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Cost-effectiveness of colorectal cancer screening – an overview

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Abstract

There are several modalities available for a colorectal cancer (CRC) screening program. When determining which CRC screening program to implement, the costs of such programs should be considered in comparison to the health benefits they are expected to provide. Cost-effectiveness analysis provides a tool to do this. In this paper we review the evidence on the cost-effectiveness of CRC screening. Published studies universally indicate that when compared with no CRC screening, all screening modalities provide additional years of life at a cost that is deemed acceptable by most industrialized nations. Many recent studies even find CRC screening to be cost-saving. However, when the alternative CRC screening strategies are compared against each other in an incremental cost-effectiveness analysis, no single optimal strategy emerges across the studies. There is consensus that the new technologies of stool DNA testing, computed tomographic colonography and capsule endoscopy are not yet cost-effective compared with the established CRC screening tests.

Keywords

colorectal neoplasms; mass screening; cost-benefit analysis; occult blood; colonoscopy; sigmoidoscopy; colonography; computed tomographic; stool DNA; capsule endoscopy

Introduction

The aim of population screening, such as colorectal cancer (CRC) screening, is to discover latent disease in its early stages to treat it adequately before it poses a threat to the individual. [1] As such, screening is a commendable method to fight disease. However, a screening program targets an (apparently) healthy population, and should therefore only be implemented after a careful consideration of both the harms and benefits of such a program. Cost-effectiveness analysis provides a tool to weigh and synthesize benefits, harms and costs of

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interventions and thus can inform the decision process for adopting population screening. In this paper we provide a brief overview of cost-effectiveness analysis and summarize the evidence on the cost-effectiveness of CRC screening in the average-risk population.

Cost-effectiveness analysis

Cost-effectiveness analysis, a form of decision analysis, is an analytic tool that formally compares the health and economic consequences of different interventions, thereby assisting decision makers to identify the interventions that will yield the greatest health benefits, given their resource constraints.[2] Cost-effectiveness analysis cannot determine which the optimal intervention is, but rather which intervention will provide the greatest health benefits, given the decision maker's willingness to pay for a unit of benefit. In a cost-effectiveness analysis, a mathematical model is typically used to track the benefits and harms of an intervention. These effects are then weighed against each other to determine the net benefit (or net harm). The model also tracks the costs associated with the intervention, including those of side effects. The results of a cost-effectiveness analysis are summarized in a cost-effectiveness ratio. The (quality-adjusted) life-years gained with a particular strategy (compared with an alternative) are included in the denominator, and the additional costs of that strategy (compared with the same alternative) are included in the numerator, yielding an incremental cost per (quality-adjusted) life-year gained.[2]

Two types of cost-effectiveness ratios are often reported in the literature: 1) a cost-effectiveness ratio comparing each intervention strategy with the standard of care, often a "no intervention" scenario; and 2) an incremental cost-effectiveness ratio comparing each strategy with the next most effective alternative which may or may not be a "no intervention" scenario. Incremental cost-effectiveness ratios are only calculated for strategies that are efficient or economically rational, which means that no other strategy or combination of strategies provides more life-years for the same or lower costs.[3] Non-efficient strategies are "dominated". There are two ways in which a strategy can be dominated. A strategy is strongly dominated if an alternative strategy provides more life-years at the same or lower cost. A strategy is weakly dominated if a combination of alternative strategies provides more life-years at the same or lower cost. For more insight in this complex matter, see the visualization of cost-effectiveness analyses in Mark, 2002.[4]

Determining the balance between costs and benefits

The World Health Organization principles for population screening state that screening should only be implemented when there is a good balance between costs and benefits.[1] Unfortunately there is no universal definition for "good balance" and different institutions may have different assessments of whether the incremental cost of one intervention over another is warranted by the additional benefits it provides. An intervention that provides an additional year of life at an incremental cost of $50,000 or less is deemed acceptable in most industrialized countries, but thresholds of even $100,000 per life-year gained have been argued to be acceptable in some settings.[5]

