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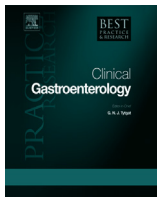

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Economic evaluation of colorectal cancer (CRC) screening

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A B S T R A C T

Because of its incidence and mortality colorectal cancer represents a serious public health issue in industrial countries. In order to reduce its social impact a number of screening strategies have been implemented, which allow an early diagnosis and treatment. These basically include faecal tests and studies that directly explore the colon and rectum. No strategy, whether alone or combined, has proven definitively more effective than the rest, but any such strategy is better than no screening at all. Selecting the most efficient strategy for inclusion in a population-wide program is an uncertain choice. Here we review the evidence available on the various economic evaluations, and conclude that no single method has been clearly identified as most cost-effective; further research in this setting is needed once common economic evaluation standards are established in order to alleviate the methodological heterogeneity prevailing in study results.

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Colorectal cancer is the second leading cause of death in developed countries, both in males and females; when both genders are considered together, it occupies the first place in incidence and represents the second leading cause of cancer-related mortality [1]. This is therefore a significant public health issue in most industrial countries [2].

Lack of awareness regarding the primary risk factors and the difficulty involved in modifying some of the known ones render the primary prevention of this disease a challenging task [3]. In order to reduce the impact of CRC multiple strategies have been suggested for early detection (secondary prevention).

This type of tumour meets the conditions required by a disease susceptible to screening: it is a common, serious health issue with a known clinical course and a symptomatic stage, and early treatment decreases mortality; furthermore, various screening tests are available those are easy to perform, simple, reproducible, valid, and in some cases also inexpensive [4].

The strategies used for population-based CRC screening may be summed up into two categories: faecal tests that identify occult blood through the use of guaiac (gFOBT) or immunological methods (iFOBT), or that identify tumour DNA (tDNA), and tests that directly examine the colon, including sigmoidoscopy, colonoscopy or virtual colonoscopy (VC).

Regarding the efficacy and effectiveness of the various screening strategies the following may be stated:

(1) There is evidence on the efficacy and effectiveness of gFOBT to reduce CRC-related mortality in a mid-risk population [5–8].
(2) iFOBT has proven more sensitive and specific than gFOBT, is more user-friendly, and provides better adherence [9–11].
(3) Regarding sigmoidoscopy, results are variable [12–14] but a decrease in CRC incidence and mortality has been recently reported with this technique [15,16].
(4) Colonoscopy has also shown a decrease in CRC incidence and mortality [17–23], but its cost, side effects, and low participation rates may be limiting this option for CRC screening despite its proven efficacy [24].
(5) Evidence is insufficient on the efficacy and effectiveness of VC [25,26] and DNAt [27–29] as an alternative for use in a screening program on a mid-risk population.
(6) CRC screening has proven effective in the secondary prevention of CRC and, given that it may detect (and excise) precursor lesions, is also effective for primary prevention, but doubts remain on which strategy works best [30]. No single technique has proven more effective than any other, but iFOBT is preferred by many patients as their primary screening strategy.

Which is the best strategy to start up a population-wide program for the prevention of CRC?

The efficacy and effectiveness of a screening test, drug, device, etc., is not enough to warrant its use or implementation. To help in decision-making, a basic tool would be economic evaluations (EE) of the various health care technologies; the latter understood as any methods employed to promote health, prevent and treat diseases, and improve rehabilitation or health care in the long term. The term 'technology' in this context does not only refer to novel medications, sophisticated devices, etc., but also includes health care interventions, care organization, and screening programs.

EE incorporates a number of instruments to achieve efficiency in resource allocation, defined as a maximization of health gains given the limited resources within reach [31].

This efficiency requirement also covers the various population-wide screening strategies for CRC, hence the goal of this paper will be to review the cumulative scientific evidence derived from EE studies assessing these strategies' cost-effectiveness, and to discuss – in the light of their results – which are the best candidates for inclusion in institutional prevention programs for CRC.

Material and methods

We performed a literature search for EE studies regarding CRC screening strategies in symptom-free populations. Strategies discussed included: gFOBT (non-hydrated, rehydrated), iFOBT, DNAt,

sigmoidoscopy, colonoscopy, and VC, either in stand-alone or combined form. The various strategies are compared between themselves and/or with the 'no screening' option.

