National Collaborating Centre for Cancer

Suspected cancer:

recognition and management of suspected cancer in children, young people and adults

Clinical Guideline

Appendices A - E

June 2015

Final version

Commissioned by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Funded to produce guidelines for the NHS by NICE

These appendicies update and replace those in NICE guideline CG27 (published June 2005).

Evidence has been reviewed on the recognition and management of suspected cancer in children, young people and adults.

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Appendices

Appendix A: The cost-effectiveness of diagnostic tests to diagnose colorectal cancer for patients aged 40 years and over with a change in bowel habit in primary care

A.1 Background

People in England and Wales with suspected colorectal cancer are usually offered a colonoscopy within two weeks to establish a diagnosis. Colonoscopy is considered the gold standard investigation for the diagnosis of colorectal cancer due to its ability to visualise the entire colon and perform biopsies. Other investigations used in the diagnosis of colorectal cancer include flexible sigmoidoscopy and barium enema. Both investigations are associated with a lower risk of adverse events compared to colonoscopy however sensitivity is considerably lower. Recently, computerised tomography colonography (CTC) has begun to replace barium enema as the investigation of choice, for patients with co-morbidities. The technology uses CT imaging of the colon to visualise tumours.

Currently, the national bowel cancer screening programme uses faecal occult blood tests (FOBT) or faecal immunochemical tests (FIT) to detect occult blood in the faeces which is indicative of colorectal cancer. These tests are given to asymptomatic people aged 60 years or older in England and Wales. They are easy to use and can be performed by the person at home. Currently these tests are not routinely available to GPs to order if they suspect their patient has colorectal cancer and falls outside the bowel cancer screening age parameters.

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A.2 Existing Economic Evidence

A systematic literature review was performed to assess the current economic literature in this area. The review identified 634 possibly relevant economic papers relating to colorectal cancer. Of these, ten full papers were obtained for appraisal. No study directly assessed the decision problem. The majority of literature in this area focuses on screening for asymptomatic patients. One study was identified, Allen et al 2004, which addressed a similar question to this decision problem; diagnostic tests to investigate rectal bleeding in patients aged 40 years and over.

This study could not be included within the economic evidence for this topic because it did not include a change in bowel habit as the main symptom and included other benign diseases of the bowel as an outcome. However it did provide a useful structure for the de novo analysis. The study used a decision tree combined with a Markov state transition model. The disease natural history section of the model was consistent with existing UK based screening economic models and divided the disease states by Dukes grading[a].

The study perspective was from a USA modified societal perspective. The investigations included in the study were; air contrast barium enema (ACBE) alone, ACBE and flexible sigmoidoscopy, flexible sigmoidoscopy, colonoscopy and watchful waiting. Faecal occult blood tests were not included in the analysis because the study was investigating people with

a Method of assessing the level of invasion and the spread of a colorectal tumour within the bowel.

visible rectal bleeding therefore occult blood tests are not relevant to this population. The authors concluded that colonoscopy was cost-effective compared to flexible sigmoidoscopy alone (ICER $5,480). Watchful waiting, defined as bleeding for one year followed by colonoscopy, was the most expensive option and was dominated by flexible sigmoidoscopy.

A.3 Aim

To estimate the cost-effectiveness of diagnostic tests for suspected colorectal cancer ordered in primary care for patients aged 40 years and over with a change in bowel habit.

A.4 De Novo Economic Model

As the current economic literature did not adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost-effectiveness.

A.4.1 Model Structure

A decision tree analysis with combined Markov states was used to capture the diagnosis and staging of colorectal cancer. The full model structure is shown in Figure 1. The cohort begins with people aged 40 years and over with a change in bowel habit who have presented to their GP for the first time. The cohort can have one of five initial investigations; FOBT, barium enema, flexible sigmoidoscopy, CTC or Colonoscopy. If the initial test result is positive they are referred for either a colonoscopy or CTC depending on the probability of them being unsuitable for colonoscopy (for those receiving a colonoscopy as a first line investigation, no further test is required). If after colonoscopy or CTC the person tests positive for colorectal cancer, a CT scan is ordered to establish the stage of the cancer.

The initial cancer stage for those people with colorectal cancer is determined by a probability of entering one of the four colorectal cancer markov states. These states are based on the Dukes grading system for colorectal cancer. Patients with diagnosed cancer can either remain in their current health state or die from colorectal cancer or another cause.

A lifetime horizon with a one year cycle length captures the probability of progression for treated and untreated colorectal cancer. For those patients with a negative result who have the underlying disease (false negatives), it is assumed that their symptoms would persist and they would be diagnosed at one year with a colonoscopy. During this time the patient has a probability of progressing to a worse cancer state. All true negative patients are discharged after either their first investigation, or, if false positive at initial stage they are discharged after their second investigation.

Estimated total costs and quality adjusted life years (QALYs) are collected over the modelled forty year time horizon for each diagnostic strategy. The total costs include all costs associated with initial and follow up investigations, staging, and treatment. These are described in more detail in the cost section of this report. QALYs are calculated by multiplying the life years that patients spend in each health state by the associated quality of life (QoL) weighting, which represent the valuation of the patient's health state. QALYs and QoL values are discussed in more detail in later sections of the report. Future costs and benefits were discounted at a rate of 3.5% per year as recommended by NICE.

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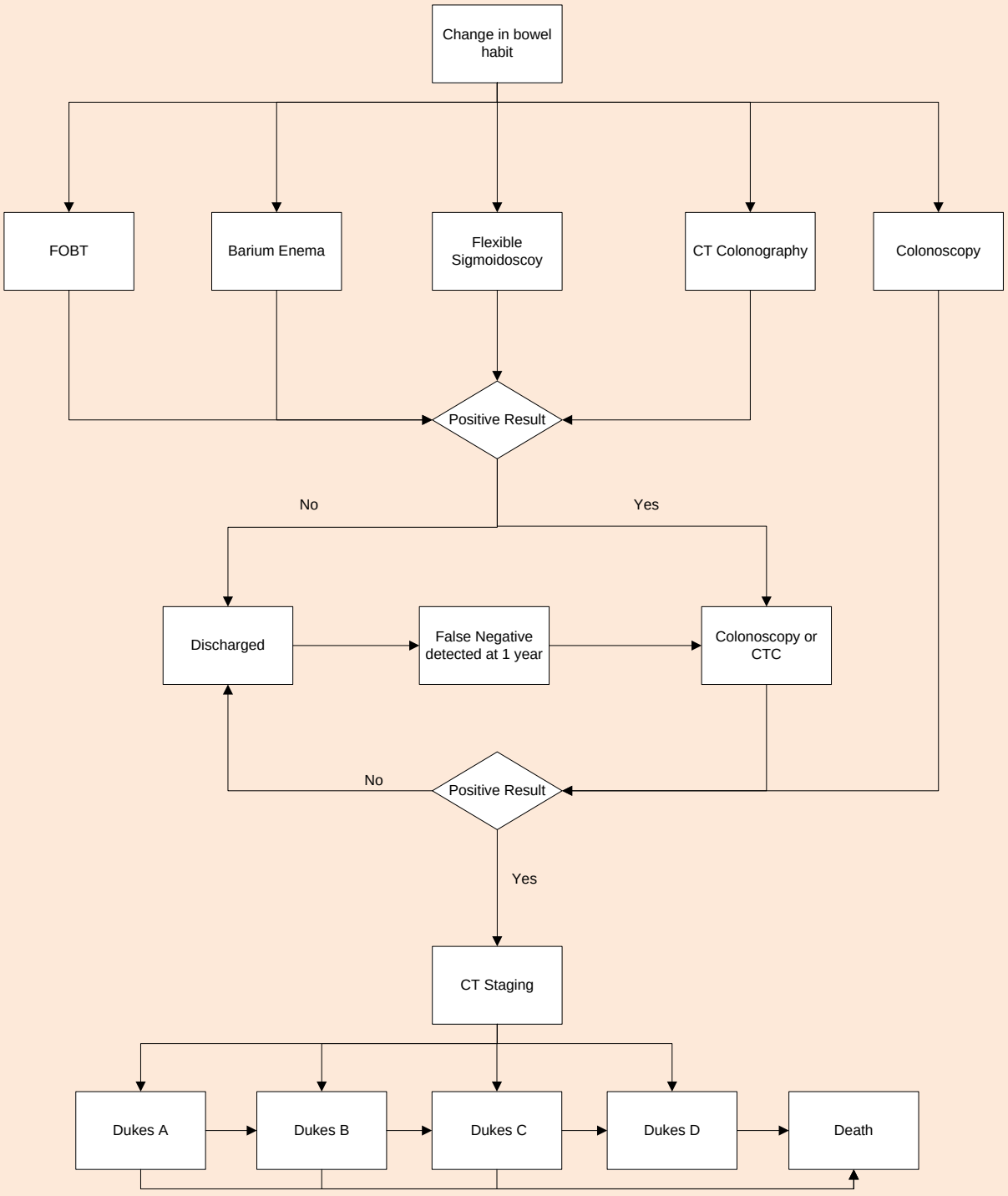
Figure 1: Basic Model Structure



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A.4.2 Prevalence of colorectal cancer

No evidence was identified to inform the prevalence of colorectal cancer in the study population. The clinical review for this guideline examined the positive predictive value (PPV) of various symptom/s associated with colorectal cancer. The PPV is the probability of colorectal cancer in a person with the specific symptom. This can be used to inform the prevalence in the absence of evidence. Twenty-two studies were identified as relevant. The evidence could not be pooled due to excessive heterogeneity. The evidence showed a PPV of colorectal cancer in men and women aged 60 years or lower with a change in bowel habit (described as diarrhoea or constipation) ranging from 0.01-15.7.

Due to the lack of evidence the guideline development group (GDG) estimated that the prevalence of colorectal cancer in the base case population is 1.5%. Prevalence was examined fully in the sensitivity analysis.

A.4.3 Natural History of Disease

The initial distribution of cancer stages at diagnosis was estimated using data from the National Cancer Intelligence Network (NCIN), which showed the percentage of patients diagnosed at each stage of colorectal cancer between 1996 and 2002. Disease specific mortality was also estimated using data from the NCIN, with the reported five year survival rates used as a starting point for extrapolation. . Table 1 outlines the NCIN data showing the five year survival rates and percentages of cases diagnosed at each stage from patients in England.

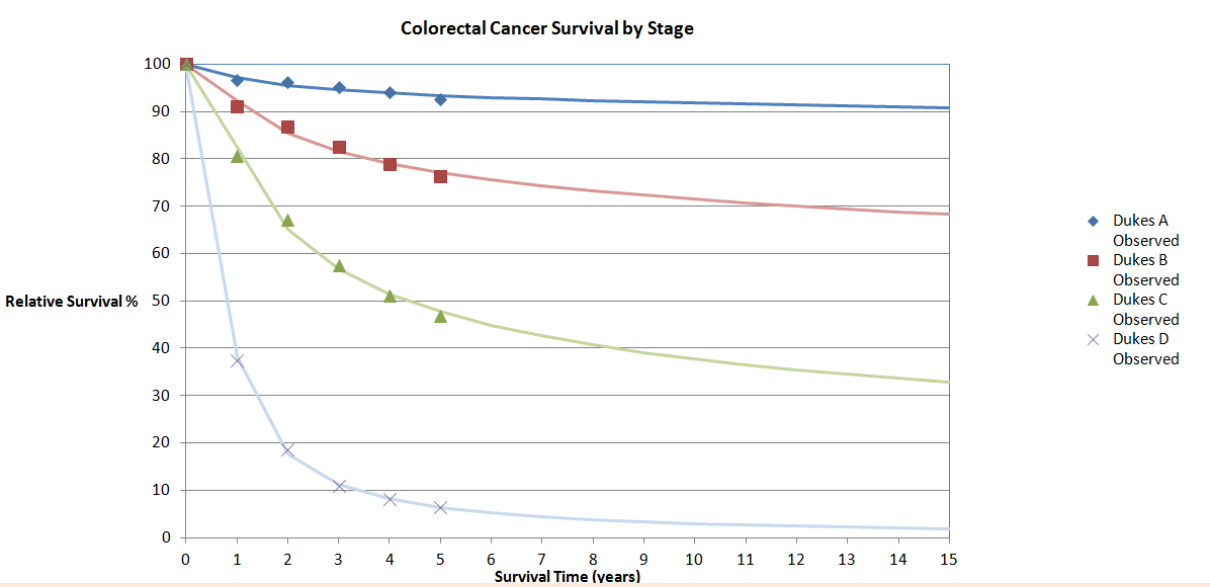
Table 1: Number of cases and 5 year relative survival of colorectal cancer patients diagnosed between 1996-2002, England (NCIN)

Stage at Diagnosis	Number of cases	5-year relative survival	Confidence Interval (95%)
Dukes A	26,727	93.2%	92.5-93.9
Dukes B	74,784	77.0%	76.4-77.5
Dukes C	72,806	47.7%	47.1-48.3
Dukes D	28,377	6.6%	6.1-7.0

For the purposes of the analysis, the five year survival rate was extrapolated over the time horizon of the model. It was not appropriate to assume an exponential mortality rate as a certain number of patients will survive after five years from all cancer stages. Figure 2 illustrates the observed five year survival data and predicted survival for colorectal cancer used in this analysis.

Data from published interim life tables for the UK Office of National Statistics 2013 were used to calculate age-related mortality probabilities.

Figure 2: Colorectal survival by stage



Data on progression between cancer stages for those people who have undiagnosed colorectal cancer were obtained from Tappenden et al 2004 (Table 2). Tappenden et al 2004

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describes the method for calibrating transition probabilities by using Monte Carlo sampling of published incidence, mortality, stage distribution and prevalence data. Each parameter was given wide uniform distributions and then sampled over 60,000 iterations. Those parameter combinations which generated the minimum mean squared errors between the model predictions and published evidence were retained for inclusion in the model.

The GDG noted that obtaining observed probabilities in colorectal cancer patients is unlikely. Therefore in the absence of evidence on progression the GDG chose the Tappenden et al values for use in the model. Using calibrated probabilities will lead to uncertainty within the model results, however this was fully explored in the one way sensitivity analysis and the probabilistic sensitivity analysis.

Table 2: Probability of progression for undiagnosed colorectal cancer

Colorectal Stage	Annual probability of progression for undiagnosed CRC (95% CI)	PSA Distribution	Reference
Dukes A – Dukes B	0.58 (0.57-0.59)	Uniform	Tappenden et al 2004
Dukes B – Dukes C	0.66 (0.64-0.67)	Uniform	Tappenden et al 2004
Dukes C – Dukes D	0.87 (0.85-0.88)	Uniform	Tappenden et al 2004

A.4.4 Diagnostic accuracy

Diagnostic accuracy was captured in the model using data on sensitivity and specificity. Sensitivity is defined as; the probability that the index test result will be positive in a diseased case. The specificity is defined as; the probability that the index test result will be negative in a non diseased case.

All included evidence for the guideline is required to be from primary care studies. Patient selection, overall clinical responsibility and setting should all have been conducted in primary care to be eligible for inclusion. Upon review of the evidence six papers were identified as relevant for faecal occult blood tests and three were relevant for barium enema.

The sensitivity and specificity reported for barium enema and FOBT could not be pooled due to excessive heterogeneity between the studies. The GDG chose to use Gillberg et al 2012 for the diagnostic accuracy of FOBT as the study included a large sample size and was conducted in a primary care setting with sensitivity and specificity reported for a range of ages. Jensen et al 1993 was chosen for barium enema. Although this study had several limitations (specificity was reported as 100%) the reported diagnostic accuracy for sensitivity matched other published non-primary care studies. These issues were fully explored in the sensitivity analysis.

