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As tests evolve and costs of cancer care rise: reappraising stool-based screening for colorectal neoplasia

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SUMMARY

Background
Colorectal cancer screening and treatment are rapidly evolving.

Aims
To reappraise stool-based colorectal cancer screening in light of changing test performance characteristics, lower test cost and increasing colorectal cancer care costs.

Methods
Using a Markov model, we compared faecal DNA testing every 3 years, annual faecal occult blood testing or immunochemical testing, and colonoscopy every 10 years.

Results
In the base case, faecal occult blood testing and faecal immunochemical testing gained life-years/person and cost less than no screening. Faecal DNA testing version 1.1 at $300 (the current PreGen Plus test) gained 5323 life-years/100 000 persons at $16 900/life-year gained and faecal DNA testing version 2 (enhanced test) gained 5795 life-years/100 000 persons at $15 700/life-year gained vs. no screening. In the base case and most sensitivity analyses, faecal occult blood testing and faecal immunochemical testing were preferred to faecal DNA testing. Faecal DNA testing version 2 cost $100 000/life-year gained vs. faecal immunochemical testing when per-cycle adherence with faecal immunochemical testing was 22%. Faecal immunochemical testing with excellent adherence was superior to colonoscopy every 10 years.

Conclusions
As novel biological therapies increase colorectal cancer treatment costs, faecal occult blood testing and faecal immunochemical testing could become cost-saving. The cost-effectiveness of faecal DNA testing compared with no screening has improved, but faecal occult blood testing and faecal immunochemical testing are preferred to faecal DNA testing when patient adherence is high. Faecal immunochemical testing may be comparable to colonoscopy every 10 years in persons adhering to yearly testing.

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INTRODUCTION

Colorectal cancer (CRC) affects up to 6% of the population and is the second leading cause of cancer-related death in the US.[1] Each year, approximately 145 000 new cases are diagnosed and approximately 55 000 deaths are attributed to CRC in the US.[2] Screening decreases CRC incidence and mortality and is cost-effective,[3–13] but only a minority of the population has been screened.[14, 15] Patient preferences for invasive vs. non-invasive screening tests vary,[16–18] and the availability of some tests may be limited.[19]

In 2004, we first explored the potential role of faecal DNA testing (F-DNA) in average-risk persons.[20] We concluded that it could not be considered a substitute for traditional screening methods, but that it could have an important impact if it attracted persons who are not currently screened for CRC.[20] A prospective trial of the original PreGen Plus faecal DNA test (EXACT Sciences Corporation, Marlboro, MA, USA and LabCorp, Burlington, NC, USA) subsequently found the test to be superior to faecal occult blood testing (FOBT) in detecting CRC and large adenomas,[21] but its performance was inferior to our original estimates and its projected effectiveness and cost-effectiveness declined.[22]

Colorectal cancer screening is a rapidly evolving field and key variables that affect estimates of effectiveness and cost-effectiveness are changing, including test performance characteristics and cost, and costs of CRC care. Technical advances in DNA stabilization,[23] DNA extraction from stool,[24] and use of gene-specific methylation[25] have improved the faecal DNA test.[26] Test cost has decreased to approximately $300 after write-offs (B. Berger, personal communication; EXACT Sciences Corporation). At the same time, bevacizumab (an antibody targeting vascular endothelial growth factor, a known regulator of tumour cell angiogenesis) and cetuximab (an antibody targeting the epidermal growth factor receptor, a tyrosine kinase important in the regulation of growth and survival pathways in CRC cells)[27–29] have emerged as novel treatments that enhance the efficacy of chemotherapy for advanced CRC,[28, 30] but also markedly increase treatment costs.[31]

Our aims were to reappraise non-invasive stool-based screening for colorectal neoplasia in persons unwilling or unable to undergo invasive screening with sigmoidoscopy or colonoscopy in light of changing faecal DNA test performance characteristics,[21, 26] lower test cost and increasing costs of CRC care. We compared F-DNA, guaiac-based FOBT and faecal immunochemical testing (FIT). Because adherence to yearly guaiac-based FOBT is poor,[15, 32–44] we examined in detail the potential impact of imperfect adherence on the effectiveness and cost-effectiveness of screening strategies. We previously examined the cost-effectiveness of other modalities, including colonoscopy.[11, 20, 22, 45] Although we focus here on stool-based testing, we report results for screening colonoscopy for purposes of comparison.

MATERIALS AND METHODS

Literature review and data sources

The sources for most model inputs have been described previously.[11, 20, 22, 45] For updated clinical information on F-DNA and FIT, we searched PubMed using the terms faecal DNA, colorectal cancer, faecal immunohistochemistry, detection, sensitivity, specificity and test performance, we reviewed national meeting abstracts, and we obtained data from EXACT Sciences Corporation and FDA submission data from Enterix Inc. (Edison, NJ, USA), maker of InSure FIT. For updated cost data, we searched PubMed using the terms colorectal cancer, chemotherapy, and cost, we reviewed national meeting abstracts, we obtained data from EXACT Sciences Corporation, and we used 2006 Medicare fee schedules, as detailed below.[46]

Decision analytic model

Our decision analytic model and its calibration and validation have been described in detail.[11, 20, 22, 45, 47] The model is constructed in TreeAge (TreeAge Software, Inc., Williamston, MA, USA) and the Natural History model is calibrated to reproduce the natural history and age-specific incidence and prevalence of colorectal adenomas and CRC in the US without screening.[11, 20, 22, 45, 47] Screening strategies are then superimposed on the Natural History model. As described previously, the model's predictions for conventional strategies are consistent with available clinical data.[11, 20, 22, 45, 47] For the current analysis, the model was modified to allow variable adherence rates every time a screening test was offered. To validate this modification, we have modelled a cohort representing the one studied by Mandel *et al.*[32, 33] with FOBT offered and followed up as in that study.[22] Our model predicts a 21% reduction in CRC incidence over

18 years vs. 20% observed in the study,[33] and a 36% reduction in CRC mortality over 16 years vs. 33% observed in the study.[32]

Natural history

The principal health states in the model are (Figure 1): normal; small (<10 mm) adenomatous polyp; large (≥10 mm) adenomatous polyp; localized, regional, or distant CRC and dead. Approximately 85% of CRCs develop through a polypoid adenoma. In the Natural History model, CRCs are diagnosed with colonoscopy once they lead to symptoms. Diagnosed CRCs are treated, resulting in stage-specific survival.[11, 20, 28, 30, 45, 48–51] Persons surviving CRC treatment enter surveillance (see below). Beginning at age 50 years, average-risk persons progress through the model for 50 1-year cycles, until age 100 years or death. Age-specific non-CRC mortality rates reflect US life table data.[52] Model inputs are shown in Table 1.

Screening strategies and surveillance

We compared Natural History, F-DNA, annual guaiac-based FOBT and annual FIT. First, a screening interval for F-DNA was selected that could be considered cost-effective compared to a shorter screening interval, as described below.

Screening strategies were superimposed on the Natural History model. In the base case, in all strategies, screening and surveillance with perfect adherence were performed up to and including age 80. Variable adherence was a principal focus of sensitivity analyses. After age 80, colonoscopy was performed only to evaluate symptoms. With colonoscopy, polyps were removed and CRCs were biopsied, if detected. If F-DNA, FOBT or FIT were positive, colonoscopy followed with polypectomy and biopsy as necessary. If colonoscopy was normal after a positive non-invasive test, the non-invasive test was assumed to be false positive and screening resumed in 10 years with the primary screening strategy. CRC was managed, and symptomatic CRC could be detected, as in the Natural History model.

In all strategies, after adenoma detection, patients underwent surveillance colonoscopy every 5 years.[53, 54] Persons developing CRC underwent colonoscopy at diagnosis, 3 years later and then every 5 years thereafter.[53, 54]

Faecal occult blood testing and faecal immunochemical testing

In the FOBT strategy, annual testing[3, 53, 55] was offered with test performance characteristics as modelled previously (Table 1).[22] FIT was evaluated with annual testing and test performance characteristics based on available literature[56–66] and FDA submission data from Enterix Inc., maker of InSure FIT.[67] Reported FIT sensitivities range from 30% to 100% for CRC and from 20% to 71% for large adenoma, with specificities of 86–99%.[56–66] In the base case for FIT, we assumed sensitivity of 76% for CRC, 40% for large adenoma and specificity of 91%.