The search covered the 1998–2013 period, and only included studies in Spanish or English corresponding to category 4 (full EEs) according to the scheme posited by Drummond et al [32] (Table 1). A total of 36 studies were selected following these criteria.

The primary information sources searched included: PubMed, the United Kingdom National Health Service Economic Evaluation Database (NHS EED; http://www.crd.york.ac.uk/crdweb/), the US Tufts Medical Center Cost Effectiveness Analysis Registry (http://www.tufts-nemc.org/cearegistry), Embase, Cochrane Central Register of Controlled Trials, Cochrane Database of Systematic Reviews, Health Technology Assessment database, INAHTA, reports by Spanish health technology assessment agencies, and the Spanish Ministry of Health.

Search terms included: Medline Index terms (MeSH): exp colorectal neoplasm, mass screening, occult blood, guaiac, immunochemistry, exp immunologic tests, costs and cost analysis, sigmoidoscopy, colonoscopy, CT colonography, and Embase index terms: exp large intestine cancer, exp rectum cancer, exp colorectal cancer, cancer screening, exp economic evaluation, exp health care cost.

Cost-effectiveness of CRC screening with gFOBT (Table 2)

Various papers conclude that gFOBT is cost-effective vs no screening and even other programs, including that for breast cancer [33,34]. Some of these studies suggest that associating CRC screening with cervical and breast screening could be most appropriate to improve participation [35].

There is consensus that CRC screening with gFOBT, regardless of chosen approach, is cost-effective vs no screening at all [36]. These programs are cost-effective if we use the informal cost-effectiveness threshold of €30,000 per QALY as a reference [37].

Uncertainties in estimations applied to 'models' and associated with CRC natural history, detected and prevented cancer rates, mortality reduction rates, etc., affect the identification of a most cost-effective strategy [38].

Cost-effectiveness of CRC screening using iFOBT (Table 3)

A study suggested that gFOBT is more cost-effective than iFOBT [39]. Subsequently, Berchi et al [40] suggest that iFOBT, although a more expensive strategy shows a more favourable cost-effectiveness ratio because of higher sensitivity. Within a screening program iFOBT may save more lives than gFOBT without an excessive incremental cost-effectiveness ratio (ICER). Lejeune et al [41] assess CRC screening cost-effectiveness by comparing various strategies – gFOBT vs iFOBT and vs no screening – and conclude that iFOBT could well be the most appropriate test.

Van Rossum LG et al [42] examine iFOBT cost-effectiveness (one single sample, positive when $\geq$100 ng/ml) and gFOBT cost-effectiveness (six samples every three days) vs no screening in a 50–75-year-old population by using real participation rates. They conclude that iFOBT is a dominant strategy, that is, a strategy more effective and less expensive than gFOBT and no screening at all.

Table 1
Classification of economic evaluations for health technologies.

	Costs and consequences are examined	
	No	Yes
Only one option considered	Partial evaluation: 1A Description of results 1B Description of costs	Partial evaluation: 2A Description of costs-results
Two or more options considered	Partial evaluation: 3A Efficacy assessment 3B Cost analysis	Complete evaluation: 4A Cost-minimization analysis (CMA) 4B Cost-effectiveness analysis (CEA) 4C Cost-utility analysis (CUA) 4D Cost-benefit analysis (CBA)

Source: adapted from Table 2.1. in Drummond et al [32]

Table 2
Studies evaluating CRC screening CE when using gFOBT alone or combined with other techniques.

