part of a more comprehensive report on the cost of the Waitemata pilot, a companion report to the present one. Some of the outputs were summarised differently in order to be suitable for use with the MoDCONZ model.

Table 19 Screening costs

Cost	Population	Value
Mailout costs	Eligible for screening	$22.92
iFOBT analysis and reporting costs	Participating in screening	
• negative		$18.73
• positive		$111.45
Colonoscopy, by type	Undergoing colonoscopies (positive iFOBT's and surveillance)	
• *In-house salaried / local anaesthetic*		*$260.59*
• *In-house - private contractor/ local anaesthetic*		*$487.51*
• *In-house salaried / general anaesthetic*		*$1,139.01*
• *private*		*$1,019.66*
• *CT*		*$427.75*
Weighted average		$754.92
Histology	All samples collected at colonoscopy	$937.14
Re-admission following colonoscopy		$5,172

Source: Sapere estimates, based on Sapere costing report of the pilot

2.9.1 Cost of colonoscopy complications

We have based the costs of readmission on the average in-patient admission costs for overnight admission in New Zealand.

We have used information published by the Ministry of Health to estimate the cost of an admission for colonoscopy. MoH report the average cost-weights for Colonoscopy with or without Catastrophic or Severe Complications as 1.91 and 1.00 respectively[52]. Using the 2014/15 cost weight of $4,681.97[52] results in the following average costs:

- Colonoscopy with Catastrophic or Severe Complication: $8,947
- Colonoscopy without Catastrophic or Severe Complication: $4,705

We have assumed those colonoscopies resulting in a perforation to be associated in the more expensive stay and the rest of the readmissions being associated with the less expensive stay. Given approximately 11% of readmissions in the pilot were due to perforation, our estimated cost for readmission is $5,172.

2.10 Modelling uncertainty

There are three sources of uncertainty which can affect the results of this analysis, the sources are:

- structural uncertainty;
- choice of data sources; and
- parameter uncertainty[53].

Structural uncertainty

Structural uncertainty relates to the uncertainty due the structure of the model. This includes which health states are included in the model, and how pathways of care are represented. We have attempted to minimise structural uncertainty by modelling the model of care to closely align with New Zealand experience.

Choice of data sources

The choice of data sources affects the inputs used in the model. For each model parameter we have searched for the most appropriate input, with consideration given to the quality of evidence and the applicability to the New Zealand setting.

In order to determine the impact of data sources, we include scenario analyses using alternative data values when there is more than one source that is a good match for the model. For example, we consider scenarios with varying participation rates.

Parameter uncertainty

Each parameter (input) included in the MoDCoNZ model is associated with uncertainty. Sensitivity analysis is used to quantify the impact of parameter uncertainty. The base microsimulation model addresses the sensitivity of the natural history parameters through the Bayesian calibration with incidence and death data. The screening intervention model

introduces a new set of parameters related to the decision points for each individual proceeding through the screening program and the performance of FIT's. We incorporate probabilistic sensitivity analysis of these screening parameters into the MoDCoNZ screening model by performing a random draw on the distributions for these screening parameters at the same time as the draw of natural history parameters for each simulation run over the cohort of individuals.

Probabilistic sensitivity analysis (PSA) runs the model many times, with each run using a different set of values for each of the parameters. This creates a range of results which represents the uncertainty of the parameters. The values for each of the parameters for each run are based on the distribution for each parameter; with each distribution based on the best available evidence. PSA is the preferred method for addressing parameter uncertainty by the UK's National Institute for Health Care and Excellence (NICE)[53].

We derived alpha and beta parameters for a beta distribution for each screening parameter from known or estimated 95% confidence intervals. For each simulation the parameters are randomly drawn from the beta distributions, with the exception of iFOBT sensitivities. It is assumed that iFOBT sensitivities are correlated, i.e. a higher degree of sensitivity to large adenomas implies a higher sensitivity to cancers, and so on. The iFOBT sensitivities are correlated by randomly drawing a percentile from a beta distribution, and determining the parameter value for that percentile using each parameter's beta distribution.

3. Summary of assumptions

The inputs in the model are summarised in the tables below. The distributions listed are used in the probabilistic sensitivity analysis; where no distribution is listed then the single value is used.

Table 20 Parameter inputs – screening parameters

Parameter	Mean (95% CI)
Screening	
Proportion invited	96% (94% - 98%)
iFOBT Participation, new to screening	Age dependent range: 43% to 70%
iFOBT Participation, participated in previous round	Age dependent range: 65% to 95%
iFOBT Participation, did not participate in previous round	Age dependent range: 18% to 30%
iFOBT sensitivity Adenoma < 10mm	7.7% (7.1% - 8.4%)
iFOBT sensitivity Adenoma ≥ 10mm	25.2% (22.2% - 28.2%)
iFOBT Sensitivity Stage 1&2 cancer	59.7% (27% - 92.5%)
iFOBT Sensitivity Stage 3&4 cancer	85.9% (67.4% - 100%)
iFOBT Specificity	94.7% (94.4% - 95%)
Rate of successful colonoscopy	92.5% (90-95%)
Colonoscopy specificity	100%
Colonoscopy sensitivity: Adenoma <10mm	76% (72% - 81%)
Colonoscopy sensitivity: Adenoma ≥ 10mm	98% (92% - 99%)
Colonoscopy sensitivity: Cancer	98% (92% - 99%)
Colonoscopy: Probability of complication resulting in re-admission	1% (0.9% - 1.1%)
Quality of life	
No diagnoses bowel cancer	0.792 (0.713 – 0.870)
Initial phase (first year following diagnosis)	

Stage I	0.74 (0.69 – 0.78)
Stage II	0.70 (0.65 – 0.75)
Stage III	0.50 (0.44 – 0.56)
Stage IV	0.25 (0.20-0.31)
Continuing care phase	0.792 (0.713 – 0.870)
Terminal phase – cancer (last year of life)	0.25 (0.20-0.31)
Cost of treating cancer (unweighted average by stage)	
Treatment cost: Stage I	$44,849
Treatment cost: Stage II	$68,917
Treatment cost: Stage III	$86,759
Treatment cost: Stage IV	$54,054
Cost of screening	
Eligible to receive a mail out	$22.92 ($19.29 – $24.73)
Return iFOBT- negative results	$18.73 ($15.54 – $20.30)
Return iFOBT - positive results	$111.45 ($91.60 – $121.19)
Colonoscopy – mode weighted average	$754.92 ($639.12 - $813.08)
Histology of samples collected at colonoscopy	$937.14 ($793.38 -$1009.34)
Re-admission following colonoscopy	$5,172 ($4,655 - $5,689)

4. Reduction in cancers and cancer related deaths

Bowel cancer screening is estimated to results in the following benefits for the entire cohort offered screening, up to the age of 84:

- 35 percent reduction in people with bowel cancer
- 45 percent reduction in bowel cancer deaths

4.1 Reduction in cancers

In the base case we estimate there would be 4,921 bowel cancers diagnosed for those in the cohort (counting cancer up to the age of 84) , i.e. 8.7 percent of the cohort who are alive at age 44[vi]. With bowel cancer screening the cancers diagnosed are estimated to reduce to 3,183, i.e. 5.6 percent of the cohort. The number needed to invite to screening to avoid a cancer is 33.

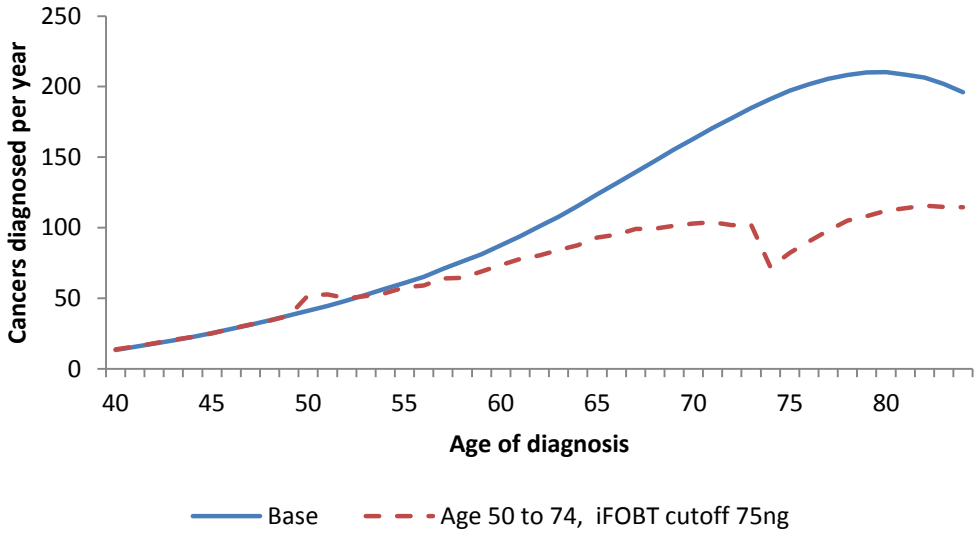
Screening results in a temporary increase in the diagnoses of cancers. In the first year of screening there are an estimated 10 additional cancers detected. This is due to some people having un-diagnosed cancers that are detected earlier due to screening. However, after the first four years of screening the number of diagnoses in the screening arm is lower for any given age; with the difference increasing with time. These results are shown in Figure 17 below, where the dotted red line represents the reduced number of people diagnosed with cancer, compared with the solid blue line that shows the number diagnosed with cancer in the base case (i.e. the absence of screening).