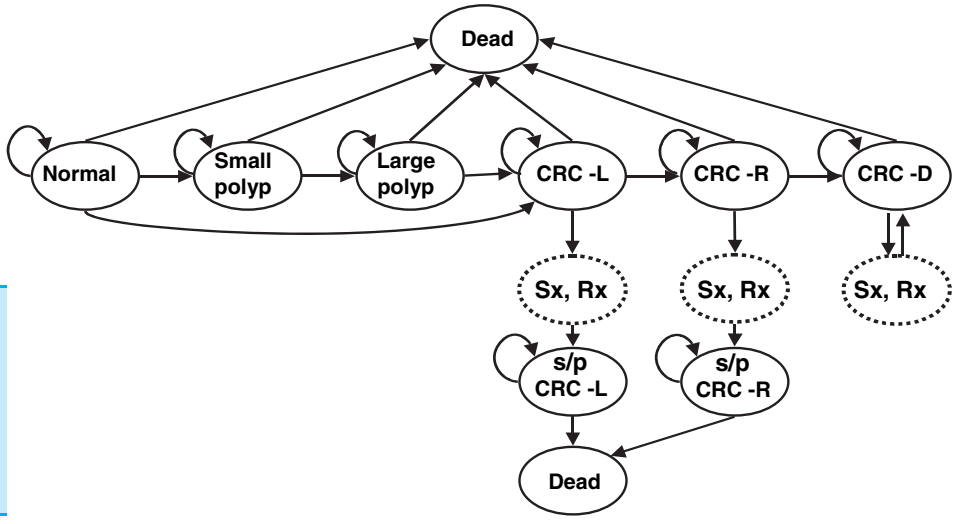

Figure 1. Markov states in the natural history model. Persons cycle between states every year from age 50 to 100. Screening strategies were superimposed on the natural history model.

Table 1. Inputs in the cost-effectiveness model

Variable	Base case value (range)*	References
Clinical		
Polyp prevalence at age 50 (%)†	15	91–93
Small polyp (%)†	95	93–95
Large polyp (%)†	5	93–95
Annual transition rate to small polyp from normal (%)†	Age specific, 1.1–1.9	91–95
Annual transition rate to large polyp from small polyp (%)†	1.5	93–96
Annual transition rate to cancer without polypoid precursor (%)†	Age specific, 0.006–0.086	9, 91–93, 97
Annual transition rate to cancer from large polyp (%)†	5	9, 91–93, 97
Symptomatic presentation of localized cancer (%)†	22/year over 2 years	97
Symptomatic presentation of regional cancer (%)†	40/year over 2 years	97
Mortality rate from treated localized cancer (%)‡	1.74/year in first 5 years	97
Mortality rate from treated regional cancer (%)‡	8.6/year in first 5 years	97
Mean survival from distant cancer (year)	1.9	28, 30, 31, 48–51, 78, 79, 97
Mortality rate from cancer treatment (%)	2	9, 10
Faecal occult blood testing sensitivity for cancer (%)	40 (30–60)	9, 10
Faecal occult blood testing sensitivity for large polyp (%)	10 (5–15)	9, 10
Faecal occult blood testing specificity (%)§	92 (90–97)	9, 10
FIT testing sensitivity for cancer (%)	76 (62–88)	56–66
FIT testing sensitivity for large polyp (%)	40 (20–67)	56–66
FIT testing specificity (%)§	91 (86–98)	56–66
Faecal DNA version 1 testing sensitivity for cancer (%)	52 (35–68)	21
Faecal DNA version 1 testing sensitivity for large polyp (%)	18 (14–22)	21
Faecal DNA version 1 testing specificity (%)§	94 (93–96)	21
Faecal DNA version 1.1 testing sensitivity for cancer (%)	73 (57–84)	26
Faecal DNA version 1.1 testing sensitivity for large polyp (%)	18 (14–22)	26
Faecal DNA version 1.1 testing specificity (%)§	89 (83–94)	26
Faecal DNA version 2 testing sensitivity for cancer (%)	88 (74–95)	26
Faecal DNA version 2 testing sensitivity for large polyp (%)	18 (14–22)	26
Faecal DNA version 2 testing specificity (%)§	82 (74–88)	26
Colonoscopy sensitivity for cancer (%)	95 (90–97)	9, 10
Colonoscopy sensitivity for large polyp (%)	90 (85–95)	9, 10
Colonoscopy sensitivity for small polyp (%)	85 (80–90)	9, 10
Colonoscopy major complication rate (%)	0.1 (0.05–0.5)	9, 10
Colonoscopy mortality rate (%)	0.01 (0.01–0.03)	9, 10
Cost ($)		
Faecal occult blood testing	15 (15–56)	46
FIT testing	22 (22–95)	46
Faecal DNA testing	300 (300–495)	**
Colonoscopy	920 (710–1350)	7, 9, 11, 20, 47, 98
Colonoscopy with lesion removal	1350 (990–2030)	7, 9, 11, 20, 47, 98
Endoscopy complication	29 000 (16 000–43 000)	71, 72
Colorectal cancer care by stage¶		
Localized	51 000 (40 000–62 000)	5, 73–75
Regional	98 000 (85 000–105 000)	5, 28, 30, 31, 48–51, 73–75, 78, 79
Distant	200 000 (175 000–230 000)	5, 28, 30, 31, 48–51, 73–75, 78, 79

* Range for test sensitivity and specificity used in Monte Carlo simulation.
† Derived from epidemiological and autopsy data.
‡ The annual mortality rate applies to those surviving to the beginning of each year, reflecting exponential decay as the fraction of persons surviving decreases at a rate proportional to its value.
§ Sensitivity for small polyp set at (1 − specificity).
¶ Derived from Centers for Medicare and Medicaid Services and published data.
** Derived from LabCorp list price and average reimbursement (B. Berger, personal communication; Exact Sciences Corp.).
FIT, faecal immunochemical testing.

Faecal DNA testing

Faecal DNA testing version 1 was defined as the strategy using the prototype test evaluated by Imperiale *et al.*[21] This test had sensitivities of 52% for CRC and 18% for large adenoma and specificity of 94%.[21] F-DNA version 2 was defined as the strategy using the test recently reported by Itzkowitz *et al.*[26] This test represents the optimal marker combination of vimentin methylation and a DNA integrity assay, with sensitivity of 88% for CRC and specificity of 82%.[26] The sensitivity of F-DNA version 2 for large adenoma has not been reported formally. We assumed that the sensitivity for large adenoma of F-DNA version 2 was 18%, the same as for version 1. For F-DNA versions 1 and 2, we assumed that F-DNA could not distinguish normal from small adenoma. Thus, F-DNA was positive when the most advanced lesion was a small adenoma at a rate defined as (100% − specificity).

The test currently available on the market is version 1.1 (PreGen Plus, LabCorp). Compared with version 1, version 1.1 includes a DNA stabilization buffer and an improved gel capture method for isolating DNA.[18, 23–25] When the version 1 test was enhanced in these ways in the recent study by Itzkowitz *et al.*, sensitivity for CRC was 73% and specificity was 89%.[26] We assumed that the sensitivity for large adenoma of F-DNA version 1.1 was 18%, the same as for the other versions of the test.

Before evaluating F-DNA strategies, an appropriate screening interval was selected. As described previously,[20] we examined F-DNA at progressively shorter screening intervals ranging from 1 to 5 years. Screening at a given interval (e.g. 4 years) was compared to screening at a longer interval (e.g. 5 years), yielding the incremental cost per life-year gained when shortening the interval. For the base case, we selected a screening interval consistent with the commonly accepted 'willingness to pay' threshold of $50 000/life-year gained.[68–70] Thus, in the base case, F-DNA was offered every 3 years (see Results).

Screening colonoscopy

The screening colonoscopy strategy included colonoscopy every 10 years (COLO), if no adenomas were detected. Polyps were removed upon detection and masses underwent biopsy. Test performance characteristics and costs are presented in Table 1. After detection of adenomas, surveillance was performed as described for all strategies above.