To ensure efficient use of resources, the incremental cost-effectiveness ratio, not the ratio of each strategy compared to standard of care, should be compared to the threshold cost per (quality-adjusted) life-year gained.[6,7] This requirement is illustrated by the following example: a recent US study found that the cost-effectiveness ratio of stool DNA testing for CRC compared with no CRC screening is $13,000–$18,000 per life-year gained.[8] With this ratio, stool DNA testing would be considered cost-effective even if the decision-maker is only willing to pay $20,000 per life-year gained. One might therefore recommend implementing a stool DNA screening program. However, annual screening with a faecal occult blood test

(FOBT) was estimated to save more life-years than stool DNA testing at a lower cost and therefore strongly dominated stool DNA testing. Implementing a stool DNA screening program would therefore lead to higher costs and fewer life-years gained compared with an FOBT screening program.

There is however a situation where the cost-effectiveness ratio compared to no screening could be considered the appropriate measure of cost-effectiveness of a screening test, namely if the test would entice a previously unscreened segment of the population to adhere to screening. For example, less than 60% of the population currently adheres to CRC screening.[9–13] Most cited reasons for nonparticipation are practical reasons (e.g., conflicts with work or family, inconvenience, being too busy, lack of interest, and cost) and not having any current health problems or symptoms of CRC.[14] These barriers exist regardless of the screening test. However, other reasons for nonparticipation are worry about pain, discomfort, or injury associated with the examination or that the test would be embarrassing or unpleasant.[14] New screening tests such as computed tomographic (CT) colonography, stool DNA tests, and serum tests aim to eliminate (some of) these barriers. If there is good evidence that these tests indeed are able to increase adherence among those who would otherwise remain unscreened, then the cost-effectiveness ratio compared to no screening would be an appropriate measure for decision-making since for these people no screening is the relevant comparator.

Cost-effectiveness of CRC screening

Since the demonstration of the efficacy of CRC screening with guaiac FOBT in 1993, [15] the economic impact of population screening for CRC has been evaluated in several cost-effectiveness analyses.

US studies

The majority of CRC screening cost-effectiveness analyses are based on the US population. CRC screening guidelines were first released in the US in 1997, recommending individuals at average risk be screened with any of the following methods: (1) annual guaiac FOBT; (2) 5-yearly sigmoidoscopy; (3) the combination of 5-yearly sigmoidoscopy and annual guaiac FOBT (4)5-yearly barium enema; or (5) 10-yearly colonoscopy.[16] These strategies are still included in the most recent US CRC screening guidelines, [17,18] and we refer to them below as the “established screening strategies”.

To date, there has been one systematic review of the cost-effectiveness of CRC screening in the US.[19] That review showed that the cost-effectiveness ratios for all established screening strategies compared to no screening were less than $50,000 per life-year gained. For guaiac FOBT the estimates were between $5,691 and $17,805 per life-year gained, for sigmoidoscopy between $12,477 and $39,359, for the combination of guaiac FOBT and sigmoidoscopy between $13,792 and $22,518 and for colonoscopy screening between $9,038 and $22,012. When the established CRC screening strategies were compared against each other, no strategy was consistently found to be the most effective or to have the best incremental cost-effectiveness ratio:[19] approximately half of the studies found the combination strategy of flexible sigmoidoscopy and guaiac FOBT to be the most effective, while the other half found colonoscopy to be the most effective strategy. At a willingness-to-pay threshold of $20,000 per life-year gained, each established screening strategy emerged as the preferred screening strategy in at least one model.

Since 2001, several new cost-effectiveness analyses of CRC screening have been published. [20–23] These studies generally confirm the findings of the systematic review that CRC screening is cost-effective compared to no screening, but no single strategy is consistently

found to be the most effective or to have the most attractive incremental cost-effectiveness ratio for a given willingness to pay per life-year gained.

Studies outside the US

Cost-effectiveness analyses have also been performed for CRC screening in Europe [24–34], Asia [35–40] Australia [41–43], and Canada [44]. The focus of European cost-effectiveness analyses has been much more on (guaiac) FOBT, [24,25,27–29,34] and to a lesser extent sigmoidoscopy[30,33]; only three European studies evaluated colonoscopy screening.[26,31, 32] In many European countries colonoscopy is not considered an option for population CRC screening. Reasons include lack of endoscopic capacity, [45,46] lack of evidence from randomized trials, [47] and population preference for non-invasive testing.[48,49] Another potential explanation is the different mechanism by which screening recommendations and policies are set between the US and Europe. In the US, guidelines have been issued by professional societies and other organizations that are not incentivized to consider cost or capacity issues, merely effectiveness. In many European countries screening decisions are implemented by a national body that must consider issues such as capacity and costs, as well as effectiveness of alternative screening options.