Author/country	EE	Screening technique	Comparator	Results
Whynes [33] UK	CEA	Biennial non-hydrated gFOBT 50–74 years of age Colonoscopy if positive	9 gFOBT strategies No screening	ICER/PLYG gFOBT vs no screening: £1,584
Gyrd–Hansen [34] Denmark	CEA	Annual/biennial non-hydrated gFOBT 45–75 years of age Colonoscopy if positive	60 strategies with varying screening intervals, and ages at both start and end	ICER/PLYG Biennial gFOBT 65–74 yrs: DK17,000; 60–74 yrs: DK18,896; 55–74 yrs: DK23,012 gFOBT/1.5 years 55–74 yrs: DK28,802 Annual gFOBT: 55–74 yrs: DK 35,471 50–74 yrs: DK42,500
Gyrd–Hansen [35] Denmark	CEA review	Annual non-hydrated gFOBT 50–74 years of age Colonoscopy if positive	Breast and cervical cancer screening.	ICER/PLYG tAnnual gFOBT (50–74 yrs): $6,570 Annual mammography (50–69 yrs): $9,060 Cytology/4 yrs (25–59 yrs): $6,455
Helm [36] USA	CEA	Biennial gFOBT (Funen-Nottingham) 45–75 years of age Annual gFOBT (Minnesota) 50–80 years of age Colonoscopy if positive	Between techniques and no screening	ICER/PLYG Biennial gFOBT (Funen-Nottingham) vs no screening: $2,500–2,700 ICER/PLYG Annual gFOBT (Minnesota) vs no screening: $20,500
Stone [38] Australia	CEA CUA	Non-hydrated gFOBT (two per day/three days) 55–69 years of age Colonoscopy if positive	No screening	ICER/QALY: gFOBT vs no screening: AUD17,000 (only costs) AUD12,000 (costs-cost savings by screening) Program extension to 74 years reduces ICER/QALY to $12,000, and to 50 years increases ICER/QALY to $29,000

Pignone et al [43] have reported that biennial iFOBT in 50-to-74-year-old individuals is cost-effective, and that a full program coverage in Australia may be reached with an investment similar to that for other screening programs, including breast cancer.

Disparities exist when considering which cut-off should be used for faecal haemoglobin, and the number of samples needed to consider iFOBT cost-effective. The answer oscillates between a single sample with a cut-off at 110 ng/ml [44], 75 ng/ml [45] and 50 ng/ml [46], and three samples with 50 ng/ml [47].

A recent report evaluated that screening with two iFOBT samples (one positive or mean positive) is more cost-effective than screening with a single sample. By increasing age range or shortening screening interval single-sample iFOBT is more effective than dual-sample iFOBT [48].

López–Bastida et al [49] performed a cost-utility analysis (CUA) by comparing several CRC strategies: iFOBT and annual/biennial gFOBT, sigmoidoscopy every five years, and colonoscopy once or every ten years. They conclude that annual iFOBT is the most cost-effective strategy.

A CUA compared annual gFOBT, annual iFOBT, flexible sigmoidoscopy every five years, colonoscopy every ten years, ADNt every three years, and VC every five years [50]. They conclude that CRC screening with annual iFOBT reduces CRC risk and CRC-related mortality, as well as health care costs when compared to no screening and the remaining strategies.

Cost-effectiveness of CRC screening using DNAt (Table 4)

A number of studies conclude that DNAt is not cost-effective mainly due to its high cost [51,52].

Table 3
Studies evaluating CRC screening CE when using iFOBT alone or combined with other techniques.

Author/country	EE	Screening technique	Comparator	Results
Gyrd–Hansen [39] Denmark	CEA	Annual/biennial non-hydrated gFOBT (55–74 yrs & 50–74 yrs) Annual/Biennial rehydrated gFOBT (55–74 yrs & 50–74 yrs) Annual/Biennial gFOBT Haemoccult II Sensa (55–74 yrs & 50–74 yrs) Annual/Biennial iFOBT (55–74 yrs & 50–74 yrs) Colonoscopy if positive	Between techniques No screening	ICER/PLYG Biennial gFOBT (55–74): DK17,500 Annual gFOBT (55–74): DK30,000 Annual gFOBT (50–74): DK39,000 Annual iFOBT (50–74): DK71,300. Annual rehydrated gFOBT (50–74): DK138,100.
Berchi [40] France	CEA	Biennial non-hydrated gFOBT (two samples/three days) (50–74 years of age) Biennial iFOBT (50–74 years of age) (one sample/two days) Colonoscopy if positive	Between techniques	ICER/PLYG iFOBT vs gFOBT over 20 years: €2,980 Same over ten years: €7,458
Lejeune [41] France	CEA	Biennial non-hydrated gFOBT (three samples) (50–74 years of age) Biennial iFOBT (50–74 years of age) (two samples) Colonoscopy if positive	Between techniques No screening	ICER/PLYG gFOBT vs no screening: €2,739 iFOBT vs no screening: €2,819 iFOBT vs gFOBT: €2,988
van Rossum [42] Netherlands	CEA	iFOBT (one sample) (50–75 years of age) 1 round gFOBT (two samples/day, three days) (50–75 years of age) 1 round Colonoscopy if positive	Between techniques No screening	iFOBT dominates over gFOBT and no screening both in cost per CRC and PLYG
Pignone [43] Australia	CEA	Biennial iFOBT (one sample) (50–74 years of age) Colonoscopy if positive	No screening	ICER/PLYG iFOBT vs no screening, from AUD25,000 to AUD41,667
Chen [44] Taiwan	CEA	Annual iFOBT (one sample) (50–80 years of age) Colonoscopy if positive	iFOBT, various cut-offs: 30–200 ng/ml No screening	El punto de corte optimo con mejor ICER/APVG tSOHi fue de 110 ng/ml Vs no cribado: 0.054 APVG y 950$USA
Berchi [45] France	CEA	Biennial iFOBT (one sample/two days) Biennial gFOBT (two samples/three days) 50–74 years of age Colonoscopy if positive	iFOBT, various cut-offs gFOBT	ICER/advanced tumour detected, iFOBT vs gFOBT: €-148 This would entail one-round savings of €6,282, with further 42 advanced adenomas detected.
Wilschut [46] Netherlands	CEA CUA	iFOBT 45–80 years of age Colosocopy if positive	iFOBT with various cut-offs (50, 75, 100, 150 & 200), ages at start (45, 50, 55, 60 yrs) and end (70, 75, 80 yrs). Various screening intervals (1, 1.5, 2 & 3 yrs)	Incremental costs per PLYG for all strategies were below €20,000 The most cost-effective option was annual iFOBT (45–80 yrs) vs 1.5 annual iFOBT (45–80 yrs) ICER €14,000/PLYG Similar results with outcome measurements on QALY

