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Which Lynch syndrome screening programs could be implemented in the “real world”? A systematic review of economic evaluations

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Purpose: Lynch syndrome (LS) screening can significantly reduce cancer morbidity and mortality in mutation carriers. Our aim was to identify cost-effective LS screening programs that can be implemented in the “real world.”

Methods: We performed a systematic review of full economic evaluations of genetic screening for LS in different target populations; health outcomes were estimated in life-years gained or quality-adjusted life-years.

Results: Overall, 20 studies were included in the systematic review. Based on the study populations, we identified six categories of LS screening program: colorectal cancer (CRC)-based, endometrial cancer-based, general population-based, LS family registry-based, cascade testing-based, and genetics clinic-based screening programs. We performed an in-depth analysis of CRC-based LS

programs, classifying them into three additional subcategories: universal, age-targeted, and selective. In five studies, universal programs based on immunohistochemistry, either alone or in combination with the *BRAF* test, were cost-effective compared with no screening, while in two studies age-targeted programs with a cutoff of 70 years were cost-effective when compared with age-targeted programs with lower age thresholds.

Conclusion: Universal or <70 years-age-targeted CRC-based LS screening programs are cost-effective and should be implemented in the “real world.”

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Key Words: colorectal cancer; cost-effectiveness; Lynch syndrome; screening program; systematic review

INTRODUCTION

Lynch syndrome (LS) is the most common cause of inherited colorectal cancer (CRC), accounting for about 3% of newly diagnosed cases, and results from a mutation in one of the DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*). As LS is associated with an increased risk of colorectal, endometrial, and other cancers, it is important to identify both the probands and their family members.¹

In 2009, the Evaluation of Genomic Applications in Practice and Prevention Working Group recommended testing for LS in individuals with newly diagnosed CRC to reduce cancer morbidity and mortality in relatives.² The working group declared that there is a moderate certainty that this would provide moderate population benefit, but it did not recommend a specific genetic testing strategy among the several examined, nor did it deal with implementation issues.² Thereafter the US Department of Health and Human Services adopted the following as a Healthy People 2020 developmental objective:³ “Increase the proportion of persons with newly diagnosed colorectal cancer who receive genetic testing

to identify Lynch syndrome (or familial colorectal cancer syndromes).”

Although genomic information has the potential to improve the delivery of patient-centered care through tailored preventive, diagnostic, and treatment strategies, there is a considerable gap between discoveries in genomics research and the translation of these findings into genetic services that benefit patients.^{4,5} A previous study highlighted the considerable variation in uptake of LS screening among health-care organizations,⁶ while other authors have stated that under-screening for LS should be considered a form of a health disparity.⁷ Some possible barriers that might hinder the successful implementation of LS screening programs are variations in local expertise, availability of laboratory and genetic counseling services, limited acceptance of genetic testing and low compliance with surveillance recommendations by the patient, psychosocial impact on the patient and family, and the costs of genetic testing.^{8,9} Therefore, the widespread implementation of a successful LS screening program will require a strongly integrated multidisciplinary

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public health approach,⁹ including a careful evaluation of the appropriate use of available economic resources.¹⁰ As evidenced by the results of a systematic review on *BRCA* genetic testing programs, economic evaluations may allow an assessment of genetic screening programs in terms of both their cost and effectiveness and their readiness for implementation.¹¹

Two previous systematic reviews^{12,13} of LS economic evaluations have argued that universal LS screening is cost-effective compared with not performing genetic testing (no screening), but not necessarily compared with selective or age-targeted testing strategies. Accordingly, there are still several issues that need to be clarified: the cost-effectiveness of universal screening relative to age-targeted screening, the comparative cost-effectiveness of different diagnostic strategies, the implications of the use of preventive strategies for endometrial and ovarian cancer in females with LS, and the cost-effectiveness of LS screening programs for other potential target populations, such as women newly diagnosed with endometrial cancer or primary care patients.

Therefore, in this systematic review, we have carried out a comprehensive assessment of LS screening programs whose cost-effectiveness has been subject to an economic evaluation. Our aim was to recognize clinically and economically feasible diagnostic and preventive strategies that may be implemented in the “real world.”