Cost inputs

Procedure cost estimates ranged from those derived from Medicare fee schedules (including professional fees and procedure reimbursement) to those reported from a health maintenance organization.[7–13, 20, 47] Based on Medicare schedules, we assumed a base case cost of $15 for each cycle of FOBT and $22 for each cycle of FIT.[46] The PreGen Plus test list price is $495 (LabCorp; test number 512094), but the average reimbursement for the test is approximately $300 after write-offs (B. Berger, personal communication; EXACT Sciences Corporation). In the base case, we assumed a cost of $300 for each faecal DNA test. Complication costs were derived from relevant diagnostic-related groups (DRG 148, major small and large bowel procedures).[9, 11, 20, 47, 71, 72]

Stage-specific costs of care for CRC were taken from published reports and available data on the costs of newer therapies for advanced CRC.[5, 9, 11, 20, 31, 47, 73–75] Our Natural History model is calibrated to SEER data on CRC stage distribution of 39% localized, 39% regional and 22% disseminated CRC.[22] After comparisons with data on CRC TNM stage distribution, we assumed that disseminated CRC in our model represented TNM Stage IV disease and that 2/3 of patients with regional CRC in our model had TNM Stage III disease.[76, 77] To account for the increasing costs of CRC care for advanced disease, we assumed that patients with TNM Stage III disease received three 8-week cycles of FOLFOX (oxaliplatin, infusional fluorouracil and leucovorin) chemotherapy,[78] resulting in an increased cost of $34 800 over the costs assumed in our previous analyses.[31] We assumed that patients with TNM Stage IV disease received four to six cycles of treatment including the emerging biological agents, bevacizumab and cetuximab,[28, 30, 48–51, 78, 79] resulting in an increased cost to $200 000.[31] Base case cost inputs incorporate these assumptions (Table 1).

Costs were updated to 2006 dollars as necessary, using the medical services component of the consumer price index.[80] For each base case cost input, we used the average of the published values. Indirect costs were not included. We used a third-party payer perspective.

Clinical and economic outcomes

For each strategy, we determined CRC cases by stage in a cohort of 100 000 persons, deaths by cause and average life-years and costs per person (both discounted at 3% annually).[81]

Cost-effectiveness of screening strategies

If one strategy afforded more life-years than another at higher expense, an incremental cost-effectiveness ratio was calculated. One-way sensitivity analyses were performed on all model inputs, including test performance characteristics and costs. Two-way sensitivity analyses were performed on variables determined to be influential on one-way sensitivity analyses. Threshold analyses were performed to identify critical values for variables at which specific conditions of interest were met (e.g. clinical equivalence, or cost-effectiveness at a willingness to pay of $50 000–100 000/life-year gained). A Monte Carlo simulation with 1000 trials was performed with sampling for the test performance characteristics for FOBT, FIT and F-DNA versions 1, 1.1 and 2 from uniform distributions representing the 95% confidence interval ranges reported in the literature (Table 1).

In controlled trials of FOBT, adherence has been less than perfect.[32, 33, 36, 38] Initial screening rates have ranged from 53% to 78%[32, 33, 36, 38] and repeat screening has ranged from 77%[82] to 94%.[38] Adherence is lower outside controlled trials. Data from the Behavioral Risk Factor Surveillance System in 2001 reported that 45% of adults aged 50 or greater had undergone FOBT at least once and 24% had FOBT within the past 12 months.[15] Others have reported initial rates of screening with FOBT from 35% to 47%[34, 41–43, 61] and rates of FOBT within 1 year (considered up to date) from 10% to 26%.[37, 39, 40, 43, 44] Data on annual follow-up, or serial screening, are very limited. Myers *et al.* reported initial response to a screening programme of 41% (647 of 1565 subjects) and then subsequent serial screening by 56% of initial responders (362 of 647).[42] Using data from Liang *et al.*, adherence to annual screening can be estimated at 61%.[39] Thus, imperfect adherence was explored in detail in sensitivity analyses.

In the base case, we assumed perfect adherence for all strategies. This reflects the optimal possible 'efficacy' of the strategies. The results are useful because they reflect a strategy's impact in persons who adhere to it. Because imperfect adherence limits true 'efficacy' in larger cohorts, we performed extensive sensitivity analyses on adherence to estimate real-world 'effectiveness' with imperfect adherence.

RESULTS

Base case

Selection of screening interval for F-DNA. Faecal DNA testing version 1 every 3 years compared with every 4 years cost $39 200/life-year gained, and every 2 years compared with every 3 years it cost $52 600/life-year gained (Table 2). Similarly, F-DNA version 2 every 3 years compared with every 4 years cost $47 700/life-year gained, and every 2 years compared with every 3 years it cost $57 100/life-year gained. Therefore, we selected a screening interval of 3 years for F-DNA.

Clinical outcomes with perfect adherence. Compared with no screening, all strategies reduced CRC incidence and mortality (Table 3). FIT yielded the greatest number of discounted life-years/person, followed by COLO, F-DNA version 2, FOBT, F-DNA version 1.1 and F-DNA version 1. Without screening, a cohort of

Table 2. Effectiveness, cost and incremental cost-effectiveness of faecal DNA testing (F-DNA) version 1 at progressively shorter intervals

F-DNA interval (years)	Discounted life-years/ person	Discounted cost/ person ($)	Incremental cost/ life-year gained compared to next shorter interval ($)
5	18.7197	3531	–
4	18.7244	3627	20 400
3	18.7305	3867	39 200
2	18.7394	4339	52 600
1	18.7478	5658	158 000

Table 3. Base case clinical and economic results and incremental cost-effectiveness ratios

	Natural history	F-DNA version 1	F-DNA version 1.1	FOBT	F-DNA version 2	Colonoscopy	FIT
CRC cases per 100 000 persons from age 50 to 100 years	5927	3989	3711	3009	3403	1584	2015
CRC stage							
Local	2373	2191	2231	1876	2148	882	1291
Regional	2210	1266	1086	813	943	509	504
Distant	1345	532	393	320	312	193	220
Deaths attributable to CRC	2.4%	1.2%	1.0%	0.8%	0.9%	0.5%	0.5%
Life-years/person*	18.686	18.730	18.739	18.742	18.744	18.748	18.751
Cost/person*	$2921	$3867	$3821	$2683	$3833	$3489	$2428
Incremental life-years gained per 100 000 persons compared to							
Natural history	–	4466	5323	5623	5795	6185	6542
F-DNA version 1	–	–	857	1157	1329	1719	2076
F-DNA version 1.1	–	–	–	300	472	862	1219
FOBT	–	–	–	–	172	562	919
F-DNA version 2	–	–	–	–	–	390	747
Colonoscopy	–	–	–	–	–	–	357
Increment cost per life-year gained compared to							
Natural history	–	$21 200	$16 900	Dominates†	$15 700	$9200	Dominates†
F-DNA version 1	–	–	Dominates†	Dominates†	Dominates†	Dominates†	Dominates†
F-DNA version 1.1	–	–	–	Dominates†	$2700	Dominates†	Dominates†
FOBT	–	–	–	–	$669 000	$144 000	Dominates†
F-DNA version 2	–	–	–	–	–	Dominates†	Dominates†
Colonoscopy	–	–	–	–	–	–	Dominates†

CRC, colorectal cancer; F-DNA, faecal DNA testing every 3 years; FOBT, annual guaiac-based faecal occult blood testing; FIT, annual faecal immunochemical testing.
* Discounted at 3% per year.
† Strategy in top row is more effective and less costly than strategy in left column to which it is being compared.

100 000 persons experienced 5927 CRC cases, and CRC accounted for 2.4% of deaths. Compared with no screening, F-DNA version 1 decreased CRC incidence by 33% and CRC-related mortality by 49%, F-DNA version 1.1 decreased CRC incidence by 37% and CRC-related mortality by 57%, FOBT decreased CRC incidence by 49% and CRC-related mortality by 66%, F-DNA version 2 decreased CRC incidence by 43% and CRC-related mortality by 63%, COLO decreased CRC incidence by 73% and CRC-related mortality by 80% and FIT decreased CRC incidence by 66% and CRC-related mortality by 78%.

Cost-effectiveness with perfect adherence. Compared with no screening, all screening strategies increased life-expectancy at reasonable costs (Table 3). FOBT and FIT yielded more average life-years per person than no screening, and achieved this at a lower cost – i.e. they were dominant compared with no screening. Compared with no screening, F-DNA version 1 gained 4466 life-years/100 000 persons at an incremental cost of $21 200/life-year gained, F-DNA version 1.1 gained 5323 life-years/100 000 persons at an incremental cost of $16 900/life-year gained and F-DNA version 2 gained 5795 life-years/100 000 persons at an incremental cost of $15 700/life-year gained. COLO gained 6185 life-years/100 000 persons at an incremental cost of $9200/life-year gained.

Faecal occult blood testing and FIT were preferred over all F-DNA versions. F-DNA versions 1 and 1.1 were dominated by FOBT and FIT. F-DNA version 2 was slightly more effective than FOBT, but at a very high incremental cost of $669 000/life-year gained. FIT was dominant over all other strategies, including F-DNA version 2 (Table 3). COLO was dominated by FIT and it cost $144 000/life-year gained compared to FOBT.