At the end of screening, there is a temporary drop in the number of people diagnosed with cancer in the screening group. This drop is due to no longer actively looking for cancers. The drop is illustrated in Figure 17 below by the drop in the dashed red line at age 75.

The number of diagnoses each year increase with age, until about age 80 when it starts to decline. The number of diagnoses for those aged 80 is over four times higher for those aged 50. Therefore the greatest reduction in cancers is in those around the age of 80. While screening only runs until age 75, the reduction in diagnosed cancers extends beyond the age of 75 due to the prevention of cancers from the removal of adenomas.

[vi] Based in a cohort of 56,552

Figure 17 Diagnoses of cancers age of diagnosis - cohort followed to age 84 - whole population



Source: MoDCoNZ

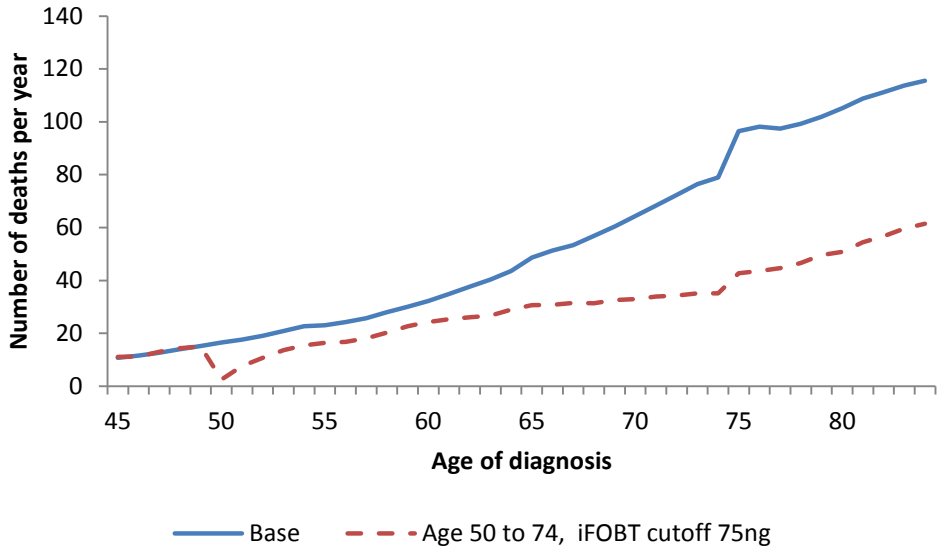
4.2 Reduction in cancer deaths

In the base case we estimate there would be 2,176 people who die from bowel cancer, i.e. 3.8 percent of the cohort[vi] (This aligns closely with the figure that 4.2 percent[vii] of people who died in 2013 in New Zealand died from bowel cancer[54]). With bowel cancer screening the number of people diagnosed with cancer would reduce to 1,196, i.e. 2.1 percent of the cohort. The number needed to invite to screening to avoid a cancer deaths is 58 i.e. 1 in 58 people invited will avoided having a bowel cancer death.

The age profile of cancer deaths, and the reduction due to screening, is similar to the age profile for cancers diagnosed. The cancer deaths by age for the base case and for screening are shown in Figure 18 below.

[vii] In 2013, 1252 people had their cause of death recorded as bowel cancer (based on ICD codes C18 – C20, this represents 4.2 percent of the 29,636 deaths recorded in 2013. Figures based on Ministry of Health's provisional statistics.

Figure 18 Cancer deaths by age of death - cohort followed to age 84 – whole population



Source: MoDCoNZ

4.3 Estimated impact for Maori

Bowel cancer screening in the Maori population is estimated to results in in the following benefits for the entire cohort offered screening:

- 34 percent reduction in people with bowel cancer
- 42 percent reduction in bowel cancer deaths

Although the relative reduction is the same for Maori and for the whole population, the absolute number of cancers avoided per person invited is fewer for Maori, while the number of cancer deaths avoided per person invited is the slightly higher for Maori and the whole population. The reduced number of cancers avoided is due to a lower rate of bowel cancer in Maori. The number needed to invite to screening to avoid a cancer is 39, a fifth more than for the whole population. The number needed to invite to screening to avoid a cancer death is 53, lower than the whole population result of 58.

The reduction in cancers and cancer deaths is similar for Maori and the whole population. While more Maori have to be invited to screening to avoid a cancer, the number needed to invite to avoid a bowel cancer death is similar across the whole population. We interpret this as due to Maori having lower rates of bowel cancer, but similar rates of bowel cancer deaths.

5. Cost effectiveness results

5.1 Cohort

The results presented in this section are based on following the cohort modelled in MoDCONZ from the age of forty through to death, with a maximum age of 111. This means that our cost effectiveness estimates are based upon following a cohort through their entire experience of screening, rather than on the basis of a whole, changing, population over a notional period of time. In effect, our analysis reflects the underlying steady state impact of screening, rather than the simulating the absolute number of events which a screening programme would encounter over a given time period.

5.2 National generalisation of the pilot

In the previous sections of this report we have reported the components of the cost-utility results. In this section we combine the components to estimate the cost per QALY, i.e. the cost-effectiveness ratio. Further, we report the uncertainty of the results using probabilistic and univariate analysis.

If bowel cancer screening was rolled out nationally in New Zealand in the same way that it was undertaken in the pilot, it is estimated to dominate no screening; i.e. be cost saving with QALY gains. The comparison of the outcomes for screening and no screening are included in Table 21 below.

Our best estimate of the cost-per QALY for this scenario is -$1,344, i.e. cost saving with health benefits. There is some uncertainty in the result: we estimate the cost per QALY to fall in the range of -$5,786 to $4,850. This is a negative cost per QALY, which dominates all other scenarios, since there is no tradeoff between cost and outcome.

Table 21 Cost-effectiveness of bowel cancer screening - based on national generalisation of the Pilot – life time costs and benefits of the average person – Whole population

Treatment	Costs	QALYs	Incremental		Cost per QALY (95%CI)
			Costs (95% CI)	QALYs (95%CI)	
No screening	$2,643	17.661	-$98 (-$627 - $219)	0.0730 (0.0451 - 0.1084)	Dominates* (-$5,786 - $4,850)
Screening	$2,544	17.734			

5.2.1 Cost-effectiveness for Maori

For the Maori population, if bowel cancer screening was rolled out nationally in New Zealand in the same way that it was undertaken in the pilot, our best estimate is a cost-effectiveness ratio of $381 per QALY, i.e. small cost for health gains. There is some uncertainty in the result: we estimate the cost per QALY to fall in the range of -$4,570 (Cost saving) to $5,592.

The estimated QALY gains per person are very similar for Maori and the whole population. The cost-saving per person for Maori are not as great as for the whole population, which results in an estimated slight net cost for Maori. Although our estimated range of the net cost of screening includes cost-saving, with a range of -$430 to $307.

Table 22 Cost-effectiveness of bowel cancer screening - based on national generalisation of the Pilot – life time costs and benefits of the average person – Maori population

Treatment	Costs	QALYs	Incremental		Cost per QALY (95%CI)
			Costs (95% CI)	QALYs (95%CI)	
No screening	$2,233	16.901	$29 (-$430 - $307)	0.0759 (0.0463 - 0.1142)	$381 (-$3,762- $6,288)
Screening	$2,262	16.977			

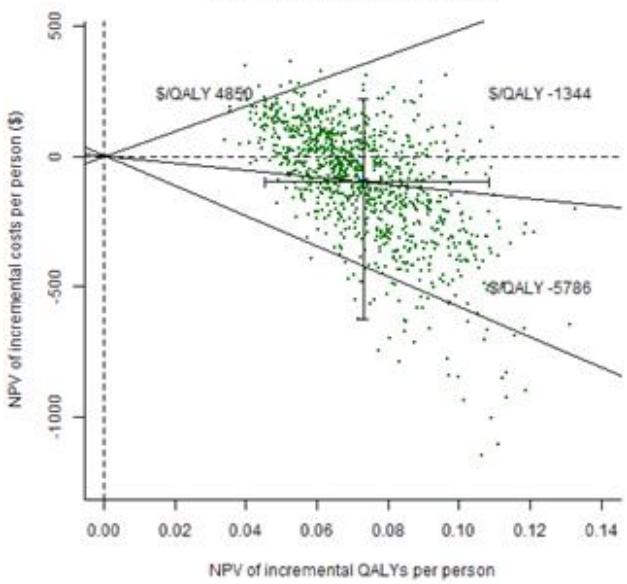
5.2.2 Probabilistic sensitivity analysis

We use probabilistic sensitivity analysis to estimate the range of the cost per QALY due to parameter uncertainty. This analysis provides us with 1,000 results, with each representing the estimated cost per QALY for the modelled cohort. Each result is based on different values used for each of the parameters.