In general, the cost-effectiveness of CRC screening in Europe and Asia is more favourable than in the US, with cost-effectiveness ratios compared with no screening mostly less than $10,000 per life-year gained, [24,25,27–30,34,39] and in many studies even cost-saving.[26, 31,33,35,40] The lower test costs in Europe and Asia provide an important explanation for this difference. Studies in Australia and Canada find similar cost-effectiveness ratios as in the US. [41–44] These difference illustrate the necessity to tailor cost-effectiveness analyses for specific countries. Generalization of cost-effectiveness analyses from one country to another cannot be done, because screening costs, resource capacity and population preferences for different screening tests vary from country to country.

Initiatives to reconcile differences between cost-effectiveness analyses

Two collaborative modelling efforts have been undertaken to identify reasons for differences in effectiveness and cost-effectiveness of CRC screening across models.

Institute of Medicine workshop on the cost-effectiveness of CRC screening

The Institute of Medicine organized a workshop in January 2004 in which researches from five modelling teams agreed to participate.[50]. Each model was used to estimated costs and life-years gained for five screening strategies. Each estimation was performed twice: once with the original assumptions used by the modeller and once with standardized input assumptions concerning test and treatment costs, test performance, adherence to screening, follow-up, and surveillance, and the surveillance protocol. As expected, there was quite some variation in the model outcomes with the original modellers' assumptions (Table 1). No strategy was efficient in all five models, nor was there one strategy that was dominated in all five models. After standardization, there was still considerable variation in absolute levels of costs and life-years gained, but interestingly the ordering of strategies with respect to cost-effectiveness were comparable across models (Table 2). Based on these results, the workshop organizers concluded that variation in results between CRC models could be reduced when standardizing inputs for costs, test performance, adherence and surveillance. This implies that consensus is needed regarding the best estimates for these parameters.

Cancer Intervention and Surveillance Modeling Network

In September of 2000 the National Cancer Institute in the US established the Cancer Intervention and Surveillance Modeling Network (CISNET), a large-scale modelling effort

with the goal of using comparative modelling to inform cancer-control interventions.[51] Three CRC models were funded by CISNET. The CISNET CRC models were developed independently, but the modellers collaborated to identify the best-available data to inform the natural history components of the models and to standardize assumptions about screening and surveillance. In spite of the fact that the three models are informed by a common set of data and yield similar predictions for adenoma prevalence, CRC incidence, and CRC mortality in the absence of screening, the models differ with respect to which screening strategy is the most effective in terms of the number of life-years saved.[23] They determined that this discrepancy is mainly caused by differences in the simulated duration of the adenoma-carcinoma sequence. It is difficult to measure this duration in patients because, by definition, it is the period during which the condition is undiagnosed. Longitudinal data of CRC incidence after a negative sigmoidoscopy and colonoscopy from randomized trials will shed light on the true duration of the adenoma carcinoma sequence.

Future developments likely to affect the cost-effectiveness of CRC screening

Three factors are likely to greatly influence the cost-effectiveness of CRC screening in the coming years: new CRC screening tests, personalized screening recommendations based on CRC risk and rising CRC treatment costs.

New CRC screening tests

In the latest version of the US Multi-Society Task Force guidelines, immunochemical FOBT, CT colonography and stool DNA testing are included as viable options for CRC screening.[17] A fourth emerging test for CRC screening is capsule endoscopy.

Several studies have shown that immunochemical FOBT has a higher CRC and adenoma detection rate than Hemoccult II, while having the same or a better positive predictive value.[52–63] Its sensitivity is comparable to that of Hemoccult Sensa, while having better specificity.[64] However in the US, immunochemical FOBT is also considerably more expensive than these guaiac FOBTs. Approximately half of the cost-effectiveness analyses that evaluated immunochemical FOBT conclude that it is a cost-effective screening strategy, [20, 24,35,37] whereas in the other half it is dominated by Hemoccult Sensa.[23,39] This result is mainly dependent on the price difference between the immunochemical FOBT and Hemoccult Sensa.