One-way and two-way sensitivity analyses

Changes in most variables did not significantly affect the comparisons between the F-DNA strategies and FOBT or FIT (Table 4). If we assumed significantly worse test performance characteristics for FOBT than in the base case, the F-DNA strategies compared more favourably but still cost >$50 000/life-year gained compared with FOBT. When we examined the low end of reported values for FIT test performance, it was still dominant over the F-DNA strategies. If FIT test cost increased to $95, the strategy was no longer cost-saving compared with no screening (it cost $8300/life-year gained) and it cost $135 000/life-year gained compared with FOBT, but it was still dominant over the F-DNA strategies. Changes in colonoscopy test performance, complication rate and costs did not affect the results significantly.

As the sensitivity for large adenoma of the F-DNA version 2 test improved, this strategy became progressively more effective than FOBT (Figure 2a). With a sensitivity for large adenoma of 80%, F-DNA version 2 cost $87 500/life-year gained compared with FOBT, but this incremental cost/life-year gained rose sharply as sensitivity for large adenoma decreased (Figure 2b). At a test cost of $200, F-DNA version 2 cost <$50 000/life-year gained compared with FOBT when F-DNA test sensitivity for large adenoma was >60% (Figure 2b).

If we assumed lower CRC care costs because the novel, costly therapies were not used, no screening strategy was cost-saving anymore. Compared with no screening, FOBT cost $8000/life-year gained, FIT cost $43 000/life-year gained, F-DNA version 1 cost $33 100/life-year gained, F-DNA version 1.1 cost $28 800/life-year gained and F-DNA version 2 cost $27 700/life-year gained. However, the incremental cost-effectiveness ratios comparing the F-DNA strategies to FOBT and FIT were not affected significantly (Table 4).

Threshold analyses on F-DNA test cost

Faecal DNA testing test cost would need to be significantly lower than the $300 assumed in the base case to make any of the F-DNA strategies competitive with FOBT. F-DNA test cost would need to fall to $40 for FOBT to cost >$50 000/life-year gained compared to F-DNA version 1.1. F-DNA test cost would need to fall to $60 for F-DNA version 2 to cost <$50 000/life-year gained compared to FOBT.

Even when the F-DNA test was assumed to be free, FIT cost only $9200/life-year gained compared to F-DNA version 1 and $8100/life-year gained compared to F-DNA version 1.1, and it still dominated F-DNA version 2.

Monte Carlo simulation focusing on test performance characteristics

When test performance characteristics for all stool-based tests were varied within the ranges reported in the literature (Table 1), FOBT was dominant over no screening in >95% of iterations and FIT was dominant over no screening in 100% of iterations. Compared with no screening, the mean (and 95% confidence interval) for the cost/life-year gained was $21 500 ($16 000–29 200) for F-DNA version 1, $17 600 ($13 900–21 700) for F-DNA version 1.1 and $16 500 ($13 700–19 200) for F-DNA version 2.

Compared with F-DNA version 1.1, FOBT was dominant in 88% of iterations, it cost between $100 000 and $1 000 000/life-year gained in 18% of iterations, and it was more costly in the remainder. Compared with FOBT, F-DNA version 2 was dominant in 64% of iterations, it cost <$100 000/life-year gained in 1% of iterations, it cost between $100 000 and $1 000 000/life-year gained in 28% of iterations, and it was more costly in the remainder. Compared with F-DNA version 2, FIT was dominant in 100% of iterations.

Sensitivity analyses on adherence with testing

As the per-cycle (per-year) adherence with testing decreased with FOBT and FIT, the effectiveness of FOBT decreased steadily, and the effectiveness of FIT began to decrease significantly when the per-cycle adherence fell below approximately 60% (Figure 3).

Faecal DNA testing version 1.1 (with 100% adherence) became more effective than FOBT when the per-cycle adherence with FOBT fell below 85%. F-DNA version 1.1 cost $100 000/life-year gained compared with FOBT when per-cycle adherence with FOBT was 49%, and $50 000/life-year gained when the per-cycle adherence with FOBT was 31% (Figure 4).

Faecal DNA testing version 2 (with 100% adherence) became more effective than FIT when the per-cycle adherence with FIT fell below 50%. F-DNA version 2 cost $100 000/life-year gained compared with FIT

Table 4. One-way sensitivity analyses

Subject of sensitivity analysis	Base case value(s)	Value(s) in sensitivity analysis	FOBT vs. F-DNA version 1		FOBT vs. F-DNA version 1.1		F-DNA version 2 vs. FOBT		FIT vs. F-DNA version 2	
			Life-years gained per 100 000 persons	Cost/ life-year gained	Life-years gained per 100 000 persons	Cost/ life-year gained	Life-years gained per 100 000 persons	Cost/ life-year gained	Life-years gained per 100 000 persons	Cost/ life-year gained
Faecal DNA test										
Cost	$300	$200	1157	Dominates	300	Dominates	172	$410 000	747	Dominates
		$495	1157	Dominates	300	Dominates	172	$1 170 000	747	Dominates
Colonoscopy										
Sensitivity for CRC	95%	90%	1136	Dominates	273	Dominates	192	$596 000	720	Dominates
		97%	1156	Dominates	242	Dominates	240	$474 000	612	Dominates
Sensitivity for large polyp	90%	85%	1157	Dominates	289	Dominates	194	$592 000	658	Dominates
		95%	1166	Dominates	313	Dominates	154	$745 000	818	Dominates
Sensitivity for small polyp	85%	80%	1135	Dominates	286	Dominates	178	$647 000	745	Dominates
		90%	1168	Dominates	308	Dominates	167	$688 000	748	Dominates
Probability of complication	0.1%	0.05%	1157	Dominates	300	Dominates	172	$670 000	747	Dominates
		0.5%	1157	Dominates	300	Dominates	172	$663 000	747	Dominates
Probability of death related to colonoscopy	0.01%	0.005%	1204	Dominates	328	Dominates	169	$690 000	761	Dominates
		0.05%	751	Dominates	61	Dominates	217	$531 000	632	Dominates
Cost (diagnostic/with lesion removal)	$920/$1350	$710/$990	1157	Dominates	300	Dominates	172	$688 000	747	Dominates
		$1350/$2030	1157	Dominates	300	Dominates	172	$632 000	747	Dominates
Cost of complication	$29 000	$16 000	1157	Dominates	300	Dominates	172	$669 000	747	Dominates
		$43 000	1157	Dominates	300	Dominates	172	$668 000	747	Dominates
FOBT										
Sensitivity for CRC/ large polyp/ small polyp/specificity	40%/10%/8%/ 92%	30%/5%/3%/97%	527	Dominates	−330 (F-DNA version 1.1 is more effective)	$385 000 (F-DNA version 1.1 vs. FOBT)	802	$160 000	747	Dominates
		60%/15%/10%/90%	1747	Dominates	890	Dominates	−418 (FOBT is more effective)	$286 000 (FOBT vs. F-DNA version 2)	747	Dominates
		13%/11%/5%/95% (as in Imperiale *et al.* [21])	−407 (F-DNA version 1 is more effective)	$303 000 (F-DNA version 1 vs. FOBT)	−1264 (F-DNA version 1.1 is more effective)	$94 000 (F-DNA version 1.1 vs. FOBT)	1736	$69 000	747	Dominates
Cost	$15	$56	1157	Dominates	300	Dominates	172	$413 000	747	Dominates
FIT										
Sensitivity for CRC/ large polyp/ small polyp/specificity	76%/40%/9%/ 91%	62%/20%/ 14%/86%	1,157	Dominates	300	Dominates	172	$669 000	385	Dominates
Cost	$22	$95	1,157	Dominates	300	Dominates	172	$669 000	747	Dominates
CRC care costs										
Local/regional/ distant	$51 000/98 000/ 200 000	$40 000/85 000/175 000	1157	Dominates	300	Dominates	172	$657 000	747	Dominates

Table 4. Continued

Subject of sensitivity analysis	Base case value(s)	Value(s) in sensitivity analysis	FOBT vs. F-DNA version 1		FOBT vs. F-DNA version 1.1		F-DNA version 2 vs. FOBT		FIT vs. F-DNA version 2	
			Life-years gained per 100 000 persons	Cost/ life-year gained	Life-years gained per 100 000 persons	Cost/ life-year gained	Life-years gained per 100 000 persons	Cost/ life-year gained	Life-years gained per 100 000 persons	Cost/ life-year gained
	$62 000/105 000/230 000 $51 000/75 000/78 000 (without use of novel chemotherapy)	1157 1157	Dominates Dominates	300 300	Dominates Dominates	172 172	$678 000 $674 000	747 747	Dominates Dominates	

CRC, colorectal cancer; F-DNA, faecal DNA testing every 3 years; FOBT, annual guaiac-based faecal occult blood testing; FIT, annual faecal immunochemical testing.
'Dominates' denotes situation where first strategy is more effective and less costly than second strategy.

when per-cycle adherence with FIT was 22%, and $50 000/life-year gained when the per-cycle adherence with FIT was 13% (Figure 5).