The 95 percent confidence interval, is cost–saving (-$5,786) to $4,850 per QALY. These values are represented by the lower and upper diagonal lines in Figure 19 below. The 95 percent confidence interval for the net cost of screening per eligible person represented by the vertical error bars in Figure 19 is -$627 to $291. The 95 percent confidence interval for the QALYs gained per eligible person represented by the horizontal error bars in Figure 19 is 0.0451 to 0.1084.

All of the simulations estimated a positive QALY gain. In terms of cost, 63 percent of simulations were cost-saving and the remaining 37 percent had a positive cost; i.e. in approximately two thirds of the simulations bowel cancer is estimated to be cost-saving with QALY gains for the New Zealand population.

Figure 19 Probabilistic sensitivity analysis: national rollout of the pilot



5.2.3 Univariate sensitivity analysis

In order to understand what drives the uncertainty we have varied each parameter, or each set of parameters, one by one. This analysis shows that our result is most sensitive to the uncertainty in the natural history of bowel cancer.

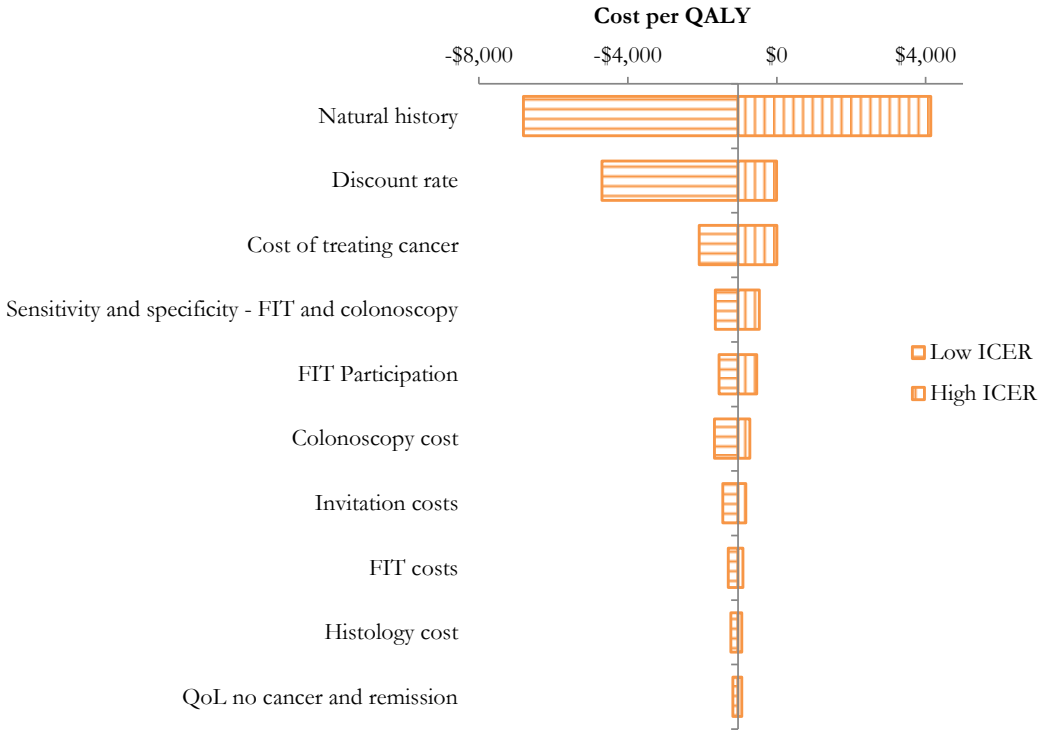
The results of this analysis are shown in Figure 20 as a tornado diagram. The tornado diagram makes it clear to see the parameters which create the largest uncertainty, as shown by the wide bars for natural history. In this report we limit the number of parameters, or sets of parameters, to the 10 that have the biggest impact on the results.

The uncertainty in the natural history of adenomas, and corresponding bowel cancers, creates the largest uncertainty in the cost-effectiveness. The greater the number of adenomas the more cost-effective bowel screening is. A low rate of adenoma results in a cost per QALY of $4,138, and a high rate of adenomas results in a cost per QALY of -$6,799.

While the discount rate isn't uncertain, the value chosen has a relatively large impact. A lower discount rate improves the cost-effectiveness as the future benefits of screening are discounted less. A discount rate of 0% results in a cost per QALY of -$4,692. A discount rate of 5% results in a cost per QALY of -$5.

The discount rate applied during analysis and the cost of cancer also had an impact, although a lesser one, upon cost effectiveness. In neither case does a plausible range of alternative values reduce the cost effectiveness to a level at which screening would not be considered a highly cost effective intervention.

Figure 20 Univariate sensitivity analysis - Tornado diagram



5.3 Cost-effectiveness of different scenarios

In this section we explore the impact on the cost-effectiveness of varying the following parameters:

- iFOBT cut-off;
- age band for screening;
- iFOBT participation rate.

iFOBT cut-off and the age band for screening are two design parameters that can be changed if bowel cancer screening is rolled out nationally. We have varied these parameters to inform views on the different options for a national rollout. iFOBT participation rate was included since it helps to inform the value of improving, or retaining, the participation rate seen in the pilot.

5.3.1 iFOBT cut-off

Bowel cancer screening is estimated to be less cost-effective at higher cut-off levels. Increasing the iFOBT cut-off reduces the net savings and reduces the QALY gains.

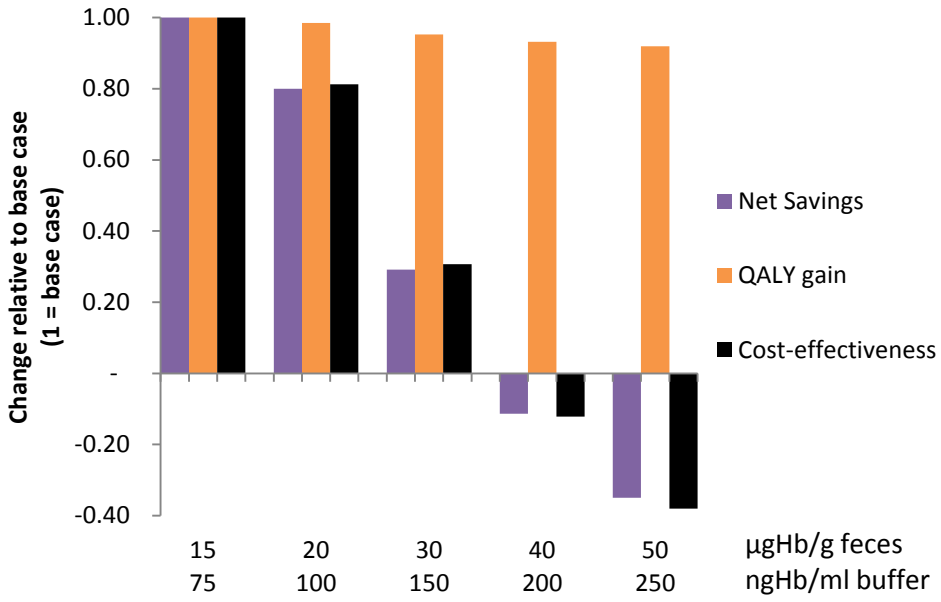
Increasing the iFOBT cut-off from 75 to 250 results in a cost per QALY of $510, i.e. no longer cost saving (although close to cost-saving). The cost per QALY for a range of iFOBT cut-off values are shown in Table 23 below.

Table 23 Cost-effectiveness at differing FIT cut-off levels

FIT cut-off (ng HB/mL)	Cost per QALY
75	Dominates
100	Dominates
150	Dominates
200	$160
250	$510

The reduction in net savings and QALY gains at higher iFOBT cut-offs is shown in Figure 21 below. Increasing the iFOBT cut-off to 250ng results in a net cost of $34 compared with a net saving of $98 in the base case. Increasing the iFOBT cut-off decreases the QALY gain by 8 percent. The changes in the cost per QALY are driven by the changes in the net savings.

