Cost-effectiveness of population-based screening for colorectal cancer: a comparison of guaiac-based faecal occult blood testing, faecal immunochemical testing and flexible sigmoidoscopy.

Sharp L[1], Tilson L[2], Whyte S[3], O Ceilleachair A[1], Walsh C[2,4], Usher C[2], Tappenden P[3], Chilcott J[3], Staines A[5], Barry M[2], Comber H[1]

[1] National Cancer Registry Ireland, Cork Airport Business Park, Cork, Ireland

[2] National Centre for Pharmacoeconomics, St James's Hospital, Dublin, Ireland

[3] School for Health and Related Research, University of Sheffield, Sheffield, England

[4] Department of Statistics, Trinity College Dublin, Dublin, Ireland

[5] School of Nursing, Dublin City University, Dublin, Ireland

Corresponding author: Linda Sharp, National Cancer Registry Ireland, Building 6800, Cork Airport Business Park, Kinsale Road, Cork, Ireland. Email: linda.sharp@ncri.ie

Running title: Cost-effectiveness of colorectal cancer screening

Key words: colorectal cancer, adenomatous polyps, mass screening, cost-effectiveness, FOBT, faecal immunochemical test, flexible sigmoidoscopy

Word count: 3,991

ABSTRACT

Objective: Several colorectal cancer screening tests are available. Each has its own strengths and limitations, making it uncertain which would provide the best balance of risks and benefits if implemented in a screening programme. We evaluated the cost-effectiveness of a population-based screening programme in Ireland based on (i) biennial guaiac-based occult blood testing (gFOBT) at ages 55-74, with reflex faecal immunochemical testing (FIT); (ii) biennial FIT at ages 55-74; and (iii) once-only flexible sigmoidoscopy (FSIG) at age 60.

Design: A state-transition model of the natural history of colorectal neoplasia was used to estimate costs and outcomes for a policy of no screening (the status quo) and each screening scenario.

Setting: Ireland

Main outcome measures: Incremental cost-effectiveness ratios (ICER) were computed for each screening scenario versus no screening. Direct costs incurred from 55 years and associated with screening (including screening tests, colonoscopies, adenoma surveillance and harms) and cancer management were included. Outcomes were expressed as quality adjusted life-years gained (QALYs).

Results: All screening scenarios would be considered highly cost-effective compared to no screening. FSIG had the lowest ICER (€589 per QALY gained), followed by FIT (€1,696) and gFOBT (€4,428). gFOBT was dominated. Compared to FSIG, FIT was associated with greater gains in QALYs and reductions in lifetime cancer incidence and mortality. FIT was also more costly, required more colonoscopies and resulted in more complications. The ICER for FIT versus FSIG was €2,058 per QALY gained. Results were robust to variations in parameter estimates.

Conclusions: A screening programme based on FIT is expected to result in greater health gains than a policy of gFOBT (with reflex FIT) or once-only FSIG, but would require considerably more colonoscopy resources and result in more harm. The challenge for policy-makers is to balance these benefits and harms while meeting health service capacity requirements.

INTRODUCTION

Each year, there are more than one million new cases of colorectal cancer and 500,000 deaths worldwide.[1] In developed countries it is the third most common cancer in men and second most common in women. In light of this burden, various international organisations have strongly recommended implementation of colorectal cancer screening.[2-4]

Several screening tests are available which, by detecting either benign adenomas or early cancers, might reduce colorectal cancer mortality and, potentially, incidence in the population. Until very recently the only test for which there was robust evidence of efficacy from randomised controlled trials (RCTs) was the guaiac-based faecal occult blood test (gFOBT); repeated screening with gFOBT results in a 16% mortality reduction.[5] This evidence underpinned the decision to base the UK colorectal cancer screening programmes on gFOBT.[6] However, gFOBTs have several weaknesses, including limited sensitivity (even when used biennially) and a high positivity rate,[7,8] the latter meaning that, in practice, substantial proportions of screened individuals need to complete a second (reflex) test before a decision is taken on referral for colonoscopy. Recent years have seen the development of faecal immunochemical tests (FIT) which are specific for bleeding of colorectal origin.[7] Reports of higher sensitivity in some studies[8] have led commentators to suggest that FIT might be a better primary screening test than gFOBT.[7] However, qualitative FITs have a lower analytic detection limit than gFOBTs, resulting in a high colonoscopy referral rate, and the kits are generally more expensive,[9] both key considerations for publicly-funded screening programmes. In Scotland, FIT is used as for reflex testing following a positive gFOBT. This has resulted in a large reduction in the proportion of screened individuals referred for colonoscopy compared with second-line gFOBT,[9-11] but the potential impacts on cancer incidence and mortality are unclear.

An alternative approach is to use an endoscopy-based screening test. The invasive nature and risk of serious complications, including death, resulting from colonoscopy,[12] may render it unsuitable for

primary screening.[13] A more acceptable alternative is likely to be flexible sigmoidoscopy (FSIG). The recently published results of the UK FSIG RCT, which showed that a single examination between age 55 and 64 was associated with reductions of 23% reduction in incidence and 31% in mortality,[14] have put endoscopy-based screening firmly back on the agenda.

The relative costs and benefits of a screening programme based on primary FIT, compared with primary gFOBT with reflex FIT, and once-only FSIG, have not been assessed. Cost-effectiveness analysis provides a methodology for comparing such alternative strategies.[15] The purpose of this study was to estimate the incremental cost-effectiveness of population-based colorectal cancer screening in Ireland using once-only FSIG, gFOBT (with reflex FIT testing) and FIT.

METHODS

Screening scenarios

The tests, screening intervals and age-groups considered were guided by an expert clinical group.[16] Three primary screening scenarios were evaluated: (1) biennial gFOBT, with reflex FIT, in those aged 55-74 years; (2) biennial FIT in those aged 55-74 years; and (3) once-only FSIG at age 60. In secondary analyses, five age-variant scenarios were considered: (1) biennial gFOBT, with reflex FIT, at 55-64 years; (2) biennial gFOBT, with reflex FIT, at 65-74 years; (3) biennial FIT at 55-64 years; (4) biennial FIT at 65-74 years; and (5) once-only FSIG at age 55. It was assumed that investigation of positive screening tests would be by colonoscopy, with CT colonography in those unfit for colonoscopy, or in whom colonoscopy was incomplete. Follow-up of individuals who had adenomas detected and removed was assumed to follow existing guidelines;[16,17] those who had intermediate or high-risk adenomas removed would enter ongoing colposcopic surveillance and those who had low-risk adenomas removed would return to routine screening.

Economic model structure

The economic model is described in detail elsewhere.[16,18] Briefly it was a state transition (Markov process) model[19] with three interlinked components relating to the: (1) natural history progression of colorectal neoplasia; (2) impact of screening and subsequent adenoma surveillance; and (3)impact of mortality.