Imperfect adherence with F-DNA affected the comparisons with FOBT and FIT. To illustrate, when the per-cycle adherence with F-DNA version 1.1 was 50%, F-DNA version 1.1 became more effective than FOBT when the per-cycle adherence with FOBT fell below 35% and it cost $100 000/life-year gained compared with FOBT when per-cycle adherence with FOBT was 26%. Similarly, when the per-cycle adherence with F-DNA version 2 was 50%, F-DNA version 2 became more effective than FIT when the per-cycle adherence with FIT fell below 19% and it cost $100 000/life-year gained compared with FIT when per-cycle adherence with FIT was 12%.

DISCUSSION

Colorectal cancer screening and treatment are rapidly evolving fields, necessitating reappraisal of the effectiveness and cost-effectiveness of screening strategies as key variables change. Our current analyses focused on the latest test performance characteristics and costs of non-invasive, stool-based tests, and the increasing costs of care for advanced CRC. Our results lead to four major conclusions. First, if CRC treatment costs increase significantly because of the use of novel biological therapies, FOBT and FIT could improve clinical outcomes while also achieving cost savings. Secondly, recent improvements in test performance and lower test cost have translated into enhanced cost-effectiveness for F-DNA compared with no screening, but FOBT and FIT are likely to be preferred to F-DNA when patient adherence with yearly testing is high. Thirdly, adherence over time is a key determinant of the effectiveness of strategies that rely on frequent testing, and F-DNA with screening every 3 years could be cost-effective compared with FOBT and FIT in populations with poor adherence to yearly testing. Fourthly, in persons who can adhere to yearly testing, highly sensitive and relatively inexpensive stool-based testing such as FIT may be comparable to screening COLO.

Before the current era of novel but costly treatments for advanced CRC, multiple analyses concluded that CRC screening is cost-effective.[3–13, 20, 22] Screening had been estimated to be cost-saving only when very low screening costs were assumed.[83] Our current analyses demonstrate how FOBT and FIT could not only decrease CRC incidence and mortality, but could

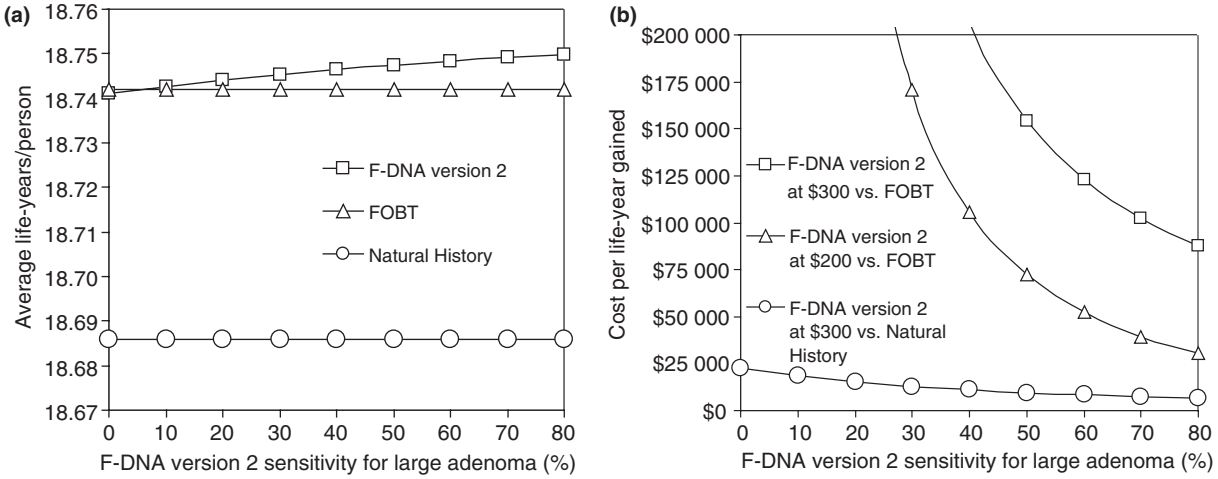

Figure 2. (a) Impact of sensitivity for large adenoma on the effectiveness of faecal DNA testing (F-DNA). The effectiveness of F-DNA increases as sensitivity for large adenoma improves. (b) Impact of sensitivity for large adenoma and test cost on the cost-effectiveness of F-DNA. At a test cost of $200 and test sensitivity for large adenoma of >60%, F-DNA version 2 cost <$50 000/life-year gained compared with faecal occult blood testing.

actually decrease total overall CRC-related costs (screening, testing, complications and CRC care) if advanced CRC is treated with novel, costly therapies.[28, 30, 31, 48–51, 78, 79] It is rare for medical interventions to improve outcomes as well as decrease costs. Therefore, the question is often whether an intervention is 'cost-effective'. We have previously estimated that screening 75% of the US population with conventional methods could increase overall CRC-related costs by $1–3 billion/year, accounting for savings in CRC care.[22] However, if costly therapies for advanced CRC become widely used, the economic benefit of prevention and early detection may become large enough that overall savings could be realized by screening.

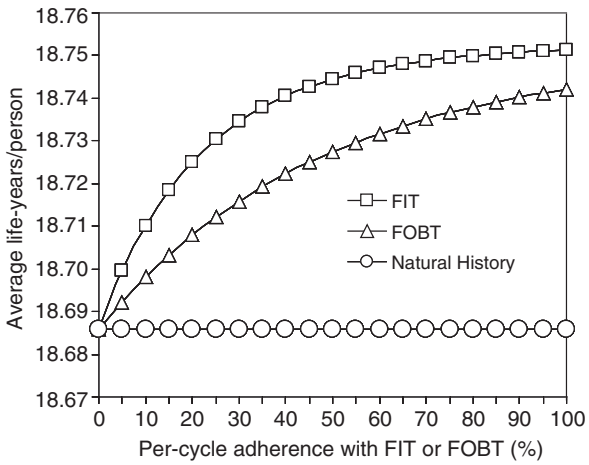

Figure 3. Impact of adherence on the effectiveness of faecal occult blood testing (FOBT) and faecal immunochemical testing (FIT). As adherence with yearly testing decreased, the effectiveness of FOBT decreased steadily, and the effectiveness of FIT decreased significantly with per-cycle adherence below 60%.

With current test cost of $300, F-DNA version 1.1 (the currently available test PreGen Plus, LabCorp) and F-DNA version 2 (the refined test as in Itzkowitz *et al.*[26]) were both cost-effective compared with no screening. Assuming the high advanced CRC care costs associated with novel biological therapies, these strategies cost approximately $17 000/life-year gained (upper 95% confidence interval of approximately $22 000/life-year gained). Without the use of novel therapies for advanced CRC, these strategies were still cost-effective compared with no screening (<$30 000/life-year gained). However, FOBT and FIT were preferred to all F-DNA strategies when they were not compromised by poor adherence.

With current test performance characteristics and good adherence, substantial decreases in test cost would be required for any F-DNA test to become cost-effective compared with FOBT. F-DNA test cost would need to be $40–60 for F-DNA versions 1.1 and 2 to compare favourably with FOBT at a threshold of $50 000/life-year gained. More dramatically, FIT dominated F-DNA strategies in most sensitivity analyses,

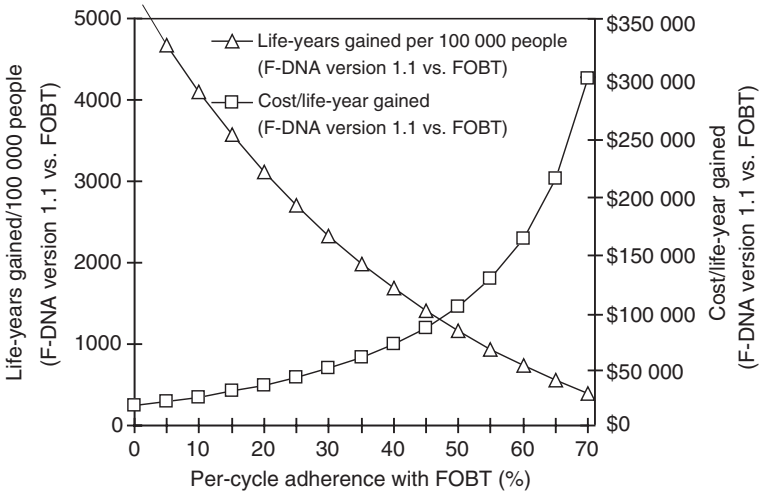

Figure 4. Impact of adherence on the effectiveness and cost-effectiveness of faecal DNA testing (F-DNA) version 1.1 compared with faecal occult blood testing (FOBT). F-DNA version 1.1 became more effective than FOBT when the per-cycle adherence with FOBT fell below 85%, and it cost an incremental $50 000/life-year gained when the per-cycle adherence with FOBT was 31%.

