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Cost Effectiveness of CT Colonography for UK NHS Colorectal Cancer Screening of Asymptomatic Adults Aged 60–69 Years

David Lee,[1] *Dominic Muston*,[2] *Alison Sweet*,[3] *Chris Cunningham*,[4] *Andrew Slater*[4] and *Kevin Lock*[2]

1 GE Healthcare, Waukesha, Wisconsin, USA
2 Heron Evidence Development, Luton, Bedfordshire, UK
3 GE Healthcare, Chalfont St Giles, Buckinghamshire, UK
4 Oxford Radcliffe Hospitals NHS Trust, Oxford, UK

Abstract

Background: Screening of populations at risk for colorectal cancer (CRC) allows the detection and successful treatment of tumours and their precursor polyps. The current UK CRC screening programme is faecal occult blood testing (FOBT), despite evidence from modelling studies to suggest that more cost-effective technologies exist.

Objective: To assess the cost effectiveness of CT colonography (CTC) for colorectal cancer screening from the perspective of the UK NHS.

Methods: A state-transition Markov model was constructed to estimate lifetime costs and health outcomes of a cohort of individuals screened at age 60–69 years using four different CRC screening technologies: FOBT, flexible sigmoidoscopy, optical colonoscopy and CTC.

Results: CTC screening offered every 10 years was cost saving compared with the current UK programme of biennial FOBT screening. This strategy also yielded greater health benefits (QALYs and life-years) than biennial FOBT screening. The model fit observed CRC epidemiology data well and was robust to changes in underlying parameter values. CTC remained cost effective under a range of assumptions in the univariate sensitivity analysis. However, in the probabilistic sensitivity analysis, CTC dominated FOBT in only 5.9% of simulations and was cost effective at a threshold of £30 000 per QALY gained in 48% of simulations.

Conclusions: CTC has the potential to provide a cost-effective option for CRC screening in the UK NHS and may be cost saving compared with the current programme of biennial FOBT. Further analysis is required to assess the impact of introducing CTC to the UK CRC screening programme on the NHS budget and capacity.

Background

Colorectal cancer (CRC) is the third most common cancer in the UK, with 29 565 new cases diagnosed in 2005,[1] resulting in 16 200 CRC-related deaths.[2] The total annual cost of diagnosis and treatment of CRC in England has been estimated to be £1.1 billion, with a mean annual total cost per patient of over £8000 (year 2004–5 values).[3]

The natural history of CRC supports the detection and successful treatment of both precursor polyps and localized tumours through population-wide screening programmes. The majority of CRCs arise from adenomatous polyps, and the malignant transformation occurs through a predictable and prolonged polyp-cancer pathway.[4,5] Consequently, cancer can be prevented by detecting and removing polyps,[6] and early-stage detection is associated with lower cancer mortality.[7] Screening tests for CRC broadly fall into two categories: stool tests (including tests for occult blood or exfoliated DNA) and structural examinations (including flexible sigmoidoscopy [FSIG], double-contrast barium enema [DCBE], optical colonoscopy [OC] and CT colonography [CTC]).

CTC allows a minimally invasive and rapid structural evaluation of the entire colon, with no requirement for sedation and a low risk for serious adverse events.[8,9] Some studies have demonstrated a patient preference for CTC over OC, despite similar levels of reported discomfort, with faster procedures and avoidance of sedation cited as the patient-perceived advantages of CTC.[10,11] Preparation of the bowel prior to screening is the most demanding aspect of CTC currently, but may become obsolete in the future with the development of novel faecal tagging techniques.[12]

In a cost-effectiveness analysis of CRC screening strategies for the UK NHS, Tappenden and colleagues[13,14] concluded that, compared with a policy of no screening, all five screening options studied (biennial faecal occult blood test [FOBT] between either ages 50 and 69 years or 60 and 69 years, FSIG at age 55 or 60 years, or a combination of FSIG at 60 years with biennial FOBT between 61 and 70 years) were expected to produce health gains at a reduced cost or at a cost acceptable to the NHS. The authors concluded that a once-only FSIG screen of individuals at 55 years had the highest probability of resulting in the greatest marginal net health benefit. However, the uncertainty surrounding the natural history of CRC and the accuracy of the screening options had a considerable impact on the estimates of cost effectiveness. These considerations, and the predicted impact of FSIG on endoscopy services, influenced the NHS decision to introduce a biennial FOBT screening programme for individuals aged 60–69 years.

Although it has been estimated that FOBT detects only about 40% of cancers,[14] it has been shown that biennial screening of asymptomatic individuals can reduce mortality rates by 15%.[15-17] A recent UK-based pilot study found that only about half (52%) of the more than 125 000 subjects aged between 50 and 69 years who were invited for FOBT screening actually returned an adequate kit in the first screening phase.[18] This low 'uptake' rate would, of course, substantially limit screening benefit, and the uptake rate may presumably be even lower in the general target population than in this pilot study population.

Several recent studies have attempted to estimate the cost effectiveness of CTC for CRC screening,[19-23] concluding that it is cost effective compared with no screening,[21] and more effective than FOBT or FSIG alone.[19] Hassan et al.[22] found that the main variables affecting the cost effectiveness of these technologies were accuracy for detection of mid-size polyps, as well as the cost, uptake and frequency of screening.

