

## RESEARCH ARTICLE

# Is there a place for sigmoidoscopy in colorectal cancer screening? A systematic review and critical appraisal of cost-effectiveness models

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## Abstract

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## Introduction

Screening for colorectal cancer (CRC) is effective in reducing both incidence and mortality. Colonoscopy and stool tests are most frequently used for this purpose. Sigmoidoscopy is an alternative screening measure with a strong evidence base. Due to its distinct characteristics, it might be preferred by subgroups. The aim of this systematic review is to analyze the cost-effectiveness of sigmoidoscopy for CRC screening compared to other screening methods and to identify influencing parameters.

## Methods

A systematic literature search for the time frame 01/2010–01/2023 was conducted using the databases MEDLINE, Embase, EconLit, Web of Science, NHS EED, as well as the Cost-Effectiveness Registry. Full economic analyses examining sigmoidoscopy as a screening measure for the general population at average risk for CRC were included. Incremental cost-effectiveness ratios were calculated. All included studies were critically assessed based on a questionnaire for modelling studies.

## Results

Twenty-five studies are included in the review. Compared to no screening, sigmoidoscopy is a cost-effective screening strategy for CRC. When modelled as a single measure strategy, sigmoidoscopy is mostly dominated by colonoscopy or modern stool tests. When combined with annual stool testing, sigmoidoscopy in 5-year intervals is more effective and less costly than the respective strategies alone. The results of the studies are influenced by varying assumptions on adherence, costs, and test characteristics.

## Conclusion

The combination of sigmoidoscopy and stool testing represents a cost-effective screening strategy that has not received much attention in current guidelines. Further research is needed that goes beyond a narrow focus on screening technology and models different, preference-based participation behavior in subgroups.

## Introduction

Colorectal cancer (CRC) is one of the most common tumorous diseases in developed countries: in 2020, it accounted for 10.3% of cancer cases and 9.9% of cancer-associated deaths in Europe, ranking third and second respectively [1]. Screening has the potential to reduce both CRC incidence and CRC mortality. Since most intestinal tumors develop along the adenoma-carcinoma sequence over a long period of time, CRC can be detected at early stages or even be prevented by removing precursor lesions [2]. The majority of European countries have implemented organized or opportunistic screening following the recommendation of the European Council [3]. The most common screening methods in Europe include immunochemical or guaiac-based fecal occult blood tests (FIT / gFOBT), as well as structural examinations of the bowel by colonoscopy. Newer methods, such as DNA testing or CT-colonography, are not regularly used in Europe [4, 5]. The European Colorectal Cancer Screening Guidelines Working Group recommends that individuals aged 50 to 74 years undergo annual to biennial FIT or gFOBT, which is low-cost and approved as a screening measure throughout the entire European Union [6, 7]. A meta-analysis of randomized controlled trials (RCTs) shows a significant reduction in CRC mortality with stool tests [8]. With their low sensitivity for adenomas, stool tests are primarily detection tests for cancer. A positive finding must be followed by a complete colonoscopy [9].

Endoscopic procedures, such as colonoscopy or sigmoidoscopy, are superior to non-invasive stool tests in terms of detecting CRC and adenomas [9]. Colonoscopy is considered the gold standard, as the procedure can be both diagnostic and therapeutic. During colonoscopy, which consists of an endoscopic visualization of the entire colon, precursor lesions can be directly removed. Sigmoidoscopy is an alternative endoscopic procedure during which only the distal segment of the bowel is examined. Although colonoscopy is part of CRC screening in several European countries, such as Germany or Poland, incidence and mortality reductions as a result of colonoscopy have so far been demonstrated only by observational studies [5, 10]. First results of an RCT examining colonoscopy in Poland, the Netherlands, and Sweden published in October 2022 indicated that, over a 10-year period, colonoscopy resulted in a smaller reduction in incidence compared with results from observational studies [11]. A reduction in mortality was not clearly demonstrated. However, it is possible that the effectiveness of colonoscopy could not be adequately surveyed because of the relatively short follow-up period and low participation rate (42%). Per-protocol analysis showed a greater incidence and mortality reduction [11]. For sigmoidoscopy, recent RCTs are available, which in a meta-analysis result in an incidence and mortality reduction of 24% and 26%, respectively [12].

Over the past few decades, with the growing implementation of colonoscopy in health care, sigmoidoscopy has increasingly fallen into disuse. In Europe, sigmoidoscopy is used for population-based screening only in the Italian region Piedmont [3], although it is stated in several European guidelines as a reasonable measure [4]. A possible reason for the shift away from sigmoidoscopy is its weakness in detecting proximal lesions compared to colonoscopy. However, due to a lack of evidence demonstrating the relevance of proximal lesions for CRC screening,

it is questionable whether colonoscopy can be considered superior to sigmoidoscopy as a result of its ability to detect such neoplasms. When differentiated by location, colonoscopy is associated with no significant incidence and mortality reduction of proximal neoplasms [10, 13–15] or a significantly smaller reduction compared with distal carcinomas [16]. The reason for this may be the histological nature of the upper intestinal segment. This area more frequently sees the growth of sessile serrated adenomas, which are more difficult to detect and at the same time associated with a more rapid carcinogenesis. As a consequence, CRC is mostly detected at a higher stage in this bowel section. Only a minority of carcinomas arise from this form of precursor lesions along the alternated serrated pathway [17].

As all screening strategies incorporate specific advantages and disadvantages, there is no universally ideal method. The appropriateness of a screening strategy depends on many factors. For example, the setting, the available resources, and the willingness of the respective target population to participate must be taken into account [18]. In particular, participation rates are still low in Europe and often below the minimum target of 45% as defined by the European Union [6, 19].

Because the choice of screening modality is highly preference-sensitive, procedural characteristics are a critical determinant of anticipated participation. Reservations seem to be more prevalent with invasive procedures than with stool tests [20]. In the case of colonoscopy, patients often describe the extensive preparation (drinking up to 2 liters or more of laxatives and concurrent dietary restrictions) as burdensome. Furthermore, the necessary sedation leads to an inability to work on the day of the examination, and the need for an accompanying person creates additional organizational effort [21]. For sigmoidoscopy, on the other hand, an enema is usually sufficient as preparation and sedation is not strictly necessary [22]. Risks such as major bleeding or perforations are less pronounced compared to colonoscopy [23]. Due to its inherent characteristics, sigmoidoscopy may be better accepted by patients and is thus more likely to be utilized.

In the face of ever-evolving medicine, scarce resources, and low participation, the question emerges to which extent it may be appropriate to shift focus to sigmoidoscopy, an evidence-based strategy which is possibly preferred by subgroups. Decision-analytical modeling provides valuable information on optimal resource allocation, especially when the events of interest are far in the future. When costs and effects are contrasted, all current CRC screening methods appear to be cost-effective or even cost-saving compared to no screening offer. There is disagreement about which strategy is optimal in terms of cost-effectiveness [24–28]. Previous systematic reviews have focused on the question of the most cost-effective single strategy, mostly assuming perfect adherence. Since the potential of sigmoidoscopy lies in complementing less-sensitive procedures (stool test) or strategies with preference-related low participation (colonoscopy), such a consideration is insufficient. It is therefore useful to consider the performance of sigmoidoscopy in combination with other strategies, as well as to identify the most influential modeling parameters. The validity of the results depends on the representation of the natural history of the disease, the modeled effectiveness of screening, and the data used [29]. There are significant underlying structural and qualitative differences between models. However, this was only captured narratively [18] or pertained primarily to reporting quality [26, 28].

The aim of this systematic review is to analyze the cost-effectiveness of sigmoidoscopy for CRC screening either alone or in combination with other strategies compared to current and newer screening methods and to identify relevant influencing parameters. It is also the first review in the field of CRC screening to provide a comprehensive quality assessment of modeling studies using instruments by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [30].

## Methods

The protocol for this systematic review was registered in Prospero (CRD42020189934). The methodology was based on the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA), though not all items are applicable to economic evaluations [31]. The research question was worded as follows:

*Is sigmoidoscopy in colorectal cancer screening cost-effective compared to other commonly used screening strategies and what are relevant factors influencing the results?*

## Search strategy

The databases MEDLINE, Embase, EconLit, Web of Science, the British National Health Service Economic Evaluation Database (NHS EED), as well as the Cost-Effectiveness Registry (Tufts Medical Center) were systematically searched in March 2020. The search was updated in August 2021 and January 2023, ultimately covering the time frame of 01/2010 to 01/2023. The search strategy consisted of 2 blocks, describing Colorectal Cancer Screening and Economic Evaluation respectively (S1 Fig). In each block, various search terms, including both controlled vocabulary (MeSH Terms) and free terms, were linked with the Boolean operator “OR”. The blocks were then combined with the operator “AND”. The search syntax for each database can be found in the appendix (S2 Table).

## Study selection

Studies were considered if they met the a priori defined inclusion criteria. Only full economic analyses that examined the general population at average risk for CRC and compared sigmoidoscopy as a screening strategy to either no screening or at least one other generally available screening measure were eligible for inclusion. Studies were included if they reported long-term outcomes such as life years gained (LYG) or quality-adjusted life years (QALY). Accordingly, studies were excluded if they investigated a non-screening population (e.g., CRC patients) or a specific target group (e.g., high risk population), or if they had no adequate comparator. Partial economic evaluations and studies that only reported non-comparable outcomes, such as cost per patient screened or cost per cancer detected, were also excluded. Congress abstracts, duplicate publications, and gray literature were not eligible for inclusion. The language was limited to English or German.

Two independent researchers screened the retrieved results. After all duplicate items were removed, title and abstract were assessed for eligibility. If the studies appeared suitable, full texts were obtained and reviewed based on the inclusion and exclusion criteria. Disagreement on inclusion was discussed within the research team and a final consensus was reached.

## Data extraction and analysis

Data extraction was performed by one reviewer and checked for accuracy by a second reviewer. Discrepancies were resolved within the research team, if necessary. The data was recorded in tabular form and included study population, investigated screening strategies, methodological approach and structure, perspective, time horizon, adherence rate, discount rate, and methods for sensitivity analysis. Discounted cost and effectiveness measures were extracted per person for each CRC screening strategy, including only base case values. The incremental costs and effectiveness (LYG or QALY gained) of other commonly analyzed strategies compared to sigmoidoscopy were calculated. If a strategy was equally or more costly and

less effective, it was considered as dominated. Similarly, if a strategy was less costly and equally or more effective, that strategy was referred to as cost-saving. For non-dominated comparisons, the incremental cost-effectiveness ratio (ICER) was derived, stating the incremental cost per LYG or per QALY gained. Alternatively, ICERs were extracted when reported in the study.

$$ICER = \frac{Cost_{Sigmoidoscopy} - Cost_{Comparator}}{Effectiveness_{Sigmoidoscopy} - Effectiveness_{Comparator}}$$

### Cost conversion

To improve the comparability of the studies, all cost estimates were adjusted to 2019 US-\$ using country-specific consumer price indices (CPI). If a study did not state the base year for costs, 2 years prior to publication was assumed as the base year. When necessary, local currency units were subsequently converted to US-\$ using Purchasing Power Parity (PPP) conversion factors [32, 33]. CPI and PPP data were obtained from the World Bank Database [34].