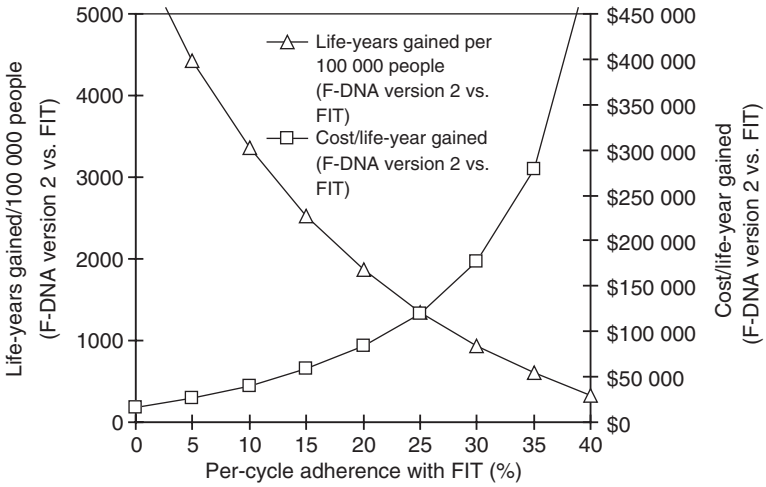

Figure 5. Impact of adherence on the effectiveness and cost-effectiveness of faecal DNA testing (F-DNA) version 2 compared with faecal immunochemical testing (FIT). F-DNA version 2 became more effective than FIT when the per-cycle adherence with FIT fell below 50%, and it cost an incremental $100 000/life-year gained when per-cycle adherence with FIT was 22%.

and it was preferred even when the F-DNA test was assumed to be free.

Early detection of CRC, as well as CRC prevention through removal of adenomas, underlies the benefit of screening. In the base case, we assumed low F-DNA sensitivity for large adenoma. Better sensitivity for large adenoma would improve F-DNA's effectiveness (Figure 2a), but the effect appears less dramatic than we expected initially. This result depends on the assumption that most CRCs remain localized or regional for several years, and can therefore be detected at a high rate with a relatively sensitive test that is performed every 3 years. Similarly, for adenomas that 'dwell' for many years, repeated testing with only a fair test has a reasonably high cumulative sensitivity. The predictions of our model as regards the effectiveness of FOBTs are very close to the results of clinical trials,[22, 32, 33] giving us confidence as regards our predictions for F-DNA. However, if the fraction of rapidly advancing adenomas or tumours is higher than reflected in our current model, the benefit of improved sensitivity for large adenoma may be underestimated.

Not surprisingly, we found that adherence over time is a key determinant of the effectiveness of strategies that rely on frequent testing (Figure 3). Even in the idealized setting of a controlled trial, adherence to annual or biannual FOBT is less than ideal.[32, 33, 36, 38] In clinical practice, it has been difficult to achieve ongoing high rates of adherence with FOBT,[39, 42] and the follow-up of abnormal tests is difficult to ensure.[32, 33, 36, 38, 41, 61] Furthermore, patient preferences for screening options vary.[16, 84–90] Because changing the adherence rates of multiple strategies simultaneously is cumbersome, we compared F-DNA with perfect adherence against FOBT and FIT with imperfect adherence (Figures 4 and 5). It is

conceivable that F-DNA could be considered cost-effective compared with FOBT or FIT in populations that demonstrate good to excellent adherence with testing every 3 years, but which would otherwise have very poor adherence with yearly testing. Further study is required in this area.

In persons adhering perfectly with screening, which reflects optimal efficacy, screening COLO decreased CRC incidence more than annual FIT, but the average life-expectancy with FIT was higher than with screening colonoscopy. This is explained by the fact that most CRCs were diagnosed at treatable stages. The generalizable conclusion is that among persons who can comply with frequent testing, highly sensitive and inexpensive non-invasive testing may be comparable to much less frequent screening with colonoscopy.

The current reappraisal raises important points when compared with our first analysis of F-DNA.[20] As F-DNA's test performance has improved and its cost has decreased, it has become more cost-effective when compared with no screening, an effect that is accentuated as the cost of CRC care increases. However, colonoscopy remains preferred over F-DNA with current parameters. In our first analysis, we did not focus on the comparison between stool-based tests, which is the principal subject of our current reappraisal. Our current results highlight that, in the setting of good adherence, FOBT and FIT are likely to be preferred to F-DNA.

Our analysis has some limitations. Indirect costs were not included. Patterns of adherence over time are likely to be complex, and such considerations are beyond the scope of the current analyses. Finally, as in all decision analyses, there is uncertainty surrounding important inputs. However, we have addressed the key variables in extensive sensitivity analyses to be able to draw conclusions that may focus future clinical research and inform policy decisions.

In conclusion, our analyses suggest that as the costs of care for advanced CRC increase because of use of novel but costly biological therapies, screening with reasonably effective and inexpensive methods such as FOBT and FIT can be not only cost-effective, but also potentially cost-saving. The evolution of test performance characteristics and decrease in test cost for F-DNA have translated into improved cost-effectiveness for F-DNA compared with no screening, but presently FOBT and FIT remain preferred to F-DNA in populations with high adherence to yearly testing. F-DNA with excellent adherence can be considered cost-effective compared with FOBT or FIT in populations with very poor adherence to yearly testing. With excellent annual adherence, sensitive and inexpensive stool-based testing such as FIT may be comparable to screening colonoscopy.

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REFERENCES

1 Levin B, Brooks D, Smith RA, Stone A. Emerging technologies in screening for colorectal cancer: CT colonography, immunochemical fecal occult blood tests, and stool screening using molecular markers. *CA Cancer J Clin* 2003; **53**: 44–55.

2 Jemal A, Murray T, Ward E, *et al.* Cancer statistics, 2005. *CA Cancer J Clin* 2005; **55**: 10–30.

3 Pignone M, Rich M, Teutsch SM, Berg AO, Lohr KN. Screening for colorectal cancer in adults at average risk: a summary of the evidence for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; **137**: 132–41.

4 Pignone M, Saha S, Hoerger T, Mandelblatt J. Cost-effectiveness analyses of colorectal cancer screening: a systematic review for the U.S. Preventive Services Task Force. *Ann Intern Med* 2002; **137**: 96–104.

5 Eddy DM. Screening for colorectal cancer. *Ann Intern Med* 1990; **113**: 373–84.

6 Lieberman DA. Cost-effectiveness model for colon cancer screening. *Gastroenterology* 1995; **109**: 1781–90.

7 Frazier AL, Colditz GA, Fuchs CS, Kuntz KM. Cost-effectiveness of screening for colorectal cancer in the general population. *JAMA* 2000; **284**: 1954–61.

8 Sonnenberg A, Delco F, Inadomi J. Cost-effectiveness of colonoscopy in screening for colorectal cancer. *Ann Intern Med* 2000; **133**: 573–84.

9 Wagner JL, Tunis S, Brown M, Ching A, Almeida R. Cost-effectiveness of colorectal cancer screening in average risk adults. In: Young G, Rozen P, Levin B, eds. *Prevention and Early Detection of Colorectal Cancer*. Philadelphia: WB Saunders, 1996: 321–56.