The current study extends this previous work and uses updated data on disease staging and progression to estimate the cost effectiveness of CRC screening technologies (CTC, OC, FOBT, FSIG) from the perspective of the UK NHS.

Methods

Modelling Methodology and Structure

The model structure was based on that described by Tappenden et al.[13] and all inputs and assumptions were taken from that study unless

stated otherwise (tables I and II). In particular, selected assumptions about the natural history of polyp progression to CRC were recalibrated to reflect recent observational data on CRC incidence,[1] mortality[2] and staging of cancer at time of diagnosis.[34,35] The parameter values for the natural history of CRC from Tappenden et al.[14] were optimized in the original study by comparison of over 60 000 iterations of the model with contemporary data. The central estimates used in the Tappenden et al.[14] model were varied systematically in the current study to produce outcomes that more closely approximated current data reported by the Office of National Statistics (ONS).[1] The Tappenden et al.[14] model was also extended by including CTC and OC as screening tests, in addition to FOBT and FSIG (table II).

The model utilized a state-transition Markov structure, with 23 mutually exclusive health states that characterize disease progression and staging, as well as type of presentation and clinical

Table I. Summary of inputs used in the model[a]

Parameter description	Value	
	original[14]	recalibrated
Proportion of low-risk polyps in the distal colon[24]	0.91	
Probability of progression		
From normal epithelium to low-risk polyp	0.016	0.012
From low-risk to high-risk polyp	0.0212	0.024
From high-risk polyp to asymptomatic Dukes' A	0.0326	0.034
From asymptomatic Dukes' A to Dukes' B	0.5829	0.583
From asymptomatic Dukes' B to Dukes' C	0.6555	0.656
From asymptomatic Dukes' C to stage D	0.8648	0.865
Probability of death from colorectal cancer		
Dukes' A	0.0000	
Dukes' B	0.0100	
Dukes' C	0.0602	
Stage D	0.3867	
Probability of symptomatic presentation		
Dukes' A presentation	0.070	0.065
Dukes' B presentation	0.320	0.26
Dukes' C presentation	0.490	0.46
Stage D presentation	0.854	0.92
Probability of developing adenomas following a history of polyps		
After polypectomy of a low-risk polyp (first year)	0.18	
After polypectomy of a low-risk polyp (subsequent years)	0.05	
After polypectomy of a high-risk polyp (first year)	0.25	
After polypectomy of a high-risk polyp (subsequent years)	0.06	
Utility values[b] [25]		
No symptomatic cancer	0.91	
Symptomatic Dukes' A cancer	0.74	
Symptomatic Dukes' B cancer	0.70	
Symptomatic Dukes' C cancer	0.50	
Symptomatic stage D cancer	0.25	

a Probabilities are annual.

b A utility value is applied to surviving individuals and is used to calculate the average QALY, a tool widely used to enable comparison of cost effectiveness across technologies.[26]

outcome. Owing to a lack of evidence, the model assumed that all cancers arise from pre-existing adenomatous polyps[4,5] and, although the incidence rates of distal polyps and cancers are greater than those in the proximal colon, it was assumed that progression rates are identical. In our model, it was assumed that polyps between 6 and 9 mm are 'low risk' and that those >10 mm represent 'high risk'.[36] It was assumed that polyps <6 mm are either not removed, as they are assumed to present such low risk,[36] or, in the case of CTC and FOBT, they are not detected. Figure 1 presents a simplified illustration of the way that the natural progression of CRC is modelled, and shows CRC mortality and other mortality among the mutually exclusive health states. The probability of dying from other causes was modelled as an age-dependent probability

Table II. Screening characteristics and parameter boundaries used in sensitivity analysis[a]

Parameters: base-case estimate (range)	Screening strategy			
	FOBT	FSIG	OC	CTC
Screening frequency (y)	2	10 (5)	10 (5)	10 (5)
Uptake of screening invitation (%)	60 (40–80)[b]	60 (40–80)[b]	60 (40–80)[b]	60 (40–80)[b]
Follow-up for positive screening test	OC polypectomy	Polyp removal during screening procedure	Polyp removal during screening procedure	OC polypectomy
Per-person sensitivity for polyps (%)				
low-risk proximal	5 (0–10)[13]	0[c]	92.4 (88.3–96.5)[11,27]	65.3 (56.1–74.6)[28]
low-risk distal	5 (0–10)[13]	95 (90.8–99.2)[11,27] [c]	95 (90.8–99.2)[11,27]	65.3 (56.1–74.6)[28]
high-risk proximal	5 (0–10)[13]	0[c]	85.9 (76.8–94.9)[11,27]	89.9 (84.3–95.5)[28]
high-risk distal	5 (0–10)[13]	88.3 (78.9–97.6)[11,27] [c]	88.3 (78.9–97.6)[[11,27]	89.9 (84.3–95.5)[28]
Per-person sensitivity for cancer (%)				
proximal cancer	41 (30–50)[13]	0[c]	85.9 (76.8–94.9)[11,27]	89.9 (84.3–95.5)[28]
distal cancer	41 (30–50)[13]	88.3 (78.9–97.6)[11,27] [c]	88.3 (78.9–97.6)[11,27]	89.9 (84.3–95.5)[28]
Per-person specificity (%)	99[13]	100[c]	100[13]	88[28]
Risk of perforation (%)				
from screening	0[13]	0.0025 (0.00006–0.0137)[29]	0.08 (0.046–0.430)[29]	0.06 (0.02–0.1)[29,30]
from polypectomy	0.17 (0.092–0.861)[29]	0.0025 (0.00006–0.0137)[29]	0.17 (0.09–0.86)[29]	0.17 (0.09–0.86)[29,30]
Risk of bleeding from screening (%)	0[13]	0.0295 (0.0153–0.0515)[29]	0.439 (0.201–0.831)[29]	0
Risk of mortality following perforation (%)	5.82 (2.07–11.7)[31]	5.82 (2.07–11.7)[31]	5.82 (2.07–11.7)[31]	5.82 (2.07–11.7)[31]
Unit cost of screening (£, year 2007 values)	13[d] (±20%)	304[e] (±20%)	488[f] (±20%)	128[g] (±20%)