MATERIALS AND METHODS

This systematic review was performed according to the guidelines set by the Center for Reviews and Dissemination and by the Cochrane Collaboration.^{14,15}

Inclusion criteria

We included full economic evaluations of LS screening programs containing genetic testing strategies aimed at identifying and managing LS in different target populations. The included studies were required to have evaluated the costs and benefits of each strategy provided by the screening program and to have reported the health outcomes in terms of either life-years gained (LYG) or quality-adjusted life-years (QALYs) gained. As in the review by Grosse,¹³ we excluded partial cost-effectiveness analyses (CEAs) that reported only estimates of cost per case detected because they did not consider the impact of preventive strategies and did not quantify the willingness-to-pay to achieve an improvement in health status.

Search strategy

The literature search comprised all studies published in English from inception to August 2017 and present in the following databases: MEDLINE, Scopus, Web of Science, the National Health Service Economic Evaluation Database, the Database of Abstracts of Reviews of Effects, the Health Technology Assessment Database, the Economics Literature Index, and the CEA Registry. The search strings were built up and adapted for each database using the following search

terms: “hereditary nonpolyposis colorectal cancer OR Lynch syndrome” AND “screening OR genetic test*” AND “health technology assessment OR economic evaluation OR cost-benefit OR cost-utility OR cost-effectiveness.” The search terms used covered information relating to the clinical condition, the health technology used, and the study design. The literature search was carried out by two researchers (M.D.M., E.D.A.), and it also included the examination of reference lists of previous systematic reviews of LS economic evaluations to identify further potentially relevant studies.

Selection of studies

Two researchers (M.D.M., E.D.A.) independently screened the titles and abstracts of the retrieved studies and identified those eligible for a more comprehensive assessment. The full text of each eligible article was examined and the article was included in the review if it passed the inclusion criteria.

Data extraction and quality assessment

The information extracted comprised article data (authors, country, journal, year of publication), methodological features of the study (type of economic evaluation, analytical model, outcome measures, time horizon, study perspective, incremental cost and effectiveness data, discount rates, cost-effectiveness threshold, type of sensitivity analyses), basic components of the program (clinical condition, target population, clinical criteria, age cutoffs, tumor testing, genetic counseling, gene sequencing, preventive strategy, screening of relatives), and assumptions relating to key model parameters and cost data used within the model. Data extraction was performed by two researchers (M.D.M., N.P.) independently and was reviewed by a third researcher (E.D.A.).

The methodological quality of the included studies was assessed using the BMJ checklist¹⁶ and the Quality of Health Economic Studies (QHES) list.¹⁷ The BMJ tool allows a detailed qualitative assessment, whereas the QHES tool provides an overall score for each study. Quality assessment of all included studies was performed independently by two researchers (M.D.M., N.P.). Potential differences in the assessors’ results were resolved by discussion.

Data synthesis

A classification of the LS screening programs evaluated was carried out to identify and summarize all those studies in which the authors judged the programs to be cost-effective. We did not adjust the costs and discount rates of the included studies to directly compare the retrieved incremental cost-effectiveness ratios (ICERs). Because assumptions relating to key model parameters strongly depend on the intervention context, a direct comparison of ICERs is likely to be inappropriate to fully assess the cost-effectiveness of screening programs.¹⁸ The classification process was made in five steps: (i) the structure of each program was summarized in terms of target population, diagnostic strategy (age cutoff, clinical criteria, tumor testing, gene sequencing), cascade testing of the relatives, and preventive strategy; (ii) the outlined