The natural history model simulated the experience of a cohort of individuals over their lifetime through health states relating to the progression from normal colorectal epithelium, through the adenoma-carcinoma sequence, to death (figure 1). During each annual Markov cycle the model cohort was distributed across the health states, with these transitions governed by a series of transition matrices (probabilities). Health states were defined in terms of an "index" lesion, that is the greatest malignant potential of the adenoma(s) present, or most advanced cancer present. Individuals with adenomas were classified as low-risk (<10mm) or higher-risk (≥10mm), with the latter category broadly corresponding to the combination of intermediate and high-risk described by Atkins & Saunders.[17] Intermediate and high-risk were not modelled separately due to limitations in the evidence relating to progression rates through low-intermediate-high risk.[18] Discrete cancer states were modelled individually according to AJCC staging.[20] Adenomatous polyps and cancers located in the distal and proximal colon were considered separately to account for the reach of FSIG, with some correlation implicitly modelled by assuming 70% arose in the distal, and 30% in the proximal, colon.[21] Some cancers were assumed to develop without a prior adenoma (i.e. in individuals with inflammatory bowel disease, or flat or serrated adenomas)[22-24] and modelled as direct progression from normal epithelium to stage I cancer.

The screening intervention model was superimposed upon the natural history model. The characteristics of the screening (gFOBT, FIT, FSIG) and diagnostic (colonography, CT colonography) tests were defined in terms of true sensitivity and specificity. The impact of the screening and diagnostic tests, and clinical management of adenomas and cancers, was modelled by re-distributing the cohort across the health states at the point of screening or surveillance. Individuals in whom

adenomas were detected were assumed to undergo polypectomy and enter surveillance as described above. Individuals in whom cancer was detected entered a stage-specific clinical management state. Individuals in whom neither cancer nor adenoma was detected were re-invited for screening in the next round, if applicable. Owing to a lack of data, the model assumed that performance characteristics of gFOBT and reflex FIT were independent, and that everyone who had a positive gFOBT completed a reflex FIT.

The mortality model allowed for deaths due to colorectal cancer, endoscopic bowel perforation, or other causes. The probability of dying from other causes was based on Irish life tables[25] and modelled as an age-dependent probability during each Markov cycle. The risk of death from endoscopic perforation was applied during screening (FSIG only), diagnostic investigation and adenoma surveillance. The probability of dying from colorectal cancer was assumed to be higher for more advanced disease.

The cohort entered the simulation at age 30, at which point it was assumed that prevalence of pre-clinical cancers and adenomas was zero, which is likely to be reasonable for cancers which arise in individuals without specific genetic syndromes ("sporadic" cancers). Thus, the prevalence of disease accumulated over the pre-screening period (30-54 or 30-59). The simulation ended at age 100, by which time almost all member were absorbed into the "death" health state.

Model parameters and calibration

Full details of the model inputs are given elsewhere.[16] Briefly, comprehensive literature reviews were undertaken, with published papers supplemented by data from ongoing population-based screening programmes, pilot programmes and RCTs. When relevant data was not available, estimates were based on expert clinical opinion. Costs of screening and managing screening-detected and symptomatic colorectal cancer were estimated for Ireland from diagnostic-related group costs,[26] hospital finance and pharmacy departments, clinical opinion and literature review. For each

parameter, a base-case, range and distribution, for use in sensitivity analyses, were identified (see below; table 1).

Estimates for several model parameters, including the natural history transition probabilities, could not be empirically observed and were obtained by calibration. The model was fitted to colorectal cancer incidence and mortality in Ireland (www.ncri.ie) and the likely prevalence of adenomas and undiagnosed cancers (estimated from[27,28]). Parameters were estimated using Markov Chain Monte Carlo (MCMC) methods and the Metropolis-Hastings algorithm.[29] A normal likelihood function was used for the observations about mortality, incidence and prevalence and non-informative Beta(1,1) priors were used for all parameters. The model was run using three independent chains with a burn-in of 2,000 iterations for each (Whyte, manuscript submitted). The parameter set obtained are samples from the joint posterior distribution, so they reflect the residual uncertainty about the natural history parameters conditional on the data available for the fitting process. The set of transition probabilities with the highest likelihood was used in the base-case analysis.

Analysis

Costs and health outcomes associated with spending time in each health state were aggregated over the time horizon to estimate the total cost and health gain associated with each screening option.
A healthcare payer perspective was adopted, in this case the Health Service Executive. Direct costs incurred from the age of 55 and associated with screening (including screening tests, colonoscopy and CT colonography, adenoma surveillance and harms, including major episodes of bleeding, bowel perforation and deaths from perforation) and cancer management (diagnosis, treatment and follow-up) were included. Health outcomes were measured as quality-adjusted life years (QALYs). Costs and health outcomes were discounted at 4% per annum (as recommended for Ireland) starting at age 55.[16]

In the base-case analysis, the marginal cost-effectiveness of each screening scenario compared to the status quo (i.e. a policy of no screening) was assessed using incremental cost-effectiveness ratios (ICERs). Scenarios which were not dominated were compared. While there is no formal cost-

effectiveness threshold in Ireland, the Health Service Executive have reimbursed most interventions with an ICER < €45,000 per QALY gained.[30]

Model parameters (including sensitivity of screening and diagnostic tests, screening uptake, costs of screening tests, lifetime costs of cancer, utilities and discount rate) were varied in one-way and multi-way sensitivity analyses. In addition, probabilistic sensitivity analysis (PSA) was undertaken using Monte Carlo simulation to sample simultaneously from all uncertain model parameters(table 1). This joint uncertainty was propagated through the model over 1,200 iterations to estimate the probability that each screening option was optimal: 1,200 iterations was sufficient for convergence. The natural history parameters were sampled from the parameter sets obtained in the calibration process across the three chains, thus correlation between these parameters is incorporated. Most other parameters were treated as independent, but a few which were considered inter-dependent (e.g. sensitivities of a screening test for adenomas and cancers) were assigned perfectly correlated distributions.

RESULTS

Base-case analysis: core screening scenarios

No screening was the least expensive option. In the base-case analysis, once-only FSIG at age 60 was expected to be associated with the smallest marginal cost compared with no screening (€3.43 per person); this was followed by biennial gFOBT at age 55-74 (€33.63 per person), and biennial FIT at age 55-74 (€40.17 per person; table 2). The cost of screening (including test kits/examinations, diagnostic procedures, perforations and bleeds, and adenoma surveillance) was similar for gFOBT and FSIG (€56 and €61 per person, respectively), and more than three times higher for FIT (€222 per person).

Compared to no screening, all three screening scenarios were associated with a gain in QALYs, which was greatest for FIT (table 2). All three scenarios appeared to have favourable cost-effectiveness profiles when compared marginally against no screening (i.e. the ICER was

significantly lower than the notional cost-effectiveness threshold of €45,000 per QALY). The lowest ICER was for once only FSIG at age 60 (€589 per QALY gained), followed by FIT at age 55-74 (€1,696 per QALY gained) and gFOBT at age 55-74 (€4,428 per QALY gained; €3,332 per LYG). gFOBT was eliminated by extended dominance: it was more costly than FSIG and less effective than FIT. The ICER for FIT at age 55-74 versus once only FSIG at age 60 was €2,058 per QALY, which would be considered favourable.

Over the lifetime of the cohort, compared with no screening, all three scenarios would result in a modest fall in colorectal cancer incidence and a larger fall in colorectal cancer mortality (table 3). These decreases were expected to be greatest for FIT-based screening based (15% fall in incidence, 36% fall in mortality). FIT would also result in the largest percentage of screen-detected cases (29.8%), and smallest percentage of symptomatic cases (68.4%), in the population (table 3). All three screening scenarios have the potential to change the stage distribution of cancers in the population, such that a greater proportion would be diagnosed at an early stage. With no screening, the model predicted 12% of cancers would be stage I at diagnosis, 25% stage II, 35% stage III and 29% stage IV. With FIT-based screening, 79% of screen-detected and 42% of symptomatic cancers were predicted to be stage I or II; the comparable figures for gFOBT-based screening were 73% and 39% and for FSIG screening were 71% and 37%.