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Table 3 (*continued*)

Author/country	EE	Screening technique	Comparator	Results
Sobhani [47] France	CEA CUA	iFOBT (semiquantitative and quantitative) gFOBT Colonoscopy if positive 50–74 years of age	Semiquantitative iFOBT (1 sample) Quantitative iFOBT (1, 2, 3 samples) Different cut-offs at 50, 75, 100, 150 gFOBT	ICER/QALY iFOBT (three samples with cut-off at 50 ng/ml) vs gFOBT over 12 yrs: €8,821 Same over 24 yrs: €310
Goede [48] Netherlands	CEA	iFOBT gFOBT Colonoscopy if positive 55–75 years of age	2 iFOBT samples vs 1 iFOBT sample Cut-off at 50–200 ng/ml Positive 1, 2 or mean	ICER/PLYG Biennial iFOBT (1 sample) vs no screening: €2,690–3,473 Biennial iFOBT (two samples/ 1 positive) vs iFOBT (1 sample): €4,024–8,041
López Bastida [49]. Spain	CUA	Annual and biennial iFOBT Annual and biennial gFOBT Sigmoidoscopy/five years Colonoscopy/ten years or once From 50 years onwards	Between techniques and no screening	ICER/QALY Annual iFOBT vs no screening: €2,154 All strategies were cost-effective vs no screening
Heitman [50] Canada	CUA	Annual gFOBT Annual iFOBT DNAt/three years Sigmoidoscopy/five years VC/five years Colonoscopy/ten years	Between techniques and no screening.	ICER/QALY iFOBT (mean yield in adenoma detection) vs all stratgegies, including no screening, is most cost-effective. iFOBT (high yield) vs iFOBT (mid yield): CAD85,150 Colonoscopy vs iFOBT (high yield) with 20% participation rate: CAD32,912

Cost-effectiveness of CRC screening using sigmoidoscopy (Table 5)

Sigmoidoscopy as only strategy every five [53] or ten years [54] has proven cost-effective vs no screening (less than $20,000 per potential life year gained (PLYG)).

A study comparing sigmoidoscopy with FOB tests – either alone or in combination – and with colonoscopy showed that annual gFOBT plus sigmoidoscopy every five years would be most cost-effective; however, colonoscopy every ten years is more effective in reducing mortality rates [55].

Participation rates significantly impact on cost-effectiveness when various strategies are compared [56].

Tappenden et al [57] performed a cost-effectiveness and cost-utility study of CRC screening, based on UK data from CRC screening trials and the UK FOBT pilot, under hearth service perspective and lifetime time horizon; and using five different strategies and no screening. gFOBT and sigmoidoscopy are both cost-effective options.

