Faecal DNA testing compared with conventional colorectal cancer screening methods: a decision analysis

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Record Status
This is a critical abstract of an economic evaluation that meets the criteria for inclusion on NHS EED. Each abstract contains a brief summary of the methods, the results and conclusions followed by a detailed critical assessment on the reliability of the study and the conclusions drawn.

Health technology
The use of faecal DNA tests (F-DNA) versus conventional screening strategies for the detection of colorectal cancer (CRC). The conventional strategies were faecal occult blood testing (FOBT) and/or sigmoidoscopy, and colonoscopy (COLO).

Type of intervention
Screening.

Economic study type
Cost-effectiveness analysis.

Study population
The study population comprised a hypothetical cohort of 50-year-old persons at average risk of CRC.

Setting
The setting of the study was likely to be primary and secondary care. The study was conducted in the USA.

Dates to which data relate
The effectiveness data were obtained from literature published from 1964 to 2003. The cost data referred to 1987 to 2004. Year 2003 prices were used.

Source of effectiveness data
The effectiveness data were derived from a review or synthesis of completed studies.

Modelling
A Markov model was developed, using DATA Pro (TreeAge software), to estimate the costs and outcomes associated with each screening strategy assessed. The principal health states in the model were normal, small polyp, large polyp, CRC (localised, regional or distant) and death (both CRC and non-CRC related). A hypothetical cohort of 50-year-old persons progressed through the model for 50 1-year cycles, until age 100 or death. CRC arose from polyps but could also develop without a polypoid precursor. If people undergoing screening were found positive, then COLO followed, with polypectomy or biopsy as necessary. In the case of a normal COLO after a positive F-DNA, it was assumed that patients and clinicians would opt for screening COLO as the 'gold' standard. The diagnosis of CRC was followed by treatment and patients surviving entered surveillance, characterised by COLO 3 years after diagnosis and every 5 years thereafter. After polyp detection, surveillance consisted of COLO every 5 years. In all strategies, screening and surveillance were performed up to age 80 years. After that age, COLO was performed only to evaluate symptoms.
Outcomes assessed in the review
The outcomes assessed were:

the polyp prevalence at age 50;

the annual transition rates to large polyp from small polyp, to CRC from large polyp, and to CRC without polypoid precursor;

the symptomatic presentation of localised and regional CRC;

the mortality rate from treated CRC (both localised and regional) and from CRC treatment;

the age-specific non-CRC mortality rates;

the mean survival from distant cancer;

the test characteristics (sensitivity and specificity) of F-DNA, FOBT, FS and COLO for CRC, large and small polyps;

the percentage of polyps or CRC within reach of a sigmoidoscope;

the rate of major complications for COLO and FS; and

the mortality rates related to COLO and FS.

Study designs and other criteria for inclusion in the review
English language literature using the terms colorectal neoplasm, colorectal polyp, screening, occult blood, sigmoidoscopy, colonoscopy, faecal DNA testing, cost and cost-effectiveness was identified. No further inclusion criteria were reported.

Sources searched to identify primary studies
MEDLINE was searched from 1980 to 2003. The authors also reviewed abstracts from national meetings, data from Medicare, and relevant unpublished data from EXACT Sciences Corporation (a company marketing an F-DNA test). Finally, published literature reviews from a multidisciplinary expert panel from the Agency for Health Care Policy and Research and by the Office of Technology Assessment were considered.

Criteria used to ensure the validity of primary studies
The criteria used were not specified.

Methods used to judge relevance and validity, and for extracting data
The methods used were not specified.

Number of primary studies included
Approximately 15 primary studies were included in the review.

Methods of combining primary studies
The results of primary studies referring to F-DNA test characteristics were combined by pooling all studies. Also, by using the mean between average values calculated after the exclusion of unpublished data, and average values estimated after the exclusion of the above data, plus the exclusion of one report with particularly high sensitivities. Results referring to other input parameters were possibly combined, but the methods used were not specified.
Investigation of differences between primary studies
Differences between the primary studies were not discussed.

Results of the review
The polyp prevalence at age 50 was 15% (95% of these were small polyps and 5% were large polyps).

The annual transition rate to large polyp from small polyp was 1.5%, to CRC from large polyp 5%, and to CRC without polypoid precursor 0.006 to 0.086%, depending on age.

Over 2 years, the symptomatic presentation of localised CRC was 22% per year and that for regional CRC 40% per year.

In the first 5 years, the mortality rate of treated localised and regional CRC was 1.74% (localised) and 8.6% (regional), respectively, per year.

The mortality rate from CRC treatment was 2%.

The mean survival from distant CRC was 1.9 years.

The sensitivity of F-DNA was 65% for CRC and 40% for large polyps. The specificity of F-DNA was 95%.

The sensitivity of FOBT was 40% for CRC, 10% for large polyps and 8% for small polyps. The specificity of FOBT was 92%.

The sensitivity of FS for lesions within reach of a sigmoidoscope was 90% for CRC, 80% for large polyps and 70% for small polyps. The specificity of FS for lesions within reach of a sigmoidoscope was 95%.