FSIG-based screening would result in a higher lifetime rate of endoscopy procedures than screening based on faecal testing, but most of these would be FSIG screening examinations (table 4). The rate of colonoscopies over the lifetime of the cohort would be ten-times higher (34,632 vs 3,386 per 100,000), and that of polypectomies eight-times higher (9,486 vs 1,125 per 100,000), for FIT-based screening than for screening based on gFOBT. A consequence of this would be a higher rate of complications with FIT-based screening than the other options (table 4).

Sensitivity analyses

Figure 2 shows the results of the one-way and multi-way sensitivity analysis for FIT; the effect of varying the parameters on the ICERs for FSIG and gFOBT were similar (not shown). The most influential parameters were: discount rate, costs of screening tests and costs of managing colorectal cancer. However, when these were varied, all three screening scenarios remained very much below the notional cost-effectiveness threshold, and in some instances became cost saving (ICER<0), versus no screening.

In the probabilistic sensitivity analysis (figure 3), although there was variability in the marginal costs and effects of all three scenarios, the findings from the base-case analysis were confirmed i.e. (1) all three scenarios were almost always likely to be considered highly cost-effective compared to no screening; and (2) there was a clear distinction in terms of incremental QALYs between FIT-based screening and the other two options. Therefore, FIT would be considered the optimal strategy.

Age-variant scenarios

The cost-effectiveness results of the base-case analysis for the five age-variant scenarios are shown in table 2. All variant scenarios had favourable cost-effectiveness profiles compared to no screening. For faecal testing, the ICER was lower for screening restricted to the younger (55-64 years), compared to the full (55-74) age group. The FIT-based scenarios were more cost-effective, versus no screening, than the gFOBT scenarios. For FSIG, offering screening at 55 years was less cost-effective than at age 60. The only strategies not eliminated by extended dominance were, in order of incremental QALYs gained: FSIG at age 60, FIT at 55-64 years, and FIT at 55-74 years. The ICER for FIT at 55-64 years vs FSIG at 60 years was €1,436 per QALY gained. The ICER for FIT at 55-74 compared to FIT at 55-64 was €3,221 per QALY gained, indicating that FIT in the full age group (55-74) remained the most cost-effective strategy. This was confirmed in probabilistic sensitivity analysis (not shown). The cost-effectiveness acceptability curve showed that if decision-makers were willing-to-pay a maximum of around €1,000 per additional QALY, the most cost-effective strategy would be

expected to be FSIG at age 60 (not shown).[16] At a threshold of ≥€4,000 per additional QALY, the optimal option would be biennial FIT at 55-74 years.

DISCUSSION

The key issues in deciding whether to introduce a new screening programme include whether: (1) screening represents a cost-effective intervention (that is, the health gains are likely to be significant compared to the costs involved); (2) uptake is likely to be sufficiently high for screening to be effective; and (3) implementation is feasible (that is, sufficient health service resources are available to diagnose, treat and follow-up those found to have adenomas and cancer).

Cost-effectiveness

This analysis clearly shows that a population-based colorectal cancer screening programme in Ireland - using gFOBT, FIT, or FSIG - would be likely to be considered highly cost-effective compared to no screening. Screening based on FIT at 55-74 years is associated with the greatest health gains, both in terms of QALYs and reductions in population cancer incidence and mortality rates, and would be considered the optimal option. Most previous evaluations have concluded that colorectal cancer screening, by a range of different modalities, is likely to be cost-effective ([16] and references therein). Although estimates from individuals studies are not entirely comparable, the ICERs in the current study were low compared to those reported elsewhere, probably because of rising costs of colorectal cancer treatment.[31] We included costs of combination chemotherapies and monoclonal antibodies, which are expensive but now part of standard care, and our estimated treatment costs were higher than those reported in slightly older studies from other European countries.[18,32-34] One consequence of the rising treatment costs is that screening could be considered desirable not only in terms of reducing colorectal cancer incidence and morality, but also as a means to control treatment costs.[35]

Uptake

The relative cost-effectiveness of screening changes little as uptake changes because, as well as reducing costs, lower uptake also reduces effectiveness. High uptake rates are essential if screening is to be effective in reducing mortality in the population. Our base-case estimate of 53% uptake for screening by faecal testing was based on the UK pilot programmes.[11,36] Although some studies have suggested that uptake could be higher with FIT than gFOBT,[37,38] evidence at the population-level is inconsistent so we assumed the same uptake for both tests. The assumption of 39% uptake for FSIG was based on the UK Flexible Sigmoidoscopy Screening Trial.[14,39] Whether these levels of participation are achievable in Ireland is unclear. In two small pilot studies of faecal testing in Dublin uptake was 47-50% (C O'Morain, personal communication). In most settings, uptake varies by socio-demographic factors,[40-42] making it uncertain whether these figures would apply across Ireland. Moreover, the base-case estimates were higher than uptake levels achieved elsewhere in European.[43-37]

Feasibility

Cost-effectiveness should not be considered in isolation to issues relating to service delivery, and while FIT in age 55-74 was considered the optimal option, such a programme would require substantial more resources for colonoscopy (and CT colonography and other diagnostic procedures) than one based on gFOBT or FSIG. An option appraisal in England, based on a similar economic model to the current analysis, recognised the importance of endoscopy resource and capacity issues and suggested that gFOBT-based, although less cost-effective, was probably more feasible than a programme based on FSIG (FIT was outwith the scope of the analysis).[18] In the UK pilot programmes, which are likely to be much less resource intensive than a programme based on FIT, achieving sufficient colonoscopy capacity has been a major challenge, and has underpinned the age and area-based roll-out. Hence, any programme which adopts primary screening by FIT will have to consider very carefully how to deliver sufficient capacity for diagnosis and surveillance. One option to address capacity issues would be to consider restricting screening to a narrower age-range: we found that screening at 55-64 years had a lower ICER than screening over 55-74 years.

A related issue concerns adverse effects of endoscopy among screening participants. Because of the high rate of colonoscopies and polypectomies, screening based on FIT would be associated with a much higher lifetime risk of major abdominal bleeding, bowel perforation and death than screening with gFOBT or FSIG. However, even with FIT-based screening the absolute risk to an individual of experiencing one of these complications is low, and in ongoing programmes major complications of colonoscopy are rare.[11,48]

FIT versus gFOBT

FIT is increasingly being adopted as a primary test in screening programmes.[49] We found that that this strategy was more cost-effective than screening by gFOBT with reflex FIT (currently implemented in Scotland) which raises the question of whether the UK screening programmes should use primary FIT testing. Dealing with advances in the evidence-base is always a challenge for existing screening programmes. The efficacy of gFOBT in reducing colorectal cancer mortality is established,[5] but FIT may (or may not) be more sensitive and more cost-effective. We derived our estimates of the performance characteristics of gFOBT from diagnostic cohort studies of Hemoccult® and Hemoccult II®.[16] Other, newer, gFOBTs may have higher sensitivity and the potential to be more effective. We repeated our analysis using higher estimates of gFOBT sensitivity (adenomas, 20%, cancers, 64%),[50] and obtained an ICER compared to no screening of €1,701 per QALY gained, which was very close to that for FIT (€1,696 per QALY gained). Therefore, it is entirely possible that a screening programme based on gFOBT could achieve similar health gains to one based on FIT, depending on the test used.