US studies have estimated that screening for CRC with a stool DNA test every 2–5 years has a cost-effectiveness ratio compared to no screening of $13,000–$30,000 per life-year gained. However, the established screening options are estimated to save more life-years at lower costs and therefore stool DNA testing is strongly dominated.[8,65] In order for stool DNA testing to be cost-effective, its unit cost would need to fall and/or adherence with stool DNA testing would need to be substantially higher than with the established screening tests. There is some evidence that the price of stool DNA testing can be reduced: the first stool DNA assay that reached the market cost almost $800, whereas a more recent stool assay for vimentin methylation alone was introduced at a cost of $220.[66] These numbers offer hope that further technological refinements will permit significant cost reductions.

Screening for CRC with CT colonography every 5–10 years has been estimated to be more expensive and in many (US) cost-effectiveness studies also less effective than colonoscopy. It is either dominated by colonoscopy or has a high incremental cost-effectiveness ratio.[67] The studies suggest that if the cost of a CT scan were a quarter to half the cost of a colonoscopy, then the incremental cost-effectiveness ratio of CT colonography screening would be similar to colonoscopy and/or the established CRC screening techniques. An important deficiency of most cost-effectiveness analyses of CT colonography to date is that they have not incorporated

the potential harms of the radiation exposure from CT exams and/or costs and potential health effects associated with extracolonic findings. Only one study incorporated health benefits of abdominal aortic aneurysm detection, extracolonic cancer detection, and long-term radiation effects. In this study, CT colonography was dominant over both colonoscopy and colonoscopy with 1-time ultrasonography.[68] However, this study did not include costs of follow-up of other extracolonic findings and the benefits of finding abdominal aortic aneurysms were very favourable. A more careful examination of radiation risks and extra-colonic findings is needed. [67]

Finally, capsule endoscopy is the least developed of the emerging CRC screening tests.[69, 70] To date, only one study has evaluated the cost-effectiveness of capsule endoscopy.[71] Although the cost-effectiveness ratio comparing capsule endoscopy to no screening was found to be $25,000–$29,000 per life-year gained, colonoscopy saved more life-years at a lower cost than capsule endoscopy and capsule endoscopy was therefore dominated. The authors concluded that the cost-effectiveness of capsule endoscopy was mainly dependent on its ability to improve adherence to CRC screening.

These studies show that there is general consensus that the developing screening methods are not cost-effective compared to the established screening strategies, but that they are cost-effective compared to no screening. Accordingly, from an efficiency perspective, these tests should only be implemented if they entice individuals who would not otherwise be screened to adopt screening. Although some studies suggest that patients prefer CT colonography or stool DNA testing over the established screening strategies, there is no direct evidence showing that CT colonography and stool DNA increase CRC screening uptake among subjects who have been unwilling to perform any of the established tests.[8,23] Stool DNA testing still requires contact with stool and may therefore present the same barrier as FOBT. Although CT colonography and capsule endoscopy are less invasive than endoscopy, they both require extensive bowel preparation which is generally considered to be one of the most important barriers to CRC screening.

Personalized screening

Personalized medicine is a general trend in medical care. Separate CRC screening guidelines already exist for individuals at increased risk of the disease because of a family history of CRC, a genetic predisposition (e.g., familial adenomatous polyposis and hereditary nonpolyposis CRC), or a personal history of CRC, adenomas, or inflammatory bowel disease.[17,18] But differences in CRC risk exist even within the average-risk population. African Americans and men have higher CRC risk than whites and women respectively.[72] Furthermore, several risk factors are known to increase CRC incidence, such as smoking, diet, obesity, and physical inactivity.[73] To date, screening recommendations have not been tailored across different subgroups of the average-risk population. However, the American College of Gastroenterology has advocated that screening should start earlier in blacks because of the higher incidence and younger age at presentation of CRC in this population subgroup.[74] Studies have shown that CRC screening in African Americans has a lower cost per life-year gained than in whites, [75–77] and that African Americans should be screened earlier in life and with higher frequency than whites.[75] However, the benefit of tailoring of screening strategies by race was modest. Personalization of CRC screening recommendations is complex, and it might confuse providers and consumers to the point of decreasing adherence. A decrease in adherence would easily offset the gains from personalization. Given the low adherence to current screening guidelines, more benefit could be obtained from increasing adherence to existing guidelines than from personalizing them. On the other hand, individualization of screening guidelines must be considered in the context of a general trend towards personalized medical care.[78,79] If

personalization of medical care becomes the standard, it would be only natural to account for risk differences by race and gender.