Figure 21 Impact of iFOBT cut-off on, net savings, QALY gain and cost-effectiveness

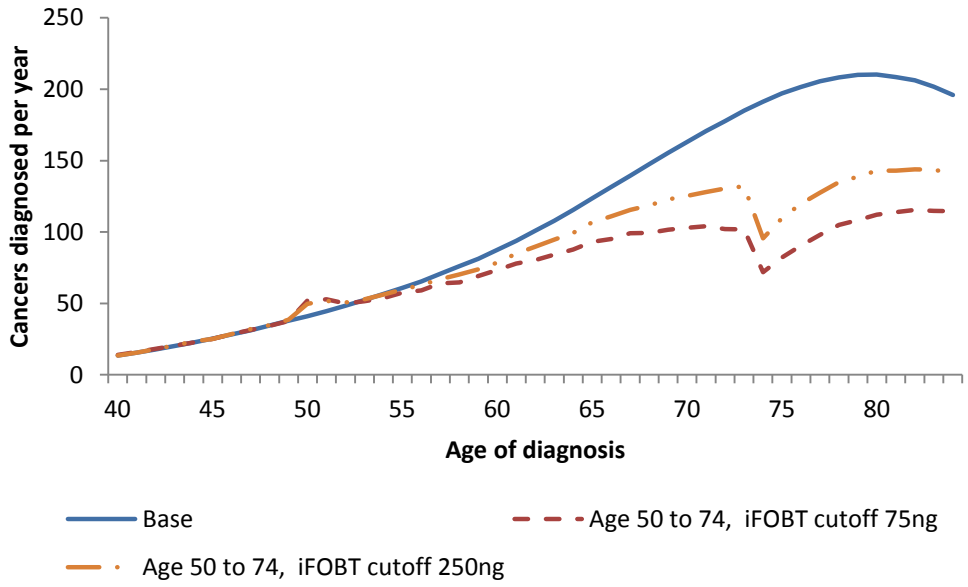


Increasing the iFOBT cut-off decreases the number of positive iFOBT tests. This leads to lower screening costs and reduced cost-offset; although the larger effect is a reduction in cost-offsets which leads to a decrease in net savings (as shown in Figure 21 above).

Increasing the iFOBT cut-off reduces the number of adenomas and cancers detected; which results in fewer cancers and cancer deaths avoided from screening. This reduction in cancers and cancers deaths avoided is what drives the reduction in QALYs shown in Figure 21 above.

Using an iFOBT cut-off of 250ng results in a 24 percent reduction in cancers, compared with a 35 percent reduction with a cut-off of 75ng (i.e. one third fewer cancers avoided than when using the higher iFOBT-cut off). The estimated number of cancers with no screening and screening using different iFOBT cut-offs is shown in Figure 22 below. The top line in the figure below represents the number of cancers diagnosed without screening, by age. The lines in the figure below represent the number of cancers with screening with an iFOBT cut-off of either 75ng or 250ng, with 75ng iFOBT cut-off represented by lower line due to the greater reduction in cancers.

Figure 22 Diagnoses of cancers by age of diagnosis - cohort followed to age 84 – comparing different iFOBT cut-off values



The impact of using a higher iFOBT cut-off is smaller for the reduction in cancer deaths, compared with cancers. Using a iFOBT cut-off of 250ng results in a 34 percent reduction in cancer deaths, compared with a 45 percent reduction with a cut-off of 75 (i.e. a quarter fewer cancer deaths avoided when using the higher iFOBT-cut off).

In this section we compared the sensitivity and specificity using different cut-off values of a single iFOBT test. Another way to increase the performance of iFOBT is to perform multiple tests. We have identified one study that reported that taking the highest values of multiple iFOBT increased the sensitivity while decreasing the sensitivity; this pattern was

consistent at different cut-off values[55]. However, we have not assessed the impact of performing multiple tests, which could be an area for further research.

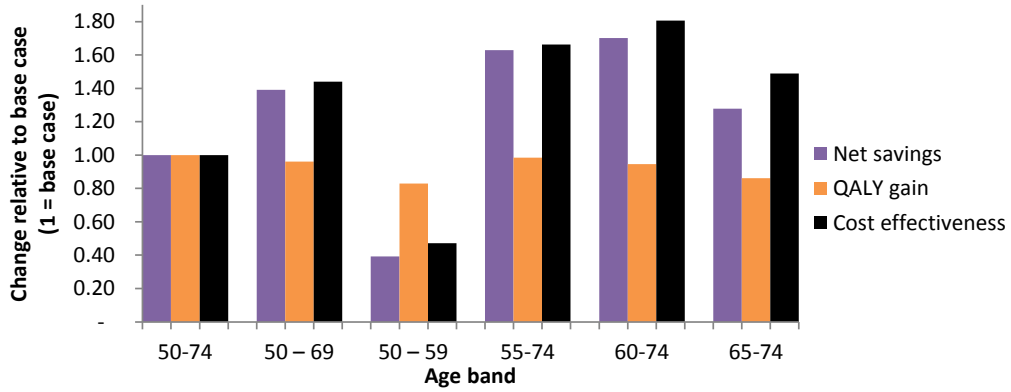
5.3.2 Age band for screening

Using a narrower age band is more cost-effective, up to a point. Five of the six narrower age bands we assessed resulted in increased cost-effectiveness. However, there is reduced efficacy from screening when narrowing the age bands.

Using a narrower age band is usually more cost-effective because the efficacy of screening reduces with each additional episode of screening. The reduction in efficacy is due to people being less likely to have a cancer or adenoma if they have previously taken part in screening.

The reduction in QALY gains and increase in net savings from using narrower age bands are shown in Figure 23 below. The most cost-effective age band is estimated to be 60-74. Narrowing the age band to 60-74 increases the saving 69 percent and the decreases the QALY gain by 5 percent; given the increase in net saving, the cost–effectiveness improves by 79 percent.

Figure 23 Impact of age band on, net savings, QALY gain and cost-effectiveness

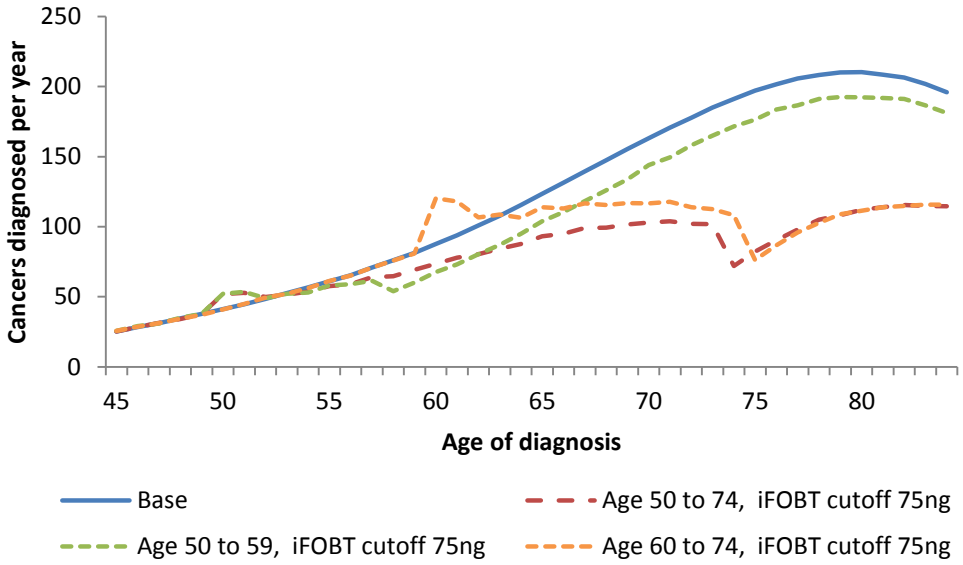


Narrowing the age bands decreases the number of rounds people can participate in. This leads to lower screening costs and reduced cost-offset; although the larger effect is a reduction in screening costs which leads to a reduction in net costs (as shown in Figure 23 above).

Narrowing the age band reduces the number of adenomas and cancers detected; which results in fewer cancers and cancer deaths avoided from screening. This reduction in cancers and cancer deaths avoided is what drives the reduction in QALYs gained shown in Figure 23 above.

Using an age band of 60-74 results in a 28 percent reduction in cancers, compared with a 35 percent reduction with an age band of 50-74, i.e. a fifth of a reduction in the number of cancers avoided when using a narrower age band. The estimated number of cancers with no screening and screening using age bands is shown in Figure 24 below. The top line in the figure below represents the number of cancers diagnosed without screening, by age. The lower lines in the figure below represent the number of cancers with screening.

Figure 24 Diagnoses of cancers by age of diagnosis - cohort followed to age 84 – comparing different age bands



The impact of using a narrower age band is a smaller reduction in cancer deaths, compared with cancers. Using an age band of 60-74 results in a 42 percent reduction in cancer deaths, compared with a 45 percent reduction with an age band of 50-74, i.e. a thirteenth reduction in the number of cancer deaths avoided when using a narrow age band.