Combining screening strategies with gFOBT, iFOBT and/or sigmoidoscopy may result in additional clinical benefits in a cost-effective manner, but this is dependent on the supplemental resources that might be required [58].

A study compared biennial gFOBT with biennial iFOBT and sigmoidoscopy only once, and found that the latter is the most cost-effective strategy when the endpoints considered include decreased CRC incidence and mortality. However, in terms of quality of life, biennial iFOBT is the preferable strategy even though more resources are used [59].

Cost-effectiveness of CRC screening using colonoscopy (Table 6)

While colonoscopy is the gold-standard strategy in terms of effectiveness, the results of studies economically assessing this approach are conditioned by participation rates, test specificity and sensitivity, and frequency of repeats when negative.

Table 4
Studies evaluating CRC screening CE when using fecal DNAt.

Author/country	EE	Screening technique	Comparator	Results
WU [51] Taiwan	CEA	DNAt (3/5/10 years) Colonoscopy if positive 50–75 years of age	DNAt (3/5/10 yrs) Annual FOBT No screening	ICER/PLYG Annual FOBT vs no screening: $2,376 Sigmoidoscopy every five yrs vs no screening: $20,206 Colonoscopy every 10 yrs vs no screening: $13,831 DNAt (all strategies) vs no screening: $115,000
Zauber [52] USA	CEA	DNAt (3/5 years) Colonoscopy if positive	Annual gFOBT Annual iFOBT Sigmoidoscopy every five years Colonoscopy every ten years No screening	All DNAt strategies were dominated by all other approaches

Regarding participation rates, Sonnenberg et al [60] conclude that colonoscopy every ten years represents a cost-effective option for CRC detection, as it reduces mortality with a relatively low cost-incremental rate. Low participation rates have a greater impact on CRC screening using FOBT vs colonoscopy every ten years. In case of low participation colonoscopy may well be a first-choice strategy for CRC detection. Vijan et al [61] state that CRC screening using colonoscopy seems to be the best strategy as it remains cost-effective even with low participation levels.

A study comparing only colonoscopy at varying ages vs no screening concludes that colonoscopy once, between 50 and 54 years, is the most cost-effective strategy (less than $10,000 per QALY) as compared to colonoscopy between 55 and 60 years, and that starting screening at an earlier age depends on the society's willingness to pay [62].

Technique-related costs also have a considerable impact on screening cost-effectiveness with colonoscopy. Vijan et al [67] suggest that a reduction in colonoscopy costs would increase the cost-effectiveness of this strategy every ten years. If not feasible, a single colonoscopy at 65 would be a reasonable alternative [63].

In their review, Pignone et al [64] conclude that all CRC screening strategies starting at 50 years in mid-risk individuals are cost-effective vs no screening. Colonoscopy would be the most favourable strategy from the perspective of how much is one willing to pay. The author finds difficulties defining which is the most appropriate age for initial screening, and points out that the cost-effectiveness ratio is highly sensitive to participation levels.

Hassan C et al [65] assessed the cost-effectiveness of endoscopic techniques vs FOBT in France, and colonoscopy every ten years was found to be more costly and less effective than annual iFOBT with a presumed participation of 40%. Colonoscopy improves its incremental cost-effectiveness ratio with respect to the best strategy when anaesthesia costs are not excluded.

In a recent review by Lansdor–Vogelaar et al [66], with the purpose of assessing cost-effectiveness for carious CRC detection strategies, the authors found that all studies are cost-effective, even cost-saving, as compared to no screening at all. There is no consensus on which strategy is more cost-effective or preferred according to 'willingness to pay'.

A CUA [67] showed that, of all strategies reviewed, annual gFOBT and iFOBT, sigmoidoscopy every five years, sigmoidoscopy and iFOBT every three years, colonoscopy every ten years, and sigmoidoscopy once at 60 are cost-effective. The best strategy under 'optimal adherence' conditions would be iFOBT. Colonoscopy may be a cost-effective strategy depending on participation and adherence rates. The cost-effectiveness of colonoscopy vs sigmoidoscopy would depend on its ability to detect at least 50% CRCs in the proximal colon.

Table 5
Studies evaluating CRC screening CE when using sigmoidoscopy alone or combined with other techniques.