10 Winawer SJ, Fletcher RH, Miller L, *et al.* Colorectal cancer screening: clinical guidelines and rationale. *Gastroenterology* 1997; **112**: 594–642.
11 Ladabaum U, Chopra CL, Huang G, Scheiman JM, Chernew ME, Fendrick AM. Aspirin as an adjunct to screening for prevention of sporadic colorectal cancer. A cost-effectiveness analysis. *Ann Intern Med* 2001; **135**: 769–81.
12 Vijan S, Hwang EW, Hofer TP, Hayward RA. Which colon cancer screening test? A comparison of costs, effectiveness, and compliance. *Am J Med* 2001; **111**: 593–601.
13 Khandker RK, Dulski JD, Kilpatrick JB, Ellis RP, Mitchell JB, Baine WB. A decision model and cost-effectiveness analysis of colorectal cancer screening and surveillance guidelines for average-risk adults. *Int J Technol Assess Health Care* 2000; **16**: 799–810.
14 Chao A, Connell CJ, Cokkinides V, Jacobs EJ, Calle EE, Thun MJ. Underuse of screening sigmoidoscopy and colonoscopy in a large cohort of US adults. *Am J Public Health* 2004; **94**: 1775–81.
15 Colorectal cancer test use among persons aged > or = 50 years – United States, 2001. *MMWR Morb Mortal Wkly Rep* 2003; **52**: 193–6.
16 Schroy PC, Heeren TC. A comparative study of patient perceptions and screening preferences for stool-based DNA testing (SBDNA), fecal occult blood testing (FOBT) or colonoscopy (CS) (Abstract). *Gastroenterology* 2003; **124**: A-77.
17 Schroy PC, Heeren TC. Patient perceptions of stool-based DNA testing for colorectal cancer screening. *Am J Prev Med* 2005; **28**: 208.
18 Berger BM, Schroy PC 3rd, Rosenberg JL, *et al.* Colorectal cancer screening using stool DNA analysis in clinical practice: early clinical experience with respect to patient acceptance and colonoscopic follow-up of abnormal tests. *Clin Colorectal Cancer* 2006; **5**: 338–43.
19 Seeff LC, Manninen DL, Dong FB, *et al.* Is there endoscopic capacity to provide colorectal cancer screening to the unscreened population in the United States? *Gastroenterology* 2004; **127**: 1661–9.
20 Song K, Fendrick AM, Ladabaum U. Fecal DNA testing compared to conventional colorectal cancer screening methods: a decision analysis. *Gastroenterology* 2004; **126**: 1270–9.
21 Imperiale TF, Ransohoff DF, Itzkowitz SH, Turnbull BA, Ross ME. Fecal DNA versus fecal occult blood for colorectal-cancer screening in an average-risk population. *N Engl J Med* 2004; **351**: 2704–14.
22 Ladabaum U, Song K. Projected national impact of colorectal cancer screening on clinical and economic outcomes and health services demand. *Gastroenterology* 2005; **129**: 1151–62.
23 Olson J, Whitney DH, Durkee K, Shuber AP. DNA stabilization is critical for maximizing performance of fecal DNA-based colorectal cancer tests. *Diagn Mol Pathol* 2005; **14**: 183.
24 Whitney D, Skoletsky J, Moore K, *et al.* Enhanced retrieval of DNA from human fecal samples results in improved performance of colorectal cancer screening test. *J Mol Diagn* 2004; **6**: 386.
25 Rashid A, Issa JP. CpG island methylation in gastroenterologic neoplasia: a maturing field. *Gastroenterology* 2004; **127**: 1578.
26 Itzkowitz SH, Jandorf L, Brand R, *et al.* Improved fecal DNA test for colorectal cancer screening. *Clin Gastroenterol Hepatol* 2007; **5**: 111–7.
27 Gerber HP, Ferrara N. Pharmacology and pharmacodynamics of bevacizumab as monotherapy or in combination with cytotoxic therapy in preclinical studies. *Cancer Res* 2005; **65**: 671–80.
28 Hurwitz H, Fehrenbacher L, Novotny W, *et al.* Bevacizumab plus irinotecan, fluorouracil, and leucovorin for metastatic colorectal cancer. *N Engl J Med* 2004; **350**: 2335–42.
29 Mendelsohn J, Baselga J. Status of epidermal growth factor receptor antagonists in the biology and treatment of cancer. *J Clin Oncol* 2003; **21**: 2787–99.
30 Cunningham D, Humblet Y, Siena S, *et al.* Cetuximab monotherapy and cetuximab plus irinotecan in irinotecan-refractory metastatic colorectal cancer. *N Engl J Med* 2004; **351**: 337–45.
31 Schrag D. The price tag on progress – chemotherapy for colorectal cancer. *N Engl J Med* 2004; **351**: 317–9.
32 Mandel JS, Bond JH, Church TR, *et al.* Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. *N Engl J Med* 1993; **328**: 1365–71.
33 Mandel JS, Church TR, Bond JH, *et al.* The effect of fecal occult-blood screening on the incidence of colorectal cancer. *N Engl J Med* 2000; **343**: 1603–7.
34 Bat L, Pines A, Ron E, Niv Y, Arditi E, Shemesh E. A community-based program of colorectal screening in an asymptomatic population: evaluation of screening tests and compliance. *Am J Gastroenterol* 1986; **81**: 647–51.
35 Bond JH. The place of fecal occult blood test in colorectal cancer screening in 2006: the U.S. perspective. *Am J Gastroenterol* 2006; **101**: 219–21.
36 Hardcastle JD, Chamberlain JO, Robinson MH, *et al.* Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996; **348**: 1472–7.
37 Ioannou GN, Chapko MK, Dominitz JA. Predictors of colorectal cancer screening participation in the United States. *Am J Gastroenterol* 2003; **98**: 2082–91.
38 Kronborg O, Fenger C, Olsen J, Jorgensen OD, Sondergaard O. Randomised study of screening for colorectal cancer with faecal-occult-blood test. *Lancet* 1996; **348**: 1467–71.
39 Liang SY, Phillips KA, Nagamine M, Ladabaum U, Haas JS. Rates and predictors of colorectal cancer screening. *Prev Chronic Dis* 2006; **3**: A117.
40 Meissner HI, Breen N, Klabunde CN, Vernon SW. Patterns of colorectal cancer screening uptake among men and women in the United States. *Cancer Epidemiol Biomarkers Prev* 2006; **15**: 389–94.
41 Morris JB, Stellato TA, Guy BB, Gordon NH, Berger NA. A critical analysis of the largest reported mass fecal occult blood screening program in the United States. *Am J Surg* 1991; **161**: 101–5; discussion 105–6.
42 Myers RE, Balshem AM, Wolf TA, Ross EA, Millner L. Adherence to continuous screening for colorectal neoplasia. *Med Care* 1993; **31**: 508–19.
43 Seeff LC, Nadel MR, Klabunde CN, *et al.* Patterns and predictors of colorectal cancer test use in the adult U.S. population. *Cancer* 2004; **100**: 2093–103.
44 Shapiro JA, Seeff LC, Nadel MR. Colorectal cancer-screening tests and associated health behaviors. *Am J Prev Med* 2001; **21**: 132–7.
45 Ladabaum U, Song K, Fendrick AM. Colorectal neoplasia screening with virtual colonoscopy: when, at what cost, and with what national impact? *Clin Gastroenterol Hepatol* 2004; **2**: 554–63.
46 CMS Clinical Laboratory Fee Schedule. Available at: http://www.cms.hhs.gov/ClinicalLabFeeSched/02_clinlab.asp#TopOfPage, accessed on 19 April 2007.

47 Ladabaum U, Scheiman JM, Fendrick AM. Potential effect of cyclooxygenase-2-specific inhibitors on the prevention of colorectal cancer: a cost-effectiveness analysis. *Am J Med* 2003; **114**: 546–54.

48 Bernold DM, Sinicrope FA. Advances in chemotherapy for colorectal cancer. *Clin Gastroenterol Hepatol* 2006; **4**: 808–21.

49 Kabbinavar F, Hurwitz HI, Fehrenbacher L, *et al.* Phase II, randomized trial comparing bevacizumab plus fluorouracil (FU)/leucovorin (LV) with FU/LV alone in patients with metastatic colorectal cancer. *J Clin Oncol* 2003; **21**: 60–5.

50 Meyerhardt JA, Mayer RJ. Systemic therapy for colorectal cancer. *N Engl J Med* 2005; **352**: 476–87.

51 Saltz LB, Meropol NJ, Loehrer PJ Sr, Needle MN, Kopit J, Mayer RJ. Phase II trial of cetuximab in patients with refractory colorectal cancer that expresses the epidermal growth factor receptor. *J Clin Oncol* 2004; **22**: 1201–8.

52 Life tables. In: *Vital Statistics of the United States. Preprint of Vol. II, Mortality, Part A, Section 6*. Hyattsville, MD: National Center for Health Statistics, 1998: Section 6, pp. 1–18.

53 Winawer S, Fletcher R, Rex D, *et al.* Colorectal cancer screening and surveillance: clinical guidelines and rationale – update based on new evidence. *Gastroenterology* 2003; **124**: 544–60.

54 Winawer SJ, Zauber AG, Fletcher RH, *et al.* Guidelines for colonoscopy surveillance after polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer and the American Cancer Society. *Gastroenterology* 2006; **130**: 1872–85.

55 Smith RA, Cokkinides V, Eyre HJ. American Cancer Society guidelines for the early detection of cancer, 2003. *CA Cancer J Clin* 2003; **53**: 27–43.