Rising treatment costs

CRC treatment costs have increased dramatically over the past years. From the early 1990s to 2003, treatment costs per person have increased by up to 200%, depending on the stage of disease at diagnosis, [80,81] whereas unit screening costs have not.[65,82] With the US Food and Drug Administration's approval of oxaliplatin in 2003 and the monoclonal antibodies bevacizumab and cetuximab for metastatic CRC in 2004, treatment costs have risen even higher.[83] We do not expect to have seen the end of developments in chemotherapy for CRC. The second-line treatment of bevacizumab for recurrent disease is already being investigated as first-line treatment for stage IV disease [84] and as adjuvant therapy for stage III and advanced stage II disease.[85] An important consequence of this development is that the savings from preventing (advanced) CRC and CRC deaths by screening also increase dramatically. Two studies have explicitly evaluated the consequence of the increasing CRC treatment costs on the cost-effectiveness of CRC screening. They showed that the cost-effectiveness of CRC screening is becoming more favourable compared to no screening and that most CRC screening strategies even become cost-saving, because the treatment savings from preventing (advanced) CRC and CRC deaths by screening outweigh the screening costs. [20,86] The vast majority of the cost-effectiveness analyses have not included this spectacular increase in treatment costs, and are therefore outdated.

The best test is the test that gets done

The discrepancies in the outcomes of the different cost-effectiveness analyses seem to indicate that no conclusion can be drawn concerning which CRC screening program should be implemented. However, the fact that no strategy emerges across the models as being the most effective or having the best incremental cost-effectiveness ratio suggests that, assuming perfect adherence across all modalities, the differences in life-years gained between strategies are quite small. This result triggers the question of whether test-specific adherence predicts the best CRC screening strategy, rather than cost-effectiveness.[87] As the prominent gastroenterologist Dr. Sidney Winawer said a long time ago, the best test is the test that gets done.[Personal Communication]

Most cost-effectiveness analyses to date assume either perfect adherence or comparable imperfect adherence among all screening strategies. European randomized controlled trials have shown that adherence with immunochemical FOBT is significantly higher than with guaiac FOBT or endoscopy.[48,49] However, these studies have only compared adherence with the first round of screening. FOBT is generally repeated every (other) year, whereas the recommended interval for colonoscopy screening is 10 years. Although trials have shown that initial adherence with immunochemical FOBT is higher than with colonoscopy, high adherence with repeat immunochemical FOBT is required to reach similar life-years gained as with colonoscopy screening.[88] Given the frequent nature of immunochemical FOBT testing, adherence may decline over time. If small advantages in adherence for FOBT are associated with better projected outcomes relative to colonoscopy, then trials that compare both adherence and clinical outcomes after invitation to an FOBT versus colonoscopy screening program are warranted. Longer-term trials measuring adherence with FOBT in repeat screening rounds are required to finally determine which test gets done and thus what the best CRC screening strategy is. Since attitudes toward screening may differ across countries, adherence patterns observed in one country may not be applicable to other countries and should therefore be evaluated in each country.