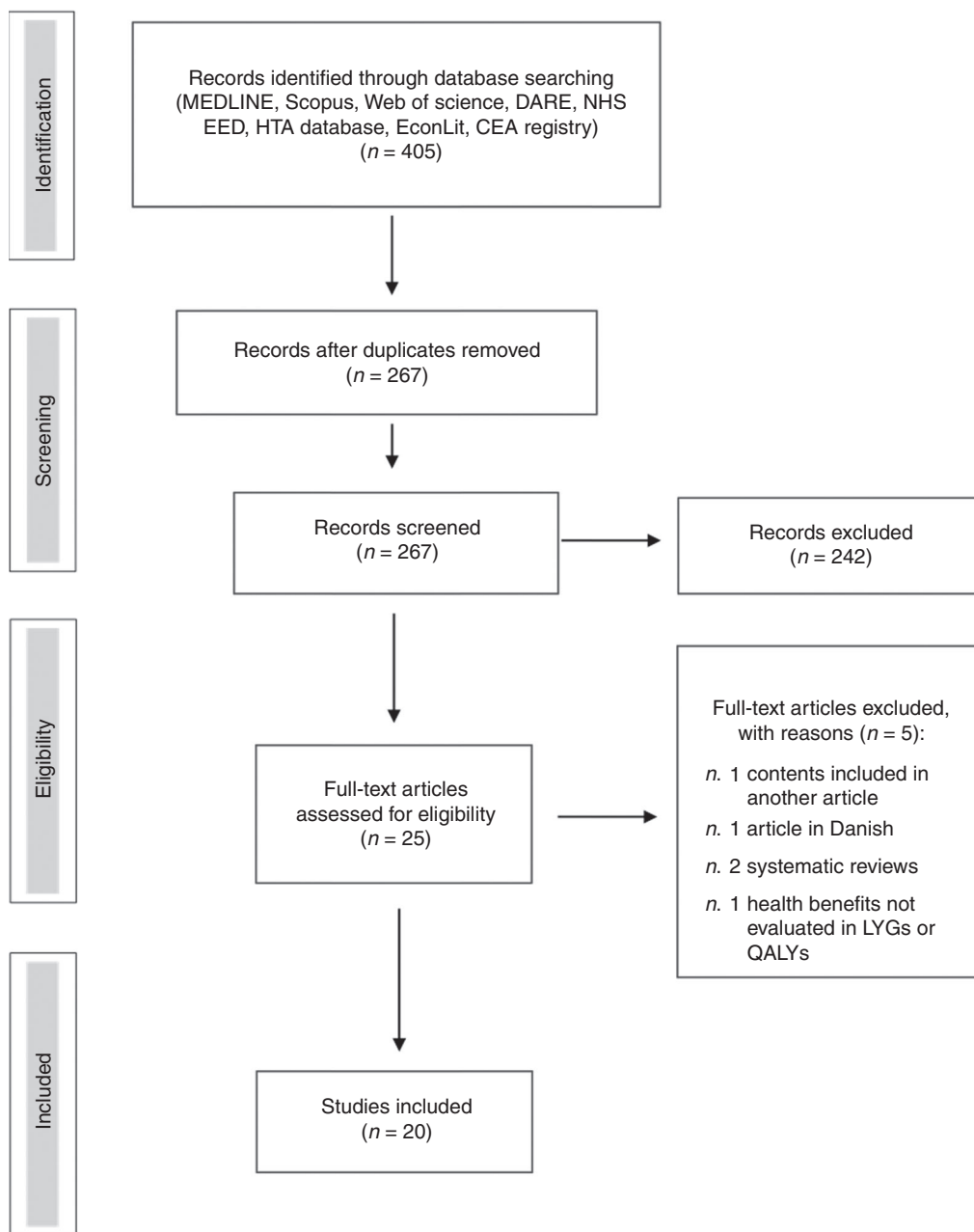


Figure 1 Flow diagram for selection of economic evaluations of LS screening programs. (Adapted from PRISMA⁶⁵.) CEA Registry, Cost-Effectiveness Analysis Registry; DARE, Database of Abstracts of Reviews of Effects; EconLit, Economics Literature Index; HTA Database, Health Technology Assessment Database; LYG, life-years gained; NHS EED, National Health Service Economic Evaluation Database; QALY, quality-adjusted life-years.

programs were listed in a table in chronological order and were tagged according to the Centers for Disease Control and Prevention (CDC) classification of genomic applications (Tier)^{19,20} (iii) the ICERs extracted from each study were listed in the table according to the specific comparisons made between programs and were marked as accepted or not accepted according to the willingness-to-pay thresholds specified in their studies; (iv) based on their target population, programs were assigned to specific screening categories and were listed in different tables; and (v) programs were ranked in ascending order of ICER and divided into two sections: one

for those with accepted ICERs, the other for those for which ICERs were not accepted.

Because of the lack of a universally accepted ICER threshold and the different health-care resources and preferences among different countries,²¹ we counted as cost-effective programs all those with an ICER under the willingness-to-pay threshold specified in their studies. When the ICER threshold was not stated in the study, we adopted a threshold we judged to be appropriate after considering either the economic literature or the institutional guidelines of the selected country.