### Quality assessment

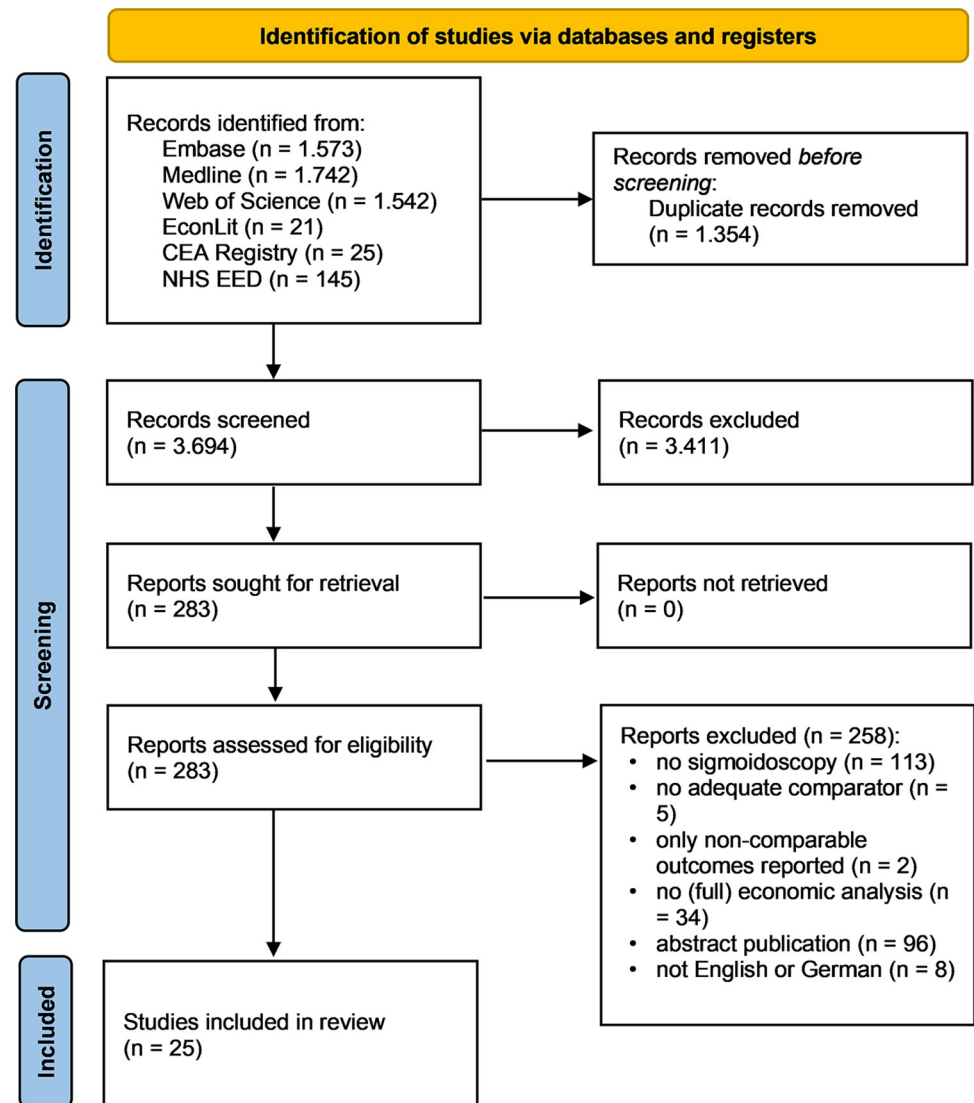
The critical appraisal of the studies was undertaken by 2 independent researchers with a questionnaire by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) [30]. The questionnaire is a recommended tool for assessing the relevance and credibility of modeling studies based on the 7 main dimensions: validation, design, data, analysis, reporting, interpretation, and conflict of interest. Each domain consists of 1 or more questions and can be judged as strength, neutral or weakness depending on the responses. If the study demonstrated convincing credibility in all sub-questions, the domain was rated as a strength. If there were minor concerns but they did not limit the overall credibility, the domain was rated as neutral. In the case of issues that were a potential constraint on credibility, the domain represented a weakness. Disagreement between the reviewers was resolved by discussion within the research team. Based on the domain ratings, the credibility of each study was assessed as sufficient or insufficient for the review.

## Results

The database search yielded 5,048 records (Fig 1). After removing duplicates, 283 full-text articles were assessed for eligibility. The majority of articles were excluded because sigmoidoscopy was not evaluated or no (full) economic analysis was conducted. Other reasons included lack of an adequate comparator group, non-comparable outcomes according to the exclusion criteria, publication of an abstract with no full article, and language other than English or German. For articles excluded after full-text review, see S2 Table in the supplement. Ultimately, 25 articles could be included in the systematic review.

### 1.1 Study characteristics

The majority of the included studies were conducted in the USA [35–46], and 2 in Canada [47, 48] (Table 1). In 7 models investigated CRC screening in European countries, namely France [49, 50], UK [51, 52], Ireland [53], Italy [54], and Ukraine [55]. A total of 3 studies came from Asian countries: 2 from Hong Kong [56, 57] and 1 from Singapore [58]. A single study was conducted in Australia [59]. Fifteen studies employed a Markov Model to estimate the cost-effectiveness. The remaining 10 studies used microsimulation as a modeling approach. The majority of these 10 studies utilized at least 1 of 3 models developed by the US Cancer Intervention and Surveillance Modeling Network (CISNET) named CRC-SPIN, MISCAN and Sim-CRC [38, 42, 43, 45, 46]. US studies using microsimulation thus applied identical



**Fig 1. Flow diagram of study selection.**

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modeling techniques and assumptions and differed mainly in the input parameters or populations examined. To reduce the risk of ‘double counting’ and overestimating single models, studies were grouped by modeling approaches.

In 6 studies, the analyses were conducted from a societal perspective [36, 37, 45, 46, 50, 58]. The other studies took a third-party payer perspective, with the exception of 2 studies where the perspective was not declared and remained unclear [56, 57]. Almost all studies followed the modeled cohort for a lifetime to capture the long-term effects of CRC screening. Shorter time horizons varied between 12 and 35 years [35, 36, 54, 56]. The discount rate was between 3% and 5% among all studies that reported discounting. QALY gained were the most frequently analyzed outcome, described by 13 studies [36, 37, 39–41, 44, 45, 47, 48, 50, 53, 55, 58]. A further 9 studies reported LYG [35, 38, 42, 43, 46, 49, 54, 57, 59]. Both LYG and QALY were reported in 3 studies [51, 52, 56]. The screening period, meaning the time frame where screening measures were actively performed, covered at least the period from 55 to 70 years of age in

Table 1. Characteristics of the studies.

Author, Year	Country	Model Type	Model Name	Perspective	Time Horizon	Discount Rate	Outcome Measure	Screening Period	Route of Carcinogenesis	Types of precursor lesions	Consideration of the localization of lesions
Barré 2020 [50]	FR	Microsimulation	-	Societal	Lifetime	4%	QALY	50–74	100% Adenoma-Carcinoma-Sequence	Polyp or adenoma (6–9 mm; ≥ 10mm)	Consideration of proximal and distal lesions separately
Barzi 2017 [35]	US	Microsimulation	-	Societal	35 years or Lifetime	3%	LYG	50–75	100% Adenoma-Carcinoma-Sequence	Adenoma	n/a
Dan 2012 [58]	SG	Markov	-	Societal	Lifetime	3%	QALY	50–75	100% Adenoma-Carcinoma-Sequence	Polyp	n/a
Dinh 2013 [36]	US	Microsimulation	Archimedes	Societal	30 years	3%	QALY	50–75	100% Adenoma-Carcinoma-Sequence	benign polyps or adenomatous polyps	Differentiation of cecum, ascending, transverse, descending and sigmoid colon and rectum
Hassan 2011 [49]	FR	Markov	-	Third-Payer	Lifetime	3%	LYG	50–75	85% Adenoma-Carcinoma-Sequence, 15% de novo	diminutive (≤ 5 mm), medium (6–9 mm) or large (≥ 10 mm) adenomatous polyp	n/a
Heitman 2010 [47]	CA	Markov	-	Third-Payer	Lifetime	5%	QALY	50–75	100% Adenoma-Carcinoma-Sequence	nonadvanced or advanced adenoma	n/a
Kingsley 2016 [37]	US	Microsimulation	-	Societal	Lifetime	3%	QALY	50–80	Adenoma-Carcinoma-Sequence, de novo <sup>s</sup>	high-grade (>1cm, 3 or more in number or with villous dysplastic features on histology) or low-grade adenomas (all other)	n/a
Knudsen 2010 [38]	US	Microsimulation	CRC-SPIN MISCAN Sim-CRC	Third-Payer	Lifetime	3%	LYG	65–80	100% Adenoma-Carcinoma-Sequence	small (1–5 mm), medium (6–9 mm), and large (≥10 mm) adenoma (MISCAN and Sim-CRC), continuous adenoma growth from 1–50mm (CRC-SPIN)	Differentiation of cecum, ascending, transverse, descending and sigmoid colon and rectum
Lansdorp-Vogelaar 2010 [42]	US	Microsimulation	MISCAN Sim-CRC	Third-Payer	Lifetime	3%	LYG	65–80	100% Adenoma-Carcinoma-Sequence	small (1–5 mm), medium (6–9 mm), or large (≥10 mm) adenoma	
Naber 2019 [43]	US	Microsimulation	CRC-SPIN MISCAN Sim-CRC	Third-Payer	Lifetime	3%	LYG	65–75	100% Adenoma-Carcinoma-Sequence	small (1–5 mm), medium (6–9 mm), and large (≥10 mm) adenoma (MISCAN and Sim-CRC), continuous adenoma growth from 1–50mm (CRC-SPIN)	
Van Hees 2014 [45]	US	Microsimulation	MISCAN	Societal	Lifetime	3%	QALY	76–90	100% Adenoma-Carcinoma-Sequence	small (1–5 mm), medium (6–9 mm), or large (≥10 mm) adenoma	
Vanness 2011 [46]	US	Microsimulation	CRC-SPIN MISCAN Sim-CRC	Third-Payer	Lifetime	3%	LYG	50–80	100% Adenoma-Carcinoma-Sequence	small (1–5 mm), medium (6–9 mm), and large (≥10 mm) adenoma (MISCAN and Sim-CRC), continuous adenoma growth from 1–50mm (CRC-SPIN)	

(Continued)

Table 1. (Continued)