Strengths and limitations

Unlike most previous natural history models, we assumed that some cancers (14%) would arise without a prior adenoma. However, the frequency and malignant potential of hyperplastic and flat polyps in European populations is uncertain.[24,51-53] Thus, if more than 86% of cancers develop though

the adenoma-carcinoma sequence, our model is likely to have under-estimated screening effectiveness, with the extent of under-estimation differing for faecal and endoscopic tests.

Important questions remain about the efficacy and effectiveness of the screening and diagnostic tests considered in this analysis. Even for gFOBT, which has been extensively investigated, there remains a lack of certainty about true performance characteristics, particularly for the newer versions of the test .[8] As regards FSIG, there are few studies of sensitivity and specificity,[54-56] and the gold standard (colonoscopy) misses lesions.[57] The estimation of sensitivity and specificity of FIT in population-based screening is hampered by the fact that numerous tests are available with heterogeneous performance characteristics, and various approaches have been taken to estimate sensitivity.[8] In addition, although quantitative FITs, theoretically, allow the level to define a "positive" result to be set for individual populations and in accordance with local circumstances (e.g. to suit available colonoscopy capacity),[58] the absence of consistent, high-quality, data meant that we could not estimate cost-effectiveness of different cut-offs. Chen et al[59] reported that average life years gained increased as the cut-off decreased, but the lowest ICER was at a threshold of 100ng/mL. In light of this uncertainty, it was reassuring that our overall conclusions were unchanged after extensive sensitivity analyses.

In common with similar analyses, we did not include costs of setting-up programme infrastructure and some costs associated with ongoing programme administration and delivery. Many of these depend on the business model used for programme organisation and delivery. It is important, however, to acknowledge that they exist and are likely to vary for different screening modalities. Because of the limited evidence-base, costs incurred by screening participants and societal costs, such as lost production, were not included. This would tend to mean that our cost estimates are conservative.

A major area of uncertainty in this, and other similar, models relates to the true underlying population prevalence of adenomas. We estimated prevalence based on data from a recent, large, well-conducted,

autopsy study and the first round of the pilot screening programmes in Scotland and England.[27,28] Our estimates of prevalence were lower than those from older autopsy series, which other analyses have used (Whyte, manuscript submitted). The prevalence estimates from these older studies vary greatly[18] and they have been criticised for being small, providing little information on the source population, and not always clearly distinguishing between different types of polyps.[60] It is impossible to be sure which of the sources is closer to the true prevalence of adenomas.

Conclusions

This analysis suggests that a screening programme based on biennial screening at 55-74 years with FIT would be preferable to one based on biennial gFOBT (with reflex FIT) at 55-74 years or once-only FSIG at 60. Although a programme based on FIT is expected to result in the greatest health improvement, it would require more colonoscopy resources and result in more individuals suffering adverse effects. The major challenges for policy-makers are, therefore, balancing the benefits and harms of screening while ensuring sufficient capacity for follow-up of screen-detected adenomas and cancers.

ACKNOWLEDGEMENTS

We are grateful to the Expert Advisory Group, HTA secretariat and Board of the Health Information and Quality Authority, and the National Cancer Screening Service, for their input to this project. We would also like to thank numerous individuals for helpful discussions or for supplying data or other information; these individuals are listed in the full project report.[16]

FUNDING

This project was funded by the Health Information and Quality Authority and the Health Research Board, Ireland.

COMPETING INTERESTS

None declared

REFERENCES

1. Parkin DM, Bray F, Pisani P. Global cancer statistics, 2002. *CA Cancer J Clin* 2005;55:74-108.
2. Boyle P, Vainio H, Smith R, et al. Workgroup I: criteria for screening. UICC International Workshop on Facilitating Screening for Colorectal Cancer, Oslo, Norway (29 and 30 June 2002). *Ann Oncol* 2005;16:25-30.
3. Boyle P, Autier P, Bartelink H, et al. European Code Against Cancer and scientific justification: third version (2003). *Ann Oncol* 2003;14: 973-1005.
4. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627-37.
5. Hewitson P, Glasziou P, Irwig L, et al. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev* 2007;(1):CD001216.
6. UK Colorectal Cancer Screening Pilot Group. Results of the first round of a demonstration pilot of screening for colorectal cancer in the United Kingdom. *Br Med J* 2004;329:133.
7. Young GP, Cole S. New stool screening tests for colorectal cancer. Digestion 2007;76:26-33.
8. Burch JA, Soares-Weiser K, St John DJ, et al. Diagnostic accuracy of faecal occult blood tests used in screening for colorectal cancer: a systematic review. *J Med Screen* 2007;14:132-7.
9. Fraser CG, Matthew CM, Mowat NA, et al. Evaluation of a card collection-based faecal immunochemical test in screening for colorectal cancer using a two-tier reflex approach. *Gut* 2007;56:1415-8.
10. Fraser CG, Matthew CM, Mowat NA, et al. Immunochemical testing of individuals positive for guaiac faecal occult blood test in a screening programme for colorectal cancer: an observational study. *Lancet Oncol* 2006;7:127-31.
11. Information Services Division. Summary of the key performance indicators (KPIs) used to monitor and evaluate the Scottish bowel screening pilot. NHS National Services Scotland: Edinburgh, 2008.
12. Warren JL, Klabunde CN, Mariotto AB, et al. Adverse events after outpatient colonoscopy in the Medicare population. *Ann Int Med* 2009;150:849-57.