RESULTS

The literature search initially identified 405 studies. After title and abstract screening, 25 full-text articles were assessed for eligibility. A further five studies were subsequently excluded for the following reasons: one article referred to the same results contained in another included study,²² one model did not evaluate health benefits in terms of LYGs or QALYs,²³ one article was written in Danish,²⁴ and two studies were systematic reviews.^{12,13} Twenty economic evaluations^{25–44} were finally included in our systematic review. A flow diagram of literature search results is shown in **Figure 1**.

General characteristics of studies

The methodological features of the economic evaluations included are described in **Supplementary Table S1** online.

Ten studies were carried out in the United States,^{25–27,30–34,39,40} four in the Netherlands,^{28,36,41,44} and one each in Denmark,²⁹ Singapore,³⁵ the United Kingdom,³⁷ Germany,³⁸ Taiwan,⁴² and Canada.⁴³ Fifteen studies employed a CEA,^{25–30,32,33,35,36,38,39,41,42,44} three employed a cost–utility analysis (CUA),^{31,34,37} and two employed both CEA and CUA.^{40,43} All studies assumed a lifetime time horizon.^{25–44} The health-care system perspective was adopted as the viewpoint of analysis in most studies.^{25,27–30,35–37,40,41,43,44} Four studies declared a societal perspective, but none of these included social costs.^{26,31,32,39} Most economic models used were based on a decision analysis,^{26–40,42,43} while a Markov model was applied in 11 studies.^{28,29,32–35,38,39,42,43} The most frequently used discount rate for costs and benefits was 3%.^{26,27,30–35,38–42,44} The ICER thresholds stated in the studies were in the range 50,000–100,000 for US dollar–based economic models^{27,30–34,39,40,42} and in the range 40,000–80,000 for euro-based economic models.^{36,38,41,44} The lowest ICER threshold was 20,000 pounds sterling,³⁷ whereas the highest was 159,000 Singapore dollars.³⁵

Quality assessment

In general, the quality of the economic evaluations included was good and all but two studies^{26–39,41–44} achieved a score greater than 80 according to the QHES checklist (**Supplementary Table S1**). Nevertheless, several models did not comply with some of the methodological requirements listed in the BMJ checklist (**Supplementary Table S2**). Regarding aspects of study design, the viewpoint of analysis was clearly stated and justified in 11 of 20 economic evaluations,^{27,28,30,33–35,37,38,41–43} but the perspective declared by the authors was not consistent with the costs included in the analysis in four studies.^{26,31,32,39} Although adjusting for health-related quality of life would generally be recommended for cost-effectiveness analysis,⁴⁵ 10 economic evaluations did not explain the lack of outcomes in terms of QALYs.^{26–29,32,35,38–40,42} Regarding data collection, almost all studies stated the effectiveness of the health interventions, but only one^{43,46} reported the methods of data synthesis. Only two of five studies using outcomes measured in QALYs

specified the details of the methods used and the subjects from whom valuations were obtained.^{34,37} In general, costs were properly quantified, but only seven studies considered adjustments for inflation or currency conversion.^{29,35,37,40–42,44} Although to different degrees, most studies gave details of the modeling and parameters used.^{26–28,30–39,42,43} The time horizon of the analysis was not always clearly defined, although it could be deduced from the model.^{29,31,40,41,44} Sensitivity analysis was performed in all economic evaluations.^{25–44} six studies used only univariate analysis,^{25,28,31,39,41,44} while nine studies performed probabilistic sensitivity analysis.^{26,27,33,34,36,38,40,42,43} Furthermore, most studies reported the range over which variables varied.^{25–30,33–35,37–44} All economic evaluations provided an incremental analysis.^{25–44}