Autor/país	EE	Screening technique	Comparator	Results
Khandker [53] USA	CEA	Annual FOBT Sigmoidoscopy (3/5 years) Annual FOBT + sigmoidoscopy (3/5 years) Double contrast barium (five years) Colonoscopy if positive Colonoscopy (5–10 years) 50–85 years of age	Between all eight strategies and no screening	ICER/PLYG for sigmoidoscopy (5 yrs) vs no screening: $12,636 ICER/PLYG for annual FOBT vs no screening: $14,394 If participation decreases, FOBT cost-effectiveness decreases. Should colonoscopy costs decrease, the strategy's cost-effectiveness would improve at ten years
Frazier [54] USA	CEA	Annual gFOBT Sigmoidoscopy (5/10 years) Annual FOBTl + sigmoidoscopy/five years Double contrast barium enema every five or ten years Colonoscopy if positive Colonoscopy every ten years 50–85 years onwards	Between all 22 strategies and no screening	ICER/PLYG Sigmoidoscopy/10 yrs vs no screening: $<17,000 Annual rehydrated gFOBT + sigmoidoscopy/5 yrs vs non-hydrated gFOBT + sigmoidoscopy: $92,900 Colonoscopy once vs sigmoidoscopy once: $22,400
Leshno [55] Israel	CEA	Annual gFOBT Annual gFOBT + sigmoidoscopy/five years Colonoscopy once Colonoscopy every ten yrs DNAt	Between techniques and no screening	ICER/PLYG gFOBT + sigmoidoscopy vs Colonoscopy once: $250 Colonoscopy/10 yrs reduces mortality rates most.
O'Leary [56] Australia	CEA	Sigmoidoscopy/ten years Colonoscopy if positive 54–64 years of age	Annual/Biennial gFOBT Colonoscopy every ten yrs. No screening	ICER/PLYG Sigmoidoscopy every ten years vs no screening: AUD16,801 Colonoscopy every ten years vs no screening: AUD19,285 Biennial gFOBT vs no screening: AUD41,183 Annual gFOBT vs no screening: AUD46,900
Tappenden [57] UK.	CEA CUA	Annual gFOBT 50–69 years of age Biennial gFOBT 60–69 years of age Sigmoidoscopy once 55 years of age. Sigmoidoscopy once 60 years of age Sigmoidoscopy once at 60 years followed by biennial FOBT at 61–70 years of age Colonoscopy if positive	Between all 5 strategies and no screening.	Marginal cost-effectiveness of biennial gFOBT at any age vs no screening: £<3,000/QALY. Sigmoidoscopy in any strategy vs no screening; dominated
Whyte [58] UK	CUA	gFOBT (two samples/day, three days) iFOBT (1 sample) Sigmoidoscopy Colonoscopy if positive 60–74 years of age	Between techniques (using various strategies: age at start and end, test repeats) No screening	ICER/QALY for all strategies vs no screening: £<20,000
Sharp [59] Ireland	CUA	Biennial gFOBT 55–74 years of age iFOBT 55–74 years of age Sigmoidoscopy once at 60 years Colonoscopy if positive	Between techniques No screening	ICER/QALY Sigmoidoscopy vs no screening: €589 tSOHi vs no cribado: 1.696€ tSOHg vs no cribado: 4.428€ tSOHi vs sigmoidoscopia: 2.058€

Table 6
Studies evaluating CRC screening CE when using colonoscopy alone or combined with other techniques.