Author, Year	Country	Model Type	Model Name	Perspective	Time Horizon	Discount Rate	Outcome Measure	Screening Period	Route of Carcinogenesis	Types of precursor lesions	Consideration of the localization of lesions
Ladabaum 2013 [39]	US	Markov	-	Third-Payer	Lifetime	3%	QALY	50–80	85% Adenoma-Carcinoma-Sequence, 15% de novo	small (<10 mm) or large (≥10 mm) adenomatous polyp	Differentiation of fractions of lesions within reach of endoscope
Ladabaum 2018 [40]	US	Markov	-	Third-Payer	Lifetime	3%	QALY	50–80	85% Adenoma-Carcinoma-Sequence, 15% de novo	small (<10 mm) or large (≥10 mm) adenomatous polyp	
Ladabaum 2019 [41]	US	Markov	-	Third-Payer	Lifetime	3%	QALY	45–75	85% Adenoma-Carcinoma-Sequence, 15% de novo	small (<10 mm) or large (≥10 mm) adenomatous polyp	
Sharaf 2013 [44]	US	Markov	-	Third-Payer	Lifetime	3%	QALY	50–80	85% Adenoma-Carcinoma-Sequence, 15% de novo	small (<10 mm) or large (≥10 mm) adenomatous polyp	
Lam 2015 [56]	HK	Markov	-	?	25 years	n/a	LYG, QALY	50–75	100% Adenoma-Carcinoma-Sequence	low-risk or high-risk polyps	n/a
Lee 2010 [51]	UK	Markov	-	Third-Payer	Lifetime	3.5%	LYG, QALY	60–69	100% Adenoma-Carcinoma-Sequence	low-risk (6–9 mm) or high-risk polyps (≥10 mm)	Consideration of proximal and distal lesions separately
Lew 2018 [59]	AU	Microsimulation	Policy1-Bowel	Third-Payer	Lifetime	5%	LYG	50–74	85% Adenoma-Carcinoma-Sequence, 15% Serrated Pathway	diminutive (<6mm), small (≥6mm) or large (≥10mm) adenoma; Small (<10mm) or large (≥10mm) hyperplastic polyp; small (<10mm) or large (≥10mm) sessile serrated adenoma	Differentiation of cecum, ascending, transverse, descending and sigmoid colon and rectum
Senore 2019 [54]	IT	Markov	-	Third-Payer	12 years	3%	LYG	58–70	no natural history model	n/a	n/a
Sharp 2012 [53]	IE	Markov	-	Third-Payer	Lifetime	4%	QALY	55–74	86% Adenoma-Carcinoma-Sequence, 14% de novo	low-risk (<10 mm) or higher-risk (≥10 mm) adenomas	Consideration of proximal and distal lesions separately
Telford 2010 [48]	CA	Markov	-	Third-Payer	Lifetime	5%	QALY	50–75	100% Adenoma-Carcinoma-Sequence	low-risk polyp or advanced adenoma	Differentiation of fractions of lesions within reach of endoscope
Melnitchouk 2018 [55]	UA	Markov	-	Third-Payer	Lifetime	3%	QALY	50–75	100% Adenoma-Carcinoma-Sequence	low-risk or high-risk polyps	
Whyte 2012 [52]	UK	Markov	-	Third-Payer	Lifetime	3.5%	LYG, QALY	55–74	Adenoma-Carcinoma-Sequence, de novo <sup>5</sup>	low-risk or high-risk adenomas	n/a

(Continued)



Table 1. (Continued)

Author, Year	Country	Model Type	Model Name	Perspective	Time Horizon	Discount Rate	Outcome Measure	Screening Period	Route of Carcinogenesis	Types of precursor lesions	Consideration of the localization of lesions
Wong 2016 [57]	HK	Markov	-	?	Lifetime	3%	LYG	50–70	no natural history model	n/a	n/a

FR: France; US: United States of America; SG: Singapore; CA: Canada; HK: Hong Kong; UK: United Kingdom; AU: Australia; IT: Italy; IE: Ireland; UA: Ukraine  
 ? Unclear

LYG: life years gained

QALY: quality-adjusted life years

n/a: not applicable

<sup>a</sup> distribution unclear

<https://doi.org/10.1371/journal.pone.0290353.t001>

18 studies. Screening started as early as 45 years of age in 1 study [41], while the earliest screening age in another study was as high as 76 [45], with 50 being the most common starting age. Most studies had a screening period of either 26 or 31 years.

### Structural assumptions

When comparing the validity of the models, some structural aspects are of particular importance: the displayed carcinogenesis and the type and localization of lesions modeled. These aspects can lead to crucial differences in CRC detection between endoscopic procedures and stool tests, but also between colonoscopy and sigmoidoscopy.

In 2 studies, the natural history of CRC was not modeled [52, 54] (Table 1). All other models depicted the adenoma-carcinoma sequence. De novo carcinoma without previous adenomatous lesions were additionally included in 8 studies [37, 39–41, 44, 49, 52, 53]. Only 1 microsimulation also modeled the serrated pathway and therefore explicitly included sessile serrated adenoma as a precursor lesion of CRC [59]. Moreover, modeling of lesions was performed differently across models. Most studies classified either 2 (14 studies) [36, 37, 39–41, 44, 47, 48, 50–53, 55, 56] or 3 types of adenomas (7 studies) [38, 42, 43, 45, 46, 49, 59]. Two studies modelled only 1 stage of adenoma [35, 58]. While 11 studies differentiated adenomas solely by size [38–46, 49, 59], 9 studies composed risk types, some of which also included histology [36, 37, 47, 48, 51–53, 55, 56]. The CRC-SPIN microsimulation modeled adenoma growth as continuous growth rather than set health states. 16 studies that modeled the natural history explicitly addressed the localization of lesions. A separate modeling of all sections of the intestine was only conducted in microsimulations [36, 38, 42, 43, 45, 46, 59]. Two Markov models and 1 microsimulation included distal and proximal adenomas as different health states [50, 51, 53]. An indirect approach to localization using different fractions of lesions within reach of the respective endoscope was performed in 6 articles, which are primarily adaptations of 2 modeling approaches [39–41, 44, 48, 55].

### Quality assessment

The overall credibility of the studies was sufficient (Fig 2). Only the study by Lam et al. [56] was excluded from the result synthesis due to severe weaknesses in almost all domains. The most critical domain across the models was validation, even though most authors ensured sufficient external validity. In 3 studies, serious concerns for validity were present, as it was unclear whether the results of the models are coherent with independent data [54, 55, 57]. Validation issues were mostly based on the lack of internal validity, as almost no model documented technical verification of equations and debugging exercises ensuring all assumptions were correctly implemented in code. While the model designs and included data were generally appropriate for the course of CRC, limitations resulted from the often unclear process of model development and data identification. Analysis was assessed as a strength in 11 studies [37, 39, 40, 44, 47, 49–54] and as neutral in 12 studies [35, 36, 38, 41–43, 45, 46, 55, 57–59], due for example to lack of probabilistic sensitivity analysis. Reporting and interpretation was predominantly satisfactory. Only the technical documentation was absent in the majority of models, making replication of the results difficult. Eight studies raised the distinct possibility of a conflict of interest [39–41, 43, 46, 48, 51, 54].

### 1.2 Cost-effectiveness results

In the models, sigmoidoscopy was explored within different screening strategies. As a single-intervention strategy, a 5-year interval was the most common (13 studies) [35–40, 42, 43, 47–49, 57, 58]. A number of 5 studies investigated sigmoidoscopy at a 10-year interval [49–52, 59]

	Validation	Design	Data	Analysis	Reporting	Interpretation	Conflict of interest	Included in Review
Barré 2020	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Barzi 2017	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Dan 2012	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Dinh 2013	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Hassan 2011	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Heitman 2010	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Kingsley 2016	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Knudsen 2010	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Lansdorp 2010	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Naber 2019	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Van Hees 2014	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Vanness 2011	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Lam 2015	⊕	⊕	⊕	⊕	⊕	⊕	⊕	No
Lee 2010	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Lew 2018	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Senore 2019	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Sharp 2012	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Whyte 2012	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Wong 2016	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Telford 2010	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Melnitchouk 2018	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Sharaf 2013	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Ladabaum 2013	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Ladabaum 2018	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes
Ladabaum 2019	⊕	⊕	⊕	⊕	⊕	⊕	⊕	Yes



 : Strength  
 : Neutral  
 : Weakness

Fig 2. Results of the quality assessment of the retrieved modelling approaches based on the ISPOR “Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making” [30].

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and 7 as a once-only measure [44, 45, 52–54, 58, 59]. Cost-effectiveness results of these other intervals are displayed in the appendix (S1 File). In addition, sigmoidoscopy was assessed in combination with stool testing (8 studies) [35, 38–40, 46, 48, 55, 58]. Models with a societal perspective did not differ in the overall results from third-party payer models.

### Sigmoidoscopy every 5 years

Compared to ‘no screening’, 5-yearly sigmoidoscopy was in the majority of studies less costly and more effective, and therefore cost-saving (Table 2). Sigmoidoscopy always yielded higher QALY or LYG than no screening, with the highest ICER being \$50,027.19 per LYG [57]. Sigmoidoscopy was in all studies less effective than the gold-standard endoscopic procedure colonoscopy and in 5 studies associated with higher cost per patient [35, 36, 38, 43, 47]. ICER were mostly below \$67,000, favoring colonoscopy. One study reported significantly higher incremental cost of approximately \$107,365.00 per LYG with colonoscopy compared to sigmoidoscopy [49]. Regarding stool tests, the results were less consistent. Annual guaiac-based FOBT dominated sigmoidoscopy in 7 comparisons within 4 studies [38, 40, 43, 48], but in 6 cases sigmoidoscopy was associated with higher effectiveness and incremental cost below \$26,000 per LYG or QALY [38, 47, 49]. Most models showed that modern annual FIT was more effective and less costly than sigmoidoscopy [36, 38–40, 43, 47]. In 4 non-dominated comparisons with FIT, incremental cost varied between \$20,182.42 and \$194,487.07 per LYG [43, 47, 49, 58]. Only the studies by Barzi et al. [35] and Telford et al. [48] showed that sigmoidoscopy was cost-saving compared to both FOBT and FIT. Biennial FOBT or FIT was evaluated in only a few studies with mixed results when compared to sigmoidoscopy (S1 File). Overall, there was a tendency for sigmoidoscopy to be favored over low-sensitivity FOBT but dominated by higher sensitivity FOBT and FIT. Most of the variability of the stool test results was therefore attributable to differences in sensitivity assumptions.

In 10 different models, sigmoidoscopy was analyzed alongside newer screening strategies, such as DNA testing [35, 37, 39, 42, 43, 47, 48, 58], CT-colonography [35, 38, 47, 48, 58] or capsule endoscopy [49] (Table 3). DNA (stool) tests were conducted at an interval of either 2 [35, 39], 3 [37, 42, 43, 47, 48] or 5 years [42, 58]. While sigmoidoscopy was cost-saving in most comparisons, some studies came to the opposite conclusion, with sigmoidoscopy being associated with a smaller effect than DNA testing. However, ICERs for DNA testing were rather high, between \$61,310.88 and \$200,018.32 per QALY or per LYG, respectively [37, 42, 43, 58]. Compared to CT-colonography, 5-yearly sigmoidoscopy was associated with lower cost, but also lower effectiveness. The lowest incremental costs were \$21,407.95 per LYG [38]. Barzi et al. analyzed the only modeling approach where sigmoidoscopy was dominated by CT-colonography [35]. This was also the only study where the interval of the comparator intervention was 10 years. In all other studies examining this strategy as a comparator, both CT-colonography and sigmoidoscopy were conducted every 5 years. Only Hassan and colleagues included capsule endoscopy, generating no conclusive results [49].