No relevant evidence was identified for the remaining interventions for the decision problem. Data for the remaining investigations was collected by removing the primary care filter from the clinical review and sifting the remaining articles for relevant papers. Colonoscopy was included in the base case analysis as a comparator due it being the gold standard investigation for colorectal cancer. The remaining investigations were not included in the base case but were considered as part of a supplementary analysis. Table 3 below outlines the values used in this analysis for diagnostic accuracy.

Table 3: Key Diagnostic Accuracy Data

Investigation	Sensitivity (95% CI)	Specificity (95% CI)	Beta PSA Distribution (alpha, beta)	Reference
FOBT	50.0% (15.0%,85.0%)	88.0% (85.0%,89.0%)	Sensitivity = 3,3 Specificity =963,138	Gillberg et al 2012

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Investigation	Sensitivity (95% CI)	Specificity (95% CI)	Beta PSA Distribution (alpha, beta)	Reference
FITb	74.7% (64.5%,83.3%)	86.4% (84.1%,88.4%)	Sensitivity = 69,24 Specificity = 849,135	Oono et al 2010
Barium Enema	60.0% (15.0%,95.0%)	100.0% (97.0%,100.0%)	Sensitivity = 2,2 Specificity = 21,1	Jensen et al 1993.
Flexible Sigmoidoscopy	68.6% (65.5%,71.6%)	100.0%	Sensitivity = 648,297 Specificity = not varied	Thompson et al 2008
CT Colonography	96.1% (93.8%,97.7%)	79.2% (76.8%,81.5%)	Sensitivity = 398,16 Specificity =921,242	Pickhardt et al 2011 (only reported sensitivity) & Halligan et al 2013
Colonoscopy	94.7% (90.4%,97.2%)	100.0%	Sensitivity = 178,10 Specificity = not varied	Pickhardt et al 2011

A.4.5 Adverse Events

Adverse events associated with each diagnostic test were collected from various sources. A UK colonoscopy audit by Gavin et al 2012 provided data on colonoscopy completion rates and associated adverse events (Table 4). No data was available to inform the probability of adverse events for flexible sigmoidoscopy. This was estimated to be of the same risk as colonoscopy by the co-opted clinical expert[c]. No other procedures were deemed to require inpatient treatment for adverse events.

Bleeding was assumed to be gastrointestinal and require hospitalisation and occur in both investigations. Bowel perforation is only a risk in colonoscopy.

Table 4: Adverse event profiles

Adverse Event	Probability of occurrence (95%CI)	PSA Distribution	Reference
Bleeding	0.26 (0.20-0.36)	Uniform	Gavin et al 2012
Perforation	0.04 (0.02-0.08)	Uniform	Gavin et al 2012

A.4.6 Costs

NHS Reference Costs 2012/13 and the Personal and Social Services Research Unit (PSSRU) 2013 were used to inform the price of tests and consultations (Table 5). FOBT is not routinely available in primary care outside the parameters of the screening programme, therefore the price used was sourced from the screening programmes Southern Hub. Costs on adverse events were taken from NHS Reference Costs 2012/13.

Any patient found to have colorectal cancer first incurs the cost of a CT scan for staging (as per existing CG 131 NICE guidance[d]). The patient then incurs a lifetime cost of the disease based on their disease stage at the time of diagnosis. This cost includes the various treatments that the average patient would receive, including costs for surgery, radiotherapy and chemotherapy. Data on lifetime costs were taken from Tappenden et al 2004 and inflated to 2014 prices.

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[b] Examined in supplementary analysis
c Dr Rachel Hargest, Consultant Colorectal Surgeon at University Hospital of Wales and NCC-C Management Board Member.
d http://www.nice.org.uk/guidance/CG131

Table 5: List of all costs included in analysis

Type of Cost	Mean Cost (Standard error)	Gamma PSA Distribution (alpha, beta)	Reference
Investigations			
FOBT	£4.86 (4.45)	(1.19, 4.07)	Estimated[e]
FIT	£9.42 (7.41)	(1.61,5.83)	Estimated[f]
Colonoscopy	£368.00 (145.88)	(6.36, 57.83)	NHS Reference Costs 2012/13
CT colonography	£275.00 (29.65)	(86.01,3.19)	NHS Reference Costs 2012/13
Barium Enema	£101.00 (32.55)	(9.63,10.49)	NHS Reference Costs 2012/13
Flexible Sigmoidoscopy	£351.00 (130.10)	(7.28,48.21)	NHS Reference Costs 2012/13
CT Scan	£146.53 (68.94)	(4.52,32.43)	NHS Reference Costs 2012/13
Adverse Event			
Gastro intestinal bleeding	£265 (148.26)	(3.19, 82.95)	NHS Reference Costs 2012/13
Bowel Perforation	£2,240 (593.03)	(14.27, 157.00)	NHS Reference Costs 2012/13
Referral			
GP visit	£45.00 (not reported)	n/a	PSSRU 2013.
Lower Gastrointestinal appointment	£171.00 (60.79)	(7.91,21.61)	NHS Reference Costs 2012/13.
Cancer Stage			
Dukes A	£8,221 (3047.24)	(7.28,1129.44)	Tappenden et al 2004
Dukes B	£13,863 (5138.60)	(7.28,1904.60)	Tappenden et al 2004
Dukes C	£22,428 (8313.13)	(7.28,3081.22)	Tappenden et al 2004
Dukes D	£14,925 (5531.89)	(7.28,2050.37)	Tappenden et al 2004

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A.4.7 QoL valuations (utilities)

The model estimates effectiveness in terms of quality adjusted life years (QALYs). QALYs are estimated by combining the life year estimates with utility values (or QOL weights) associated with being in a particular health state. These utility values were identified through a search of the available literature (Table 6).

There is a paucity of quality of life (QoL) data available in colorectal cancer. One study by Ness et al 1999 assessed quality of life values associated with the various stages of cancer and treatment in the USA using the standard gamble technique. These results were not valued by the UK public. The NICE reference case requires QoL to be based on public preferences and measured in patients (and ideally measured using the EQ-5D survey). However, in the absence of such high quality data, the utilities from the Ness et al 1999 study were utilised. QoL for healthy patients was taken from a large UK based study on population health using the EQ-5D survey.

e Estimated from UK bowel screening Southern hub contract prices 2011.
f Estimated from UK bowel screening Southern hub contract prices 2011.

Table 6: Quality of life valuations

Model State	QoL	Beta distribution (alpha, beta)	Reference
Healthy	0.79	(267.00,71.00)	Kind et al 1999
Dukes A	0.74	(145.00,51.69)	Ness et al 1999
Dukes B	0.70	(56.60,24.53)	Ness et al 1999
Dukes C	0.50	(33.78,32.28)	Ness et al 1999
Dukes D	0.25	(1.03,2.35)	Ness et al 1999

A.4.8 Base case results

The results of the economic model are presented as expected costs and QALYs for intervention along with an incremental cost-effectiveness ratio (ICER) for each comparison. The ICER is used to measure the cost-effectiveness of one intervention over another; it is calculated as shown in Figure 3.

Figure 3: Calculation of the incremental cost-effectiveness ratio (ICER)

ICER = (Δ Cost) / (Δ QALYs)

ICER = (Cost Intervention A − Cost Intervention B) / (QALYs Intervention A − QALYs Intervention B)

It can be seen that by dividing the difference in costs of each intervention by the difference in benefits (in QALY terms), a cost per QALY can be calculated for each comparison. NICE typically has a cost effectiveness (CE) threshold of £20,000 for one additional QALY gained. Thus, an intervention with ICER < £20,000 can usually be considered cost-effective. Interventions with ICER values above £30,000 are not typically considered cost-effective. For ICER values between £20,000 and £30,000, an intervention may be considered cost-effective if it is associated with significant benefits.

An alternative way of presenting the results of economic analyses is in the form of net monetary benefit (NMB), which is calculated as shown in figure 4. It can be seen that by employing a fixed NICE threshold of £20,000 per QALY and re-arranging the ICER formula it is possible to express both effectiveness and costs in monetary terms. When the calculated result is found to be positive then the benefits are found to outweigh the costs and those interventions that have higher NMBs are preferred to those with lower NMBs.

Figure 4: Calculation of net monetary benefit (NMB)

$$\mathbf{NMB} = \lambda \times \Delta\text{QALYs} - \Delta\text{Costs}$$

Where λ = NICE threshold of £20,000 per QALY

The model was run over a time horizon of forty years as this was expected to be the time period over which the outcomes were most likely to differ for patients with colorectal cancer. Costs and QALYs are calculated for a cohort of 1000 people. The base case deterministicresults of the model are presented in the tables below. The table shows the total cost, incremental (incr) cost, total QALYs, incremental QALYs, ICER (cost per QALY) and NMB.

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Table 7 shows the results of FOBT and barium enema compared against colonoscopy. It can be seen that both FOBT and barium enema are cost effective compared to colonoscopy at a threshold of £20,000 per QALY gained.

Table 8 presents the results in a dominance rank format. In this analysis the tests are rearranged in order of total cost, from cheapest to most expensive. Incremental costs and QALYs are then calculated for each intervention by comparing it against the previous intervention that was found to be cost-effective (at a threshold of £20,000 per QALY).Upon analysis of results using the dominance rank method, FOBT was found to be the most cost-effective test.

Table 7: Base case deterministic results, FOBT and barium enema compared to colonoscopy

Test	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
Colonoscopy	£810,397	-	814.24	-	-	£15,474,474
FOBT	£343,244	-£467,153	809.99	-4.25	£109,860[g]	£15,856,582
Barium Enema	£365,818	-£444,578	810.94	-3.30	£134,681	£15,853,033

Table 8: Base case deterministic results - dominance rank

Test	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
FOBT	£343,244	-	809.99	-	-	£15,856,582
Barium Enema	£365,818	£22,575	810.94	0.95	£22,580	£15,853,033
Colonoscopy	£810,397	£467,153	814.24	4.25	£116,750	£15,474,474

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In addition to the deterministic results above, the base case results were also generared probabilisticly. In this analysis the mean total costs and QALYs were recorded after 10,000 probabilistic runs of the analysis. The probabilistic base case results are presented in tables 9 and 10 below showing a comparison against a common baseline (colonoscopy) and a dominance rank, respectively.

As in the deterministic analysis, it can be seen that both FOBT and barium enema are cost effective compared to colonoscopy at a threshold of £20,000 per QALY gained. Furthermore, when using the dominance rank method, FOBT was again found to be the most cost-effective test. However, one difference that can be noted is that barium enema was found to be dominated by FOBT in the probabilistic analysis.

Table 9: Base case probabilistic results, FOBT and barium enema compared to colonoscopy

Test	Costs		QALYs		ICER	NMB
	Total	Incr	Total	Incr		
Colonoscopy	£836,201	-	812.12	-	-	£15,407,830
FOBT	£350,045	-£486,157	808.03	-4.17	£116,641	£15,810,627
Barium Enema	£390,076	-£446,125	808.03	-4.17	£107,034	£15,770,593

g When incremental QALYs & Costs are negative anything above the CE threshold (£20,000 per QALY) is cost-effective

Table 10: Base case probabilistic results - dominance rank

	Costs		QALYs		ICER	NMB
Test	Total	Incr	Total	Incr		
FOBT	£350,045	-	808.03	-	-	£15,810,627
Barium Enema	£390,076	£40,031	808.03	0.00	Dominated	£15,770,593
Colonoscopy	£836,201	£486,157	812.12	4.17	£116,641	£15,407,830,

A.4.8.1 Scenario Analysis

Further analysis was undertaken to examine the cost-effectiveness of flexible sigmoidoscopy and CTC. Table 11 shows the ICERs for CTC and flexible sigmoidoscopy compared to colonoscopy. Both investigations were cost-effective compared to colonoscopy.

Table 11: Comparison of flexible sigmoidoscopy and CTC to colonoscopy

	Costs		QALYs		ICER	NMB
Investigation	Total	Incr	Total	Incr		
Colonoscopy	£810,397	-	814.24	-	-	£15,474,474
Flexible Sigmoidoscopy	£690,542	-£119,855	811.76	-2.48	£48,291h	£15,544,691
CTC	£710,146	-£100,250	814.38	0.13	Dominant	£15,577,388

Upon analysis (using the dominance rank method) including all investigations, FOBT is shown to be the most cost-effective investigation (Table 12).

Table 12: Dominance rank for all investigations

	Costs		QALYs		ICER	NMB
Investigation	Total	Incr	Total	Incr		
FOBT	£343,244	-	809.99	-	-	£15,856,582
Barium enema	£365,818	£22,575	810.94	0.95	£23,730	£15,853,033
Flexible Sigmoidoscopy	£690,542	£347,298	811.76	1.77	£196,176	£15,544,691
CTC	£710,146	£366,903	814.38	4.39	£83,664	£15,577,388
Colonoscopy	£810,397	£467,153	814.24	4.25	£109,860	£15,474,474

The results of the dominance rank are also presented in Figure 4. It demonstrates that the ICER between FOBT and Barium Enema is higher than the CE threshold of £20,000 per QALY.

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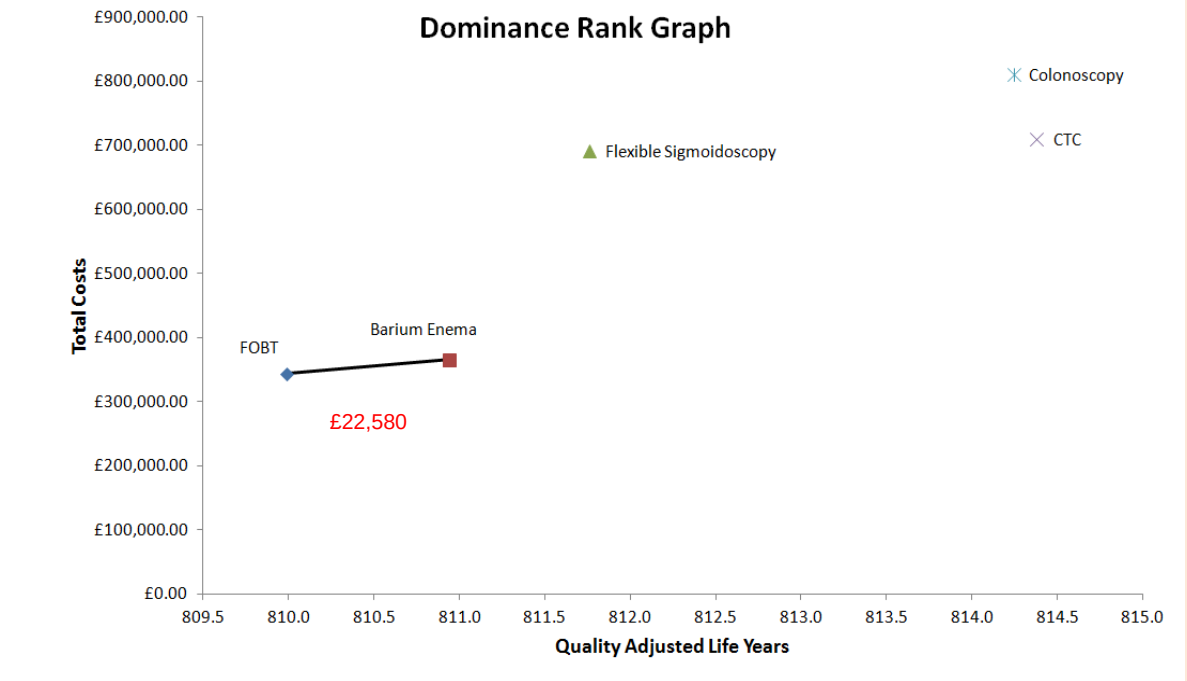
h When incremental QALYs & Costs are negative anything above the CE threshold (£20,000 per QALY) is cost-effective

Figure 5: Dominance Rank for all investigations



A.4.9 One-way sensitivity analysis results

A series of one-way sensitivity analyses were conducted, whereby the value of one input parameter is changed and its effect on the overall outcome is recorded and assessed. The tables below shows the results of a range of one-way sensitivity analyses that were conducted. Part 1 (Table 13) focuses on none- test specific parameters (lifetime costs, age, QoL etc); Part 2 (Table 14) focuses on changing parameters associated with FOBT and barium enema. This includes using data from a recent large multi centre trial on CTC versus barium enema for the diagnosis of colorectal cancer (Halligan et al 2013).