Author/ country	Economic evaluation	Screening technique	Comparator	Results
Sonnenberg [60] USA	CEA	Annual FOBT Sigmoidoscopy/five years Colonoscopy when positive Colonoscopy every ten years when negative From 50 years onwards	Between techniques No screening	ICER/PLYG Annual gFOBT vs no screening: $9,705 Colonoscopy vs no screening: $10,983 Colonoscopy vs annual gFOBT: $11,382 With participation rate at 75% Annual gFOBT vs no screening: $14,071 Colonoscopy vs no screening: $13,081
Vijan [61] USA	CEA	Annual gFOBT Annual gFOBT + sigmoidoscopy Sigmoidoscopy/five years Colonoscopy/ten years From 50 years onwards	Between techniques (using various strategies: age at start and end, repeat test) No screening	ICER/PLYG All strategies vs no screening < $20,000 Regardless of participation level, sigmoidoscopy & annual FOBT dominated by colonoscopy If participation at 100% Colonoscopy at 60 yrs: $150 Colonoscopy at 55 & 65 yrs: $14,870 If participation 75% Colonoscopy at 60 yrs: $130 Colonoscopy at 55 & 65 yrs: $6,500
Ness [62] USA	CUA	Colonoscopy once	Colonoscopy once between 40 and 64 years of age No screening	Marginal cost/QALY Men: Colonoscopy at 55–59 dominates over colonoscopy at 60–64 and no screening. Colonoscopy at 50–54 vs 55–59 yrs: $3,625 Women: Colonoscopy at 60–64 dominates over no screening Colonoscopy at 55–59 vs 60–64: $366 Both genders Colonoscopy once at 50–54 yrs vs 55–60 yrs: < $10,000/QALY
Sonnenberg [63] USA	CEA	Colonoscopy once at 65 years. Colonoscopy/ten years From 50 years onwards	Between techniques No screening	ICER/PLYG Colonoscopy once vs no screening: $2,981 Colonoscopy/ten years vs no screening: $10,983 Colonoscopies every ten years vs colonoscopy once: $14,878 .
Pignone [64] USA	Systematic review CEA	Annual gFOBT gFOBT + sigmoidoscopy. Sigmoidoscopy/five years Double contrast enema/ five years Colonoscopy/ten years	Between techniques No screening	ICER/PLYG for all strategies vs no screening fall between $10,000 and $25,000 Most cost-effective method is unclear
Hassan [65] France	CEA	Colosnoscopy/ten years Sigmoidoscopy/five or ten years Capsule endoscopy/five or ten years Annual or biennial gFOBT Annual or biennial iFOBT 50–75 years	Between techniques No screening	All strategies vs no screening were cost-effective ICER/PLYG Biennial gFOBT: €1,139 Biennial iFOBT: €8,598 Annual iFOBT: €48,165; the strategy with a greater benefit
Lansdor–Vogelaar [66] Netherlands	Systematic review CEA	gFOBT iFOBT DNAt Sigmoidoscopy Colonoscopy Virtual colonoscopy	Between techniques No screening	All studies confirm that any CRC screening strategy is cost-effective vs no screening

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Table 6 (*continued*)

Author/ country	Economic evaluation	Screening technique	Comparator	Results
Sharaf [67] USA	CUA	Colonoscopy/ten years Sigmoidoscopy/five years Sigmoidoscopy and iFOBT/three years Sigmoidoscopy once at 60 years of age Annual iFOBT Annual gFOBT 50–80 years	Between techniques No screening	ICER/QALY Optimum participation and follow-up rate: iFOBT vs rest of strategies: coloscopy dominant vs sigmoidoscopy: $56,800 If participation<50% sigmoidoscopy and colonoscopy vs iFOBT <$50,.000

Cost-effectiveness of CRC screening using VC (Table 7)

The studies reviewed [68,69] confirmed that a cost-effectiveness ratio similar to that provided by colonoscopy would require a reduction in the technique's price (which is 43% above that of colonoscopy) and/or very high participation and adherence rates with this strategy. In all, CRC screening with VC needs improved diagnostic accuracy and reliability, as well as reduced costs, to become a cost-effective option.

Discussion

The most commonly used economic tool in the aforementioned studies was the cost-effectiveness analysis. All of them found that CRC screening, regardless of approach, are both effective and cost-effective when compared to no screening. However, which strategy is most cost-effective cannot be determined yet.

Few randomized clinical trials (RCTs) for CRC screening provide real participation and adherence data on the various strategies employed. It is a well-known fact that participation rates are a significant factor when it comes to estimate cost-effectiveness. Preferences for one or another screening test are known to have an influence on participation. Lastly, test pricing and/or availability has an impact among studies and represents a relevant limitation when implementing one particular screening strategy. Similarly, pressures from endoscopy services also limit any screening strategies.

Limitations in these studies are varied. Economic models include structural and parametric 'assumptions' with an impact on cost estimations and the potential consequences of CRC screening options. Disease process is usually excessively simplified, and a comprehensive list of factors present in the real world is usually absent. Costs are insufficiently specified, and many are not taken into account.

Table 7
Studies evaluating CRC screening CE when using VC alone or combined with other techniques.