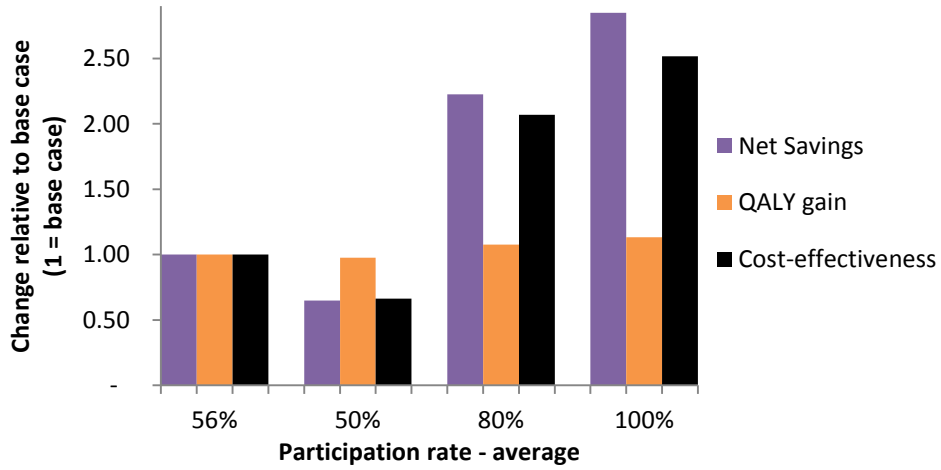
5.3.3 Participation rates

Increasing the participation rate improves the cost-effectiveness. A higher participation rate results in increased net savings, and increased QALY gains. Although the cost of screening increases with increased participation rates, the cost-offsets increase at a greater rate, which then leads to an increase in net savings.

We estimated the cost-effectiveness using differing participation rates. All the participation rates were varied to obtain a specified average participation rate. The average rate is the average for the cohort from when they enter screening at age 50 to when screening end at age 74. The results for each of the participation rates are shown in Figure 24 below.

Increasing the participation rate from 56 percent (i.e. the base case) to 100 percent increases the QALY gains by 16 percent. While the participation rate is nearly doubled the QALY gains only increase by 16 percent because increasing the participation rates also increases the number of rounds of screening people attend, and the efficacy of screening reduces with each additional episode of screening a person participates in. The net savings more than triple when the participation rate is increased to 100 percent; this is because the increase in cost-offsets significantly outweighs the increase in screening costs.

Figure 25 Impact of age band on, net savings, QALY gain and cost-effectiveness



5.4 Comparison of results

The cost-effectives results of bowel cancer screening compare very favourably with cost effectiveness results both nationally and internationally. Many health interventions have a positive cost-effectiveness, i.e. an increase in cost for improved health outcomes. However, we estimate bowel cancer screening to be cost-saving with improved health outcomes. In decision analysis terms, this is a highly attractive intervention.

5.4.1 Pharmaceutical funding in New Zealand

The funding of pharmaceuticals (and some devices) in New Zealand is managed by PHARMAC. PHARMAC have reported the average cost-effectiveness of the investments they have made in each of the last four years. The cost-effectiveness ranges from $16,000[56] to $45,000[57] per QALY[viii]. These values represent the average for the investments made in the year: the highest cost-per QALY invested in will be higher than these average values.

5.4.2 WHO recommendations

The World Health Organisation (WHO) uses the following definitions of cost-effectiveness:

- Very cost-effective: less than GDP per capita;
- Cost effective: between 1 – 3 times GDP;
- Not cost effective: over 3 times GDP per capita.[58]

In 2015 New Zealand's GDP per capita was $53,000[59]. Using the WHO definitions, bowel cancer screening would be considered very cost-effective.

[viii] PHARMAC reports cost-effectiveness in terms of QALYs per million, which is the inverse of cost per QALY. The average QALYs per million were reported be 22 and 61 in the 2011/12 and 2014/15 years respectively

6. Comparison of results with existing screening programmes

We reviewed published cost-effectiveness analyses and compared their results with our analysis. There is significant variation in the assumptions and results of the analyses we reviewed, however our result is within the range of the existing reported results from the international literature.

The results of published analyses were summarised by Lansdorp-Vogelaar et al, reported as: *"All [32] studies found that colorectal cancer screening was cost-effective or even cost-saving compared with no screening. However, the studies disagreed as to which screening method was most effective or had the best incremental cost-effectiveness ratio for a given willingness to pay per life-year gained."*[60] This finding was based on an exhaustive review of publications between 1993 and 2009. There is significant variation between the results, and the authors conclude it is difficult to determine the cause of the variation as assessments with very similar assumptions have differing results.

There is limited analysis on the impact of screening on quality of life. Most of the analyses report life years gained, rather than quality adjusted life years (QALYs) gained.

We undertook a detailed comparison of our model with four published analyses. We identified analyses that were most relevant and had sufficient details reported in order to make a meaningful comparison. Amongst these analyses there was a wide range in the inputs, for example participation rates varied between 37% and 100%. There was also a wide range in the results, from cost-saving to $53,000 per life year saved. A high level summary is included in the following section, with further details included in Appendix 3.

6.1 Summary of individual cost-effectiveness analyses

We searched for cost-effectiveness analyses that met the following criteria

- FIT or iFOBT screening compared with no screening
- Report in detail in terms on basis for assumptions and results

We identified four studies meeting these criteria[27,28,29,30]. One of the studies had limited details reported;[27] however, we included this study because it is relatively recent, and provides an interesting comparison with the Australian setting.

The most descriptive report we identified was by Tappenden et al,[29] which appraised screening options in the UK setting. The assessment is relatively similar to our analysis, with key differences being the use of FOBT rather than iFOBT, and differing methods for estimating QALYs.

The analyses reported by Goede et al[28] used the MISCAN-Colon model, which has also been used by a number of other researchers. The primary objective of the study was to compare one versus two sample iFOBT; however they also reported the cost-effectiveness of using

different cut-off values. A key difference to our study is that they did not estimate QALYs, but focused on life years saved.

Our model has a number of similarities with the MISCAN-Colon model used by Goede et al. A number of the input values are similar and the results of the models are comparable. A comparison of the inputs is made throughout section 2 above, and the comparison of the results is in section 6.2 below.

Ladabaum et al[30] compare the cost-effectiveness of a particular screening method with current screening methods. While the reporting is relatively detailed, the reporting of the cost-effectiveness of iFOBT compared with no screening is somewhat limited. A key difference from our analysis is that 100 percent participation (for iFOBT and all follow up) is assumed in the base case.

Tran et al[27] estimate the cost-effectiveness of the Australian National Bowel Cancer Screening Program. Of the four analyses we reviewed in detail this had the most limitations, both in limited reporting and in differences to our model. One of the key differences from our study assessment was the relatively low participation rate of 37 percent. Tran et al note in their report that they have taken a conservative approach on a number of fronts.

A high level comparison of these four analyses and our analysis is included Table 24 below. There is a range of combinations of screening tests and frequency used, with the least effective being FOBT biannual and the most effective being iFOBT annual. The age bands vary from 15 to a 30 year ranges, with all assessments included those aged 55. The participation rates vary greatly, from 37% to 100%.

Ladabaum et al[30] included the most effective screening test, widest age band and highest participation rate, they also reported the most cost-effective results of cost-saving. Tran et al[27] had the least effective screening option, narrowest age band, and lowest participation rate, which resulted in the lest cost-effective result of $53,300 per life year. Despite having the least cost-effective result, Tran et al had a relatively low net cost per person of $98, so it seems the relatively low level of benefit per person invited is the driver of result.

The base line bowel cancer incidence (and bowel cancer mortality) in our analysis is higher than found by Tappenden and Ladabaum (the other two studies did not report this data), although the extent of the difference is difficult to estimate given the differing measures used for incidence. For our cohort, we estimate that, without screening, 87 cancers would develop per 1,000. Tappenden and Ladabuam provide figures on the number of people who develop cancer, with rates of 41 and 59 per 1,000 respectively.

Our model also included a reducing incidence of bowel cancer over time. The analyses we reviewed do not report taking such an effect in to account. Tappenden et al calibrated their model again 2001 UK data. Over the 20 years prior to 2005 the NZ bowel cancer mortality rate for men decreased by 35 percent. If this New Zealand trend continued, then if could explain a significant amount of the variation in base case cancer incidence between our model and that reported by Tappenden.

A more detailed comparison of the four studies and our study is included in Table 27 in Appendix 3.