Influential parameters and basic assumptions

Basic assumptions of key model parameters were extracted to evaluate their impact on ICER estimates (**Supplementary Table S3**). In general, parameters and assumptions included in the economic models differed according to the features of the screening programs evaluated. According to the results reported by the authors, the most influential parameters were prevalence of LS, uptake of genetic testing, cost of gene sequencing, number of relatives tested per proband, uptake of genetic counseling among relatives, uptake of LS surveillance, the cost of colonoscopy, risk of CRC for mutation carriers, risk reduction of CRC with LS surveillance, and discount rate for cost and benefit (**Supplementary Table S4**). Most studies assumed a LS prevalence between 2 and 3% in new CRC patients,^{26,27,30,33,34,38,39,42,43} whereas Snowsill³⁷ and Leenen⁴¹ assumed respectively a LS prevalence of 8.4% and 4.9% for new CRC patients up to age 50. Uptake of genetic testing among cancer patients ranged from 60 to 100%,^{26–28,30,33,34,36–39,42–44} notably, Dinh³¹ assumed 100% of genetic testing uptake in the general population. Excluding the two studies by Ramsey,^{26,27} the overall number of relatives tested per proband ranged from one to eight.^{30,33,34,36–40,42,43} The most favorable assumption, by Sie,³⁶ of eight relatives tested per proband resulted from a 100% uptake of genetic testing among relatives. Conversely, Severin³⁸ made the most conservative assumptions of a 29.5% uptake of genetic testing among relatives and 1.1 relatives tested per proband. The prevalence of LS among tested relatives varied between 37 and 50%.^{26,27,30,33,34,36–39,42–44} Conservative assumptions for this parameter were used by Mvundura³⁰ and Snowsill^{12,37} since some tested relatives might not be first-degree biological relatives, while other authors^{36,43,44} calculated prevalence estimates less than 50% because they used data from studies or databases on LS screening that included also second- or higher-degree relatives in the cascade testing. Most studies assumed roughly an 80% uptake of LS surveillance,^{30,31,33,34,36–39,41–44} but two studies proposed a 100% uptake.^{32,35} Estimates of the lifetime risk of CRC for mutation carriers in the absence of prevention strategies varied widely among the studies. It was higher in the least

recent analyses (80%)^{26,27,29} and considerably lower in the latest studies.^{30,32–35,37–39,41,43,44} Estimates of reduction in risk of CRC in mutation carriers adhering to LS surveillance programs was assumed to be 56–62% in most studies.^{26,27,29,30,32–37,39–42,44} Severin adopted the most conservative percentage of 52%,³⁸ whereas the Canadian Agency for Drugs & Technologies in Health model assumed the most favorable percentage of 68% CRC risk reduction.⁴³ Several studies reported percentages greater than 99% for both sensitivity and specificity of MMR genes sequencing^{30,38–40,43,44} (**Supplementary Table S5**), but a lower sensitivity was assumed by Ramsey (87%),^{26,27} Dinh (90%),³¹ and Snowsill (90%).³⁷ The sensitivity ranges of microsatellite instability (MSI) and immunohistochemistry (IHC) tests were respectively 76–91%^{26,27,30,33,34,37–39,42} and 77–92%,^{30–34,37–40,42,43} whereas specificity ranges were 79–93% for MSI^{26–28,30,33,34,37–39,42} tests and 70–91% for IHC tests.^{30–34,37–40,42,43} Being context-specific, cost assumptions (**Supplementary Table S6**) are not directly comparable; single-gene sequencing costs ranged from 600 to 1,200 dollars in American studies,^{30–34,39,40} whereas, with euro-based models, it was much more expensive in the German study (3,836 euros)³⁸ than in Dutch studies (538–814 euros).^{36,41,44} In general, family mutation testing was far less expensive than single-gene sequencing.^{30,31,33,34,36–44} Colonoscopy costs ranged from 500 to 950 dollars in American studies^{25,30–34,39} and from 144 to 393 euros in European studies,^{28,29,36,38,41,44} excepting the model by Snowsill (395 pounds sterling).³⁷

Classification of LS screening programs

We classified the screening programs with reference to the basic design components for each program (**Supplementary Table S7**). All studies included programs that considered CRC,^{25–44} while endometrial cancer and ovarian cancer were addressed respectively in nine^{31–34,37,39,41,43,44} and in five studies.^{33,34,39,41,43} Most studies focused on newly diagnosed CRC patients,^{26–28,30,33,34,36–39,41–43} but five additional different target populations were also considered.^{25,29,31,32,35,39,40,44}