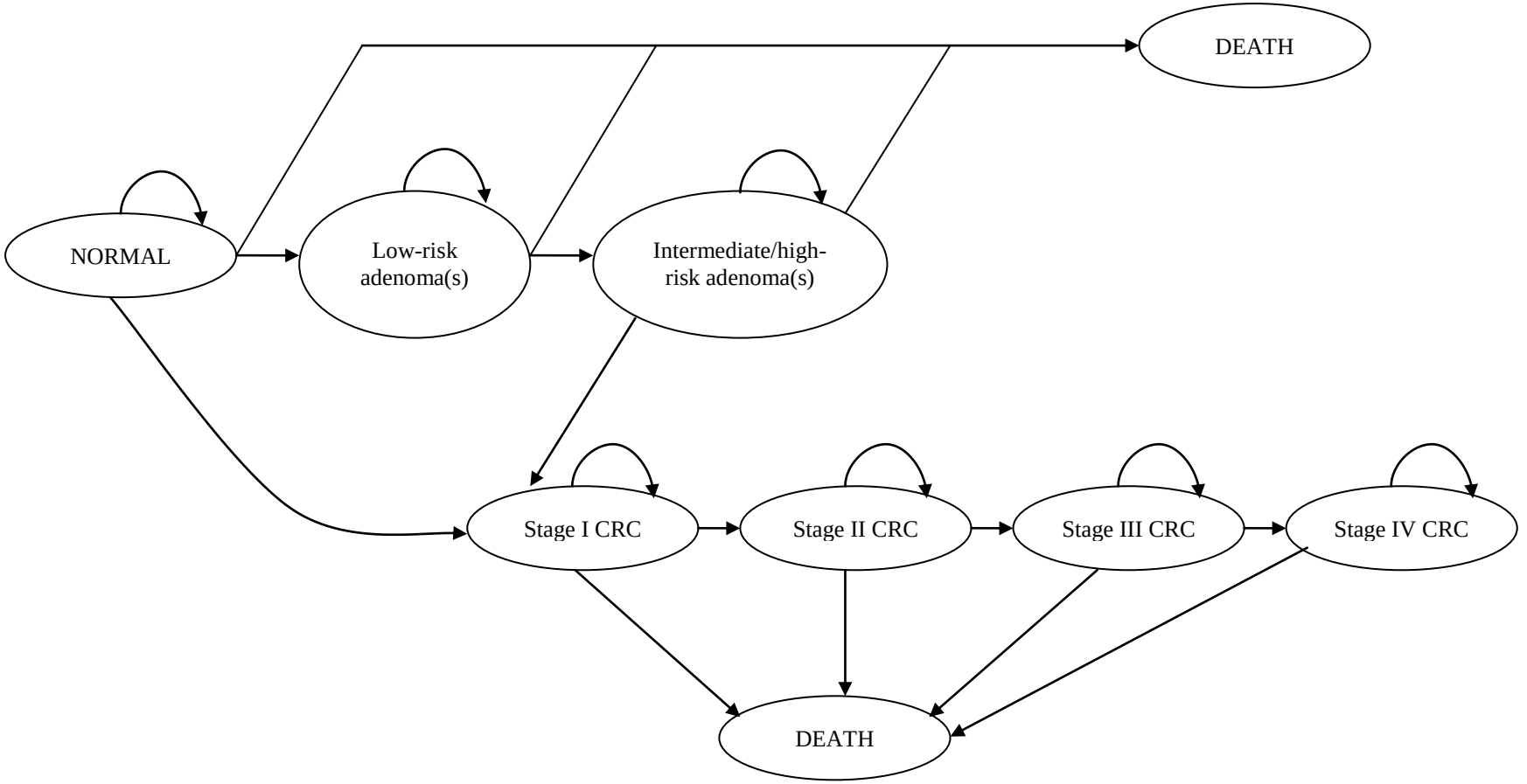
13. Ransohoff DF. Screening colonoscopy in balance. Issue of implementation. *Gastroenterol Clin N Am* 2002;31:1031-44.
14. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in the prevention of colorectal cancer: a multicentre randomised controlled trial. *Lancet* [Epub ahead of print]
15. Drummond M, Sculpher M, Torrance G, et al. Methods for the economic evaluation of healthcare programmes. Third Edition. Oxford University Press USA: New York, 2005.
16. Health Information and Quality Authority. Health Technology Assessment (HTA) of a population-based colorectal cancer screening programme in Ireland. HIQA: Cork, 2009.
17. Atkin WS, Saunders BP. Surveillance guidelines after removal of colorectal adenomatous polyps. *Gut* 2002;51:v6-v9 (Supplement 5).
18. Tappenden P, Eggington S, Nixon R, et al. Colorectal cancer screening options appraisal: cost-effectiveness, cost-utility and resource impact of alternative screening options for colorectal cancer. School of Health & Related Research: Sheffield, 2004.
19. Sonnenberg FA, Beck JR. Markov models in medical decision making: a practical guide. *Med Decis Making* 1993;13:322-38.
20. O'Connell JB, Maggard MA, Ko CY. Colon cancer survival rates with the new American Joint Committee on Cancer sixth edition staging. *J Natl Cancer Inst* 2004;96:1420-5.
21. Mandel JS. Screening of patients at average risk for colon cancer. *Med Clin North Am* 2005;89:43-59.
22. Jass JR. Hyperplastic polyps of the colorectum-innocent or guilty? *Dis Colon Rectum* 2001;44:163-6.
23. Munkholm P. Review article: the incidence and prevalence of colorectal cancer in inflammatory bowel disease. *Aliment Pharmacol Ther* 2003;18:1-5.
24. Speake D, Biyani D, Frizelle FA, Watson AJ. Flat adenomas. *ANZ J Surg* 2007; 77: 4-8
25. Central Statistics Office. Irish Life Tables No. 14 (2001-2003). Central Statistics Office: Cork, 2004.

26. HSE Casemix Unit. Ready reckoner of acute hospital inpatient activity & costs (summarised by DRG) relating to 2006 costs & activity. Annual report. part 3. Health Services Executive: Naas, 2008.
27. Alexander F, Weller D. Evaluation of the UK colorectal cancer screening pilot. Final report by the UK CRC Screening Pilot Evaluation Team. University of Edinburgh: Edinburgh, 2003.
28. Pendergrass CJ, Edelstein DL, Hylind LM, et al. Occurrence of colorectal adenomas in younger adults: an epidemiologic necropsy study. *Clin Gastroenterol Hepatol* 2008;6:1011-5.
29. Chib S, Greenberg E. Understanding the Metropolis-Hastings algorithm. *Am Stat* 1995;49:327-35.
30. Health Information and Quality Authority. The role of human papillomavirus vaccines in reducing the risk of cervical cancer in Ireland. A health technology assessment. Health Information & Quality Authority: Cork, 2008.
31. Schrag D. The price tag on progress – chemotherapy for colorectal cancer. *N Engl J Med* 2004;351: 317-9.
32. Neymark N, Adriaenssen I. The costs of managing patients with advanced colorectal cancer in 10 different European centres. *Eur J Cancer* 1999;35:1789-95.
33. Delco F, Egger R, Bauerfeind P, Beglinger C. Hospital health care resource utilization and costs of colorectal cancer during the first 3-year period following diagnosis in Switzerland. *Aliment Pharmacol Ther* 2005;21:615-22.
34. Clerc L, Jooste V, Lejeune C, et al. Cost of care of colorectal cancers according to health care patterns and stage at diagnosis in France. *Eur J Health Econ* 2008;9:361-7.
35. Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG, et al. Effect of rising chemotherapy costs on the cost savings of colorectal cancer screening. *J Natl Cancer Inst* 2009;102:1412-22.
36. Weller D, Moss S, Butler P, et al. English pilot of bowel cancer screening: an evaluation of the second round. Final report to the Department of Health. University of Edinburgh: Edinburgh, 2006.
37. Cole SR, Young GP. Effect of dietary restriction on participation in faecal occult blood test screening for colorectal cancer. *Med J Aust* 2001;175:195-8.