The best test is the test that gets done *well*

Although for any test to be effective it first must be done, there is another important aspect to the effectiveness of any screening program: quality. Efficacy of tests is established in trial settings, and cost-effectiveness analyses are almost always based on estimates from these trials. However, the *efficacy* of a screening test in a trial setting may differ from its *effectiveness* in real-world settings. Randomized controlled trials generally have detailed screening and follow-up protocols that include quality assurance and control measures; these high standards are not always followed in real-world screening settings. For example, while adherence to follow-up colonoscopy after a positive FOBT was over 80% in randomized trials, [10,11,15] only 50% undergo follow-up in US clinical practice.[89] Additionally, several studies have shown that there is wide variation in adenoma detection rates between endoscopists, even within a trial setting.[90,91] Outside a trial setting, endoscopists generally perform fewer screening procedures and are less experienced. These provider-specific factors will influence detection rates and thus effectiveness of endoscopy screening. It is therefore important for any screening program to have good quality assurance protocols in place. Accordingly, Dr. Winawer has updated his quote to: “The best screening test is the test that gets done *well*”.[Personal Communication]

Summary

Cost-effectiveness analysis is a useful tool for weighing the costs and benefits of alternative screening programs. Many cost-effectiveness analyses have been performed for CRC screening. All studies show that when compared with no CRC screening, all screening modalities provide additional years of life at a cost that is deemed acceptable by most industrialized nations. However even with standardization of assumptions, no one screening program emerges as the most effective in terms of life-years saved or as the preferred strategy for a given willingness to pay. There is good consensus that CT colonography, stool DNA and capsule endoscopy testing are currently more costly than alternative strategies that provide comparable, if not greater, health benefits and accordingly are not cost-effective. Studies of test-specific adherence patterns are needed, as these strategies could be cost-effective if they entice previously unscreened individuals to adopt screening. With the dramatic rise in the costs of CRC screening, the cost-effectiveness of CRC screening programs will further improve and CRC screening is likely to become cost-saving. Assuming perfect adherence across all screening modalities, life-years gained with annual screening with a highly sensitivity FOBT, 10-yearly colonoscopy, or with a combination of annual FOBT and 5-yearly sigmoidoscopy are nearly equivalent. This result implies that test-specific adherence predicts the best CRC screening strategy, rather than cost-effectiveness. Longer-term trials measuring adherence and detection rates with FOBT in repeat screening rounds are required to determine the relative benefit of FOBT versus endoscopy.

Practice points

- All CRC screening strategies are cost-effective compared to no screening
- There is no consensus on what is the preferred CRC strategy for a given willingness to pay
- Generalization of cost-effectiveness analyses from one country to another cannot be done, because screening costs, resource capacity and population preferences differ
- CT colonography, stool DNA and capsule endoscopy are not (yet) cost-effective compared to FOBT and endoscopy screening

- Rising CRC treatment costs will make CRC screening even more cost-effective and possibly cost-saving
- Test-specific adherence may be the key determinant of the (cost-)effectiveness of a CRC screening strategy

Research agenda

- Evidence is needed regarding whether stool DNA, CT colonography and/or capsule endoscopy entice a previously unscreened segment of the population to adhere to screening
- Studies investigating the effect of personalized screening on CRC screening adherence are necessary
- Detailed studies are required to determine the best estimates for CRC test and treatment costs, screening test performance, adherence and surveillance
- Longitudinal data of CRC incidence after a negative sigmoidoscopy and colonoscopy from randomized trials are needed to obtain a better estimate of the duration of the adenoma carcinoma sequence
- Longer-term trials measuring adherence and detection rates with FOBT in repeat screening rounds are required to determine the relative benefit of FOBT versus endoscopy

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TABLE 1

Preferred CRC Screening Strategy at different levels of willingness to pay: Original Assumptions [50]

	Model 1	Model 2	Model 3	Model 4	Model 5
$20,000	FOBT	FOBT	F/S	FOBT	R
$50,000	F/S	R	F/S	R	C
$100,000	F/S	R	F/S	R	C

NOTES: FOBT = annual guaiac faecal occult blood test; F/S = annual guaiac faecal occult blood test; sigmoidoscopy every 5 years; R = prototype radiology procedure every 5 years; C = colonoscopy every 10 year.

TABLE 2

Preferred CRC Screening Strategy at Different Levels of Willingness to Pay: Standardized Assumptions [50]

	Model 1	Model 2	Model 3	Model 4	Model 5
$20,000	FOBT	FOBT	FOBT	FOBT	FOBT
$50,000	FOBT	FOBT	FOBT	FOBT	FOBT
$100,000	F/S	F/S	F/S	FOBT	F/S

NOTES: F/S = annual faecal occult blood test; sigmoidoscopy every 5 years; FOBT = annual guaiac faecal occult blood test.