### Sigmoidoscopy in combination with stool tests

Similarly to sigmoidoscopy alone, combinatorial strategies were also more effective or even cost-saving compared to no screening (S1 File). Seven models evaluated 5-yearly sigmoidoscopy in combination with annual guaiac-based FOBT [35, 38–40, 46, 48, 55, 58] (Table 4). When comparing this strategy to the standard colonoscopy, results were mixed. Although sigmoidoscopy was cost-saving in 5 cases compared to colonoscopy [38–40, 46], it was dominated in 3 studies [35, 38, 55] and both less expensive and less effective in the remaining models [38, 46, 48]. The highest incremental cost was \$78,776.30 per LYG [38]. When comparing the



**Table 3. Incremental cost, life years gained, quality-adjusted life years and incremental cost-effectiveness ratios of 5-yearly sigmoidoscopy compared with newer screening measures (in 2019 \$).**

Author, Year	Country	Model Name	Screening Period	5-yearly sigmoidoscopy												
				vs. DNA Test			vs. CT-Colonography			vs. Capsule Endoscopy						
				ΔCost	LYG	ΔQALY	ICER	ΔCost	LYG	ΔQALY	ICER	ΔCost	LYG	ΔQALY	ICER	
Barzi 2017 [35]	US	Markov	50–75	-1,095.904	0.002	-0.002	CS <sup>a</sup>	89.528	-0.004	-	-	-	-	-	-	-
Dan 2012 [58]	SG	Markov	50–75	-161.665	-	-0.002	80,832.366 <sup>b</sup>	-796.259	-	-0.012	66,354.927 <sup>b</sup>	-	-	-	-	-
Hassan 2011 [49]	FR	Markov	50–75	-	-	-	-	-	-	-	-	-	-	-644.995	-0.004	167,967.503 <sup>b</sup>
Heitman 2010 [47]	CA	Markov	50–75	-650.240	-	0.026	CS <sup>c</sup>	-207.735	-	-0.005	41,547.032 <sup>b</sup>	-	-	-	-	-
Kingsley 2016 [37]	US	Markov	50–80	-324.408	-	0.013	CS <sup>d</sup>	-	-	-	-	-	-	-	-	-
Knudsen 2010 [38]	US	CRC-SPIN	65–80	-1,741.229	-	-0.028	61,310.867 <sup>e</sup>	-	-	-	-	-	-	-	-	-
Naber 2019 [43]	US	CRC-SPIN	65–75	-810.404	-0.008	-	95,341.61 <sup>e</sup>	-	-	-	-	-	-	-	-	-
Knudsen 2010 [38]	US	MISCAN	65–80	-	-	-	-	-797.764	-0.010	-	77,452.831 <sup>i</sup>	-	-	-	-	-
Lansdorp-Vogelaar 2010 [42]	US	MISCAN	65–80	-1,048.437	0.006	-	CS <sup>e</sup>	-821.192	-0.006	-	130,347.864 <sup>i</sup>	-	-	-	-	-
Naber 2019 [43]	US	MISCAN	65–75	-690.245	0.016	-	CS <sup>b</sup>	-	-	-	-	-	-	-	-	-
Knudsen 2010 [38]	US	Sim-CRC	65–80	-1,054.463	0.007	-	CS <sup>e</sup>	-	-	-	-	-	-	-	-	-
Lansdorp-Vogelaar 2010 [42]	US	Sim-CRC	65–80	-1,100.101	-0.006	-	200,018.317 <sup>e</sup>	-623.908	-0.027	-	23,280.160 <sup>i</sup>	-	-	-	-	-
Naber 2019 [43]	US	Sim-CRC	65–75	-770.884	0.007	-	CS <sup>b</sup>	-662.132	-0.022	-	30,096.906 <sup>i</sup>	-	-	-	-	-
Ladabaum 2013 [39]	US	Markov	50–80	-948.078	-0.008	0.015	121,548.518 <sup>c</sup>	-	-	-	-	-	-	-	-	-
Telford 2010 [48]	CA	Markov	50–75	-848.848	-	0.007	CS <sup>f</sup>	-	-	-	-	-	-	-	-	-
				-952.596	-	0.016	CS <sup>e</sup>	-1,124.471	-	0.003	CS <sup>b</sup>	-	-	-	-	-

FR: France; US: United States of America; SG: Singapore; CA: Canada; HK: Hong Kong; UK: United Kingdom; AU: Australia; IT: Italy; IE: Ireland; UA: Ukraine

CS: cost saving, when a strategy was less costly and equally or more effective

D: dominant, when a strategy was equally or more costly and less effective

LYG: life years gained

QALY: quality-adjusted life years

ICER: incremental cost-effectiveness ratio

n/a: not applicable

<sup>a</sup> Comparator intervention biennial

<sup>b</sup> Comparator intervention every 5 years

<sup>c</sup> Comparator is first generation fecal DNA test every 3 years

<sup>d</sup> Comparator is second generation fecal DNA test every 3 years

<sup>e</sup> Comparator intervention triennial

<sup>f</sup> Comparator intervention is biennial <sup>m</sup>SEPT9-2well test

<sup>g</sup> Comparator intervention is biennial <sup>m</sup>SEPT9-3well test

<sup>h</sup> Comparator intervention every 10 years

<sup>i</sup> Different performance assumptions of CT-colonography

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**Table 4. Incremental cost, life years gained, quality-adjusted life years and incremental cost-effectiveness ratios of 5-yearly sigmoidoscopy combined with annual stool tests compared with single measure strategies (in 2019 \$).**

Author, Year	Country	Model Name	Screening Period	5-yearly sigmoidoscopy + annual FOBT														
				vs. 10-yearly colonoscopy					vs. 5-yearly sigmoidoscopy					vs. annual FOBT				
				ΔCost	LYG	ΔQALY	ICER	ICER	ΔCost	LYG	ΔQALY	ICER	ICER	ΔCost	LYG	ΔQALY	ICER	ICER
Barzi 2017 [35]	US	Markov	50–75	333.302	-0.010	-	D	D	26,966	-0.004	-	D	D	6,472	0.002	-	3,235.938	
Dan 2012 [58]	SG	Markov	50–75	-	-	-	-	-	-	-	-	-	-	-	-	-	-	
Knudsen 2010 <sup>a</sup> [38]	US	CRC-SPIN	65–80	69.049	-0.013	-	D <sup>b</sup>	D <sup>b</sup>	-73.981	0.017	-	CS <sup>b</sup>	CS <sup>b</sup>	147.962	0.029	-	5,119.808 <sup>b</sup>	
Vanness 2011 [46]	US	CRC-SPIN	50–80	82.612	-0.006	-	D <sup>c</sup>	D <sup>c</sup>	-60.418	0.024	-	CS <sup>c</sup>	CS <sup>c</sup>	228.109	0.013	-	18,103.870 <sup>c</sup>	
Knudsen 2010 <sup>a</sup> [38]	US	MISCAN	65–80	-109.739	-0.004	-	27,434.703	27,434.703	-	-	-	-	-	-	-	-	-	
Knudsen 2010 <sup>a</sup> [38]	US	MISCAN	65–80	-141.797	-0.002	-	78,776.299 <sup>b</sup>	78,776.299 <sup>b</sup>	-39.457	0.010	-	CS <sup>b</sup>	CS <sup>b</sup>	196.050	0.019	-	10,210.945 <sup>b</sup>	
Vanness 2011 [46]	US	MISCAN	50–80	-56.719	0.001	-	CS <sup>c</sup>	CS <sup>c</sup>	45.622	0.013	-	3509.366 <sup>c</sup>	3509.366 <sup>c</sup>	177.555	0.007	-	25,732.598 <sup>c</sup>	
Knudsen 2010 <sup>a</sup> [38]	US	Sim-CRC	65–80	-41.923	0.004	-	CS	CS	-	-	-	-	-	-	-	-	-	
Knudsen 2010 <sup>a</sup> [38]	US	Sim-CRC	65–80	-108.506	-0.008	-	13,395.777 <sup>b</sup>	13,395.777 <sup>b</sup>	-102.341	0.021	-	CS <sup>b</sup>	CS <sup>b</sup>	3.699	0.026	-	143.374 <sup>b</sup>	
Vanness 2011 <sup>d</sup> [46]	US	Sim-CRC	50–80	-27.126	-0.001	-	20,866.498 <sup>c</sup>	20,866.498 <sup>c</sup>	-20.961	0.027	-	CS <sup>c</sup>	CS <sup>c</sup>	134.399	0.011	-	11,789.405 <sup>c</sup>	
Vanness 2011 <sup>d</sup> [46]	US	Sim-CRC	50–80	-219.478	0.001	-	CS	CS	-	-	-	-	-	-	-	-	-	
Ladabaum 2013 [39]	US	Markov	50–80	-182.901	0.003	-	CS	CS	290.766	0.010	-	27,691.962	27,691.962	533.461	0.012	-	42,676.887	
Ladabaum 2018 [40]	US	Markov	50–80	-816.294	0.003	-	CS	CS	-239.526	0.029	-	CS	CS	1,101.104	0.012	-	88,088.284	
Melnitchouk 2018 [55]	UA	Markov	50–75	117.117	-0.007	-	D	D	-	-	-	-	-	-	-	-	-	
Telford 2010 [48]	CA	Markov	50–75	-864.094	-0.046	-	18,784.645	18,784.645	340.837	0.032	-	10,651.159	10,651.159	351.033	0.013	-	27,002.544 <sup>e</sup>	

Author, Year	Country	Model Name	Screening Period	5-yearly sigmoidoscopy + annual FIT														
				vs. 10-yearly colonoscopy					vs. 5-yearly sigmoidoscopy					vs. annual FIT				
				ΔCost	LYG	ΔQALY	ICER	ICER	ΔCost	LYG	ΔQALY	ICER	ICER	ΔCost	LYG	ΔQALY	ICER	ICER
Barzi 2017 [35]	US	Markov	50–75	514.514	-0.013	-	D	D	208.179	-0.007	-	D	D	37.753	0.003	-	12,584.202	
Dan 2012 [58]	SG	Markov	50–75	-360.730	-0.010	-	36,072.951	36,072.951	113.407	0.002	-	56,703.301	56,703.301	211.129	0.003	-	70,376.438	
Knudsen 2010 <sup>a</sup> [38]	US	CRC-SPIN	65–80	208.380	-0.006	-	D	D	65.350	0.023	-	2,792.738	2,792.738	239.206	0.015	-	16,496.962	
Vanness 2011 [46]	US	CRC-SPIN	50–80	19.728	-0.004	-	D	D	-	-	-	-	-	-	-	-	-	
Knudsen 2010 <sup>a</sup> [38]	US	MISCAN	65–80	143.030	0.001	-	102,164.542	102,164.542	245.371	0.013	-	18,730.614	18,730.614	302.090	0.008	-	37,761.248	
Vanness 2011 [46]	US	MISCAN	50–80	56.719	0.004	-	14,179.734	14,179.734	-	-	-	-	-	-	-	-	-	
Knudsen 2010 <sup>a</sup> [38]	US	Sim-CRC	65–80	86.311	-0.002	-	D	D	92.477	0.027	-	3,412.418	3,412.418	156.594	0.013	-	12,527.487	
Vanness 2011 <sup>d</sup> [46]	US	Sim-CRC	50–80	-97.409	0.001	-	CS	CS	-	-	-	-	-	-	-	-	-	
Ladabaum 2013 [39]	US	Markov	50–80	-179.384	0.006	-	CS	CS	294.283	0.013	-	23,355.788	23,355.788	638.981	0.004	-	152,138.301	
Ladabaum 2018 [40]	US	Markov	50–80	-551.743	0.006	-	CS	CS	25.025	0.031	-	796.977	796.977	1,089.187	0.004	-	259,330.202	

FR: France; US: United States of America; SG: Singapore; CA: Canada; HK: Hong Kong; UK: United Kingdom; AU: Australia; IT: Italy; IE: Ireland; UA: Ukraine

CS: cost saving, when a strategy was less costly and equally or more effective

D: dominant, when a strategy was equally or more costly and less effective

LYG: life years gained

QALY: quality-adjusted life years

ICER: incremental cost-effectiveness ratio

FOBT: guaiac-based fecal occult blood test

FIT: fecal immunochemical tests

<sup>a</sup> Identical model and input data to Lansdorp-Vogelaar 2010, therefore only Knudsen 2010 reported

<sup>b</sup> Hemoccult II Test

<sup>c</sup> Hemoccult SENS A

<sup>d</sup> Sigmoidoscopy without biopsy

<sup>e</sup> High sensitivity FOBT

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combinatorial strategy of sigmoidoscopy plus annual FOBT with the respective strategies alone, the evaluations showed a clear improvement of LYG or QALYs. In 4 models, the addition of FOBT annually resulted in cost-savings while gaining LYG or QALY per patient compared to sigmoidoscopy alone [38, 40]. Compared with FOBT alone, the combination with sigmoidoscopy resulted in incremental cost of \$143.37 to \$88,088.28 per LYG or QALY [38, 40].