Table 24 Summary of individual cost-effectiveness analysis: Results compared to no screening, reported in 2016 NZD

First author , year (Setting)	Tappenden 2004 (UK)	Goede 2013 (Dutch)	Tran 2011 (Australia)	Ladabaum 2013 (US)	This analysis (New Zealand)
Screening test	FOBT Biannual	FIT Biannual	FOBT One off	FIT Annual	FIT Biannual
Age band	50-69	55-75	50-65 as per Australian Screening programme	50-80	50 – 74
Bowel cancer incidence – No screening (per 1,000)	41			59	87 (counting cancers, rather than people with cancer)
Participation	60%	60%	~37%[α]	100%	56%
Net Cost (per invitee)	$243	$427	$98	-$753	-$98
Headline result	$11,000 per QALY*	$5,000 per life year	$53,000 per life year	Cost-saving with QALY gains	Cost-saving with QALY gains

[α] Tran et al reported the participation rates for the age groups 50, 55 and 65 as 28.0%, 37.7% and 46.4% respectively

6.2 Comparison of impacts

In this section we compare how the results of our analysis and the four analyses we reviewed are impacted when we change the following:

- Participation rate;
- FIT-cut-off;
- Age band.

6.2.1 Participation rate

There is variation in how the participation rates impact the results of published analyses. The impact of participation rates in our model is similar to the impact reported by Tran et al.

Tappenden et al find a very small impact when participation is reduced. When they assumed that 40% of people never participate in screening, the cost per QALY increased by only half a percent

They noted *'As fewer individuals comply with FOB tests, fewer adenomas and cancers would be found. Although non-compliers are assumed to continue to accrue the costs of sending FOB tests kits, the total cost of the programme is slightly offset by the reduction in colonoscopy costs'* pg 103

Tran et al included alternative participation rates in their scenario analysis. When the participation rate was increased by 50 per cent (up to a level of 75 percent) the cost-effectiveness result improved by 25 percent.

Ladabaum et al did not report on the impact of varying the participation rate on the cost-effectiveness of screening with iFOBT compared to no screening. Participation was assessed in detail for other screening comparisons.

Goede et al did not report on the impact of varying the participation rate.

6.2.2 iFOBT cut-off

Goede et al was the only study of the four we assessed in detail that evaluated the impact of differing iFOBT cut-offs. Both our analysis and that reported by Goede et al, found that a lower iFOBT cut-off is more cost-effective.

While both analyses report low iFOBT cut-off being associated with greater heath gains, the impact of net cost differed. Goede et al estimated the net cost to be higher at lower cut-offs. This difference is results is likely to be due to the difference in the ratio of cost of screening and cost off-sets.

6.2.3 Age range

Our results are in line with the two published analyses that reported the cost-effectiveness for different age bands, where both reported that narrower age bands were more cost-effective. Tappenden included two age bands for biannual FOBT, 50-69 and 60-69. The narrower age band of 60-69 year olds was reported to be 20 percent more cost-effective.

Goede et al include a number of age bands in their analysis. For biannual iFOBT with a 50ng cut off they report the cost-effectiveness for the age bands: 60 -70; 60 – 74; and 55 – 75. They found that the age band 60-70 was the most cost-effective, with 55-75 being the least cost-effective.

7. Discussion

This cost utility analysis has used data from a New Zealand pilot of a bowel screening programme, and data from the international literature. We applied an explicitly defined set of assumptions to a microsimulation model of bowel screening in the New Zealand population.

We have found that, in a New Zealand setting, bowel screening is a highly cost effective intervention and under some scenarios is not only cost effective, but directly cost saving. This very strong result suggests that from a perspective of New Zealand health sector costs, bowel screening can avoid more costs than are involved in delivering the programme. This result is not unprecedented in the international literature on bowel screening, but it does lie at the more cost effective end of the range of published results. This highly cost effective result applies both to the New Zealand population overall, and to people of Maori ethnicity.

More generally, the patterns of results from our analysis fit within the range of results observed in other cost benefit analyses of bowel screening programmes internationally – for example, our estimated cost of treating Stage III bowel cancer is close to the costs used by UK analysts. This consistency with international results adds a level of confidence in the findings, and sets our results in context.

We conducted a full probabilistic sensitivity analysis within our microsimulation model. While the detail of reported results from other cost benefit analyses means that there is only one comparison which can be made to our study for the width of the credible limits of the cost effectiveness results, we have found a narrower range than that comparator, further supporting the strength of the results.

An important and novel part of our analysis has been the ability to report a subset of results for Maori. The ability to confirm that bowel screening is also cost effective in a key, high need, ethnic population is an important piece of information to support policy debate about the implementation of a programme, in light of the differential impacts which could arise for vulnerable populations. We intended to conduct the analysis for Maori from the beginning of the project, and believe that this result is an important facet of the overall assessment of the effectiveness of the New Zealand bowel screening pilot. Reporting the cost effectiveness of programmes for vulnerable populations, as well as for the population as a whole, can help to identify any risks of increasing health inequalities which may arise from well intentioned health care programmes, and to ensure that such risks are appropriately debated and mitigated.

The results we have reported here inform policy decisions by providing cost and cost effectiveness information for health system planners. But it should be noted that cost effectiveness is not the only parameter which informs decision on investment in health services and interventions. In this case the absolute level of resource needed to implement the programme, the absolute sensitivity and specificity of the programme, and the expected impact on vulnerable populations as well as the population of New Zealand overall are important components of the decisions which will be made about the future of any bowel screening programme.

We have conducted this project in close cooperation with our research partners: Litmus, and Massey University. The ability to set our cost effectiveness results within a wider evaluation of New Zealand's pilot bowel screening programme means that a technical cost utility result can be interpreted within the context of a comprehensive analysis of the pilot and what it has achieved.

We have been lucky to be able to draw upon the work of two New Zealand research groups for elements of our analysis. These are the cost of cancer results provided to us by the BODE research team, and the microsimulation code provided to us by the MoDCONZ team. We would like to acknowledge the important work of these teams, and in particular thank the MoDCONZ group for allowing us to participate in some aspects of the development of the model. While we have built upon the work of these two research groups, responsibility for the results reported here lies with Sapere Research Group.

Appendix 1: MoDCONZ

Natural History Model

The natural history model in MoDCONZ is derived from the Janoshek model as described in Rutter.[61] This model has two major components.

1. Across the sample population the number of adenomas for each person is determined by an adenoma risk model (modified from Rutter). This is determined in the main component of the MoDCONZ algorithm to divide the population into those with and without adenomas for further processing.

2. For each individual the evolution of these adenomas is modelled through growth of the adenoma, transition from adenoma to cancer, and the sojourn time from preclinical to clinical cancer. These are determined within the natural history function called for each individual.

The natural history of colorectal cancer is based on the adenoma–carcinoma sequence and assumes that all CRCs arise from an adenoma. [62] Four model components describe the natural history of CRC: adenoma risk, adenoma growth, transition from adenoma to preclinical cancer, and transition from preclinical to clinical cancer.

Adenoma Risk Model

The adenoma risk model is evaluated using a modified Rutter log hazard model:

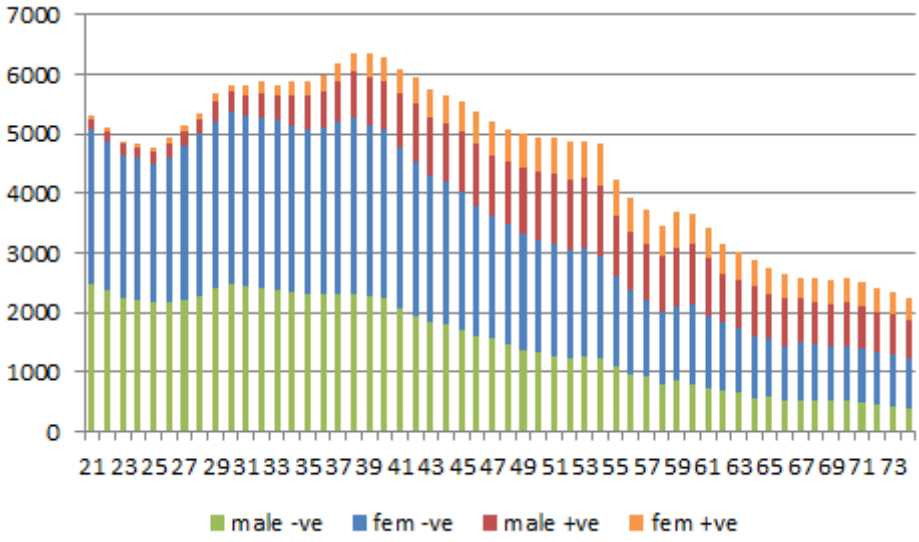
$$\begin{aligned}\log\_hazard(i) = \; & \alpha_0 + \alpha_1 sex_i + \alpha_2 age_i + \alpha_3 family\ history2_i \\ & + \alpha_4 family\ history\ 3_i + \alpha_5 (YOB_i - 1940) \\ & + \alpha_6 YOB_i^2 \delta(sex_i = male) + \alpha_7 YOB_i^2 \delta(sex_i = female)\end{aligned}$$

The cohort (YOB) components have been added to account for a reduction of incidence in post war generations, calibrated to observed changes in bowel cancer incidence in New Zealand.