Regarding the diagnostic strategies covered by the evaluated programs, 14 studies included clinical criteria,^{26–29,31–34,37–39,41,43,44} specifically, the Amsterdam criteria were used in eight studies,^{28,29,32–34,37–39} Bethesda guidelines in nine studies,^{26,27,33,34,38,39,41,43,44} and computational models in four studies.^{31,33,34,39} Seven studies used a specific age cutoff to select people for inclusion in the screening program,^{30,32,36,37,41,43,44} while preliminary tumor testing was employed in 15 studies.^{26–28,30,32–34,36–39,41–44} When we examined diagnostic strategies in more detail, we discovered that MSI testing was used in 13 studies,^{26–28,30,33,34,36–39,41,42,44} IHC testing in 12 studies,^{30,32–34,36–39,41–44} *BRAF* testing in 8 studies,^{30,33,34,37–39,42,43} and *MLH1* hypermethylation testing in four studies.^{36,41,43,44} All studies but one³¹ included genetic counseling of individuals involved in the screening. Genetic testing involving all four *MMR* genes was performed in 15 studies,^{30–44} whereas *EPCAM* sequencing was included in

only three studies.^{40,41,44} Genetic counseling and cascade testing of relatives of affected patients were included respectively in 15 (ref. 26–28,30,33,34,36–44) and 16 (ref. 26–28,30,31,33,34,36–44) economic models.

Regarding preventive strategies, colonoscopy was included in all studies,^{25–44} gynecological surveillance and/or prophylactic total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAHBSO) in eight,^{31,33,34,37,39,41,43,44} and aspirin chemoprevention in one study.³⁸ Use of tumor *MMR* genes status to support adjuvant chemotherapy choices was modeled in only one study.⁴³

Taking into account the target populations included in the programs, we were able to identify six categories of screening program for LS (**Supplementary Table S8**): (i) CRC-based, i.e., screening of newly diagnosed CRC patients;^{26–28,30,33,34,36–39,41–43} (ii) endometrial cancer (EC)-based, i.e., screening of newly diagnosed EC patients;^{32,44} (iii) general population-based, i.e., screening of all individuals of a specific age;^{25,31,39} (iv) LS family registry-based, i.e., screening of individuals from families referred to a LS registry;²⁹ (v) cascade testing-based, i.e., screening of first-degree relatives (FDRs) of LS carriers;³⁵ and (vi) genetics clinic-based, i.e., screening of patients referred to a genetics clinic for evaluation of hereditary CRC and polyposis (CRCP) syndromes.⁴⁰ For the first category, i.e., CRC-based LS screening programs, three additional specific approaches or subcategories were identified: (ia) universal CRC-based, i.e., screening of all newly diagnosed CRC patients, without performing a preliminary selection in terms of age or clinical criteria;^{27,30,33,34,38,39,42,43} (ib) age-targeted CRC-based, i.e., screening of only those newly diagnosed CRC patients who fall below specific age cutoffs such as 50, 60, or 70 years;^{30,36,37,41,43} (ic) selective CRC-based, i.e., screening of only those newly diagnosed CRC patients who meet clinical criteria such as the Amsterdam II criteria or the Revised Bethesda Guidelines (RBG) criteria.^{26–28,33,34,38,39,43}

Screening programs accepted as cost-effective

LS screening programs were accepted as cost-effective if their ICERs fell under the willingness-to-pay thresholds reported in their studies (**Supplementary Table S9**). For studies without stated ICER thresholds, we selected the following thresholds by reviewing the relevant economic literature and institutional guidelines: US dollars 100,000/QALY or LYG⁴⁷ for both Brown's study²⁵ and Ramsey's study,²⁶ euros 80,000/QALY or LYG^{36,48} for Kievit's study,²⁸ and Canadian dollars 50,000/QALY or LYG⁴⁹ for the Canadian Agency for Drugs & Technologies in Health study.⁴³ Since there was no defined or proposed ICER threshold in Denmark,^{50,51} we accepted all the cost-effective programs extracted by Olsen's study²⁹ because their ICERs were well below the thresholds used in the other European studies included.^{36–38,41,44}

Depending on their category, cost-effective programs were listed in different tables and were ranked in ascending order of ICER. Each specific category table was split into two