Five-yearly sigmoidoscopy in combination with annual FIT was evaluated in 6 models [35, 38–40, 46, 58]. Results of the comparison of this strategy with colonoscopy were similar to those of the combination with FOBT. Incremental cost varied even within 1 modeling approach between \$14,179.73 and \$102,164.54 [38, 46]. Compared with 5-yearly sigmoidoscopy, the combination with FIT was not cost-saving, but in almost all models yielded higher effectiveness levels with ICERs between \$796.98 and \$56,703.30 [38–40, 58]. Sigmoidoscopy in conjunction with FIT was more expensive, but also more effective than FIT alone. The incremental cost ranged between \$12,527.49 per LYG and \$259,330.20 per QALY [38, 40].

The evaluation of 5-yearly sigmoidoscopy plus biennial or triennial stool tests was not significantly different from combinations with annual FOBT and FIT, although only 3 models considered these strategies (S1 File).

### 1.3 Contributing factors and drivers of cost-effectiveness

In comprehensive modeling approaches, certain parameters have greater influence on cost-effectiveness results, which is estimated in sensitivity analyses (SA). The most often investigated parameters in the included articles are displayed in Table 5. All models conducted deterministic sensitivity analysis (DSA), including one-way, multi-way or scenario SA. Additionally, in about half of the studies, probabilistic sensitivity analysis (PSA) was performed to represent uncertainty in parameter estimation.

Adherence rate as well as costs of screening measures and cancer treatment varied in most models. The adherence rate to screening varied between 19% and 100%. Perfect or near perfect conditions with uptake rates over 90% across all strategies were assumed in 6 models (11 articles) [36, 38–46, 57], and only 9 studies differentiated adherence between screening measures [35, 37, 47, 50, 52–55, 57]. Unit cost of screening measures was heterogeneous among models. The lowest cost of sigmoidoscopy was \$ 71.24 [50], while the highest cost assumption was over 25-fold more costly [59]. The sources for the unit costs were based on Medicare reimbursement values between the years 2007 and 2014 in 9 studies [35–41, 43, 45]. Other costing sources used were local schemes [47–54, 57, 58] as well as expert opinions [55] or unspecified assumptions [51]. Another influential parameter was the cost of cancer treatment. In particular, the cost in higher stages differed significantly across models. For example, the cost of treating stage IV or distant CRC ranged from \$12,171.14 [51] to \$190,680.95 [47]. Also, the difference within a model between localized/stage I CRC and the highest stage was extremely heterogeneous, ranging from barely doubling to a 40-fold increase in cost.

Different assumptions about test performance characteristics of sigmoidoscopy influenced the cost-effectiveness results, which were investigated in several sensitivity analyses. For both sensitivity and specificity, there was a wide variation in the values assumed, with possible implications for detection rates and thus the effectiveness of the screening measures evaluated. Most models differentiated sensitivity for different types of precursor lesions as well as for CRC. For adenomas, sensitivity of sigmoidoscopy ranged from 22% to 97%, and for CRC from 48% to 95%. Specificity was mostly close to 100% with the lowest assumption being 60%.

The modeled risk reduction through screening measures indicates important information about the effectiveness of CRC screening strategies, as endoscopic measures may prevent CRC



Table 5. Influential variables and indicators.

Author, Year	Country	Model Type	PSA	Test characteristics of sigmoidoscopy			Adherence		Cost of sigmoidoscopy (2019 US-\$)	Cost Components				Effect indicators	
				Base Case Sensitivity for precursor lesions	Base Case Sensitivity for CRC	Base Case Specificity	General Adherence rates	Adherence rate specific to sigmoidoscopy		Stage I Localized CRC	Stage II Regional CRC	Stage III Distant CRC	Stage IV Distant CRC	Baseline CRC risk	CRC incidence reduction attributed to 5-yearly sigmoidoscopy
Barzì 2020 [50]	FR	Microsimulation	✓	Adenoma ≤ 6 mm: 45% Adenoma > 6 mm: 90%	95%	95%	25%-65%	25%	71.24	9,663.53	12,440.73	17,466.67	20,843.50	n/a	n/a
Barzi 2017 [35]	US	Microsimulation		75%	75%	92%	46%-63%	63%	177.08	38,905.68	38,905.68	38,905.68	101,102.56 <sup>c</sup>	4.50%	11.00%
Dan 2012 [58]	SG	Markov		65%	95%	60%	50%	-	241.29	12,064.53	24,129.06	28,954.88	21,716.16	2.03%	28%
Dinh 2013 [36]	US	Archimedes		n/a	n/a	n/a	100%	-	188.76	31,425.99	43,369.02	52,878.08	69,049.14	6.00%	53.00%
Hassan 2011 [49]	FR	Markov	✓	Diminutive (<= 5 mm) polyps: 45% Medium (6-9 mm) polyps: 65% Large (>= 10 mm) polyps: 65%	65%	90%	40%	-	368.80	15,628.05	-	24,699.05	29,474.11	5.36%	27.00%
Heitman 2010 [47]	CA	Markov	✓	Nonadvanced adenoma: 65% Advanced adenoma: 75%	75%	100%	63%-68%	-	924.85	35,640.81	51,425.83	137,685.72	190,680.95	4.86%	58.08%
Kingsley 2016 [37]	US	Microsimulation	✓	Low Grade polyp: 85% High Grade polyp: 90%	95%	92%	65%-95%	-	200.62-252.43	n/a	n/a	n/a	n/a	n/a	n/a
Knudsen 2010* [38]	US	CRC-SPIN		Small (1-5mm) adenoma: 75% Medium (6-9mm) adenoma: 85% Large (>=10 mm) adenoma: 95%	95%	100%	100%	-	429.09	31,425.99	43,369.02	52,878.08	69,049.14 <sup>d</sup>	5.30%	60.38%
Naber 2019 [43]	US	CRC-SPIN		Small (1-5mm) adenoma: 75% Medium (6-9mm) adenoma: 85% Large (>=10 mm) adenoma: 95%	95%	87%	100%	-	351.20	34,850.49	49,315.72	70,193.27	102,141.11 <sup>d</sup>	6.40%	54.69%
Knudsen 2010* [38]	US	MISCAN		Small (1-5mm) adenoma: 75% Medium (6-9mm) adenoma: 85% Large (>=10 mm) adenoma: 95%	95%	100%	100%	-	429.09	31,425.99	43,369.02	52,878.08	69,049.14 <sup>d</sup>	5.70%	47.37%
Naber 2019 [43]	US	MISCAN		Small (1-5mm) adenoma: 75% Medium (6-9mm) adenoma: 85% Large (>=10 mm) adenoma: 95%	95%	92%	100%	-	351.20	34,850.49	49,315.72	70,193.27	102,141.11 <sup>d</sup>	6.10%	50.82%
Van Hees 2014 [45]	US	MISCAN		Small (1-5mm) adenoma: 75% Medium (6-9mm) adenoma: 85% Large (>=10 mm) adenoma: 95%	95%	87%	100%	-	611.28	40,257.55	54,031.57	65,582.17	85,370.19 <sup>d</sup>	n/a	-0.62% - 1.2% <sup>h</sup>
Knudsen 2010* [38]	US	Sim-CRC		Small (1-5mm) adenoma: 75% Medium (6-9mm) adenoma: 85% Large (>=10 mm) adenoma: 95%	95%	100%	100%	-	429.09	31,425.99	43,369.02	52,878.08	69,049.14 <sup>d</sup>	6.00%	51.67%
Naber 2019 [43]	US	Sim-CRC		Small (1-5mm) adenoma: 75% Medium (6-9mm) adenoma: 85% Large (>=10 mm) adenoma: 95%	95%	87%	100%	-	351.20	34,850.49	49,315.72	70,193.27	102,141.11 <sup>d</sup>	6.40%	56.25%

(Continued)

Table 5. (Continued)

Author, Year	Country	Model Type	PSA	Test characteristics of sigmoidoscopy			Adherence		Cost Components				Effect indicators		
				Base Case Sensitivity for precursor lesions	Base Case Sensitivity for CRC	Base Case Specificity	General Adherence rates	Adherence rate specific to sigmoidoscopy	Cost of sigmoidoscopy (2019 US-\$)	Stage I Localized CRC	Stage II Regional CRC	Stage III Distant CRC	Stage IV Distant CRC	Baseline CRC risk	CRC incidence reduction attributed to 5-yearly sigmoidoscopy
Ladabaum 2013 <sup>a</sup> [39]	US	Markov	✓	Small polyp: 85% Large polyp: 90%	95%	92%	100%	-	198.14	33,320.80	-	56,066.17	73,211.97	5.93%	68.23%
Ladabaum 2018 [40]	US	Markov	✓	Large polyp: 90%		92%		-	391.98-470.37	44,216.93	-	74,400.76	97,154.51 <sup>e</sup>	5.93%	46.53%
Ladabaum 2019 [41]	US	Markov	✓			87%		-	391.98-470.37	32,749.49	-	82,999.35	108,382.15 <sup>e</sup>	n/a	n/a
Lee 2010 [51]	UK	Markov	✓	Low-risk proximal polyps: 0% Low-risk distal polyps: 95% High-risk proximal polyps: 0% High-risk distal polyps: 88.3%	Proximal CRC: 0% Distal CRC: 88.3%	100%	60%	-	267.66	6,156.57	11,381.75	17,806.37	12,171.14	n/a	n/a
Low 2018 [59]	AU	Policy-Bowel		Adenoma of any size: 40.9% Adenoma >5mm: 46.2% Adenoma >10mm: 47.6%	47.90%	93.20%	40%	15%	1,847.32	56,826.56	87,114.87	136,547.54	112,997.32	0.06%	8%-52%
Meinitchouk 2018 [55]	UA	Markov		Low risk polyp: 92% High risk polyp: 97%	93%	100%	75%-84%	75%	111.54	2,788.50	-	50,193.05	111,540.10	n/a	n/a
Senore 2019 [54]	IT	Markov	✓	n/a	n/a	n/a	19%-42%	30%	109.21	11,218.27	14,240.07	20,371.73	25,452.20	n/a	32% <sup>g</sup>
Sharp 2012 [53]	IE	Markov	✓	Low-risk distal adenomas: 65% Intermediate / high-risk distal adenomas: 7.4%	90%	92%	39%-53%	39%	120.49	18,382.27	29,219.65	38,581.48	28,755.38	5.16%	n/a
Telford 2010 [48]	CA	Markov	✓	Low risk polyp: 92% Advanced adenoma: 97%	93%	100%	73%	-	281.12	20,004.52	39,465.73	51,038.17	105,282.25	n/a	63.00%
Whyte 2012 [52]	UK	Markov	✓	Low-risk adenoma: 22% High-risk adenoma: 71%	62%	100%	54%-85%	85%	162.66	10,389.30	14,294.78	19,604.12	21,440.08	n/a	n/a