38. Hol L, van Leerdam ME, van Ballegooijen M, et al. Screening for colorectal cancer: randomized trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut* 2010;59:62-8.
39. UK Flexible Sigmoidoscopy Screening Trial Investigators. Single flexible sigmoidoscopy screening to prevent colorectal cancer: baseline findings of a UK multicentre randomised trial. *Lancet* 2002;359:1291-300.
40. Trivers KF, Shaw KM, Sabatino SA, et al. Trends in colorectal cancer screening disparities in people aged 50-64 years, 2000-2005. *Am J Prev Med* 2008;35:185-93.
41. von Wagner C, Good A, Wright D, et al. Inequalities in colorectal cancer screening participation in the first round of the national screening programme in England. *Br J Cancer* 2009;101:S60-S63.
42. von Euler-Chelpin M, Brasso K, Lynge E. Determinants of participation in colorectal cancer screening with faecal occult blood testing. *J Pub Health* 2009 [Epub ahead of print]
43. Segnan N, Senore C, Andreoni B, et al. Randomized trial of different screening strategies for colorectal cancer: patient response and detection rates. *J Natl Cancer Inst* 2005;97:347-57.
44. Segnan N, Senore C, Andreoni B, et al. Comparing attendance and detection rate of colonoscopy with sigmoidoscopy and FIT for colorectal cancer screening. *Gastroenterol* 2007;132:2304-12.
45. Peris M, Espinas JA, Munoz L, et al. Lesson learnt from a population-based pilot programme for colorectal cancer screening in Catalonia (Spain). *J Med Screen* 2007;14:81-86.
46. Power E, Miles A, von Wagner C, et al. Uptake of colorectal cancer screening: system, provider and individual factors and strategies to improve participation. *Future Oncol* 2009;5:1371-88.
47. Zorzi M, Fedato C, Naldoni C, et al. Screening for colorectal cancer in Italy: 2007 survey. *Epidemiol Prev* 2009;33(3 Suppl 2):57-74.
48. Regula J, Rupinski M, Kraszewska E, et al. Colonoscopy in colorectal-cancer screening for detection of advanced neoplasia. *N Engl J Med* 2006;355:1863-72.
49. International Colorectal Cancer Screening Network. Inventory of colorectal cancer screening activities in ICSN countries, May 2008. Available at http://appliedresearch.cancer.gov/icsn/colorectal/screening.html#france. [Accessed 13/04/2010]

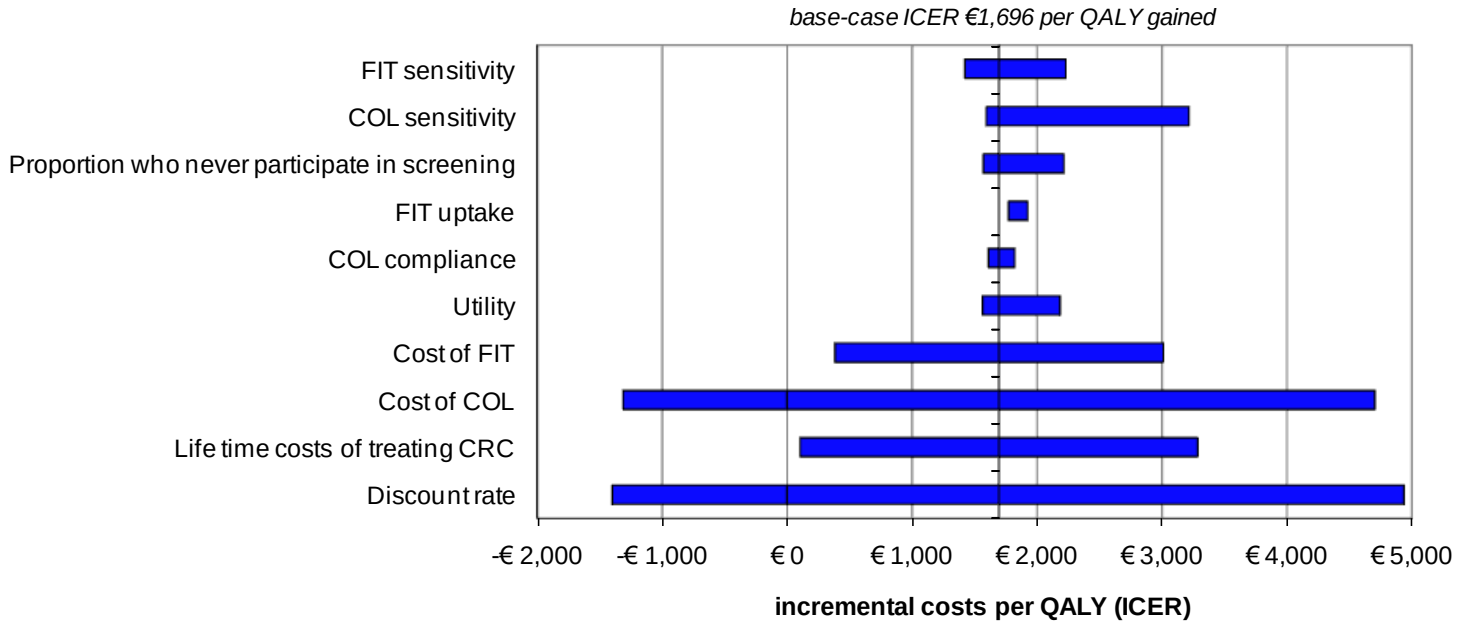
50. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *J Natl Cancer Inst* 2007;99:1462-70.
51. Bensen SP, Cole BF, Mott LA, et al. Colorectal hyperplastic polyps and the risk of recurrence of adenomas and hyperplastic polyps. *Lancet* 1999;354:1873-4.
52. Chandra A, Sheikh AA, Cerar A, Talbot IC. Clinico-pathological aspects of colorectal serrated ademomas. *World J Gastroenterol* 2006;12:2770-72.
53. Lin OS, Gerson LB, Soon MS, et al. Risk of proximal colon neoplasia with distal hyperplastic polyps: a meta-analysis. *Arch Intern Med* 2005;165:382-90.
54. Rozen P, Ron E, Fireman Z, et al. The relative value of fecal occult blood tests and flexible sigmoidoscopy in screening for large bowel neoplasia. *Cancer* 1987;60:2553-8.
55. Lieberman DA, Weiss DG, Veterans Affairs Cooperative Study Group 380. One-time screening for colorectal cancer with combined fecal occult-blood testing and examination of the distal colon. *N Engl J Med* 2001;345:555-60.
56. Sung JJ, Chan FK, Leung WK, et al. Screening for colorectal cancer in Chinese: comparison of fecal occult blood test, flexible sigmoidoscopy, and colonoscopy. *Gastroenterol* 2003;124:608-14.
57. Rex DK, Cutler CS, Lemmel GT, et al. Colonoscopic miss rates of adenomas determined by back-to-back colonoscopies. *Gastroenterol* 1997;112:24-8.
58. Fraser CG, Matthew CM, McKay K, et al. Automated immunochemical quantitation of haemoglobin in faeces collected on cards for screening for colorectal cancer. *Gut* 2008;57:1256-60.
59. Chen LS, Liao CS, Chang SH, et al. Cost-effectiveness analysis for determining optimal cut-off of immunochemical faecal occult blood test for population-based colorectal cancer screening (KCIS 16). *J Med Screen* 2007;14:191-9.
60. Jass JR, Young PJ, Robinson EM. Predictors of presence, multiplicity, size and dysplasia of colorectal adenomas. A necropsy study in New Zealand. *Gut* 1992;33:1508-14.