The percentage of polyps or CRC within reach of a sigmoidoscope was 50%.

The sensitivity of COLO was 95% for CRC, 90% for large polyps and 85% for small polyps.

The rate of major complications was 0.1% for COLO and 0.01% for FS.

The mortality rates related to COLO and FS were 0.01% (COLO) and 0.001% (FS), respectively.

The age-specific non-CRC mortality rates were not reported.

Methods used to derive estimates of effectiveness
Assumptions were made in the model.

Estimates of effectiveness and key assumptions
The model assumed perfect adherence of the study population in terms of screening strategies and surveillance.

Measure of benefits used in the economic analysis
The measure of benefits used was the average number of life-years (LY) gained per person. This measure was discounted at an annual rate of 3%. In addition, the number of CRC cases by stage and the number of deaths by cause were estimated for each screening strategy assessed. Finally, the average number of COLO procedures that a person underwent between 50 and 80 years of age with each strategy was determined for both the total cohort and for persons reaching or surpassing 80 years of age.

Direct costs
The perspective of the study was not stated, but it was consistent with that of a third-party payer. The costs covered screening (F-DNA, FOBT, FS, COLO), FS with biopsy, COLO with lesion removal, endoscopy complications, and CRC care by stage (localised, regional and distant). The costs and the quantities were not analysed separately. Procedural costs were estimated from Medicare fee schedules, which included professional fees and procedure reimbursement, and also from a published study that reported the costs incurred in a health maintenance organisation. The base-case cost of F-DNA was equal to the lowest available laboratory charge at the time of the study. The costs of complications were derived from relevant diagnostic-related groups. The costs associated with CRC care were taken from published reports. For each base-case cost input (with the exception of F-DNA cost), the average value reported in the published sources was used.

The total costs were derived using modelling. All the costs were updated to 2003 prices using the medical services component of the Consumer Price Index. The costs were appropriately discounted at an annual rate of 3% because they were incurred over lifetime or 50 years of follow-up.

**Statistical analysis of costs**
The costs were treated deterministically. No statistical analysis of the costs was undertaken.

**Indirect Costs**
The indirect costs were not included in the analysis.

**Currency**
US dollars ($).

**Sensitivity analysis**
A sensitivity analysis was conducted to test the robustness of the results under a range of input values reported in the published literature. A one-way sensitivity analysis was performed on all model inputs. Two-way sensitivity analyses were carried out on critical variables. A Monte Carlo simulation was also performed, in which the model inputs varied simultaneously and randomly for 3,000 iterations, assuming flat distributions for all variables. In addition, a threshold analysis was undertaken to determine the attributes of F-DNA under which the test would approximate the effectiveness and cost of COLO. First, the base-case test characteristics were held constant and the screening interval and test cost were altered. Second, the attributes of the “ideal test” were determined.

**Estimated benefits used in the economic analysis**
The discounted average LY per person were 18.686 with no screening, 18.731 with F-DNA, 18.734 with FS, 18.742 with FOBT, 18.748 with COLO and 18.749 with FS-FOBT.

The incremental LY gained per 100,000 persons were 4,560 for F-DNA versus no screening, 260 for FS versus F-DNA, 810 for FOBT versus FS, 560 for COLO versus FOBT and 90 for FS-FOBT versus COLO.

The total number of CRC cases per 100,000 persons from age 50 to 80 years was 4,200 for no screening, 2,740 for F-DNA, 1,860 for FS, 2,290 for FOBT, 1,230 for COLO and 1,480 for FS-FOBT.

The proportion of deaths attributable to CRC was 2.9% for no screening, 1.4% for F-DNA, 1.0% for FS, 0.9% for FOBT, 0.6% for COLO and 0.6% for FS-FOBT.

The average number of COLO procedures that a person underwent from age 50 to 80 years in the total cohort of persons was 0.8 with F-DNA, 1.3 with FS, 1.8 with FOBT, 2.3 with FS-FOBT and 3.8 with COLO.

In patients reaching or exceeding 80 years of age, these numbers were 1.3 for F-DNA, 1.9 for FS, 2.4 for FOBT, 2.9 for FS-FOBT, and 4.8 for COLO.
With the exception of deaths related to COLO and FS, the side effects of screening strategies were not considered in the estimation of the benefits.

Cost results
The discounted, average total cost per person was $1,813 for no screening, $3,987 for F-DNA, $2,557 for FS, $2,215 for FOBT, $2,865 for COLO and $2,879 for FS-FOBT.

These costs were associated with screening until the age of 80 years, COLO for evaluation of symptoms over lifetime, and CRC care over lifetime.

The costs of treating endoscopy complications were included in the analysis.

Synthesis of costs and benefits
The costs and benefits were combined in the form of incremental cost-effectiveness ratios (ICERs), which expressed the incremental costs per LY gained. When a strategy resulted in more LY and was less costly than another (i.e. it dominated), it was not necessary to calculate the ICER.