The results of the analysis show that small changes in prevalence, cost and diagnostic accuracy result in barium enema becoming the most cost-effective test. The discount rate also has an effect on the overall result however no other parameter resulted in a change to the overall results.

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Table 13: One Way Sensitivity Analysis Results Part 1

Parameter	Change Made	Most Cost Effective Test
Prevalence	Prevalence = 3.0%	Barium enema
	Prevalence = 5.0%	Barium enema
Age	50 years	FOBT
	60 years	FOBT
Lifetime cost of Dukes A	Lower 95% CI= £6166.00 Upper 95% CI = £10276.00	FOBT
Lifetime cost of Dukes B	Lower 95% CI= £10397.00 Upper 95% CI = £17329.00	FOBT
Lifetime cost of Dukes C	Lower 95% CI= £16821.00 Upper 95% CI = £28036.00	FOBT
Lifetime cost of Dukes D	Lower 95% CI= £11193.00 Upper 95% CI = £18656.00	FOBT
Probability of undetected	Lower 95% CI = 0.57	FOBT

Parameter	Change Made	Most Cost Effective Test
CRC Dukes A – B	Upper 95% CI =0.59	
Probability of undetected CRC Dukes B - C	Lower 95% CI = 0.64 Upper 95% CI =0.67	FOBT
Probability of undetected CRC Dukes C-D	Lower 95% CI = 0.85 Upper 95% CI =0.88	FOBT
QoL	Lower and Upper 95% CI	FOBT
Discount Rate	Lower = 0% Upper = 5%	Barium Enema FOBT

Table 14: Sensitivity Analysis Results Part 2

Investigation	Parameter	Change Made	Most Cost Effective Test
FOBT	Costs	Lower 95% CI = £2.00	FOBT
		Upper 95% CI = £8.00	FOBT
		Increase cost = £8.50	Barium Enema
	Sensitivity	Lower 95% CI = 15%	Barium Enema
		Upper 95% CI = 65%	FOBT
	Specificity	Lower 95% CI = 85%	Barium Enema
		Upper 95% CI = 89%	FOBT
Barium Enema	Costs	Lower 95% CI = £78.16	Barium Enema
		Upper 95% CI = £122.07	FOBT
	Sensitivity	Lower 95% CI = 35%	FOBT
		Upper 95% CI = 61%	Barium Enema
	Specificity	Upper 95% CI = n/a	n/a[i]
		Lower 95% CI = 87%	FOBT
	Sensitivity (Halligan et al 2013)	86%	FOBT
	Specificity (Halligan et al 2013)	79%	FOBT

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A.4.9.1 Scenario Analysis

A scenario analysis was undertaken to examine the effect of modelling an emergency presentation into secondary care for those people who had a false negative result after the initial test (Table 15). The analysis modelled the probability of emergency presentation and the cost of emergency surgery. The results show that even though the cost of emergency surgery was high, because the probability of the occurrence was low it had no overall effect on the results.

Table 15: Emergency presentation scenario analysis

Parameter	Value	Most Cost Effective Test	Reference
Probability of an emergency presentation	0.22	FOBT	Tappenden 2013
Cost of emergency surgery presentation	£7079.93		NHS Reference Cost 2013

i Barium enema specificity is 100% therefore no upper level reported

A further analysis was undertaken to examine the effect of shorter times to diagnosis for false negative patients (Table 16). Modelling this change directly was not possible within the confines of the existing model structure and so the influence of such a change was instead estimated by reducing the probability of progression for patients with undiagnosed CRC such that it reflected a shorter time to diagnosis. The results showed that being diagnosed early also had no overall effect on the results with FOBT still shown to be the most cost-effective test.

Table 16: Time to diagnosis scenario analysis

Parameter	Change Made	Most Cost Effective Test
6 Months to diagnosis	Probability of undetected CRC Dukes A – B = 0.17	FOBT
	Probability of undetected CRC Dukes B – C = 0.21	FOBT
	Probability of undetected CRC Dukes C-D = 0.35	FOBT
2 Months to diagnosis	Probability of undetected CRC Dukes A – B = 0.06	FOBT
	Probability of undetected CRC Dukes B – C = 0.07	FOBT
	Probability of undetected CRC Dukes C-D = 0.14	FOBT

A.4.10 Faecal immunochemical tests and safety netting analysis

In addition to the main analysis, the GDG wanted to explore the use of newer faecal occult blood tests. Faecal immunochemical tests (FIT) are similar to guaiac based FOBT in their design and sample collection however FIT detects globin in stool samples rather than heam. FIT has been associated with a higher sensitivity and specificity than FOBT.

A literature review was undertaken to ascertain diagnostic accuracy of FIT. One paper was identified in the additional literature review examining the diagnostic accuracy of FIT in a symptomatic population. Oono et al 2010 conducted a retrospective analysis in symptomatic patients and reported sensitivity of 74% and specificity of 86% for colorectal cancer. The results of the additional analysis are presented in Table 17. It is shown that FIT is cost-effective compared to colonoscopy.

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Table 17: FIT compared to Colonoscopy

	Costs		QALYs		ICER	NMB
Investigation	Total	Incr	Total	Incr		
Colonoscopy	£810,397	-	814.24	-	-	£15,474,474
FIT	£377,839	-£432,558	812.34	-1.90	£227,696	£15,869,038

The GDG also wanted to analyse a safety netting strategy for people considered low risk for colorectal cancer. In the previous suspected cancer guidance (CG27) people with a change in bowel habit less than 50 years of age were not included in the recommendations for colonoscopy. To reflect this, a safety net strategy was devised. No relevant evidence was identified on safety netting therefore the GDG defined safety netting as; a referral for colonoscopy if symptoms persist up to 4 weeks from initial presentation. The group estimated that this strategy would be 100% sensitive but only 5% specific. The results of the additional analysis are presented in Table 18. It is shown that safety netting is dominated by colonoscopy. This means it is not cost-effective for this population.

Table 18: Safety netting compared to colonoscopy

Investigation	Costs	QALYs	ICER	NMB

	Total	Incr	Total	Incr		
Colonoscopy	£810,397	-	814.24	-	-	£15,474,474
Safety netting	£855,397	£45,000	814.24	0.00	Dominated	£15,429,474

Figure 6 shows the difference in costs and QALYS of all investigation strategies from the analysis compared to colonoscopy. The red line indicates the CE threshold of £20,000 per QALY gained. It shows all investigations, apart from safety netting, sitting below the cost-effectiveness threshold indicating cost effectiveness.

Figure 6: Cost-effectiveness Plane - All strategies

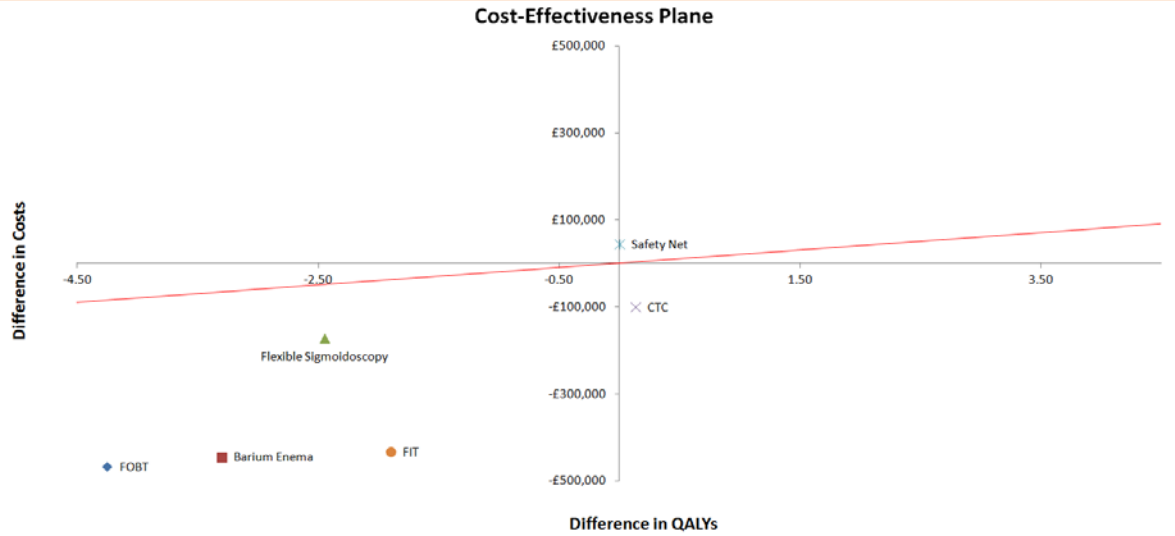

Table 19 uses the dominance rank method to establish the most cost-effective investigation. It is shown that FIT becomes the most cost-effective investigation when compared to all investigations. This is because the sensitivity and specificity of the test is higher than FOBT resulting in more QALYs even though FIT is marginally more expensive. The results also show that safety netting is the most expensive method of investigation due to the additional GP visit and high number of false positives receiving colonoscopy.

Table 19: Dominance rank for all investigations

	Costs		QALYs		ICER	NMB
Investigation	Total	Incr	Total	Incr		
FOBT	£343,244	-	809.99	-	-	£15,856,582
Barium enema	£365,818	£22,575	810.94	0.95	£23,731	£15,853,033
FIT	£377,839	£34,595	812.34	2.35	£14,705	£15,869,038
Flexible Sigmoidoscopy	£690,542	£312,703	811.76	-0.58	Dominated	£15,544,691
CTC	£710,146	£332,308	814.38	2.034	£163,465	£15,577,388
Colonoscopy	£810,397	£432,558	814.24	1.90	£227,696	£15,474,474
Safety net	£855,397	£477,558	814.24	1.90	£251,851	£15,429,474

A.4.11 Probabilistic sensitivity analysis results

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are utilised in the base case are replaced with values drawn from distributions around the mean values (see input tables detailed in above sections for distribution parameters used in analysis).

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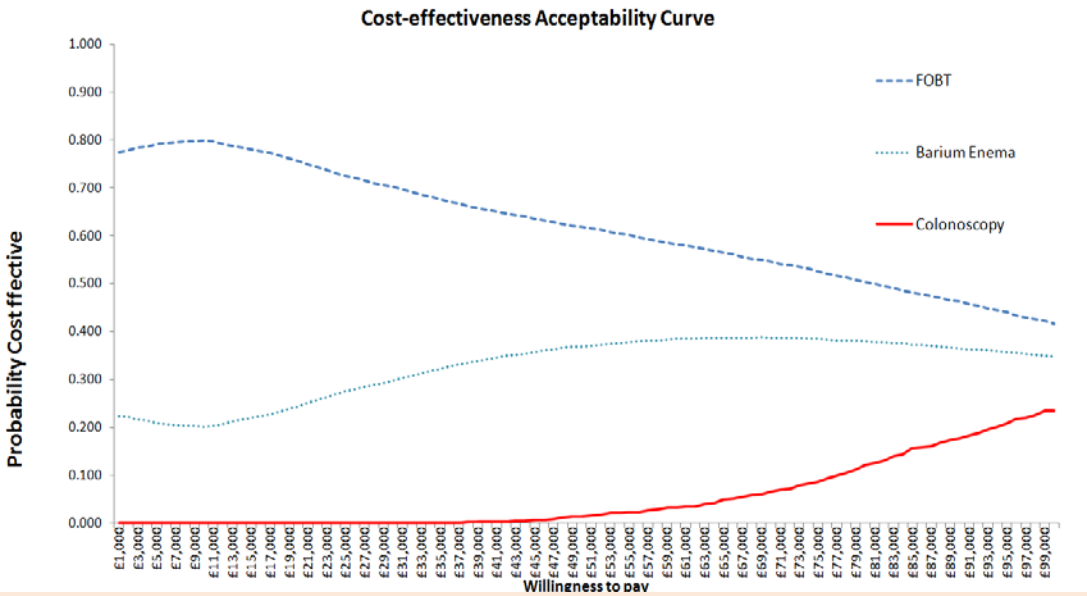
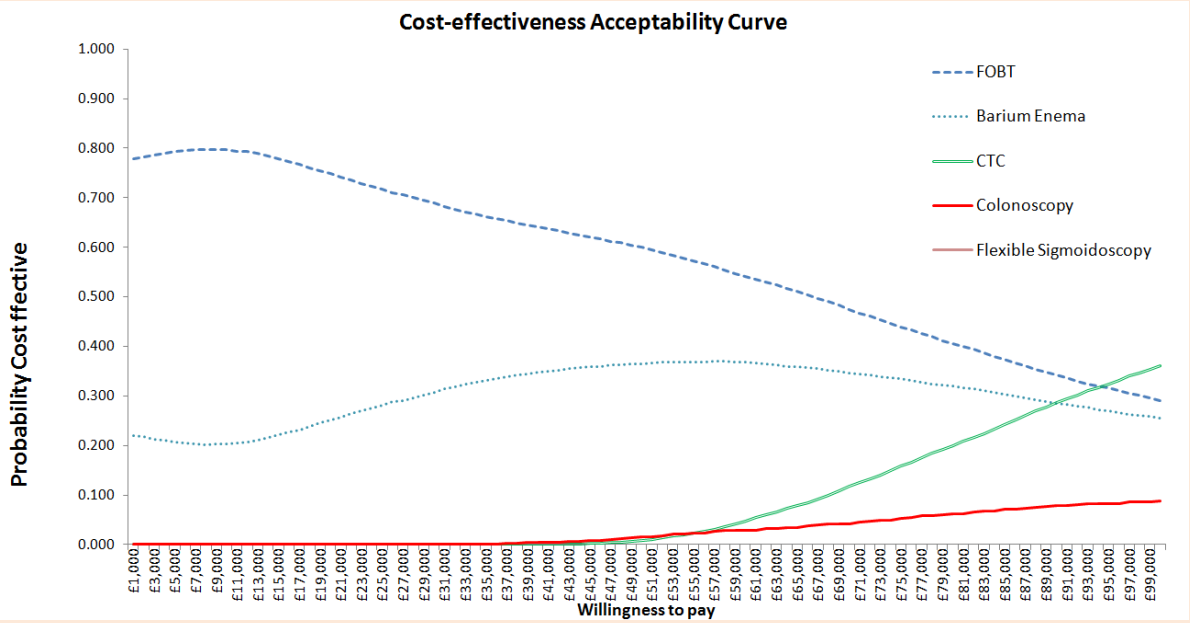
The results of 10,000 runs of the probabilistic sensitivity analysis are shown using a cost-effectiveness acceptability curve (CEAC). The graph shows the probability of each diagnostic strategy being considered cost-effective at the various cost-effectiveness thresholds on the x axis. It can be seen in Figure 7 that at a CE threshold of £20,000 per QALY, FOBT has a high probability of being cost-effective (77%). As the CE threshold increases beyond £20,000 per QALY CTC has a higher probability of being cost-effective.