Figure 1. Simplified schematic of natural history model states and transitions



low-risk polyp(s): <10 mm; intermediate/high-risk adenomas: ≥10mm; CRC=colorectal cancer

Figure 2. Incremental costs per QALY compared to no screening, when selected parameters are varied independently, for FIT at 55-74 years



COL=colonoscopy; CRC=colorectal cancer; FIT=feacal immunochemical test

Figure 3. Probabilistic sensitivity analysis: incremental costs and incremental QALYs with 95% confidence ellipses, for core screening scenarios compared to no screening,

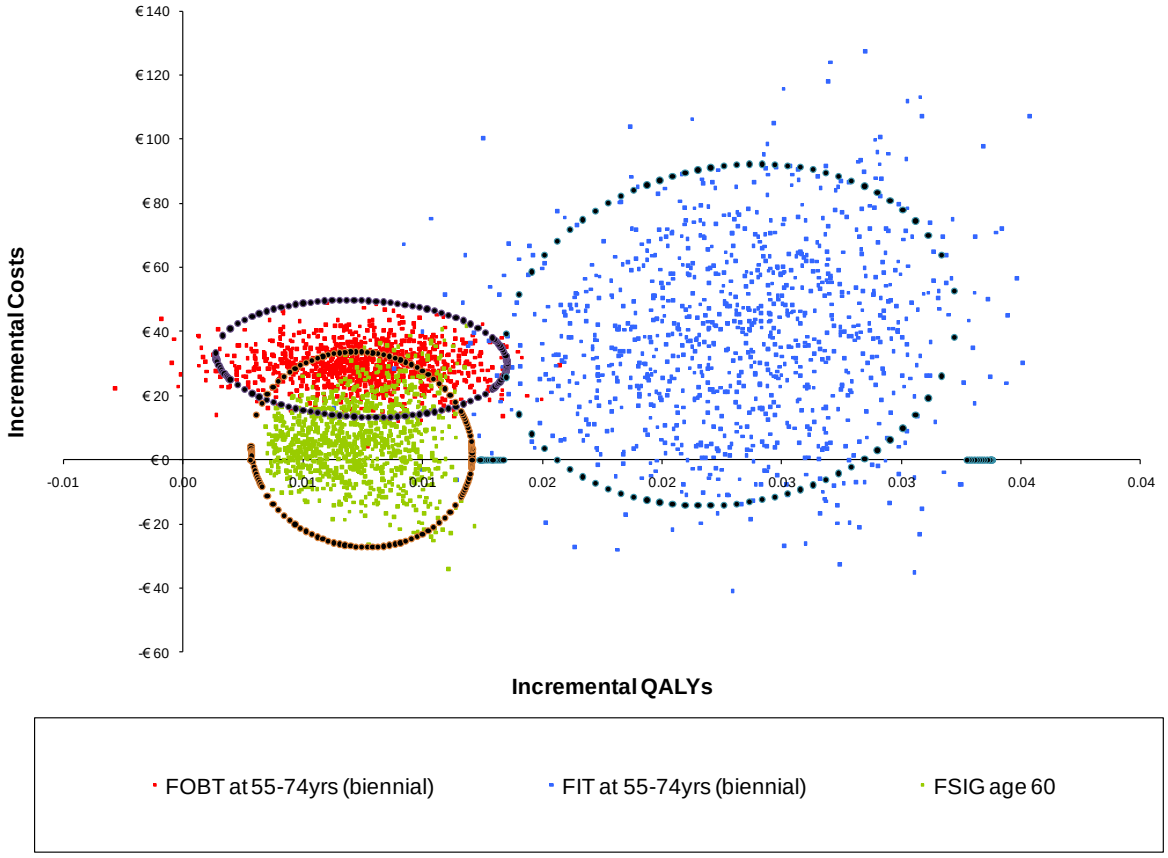


Table 1 Parameter estimates, with base-case values, ranges and distributions[1]

Model parameter	*Base-case estimate*	*Range for SA*	*Distribution for PSA[2]*
Performance of screening tests			
gFOBT sensitivity for adenomas	11%	10% - 12%	Beta(11.40,92.10)
gFOBT sensitivity for CRC	36%	31% - 42%	Beta(105.00,186.60)
gFOBT specificity for adenomas and CRC	97%	96% - 98%	Beta(1083.40,33.50)
FIT sensitivity for adenomas	21%	19% - 22%	Beta(594.62,2236.92)
FIT sensitivity for CRC	71%	67% - 75%	Beta(35.29,143.08)
FIT specificity for adenomas and CRC	95%	94% - 96%	Beta(1732.57,91.19)
FSIG sensitivity for low-risk distal adenomas	65%	60% - 70%	Beta(235.00,126.54)
FSIG sensitivity for intermediate/high-risk distal adenomas	74%	68% - 78%	Beta(180.00,63.24)
FSIG sensitivity for distal CRC	90%	85% - 95%	Beta(90.00,10.00)
FSIG specificity for distal adenomas and CRC	92%	90% - 95%	Beta(250.00,21.74)
Uptake and compliance with screening and diagnostic tests			
gFOBT uptake	53%	32% - 70%	Uniform(32%,70%)
FIT uptake	53%	32% - 70%	Uniform(32%,70%)
FSIG uptake	39%	24% - 67%	Uniform(24%,67%)
% of individuals who never accept an offer of screening[3]	13%	0% - 41%	-
COL compliance (diagnostic test)	86%	81% - 90%	Uniform(81%,90%)
Performance of diagnostic tests and related parameters			
COL sensitivity for low-risk adenomas	77%	73% – 80%	Beta(350.00,104.55)
COL sensitivity for intermediate/high-risk adenomas	98%	93% – 99%	Uniform(93%,99%)
COL sensitivity for CRC	98%	95%-99%	Uniform(95%,99%)
COL specificity for adenomas and CRC	97%	96% - 98%	Beta(970.00,30.00)
CTC sensitivity for low-risk adenomas	53%	45% - 60%	Beta(80.00,70.94)
CTC sensitivity for intermediate/high-risk adenomas	85%	48% - 100%	Beta(4.50,0.79)

CTC sensitivity for CRC	85%	75% - 95%	Beta(50.00,8.82)
CTC specificity for adenomas and CRC	86%	80% - 90%	Beta(140.00,22.79)
Average number of adenomas removed per person	1.9	-	-
Surveillance of screening-detected adenomas			
% of those in with intermediate/high-risk adenomas removed in whom the adenoma was high-risk	29%	-	-
COL compliance (surveillance)	86%	81% - 90%	Uniform(81%,90%)
Harms of screening			
FSIG probability of perforation (with or without polypectomy)	0.002%	0% - 0.051%	Uniform(0%,0.051%)
FSIG probability of death following perforation	6.452%	0% - 9.070%	Uniform(0%,9.070%)
Probability of (major) bleeding following FSIG	0.029%	0.002% - 0.054%	Uniform(0.002%-0.054%)
COL probability of perforation (with polypectomy)	0.216%	0.168% - 0.298%	Uniform(0.168%,0.298%)
COL probability of perforation (without polypectomy)	0.107%	0.010% - 0.249%	Uniform(0.010%,0.249%)
COL probability of death following perforation	5.195%	0% - 9.070%	Uniform(0%,9.070%)
Probability of (major) bleeding following COL	0.379%	0.065% - 0.412%	Uniform(0.065%,0.412%)
Health-related QoL			
Utility cancer free	0.94	-	-
Utility stage I, II, III, IV cancer	0.80	0.43-0.94	0.94*Beta(3.92,0.69)
Resource use parameters *Inadequate or incomplete endoscopic procedures*[4]			
FSIG probability of incomplete/inadequate procedure	9%	5%-14%	Beta(14.00,141.56)
COL probability of incomplete/inadequate procedure	13%	8% -16%	Uniform(8%,16%)
Costs			
gFOBT kit[5]	€1.70	€1.36-€2.04	Uniform(€1.36,€2.04)
gFOBT processing/analysis[6]	€7.81	€6.25-€9.37	Uniform(€6.25,€9.37)
FIT kit[5]	€3.75	€3-€4.50	Uniform(€3,€4.50)
FIT processing/analysis[6]	€11.60	€9.28-€13.92	Uniform(€9.28,€13.92)
Cost of FSIG (with/without polypectomy)	€150	€120-€180	Uniform(€120,€180)
Cost of COL	€650	€520-€780	Uniform(€520,€780)
Cost of CTC	€550	€440-€660	Uniform(€440,€660)
Cost of treating bowel perforation	€10,200	€8,160-€12,240	Uniform(€8,160,€12,240)
Cost of admittance for bleeding	€3,079	€2,463-€3,695	Uniform(€2,463,€3,695)
Pathology cost for adenoma	€65	€52-€78	Uniform(€52,€78)
Pathology cost for cancer	€530	€424-€636	Uniform(€424,€636)
Lifetime cost stage I CRC- symptomatic	€23,688	€18,950–€28,425	Uniform(€18,950,€28,425)
Lifetime cost stage II CRC -symptomatic	€37,180	€29,744–€44,616	Uniform(€29,744,€44,616)
Lifetime cost stage III CRC- symptomatic	€48,835	€39,068–€58,602	Uniform(€39,068,€58,602)