Compared with no screening, the ICERs were $47,700/LY gained for F-DNA, $15,500/LY gained for FS, $7,200/LY gained for FOBT, $17,010/LY gained for COLO and $17,000/LY gained for FS-FOBT. F-DNA was dominated by all other screening strategies included in the analysis. FS was dominated by FOBT.

COLO incurred an additional $22,500/LY gained compared with FS and $115,600/LY gained compared with FOBT.

FS-FOBT resulted in an additional $22,100/LY gained compared with FS, $102,100/LY gained compared with FOBT and $16,300/LY gained compared with COLO.

The results were generally robust in the one-way sensitivity analysis. F-DNA remained reasonably cost-effective in comparison with no screening for all scenarios examined.

COLO dominance over F-DNA remained nearly in all scenarios. The exception was a 50% reduction in F-DNA cost that resulted in an additional $6,000/LY gained incurred by COLO.

FOBT dominance over F-DNA was also robust, except when F-DNA sensitivity was substantially improved (91% and 82% for CRC and large polyps, respectively), in which case F-DNA became more effective and incurred an additional cost of $307,700/LY gained compared with FOBT.

In the two-way sensitivity analysis, COLO had an ICER of $59,300/LY gained versus F-DNA when the cost of F-DNA was reduced by 50% and the cost of COLO was increased by 50%.

The Monte Carlo simulation showed that COLO dominated F-DNA in 94% of the iterations and FOBT dominated F-DNA in 84% of the iterations.

The threshold analysis demonstrated that, holding constant the F-DNA characteristics, its screening interval would need to reduce to 2 years and its cost would need to decrease to $195 (from $695, which was the base-case value) to make F-DNA comparable to COLO.

Assuming a screening interval of 5 years and a specificity of 95%, the sensitivity of F-DNA would need to increase to 95% for CRC and 81% for large polyps, and its cost would need to fall to $455, to make the effectiveness and cost of F-DNA nearly identical to those of COLO.

Authors' conclusions
Faecal DNA testing (F-DNA) every 5 years appears to have been effective and cost-effective compared with no screening, but inferior to other strategies such as faecal occult blood testing (FOBT) and colonoscopy (COLO). F-DNA
could decrease the national colorectal cancer (CRC) burden if it could improve adherence with screening, particularly where the capacity to perform screening COLO is limited.

**CRD COMMENTARY - Selection of comparators**
The selection of the comparators was implicitly justified, as all of them represented established screening strategies for the detection of CRC. The comparison with no screening allowed the active value of F-DNA screening to be evaluated. Barium enema was not considered because of its significantly poorer sensitivity compared with COLO. You should consider whether any of the comparators used in the analysis represent widely used health technologies in your own setting.

**Validity of estimate of measure of effectiveness**
Although not explicitly stated, it was likely that a systematic review of the literature was undertaken. The methods and conduct of the review were adequately reported. The effectiveness estimates from the primary studies were apparently combined, although the method used was not explicitly reported in all cases. The criteria used to ensure the validity of the primary studies and the method used to judge the relevance and validity of the data were not reported. The authors did not consider the impact of differences between the primary studies when estimating the effectiveness. Sensitivity analyses, which varied the values of the effectiveness estimators, were performed and these enhanced the validity of the results.

**Validity of estimate of measure of benefit**
The estimation of benefits was modelled. The Markov model used for this purpose was appropriate because it estimated the long-term outcomes resulting from CRC screening, and it included all potential steps of screening and stages of CRC development, with transition probabilities derived from the review of the literature.

**Validity of estimate of costs**
The perspective of the study was not explicitly stated, but it was consistent with that of a third-party payer. All the categories of cost relevant to this perspective were included in the analysis. The costs and the quantities were not reported separately, which hinders the generalisability of the results. A sensitivity analysis of the costs was undertaken, using a range of values derived from published sources. Charges were used to proxy prices, therefore the costs did not reflect opportunity costs, but the use of charges in the analysis was consistent with the perspective adopted. Discounting was appropriately undertaken since the costs were incurred over lifetime or 50 years of follow-up. The year to which the prices referred was reported, which enables the results to be reproduced.

**Other issues**
The authors compared their findings with those of other studies and found them consistent. The issue of generalisability to other settings was not addressed. The authors emphasised that the gains related to screening strategies, as predicted by their model, reflected the ideal situation of perfect adherence. However, this was not the case in routine US practice since the participation rates in CRC screening programmes were low. The results of the analysis were reported in full and the authors' conclusions reflected the scope of the analysis.

**Implications of the study**
The authors expressed the opinion that their analysis could help inform policy and clinical decisions pertaining to the available F-DNA test and any improved tests available in the future. They recommended screening COLO as the method of choice for people willing and able to undergo this test and for medical environments with the required infrastructure, followed by frequent FOBT and/or FS. However, they suggested that if Americans who were reluctant to accept conventional CRC screening at the time of the study were persuaded to undergo the non-invasive F-DNA testing, this method should be considered as an alternative screening strategy that could make a valuable contribution to public health.
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None stated.

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Other publications of related interest


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