a The values in parentheses are ranges. For the probabilistic sensitivity analysis, it was assumed that all parameters had a Beta distribution, except costs, which were assumed to have a log-Normal distribution.[32] The model was run 1000 times in order to generate a distribution of expected costs and health outcomes.

b Assumption.

c Accuracy of FSIG assumed to be the same as OC; FSIG assumed to reach only the distal colon.

d Inflated from 2004 costs by the HCHS Pay and Prices index.[29]

e PbR tariff OPFSI1.[33]

f PbR tariff F35.[33]

g Average of PbR tariffs RA CT1-7.[33]

CTC = CT colonography; **FOBT** = faecal occult blood test; **FSIG** = flexible sigmoidoscopy; **OC** = optical colonoscopy; **PbR** = Payment by Results.

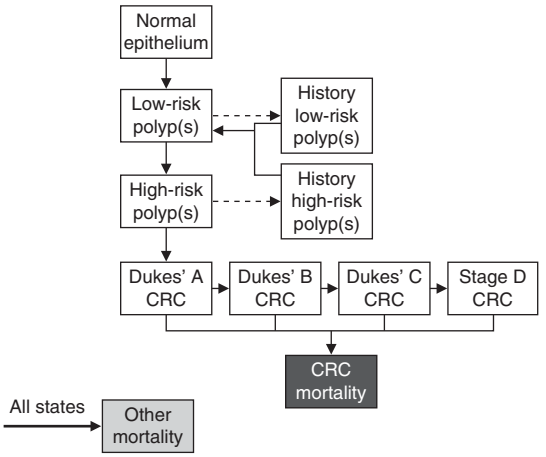

Fig. 1. Simplified colorectal cancer (CRC) natural history progression diagram.

based on UK life tables,[2] and the probability of dying as a result of endoscopic perforation from either the screening procedure or polyp removal (polypectomy) was included in the model as a potential complication of the interventions.[31]

The progress of a cohort of individuals through the health states was governed by transition probabilities that determined, during each 1-year model cycle, the probability of transition from one state to another (table I). At age 30 years, all individuals were assumed to reside in the non-disease or 'normal epithelium' state then, following a 20-year run-in, individuals were followed from age 50 years for the remainder of their expected lifetime.

The outputs of the model included number of individuals with polyps and cancers detected through screening, symptomatic cancers diagnosed, CRC-related deaths, certain adverse events, total costs, life-years (LYs), QALYs and marginal cost-effectiveness ratios (CERs). Utility estimates were derived from a Standard Gamble health utility study in 90 subjects who had previously undergone removal of colorectal adenoma.[25]

Screening Strategies

Four screening strategies were evaluated, with each option characterized by the per-person sensitivity and specificity of the screening technology (table II). Although pooled estimates of the accuracy of CTC for detecting polyps have been published,[37] this meta-analysis included a majority of studies investigating high-risk populations and a number of early studies that may not represent the evolution of CTC technology to the contemporaneous standards observed in the ACRIN (American College of Radiology Imaging Network) National CTC trial.[28] For CTC sensitivity and specificity, the results of the ACRIN study were used because, unlike previous studies, they reflect the accuracy of CTC when performed by a large number of radiologists from different centres.[28] In this study, almost 2600 asymptomatic individuals aged at least 50 years, from 15 study centres were examined by trained radiologists who reported all lesions measuring ≥5 mm in diameter. OC was performed following examination by CTC and served as the reference standard.

Similar to CTC, the pooled estimates of OC accuracy available from the literature are from predominantly high-risk populations.[38] Thus, per-person estimates for OC accuracy in the model were based on a prospective study of an average-risk population in which OC was calculated to detect 87.5% of high-risk polyps and 94.2% of low-risk polyps.[11] Sensitivity of OC was adjusted for greater sensitivity for polyps and cancer in the distal compared with the proximal colon (by a factor of 1.009 and 0.9812, respectively) according to the results of a retrospective study of colonoscopic miss rates.[27] The use of alternative estimates of screening accuracy was further explored through sensitivity analysis.