Figure 26 illustrates the 2001 population profile produced by this model for the natural history baseline population arrays with and without adenomas.[ix] The α_2 age component of the risk model is integrated over the individual's lifetime, hence is largely the same for each age cohort. The variation in adenoma positive population between age cohorts reflects the $\alpha_{6/7}$ quadratic term of the cohort effect. Figure 26 the relative impact of the quadratic term reducing the adenoma risk from 28 percent for 45 years to 13 percent for 35 years and 5.6percent for 25years.

[ix] This is collected as the number of rows in the arrays: male_adeneg_sub_a, male_adepos_sub_a, female_adeneg_sub_a, and female_adepos_sub_a.

Figure 26 Adenoma risk profile by gender



Source: MoDCONZ

Running MoDCONZ as a cohort model

To support the cost utility analysis, we run MoDCONZ as a cohort model examining the total life histories for a particular cohort for various scenarios of bowel screening. Table 25 provides some key characteristics of cohorts supporting the choice of the 1957 cohort for analysis. The cohort effect in the adenoma risk model for this cohort is significant but not dominant, while program options targeting ages 50 and above or 60 and above provide reasonable program years.

Table 25 Cohort adenoma risk characteristics

2001 age	Ade –ve	Ade +ve	Ade %	YOB	Year 50	Year 60
39	5170	1197	18.8%	1962	2012	2022
40	5089	1191	19.0%	1961	2011	2021
41	4797	1291	21.2%	1960	2010	2020
42	4524	1434	24.1%	1959	2009	2019
43	4297	1456	25.3%	1958	2008	2018
44	4230	1425	25.2%	1957	2007	2017
45	4015	1529	27.6%	1956	2006	2016
46	3823	1541	28.7%	1955	2005	2015
47	3690	1522	29.2%	1954	2004	2014

Source: MoDCONZ

Appendix 2: Details of FIT performance

Details of studies assessing the performance of FIT

Table 6 in section 2.5 of this report provides a summary of the studies we reviewed that assess the performance of FIT. This part of the report provides further details of the studies that we did not use as to base our estimate of sensitivity and specificity.

Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening – Park et al[32]

The report provides information on the sensitivity and specificity of the FIT. 770 patients who were undergoing colonoscopy also undertook FIT and gFOBT.

For each person undertook 3 FITs and 6 FOBTs. The headline results are for the performance of FIT is of all 3 tests, but the performance of the first test is also reported. It is the performance of the first test that provides us with expected efficacy of bowel screening as it is currently done in New Zealand.

The authors report the performance of FIT at different cut offs, ranging from 50 to 150ng. The reporting of the sensitivity and specificity for a single FIT test was limited to 75 and 100ng cut-off. Cohort of average risk patients aged 50 -74 in south Korea. Observations were between 2007 and 2008 for patients undergoing screening colonoscopy.

Immunochemical fecal occult blood testing is equally sensitive for proximal and distal advanced neoplasia - de Wijkerslooth 2012[33]

The report provides information on the sensitivity and specificity of the FIT. 1,256 patients who were undergoing colonoscopy also undertook FIT.

The authors report the performance of FIT at different cut offs, ranging from 50 to 100ng. Cohort of average risk patients aged 50 -74 in Amsterdam. Observations were between 2009 and 2010 for patients undergoing screening colonoscopy.

Superior diagnostic performance of faecal immunochemical tests for haemoglobin in a head-to-head comparison with guaiac based faecal occult blood test among 2,235 participants of screening colonoscopy – Brenner 2013[34]

The report provides information on the sensitivity and specificity of the FIT. 2,235 patients who were undergoing colonoscopy also undertook FIT. The study assessed the performance of four stool based tests, we report on the finding of the OC sensor FIT test.

The authors report the performance of FIT at a cut off of 100 ng. Cohort of average risk patients aged 50 –79 in Germany. Observations were between 2005 and 2009 for patients undergoing screening colonoscopy for the first time.

Accuracy of Faecal Immunochemical Tests for Colorectal Cancer: Systematic Review and Meta-analysis - Lee 2015[63]

The sensitivity and specificity of FIT in detecting bowel cancers has been estimated using a meta-analysis. The meta-analysis combined the results of 19 studies that were published between 1996 and 2013. The analysis did not assess the performance FIT in detecting adenomas.

The performance of FIT varied due a number of factors including the cut-off level used. The authors compared the performance at three different bands of cut offs, the results are shown in Table 26 below. As expected as the cut-off increased the sensitivity decreased and the specificity increased.

Table 26 Performance of FIT in detecting cancers, at different cut off levels – Lee et al 2014

Cut-off	Sensitivity (95% CI)	Specificity (95% CI)	Number of studies
Under 100 ng/ml (20 µg/g)	0.86 (0.75 - 0.92)	0.91 (0.89 – 0.93)	11
100 to 250 ng/ml (20 – 50 µg/g)	0.63 (0.43 – 0.79)	0.96 (0.94 – 0.97)	6
Over 250 ng/ml (50 µg/g)	0.67 (0.59 – 0.74)	0.96 (0.94 - 0.98)	4

Source: Lee et al 2014[63]

There was significant amount of variation in estimates by different studies. Reported sensitivity for the 6 studies with a cut-off between 100 to 250 ng/ml ranged between 0.25 and 0.60. Part of this variation is in part due to how the studies were conducted. One difference in how the studies were conducted is the reference standard, i.e. how it was determined if a patient had a cancer. Some studies used colonoscopy while others used at least 2 years of follow-up with medical records or cancer registry. Studies using colonoscopy reported lower sensitivity and no difference in specificity.

FIT cut-off: Comparison with studies FIT positivity at different cut-offs

We have estimated increasing the FIT cut-off will result in a lower sensitivity and a higher specificity, which will result fewer positive FITs and fewer adenomas and cancers detected. This is supported by clinical studies; which are summarised below.

Faecal immunochemical tests compared with guaiac fecal occult blood test for population-based colorectal cancer screening - Rabeneck 2012[64]

The review was informed by 2 systematic reviews and three RCTs.

The focus of the review was comparing FIT with guaiac-based FOBT, the authors concluded that FIT is superior in terms of participation rate and detection of cancers and advanced adenomas.

The review also summarised the performance of FIT at different cut-off levels, based on the results of four studies. At higher cut-off values the positivity decreased and the positive predictive value increased; i.e. fewer adenomas and cancers detected but a more chance that a positive FIT results in the detection of an adenoma or cancer. Only one study included the review reported outcomes for both adenomas and cancers detected over a range of cut-off values, Hol et al 2009.

The two larger studies (Hol et al and Grazzini et al) reported positivity rate of 5.7 and 5.5 percent at (or close to) a cut-off of 75ng. The smaller study (Park et al) reported a much higher positivity rate, Part et al provide reasons for the higher rate in their article.[32] Only Hol et al reported results at a cut-off of 200ng, the positivity rate was 3.5 percent. Further details of the performance of FIT at different cut-off levels are included in Figure 27 below.

The study reported by Hol et al is further discussed in the following section.

Figure 27 Summary of performance characteristics of FIT at different cut-offs

Author (ref), year	Study population	Cut-off value	Sensitivity		Specificity		Positivity	PPV	
van Rossum et al (18), 2009	428 participants				CRC + AA[1]			CRC	AA[1]
	50–75 years of age using OC-Sensor*	≥50 ng/mL	NR		96.0		8.5	NR	NR
		≥75 ng/mL	NR		97.1		NR	NR	NR
		≥100 ng/mL	NR		97.8		NR	NR	NR
		≥125 ng/mL	NR		98.1		NR	NR	NR
		≥150 ng/mL	NR		98.3		NR	NR	NR
		≥175 ng/mL	NR		98.4		NR	NR	NR
		≥200 ng/mL	NR		98.6		NR	NR	NR
		≥225 ng/mL	NR		98.7		NR	NR	NR
Hol et al (17), 2009	5007 participants				CRC	AA[2]		CRC	AA[2]
	50–74 years of age using OC-Sensor	≥50 ng/mL	NR		92.9	95.5	8.1	7	42
		≥75 ng/mL	NR		95	97.2	5.7	9	49
		≥100 ng/mL	NR		95.8	97.8	4.8	10	53
		≥125 ng/mL	NR		96.3	98.2	4.1	11	57
		≥150 ng/mL	NR		96.6	98.4	4	11	60
		≥175 ng/mL	NR		97	98.7	3.6	12	63
		≥200 ng/mL	NR		97.1	98.8	3.5	12	62
Grazzini et al (22), 2009	20,596 participants				CRC	AA[3]		CRC	AA[3]
	50–69 years of age using OC-Hemodia* and OC-Sensor	≥80 ng/mL	NR		NR	NR	5.5	5.9	NR
		≥100 ng/mL	NR		NR	NR	4.5	6.9	NR
		≥120 ng/mL	NR		NR	NR	4.0	7.6	NR
Park et al (23), 2010	770 participants		CRC	AA[4]	CRC	AA[4]	–	CRC	AA[4]
	50–75 years of age using OC-Sensor Micro*	≥50 ng/mL	92.3	44.1	87.2	88.3	NR	NR	NR
		≥75 ng/mL	92.3	37.3	89.0	89.7	12.2	NR	NR
		≥100 ng/mL	92.3	33.9	90.1	90.6	11.2	12.8	23.3
		≥125 ng/mL	84.6	28.8	91.3	91.6	NR	NR	NR
		≥150 ng/mL	84.6	27.1	91.9	92.1	NR	NR	NR