Figure 7: Cost-effectiveness acceptability curve (CEAC): Base case results



In Figure 8 CTC and flexible sigmoidoscopy are included in the PSA analysis. It is shown that FOBT is still the most cost-effective test and £20,000 per QALY however as the CE threshold increases CTC starts to become more cost-effective.

Figure 8: Cost-effectiveness acceptability curve (CEAC): All included investigations



Further analysis was undertaken to observe the influence of varying prevalence (Figure 9) using a uniform distribution between the reported PPVs (0.02-15.7) from the literature review. The probability of FOBT being the most cost effective test at £20,000 per QALY is greatly

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reduced to 48%. This reflects the wide uncertainty within estimated prevalence for this cohort of people.

Figure 9: Cost-effectiveness acceptability curve (CEAC): Prevalence variation

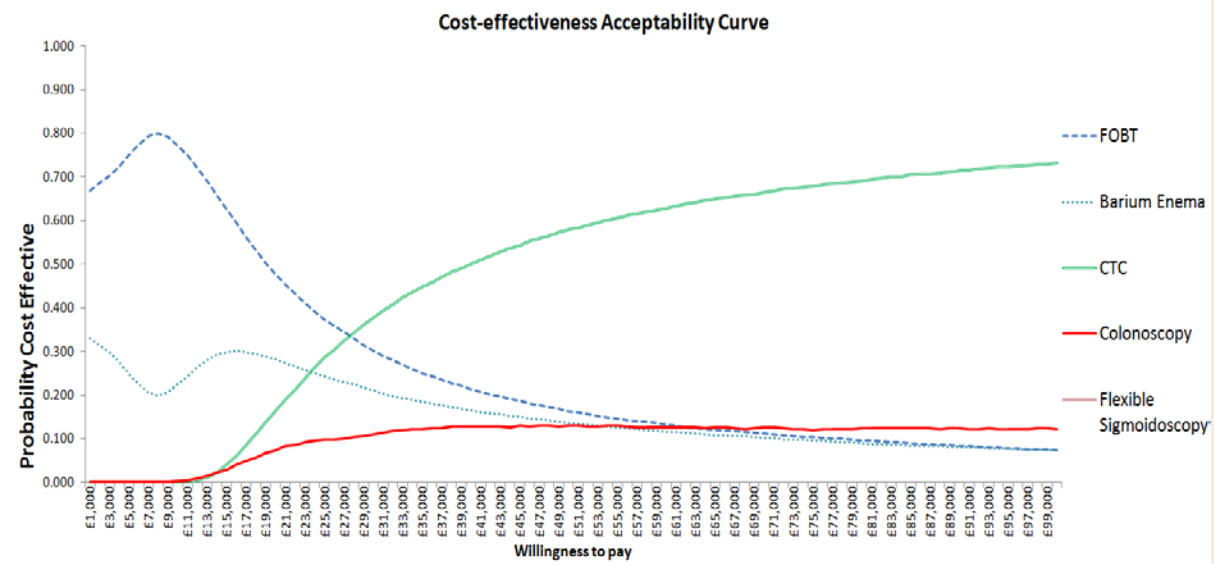
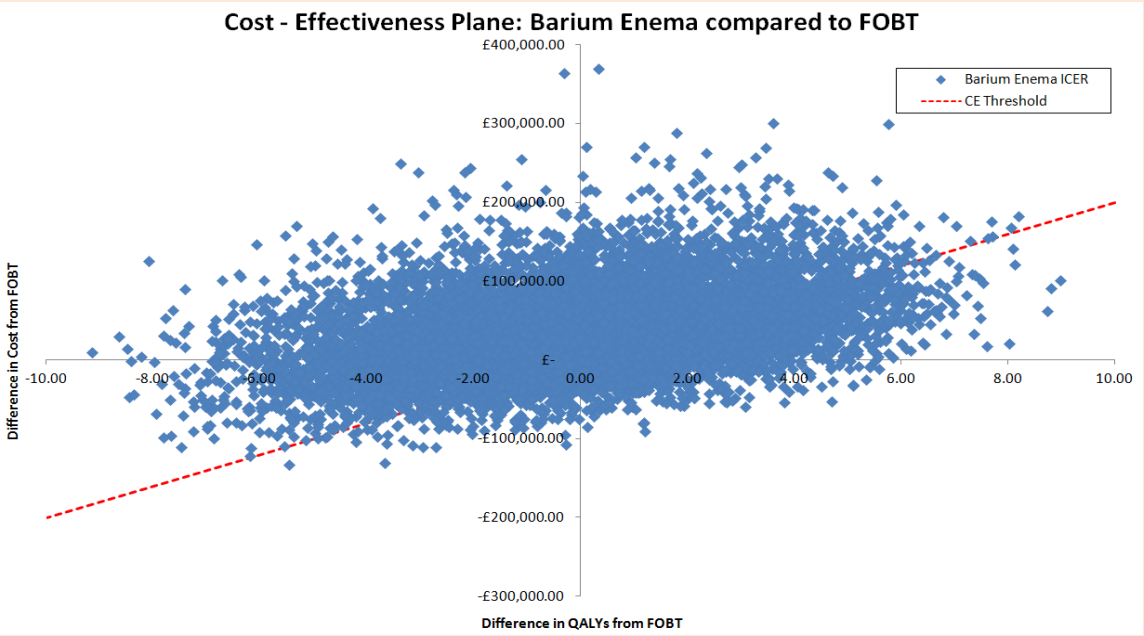


Figure 10 demonstrates the incremental costs and QALYs between barium enema and FOBT. It demonstrates that the majority of incremental costs and QALYs for barium enema compared to FOBT generated in the PSA fall above the cost-effectiveness threshold demonstrating the strength of FOBT cost-effectiveness.

Figure 10: Cost-effectiveness plane: Barium Enema compared to FOBT



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A.4.12 Discussion

This analysis aimed to estimate the cost-effectiveness of diagnostic tests to diagnose colorectal cancer for patients aged 40 years and over with a change in bowel habit in primary care. The base case results of the model suggest FOBT and barium enema are cost-effective compared to colonoscopy in people aged 40 and over with a change in bowel habit. Using a dominance rank, FOBT was found to be the most cost-effective strategy.

The remaining investigations examined in the additional analysis were; CT colonography and flexible sigmoidoscopy. Both were shown to be cost-effective compared to colonoscopy. Upon analysis using the dominance rank method FOBT was again found to be the most cost-effective strategy. The results of the analysis were mainly influenced by sensitivity, specificity, prevalence and costs. Tests with a high specificity reduce the overall cost of the strategy due to the low number of false positives receiving further unnecessary expensive investigations. Tests with high sensitivity increase the overall number of people diagnosed with cancer thus increasing overall QALYs. FOBT was the most cost-effective investigation because of its low cost and moderately high sensitivity and specificity. The increase in cancer diagnosis between FOBT and the next cheapest, more specific investigation (barium enema) was minimal meaning FOBT was more cost-effective than barium enema.

Further analysis included examining the cost effectiveness of FIT and safety netting. FIT was found to be cost-effective compared to colonoscopy. Even though the group being examined in this analysis have a very low probability of colorectal cancer, probably similar to a screening population, the majority of evidence for this investigation is related to asymptomatic people which are outside the scope of this analysis. When comparing FIT against all investigations in the analysis it was shown to be the most cost-effective. FIT sensitivity and specificity is reported as higher than FOBT but it is only marginally more expensive meaning it was the most cost-effective test. Safety netting was also examined and the results showed that safety netting is not cost-effective compared to colonoscopy. However the result of this strategy needs to be interpreted with caution as no evidence was found to support the assumptions made.

The results of the one-way sensitivity analysis suggested that the base case results were sensitive to key parameters, these were; sensitivity, specificity, cost and prevalence. However, the probabilistic sensitivity analysis showed that, at a threshold of £20,000 per QALY, the probability of FOBT being the most cost-effective investigation was 76%.

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It should be noted however that there are limitations to the analysis. As with most economic analyses, the analysis is highly dependent upon the data on which it is based. The prevalence of cancer in the population is one such uncertainty. In the base case analysis it was assumed that the prevalence was 1.5%. The guideline group estimated this figure based on the positive predicative value of the symptoms for colorectal cancer reported in the clinical review. The true prevalence is likely to be somewhere within the reported range from the literature. This was explored within the one way and probabilistic sensitivity analysis. The analysis found that as prevalence increases tests which have a higher sensitivity become more cost-effective.

Another uncertainty within the model is the diagnostic accuracy of barium enema. The results of the analysis show that barium enema becomes the most cost-effective test if FOBT price increases beyond its 95% upper confidence interval. Although the study used to inform sensitivity and specificity was deemed suitable for inclusion due to its design and primary care focus other high quality evidence on patients in secondary care show a much lower specificity. This will reduce the likelihood of barium enema becoming the most cost-effective test if the price of FOBT increases.

Furthermore all of the diagnostic accuracy values included in the model were associated with a number of bias and validity issues. Two of the main issues to note relate to the patient selection methods employed, some of which were not clearly consecutive or random and may therefore bias the results. The other issue of concern relate to sub-optimal reference standards, which may influence the results to an unknown extent.

There was also found to be a paucity of quality of life data in this area. This is a common issue in cost-effectiveness evaluations but is nevertheless a significant one. The QoL values applied in the model are all of generally low quality and so the estimated QALYs may not be robustly estimated. However, the model is primarily driven by costs and diagnostic accuracy and the influence of the QoL values is likely to be limited.

Other areas of uncertainty relate to the disease outcome in the model. Colorectal cancer was the only outcome analysed as a consequence of the symptom profile. Other models in this area include adenoma detection which would result in annual colonoscopic surveillance as there is an increased risk of patients with adenomas developing colorectal cancer. However the guideline group felt that patients with adenomas would not necessarily present with a change in bowel habit therefore it would be inappropriate to link these symptoms to the outcomes of interest.

A.4.13 Conclusion

The results of the analysis suggest that faecal occult blood testing is cost-effective to detect colorectal cancer in people aged 40 years and older with a change in bowel habit in primary care. Barium enema, flexible sigmoidoscopy and computed tomography colonography were all found to be cost-effect compared to colonoscopy however FOBT was the most cost effective for this low risk population.

A.4.14 References

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Appendix B: Abbreviations

CI	Confidence Interval
CT	Computed Tomography
FNA	Fine Needle Aspiration
GDG	Guideline Development Group
ICER	Incremental Cost Effectiveness Ratio
LETR	Linking Evidence to Recommendations
NPV	Negative Predictive Value
PPV	Positive Predictive Value
PSA	Prostate-specific antigen
QALY	Quality Adjusted Life Years
QADAS	Quality Assessment of Diagnostic Accuracy Studies

Update 2015

Appendix C: Glossary

Acid Reflux
A condition where acid from the stomach flows back into the oesophagus (gullet)

Anaemia
An abnormally low haemoglobin in the blood.

Axilla
The underarm area. It contains several nerves, blood vessels and other structures

Barium enema
An x-ray examination where a substance containing barium, which appears white on x-rays, is given as an enema so that the outline of the bowel can be seen more clearly.

Barium swallow
An x-ray examination where a substance containing barium, which is white on x-rays, is swallowed so that the oesophagus (gullet) and stomach can be seen more clearly.

Barrett's oesophagus
This is a condition where the lining of the lower oesophagus(gullet) changes. This may make oesophageal cancer more likely in the future.

Benign
Non-cancerous. Does not metastasise (spread to other organs) and treatment or removal is usually curative.

Benign prostatic hyperplasia
A non-cancerous condition, common in older men, where the prostate gland enlarges. It can affect the flow of urine and lead to urinary symptoms.

Bias
Influences on a study that can lead to invalid conclusions about a treatment or intervention. Bias in research can make a treatment look better or worse than it really is. Bias can even make it look as if the treatment works when it actually doesn't. Bias can occur by chance or as a result of systematic errors in the design and execution of a study. Bias can occur at different stages in the research process, e.g. in the collection, analysis, interpretation, publication or review of research data.

Bilateral
On both the left and the right sides of the body

Biopsy
Removal of a sample of tissue from the body to assist in diagnosis of a disease.

Blood film
A thin layer of blood put on a microscope slide so that the individual blood cells can be examined

Bone marrow
An organ that exists in the hollow centres of bones and produces blood cells

Bone marrow biopsy
The removal of a sample of bone marrow for examination. This is usually done by putting a needle into the inside of a bone such as the pelvis

Update 2015

Bronchoscopy
An examination where a device is inserted through the nose or mouth into the airways of the lung so that they can be seen directly. A biopsy can be taken.

Cerebellar
Pertaining to the cerebellum, a region of the brain that is involved in coordination and balance

Children
From birth to 15 years

CT Colonography
A test where a CT scanner is used to provide detailed x-ray images of the colon and rectum.

Colonoscopy
An examination where a device is inserted through the anus into the rectum and colon so that they can be seen directly. A biopsy may be taken.

Consistent with
The finding has characteristics that could be caused by many things, including cancer.

Cost benefit analysis
A type of economic evaluation where both costs and benefits of health care treatment are measured in the same monetary units. If benefits exceed costs, the evaluation would recommend providing the treatment.

Cost effectiveness analysis
A type of economic evaluation that compares the costs and benefits of different treatments. In cost-effectiveness analysis benefits are measured in clinical outcome units, for example, additional heart attack prevented, life years gained, etc. When a new treatment is compared with current care, its additional costs divided by its additional benefits is called the cost effectiveness ratio.

Cost utility analysis
A special form of cost effectiveness analysis where benefit is measured in quality adjusted life years. A treatment is assessed in terms of its ability to extend or improve the quality of life.

Cystoscopy
An examination where a device is inserted through the opening of the urethra (urine tube) and into the bladder so that the inside of the bladder can be seen directly. A biopsy may be taken.

Dermatoscopy
An examination with a magnifying instrument so that areas of the skin can be seen more clearly

Digital rectal examination (DRE)
An examination where a gloved finger is inserted into the anus so that nearby structures can be felt.

Direct access
When a test is performed and primary care retain clinical responsibility throughout, including acting on the result.

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Duodenum
The part of the intestine into which the stomach empties.

Dyspepsia
Also known as indigestion, dyspepsia is the feeling of a disturbance of acid levels in the stomach or the oesophagus (gullet). This is often experienced as a burning sensation in the upper abdomen or the chest.

Dysphagia
Pain or difficulty in swallowing, particularly a feeling of food sticking in the gullet

Dysuria
Pain on passing urine

Economic evaluation
Economic evaluation is a comparative analysis of costs and consequences of each alternative in order to provide explicit criteria for making choices.

Endocrine
Relating to the production by organs in the body of hormones that go into the blood stream

Equivocal
A symptom and/or sign that has more than one equally plausible explanation, or in which the explanation is uncertain.

Erectile dysfunction
The inability to develop or maintain an erection of the penis.

Erythrocyte sedimentation rate
A blood test that measures inflammation.