Screening uptake was defined as the percentage of the population who attended the screening appointment (or, in the case of FOBT, returned an adequate kit) following invitation to participate in the screening programme. The baseline assumption was that a random 60% of those invited to attend each screening event participated. Since the sociodemographic characteristics of a population may affect the screening uptake rate, different uptake rates were tested in the sensitivity analysis.

It was assumed that subjects with positive results from FOBT or CTC screening, including

Table III. Summary of lifetime cost inputs for colorectal cancer used in the model (£, year 2007 values)[a]

Cost component	Dukes' A		Dukes' B	Dukes' C	Stage D
	symptomatic	screen detected			
Diagnosis	1221.67	1221.67	1 151.88	1 174.29	1 147.21
Chemotherapy	0.00	0.00	4 612.32	12 002.92	10 469.33
Surgery	5269.60	4057.59	5 269.45	5 269.66	1 357.66
Radiotherapy	0.00	0.00	180.23	469.88	334.46
Follow-up	1713.18	1713.18	1 713.18	1 307.18	514.94
Total	8204.45	6992.44	12 927.04	20 223.92	13 823.60

a Lifetime costs were estimated based on calculations reported by Tappenden et al.,[14] and inflated to 2007 values using the PbR tariff.[33]

PbR = Payment by Results.

those subsequently identified as false positive, were referred for a follow-up polypectomy through OC, and that 100% of recommended polypectomies were performed. Polyps identified through OC and FSIG screening were assumed to be removed at the screening event.

In addition to mortality from CRC and mortality from other causes, the model specifically assessed mortality and harm due to screening and/or removal of polyps (polypectomy). Probabilities of harm caused by screening and by follow-up polypectomies were restricted to perforation of the bowel and post-endoscopy bleeds. In the case of CTC, the risk of perforation during screening was due to use of a rectal tube or distension of the colon by balloon.[30] In the case of FSIG and OC, probabilities for perforation and bleeding during a screening event were assumed regardless of the requirement for a polypectomy during the procedure. This analysis did not model any increased risk of cancer as a result of radiation exposure from initial screening or subsequent diagnostic tests, or the impact of extracolonic findings following a CTC scan. The rationale for this is explored in the discussion.

Resources and Costs

Costs associated with screening, treating adverse events and cancer treatment are accounted for in the model. The base cost year of the model was 2007, and all future costs and outcomes were discounted at a rate of 3.5% per annum. In line with suggestions in current UK National Institute for Health and Clinical Excellence (NICE) guidance, Payment by Results (PbR) tariffs were used to estimate unit costs in this economic model, and, where these were not available, the NHS reference costs were used.[39,40] PbR tariffs are the prospective costs used to commission NHS activity, whereas reference costs are the retrospective average costs of providing activity. Therefore, unit costs of screening technologies and relevant components of the lifetime treatment costs of CRC were taken from PbR tariffs for 2007–8 where these were available (tables II and III).[33]

It was assumed that the administration costs of inviting eligible individuals to attend a screening test with FSIG, OC or CTC were identical. The cost of invitations was assumed to make a negligible contribution to overall costs of screening – particularly when compared with the screening cost of FOBT, which incorporates the cost of invitation – and also in the context of total costs of each strategy. The cost of invitation was therefore omitted from the analysis. The adverse events associated with screening in the model were assumed to be restricted to bleeds and perforations. The cost of surgery for an intestinal perforation was assumed to be equal to the cost of a major surgical procedure (procedure code FA08-11): £5269.[41] The cost of treating gastrointestinal bleeding was taken as being the average cost of admittance to an observation ward and calculated to be £261.[41]

In deriving the lifetime costs of CRC treatment, certain assumptions were made.[14] It was assumed that cancers located in the rectum attract higher costs at diagnosis through additional MRI

scans as well as being suitable for radiotherapy. The cost analysis assumed that 75% of patients present electively because of symptomatic colorectal cancer, whilst the remainder are diagnosed through emergency presentations.[14] All patients with Dukes' stage A–C and approximately 26% of those with stage D cancers were assumed to undergo surgery,[14] with an average weighted cost of £5269.[41] Adjuvant (and palliative) chemotherapy was estimated to be received by 33% (19%), 85% (50%) and 11% (76%) of patients with Dukes' B, C and stage D cancers, respectively.[14] Radiotherapy was indicated for patients with carcinomas of the rectum, invasive tumours and those at high risk of post-surgical recurrence,[7] and was estimated to apply to approximately 13% of Dukes' B, 33% of Dukes' C and 12% of stage D cancers.[14] During follow-up, patients were assumed to visit a consultant in an outpatient clinic (maximum of five visits), or a GP in a local practice, every 3 months for the first 2 years following diagnosis, followed by annual visits thereafter. It was further assumed that patients would receive a colonoscopy every 5 years and a CT scan at 12 and 24 months following diagnosis. The mean survival of patients diagnosed with Dukes' stage A, B, C or stage D was assumed to be 11, 11, 8.7 or 1.4 years, respectively.[14]

Sensitivity Analyses

Univariate sensitivity analyses were conducted to assess the impact of uncertainty around key inputs on the cost effectiveness of the screening technologies. Each parameter was varied individually around the central estimate (base case) using upper and lower estimates either based on published sources or, where published estimates were not available, 20% either side of the central estimate. The parameter boundaries used in the sensitivity analyses are presented in table II. Lifetime CRC treatment costs and the costs of treating adverse events were all varied by ±20%. All costs were assumed to have a log-Normal distribution, while all proportions and probabilities had a Beta distribution.[32] Probabilistic sensitivity analysis using 1000 cycles of a Monte Carlo simulation was also conducted using the same parameters and boundaries. To assess the impact of using unit costs based on PbR tariffs, rather than NHS reference costs (which were used in Tappenden's model), the model was also parameterized using NHS reference costs.