Table 1 Continued

| First author, year, country | N | Target population | Age cutoff/criteria | Clinical criteria | Tumor testing | Gene sequencing | Relatives cascade testing | Preventive strategy | Tier | ICERs | |
|---|--------------------|-----------------------------|---------------------|-------------------|---------------|-----------------|---------------------------|--|------|----------------------------------|----------------------|
| | | | | | | | | | | Comparisons | LYG QALY |
| | | New CRC patients | | | | 4 MMR genes | | | | | |
| Barzi 2015, USA | 15.12 | New CRC patients | — | — | IHC+BRAF | 4 MMR genes | Y | Colonoscopy every year + TAHBSO at age 40 | 1 | Vs MMRpro/IHC | 144,117 |
| Chen 2016, Taiwan | 18.4 | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs NS | 145,110 |
| Ladabaum 2011, USA ^{9,14b} Wang G 2012, USA | | New CRC patients | — | — | MSI+IHC | 4 MMR genes | Y | Colonoscopy every year or subtotal colectomy + transvaginal US and endometrial biopsy every year or TAHBSO at age 40 | 1 | Vs IHC+BRAF ^b | — |
| Ramsey 2003, USA | 3.2 | New CRC patients | — | — | MSI | MLH1, MSH2 | — | Subtotal colectomy (only for proband) or colonoscopy every 3 years | 1 | Vs NS | 213,290 |
| Mvundura 2010, USA | 6.4 | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs <50 | 237,278 |
| Severin 2015, Germany | 14.2 | New CRC patients | — | — | IHC+BRAF | 4 MMR genes | Y | Colonoscopy every year + aspirin | 1 | Vs RBG/IHC +BRAF | 258,253 |
| Chen 2016, Taiwan | 18.2 | New CRC patients | — | — | IHC | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs IHC+BRAF | 260,824 |
| Ramsey 2003, USA | 3.8 | New CRC patients | — | — | — | MLH1, MSH2 | Y | Subtotal colectomy (only for proband) or colonoscopy every 3 years | 1 | Vs NS | 267,548 |
| Ladabaum 2011, USA ^{9,16b} Wang G 2012, USA | | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every year or subtotal colectomy + transvaginal US and endometrial biopsy every year or TAHBSO at age 40 | 1 | Vs MSI+IHC ^b | — |
| Mvundura 2010, USA | 6.2 | New CRC patients | — | — | IHC | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs IHC+BRAF | 273,915 |
| Ladabaum 2011, USA ^{9,16} Wang G 2012, USA | | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every year or subtotal colectomy + transvaginal US and endometrial biopsy every year or TAHBSO at age 40 | 1 | Vs MSI+IHC +BRAF | 293,000 |
| Chen 2016, Taiwan | 18.3 | New CRC patients | — | — | MSI | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs IHC | 302,129 |
| CADTH 2016, Canada | 19.12 ^b | New CRC patients (age > 50) | — | — | IHC + BRAF | 4 MMR genes | Y | Colonoscopy every 2 years + TAHBSO at age 45 | — | Vs IHC+MLH1 Hyperm. ^a | 363,043 ^a |
| Ramsey 2003, USA | 3.6 | New CRC patients | — | — | MSI | MLH1, MSH2 | Y | Subtotal colectomy (only for proband) or colonoscopy every 3 years | 1 | Vs Bethesda/MSI | 394,067 |
| Barzi 2015, USA | 15.14 ^b | New CRC patients | — | — | MSI+IHC | 4 MMR genes | Y | Colonoscopy every year + TAHBSO at age 40 | 1 | Vs IHC+BRAF ^b | 400,728 ^b |
| Mvundura 2010, USA | 6.2 | New CRC patients | — | — | IHC | — | Y | Colonoscopy every 2 years | 1 | — | 429,973 |