Excision biopsy
The removal of an entire lesion and subsequent examination to assist diagnosis

Exocrine
Relating to the production of substances that are secreted to the outside of the body or into a hollow organ such as the intestine

Evidence based
The process of systematically finding, appraising, and using research findings as the basis for clinical decisions.

Evidence table
A table summarising the results of a collection of studies which, taken together, represent the evidence supporting a particular recommendation or series of recommendations in a guideline.

Gammopathy
An excess production of antibodies, usually of a single type

Haematemesis
Vomiting blood

Haematuria
Blood in the urine

Update 2015

Haemoptysis
Coughing up of blood or of blood-stained sputum.

Health economics
The study of the allocation of scarce resources among alternative health care treatments. Health economists are concerned with both increasing the average level of health in the population and improving the distribution of health.

Hepatitis
Inflammation of the liver. This is often caused by viral infections, alcohol or other poisonous substances or abnormal immune processes.

Hepatosplenomegaly
Enlargement of both the liver and the spleen

Immediate
An acute admission or referral occurring within a few hours, or even more quickly if necessary

Iron deficiency anaemia
An abnormally low haemoglobin in the blood accompanied by reduced iron stores in the body.

Likelihood ratio
This is the chance of someone with a particular cancer, having a particular symptom compared to the chance of someone without the particular cancer, having the same symptom.

Lymph
Almost colourless fluid that bathes body tissues and is carried by lymphatic vessels. It contains cells that help fight infection and disease.

Lymph nodes or glands
Small bean-shaped organs located along the lymphatic system. Nodes filter bacteria or cancer cells that might spread through the lymphatic system and to other parts of the body.

Lymphadenopathy
Enlargement of lymph nodes. This is commonly referred to as “swollen glands” and can affect many sites on the body

Lymphoid leukaemia
A form of blood cancer that affects lymphocytes, a sort of white blood cell.

Myeloid leukaemia
A form of blood cancer that affects granulocytes or monocytes, two sorts of white blood cell

Magnetic Resonance Imaging (MRI)
A special imaging technique used to image internal structures of the body, particularly the soft tissues. An MRI image is often superior to a normal plain x-ray image. Images are very clear and are particularly good for soft tissue, brain and spinal cord, joints and abdomen. These scans may be used for detecting some cancers or for following their progress.

Malignant
Tumours can be malignant or benign. Malignant tumours are cancerous and are likely to spread both locally and to other parts of the body. Benign tumours are not.

Mammography
An x-ray examination of breast tissue

Median sulcus
This literally means “the gully in the middle” and in this guidance refers to the groove on the prostate gland. It can also refer to grooves in other parts of the body.

Melanoma
A melanoma is, in its simplest form, a mole. Melanoma is a cancer of mole cells and is sometimes referred to just as melanoma. This can be a source of confusion.

Mesotheliomas
These are cancers of the lining of the chest cavity (the pleura) or the lining of the abdominal cavity (the peritoneum).

Meta analysis
Results from a collection of independent studies (investigating the same issue) are pooled, using statistical techniques to synthesise their findings into a single estimate of an effect. Where studies are not compatible e.g. because of differences in the study populations or in the outcomes measured, it may be inappropriate or even misleading to pool statistically results in this way.

Metastases
Where a cancer spreads from one part of the body to another, the new growths are known as metastases.

Neuroendocrine
Relating to the nervous system and the hormonal system in the body.

Nocturia
Needing to pass urine during the night.

Nodular melanomas
This is a particularly aggressive form of melanoma. It is generally raised and may have lost its pigmentation.

Nodule
A spherical or near-spherical abnormality in an organ, often seen in the lungs. They may be benign or malignant and can represent metastatic disease.

Non-urgent
The timescale generally used for a referral or investigation that is not considered very urgent or urgent.

Odds Ratio (OR)
The odds of an event among an exposed population to the odds among the unexposed.

Pallor
The appearance of looking pale.

Paraproteins
An excess amount of a single antibody protein

Peritoneal
Relating to the inner lining of the abdomen

Update 2015

Persistent
As used in the recommendations in this guideline refers to the continuation of specified symptoms and/or signs beyond a period that would normally be associated with self-limiting problems. The precise period will vary depending on the severity of symptoms and associated features, as assessed by the health professional.

Petechiae
Small bleeding points within the skin. These are usually multiple.

Pigmented lesion
An area of the skin which is darker than its surrounding skin. A mole is an example.

Plasma cells
The type of white blood cell which produces antibodies

Plasma viscosity
A blood test that measures inflammation

Platelets
The small blood cells involved in stopping bleeding

Pleural
Relating to the inner lining of the chest

Positive predictive value
This is the chance of having the disease when someone has a given symptom. It is generally expressed as a percentage. Positive predictive values are influenced by two main factors: how common the disease is and how predictive the symptom is.

Precursor lesion
An abnormality which is not cancer, but may develop into cancer

Primary care
Primary care covers a range of services provided by GPs, nurses and other health care professionals, dentists, pharmacists and opticians.

Proctoscopy
An examination where a short device is inserted through the anus into the rectum so that they can be seen directly. A biopsy may be taken.

Progressive
Getting worse over time.

Prostate specific antigen (PSA)
A blood test giving an indication of the chance of having prostate cancer

Protein electrophoresis
A test on proteins in the blood that can help to diagnose myeloma

Pruritus
Itch

Quality adjusted life years (QALYS)
A measure of health outcome. QALYS are calculated by estimating the number of years of life gained from a treatment and weighting each year with a quality of life score between zero and one.

Update 2015

Raises the suspicion of
A mass or lesion that has an appearance or a feel that makes the healthcare professional believe cancer is a significant possibility.

Rare
A disease or a cancer that affects fewer than 1 in 2000 people

Recurrent
A symptom and/or sign that resolves then returns.

Regional lymph nodes

Relative risk (RR)
Ratio of the risk of an event among an exposed population to the risk among the unexposed.

Safety netting
The active monitoring in primary care of people who have presented with symptoms. It has 2 separate aspects:
- timely review and action after investigations
- active monitoring of symptoms in people at low risk (but not no risk) of having to see if their risk of cancer changes.

Sarcomas
A particular type of cancer, usually affecting muscles or bones

Sensitivity
In diagnostic testing, it refers to the chance of having a positive test result given that you have the disease. 100% sensitivity means that all those with the disease will test positive, but this is not the same the other way around. A patient could have a positive test result but not have the disease – this is called a 'false positive'. The sensitivity of a test is also related to its 'negative predictive value' (true negatives) – a test with a sensitivity of 100% means that all those who get a negative test result do not have the disease. To judge fully the accuracy of a test, its Specificity must also be considered.

Specificity
In diagnostic testing, it refers to the chance of having a negative test result given that you do not have the disease. 100% specificity means that all those without the disease will test negative, but this is not the same the other way around. A patient could have a negative test result yet still have the disease – this is called a 'false negative'. The specificity of a test is also related to its 'positive predictive value' (true positives) – a test with a specificity of 100% means that all those who get a positive test result definitely have the disease. To judge fully the accuracy of a test, its Sensitivity must also be considered.

Suspected cancer pathway referral
The patient is seen within the national target for cancer referrals (2 weeks at the time of publication of this guideline)

Tenesmus
A sensation of repeatedly or constantly needing to open the bowels

Thrombocytopaenia
A low level of blood platelets (small blood cells involved in stopping bleeding)

Thrombocytosis
A raised level of blood platelets (small blood cells involved in stopping bleeding)

Update 2015

Thrombo-embolism
Thromboses are abnormal blood clots in the veins. These can break off and block the blood flow, especially in the lungs. This is called embolism

Trigger for referral
A symptom or sign that is sufficient to indicate the need for either urgent or non-urgent referral.

Ultrasound
A test that uses sound waves to create images of organs and structures inside your body.

Unexplained
Symptoms or signs that have not led to a diagnosis being made by the healthcare professional in primary care after initial assessment (including history, examination and any primary care investigations).

Upper gastrointestinal endoscopy
An examination where a device is inserted through the mouth and down to the oesophagus (gullet), stomach and duodenum, so that they can be seen directly. A biopsy may be taken.

Urgent
To happen within 2 weeks

Urinary frequency
Passing urine more often than normal

Urinary tract
The organs involved in the production and passing of urine

Very urgent
To happen within 48 hours

Young people
Aged 16–24 years

Appendix D: Guideline Scope

D.1 Guideline scope 2015

D.1.1 Guideline title

Suspected cancer: recognition and management of suspected cancer in children, young people and adults

D.1.1.1 Short title

Suspected cancer

D.1.2 The remit

This is a partial update of 'Referral guidelines for suspected cancer' (NICE clinical guideline 27).

This update is being undertaken as part of the guideline review cycle.

D.1.3 Clinical need for the guideline

D.1.3.1 Epidemiology

There were 309,527 people diagnosed with cancer in the UK in 2008. More than 1 in 3 people will develop some form of cancer in their lifetime.

On average less than 10% of people referred from primary care with suspected cancer are found to have cancer after definitive investigation. The proportion of suspected cancers that are actually diagnosed as cancer varies with the site, from over 50% for prostate cancer to less than 10% for laryngeal cancer. This reflects how specific the initial symptoms, examination findings and GP investigations are for identifying cancer at these two sites.

Cancer diagnosis is difficult, as the symptoms of cancer can also be the symptoms of benign conditions. No diagnostic tests or guidance can achieve 100% sensitivity (identifying all cancers) or 100% specificity (correctly identifying al those without cancer).

Update 2015

D.1.3.2 Current practice

In February 2011 NICE completed its review of 'Referral guidelines for suspected cancer'(NICE clinical guideline 27) and concluded that it needed to be updated. The reasons for this include the publication of new evidence since 2005 on signs and symptoms associated with a range of cancer types and new evidence on initial investigation. Also stakeholders highlighted a variation in the level of implementation of the recommendations and a desire for a more symptom-based guideline.

Other reasons why the original clinical guideline has not proved to be as successful as was hoped include the following:

- The symptoms of cancer are very common in primary care and usually due to non-cancer diagnoses (for example, less than 5% of people with symptoms of haemoptysis have lung cancer).
- Many people with suspected cancer are referred from primary care to secondary care using the criteria set out in 'Referral guidelines for suspected cancer' (NICE clinical guideline CG27). However this guideline was structured around cancer type rather than presenting signs and symptoms so the guideline user had to first think in terms of cancer,

then consider the site and finally compare the person's symptoms with those in the guideline.

The Department of Health Cancer Reform Strategy, published in December 2007, highlighted that cancer survival in England compares poorly with that of comparable countries. One reason for this is that symptomatic patients in England are believed to present to the health service when their disease is more advanced, which has an impact on the potential for successful treatment, on patient outcomes, and on resources.

Based on analyses of 5-year survival rates in Europe, it has been estimated that up to 10,000 deaths could be avoided per year in England if the best survival rates in Europe were achieved.

The Department of Health initiative on early diagnosis of cancer –The National Awareness and Early Diagnosis Initiative (NAEDI) –aims to enable health professionals to diagnose cancer earlier. It does this through:

- public awareness campaigns, so that people become more aware of cancer symptoms
- GP developments to improve quality, such as the national cancer GP diagnosis audit
- improving GP access to diagnostic investigations, such as scans
- research including international comparisons.

The updated clinical guideline will support NAEDI, and will be structured around the symptoms that patients present with, which complements the public awareness work of NAEDI.

Because the likelihood of cancer is low for individual symptoms, this guideline will advise on symptom clusters. In addition, there will be advice on 'safety netting' when the initial evidence for immediate referral is inadequate.

New evidence on cancer risk based on symptom clusters should allow the development of a more practical guideline that will aid rapid diagnosis of people with suspected cancer.

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D.1.4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, 'Further information').

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections.

D.1.4.1 Population

Groups that will be covered

- Children (from birth to 15 years), young adults (aged 16–24 years) and adults (aged 25 years and over) presenting to primary care with signs or symptoms of suspected cancer.
- Subgroups that are identified as needing specific consideration will be considered during development but may include:
  - older people
  - people with cognitive impairment
  - people with multiple morbidities
  - people from lower socioeconomic groups.

Groups that will not be covered

- People who have been referred to secondary care for specialist management.
- People who present for the first time outside of the primary care setting.

D.1.4.2 Healthcare setting

All primary care settings in which NHS care is delivered. This includes general practice, NHS dental services, community pharmacies and opticians carrying out NHS work.

D.1.4.3 Clinical management

Key clinical issues that will be covered

The intention is to produce a guideline structured around signs and symptoms that should prompt consideration of the likelihood of cancer in a person presenting to NHS staff in primary care.

Areas from the original guideline that will be updated

- Cancer in children and young people.
- The initial investigations that contribute to the assessment of patients prior to, or in association with, referral for suspected cancer, where clinical responsibility is retained by primary care.
- Immediate referral to secondary care using the existing fast-track (2-week wait) referral system.
- Signs and symptoms that indicate the possibility of a cancer diagnosis, including:
  - abdominal distension
  - abdominal pain
  - abnormal bleeding (including, haemoptysis, haematuria, gastrointestinal and vaginal bleeding)
  - appetite loss
  - bone or skeletal pain
  - breast signs and symptoms
  - changing skin lesions
  - chest wall or rib pain
  - confusion
  - constipation
  - cough
  - diarrhoea
  - dysphagia
  - dyspnoea
  - epigastric pain (including dyspepsia)
  - fatigue
  - focal neurological signs
  - headache
  - heartburn
  - hoarseness
  - imbalance
  - infections suggesting immunocompromise
  - jaundice

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  - lower urinary tract symptoms
  - lumps (including breast, neck, abdominal, bony and soft-tissue masses, unexplained lymphadenopathy)
  - pain at multiple sites
  - pathological fracture
  - pelvic mass
  - pelvic pain
  - persistent mouth ulceration
  - personality disturbance
  - seizures
  - shortness of breath
  - thromboembolism
  - visual disturbance
  - vomiting
  - weight loss.
- Abnormal blood test results that indicate the possibility of a cancer diagnosis, including:
  - anaemia
  - abnormal liver function tests
  - hypercalcaemia
  - raised levels of inflammatory markers
  - thrombocytosis.
- Information needs of:
  - patients who are referred for suspected cancer, and their family and carers
  - patients who are being monitored in primary care, and their family and carers.

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Areas not in the original guideline that will be included in the update

- Follow-up plans (including 'safety-netting') for patients whose care is managed in primary care without referral for definitive investigation.

Areas in the original guideline that will not be updated but will appear in the final guideline

- The diagnostic process (recommendations 1.2.5–1.2.12).

Clinical issues that will not be covered

- The organisation or effectiveness of screening programmes for cancer.
- Referral for suspected recurrence or metastases in previously diagnosed cancer, or referral for palliative care.

D.1.4.4 Main outcomes

- Health-related quality of life.
- Sensitivity of symptoms/signs and diagnostic tests
- Specificity of symptoms/signs and diagnostic tests
- Positive predictive value of symptoms/signs and diagnostic tests
- Negative predictive value of symptoms/signs and diagnostic tests

D.1.4.5 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see 'Further information').

D.1.4.6 Status

Scope

This is the final scope.

Timing

- The development of the guideline recommendations will begin in June 2012.

D.1.5 Related NICE guidance

D.1.5.1 Published guidance

NICE guidance to be updated

This guideline will update and replace the following NICE guidance:

- Referral guidelines for suspected cancer (NICE clinical guideline 27 (2005).