Author/country	EE	Screening technique	Comparator	Results
Sonnenberg [68] USA	CEA	VC/10 years; if lesions, colonoscopy Colonoscopia every 10 yrs. Follow-up/three years From age 50 onwards.	VC vs colonoscopy No screening	IVER/PLYG. VC vs no screening: $11,484. VC vs colonoscopy: $10,408.
Vijan [69] USA	CEA	VC (2D) or (3D)/5 or 10 yrs. Annual gFOBT. Sigmoidoscopy/five years. Annual gFOBT plus sigmoidoscopy. Colonoscopy/ten years. 50–80 years of age.	Between techniques No screening	ICER/PLYG VC (2D)/5–10 years vs no screening: $17,289 and $14,290 VC (3D)/5–10 years vs no screening: $8,150 and $13,460 VC (3D)/5 years vs annual gFOBT: $22,400 VC (3D)/10 years vs annual gFOBT: $13,480 VC (3D)/10 years vs annual gFOBT + sigmoidoscopy: $84,160 VC (3D)/5 years vs colonoscopy/ 10 years: $156,000

The following **methodological differences** render study comparisons difficult:

(1) Effectiveness data included in most studies do not derive from RCTs or systematic reviews, which limits validity. Strong assumptions are made in most studies in absence of real world data.
(2) Differences may be seen regarding CRC 'natural history' modelling, test accuracy, and test effectiveness as related to CRC prevention or mortality reduction, which together with differences in participation/adherence rates limits comparisons between different screening strategies.
(3) Modelled screening strategies are highly variable. For example, screening duration is estimated in a number of manners (3, 10, 20 years, etc.)
(4) Costs are underestimated. A lack of detail on cost data means it is not clear whether the cost data allowed for programme costs such as the costs of health promotion, recall systems, and for administrative overheads to be included in the analysis. Furthermore, the models did not allow for inclusion of estimates of the substantial additional capital investment which may be required for endoscopies facilities, as well as training for staff. Indirect costs such as patient time and travel costs, informal carer costs, and the effect of anxiety were not included in the estimates. This means that, if entirely recorded, results would be more expensive than reported, and some studies would probably exceed accepted cost-effectiveness thresholds. Cost allocation for each screening strategy in each study is also highly variable. Costs and numbers of used resources are not separately specified. Discount rates are not always applied to costs or benefits obtained. No study measured the true costs associated with each program, since a comprehensive analysis requires the inclusion of infrastructure costs, equipment investment, professional training, costs related to staff time allowed for screening and follow-up, and indirect costs. Some parameters are not usually included which might be associated with increased costs, including side effects brought about by the excision of non-adenomatous polyps (e.g., hyperplastic polyps).
(5) References are missing about 'under which perspective' costs are being assessed. Few studies include the social perspective in their analysis.
(6) Study comparisons are difficult because of disparity in the reporting of results. Only a few studies provided QALY results, which would have allowed better comparisons in terms of health outcomes.
(7) The peculiarities of studies performed in different countries make it difficult for results to be extrapolated, as they are conditioned by their economic structures and influenced by their healthcare models (public vs private). It looks like results from these studies are influenced by the strategies to be out of self-interest adopted in their countries.

To conclude, this review demonstrates that any CRC prevention strategy for CRC is cost-effective vs no screening. However, no single screening method (colonoscopy, sigmoidoscopy, FOBT variants) may be clearly identified as the most cost-effective of them all. Not even can the preferred strategy be discerned having recourse to 'willingness to pay' per life years gained, although recent faecal DNA tests, virtual colonoscopy, and capsule endoscopy are unanimously considered inefficient when compared to established screening options.

In real practice, individual preferences and resources available for endoscopy may influence decisions on which strategy should be adopted for CRC screening.

Further investigation is needed in this field once common EE standards are adopted in order to relieve the methodological heterogeneity found in the reviewed studies.

Practice Points

- Any population-based screening strategy is better than no screening at all.
- With the evidence available, no strategy seems to do better than the rest.
- No detection method (colonoscopy, sigmoidoscopy, any FOB variant) may seemingly be clearly identified as most cost-effective.
- There is some consensus that faecal DNA detection, virtual colonoscopy, and capsule endoscopy are not cost-effective as compared to the above-mentioned options.

Research Agenda

- Further economic studies are needed on CRC screening.
- When performing an economic evaluation, fixed common standards are needed to palliate uncertainty for results and facilitate their comparison.

Conflict of interest

No conflict of interest has been declared by the authors.

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