(Continued)

Table 5. (Continued)

Author, Year	Country	Model Type	PSA	Test characteristics of sigmoidoscopy			Adherence		Cost of sigmoidoscopy (2019 US-\$)	Cost Components			Effect indicators		
				Base Case Sensitivity for precursor lesions	Base Case Sensitivity for CRC	Base Case Specificity	General Adherence rates	Adherence rate specific to sigmoidoscopy		Stage I Localized CRC	Stage II Regional CRC	Stage III Distant CRC		Baseline CRC risk	
Wong 2016 [57]	HK	Markov	✓	-	75%	76.60%	90%-98.9%	90%	309.83	20,032.56	20,032.56	33,066.07	86,838.83	2.38%	CRC incidence reduction attributed to 5-yearly sigmoidoscopy

FR: France; US: United States of America; SG: Singapore; CA: Canada; HK: Hong Kong; UK: United Kingdom; AU: Australia; IT: Italy; IE: Ireland; UA: Ukraine

PSA: probabilistic sensitivity analysis

<sup>a</sup> Identical model and input data to Lansdorp-Vogelaar 2010 and Vanness 2011, therefore only Knudsen 2010 reported

<sup>b</sup> Identical model and input data to Sharaf & Ladabaum 2013, therefore only Ladabaum 2013 reported

<sup>c</sup> Barzi only differentiates costs between curable (Stage I to III) and non-curable CRC (Stage IV)

<sup>d</sup> This study originally differentiates costs between initial costs (first 12 months after diagnosis), continuing cost (after 12 months) and terminal cost (final 12 month of life). For better comparability with the other studies, only the initial costs are reported in this table.

<sup>e</sup> Commercial payment rates for persons under age 65

<sup>f</sup> Medicare payments for persons age 65 and older

<sup>g</sup> Incidence reduction as input-parameter

<sup>h</sup> negative incidence reduction due to over-diagnosis

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development by removing precursor lesions. While the lifetime risk for developing CRC ranged from 0.06% to 6.4% (mean 4.88%; median 5.53%), the risk reduction of sigmoidoscopy varied more significantly. While in 1 study, the use of sigmoidoscopy led up to a 68.23% lower risk of developing CRC [39], another study reported an increased CRC risk due to overdiagnosis in the elderly (-0.62% risk reduction) [45].

Although SAs mostly supported the results of the base-case analysis, the effect on sigmoidoscopy was not always considered or reported. Given the fact that the models were highly heterogeneous, it was not possible to estimate the effect of the characteristics on the results. Nonetheless, the consideration of the most influential parameters revealed potential rationales for variations in the results.

## Discussion

This systematic review included the results of 25 studies. Sigmoidoscopy, both as a stand-alone strategy and in combination with stool testing, was cost-effective and in some cases cost-saving compared to no screening. In a direct comparison of effectiveness and cost to other commonly used screening strategies, sigmoidoscopy tended to be inferior to colonoscopy and FIT and had a more favorable cost-effectiveness ratio only when compared with the low-sensitivity gFOBT. At the same time, sigmoidoscopy combined with annual stool testing was more effective and less costly than the respective individual strategies. Adherence, cost assumptions, and test characteristics had the highest impact on cost-effectiveness.

Other systematic reviews have come to similar conclusions. For example, several reviews did not identify sigmoidoscopy as the optimal (single) strategy in any case [24–28]. Some of the included studies evaluated stool testing as the preferred strategy over endoscopic procedures such as colonoscopy or sigmoidoscopy. However, this is only true when considering single strategies. For the first time, the present review also focused on combined strategies of stool testing and sigmoidoscopy, demonstrating a higher benefit at low additional cost compared to the single application of the respective screening measures. Almost all studies that considered combinations of stool test and sigmoidoscopy were conducted in the USA. Combinatorial strategies have so far been of minor interest in systematic reviews of cost-effectiveness models. Only Patel and Kilgore identified a superiority of the combination of sigmoidoscopy and stool testing compared to the respective individual strategies when exclusively considering US cost-effectiveness modeling studies from 2007–2014 [27]. It is unclear whether a combination of colonoscopy with stool tests would similarly influence cost-effectiveness compared to colonoscopy alone. No evidence is available to show whether combining sigmoidoscopy with FIT or gFOBT leads to a significantly greater reduction in incidence and mortality than sigmoidoscopy alone, as RCTs have primarily examined single sigmoidoscopy [60].

Although the overall quality of the studies was satisfactory, in some cases there was no comprehensive validation of the results, which particularly included internal validation. Consequently, the results could not be fully assessed. Furthermore, the process of data identification was not presented transparently, which gave rise to the suspicion of cherry-picking of input studies. A narrative review of the quality of CRC modeling studies revealed similar deficiencies: for studies from a period of 1999–2014, the main criticisms of the authors were the oversimplification of carcinogenesis and insufficient, as well as outdated, evidence as input to the models [18]. In an assessment of the reporting quality of recent modeling studies using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, Mendivil et al. also criticized the choice of models and the methods used to identify effectiveness data as being the least well reported [26].

It is uncertain to what extent the effects of sigmoidoscopy and specifically the differences to colonoscopy were adequately represented in models. This is also reflected in the large heterogeneity of contributing factors. Differences in modeling approaches and structural representation of CRC development, as well as the superficial consideration of localization, made it difficult to compare results. Only 1 study included alternative pathways of CRC development in its modeling [59]. In contrast, the majority reduced carcinogenesis to the adenoma-carcinoma sequence. This is particularly critical because recent analyses have found differential efficacy of sigmoidoscopy by subgroups [61]. According to this analysis, sigmoidoscopy is an effective screening measure especially for men and younger women. In women older than 60 years, the effectiveness of sigmoidoscopy in reducing mortality and incidence decreased significantly. This was attributed in part to the different incidence of distal and proximal carcinomas in men and women, which in turn is influenced by different histology and carcinogenesis. Proximal advanced neoplasms without distal lesions are more common in women than in men [62, 63]. Consequently, effectiveness of sigmoidoscopy in men and younger women as an important input parameter might be underestimated in the previous modeling approaches, leading to a systematic underestimation of its cost-effectiveness. Future models should consider the age- and sex-specific data at least in sensitivity analyses.

In addition, sigmoidoscopy is a less standardized procedure that can reach either to the descending colon or up to the left flexure [64]. In some cases, biopsies were taken during sigmoidoscopies, while in other cases this exclusively took place during colonoscopies. Often, the models left unclear what assumptions were made in this regard. There is uncertainty as to what accounts for the differences in test characteristics of sigmoidoscopy in the models. Moreover, it should be noted that, similarly to stool tests, sigmoidoscopies must be followed by a complete colonoscopy in case of abnormal findings. This is necessary because the characteristics of adenomas found in the rectum and sigmoid correlate with the likelihood of the presence of proximal neoplasia [65]. The cost of colonoscopy is assumed to be significantly variable, with implications for cost-effectiveness [28]. For example, in France, the presence of an anesthesiologist is a requirement, resulting in significantly higher colonoscopy costs in contrast to countries that do not have such a provision [49]. The overall cost structure for screening and treatment cost is affected by multiple factors, which can lead to significant international differences. Even for models from the same country, variations in costs are significant contributors to differences in cost-effectiveness.

The nature of decision-analytic models is a simplification of reality. Thus, the investigated studies often used ideal-typical assumptions, such as complete participation and adherent behavior at follow-up. Annual stool tests in particular require a high degree of reliability. Although noninvasive screening methods have higher participation than endoscopic methods [19, 66], complete participation and adherence by a large proportion of the relevant population is an idealized presumption. SAs of the models identified adherence as one of the major factors influencing cost-effectiveness. Bibliometric analysis of CRC models also supported this finding [26]. In view of this, patient behavior regarding the choice of screening method is a key determinant when considering the early detection of CRC. It is expected that the willingness to participate is higher for procedures that correspond to individual preferences. Preference elicitation for CRC screening revealed dissent on the preferred measure and differences by subgroups [67–69]. No model compared systems that offered multiple methods patients could choose between based on their age and sex. This creates a relevant research gap, as the real implications on health care systems remain vague.

The present systematic review has limitations. The restriction of the selected databases may have led to a systematic omission of studies. In addition, the review did not limit the origin of the models. The included countries differ significantly in their health care policies and in

income of the population. The majority of studies reviewed were from the USA. This could have led to a bias in the results. The models set different cost-effectiveness thresholds, which were not included in the review. As various screening strategies in terms of intervals and combinations were analyzed in the models, the number of studies per comparison was low in some cases. Comparability is therefore limited. The influencing factors and drivers of cost-effectiveness could not be evaluated quantitatively due to the great heterogeneity of the studies. This also makes general clinical application of the results rather difficult.

## Conclusions

Sigmoidoscopy is a reasonable and cost-effective method for detection and prevention of CRC. Yet, in direct head-to-head comparison with other screening methods, it is often dominated. When combined with stool testing, however, it shows a significant gain in benefit at a low cost per utility gained. Further research is necessary to examine whether this combination should be promoted more and recommended in guidelines. Particularly for health care systems where multiple methods are available, sigmoidoscopy may represent a method preferred by subgroups. However, there is a lack of policy models that extend beyond a mere comparison of technologies and include preferences of the relevant population. Future decision-analytical models should incorporate such behavioral economic considerations. The analysis of subgroups will provide an essential contribution to current understanding and thus be of particular importance for decision-makers in different health care settings.