Depending on the evidence reviewed, this guideline may update and replace parts of the following NICE guidance:

- Lung cancer. NICE clinical guideline 121 (2011). (Recommendations 1.1.1–1.1.6)

NICE guidance to be incorporated

This guideline will incorporate parts of the following NICE guidance:

- Ovarian cancer. NICE clinical guideline 122 (2011). (Recommendations 1.1.1.1–1.1.1.5 and 1.1.2.1–1.1.2.4).

Other related NICE guidance

- Ovarian cancer. NICE quality standard (2012)
- Lung cancer for adults. NICE quality standard (2012)Patient experience in adult NHS services. NICE clinical guideline 138. (2012).
- Breast cancer. NICE quality standard (2011)
- Colorectal cancer. NICE clinical guideline 131 (2011).
- Colonoscopic surveillance for prevention of colorectal cancer in people with ulcerative colitis, Crohn's disease or adenomas. NICE clinical guideline 118 (2011).
- Metastatic malignant disease of unknown primary origin. NICE clinical guideline 104 (2010).
- Lower urinary tract symptoms. NICE clinical guideline 97 (2010).
- Improving outcomes for people with skin tumours including melanoma. NICE cancer service guidance (2010).
- Advanced breast cancer. NICE clinical guideline 81 (2009).

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- Early and locally advanced breast cancer. NICE clinical guideline 80 (2009).
- Metastatic spinal cord compression. NICE clinical guideline 75 (2008).
- Improving outcomes for people with skin tumours including melanoma. NICE cancer service guidance (2006).
- Improving outcomes for people with brain and other CNS tumours. NICE cancer service guidance (2006).
- Improving outcomes for people with sarcoma. NICE cancer service guidance (2006).
- Improving outcomes in children and young people with cancer. NICE cancer service guidance (2005).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).
- Improving outcomes in head and neck cancers. NICE cancer service guidance (2004).
- Improving outcomes in colorectal cancer. NICE cancer service guidance (2004).
- Improving outcomes in haematological cancers. NICE cancer service guidance (2003).
- Improving outcomes in urological cancers. NICE cancer service guidance (2002).
- Improving outcomes in breast cancer. NICE cancer service guidance (2002).
- Guidance on commissioning cancer services: improving outcomes in lung cancer: the manual. Department of Health (1998).Available from: www.dh.gov.uk
- Improving outcomes in gynaecological cancers. Cancer service guidance (1999). Department of Health, National Cancer Guidance Steering Group.http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4005385
- Improving outcomes in upper gastro-intestinal cancers. Cancer service guidance (2001). Department of Health.http://www.dh.gov.uk/en/Publicationsandstatistics/Publications/PublicationsPolicyAndGuidance/DH_4010025

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D.1.5.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Neutropenic sepsis. NICE clinical guideline. Publication expected August 2012.
- Familial breast cancer (update). NICE clinical guideline. Publication expected April 2013.
- Prostate cancer (update). NICE clinical guideline. Publication date to be confirmed.
- Bladder cancer. NICE clinical guideline. Publication date to be confirmed.

D.1.6 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- ‘How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS’
- ‘The guidelines manual'.

Information on the progress of the guideline will also be available from the NICE website.

D.2 Guideline scope 2005

D.2.1 Guideline title

Referral guidelines for suspected cancer.

D.2.1.1 Short title

Referral guidelines for suspected cancer.

D.2.2 Background

The Institute's clinical guidelines will support the implementation of National Service Frameworks (NSFs) in those aspects of care where a Framework is to be published. The statements in each NSF reflect the evidence that was available at the time the Framework was prepared.

The National Institute for Clinical Excellence ('NICE' or 'the Institute') has commissioned the National Collaborating Centre for Primary Care to develop referral guidelines for suspected cancer for use in the NHS in England and Wales. This follows referral of the topic by the Department of Health and Welsh Assembly Government. The guideline will provide recommendations for good practice that are based on the best available evidence of clinical and cost effectiveness.

The guideline will be an update of previously published guidelines,(2) following a commitment in the NHS Cancer Plan that these guidelines would be reviewed by NICE. The new guideline will take account of new research evidence and the findings of audits undertaken since the publication of the previous guideline.

Both the Department of Health and the Welsh Assembly Government have introduced policies on the urgent referral of patients with suspected cancer.

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D.2.3 Clinical need for the guideline

Cancer was responsible for a quarter of all deaths in England and Wales in 1997, and for over half of all deaths among women between 45 and 55 years of age.(7) The incidence of new cases of cancer increased by 12% in males and 28% in females between 1960 and 1997. For some cancers, mortality rates in the UK compare unfavourably with those in other countries.

Delays of three to six months between the onset of symptoms and diagnosis are associated with worse survival rates in breast cancer.(8) However, evidence about the influence of relatively short delays in other cancers is less clear. The initial symptoms of some cancers can be difficult to distinguish from the symptoms of other more common disorders,(9) and delays can occur between the first presentation and referral for suspected cancer. In a study of the time between presentation and treatment of six common cancers in general practice, the median number of days between presentation of the first symptom or sign and initiation of referral was 0 days for breast, 28 days for large bowel, 31 days for lung, 84 days for oesophageal, 20 days for prostate and 66 days for stomach cancer.(10)

Survival rates for some cancers are lower than elsewhere in Europe, and patients in the UK may have more advanced disease at the time of diagnosis or treatment.(11;12)

D.2.4 The guideline

The guideline development process is described in detail in three booklets that are available from the NICE website (see 'Further information').

The Guideline Development Process – Information for Stakeholders describes how organisations can become involved in the development of a guideline. This document is the scope. It defines exactly what this guideline will (and will not) examine, and what the guideline developers will consider. The areas that will be addressed by the guideline are described in the following sections.

D.2.5 Population

D.2.5.1 Groups and categories that will be covered

Patients in all age groups suspected of having one of the cancers covered by the guideline will be included.

The guideline will cover the following cancers:

- lung
- upper gastrointestinal cancers
- lower gastrointestinal cancers
- breast cancer
- gynaecological cancers
- urological/renal cancers
- haematological malignancies
- skin cancers
- head and neck including oral cancers
- brain/central nervous system malignancies
- sarcomas
- children's and young people's malignancies.

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D.2.5.2 Groups and categories that will not be covered

The guideline will not cover:

- the organisation or effectiveness of screening schemes for cancer
- the tests undertaken after referral, therefore definitive diagnosis will not be covered
- referral for suspected recurrence or metastases in previously
- diagnosed cancer, or referral for palliative care.

D.2.6 Healthcare setting

- The guideline will cover the care received from primary healthcare professionals who have direct contact with, and make decisions concerning, the referral of people with suspected cancer.
- The guideline will address care in primary care prior to referral for specialist assessment, but will not address care after referral in secondary and tertiary centres.
- The guideline will also be relevant to healthcare professionals in secondary care who suspect a patient they are managing for another condition also has cancer, and in whom referral to another specialist would be indicated.
- The guideline will also be relevant to the work, but will not cover the practice, of those working in:
  - accident and emergency departments
  - walk-in centres
  - NHS Direct

- voluntary sector
- occupational health
- other health professionals who may encounter patients with symptoms of cancer, for example allied health professionals, dentists, clinicians in secondary care and pharmacists.

D.2.7 Clinical management

The guideline will address:

- the symptoms, signs and other factors that should prompt consideration of the need for referral, taking into account variation in risk by age and ethnic group
- the initial investigations that contribute to the assessment of patients prior to, or in association with, urgent referral for suspected cancer
- interventions intended to help healthcare professionals appropriately identify patients needing urgent referral for suspected cancer
- the need for urgent referral, and the consequences of delay in referral
- the information and support needs of patients who are referred for suspected cancer and their families
- the monitoring of patients after referral but before the first specialist assessment will be considered in the guideline

D.2.8 Audit support within guideline

The guideline will include review criteria and advice.

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Appendix E: People and organisations involved in production of the guideline

E.1 Members of the 2015 Guideline Development Group

GDG Chair	
Dr Steve Hajioff[j]	Consultant in Public Health Medicine, London
Dr Orest Mulka[k]	Retired General Practitioner
GDG Lead Clinician	
Professor Willie Hamilton	Professor of Primary Care Diagnostics, University of Exeter
Group Members	
Lay member [l]	Patient/carer member
Nicki Doherty	Lead Cancer Manager Rotherham NHS Foundation Trust[m], General Manager, Barnsley NHS Foundation Trust[n]
Dr Jeanne Fay	General Practitioner, Oxford
Susan Hay	Patient/carer member
Dr Georgios (Yoryos) Lyratzopoulos	Senior Clinical Research Associate/Honorary Consultant in Public Health, Department of Public Health and Primary Care, University of Cambridge[o] Clinical Reader in Cancer Epidemiology, University College London; Senior Clinical Research Associate, University of Cambridge[p]
David Martin	Patient/carer member
Dr Joan Meakins	General Practitioner, York
Dr Richard Osborne	Consultant Medical Oncologist, Dorset Cancer Centre[q]
Dr Euan Paterson	General Practitioner, Glasgow
Dr Liliana Risi	General Practitioner, London
Dr Karen Sennett	General Practitioner, London
Dr Lindsay Smith	General Practitioner, Somerset
Dr Stuart Williams	Consultant Radiologist, Norfolk & Norwich University Hospital

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[j] September 2013 - present
[k] January 2012 – June 2013
[l] June 2012 – March 2013
m January 2012 – June 2013;
n November 2013 - present
o January 2012 – February 2015)
p March 2015 - present
[q] Chaired meeting 23 & 24 July 2013

Declarations of interest

GDG member	Interest declared	Type of interest	Decision taken
Steve Hajioff	Medical director of a charity that promotes testicular self examination in young men.	Personal non-pecuniary	Declare and can participate in discussions on all topics as testicular self examination is not being investigated by the guideline.
Steve Hajioff	Member of NICEs accreditation advisory committee.	Personal non-pecuniary	Declare and can participate in discussion of all guideline topics.
Steve Hajioff	Appointed Medical Director for Totally PLC. Provider of shared decision making resources and health coaching in Europe.	Personal pecuniary, specific	Declare and will need to withdraw from discussion of any topics which include shared decision tools.
Orest Mulka	Lecture at a MacMillan GP Conference on the scope of the guideline.	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Chief medical officer for Exeter Friendly Society, LV and Friends Life. Assesses complex insurance applications and claims.	Personal pecuniary, non-specific	Declare and can participate in discussion of all guideline topics unless the chair dictates otherwise. Insurance companies not included in the health industry.
Willie Hamilton	Research grant received from Macmillan to support research activities into pathways towards diagnosis for lung, colon and pancreatic cancers.	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Research grant from CRUK: Continuity And Detection Of Cancer in Primary Care (CADOC-PC).	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Research grant from RfPB: Long term outcome in giant cell arteritis	Non-personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry and giant cell arteritis is not being investigated by the

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GDG member	Interest declared	Type of interest	Decision taken
			guideline.
Willie Hamilton	Research grant from CRUK: Improved lung cancer identification by targeted chest X-ray (CXR) – a clinical trial looking at the effect on lung cancer diagnosis of giving a CXR to smokers aged over 60 with chest symptoms.	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Funded by CRUK to undertake a systematic review of the risk of cancer posed by symptoms reported to primary care, for oesophagus, stomach, uterine and cervical cancers.,	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Research grant from CRUK: ColoRectal Early Diagnosis: Information Based Local Evaluation (CREDIBLE).	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Policy Research Unit in Cancer awareness, screening and early diagnosis. Funded by the Department of Health.	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	NIHR Programme Grant: Optimising diagnosis of symptomatic cancer.	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	NIHR School for Primary Care Research (NSPCR). Using a participant-completed questionnaire to identify symptoms that predict lung cancer: a feasibility study.	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	NIHR HTA :The role of ultrasound compared to biopsy of temporal arteries in the diagnosis and treatment of giant cell arteritis	Non-personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Glaxo Smith Kline shareholder	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as

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GDG member	Interest declared	Type of interest	Decision taken
			guideline is not investigating any interventions made by GSK
Willie Hamilton	Member and GP of the Cancer Diagnostic Advisory Board: re-design of GP access to diagnostics. Two of its subcommittees: Cancer Data Project Board - establish nationwide database of cancer diagnostic activity and help DoH write guidance for enhanced GP access to cancer diagnostic tests. No fee received. Reimbursed for travel expenses.	Personal pecuniary, non-specific	Declare and can participate in all discussions as expenses not beyond reasonable amounts
Willie Hamilton	Published Risk Assessment Tools for lung, colon, ovary, prostate, pancreas, and brain. These are charts detailing the risk of cancer in symptomatic patients. The National Cancer Action Team has piloted the use of lung and colon tools, and has disseminated them widely within the English NHS. The tools have been provided free.	Non-personal pecuniary, specific	Declare and can participate in discussions on all topics as risk assessment tools are not being investigated by the guideline.
Willie Hamilton	Commissioned by the BMJ to write an article on ‘easily missed: colorectal cancer’.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as article is based on the available evidence.
Willie Hamilton	Research grant from Macmillan: metastatic cancer symptoms	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Research grant from CRUK: OGRE –the use of risk assessment tools for suspected oesophago-gastric cancer.	Non-personal pecuniary, non-specific	Declare and can participate in discussions on all topics as risk assessment tools are not being investigated by the guideline.
Willie Hamilton	Research grant from	Non-personal	Declare and can

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GDG member	Interest declared	Type of interest	Decision taken
	CRUK: BODYSHOP – researching symptom profiles of bowel disease in young people.	pecuniary, specific	participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Research grant from CRUK: Breast cancer awareness measures	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Research grant from CRUK: ABCDEEP – creating a league table of cancers where symptomatic diagnosis is of value in terms of mortality.	Non-personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Commissioned by the BMJ to write an article on 'diagnosis of bladder cancer in women'.	Personal, non-pecuniary	Declare and can participate in discussions on all topics as article is based on the available evidence.
Willie Hamilton	Invited by the DoH to become a member of an evaluation team for the reconfiguration for delivery of cancer diagnostic services; named as a grant holder.	Non-personal pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Willie Hamilton	Awarded a grant by the DoH to look into cancer outcomes following primary care identification of thrombocytosis.	Non-personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry and the guideline does not investigate thrombocytosis in isolation.
Willie Hamilton	Consultancy with a German firm MedX, to provide information on diagnostic software (with a focus on abdominal pain, rather than cancer).	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as diagnostic software is not being investigated by the guideline.
Lay member	Received honorarium for being a member of the group creating peer review measures for hepatobiliary cancers.	Personal pecuniary, non-specific	Declare and can participate in discussion on all topics as the guideline is not looking at service configuration for hepatobiliary cancers.
Lay member	Invited to provide editorial comment on	Personal pecuniary,	Declare and can participate in