Results

Model Validation

An important validation of any economic model is its ability to predict observed outputs with accuracy. The results of the model recalibration reflect more contemporary data and are presented in the Supplemental Digital Content 1, http://links.adisonline.com/APZ/A18. Due to inconsistencies in autopsy evidence, it is difficult to determine whether the model provides a good approximation of the true underlying prevalence of adenomas in the general population; however, the model predicted slightly lower prevalence than Tappenden et al.[14] Specifically, at ages 50, 60 and 70 years, the model predicted a prevalence

Table IV. Expected lifetime health outcomes for 100 000 individuals invited to attend alternative screening programmes[a]

Technology	Screening frequency (y)	Screen-detected cancers	Screen-detected polyps	Symptomatic cancers	CRC deaths	CRC cases avoided[b]	CRC deaths avoided[b]
FOBT	2	612	3543	5363	2274	NA	NA
FSIG	10	219	11282	4758	1940	605	334
OC	10	239	12367	4606	1876	757	398
CTC	10	244	9243	4782	1940	581	334

a Future outcomes are discounted at 3.5% per annum.

b Compared with FOBT.

CRC = colorectal cancer; **CTC** = CT colonography; **FOBT** = faecal occult blood testing; **FSIG** = flexible sigmoidoscopy; **NA** = not applicable; **OC** = optical colonoscopy.

Table V. Total mean costs (£, year 2007 values), health benefits and marginal cost-effectiveness ratios (CERs) of colorectal cancer (CRC) screening technologies[a]

Technology	Frequency (y)	Total mean cost per pt (£)	Total LY per pt[b]	Total QALY per pt[b]	Marginal CER vs FOBT (£)[c]		ICER[d] (£)
					per LY gained	per QALY gained	
CTC	10	434	18.586	16.862	−918	−568	NA
FOBT	2	445	18.574	16.842	NA	NA	Dominated
FSIG	10	452	18.585	16.861	606	360	Dominated
OC	10	518	18.588	16.865	5430	3321	34 002

a Lifetime costs and benefits discounted at 3.5% per annum.

b LYs and QALYs rounded to 3 decimal places.

c Negative marginal costs per LY (or QALY) gained can arise from a technology being less costly than the comparator and more effective; such technologies 'dominate' the comparator. CERs may not be obtainable from costs and outcomes due to rounding.

d Incremental cost per QALY versus next least costly option, excluding dominated options.

CTC = CT colonography; **FOBT** = faecal occult blood testing; **FSIG** = flexible sigmoidoscopy; **ICER** = incremental CER; **LY** = life-year; **NA** = not applicable; **OC** = optical colonoscopy; **pt** = patient.

of abnormal epithelium of 15%, 24% and 36%, respectively (compared with adenoma prevalence rates of approximately 18%, 30% and 38% reported by Tappenden et al.[14]).

Health Benefits

The model predicted that CTC performs well compared with other screening technologies with regards to measured health benefits. In a population of 100 000 individuals (who are between age 60 and 69 years and of whom 60% take up the invitation to be screened every 10 years, i.e. at age 60), CTC was expected to avoid 581 cases of CRC and 334 deaths compared with biennial screening with FOBT over the same period (table IV). In other words, for every 180 people screened by CTC rather than FOBT, one more CRC-related death would be avoided. CTC had similar health benefits to FSIG when compared with FOBT, whilst the most effective strategy, OC, prevented 19% more CRC-related deaths.

Compared with biennial FOBT, the model predicted that all screening options would result in between 0.012 and 0.014 LYs gained (table V). These figures equate to an additional 1152–1400 LYs (1900–2300 QALYs) for the entire cohort of 100 000 individuals over a lifetime time horizon.

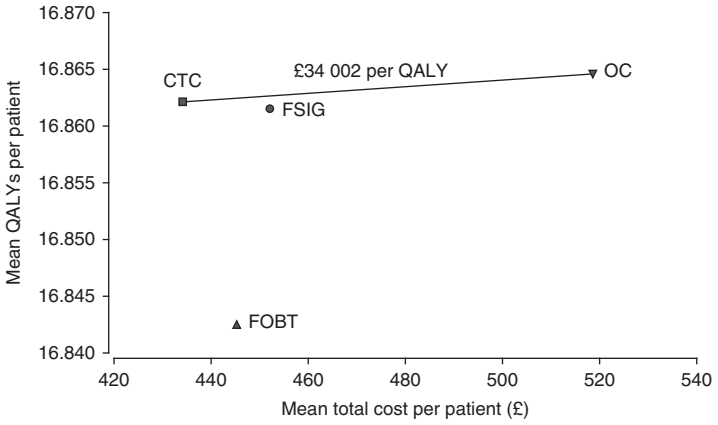

Fig. 2. Cost effectiveness of colorectal cancer screening procedures. **CTC** = CT colonography; **FOBT** = faecal occult blood test; **FSIG** = flexible sigmoidoscopy; **OC** = optical colonoscopy.