Lifetime cost stage IV CRC- symptomatic	€36,602	€29,281–€43,922	Uniform(€29,281,€43,922)
Lifetime cost stage I CRC - screen-detected	€22,885	€18,308 – €27,462	Uniform(€18,308,€27,462)
Lifetime cost stage II CRC - screen-detected	€36,377	€29,102 – €43,652	Uniform(€29,102,€43,652)
Lifetime cost stage III CRC - screen-detected	€48,032	€38,426 – €57,638	Uniform(€38,426,€57,638)
Lifetime cost stage IV CRC-screen-detected	€35,799	€28,639 – €42,959	Uniform(€28,639,€42,959)
Discount rate			
Discount rate for costs and benefits	4%	0%-6%	

COL=colonoscopy; CRC=colorectal cancer; CTC=CT colonography; FIT=faecal immunochemical test; FSIG=flexible sigmoidoscopy; gFOBT=guaiac-based faecal occult blood test; PSA=probabilistic sensitivity analysis; SA=sensitivity analysis; low-risk adenoma(s), <10mm; intermediate/high-risk adenoma(s), ≥10mm.

[1] see reference[16] for full details of sources for all parameter estimates
[2] if no distribution given, parameter was not varied in the PSA
[3] relevant to gFOBT and FIT scenarios only
[4] used in model to estimate percentage who require another procedure; if FSIG is incomplete or inadequate, the individual will have another FSIG; if COL is incomplete or inadequate, the individual will have CT colonography
[5] cost per kit dispatched (cost per individual invited to participate in screening)
[6] cost per kit completed and returned (cost per screening participant)

Table 2. Incremental cost-effectiveness ratios (ICER), based on QALYs per person, for core[1] and age-variant screening scenarios

Scenario	*Cost of screening & CRC management per person[2]*	*Incremental costs per person[3]*	*Expected QALYs per person*	*Incremental QALYs per person[3]*	*ICER -Incremental cost per QALY gained*
No screening	€ 1,074	-	10.961	-	-
gFOBT at 55-74 years	€ 1,107	€ 33.63	10.968	0.0076	€ 4,428[4,5]
gFOBT at 55-64 years	€ 1,092	€ 18.35	10.966	0.0051	€ 3,613[5]
gFOBT at 65-74 years	€ 1,089	€ 15.66	10.963	0.0026	€ 5,919[5]
FIT at 55-74 years	€ 1,114	€ 40.17	10.984	0.0237	€ 1,696
FIT at 55-64 years	€ 1,094	€ 20.06	10.978	0.0175	€ 1,153
FIT at 65-74 years	€ 1,088	€ 13.94	10.969	0.0082	€ 1,698[5]
FSIG once at 60 years	€ 1,077	€ 3.43	10.966	0.0058	€ 589
FSIG once at 55 years	€ 1,092	€ 18.19	10.968	0.0069	€ 2,659[5]

Costs and outcomes discounted at 4%.

[1] Core screening scenarios are shaded.
[2] Includes costs of screening (including faecal testing kit and processing or FSIG examination, diagnostic colonoscopy/CT colonography, pathology, perforations and bleeds, adenoma surveillance) and diagnosis, treatment and follow-up of screen-detected cancers. Costs of CRC management are weighted average of costs of managing screen-detected and symptomatic CRC.
[3] Each incremental value compares values for that strategy to common baseline of no screening
[4] In comparison of core scenarios, strategy considered dominated by combination of FIT at 55-74 years and FSIG once at 60 years
[5] In comparison of all strategies, strategy considered dominated by FSIG at age 60, FIT at age 55-74, FIT at age 55-64 or combinations of these

Table 3. Lifetime rates[1] of colorectal cancer incidence and mortality per 100,000 population, percentage of cases which would be detected by screening, surveillance and symptomatically, and percentage reductions in incidence and mortality compared to no screening, for core screening scenarios

Scenario	***Incidence***							***Mortality***	
	Screen detected CRC		*Surveillance-detected CRC[2]*		*Symptomatic CRC*		*% reduction in CRC incidence[3]*	*CRC mortality rate*	*% reduction in CRC mortality[3]*
	Rate	% of cases	Rate	% of cases	Rate	% of cases			
No screening	0	-	0	-	5158	100%	-	2287	-
gFOBT at 55-74 years	695	13.6%	11	0.2%	4401	86.2%	1.0%	2016	11.8%
FIT at 55-74 years	1313	29.8%	78	1.8%	3010	68.4%	14.7%	1465	36.0%
FSIG once at 60 years	138	2.8%	25	0.5%	4742	96.7%	4.9%	2116	7.5%

[1] Over the entire lifetime of the cohort, therefore for gFOBT and FIT includes 10 screening rounds
[2] CRC detected at surveillance among those with intermediate/high-risk adenomas found at screening
[3] Each incremental value compares values for that strategy to common baseline of no screening

Table 4. Lifetime rates[1] per 100,000 population of screening-related endoscopic procedures[2], and associated complications[3], for the core screening scenarios

Scenario	*Endoscopic procedures*			*Complications*		
	Flexible sigmoidoscopy	*Colonoscopy*	*Polypectomy*	*Major bleeding[4]*	*Bowel perforation*	*Deaths due to perforation*
gFOBT at 55-74 years	-	3,386	1,215	12	5	0.26
FIT at 55-74 years	-	34,632	9,486	132	57	3.00
FSIG once at 60 years	40,177	2,543	2,487	22	5	0.25

[1] Over the entire lifetime of the cohort, therefore for gFOBT and FIT includes 10 screening rounds
[2] Related to screening, diagnosis or surveillance
[3] Complications associated with diagnostic and surveillance colonoscopy and, where relevant, FSIG
[4] Major abdominal bleeding, requiring admission or intervention