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GDG member	Interest declared	Type of interest	Decision taken
	the pancreatic measures during December 2012 as a member of the Peer Review Measures Group for HPC cancers.	non-specific	discussion on all topics as no comments were made on issues relating to the guideline
Nicki Doherty	None declared		
Jeanne Fay	Lead primary care physician in a NAEDI 4 bid investigating ovarian cancer recognition in the Milton Keynes area.	Non-personal pecuniary, non-specific	Declare and can participate in discussion of all guideline topics as this guideline will not be investigating ovarian cancer.
Jeanne Fay	NAEDI project for GP practices to audit selected 2 week wait referrals and emergency cancer diagnoses.	Non-personal pecuniary, non-specific	Declare and can participate in discussion of all guideline topics as not funded by the healthcare industry.
Susan Hay	Appointed chairman of the Neuroblastoma Society	Personal pecuniary, specific	Declare and can participate in discussion on all topics as recommendations for neuroblastoma had been agreed before this appointment.
Susan Hay	Asked to join a Steering Group for a trial looking at bevacizumab and chemotherapy for children and young people with neuroblastoma (BEACON – Neuroblastoma)	Personal non-pecuniary	Declare and can participate in discussion on all topics as the guideline is not investigating the treatment of neuroblastoma.
Georgios (Yoryos) Lyratzopoulos	Research grant from CRUK: ABC-DEEP project (co-applicant) involving literature review, horizon scanning and a modelling study of relevance to early diagnosis research	Non-personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Georgios (Yoryos) Lyratzopoulos	Academic in the field of early diagnosis epidemiology. Postdoctoral fellowship by the NIHR on a related subject 2012-2014.	Personal non-pecuniary, specific	Declare and can participate in discussion on all guideline topics as not funded by the healthcare industry.
Georgios (Yoryos) Lyratzopoulos	Research grant from the National Awareness and Early Diagnosis Initiative 3rd	Personal non-pecuniary, specific	Declare can participate in discussion on all guideline topics as not funded by the

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GDG member	Interest declared	Type of interest	Decision taken
	funding call. "What is driving general practice variation in 'two-week wait' referrals and use of endoscopy and imaging investigations, and does it matter for cancer outcomes?" From August 2014		healthcare industry.
Georgios (Yoryos) Lyratzopoulos	Cancer Research UK Clinician Scientist Fellowship from March 2015	Non-personal pecunicary, non-specific	Declare and can participate in discussion on all guideline topics as fellowship not funded by industry
David Martin	Invited to work with the Royal Pharmaceutical Society to commission future models of care through pharmacy.	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as treatment is not being investigated by the guideline
David Martin	Invited to become a member of the evidence update group for CG138 Patient Experience for which he will receive an honorarium and expenses.	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as the guideline will not be investigating generic patient experience.
David Martin	Is a member of a steering group for research projects for HERG. Has been asked to give a presentation on 'Engagement and inclusivity in researching patients' experiences' at a symposium.	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as the guideline will not be investigating generic patient experience.
David Martin	Has been asked to join a Medicines Optimisation Reference Group.	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as the guideline will not be investigating medicines optimisation.
David Martin	Invited to give a presentation at the INVOLVE Conference on patient perspectives of engagement in research projects..	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as the guideline will not be investigating generic patient experience.
Joan Meakins	Locality lead for York	Non-personal	Declare and can

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GDG member	Interest declared	Type of interest	Decision taken
	PCG raising GP awareness of cancer using signs and symptoms. NAEDI initiative funded by DoH.	pecuniary, specific	participate in discussion on all guideline topics as not funded by the healthcare industry.
Richard Osborne	Received educational grant from Roche to attend ASCO meeting, no specific drug or disease focus.	Personal pecuniary, non-specific	Declare can participate in discussion on all guideline topics as the monies received does not exceed an unreasonable amount
Richard Osborne	Received an educational grant from Bristol Myers Squibb to attend World Melanoma Congress	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as the monies received does not exceed an unreasonable amount.
Richard Osborne	Received an honorarium from Roche for attending an advisory panel on the drug Avastin in ovarian cancer.	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as the guideline will not be investigating treatment of ovarian cancer.
Richard Osborne	Received an honorarium from Pharmar for attending an advisory panel on the drug Trabectedin in ovarian cancer	Personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as the guideline will not be investigating treatment of ovarian cancer.
Richard Osborne	Department received research contribution from Novartis. In return a Novartis pharmaceutical representative attended RJO's colon cancer clinic to gain a wider understanding of patient management. The visit was organised by RJO and did not cover drugs.	Non-personal pecuniary, non-specific	Declare can participate in discussion on all guideline topics as the guideline will not be reviewing any drug treatment.
Richard Osborne	Collaboration work with Portable Medical Technology Limited to develop a self-management app to assist in dealing with acute complications of cancer and chemotherapy.	Non-personal pecuniary, non-specific	Declare and can participate in discussion on all guideline topics as the guideline will not be investigating treatment or side effects of treatment.
Euan Paterson	Shares with GSK as part of a managed portfolio.	Personal pecuniary, nonspecific	Declare and can participate in discussion on all

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GDG member	Interest declared	Type of interest	Decision taken
			guideline topics as shares are part of a managed portfolio
Liliana Risi	None declared		
Karen Sennett	None declared		
Lindsay Smith	None declared		
Stuart Williams	None declared		

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E.2 Organisations invited to comment on the 2015 guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

A Little Wish	Abbott-Gmbh & Co KG
Abbott Molecular	Abbott Molecular UK
Action Cancer NI	Airedale NHS Trust
Alder Hey Children's NHS Foundation Trust	All Wales Dietetic Advisory Committee
Allocate Software PLC	Aneurin Bevan Health Board
Archimedes Pharma Ltd	Association of Anaesthetists of Great Britain and Ireland
Association of Breast Surgery	Association of British Insurers
Association of British Neurologists	Association of Chartered Physiotherapists in Oncology and Palliative Care
Association of Clinical Pathologists	Association of Coloproctology of Great Britain and Ireland
Association of Surgeons of Great Britain and Ireland	Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland
Astrazeneca UK Ltd	Bard Limited
Barnsley Hospital NHS Foundation Trust	Barrett's Oesophagus Campaign
BASO The Association for Cancer Surgery	Baxter Healthcare
Bayer HealthCare	Beating Bowel Cancer
Belfast Health and Social Care Trust	Biohit Healthcare Ltd
BME cancer.communities	Boehringer Ingelheim
Bolton Hospitals NHS Trust	Boots
Bowel Cancer UK	Bradford District Care Trust
Brain Tumour Research	Breakthrough Breast Cancer
Breast Cancer Campaign	Breast Cancer Care
Bristol and Avon Chinese Women's Group	British and Irish Orthoptic Society
British Association for Cytopathology	British Association of Dermatologists
British Association of Oral and Maxillofacial Surgeons	British Association of Oral Surgeons
British Association of Otorhinolaryngologists, Head and Neck Surgeons	British Association of Spinal Surgeons
British Association of Urological Surgeons	British Committee for Standards in Haematology
British Dental Association	British Dietetic Association
British Gynaecological Cancer Society	British Heart Foundation
British Liver Trust	British Lung Foundation
British Medical Association	British Medical Journal
British National Formulary	British Nuclear Cardiology Society
British Nuclear Medicine Society	British Paediatric Neurology Association
British Psychological Society	British Psychosocial Oncology Society
British Red Cross	British Society for Colposcopy and Cervical Pathology
British Society for Oral Medicine	British Society of Paediatric Radiology
British Society of Gastroenterology	British Society of Gastrointestinal and Abdominal Radiology
British Thoracic Society	British Thyroid Foundation

BUPA Foundation	C. R. Bard, Inc.
Calderstones Partnerships NHS Foundation Trust	Cambridge University Hospitals NHS Foundation Trust
Camden Link	Cancer Black Care
Cancer of Unknown Primary	Cancer Research UK
Cancer Services Collaborative Primary Care Lead	Cancer Services Co ordinating Group
Cancer Voices	Cancer52
Caper Research Unit	Capsulation PPS
Capsulation PPS	Cardiff and Vale University Health Board
Care Not Killing Alliance	Care Quality Commission
Central & North West London NHS Foundation Trust	Central London Community Health Care NHS Trust
Central Manchester and Manchester Children's Hospital NHS Trust	Chartered Society of Physiotherapy
Cheshire and Merseyside SCN	Childhood Cancer Parents Alliance
Children's Brain Tumour Research Centre	Children's Cancer and Leukaemia Group
Chronic Lymphocytic Leukaemia Support Association	City Hospitals Sunderland NHS Foundation Trust
Clarity Informatics Ltd	CLIC Sargent
Cochrane Oral Health Group	Community District Nurses Association
ConvaTec Ltd	Covidien Ltd.
Croydon Health Services NHS Trust	Croydon University Hospital
Cumbria Partnership NHS Foundation Trust	CWHHE Collaborative CCGs
Cwm Taf Health Board	Department for Communities and Local Government
Department of Health	Department of Health, Social Services and Public Safety Northern Ireland
DNU Health Protection Agency	Doncaster Council
Dudley PACT Patient Advisory Cancer Team	East and North Hertfordshire NHS Trust
East Kent Hospitals University NHS Foundation Trust	East Lancashire Hospitals NHS Trust
Eisai Ltd	Eli Lilly and Company
Equalities National Council	Ethical Medicines Industry Group
Faculty of Dental Surgery	Faculty of General Dental Practice
Faculty of Public Health	False Allegations Support Organisation
Ferring Pharmaceuticals	Fibroid Network Charity
Five Boroughs Partnership NHS Trust	Galderma
GE Healthcare	General Practice and Primary Care
George Eliot Hospital NHS Trust	Gilead Sciences Ltd
GIST Support UK	GlaxoSmithKline
Gloucestershire LINk	Gorlin Syndrome Group
GP update / Red Whale	Great Ormond Street Hospital
Great Western Hospitals NHS Foundation Trust	Greater Manchester, Lancashire and South Cumbria Strategic Clinical Network
Guerbet Laboratories Ltd	Guy Francis Bone Cancer Research Fund
Health and Care Professions Council	Health and Social Care Information Centre
Healthcare Improvement Scotland	Healthcare Infection Society
Healthcare Quality Improvement Partnership	Healthwatch East Sussex

Heartburn Cancer Awareness support	Help Adolescents With Cancer
Hertfordshire Partnership NHS Trust	Herts Valleys Clinical Commissioning Group
Hindu Council UK	Hiraeth Services Ltd
Hockley Medical Practice	HQT Diagnostics
Hull and East Yorkshire Hospitals NHS Trust	Humber NHS Foundation Trust
Humberside Oesophageal Support Group	Imaging Equipment Ltd
Impact of Neutropenia in Chemotherapy European study group	Imperial College Healthcare NHS Trust
Independent Healthcare Advisory Services	Institute of Biomedical Science
International Brain Tumour Alliance	Intuitive Surgical
IOTA International Ovarian Tumor Analysis group	James Whale Fund for Kidney Cancer
KCARE	Kidney Cancer Support Network
Kidney Cancer UK	Kings College Hospital
Lancashire Care NHS Foundation Trust	Lancashire Teaching Hospitals NHS Trust
Leeds Community Healthcare NHS Trust	Leeds Teaching Hospitals NHS Trust
Leo Pharma	Leukaemia & Lymphoma Research
Leukaemia Cancer Society	Lilly UK
Link Pharmaceuticals	Local Government Association
London Cancer	London cancer alliance
Luton and Dunstable Hospital NHS Trust	Lymphoma Association
Macmillan Cancer Support	Maidstone and Tunbridge Wells NHS Trust
Medical directorate DMS	Medicines and Healthcare products Regulatory Agency
Medway NHS Foundation Trust	Mencap
Mid Staffordshire NHS Foundation Trust	Milton Keynes Hospital NHS Foundation Trust
Ministry of Defence (MOD)	Mole Clinic Ltd, The
Mouth Cancer Foundation	Musculoskeletal Association of Chartered Physiotherapists
Myeloma UK	Myeloma UK
National Association of Primary Care	National Cancer Action Team
National Cancer Intelligence Network	National Cancer Research Institute
National Clinical Guideline Centre	National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health	National Collaborating Centre for Women's and Children's Health
National Deaf Children's Society	National Institute for Health Research Health Technology Assessment Programme
National Institute for Health Research	National Kidney Federation
National Kidney Research Foundation	National Patient Safety Agency
National Public Health Service for Wales	National Radiotherapy Implementation Group
NET Patient Foundation	NHS Barnsley Clinical Commissioning Group
NHS Choices	NHS Clinical Knowledge Summaries
NHS Connecting for Health	NHS County Durham and Darlington
NHS Cumbria Clinical Commissioning Group	NHS Doncaster CCG
NHS Dorset CCG	NHS England
NHS Halton CCG	NHS Hardwick CCG
NHS Health at Work	NHS Horsham and Mid Sussex CCG
NHS Improvement	NHS Medway Clinical Commissioning Group

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NHS Milton Keynes	NHS National Cancer Screening Programmes
NHS North Derbyshire CCG	NHS North Somerset CCG
NHS Pathways	NHS Plus
NHS Sheffield	NHS Somerset CCG
NHS South Cheshire CCG	NHS South Gloucestershire CCG
NHS South Manchester CCG	NHS St Helens CCG
NHS Vale Royal CCG	NHS Wakefield CCG
NHS Wandsworth	NHS Warrington CCG
NHS Warwickshire North CCG	NHS West Cheshire CCG
Norfolk and Suffolk Palliative Care Academy	North and East London Commissioning Support Unit
North East Lincolnshire Care Trust Plus	North of England Commissioning Support
North Staffordshire Cancer Service User Forum	North West London Hospitals NHS Trust
Northern Health and Social Care Trust	Northern Region Endoscopy Group
Nottingham City Council	Nottingham City Hospital
Nottingham University Hospitals NHS Trust	Nottinghamshire Healthcare NHS Trust
Novartis Pharmaceuticals	NS Technomed
Nursing and Midwifery Council	Nutricia Advanced Medical Nutrition
Oesophageal Patients Association	Older People's Advocacy Alliance
Ovacome	Ovarian Cancer Action
Oxford Health NHS Foundation Trust	Oxfordshire Clinical Commissioning Group
Pancreatic Cancer Action	Pancreatic Cancer UK
PERIGON Healthcare Ltd	Peterborough and Stamford Hospitals NHS Foundation Trust
Pfizer	Pharmametrics GmbH
POhWER	Primary Care Pharmacists Association
Primary Care Respiratory Society UK	Primrose Bank Medical Centre
Prostate Cancer UK	Pseudomyxoma Survivor
Public Health England	QResearch
Queen Elizabeth Hospital	Queen Elizabeth Hospital King's Lynn NHS Trust
Queen's Medical Centre Nottingham University Hospitals NHS Trust	Rarer Cancers Foundation
Robert Jones & Agnes Hunt Orthopaedic & District Hospital NHS Trust	Roche Diagnostics
Roche Products	Roy Castle Lung Cancer Foundation
Royal Berkshire NHS Foundation Trust	Royal Brompton Hospital & Harefield NHS Trust
Royal College of Anaesthetists	Royal College of General Practitioners
Royal College of General Practitioners in Wales	Royal College of Midwives
Royal College of Nursing	Royal College of Obstetricians and Gynaecologists
Royal College of Ophthalmologists	Royal College of Paediatrics and Child Health
Royal College of Paediatrics and Child Health , Gastroenetrology, Hepatology and Nutrition	Royal College of Pathologists
Royal College of Physicians	Royal College of Physicians and Surgeons of Glasgow
Royal College of Psychiatrists	Royal College of Radiologists
Royal College of Speech and Language Therapists	Royal College of Surgeons of Edinburgh