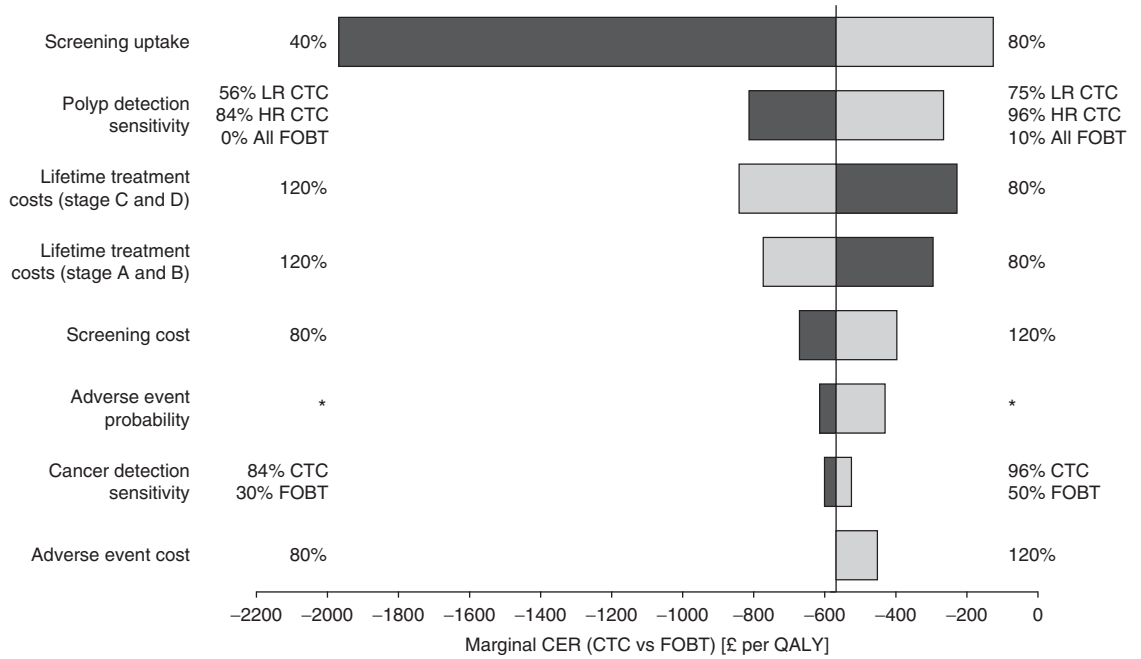

Fig. 3. Tornado diagram of the univariate sensitivity analysis on the marginal cost-effectiveness ratio (CER) of CT colonography (CTC) compared with faecal occult blood test (FOBT). Black bars = lower limits, grey bars = upper limits. * Limits for risks of perforation and bleeding are presented in table II. **HR** = high-risk polyp; **LR** = low-risk polyp.

Costs

The most costly screening technology was OC, which had an average cost of £518 per patient invited to screen (table V). CTC was the least expensive screening policy and saved £11 per person compared with biennial FOBT.

Figure 2 presents a graphical representation of the health outcome and cost for each technology, and illustrates dominance of CTC over FOBT and FSIG, with CTC being both more effective and less costly than these alternatives.

Marginal Cost-Effectiveness Ratios (CERs)

Table V presents the marginal CERs of screening technologies considered in the model compared with the current UK screening policy of biennial FOBT for ages 60–69 years. All screening alternatives were estimated to have marginal CERs well below the NICE £20 000–30 000 per QALY threshold above which new technologies are less likely to be recommended.[39]

CTC was both more effective and less costly (i.e. dominant) than a policy of biennial FOBT between ages 60 and 69 years. In contrast, OC screening was estimated to have the highest marginal CER versus FOBT, and its incremental CER (ICER) compared with CTC was £34 002 per QALY.

Sensitivity Analysis

Results of the univariate sensitivity analyses for CTC versus FOBT are shown in figure 3, with a corresponding probabilistic analysis in figure 4.

Assuming that the lifetime treatment costs of Dukes' C and stage D cancer are 20% higher than estimated in the base case decreased the marginal CER of CTC compared with FOBT, indicating that CTC is more cost effective in this scenario. Conversely, varying the adverse event probability and cost had little impact on the marginal CER. The changes in the marginal CER observed when polyp detection sensitivity of CTC and FOBT was varied are mainly a feature of the difference