## Supporting information

**S1 Checklist. PRISMA checklist.**

(PDF)

**S1 Fig. Search strategy.**

(TIF)

**S1 Table. Search syntax.**

(PDF)

**S2 Table. Articles excluded in full text screening.**

(PDF)

**S1 File. Additional results.**

(PDF)

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## References

1. Ferlay J, Ervik M, Lam F, Colombet M, Mery L, Piñeros M, et al. Global Cancer Observatory: Cancer Today [Internet]. Lyon, France; 2020 [cited 2023 Jan 9]. Available from: <https://gco.iarc.fr/>.
2. Brenner H, Altenhofen L, Stock C, Hoffmeister M. Natural history of colorectal adenomas: birth cohort analysis among 3.6 million participants of screening colonoscopy. *Cancer Epidemiol Biomarkers Prev* 2013; 22(6):1043–51. <https://doi.org/10.1158/1055-9965.EPI-13-0162> PMID: 23632815.
3. Ponti A, Anttila A, Guglielmo R, Senore C, Basu P, Segnan N, et al. Cancer screening in the European Union. Report on the implementation of the council recommendation on cancer screening [Internet]. Brussels; 2017 [cited 2019 Oct 1]. Available from: [https://ec.europa.eu/health/sites/health/files/major\\_chronic\\_diseases/docs/2017\\_cancerscreening\\_2ndreportimplementation\\_en.pdf](https://ec.europa.eu/health/sites/health/files/major_chronic_diseases/docs/2017_cancerscreening_2ndreportimplementation_en.pdf).
4. Navarro M, Nicolas A, Ferrandez A, Lanás A. Colorectal cancer population screening programs worldwide in 2016: an update. *World J Gastroenterol* 2017; 23(20):3632–42. <https://doi.org/10.3748/wjg.v23.i20.3632> PMID: 28611516; PubMed Central PMCID: PMC5449420.
5. Schreuders EH, Ruco A, Rabeneck L, Schoen RE, Sung JJY, Young GP, et al. Colorectal cancer screening: a global overview of existing programmes. *Gut* 2015; 64(10):1637–49. <https://doi.org/10.1136/gutjnl-2014-309086> PMID: 26041752.
6. Segnan N, Patrick J, Karsa L von. European guidelines for quality assurance in colorectal cancer screening and diagnosis. 1<sup>st</sup> ed. Luxembourg: Office for Official Publications of the European Communities; 2010. lx, 386.
7. Bénard F, Barkun AN, Martel M, Renteln D von. Systematic review of colorectal cancer screening guidelines for average-risk adults: Summarizing the current global recommendations. *World J Gastroenterol* 2018; 24(1):124–38. <https://doi.org/10.3748/wjg.v24.i1.124> PMID: 29358889; PubMed Central PMCID: PMC5757117.
8. Hewitson P, Glasziou P, Irwig L, Towler B, Watson E. Screening for colorectal cancer using the faecal occult blood test, Hemoccult. *Cochrane Database Syst Rev* 2007(1):CD001216. <https://doi.org/10.1002/14651858.CD001216.pub2> PMID: 17253456.
9. Quintero E, Castells A, Bujanda L, Cubiella J, Salas D, Lanás A, et al. Colonoscopy versus fecal immunochemical testing in colorectal-cancer screening. *N Engl J Med* 2012; 366(8):697–706. <https://doi.org/10.1056/NEJMoa1108895> PMID: 22356323.
10. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. *BMJ* 2014; 348:g2467. <https://doi.org/10.1136/bmj.g2467> PMID: 24922745; PubMed Central PMCID: PMC3980789.
11. Bretthauer M, Løberg M, Wieszczyn P, Kalager M, Emilsson L, Garborg K, et al. Effect of colonoscopy screening on risks of colorectal cancer and related death. *N Engl J Med* 2022; 387(17):1547–56. <https://doi.org/10.1056/NEJMoa2208375> PMID: 36214590.
12. Jodal HC, Helsing LM, Anderson JC, Lytvyn L, Vandvik PO, Emilsson L. Colorectal cancer screening with faecal testing, sigmoidoscopy or colonoscopy: a systematic review and network meta-analysis. *BMJ Open* 2019; 9(10):e032773. <https://doi.org/10.1136/bmjopen-2019-032773> PMID: 31578199.
13. Morois S, Cottet V, Racine A, Clavel-Chapelon F, Carbonnel F, Bastide N, et al. Colonoscopy reduced distal colorectal cancer risk and excess cancer risk associated with family history. *Cancer Causes Control* 2014; 25(10):1329–36. <https://doi.org/10.1007/s10552-014-0438-7> PMID: 25048603.
14. Baxter NN, Goldwasser MA, Paszat LF, Saskin R, Urbach DR, Rabeneck L. Association of colonoscopy and death from colorectal cancer. *Annals of Internal Medicine* 2009; 150(1):1–8. <https://doi.org/10.7326/0003-4819-150-1-200901060-00306> PMID: 19075198.
15. Singh H, Nugent Z, Demers AA, Kliewer EV, Mahmud SM, Bernstein CN. The reduction in colorectal cancer mortality after colonoscopy varies by site of the cancer. *Gastroenterology* 2010; 139(4):1128–37. <https://doi.org/10.1053/j.gastro.2010.06.052> PMID: 20600026.

16. Steffen A, Weber MF, Roder DM, Banks E. Colorectal cancer screening and subsequent incidence of colorectal cancer: results from the 45 and Up Study. *Med J Aust* 2014; 201(9):523–7. <https://doi.org/10.5694/mja14.00197> PMID: 25358576.
17. Leggett B, Whitehall V. Role of the serrated pathway in colorectal cancer pathogenesis. *Gastroenterology* 2010; 138(6):2088–100. <https://doi.org/10.1053/j.gastro.2009.12.066> PMID: 20420948.
18. Jeong KE, Cairns JA. Review of economic evidence in the prevention and early detection of colorectal cancer. *Health Econ Rev* 2013; 3(1):20. <https://doi.org/10.1186/2191-1991-3-20> PMID: 24229442; PubMed Central PMCID: PMC3847082.
19. Klabunde C, Blom J, Bulliard J-L, Garcia M, Hagoel L, Mai V, et al. Participation rates for organized colorectal cancer screening programmes: an international comparison. *J Med Screen* 2015; 22(3):119–26. <https://doi.org/10.1177/0969141315584694> PMID: 25967088.
20. Federici A, Marinacci C, Mangia M, Borgia P, Giorgi Rossi P, Guasticchi G. Is the type of test used for mass colorectal cancer screening a determinant of compliance? A cluster-randomized controlled trial comparing fecal occult blood testing with flexible sigmoidoscopy. *Cancer Detect Prev* 2006; 30(4):347–53. <https://doi.org/10.1016/j.cdp.2006.03.009> PMID: 16965874.
21. Hassan C, Bretthauer M, Kaminski MF, Polkowski M, Rembacken B, Saunders B, et al. Bowel preparation for colonoscopy: European Society of Gastrointestinal Endoscopy (ESGE) guideline. *Endoscopy* 2013; 45(2):142–50. <https://doi.org/10.1055/s-0032-1326186> PMID: 23335011.
22. Senore C, Ederle A, Fantin A, Andreoni B, Bisanti L, Grazzini G, et al. Acceptability and side-effects of colonoscopy and sigmoidoscopy in a screening setting. *J Med Screen* 2011; 18(3):128–34. <https://doi.org/10.1258/jms.2011.010135> PMID: 22045821.
23. Lin JS, Perdue LA, Henrikson NB, Bean SI, Blasi PR. Screening for colorectal cancer: updated evidence report and systematic review for the US Preventive Services Task Force. *JAMA* 2021; 325(19):1978–97. <https://doi.org/10.1001/jama.2021.4417> PMID: 34003220.
24. Khalili F, Najafi B, Mansour-Ghanaei F, Yousefi M, Abdollahzad H, Motlagh A. Cost-Effectiveness Analysis of Colorectal Cancer Screening: A Systematic Review. *Risk Manag Healthc Policy* 2020; 13:1499–512. <https://doi.org/10.2147/RMHP.S262171> PMID: 32982508; PubMed Central PMCID: PMC7490076.
25. Lansdorp-Vogelaar I, Knudsen AB, Brenner H. Cost-effectiveness of colorectal cancer screening. *Epidemiol Rev* 2011; 33:88–100. <https://doi.org/10.1093/epirev/mxr004> PMID: 21633092; PubMed Central PMCID: PMC3132805.
26. Mendivil J, Appierto M, Aceituno S, Comas M, Rué M. Economic evaluations of screening strategies for the early detection of colorectal cancer in the average-risk population: A systematic literature review. *PLoS ONE* 2019; 14(12):e0227251. <https://doi.org/10.1371/journal.pone.0227251> PMID: 31891647; PubMed Central PMCID: PMC6938313.
27. Patel SS, Kilgore ML. Cost Effectiveness of Colorectal Cancer Screening Strategies. *Cancer Control* 2015; 22(2):248–58. <https://doi.org/10.1177/107327481502200219> PMID: 26068773.
28. Ran T, Cheng C-Y, Misselwitz B, Brenner H, Ubels J, Schlander M. Cost-Effectiveness of Colorectal Cancer Screening Strategies-A Systematic Review. *Clin Gastroenterol Hepatol* 2019; 17(10):1969–1981.e15. <https://doi.org/10.1016/j.cgh.2019.01.014> PMID: 30659991.
29. Silva-Illanes N, Espinoza M. Critical Analysis of Markov Models Used for the Economic Evaluation of Colorectal Cancer Screening: A Systematic Review. *Value Health* 2018; 21(7):858–73. <https://doi.org/10.1016/j.jval.2017.11.010> PMID: 30005759.
30. Caro J, Eddy DM, Kan H, Kaltz C, Patel B, Eldessouki R, et al. Questionnaire to assess relevance and credibility of modeling studies for informing health care decision making: an ISPOR-AMCP-NPC Good Practice Task Force report. *Value in Health* 2014; 17(2):174–82. <https://doi.org/10.1016/j.jval.2014.01.003> PMID: 24636375.
31. Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021; 372:n71. <https://doi.org/10.1136/bmj.n71> PMID: 33782057; PubMed Central PMCID: PMC8005924.
32. Welte R, Feenstra T, Jager H, Leidl R. A decision chart for assessing and improving the transferability of economic evaluation results between countries. *Pharmacoeconomics* 2004; 22(13):857–76. <https://doi.org/10.2165/00019053-200422130-00004> PMID: 15329031.
33. Turner HC, Lauer JA, Tran BX, Teerawattananon Y, Jit M. Adjusting for Inflation and Currency Changes Within Health Economic Studies. *Value Health* 2019; 22(9):1026–32. <https://doi.org/10.1016/j.jval.2019.03.021> PMID: 31511179.
34. The World Bank. Data Bank: World Development Indicators [Internet] [cited 2021 Jan 5]. Available from: <https://databank.worldbank.org/source/world-development-indicators/preview/on>.