*Data presented as % unless otherwise indicated. *Eiken Chemical Company Ltd, Japan; AA Advanced adenoma (AA[1] Adenomas ≥10 mm with high-grade dysplasia or with a villous component ≥20%; AA[2] Adenomas ≥10 mm with high-grade dysplasia or with a villous component ≥25%; AA[3] Adenoma ≥10 mm and/ or a villous component ≥21% and/or severe dysplasia; AA[4] tubular adenomas ≥10 mm or tubulovillous or villous adenomas, or those with high-grade dysplasia regardless of size); CRC Colorectal cancer; NR Not reported; PPV Positive predictive value; ref Reference*

Source: Rabeneck 2010[64]

Key studies reporting FIT performance

Screening for colorectal cancer: random comparison of guaiac and immunochemical faecal occult blood testing at different cut-off levels[65] - Hol et al 2009

This study reported a higher cut-off results in lower positivity and higher positive predictive values. Also the positivity was higher for men and older population.

A randomised control trail was used to compare FIT with guaiac-based FOBT. The study recruited people aged 50 – 74 in the Netherlands. FIT kits were sent to 4,843 people with a 62 participation rate. At a cut-off of 50%, there was an 8.1 percent positivity rate which resulted in 241 people with a positive FIT. 226 people underwent colonoscopy. There were 95 people found to have either an advanced adenoma or cancer.

The performance of FIT at different cut-off levels is summarised in Figure 28 below. At a cut of 75ng the positivity was 5.7, of the positive tests 49 percent resulted detecting either an adenoma or cancer (advanced neoplasia). At a cut of 200ng the positivity was 3.5 percent, of the positive tests 62 percent resulted detecting either an adenoma or cancer.

Figure 28 Performance of FIT at different cut-off levels

	Cut-off	Positivity rate		PPV	
	(ng ml^{-1})	*n*	% (95% CI)	Advanced neoplasia % (95% CI)	CRC % (95% CI)
gFOBT		65	2.8 (2.2–3.6)	45 (33–58)	10 (4–20)
FIT	50	241	8.1 (7.2–9.1)*	42 (36–49)	7 (4–11)
	75	170	5.7 (4.9–6.6)*	49 (42–57)	9 (5–14)
	100	143	4.8 (4.1–5.6)*	53 (45–61)	10 (6–17)
	125	128	4.1 (3.4–4.9)*	57 (48–65)	11 (6–17)
	150	120	4.0 (3.4–4.8)*	60 (51–69)	11 (7–19)
	175	107	3.6 (3.0–4.3)*	63 (53–72)*	12 (7–20)
	200	103	3.5 (2.9–4.2)*	62 (52–71)*	12 (7–20)

Source: Hol et al 2009[65]

Although there was is sufficient information to calculate the true specificity of the FIT, the authors estimated the specificity by under the rare disease assumption as the ratio of the number of all negative screenees and the total number of screenees subtracted by the number of true positives.

Appendix 3: Detailed comparison with published analyses

Table 27 Detailed summary of individual cost-effectiveness analysis: Results compared to no screening, reported in 2016 NZD

First author , year	Tappenden 2004 (UK)	Goede 2013 Dutch	Tran 2011 Australian	Ladabaum 2013	This analysis
Underlying assumptions					
Screening test	FOBT Biannual	FIT Biannual	FOBT One off	FIT Annual	FIT Biannual
Age band	50-69	55-75	50-65	50-80	50 – 74
Perspective	Health funder (NHS in the UK)	Health funder	Government healthcare	An insurer such as Medicare	Health funder
Discount rate	3.5%	3.0%	3%	3%	3.5%
Bowel cancer incidence – No screening (per 1,000)	41 (Starting at either age 30 or 50)			59	87 (Starting at age 40)
Bowel cancer Mortality – No screening (per 1,000)	22			24	38
Key Inputs assumptions – screening					
Participation	60%	60%	~37%[α]	100%	56%
FIT cut-off	N/A - FOBT	75ng	N/A - FOBT	NR	75 ng
FIT/FOBT sensitivity - adenomas	5.00%	≤ 5mm 0%, 6-9mm 5.7% ≥10mm 14.4%	NR	< 10mm 10% ≥ 10mm 24%	< 10mm 7.7% ≥ 10mm 22.5%
FIT/FOBT sensitivity - bowel cancer	40.58%	Early 58.5% Late 87.0%	66%[θ]	70%	I or II 59.7% III or IV 85.9%
FIT/FOBT specificity	98.50%	97.05 %	NR	95%	94.7%
Key Input assumptions – costs (2016 NZ costs)					
Overhead/fixed costs	$0[‡]	$0[‡]	$0[‡]	$0[‡]	Included in other costs
FIT/FOBT cost (Including processing)	$42 (2 tests)	$25	Not stated	$36	$24

First author , year	Tappenden 2004 (UK)	Goede 2013 Dutch	Tran 2011 Australian	Ladabaum 2013	This analysis
FIT/FOBT processing and follow up	$0‡	$14	$48 positive	$0‡	$20 negative $115 positive
Colonoscopy cost – per colonoscopy	$683	$506 $657 without/with polypectomy	$1,647	$1,001 $1,571 without/with polypectomy	$960
Histology	$415†	$0‡	$0‡	$0‡	$937
Cost of treating cancer – stage III	$69,000	$58,000	$111,000	$171,000	$71,000
Input Assumptions - QoL					
No diagnoses bowel cancer	0.91	N/A	N/A	1µ	0.792
Initial phase (first year following diagnosis) Stage I Stage II Stage III Stage IV	 0.74 0.70 0.50 0.25	N/A	N/A	 0.90µ 0.80 0.80 0.76	 0.74 0.70 0.50 0.25
Continuing care phase	Same as initial phase	N/A	N/A	Same as initial phase	0.792
Terminal phase – cancer (last year of life)	N/A	N/A	N/A	N/A	0.25
Results and outputs (discounted)					
Headline result	$11,000 per QALY*	$5,000 per life year	$53,000 per life year	Cost-saving with QALY gains	Cost-saving
Headline result - Range	$2,000 – $29,000* per QALY				-$5,786 - $4,850 per QALY
Net Cost (per invitee)	$243	$427	$98	-$753	-$98
Cost of screening (FIT and colonoscopies) (per invitee)		$592	$90		$682
Cost offsets (per invitee)		$155	$26		$780
Life expectancy Gain (per invitee)	0.0260	0.0892	0.0019		

First author , year	Tappenden 2004 (UK)	Goede 2013 Dutch	Tran 2011 Australian	Ladabaum 2013	This analysis
QALY gain (per invitee)	0.0227	N/A		0.077	0.0730
Reduction in bowel cancer incidence	8.65%	10.39%	δ	62%	35%
Reduction in bowel cancer mortality	23.42%	25.98%		75%	45%

*Tappenden et al 2004 included the following results in their report, Cost per QALY of £2,949.64 with a range of £551 - £7,992. The marginal (net) cost was reported as £66.95. Costs reported in 2004 pounds

† Tappenden et al 2004 reported pathology costs of £30.00 and £250 for adenomas and cancers respectively. When we calculated the average histology cost we applied a 62% weighting to adenoma based on the five year volumes estimated by Tappenden.

‡ Assumed to be 0, as no values discussed or provided in the published reports.

Ω Ladabaum reported 40% of cancers in the base case, and 68% with FIT, would be diagnoses as localised. We use these values to approximate the stage I cancers

µLadabuam reported the utility values used as 0.90, 0.80 and 0.76 for Localised, Regional and Distant cancer.

α Tran et al reported the participation rates for the ager groups 50, 55 and 65 as 28.0%, 37.7% and 46.4% respectively

δ Tran et al reported that 1664 cases of bowel would be diagnosed with and without screening and that 225 cased of bowel cancer would be avoided.

θ Tran et al state the sensitivity of FOBT as 66%. They reference Morikawa 2005[31] as the source, which reported 66% as the sensitivity for cancers, so we assume this value was only applied to cancers and not adenomas

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