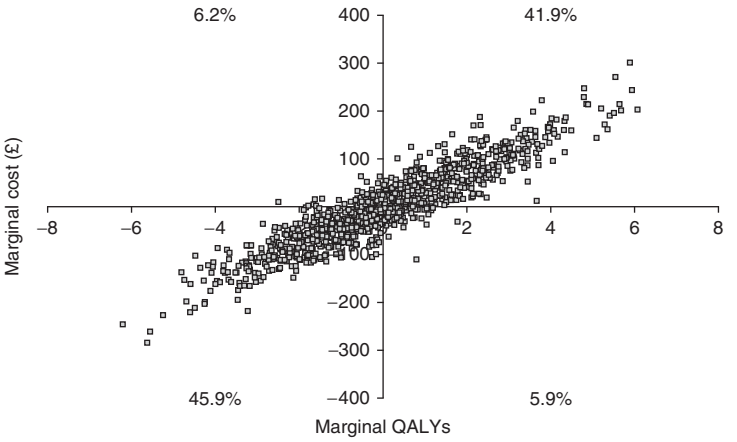

Fig. 4. Scatter plot of the probabilistic simulations on the cost-effectiveness plane for CT colonography compared with faecal occult blood test.

between lower and upper bound estimates for FOBT (table II). Reducing the uptake rates of the two screening technologies resulted in a greater cost saving for CTC compared with FOBT, but only a small QALY difference, given the different frequency of the two screening strategies. Thus, the marginal CER for CTC versus FOBT was lower when fewer individuals took up screening.

The probabilistic sensitivity analysis showed that CTC was equally likely to be cost effective versus FOBT, as not (figure 4). The mean marginal total cost per person was £0.07 (95% CI –153.13, 166.80), while the mean marginal QALY per person was 0.01 (95% CI –3.83, 4.02). The bottom-right and top-left quadrants of the cost-effectiveness plane in figure 4 illustrate that CTC dominated FOBT in 5.9% of simulations; the probability of CTC being dominated was similar (6.2%). In 48% of simulations, CTC was found to be acceptable at a cost-effectiveness threshold of £30 000 per QALY compared with FOBT.

Results of the univariate sensitivity analyses for comparisons of all screening methods versus FOBT are given in table VI. The parameters with the most impact on marginal CERs of the three alternatives were the screening uptake rate and the cost of the screening tests. When the costs of screening were reduced, either by decreasing

Table VI. Univariate sensitivity analysis of screening technologies: marginal cost (£) per QALY gained vs faecal occult blood test (FOBT)

Parameters varied	FSIG[a]	OC[a]	CTC[a]
Base case	360	3321	–568
Sensitivity for polyps	122, 617	2750, 3941	–813, –265
Sensitivity for cancer	225, 506	2927, 3716	–601, –525
Screening uptake	–1421, 802	653, 3667	–1968, –126
Adverse event probability	351, 305	3266, 3815	–614, –430
Cost of screening	–512, 1209	1840, 4607	–671, –397
Lifetime cost of Dukes' A and B	619, 79	3476, 2970	–295, –773
Lifetime cost of Dukes' C and D	671, 27	3558, 2889	–228, –841
Cost of adverse events	427, 427	3267, 3305	–482, –452
5-year screening interval	2363	5352	1064
NHS reference costs (inflated from 2004 data)	349	3223	–534

a Figures are presented as lower bound, upper bound.

CTC = CT colonography; **FSIG** = flexible sigmoidoscopy; **OC** = optical colonoscopy.

the per-test cost or by fewer individuals being screened, the marginal CER also decreased. The parameters with the least impact on cost effectiveness were the sensitivity of cancer detection and the probability and cost of adverse events associated with screening and polypectomy.

The effect of using a pooled estimate of CTC accuracy (0.63 and 0.83 for low- and high-risk polyps, respectively)[37] on the marginal CER of CTC compared with FOBT can be assessed through the sensitivity analysis results (figure 3 and table VI). Similarly, the pooled estimate of OC sensitivity (0.97 and 0.98 for low- and high-risk polyps, respectively) published by Rosman and Korsten[38] falls within, or close to, the parameter boundaries of OC sensitivity (table II). The marginal CER for OC compared with FOBT of £3941 per QALY at the upper bound was very similar to the £3321 per QALY observed in the base case (table V), thus demonstrating the limited impact of alternative sources of these inputs to the model.

Prior to the development of PbR tariffs in the UK NHS in 2004–5, NHS reference costs were the only publicly available source of NHS cost data, and, as such, were commonly used to drive economic analyses of the UK setting, including that conducted by Tappenden et al.[13] Our sensitivity analysis demonstrated that using NHS reference costs had a small impact on the marginal cost effectiveness of each of the screening programmes.

Discussion

Our analysis shows that, in the UK NHS setting, a programme of 10-yearly CTC scans for 60- to 69-year-olds has the potential to be both cost saving and more effective than the current UK screening programme of biennial FOBT, and CTC may dominate this option in terms of cost effectiveness, although there was a considerable degree of uncertainty in the probabilistic sensitivity analysis. In a group of 60 000 screened individuals, a CTC programme could avoid up to an additional 581 cases of CRC and 334 CRC-related deaths over the lifetime of the cohort compared with biennial FOBT. For every 180 people screened by CTC instead of FOBT, one more CRC-related death would be avoided.

A number of studies have measured patient preferences in subjects who have experienced both CTC and OC.[11,42-44] In general, about 50% of subjects had a preference for CTC, 40% preferred OC and 10% were undecided. Whilst it remains unclear how individuals weigh the perceived accuracy of each screening technology against the level of invasiveness, it seems reasonable to assume that the availability of a non-invasive option such as CTC has the potential to increase overall screening uptake. This could have potentially large implications, since our model has shown that patient uptake is an important factor in the cost effectiveness of CRC screening technologies.