35. Barzi A, Lenz H-J, Quinn DI, Sadeghi S. Comparative effectiveness of screening strategies for colorectal cancer. *Cancer* 2017; 123(9):1516–27. <https://doi.org/10.1002/ncr.30518> PMID: 28117881.
36. Dinh T, Ladabaum U, Alperin P, Caldwell C, Smith R, Levin TR. Health benefits and cost-effectiveness of a hybrid screening strategy for colorectal cancer. *Clin Gastroenterol Hepatol* 2013; 11(9):1158–66. <https://doi.org/10.1016/j.cgh.2013.03.013> PMID: 23542330.
37. Kingsley J, Karanth S, Revere FL, Agrawal D. Cost Effectiveness of Screening Colonoscopy Depends on Adequate Bowel Preparation Rates—A Modeling Study. *PLoS ONE* 2016; 11(12):e0167452. <https://doi.org/10.1371/journal.pone.0167452> PMID: 27936028; PubMed Central PMCID: PMC5147887.
38. Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Savarino JE, van Ballegooijen M, Kuntz KM, et al. Cost-effectiveness of computed tomographic colonography screening for colorectal cancer in the medicare population. *J Natl Cancer Inst* 2010; 102(16):1238–52. <https://doi.org/10.1093/jnci/djq242> PMID: 20664028; PubMed Central PMCID: PMC2923219.
39. Ladabaum U, Allen J, Wandell M, Ramsey S. Colorectal cancer screening with blood-based biomarkers: cost-effectiveness of methylated septin 9 DNA versus current strategies. *Cancer Epidemiol Biomarkers Prev* 2013; 22(9):1567–76. <https://doi.org/10.1158/1055-9965.EPI-13-0204> PMID: 23796793.
40. Ladabaum U, Mannalithara A, Brill JV, Levin Z, Bundorf KM. Contrasting Effectiveness and Cost-Effectiveness of Colorectal Cancer Screening Under Commercial Insurance vs. Medicare. *Am J Gastroenterol* 2018; 113(12):1836–47. <https://doi.org/10.1038/s41395-018-0106-8> PMID: 29904156; PubMed Central PMCID: PMC6768591.
41. Ladabaum U, Mannalithara A, Meester RGS, Gupta S, Schoen RE. Cost-Effectiveness and National Effects of Initiating Colorectal Cancer Screening for Average-Risk Persons at Age 45 Years Instead of 50 Years. *Gastroenterology* 2019; 157(1):137–48. <https://doi.org/10.1053/j.gastro.2019.03.023> PMID: 30930021; PubMed Central PMCID: PMC7161092.
42. Lansdorp-Vogelaar I, Kuntz KM, Knudsen AB, Wilschut JA, Zauber AG, van Ballegooijen M. Stool DNA testing to screen for colorectal cancer in the Medicare population: a cost-effectiveness analysis. *annals of internal medicine* 2010; 153(6):368–77. <https://doi.org/10.7326/0003-4819-153-6-201009210-00004> PMID: 20855801; PubMed Central PMCID: PMC3578600.
43. Naber SK, Knudsen AB, Zauber AG, Rutter CM, Fischer SE, Pabiniak CJ, et al. Cost-effectiveness of a multitarget stool DNA test for colorectal cancer screening of Medicare beneficiaries. *PLoS ONE* 2019; 14(9):e0220234. <https://doi.org/10.1371/journal.pone.0220234> PMID: 31483796; PubMed Central PMCID: PMC6726189.
44. Sharaf RN, Ladabaum U. Comparative effectiveness and cost-effectiveness of screening colonoscopy vs. sigmoidoscopy and alternative strategies. *Am J Gastroenterol* 2013; 108(1):120–32. <https://doi.org/10.1038/ajg.2012.380> PMID: 23247579.
45. van Hees F, Habbema JDF, Meester RG, Lansdorp-Vogelaar I, van Ballegooijen M, Zauber AG. Should colorectal cancer screening be considered in elderly persons without previous screening? A cost-effectiveness analysis. *annals of internal medicine* 2014; 160(11):750–9. <https://doi.org/10.7326/M13-2263> PMID: 24887616; PubMed Central PMCID: PMC4109030.
46. Vanness DJ, Knudsen AB, Lansdorp-Vogelaar I, Rutter CM, Gareen IF, Herman BA, et al. Comparative economic evaluation of data from the ACRIN National CT Colonography Trial with three cancer intervention and surveillance modeling network microsimulations. *Radiology* 2011; 261(2):487–98. <https://doi.org/10.1148/radiol.11102411> PMID: 21813740; PubMed Central PMCID: PMC3198218.
47. Heitman SJ, Hilsden RJ, Au F, Dowden S, Manns BJ. Colorectal cancer screening for average-risk North Americans: an economic evaluation. *PLoS Med* 2010; 7(11):e1000370. <https://doi.org/10.1371/journal.pmed.1000370> PMID: 21124887; PubMed Central PMCID: PMC2990704.
48. Telford JJ, Levy AR, Sambrook JC, Zou D, Enns RA. The cost-effectiveness of screening for colorectal cancer. *CMAJ* 2010; 182(12):1307–13. <https://doi.org/10.1503/cmaj.090845> PMID: 20624866; PubMed Central PMCID: PMC2934796.
49. Hassan C, Benamouzig R, Spada C, Ponchon T, Zullo A, Saurin JC, et al. Cost effectiveness and projected national impact of colorectal cancer screening in France. *Endoscopy* 2011; 43(9):780–93. <https://doi.org/10.1055/s-0030-1256409> PMID: 21623557.
50. Barré S, Leleu H, Benamouzig R, Saurin J-C, Vimont A, Taleb S, et al. Cost-effectiveness analysis of alternative colon cancer screening strategies in the context of the French national screening program. *Therap Adv Gastroenterol* 2020; 13:1756284820953364. <https://doi.org/10.1177/1756284820953364> PMID: 33014138; PubMed Central PMCID: PMC7509710.
51. Lee D, Muston D, Sweet A, Cunningham C, Slater A, Lock K. Cost effectiveness of CT colonography for UK NHS colorectal cancer screening of asymptomatic adults aged 60–69 years. *Appl Health Econ Health Policy* 2010; 8(3):141–54. <https://doi.org/10.2165/11535650-000000000-00000> PMID: 20369905.

52. Whyte S, Chilcott J, Halloran S. Reappraisal of the options for colorectal cancer screening in England. *Colorectal Dis* 2012; 14(9):e547–61. <https://doi.org/10.1111/j.1463-1318.2012.03014.x> PMID: 22390210.
53. Sharp L, Tilson L, Whyte S, O’Ceilleachair A, Walsh C, Usher C, et al. Cost-effectiveness of population-based screening for colorectal cancer: a comparison of guaiac-based faecal occult blood testing, faecal immunochemical testing and flexible sigmoidoscopy. *Br J Cancer* 2012; 106(5):805–16. <https://doi.org/10.1038/bjc.2011.580> PMID: 22343624; PubMed Central PMCID: PMC3305953.
54. Senore C, Hassan C, Regge D, Pagano E, Iussich G, Corrales L, et al. Cost-effectiveness of colorectal cancer screening programmes using sigmoidoscopy and immunochemical faecal occult blood test. *J Med Screen* 2019; 26(2):76–83. <https://doi.org/10.1177/0969141318789710> PMID: 30180780.
55. Melnitchouk N, Soeteman DI, Davids JS, Fields A, Cohen J, Noubary F, et al. Cost-effectiveness of colorectal cancer screening in Ukraine. *Cost Eff Resour Alloc* 2018; 16:20. <https://doi.org/10.1186/s12962-018-0104-0> PMID: 29977160; PubMed Central PMCID: PMC5992826.
56. Lam CLK, Law WL, Poon JTC, Chan P, Wong CKH, McGhee SM, et al. Health-related quality of life in patients with colorectal neoplasm and cost-effectiveness of colorectal cancer screening in Hong Kong. *Hong Kong Med J* 2015; 21 Suppl 6:4–8. PMID: 26645874.
57. Wong MCS, Ching JYL, Chan VCW, Lam TYT, Luk AKC, Wong SH, et al. Colorectal Cancer Screening Based on Age and Gender: A Cost-Effectiveness Analysis. *Medicine (Baltimore)* 2016; 95(10):e2739. <https://doi.org/10.1097/MD.0000000000002739> PMID: 26962772; PubMed Central PMCID: PMC4998853.
58. Dan YY, Chuah BYS, Koh DCS, Yeoh KG. Screening based on risk for colorectal cancer is the most cost-effective approach. *Clin Gastroenterol Hepatol* 2012; 10(3):266–71. <https://doi.org/10.1016/j.cgh.2011.11.011> PMID: 22100624.
59. Lew J-B, St John DJB, Macrae FA, Emery JD, Ee HC, Jenkins MA, et al. Evaluation of the benefits, harms and cost-effectiveness of potential alternatives to iFOB testing for colorectal cancer screening in Australia. *Int J Cancer* 2018; 143(2):269–82. <https://doi.org/10.1002/ijc.31314> PMID: 29441568.
60. Holme Ø, Løberg M, Kalager M, Bretthauer M, Hernán MA, Aas E, et al. Long-Term Effectiveness of Sigmoidoscopy Screening on Colorectal Cancer Incidence and Mortality in Women and Men: A Randomized Trial. *Annals of Internal Medicine* 2018; 168(11):775–82. <https://doi.org/10.7326/M17-1441> PMID: 29710125; PubMed Central PMCID: PMC6853067.
61. Holme Ø, Schoen RE, Senore C, Segnan N, Hoff G, Løberg M, et al. Effectiveness of flexible sigmoidoscopy screening in men and women and different age groups: pooled analysis of randomised trials. *BMJ* 2017; 356:i6673. <https://doi.org/10.1136/bmj.i6673> PMID: 28087510; PubMed Central PMCID: PMC5234564.
62. Schoenfeld P, Cash B, Flood A, Dobhan R, Eastone J, Coyle W, et al. Colonoscopic screening of average-risk women for colorectal neoplasia. *N Engl J Med* 2005; 352(20):2061–8. <https://doi.org/10.1056/NEJMoa042990> PMID: 15901859.
63. Forsberg AM, Kjellström L, Agréus L, Nixon Andreasson A, Nyhlin H, Talley NJ, et al. Prevalence of colonic neoplasia and advanced lesions in the normal population: a prospective population-based colonoscopy study. *Scand J Gastroenterol* 2012; 47(2):184–90. <https://doi.org/10.3109/00365521.2011.647062> PMID: 22229966.
64. Cespedes I, Seidler U, Walter U, Dreier M. Physicians’ view on sigmoidoscopy as an additionally offered method for colorectal cancer screening. *Z Gastroenterol* 2019; 57(9):1059–66. <https://doi.org/10.1055/a-0963-0433> PMID: 31525798.
65. Lewis JD, Ng K, Hung KE, Bilker WB, Berlin JA, Brensinger C, et al. Detection of proximal adenomatous polyps with screening sigmoidoscopy: a systematic review and meta-analysis of screening colonoscopy. *Arch Intern Med* 2003; 163(4):413–20. <https://doi.org/10.1001/archinte.163.4.413> PMID: 12588199.
66. Khalid-de Bakker C, Jonkers D, Smits K, Mesters I, Masclee A, Stockbrügger R. Participation in colorectal cancer screening trials after first-time invitation: a systematic review. *Endoscopy* 2011; 43(12):1059–86. <https://doi.org/10.1055/s-0031-1291430> PMID: 22135196.
67. Wortley S, Wong G, Kieu A, Howard K. Assessing stated preferences for colorectal cancer screening: a critical systematic review of discrete choice experiments. *Patient* 2014; 7(3):271–82. <https://doi.org/10.1007/s40271-014-0054-3> PMID: 24652475.
68. Lee SJ, O’Leary MC, Umble KE, Wheeler SB. Eliciting vulnerable patients’ preferences regarding colorectal cancer screening: a systematic review. *Patient Prefer Adherence* 2018; 12:2267–82. <https://doi.org/10.2147/PPA.S156552> PMID: 30464417; PubMed Central PMCID: PMC6216965.
69. Ghanouni A, Smith SG, Halligan S, Plumb A, Boone D, Yao GL, et al. Public preferences for colorectal cancer screening tests: a review of conjoint analysis studies. *Expert Rev Med Devices* 2013; 10(4):489–99. <https://doi.org/10.1586/17434440.2013.811867> PMID: 23895076.