56 Allison JE. Colon Cancer Screening Guidelines 2005: the fecal occult blood test option has become a better FIT. *Gastroenterology* 2005; **129**: 745–8.

57 Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996; **334**: 155–9.

58 Rozen P, Knaani J, Samuel Z. Performance characteristics and comparison of two immunochemical and two guaiac fecal occult blood screening tests for colorectal neoplasia. *Dig Dis Sci* 1997; **42**: 2064–71.

59 Greenberg PD, Bertario L, Gnauck R, *et al.* A prospective multicenter evaluation of new fecal occult blood tests in patients undergoing colonoscopy. *Am J Gastroenterol* 2000; **95**: 1331–8.

60 Morikawa T, Kato J, Yamaji Y, Wada R, Mitsushima T, Shiratori Y. A comparison of the immunochemical fecal occult blood test and total colonoscopy in the asymptomatic population. *Gastroenterology* 2005; **129**: 422–8.

61 Ko CW, Dominitz JA, Nguyen TD. Fecal occult blood testing in a general medical clinic: comparison between guaiac-based and immunochemical-based tests. *Am J Med* 2003; **115**: 111–4.

62 Nakama H, Yamamoto M, Kamijo N, *et al.* Colonoscopic evaluation of immunochemical fecal occult blood test for detection of colorectal neoplasia. *Hepatogastroenterology* 1999; **46**: 228–31.

63 Rozen P, Knaani J, Samuel Z. Comparative screening with a sensitive guaiac and specific immunochemical occult blood test in an endoscopic study. *Cancer* 2000; **89**: 46–52.

64 Vilkin A, Rozen P, Levi Z, *et al.* Performance characteristics and evaluation of an automated-developed and quantitative, immunochemical, fecal occult blood screening test. *Am J Gastroenterol* 2005; **100**: 2519–25.

65 Wong BC, Wong WM, Cheung KL, *et al.* A sensitive guaiac faecal occult blood test is less useful than an immunochemical test for colorectal cancer screening in a Chinese population. *Aliment Pharmacol Ther* 2003; **18**: 941–6.

66 Young GP, St John DJ, Cole SR, *et al.* Prescreening evaluation of a brush-based faecal immunochemical test for haemoglobin. *J Med Screen* 2003; **10**: 123–8.

67 Enterix Corporation. Available at: http://www.insuretest.com/professionals/invitro.html, accessed on October 2006.

68 Laupacis A, Feeny D, Detsky AS, Tugwell PX. How attractive does a new technology have to be to warrant adoption and utilization? Tentative guidelines for using clinical and economic evaluations. *CMAJ* 1992; **146**: 473–81.

69 Laupacis A, Feeny D, Detsky AS, Tugwell PX. Tentative guidelines for using clinical and economic evaluations revisited. *CMAJ* 1993; **148**: 927–9.

70 Tengs TO, Adams ME, Pliskin JS, *et al.* Five-hundred life-saving interventions and their cost-effectiveness. *Risk Anal* 1995; **15**: 369–90.

71 Eddy DM, Nugent FW, Eddy JF, *et al.* Screening for colorectal cancer in a high-risk population. Results of a mathematical model. *Gastroenterology* 1987; **92**: 682–92.

72 *The DRG Handbook: Comparative Clinical and Financial Standards*. Baltimore, MD: HCIA, Inc. and Ernst & Young LLP, 1997.

73 Brown ML, Riley GF, Potosky AL, Etzioni RD. Obtaining long-term disease specific costs of care: application to Medicare enrollees diagnosed with colorectal cancer. *Med Care* 1999; **37**: 1249–59.

74 Fireman BH, Quesenberry CP, Somkin CP, *et al.* Cost of care for cancer in a health maintenance organization. *Health Care Financ Rev* 1997; **18**: 51–76.

75 Taplin SH, Barlow W, Urban N, *et al.* Stage, age, comorbidity, and direct costs of colon, prostate, and breast cancer care. *J Natl Cancer Inst* 1995; **87**: 417–26.

76 Greene FL. *American Joint Committee on Cancer, American Cancer Society. AJCC Cancer Staging Manual*, 6th edn. New York: Springer, 2002.

77 NCDB Site by Stage Distribution of Cancer – 2003. Available at: http://www.facs.org/cancer/ncdb/ver7_site_stage_2003.htm, accessed on 20 April 2007.

78 Goldberg RM, Sargent DJ, Morton RF, *et al.* A randomized controlled trial of fluorouracil plus leucovorin, irinotecan, and oxaliplatin combinations in patients with previously untreated metastatic colorectal cancer. *J Clin Oncol* 2004; **22**: 23–30.

79 Giantonio BJ. Bevacizumab in the treatment of metastatic colorectal cancer (mCRC) in second- and third-line settings. *Semin Oncol* 2006; **5** (Suppl. 10): S15–8.

80 U.S. Department of Labor, Bureau of Labor Statistics, Consumer Price Indexes, Available at: http://www.bls.gov/cpi/, accessed on 12 February 2008, accessed on 20 April 2007.

81 Lipscomb J, Weinstein MC, Torrance GW. Time preference. In: Gold MR, Siegel JE, Russell LB, Weinstein MC, eds. *Cost-effectiveness in Health and Medicine*. New York, NY: Oxford University Press, 1996: 214–35.

82 Hardcastle JD, Thomas WM, Chamberlain J, *et al.* Randomised, controlled trial of faecal occult blood screening for colorectal cancer. Results for first 107,349 subjects. *Lancet* 1989; **1**: 1160–4.

83 Loeve F, Brown ML, Boer R, van Ballegooijen M, van Oortmarssen GJ, Habbema JDF. Endoscopic colorectal cancer screening: a cost-saving analysis. *J Natl Cancer Inst* 2000; **92**: 557–63.
84 Ling BS, Moskowitz MA, Wachs D, Pearson B, Schroy PC. Attitudes toward colorectal cancer screening tests. *J Gen Intern Med* 2001; **16**: 822–30.
85 Dominitz JA, Provenzale D. Patient preferences and quality of life associated with colorectal cancer screening. *Am J Gastroenterol* 1997; **92**: 2171–8.
86 Leard LE, Savides TJ, Ganiats TG. Patient preferences for colorectal cancer screening. *J Fam Pract* 1997; **45**: 211–8.
87 Nelson RL, Schwartz A. A survey of individual preference for colorectal cancer screening technique. *BMC Cancer* 2004; **4**: 76.
88 Pignone M, Bucholtz D, Harris R. Patient preferences for colon cancer screening. *J Gen Intern Med* 1999; **14**: 432–7.
89 Pignone M, Harris R, Kinsinger L. Videotape-based decision aid for colon cancer screening. A randomized, controlled trial. *Ann Intern Med* 2000; **133**: 761–9.
90 Sheikh RA, Kapre S, Calof OM, Ward C, Raina A. Screening preferences for colorectal cancer: a patient demographic study. *South Med J* 2004; **97**: 224–30.
91 Clark JC, Collan Y, Eide TJ, *et al.* Prevalence of polyps in an autopsy series from areas with varying incidence of large-bowel cancer. *Int J Cancer* 1985; **36**: 179–86.
92 Vatn MH, Stalsberg H. The prevalence of polyps of the large intestine in Oslo: an autopsy study. *Cancer* 1982; **49**: 819–25.
93 Williams AR, Balasooriya BA, Day DW. Polyps and cancer of the large bowel: a necropsy study in Liverpool. *Gut* 1982; **23**: 835–42.
94 Arminski TC, McLean DW. Incidence and distribution of adenomatous polyps of the colon and rectum based on 1,000 autopsy examinations. *Dis Colon Rectum* 1964; **19**: 249–61.
95 Rickert RR, Auerbach O, Garfinkel L, Hammond EC, Frasca JM. Adenomatous lesions of the large bowel: an autopsy survey. *Cancer* 1979; **43**: 1847–57.
96 Yee J, Akerkar GA, Hung RK, Steinauer-Gebauer AM, Wall SD, McQuaid KR. Colorectal neoplasia: performance characteristics of CT colonography for detection in 300 patients. *Radiology* 2001; **219**: 685–92.
97 Ries LAG, Kosary CL, Hankey BF, Miller BA, Harras A, Edwards BK (eds). *SEER Cancer Statistics Review, 1973–1994*, NIH Pub. No. 97-2789. Bethesda, MD: National Cancer Institute, 1997.
98 Winawer SJ, Zauber AG, Ho MN, *et al.* Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. *N Engl J Med* 1993; **329**: 1977–81.