Limitations and Additional Data Considerations

CRC mortality can be reduced by FOBT[15] through the detection of cancer at an earlier stage. However, there is only indirect evidence that CTC can reduce mortality from CRC and, for ethical reasons, no prospective, randomized, controlled clinical trial has been initiated to directly demonstrate the efficacy of CTC in reducing mortality from CRC.[45] Thus, studies of CTC have focussed on the detection of advanced neoplasia,[28] which provides the rationale for modelling lifetime outcomes.

The optimal time interval between CTC screening scans has not been determined. Joint guidance from the American Cancer Society, the US Multi-society Task Force on CRC and the American College of Radiology states that if no polyp larger than 5 mm is found, it is reasonable to wait 5 years before the next test (compared with 10 years between negative OCs).[45] There is also uncertainty concerning the need for follow-up OC of 'mid-size' polyps between 6 and 9 mm, which may be safe to monitor over time. The current model assumes that polyps of this size, once detected, are removed by polypectomy.

Although it was beyond the scope of this model, it is important to consider the impact of extracolonic findings that may be detected in

subjects undergoing CTC screens. A recent study suggested that, because CTC can also detect unsuspected extracolonic cancers and abdominal aortic aneurysms, considering these additional benefits makes it a dominant screening strategy over OC.[22] A recent systematic review reported that the average frequency of extracolonic findings per patient was 40%. Overall, approximately 14% of subjects underwent further investigation due to extracolonic findings and only 0.9% of subjects required immediate treatment as a result of such findings.[46] The ACRIN trial reported that extracolonic findings were observed in two-thirds of subjects and that 16% of these required follow-up or urgent care.[28] Although some of these findings are likely to have brought a clinical benefit to the patient, this would be at the expense of increased risks, anxieties and costs for those individuals undergoing follow-up investigations that prove to be clinically unnecessary.

CTC has far lower complication rates than OC, primarily due to the almost negligible risk of perforation during screening. However, the potential for harm from radiation exposure is more difficult to assess, not least because of the uncertainty of the risks associated with the typically low levels of radiation during screening and the age of subjects (>50 years). The additional lifetime risk of CRC from a CTC scan at age 50 years has been estimated to be 0.042%.[47] It was felt that this would represent a negligible and highly uncertain increase in costs and decrease in QALYs, considering that the lifetime treatment of CRC assumed in the model incorporates a number of CT scans following diagnosis, regardless of the screening technology used.

The main limitations identified by Tappenden et al.[13] in conducting their analysis were associated with the paucity of direct evidence for the natural history of CRC. Our model suffers similarly from these uncertainties. Like Tappenden et al.,[13] we have used a Markov model based on the most advanced polyp and hence the additive risk of multiple polyps is not accounted for. Furthermore, the model structure imposes an order to the events that may not accurately reflect real clinical practice. For example, the model does not allow for sequential uptake of differing screening technologies, assumes that the uptake of polypectomy is 100% and ignores the possibility that the sensitivity of some procedures is dependent on correct bowel preparation.

There is a further limitation of our model. Subjects in whom a polyp or cancer has been detected may, in clinical practice, be placed in a surveillance programme for a defined period following its removal. However, in order to provide the most straightforward assessment of the impact of the initial screening options, we chose not to include a surveillance programme in the model. In practice the nature of a surveillance protocol would depend on the characteristics of each screening programme and so surveillance would significantly complicate the model structure and assumptions.

Finally, generalizability of our results from the UK setting to other countries such as the US may not be appropriate in light of the greater cost differences between OC and CTC in other countries, as well as differing approaches to using OC in screening. Furthermore, although immunochemical-based FOBTs have been developed, we understand that there are no plans to introduce this technology in the UK due to the logistical difficulties of using it in a country-wide screening programme,[48] and so it has not been considered in this model.

Further Research and Policy Considerations

Although cost-effectiveness studies are useful tools to explore the efficiency of new healthcare technologies, the decision of whether or not to implement any particular technology must also consider resourcing requirements and specific budget limitations. For example, although FSIG was shown to be more cost effective than FOBT,[13] the impact on endoscopy services led the NHS to choose biennial FOBT screening instead.[49]

In considering the policy implications of our results, we would anticipate that uptake of CTC by the NHS would primarily result in otherwise unscreened individuals receiving CRC screening, and perhaps cause some substitution for existing screening programmes. It will be important to

understand how CTC screening can be used synergistically with the current FOBT programme to continue improving early detection and cancer prevention and to help the NHS achieve the goals of its Cancer Reform Strategy.[50] Further analysis of the potential impact of CTC screening uptake by the NHS on budgetary and/or resource constraints is therefore required.

Conclusion

CTC has the potential to provide a cost-effective option for CRC screening in the UK NHS and may be an efficient alternative to the current programme of biennial FOBT. Further analysis is required to assess the impact of introducing CTC to the UK CRC screening programme on the NHS budget and capacity.

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Correspondence: Dr *David Lee*, Head of Health Economics – Americas, GE Healthcare, 3000 N. Grandview Blvd, W460, Waukesha, WI 53188-1615, USA.
E-mail: david.w.lee@ge.com