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Royal College of Surgeons of England	Royal Cornwall Hospitals NHS Trust
Royal National Institute of Blind People	Royal National Orthopaedic Hospital NHS Trust
Royal Pharmaceutical Society	Royal Society of Medicine
Royal Surrey County Hospital NHS Trust	Royal United Hospital Bath NHS Trust
Royal West Sussex NHS Trust	Sanofi
Sarcoma Information Services Ltd.	Sarcoma UK
Schering Health Care Ltd	School of Health and Population Sciences
Scottish Intercollegiate Guidelines Network	Sheffield Teaching Hospitals NHS Foundation Trust
SNDRi	Social Care Institute for Excellence
Society and College of Radiographers	Society for Cardiothoracic Surgery of Great Britain and Ireland
Society of British Neurological Surgeons	South Asian Health Foundation
South Eastern Health and Social Care Trust	South London & Maudsley NHS Trust
South West Yorkshire Partnership NHS Foundation Trust	Southern Health & Social Care Trust
Southport and Ormskirk Hospital NHS Trust	St Mary's Hospital
Staffordshire and Stoke on Trent Partnership NHS Trust	Step4Ward Adult Mental Health
Stockport Clinical Commissioning Group	Stockport Clinical Commissioning Pathfinder
Sue Ryder	Swindon and Marlborough NHS Trust
Tameside Hospital NHS Foundation Trust	Target Ovarian Cancer
Teenage Cancer Trust	Teenagers and Young Adults with Cancer
Tenovus	Tenovus Cancer Information Centre
Tenovus The Cancer Charity	The Anthony Pilcher Bone Cancer Trust
The Brain Tumour Charity	The British In Vitro Diagnostics Association
The British Society for Haematology	The Hepatitis C Trust
The Institute of Cancer Research	The National LGB&T Partnership
The Neuro Foundation	The Neuroblastoma Society
The Patients Association	The Princess Alexandra Hospital NHS Trust
The Rotherham NHS Foundation Trust	The University of Birmingham
The Walton Centre for Neurology and Neurosurgery	Throat Cancer Foundation
UCL Partners	UK Clinical Pharmacy Association
UK Liver Alliance	UK National Screening Committee
United Response	University College London Hospital NHS Foundation Trust
University Hospital Birmingham NHS Foundation Trust	University Hospitals Birmingham
University of Nottingham	Velindre NHS Trust
Walsall Local Involvement Network	Welsh Cancer Services Coordinating Group
Welsh Government	Welsh Scientific Advisory Committee
West Suffolk Hospital NHS Trust	Western Health and Social Care Trust
Western Sussex Hospitals NHS Trust	Westminster Local Involvement Network
Whitehouse Consultancy	Wicked Minds
Wigan Borough Clinical Commissioning Group	Wirral University Teaching Hospital NHS Foundation Trust
York Hospitals NHS Foundation Trust	

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E.3 Individuals carrying out 2015 literature reviews and complementary work

Overall Co-ordinators	
Dr John Graham	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Angela Bennett	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Project Manager	
Katrina Asquith-Coe	National Collaborating Centre for Cancer, Cardiff
Senior Researcher	
Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Researchers	
Dr Mia Schmidt-Hansen	National Collaborating Centre for Cancer, Cardiff
Dr Susan O'Connell	National Collaborating Centre for Cancer, Cardiff
Dr Laura Bunting	National Collaborating Centre for Cancer, Cardiff
Dr David Jarrom	National Collaborating Centre for Cancer, Cardiff
Information Specialists	
Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Delyth Morris	National Collaborating Centre for Cancer, Cardiff
Senior Health Economist	
Matthew Prettyjohns	National Collaborating Centre for Cancer, Cardiff
Health Economist	
Victoria Kelly	National Collaborating Centre for Cancer, Cardiff

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E.4 Expert advisors to the 2015 Guideline Development Group

Dr Robert J. Dunlop	Clinical Director Infermed Ltd
Professor Willie Hamilton	Professor of Primary Care Diagnostics, University of Exeter
Professor Julia Hippisley-Cox	Professor ofclinical epidemiology & general practice. Medical Director ClinRisk Ltd
Dr Michael Horton	FGDP(UK) Board Member
Dr Tom Marshall	Reader in primary care, University of Birmingham.

Declarations of interest

Expert advisor	Interest declared	Type of interest	Decision taken
Michael Horton	General dental practitioner working within the NHS and privately, and Denplan patients.	Personal pecuniary,	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Michael Horton	Postgraduate clinical audit tutor	Personal non-pecuniary	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Michael Horton	Chair North Wales Local Dental Committee	Personal non-pecuniary	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Michael Horton	Board FGDP (UK) Royal College of Surgeons	Personal, non-pecuniary	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Michael Horton	Dental Nurse Examiner	Personal, non-pecuniary	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Michael Horton	Research Director North Wales FGDP (UK)	Personal, non-pecuniary	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Michael Horton	North Wales Oral Health Strategy Group	Personal, non-pecuniary	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Julia Hippisley-Cox	Founder and medical Directo of ClinRisk Ltd.	Personal pecuniary,	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations

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Expert advisor	Interest declared	Type of interest	Decision taken
Julia Hippisley-Cox	Received research grants to investigate cancer epidemiology.	Personal pecuniary,	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Julia Hippisley-Cox	Director of QResearch (database used for development of risk prediction algorithms). Venture between the University of Nottingham and EMIS.	Personal pecuniary,	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Julia Hippisley-Cox	Spouse is founder and Technical Director of ClinRisk Ltd.	Personal family	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Tom Marshall	None declared		
Robert Dunlop	None declared		

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E.5 Members of the 2005 Guideline Development Group

GDG Chair	
Dr Ivan Cox	General Practitioner Birmingham, West Midlands
Dr Emily Banks	Deputy Director, Cancer Research UK. Epidemiology Unit, Oxford
Dr Kathie Bynish	Director, London Cervical Screening QA Reference Centre. Charing Cross Hospital London.
Ms Ann Brown	Elderly Care Specialist Nurse, Sunderland
Ms Debbie Coats	Publications Cancer Information Nurse Specialist. CancerBacup, London
Ms Margaret Evison	Consultant Clinical Psychologist, St Thomas's Hospital, London
Dr E.D Gilby	Consultant Medical Oncologist, Royal United Hospital, Bath, Wiltshire
Professor R. Hornung	Professor of Medical Education, University of Surrey
Dr Orest Mulka	General Practitioner, Measham, Leicestershire
Dr Robert Newton	Cancer Research UK, Cancer Epidemiology Unit, Oxford University
Mr Richard Palmer	Chairman of the National Alliance for Childhood Cancer Parent Organisations, Leicestershire - Kent
Mr N.I Ramus	Consultant Breast, Endocrine and General Surgeon, Taunton and Somerset Hospital
Ms Louise Soanes	Senior Sister (Children's Services), The Royal Marsden Hospital, Sutton

E.6 Organisations invited to comment on the 2005 guideline development

The following stakeholders registered with NICE and were invited to comment on the scope and the draft version of this guideline.

Age Concern England	Leukaemia Research Fund
Airedale General Hospital	Lewisham Hospital
Anglesey Local Health Board	Link Pharmaceuticals
Association of British Neurologists	Lymphoma Association
Association of Clinical Biochemists, The	Macmillan Cancer Relief
Association of Coloproctology of Great Britain and Ireland	Medicines and Healthcare Products Regulatory Agency (MHRA)
Association of Surgeons of Great Britain and Ireland	National Alliance of Childhood Cancer Parent Organisations
Association of Upper Gastrointestinal Surgeons of Great Britain and Ireland (AUGIS)	National Cancer Alliance
AstraZeneca UK Ltd	National Cancer Network Clinical Directors Group
Aventis Pharma	National Cancer Research Institute (NCRI) Clinical Studies Group
Bard Limited	National Council for Disabled People, Black, Minority and Ethnic Community (Equalities)
Baxter Oncology	National Kidney Research Fund, The
Bayer PLC	National Public Health Service
Beating Bowel Cancer	NHS Information Authority, (PHSMI Programme)
Bedfordshire & Hertfordshire NHS Strategic Health Authority	NHS Modernisation Agency, The
Birmingham Heartlands & Solihull NHS Trust	NHS Quality Improvement Scotland
Bournemouth PCT	Novartis Pharmaceuticals UK Ltd
Breakthrough Breast Cancer	Prostate Cancer Charity, The
Breast Cancer Care	Queen Elizabeth Hospital NHS Trust
Brighton & Sussex University Hospitals Trust	Roche Products Limited
British Association of Dermatologists, The	Rotherham Primary Care Trust
British Association of Head and Neck Oncologists	Roy Castle Lung Cancer Foundation
British Association of Oral and Maxillofacial Surgeons	Royal College of General Practitioners
British Association of Oral Surgeons	Royal College of General Practitioners Wales
British Association of Otolaryngologists, Head & Neck Surgeons	Royal College of Nursing (RCN)
British Association of Urological Surgeons (BAUS)	Royal College of Obstetricians & Gynaecologists
British Committee for Standards in Haematology	Royal College of Paediatrics and Child Health
British Dental Association	Royal College of Pathologists
British Dietetic Association	Royal College of Physicians of London
British Gynaecological Cancer Society	Royal College of Psychiatrists
British National Formulary (BNF)	Royal College of Radiologists
British Nuclear Medicine Society	Royal College of Speech and Language Therapists
British Paediatric Neurology Association	Royal College of Surgeons of England
British Psychological Society, The	Royal National Orthopaedic Hospital NHS

	Trust
British Psychosocial Oncology Society	Royal Pharmaceutical Society of Great Britain
British Society for Haematology	Sanofi-Synthelabo
British Society of Gastroenterology	Sarcoma UK
British Society of Oral Medicine	Schering Health Care Ltd
British Society of Paediatric Radiology	Scottish Executive Health Department
British Thoracic Society	Scottish Intercollegiate Guidelines Network (SIGN)
British Thyroid Association BUPA	Sheffield Teaching Hospitals NHS Trust
Cancer and Leukaemia in Childhood (UK)	Society and College of Radiographers
Cancer Black Care	Society of British Neurological Surgeons
Cancer Research UK	Society of Cardiothoracic Surgeons
Cancer Services Co-ordinating Group	South Birmingham Primary Care Trust
Cancer Voices	Sue Ryder Care
CancerBACUP	Tameside and Glossop Acute Services NHS Trust
Chartered Society of Physiotherapy	Teenage Cancer Trust, The
Chelsea & Westminster Healthcare NHS Trust	Tenovus Cancer Information Centre
City Hospitals Sunderland	The Association of Breast Surgery at BASO
Cochrane Oral Health Group	The Leukaemia Society UK
Community District Nurses Association	The Neurofibromatosis Association
Department of Health	The Royal Society of Medicine
Eisai Limited	The Royal West Sussex Trust
Eli Lilly and Company Ltd	UK Breast Cancer Coalition
E-Z-EM Ltd	UK Childhood Leukaemia Working Party
Faculty of Dental Surgery	UK Children's Cancer Study Group
Faculty of Public Health	University College Londons Hospital NHS Trust
Fibroid Network Charity	Walthamstow, Leyton & Leytonstone PCT
General Practice Airways Group Limited	Wandsworth Primary Care Trust
Gorlin Syndrome Group	Welsh Assembly Government (formerly National Assembly for Wales)
Help Adolescents with Cancer	Welsh Cancer Services Coordinating Group
Independent Healthcare Association	Wirral Hospital
Independent Healthcare Forum	Women's Health Concern

E.7 Individuals carrying out 2005 literature reviews and complementary work

Overall Co-ordinators	
Professor Richard Baker	Director, NCC-PC and Project Lead. Department of Health Sciences, University of Leicester
Dr Tim Stokes	Deputy Director, NCC-PC. Department of Health Sciences, University of Leicester
Mrs Nancy Turnbull	Chief Executive, NCC-PC. Royal College of General Practitioners, London.
Ms Charmaine Larment	Centre Manager, NCC-PC. Royal College of General Practitioners, London
Dr Andres Enriquez-Puga	Clinical Lecturer, NCC-PC. Department of Health Sciences, University of Leicester
Project Manager	
Miss Gabrielle Shaw	Project Manager, NCC-PC. Royal College of General Practitioners, London.
Researchers	
Ms Elizabeth Shaw	Systematic Reviewer/Research Fellow, NCC-PC. Department of Health Sciences, University of Leicester.
Dr Kashifa Mahmood	Systematic Reviewer/Research Associate, NCCPC. Department of Health Sciences, University of Leicester. (until April 2004)
Miss Nicola Costin	Systematic Reviewer/Research Associate, NCC-PC. Department of Health Sciences, University of Leicester (January 2004 onwards)
Information Specialists	
Ms Janette Camosso-Stefinovic	Information Librarian, NCC-PC. Department of Health Sciences, University of Leicester
Health Economist	
Mrs Ariadna Juarez-Garcia	Health Economist, NCC-PC. Department of Health Sciences, University of Leicester
Administrator	
Miss Yolanda Josephs	NCC-PC. Royal College of General Practitioners, London.

E.8 Expert co-optees to the 2005 Guideline Development Group

Dr Joan Austoker	Director – CRUK Primary Care Education Research Group. Oxford.
Mr Patrick Bradley	Head and Neck Oncologic Surgeon, University Hospital Queens Medical Centre, Nottingham
Mr Andrew Brown	Consultant Maxillofacial Surgeon. Edgbaston, Birmingham.
Dr Ian Chait	General Practitioner, Hertfordshire.
Dr Helen Cox	General Practitioner (Loughborough) and Hospital Practitioner in Paediatric Oncology, Leicester Royal Infirmary
Dr Neil Cox	Dermatologist,Carlisle.
Professor Garth Cruickshank	Consultant Neurosurgeon, Birmingham.
Dr Jon Emery	General Practitioner, Cambridge
Mr John Fielding	Consultant Surgeon/National Lead for UGI Cancer. Edgbaston, Birmingham.
Mr Adrian Flower	Consultant Maxillofacial Surgeon, King's Lynn Norfolk.
Mr Robert Grimer	Consultant Orthopaedic Oncologist, Birmingham.
Dr Phil Hartropp	General Practitioner, Cambridgeshire.
Dr Graham Jackson	Consultant Haematologist and Honorary Senior Lecturer. Newcastle upon Tyne.
Dr Moyez Jiwa	General Practitioner, Retford Nottinghamshire.
Professor Sean Kehoe	Professor of Gynaecological Cancer, Oxford.
Professor Robert Mansel	Professor of Surgery, Cardiff.
Dr Donald Milligan	Consultant Haematologist, Birmingham.
Dr Richard Neal	Senior Lecturer in General Practice – Wales College of Medicine, Cardiff University, Wrexham.
Dr Michael Peake	Lead Clinician for Lung Cancer, Leicester.
Dr Sue Picton	Consultant Paediatric Oncologists, Leeds.
Dr Cliff Richards	General Practitioner, Cheshire.
Dr Leone Ridsdale	Reader in General Practice, Senior Lecturer (Honorary Consultant) in Neurology, London.
Dr Richard Stevens	Primary Care Society of Gastroenterology
Mr M.R Thompson	Consultant Colorectal Surgeon. HANTS.
Mr Michael Wallace	Consultant Urologist, Birmingham.
Professor C.E Wilkinson	Professor of General Practice, Wales College of Medicine, Cardiff University, Wrexham.

E.9 Members of the 2005 Guideline Review Panel

The Guideline Review Panel is an independent panel that oversees the development of the guideline and takes responsibility for monitoring its quality. The Panel includes experts on guideline methodology, health professionals and people with experience of the issues affecting patients and carers. The members of the Guideline Review Panel were as follows.

Professor Mike Drummond (Chair)	Director, Centre for Health Economics, University of York
Mr Barry Stables	Patient/Lay Representative
Dr Imogen Stephens	Joint Director of Public Health, Western Sussex Primary Care Trust
Dr Kevork Hopayian	General Practitioner, Suffolk
Dr Robert Walker	Clinical Director, West Cumbria Primary Care Trust
Dr John Harley	Clinical Governance and Prescribing Lead, North Tees PCT