Table 1 Continued

| First author, year, country | N | Target population | Age cutoff/criteria | Clinical criteria | Tumor testing | Gene sequencing | Relative cascade testing | Preventive strategy | Tier | ICERs | | |
|-----------------------------|---------------------|-----------------------------|---------------------|-------------------|---------------|-----------------|--------------------------|--|-------------|--------------------------|----------------------|----------------------|
| | | | | | | | | | Comparisons | LYG | QALY | |
| CADTH 2016, Canada | 19,111 ^a | New CRC patients (age > 50) | — | — | IHC | 4 MMR genes | Y | Colonoscopy every 2 years + TAHBSO at age 45 | — | Vs IHC+BRAF ^a | 610,447 ^a | 651,283 ^a |
| Mvundura 2010, USA | 6.4 | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs MSI | 737,025 | — |
| Mvundura 2010, USA | 6.3 | New CRC patients | — | — | MSI | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs IHC | 764,917 | — |
| Barzi 2015, USA | 15.16 ^b | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every year + TAHBSO at age 40 | 1 | Vs MSI+IHC ^b | 940,024 ^b | — |
| Chen 2016, Taiwan | 18.4 | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs MSI | 988,217 | — |
| Barzi 2015, USA | 15.16 | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every year + TAHBSO at age 40 | 1 | Vs MMRpro | 996,878 | — |
| Mvundura 2010, USA | 6.4 | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs < 50/MSI | 1,192,575 | — |
| Mvundura 2010, USA | 6.3 | New CRC patients | — | — | MSI | 4 MMR genes | Y | Colonoscopy every 2 years | 1 | Vs < 50/IHC | 1,355,910 | — |
| Ramsey 2003, USA | 3.8 | New CRC patients | — | — | — | MLH1, MSH2 | Y | Subtotal colectomy (only for proband) or colonoscopy every 3 years | 1 | Vs Bethesda/MSI11 | 485,640 | — |
| Ramsey 2003, USA | 3.4 | New CRC patients | — | — | — | MLH1, MSH2 | — | Subtotal colectomy (only for proband) or colonoscopy every 3 years | 1 | Vs NS | 1,625,687 | — |
| Ramsey 2003, USA | 3.8 | New CRC patients | — | — | — | MLH1, MSH2 | Y | Subtotal colectomy (only for proband) or colonoscopy every 3 years | 1 | Vs MSI | 1,989,197 | — |
| Ramsey 2003, USA | 3.8 | New CRC patients | — | — | — | MLH1, MSH2 | Y | Subtotal colectomy (only for proband) or colonoscopy every 3 years | 1 | Vs Bethesda | 2,553,345 | — |
| Severin 2015, Germany | 14.7 | New CRC patients | — | — | — | 4 MMR genes | Y | Colonoscopy every year + aspirin | 1 | Vs IHC+BRAF | 4,188,036 | — |

^a4 MMR genes, all 4 mismatch repair genes (MLH1, MSH2, MSH6, and PMS2); Bethesda, first edition of Bethesda Guidelines criteria; BRAF, BRAF testing; CADTH, Canadian Agency for Drugs & Technologies in Health; CRC, colorectal cancer; ICERs, incremental cost-effectiveness ratios; IHC, immunohistochemistry testing; LS, Lynch syndrome; LYG, life-years gained; MLH1 Hyperm., MLH1 hypermethylation testing; MMRpro, MMRpro computational model; MSI, microsatellite instability testing; New CRC patients, newly diagnosed colorectal cancer patients; NS, no screening; QALY, quality-adjusted life-years; RBG, Revised Bethesda Guidelines criteria; TAHBSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy; transvaginal US, transvaginal ultrasonography; Tier, the Centers for Disease Control and Prevention (CDC) classification of genomic applications; Y, yes; Vs, versus. ^bUsing MMR tumor status to guide chemotherapy decision making. ^cExcluding clinical criteria strategies.

Table 2 Cost-effective age-targeted CRC-based LS screening programs

| First author, year, country | N | Target population | Age cutoff | Clinical criteria | Tumor testing | Gene sequencing | Relatives cascade testing | Preventive strategy | Tier | Comparisons | ICERs | LYG | QALY |
|---|------|-------------------|------------|-------------------|------------------------|--------------------|---------------------------|---|------|----------------------------------|-------|-----|-------|
| Age-targeted CRC-based LS screening programs accepted as cost-effective | | | | | | | | | | | | | |
| Sie 2014, Netherlands | 12.2 | New CRC patients | <70 | — | MSI+IHC +MLH1 Hyperm. | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs <50/MSI+IHC +MLH1 Hyperm. | 2,703 | — | — |
| Leenen 2016, Netherlands | 17.2 | New CRC patients | <60 | — | MSI+IHC +MLH1 Hyperm. | 4 MMR genes +EPCAM | Y | Colonoscopy every 2 years + transvaginal US and endometrial biopsy every year or TAHBSO at age 40 | — | Vs <50/MSI+IHC +MLH1 Hyperm. | 4,226 | — | — |
| Snowsill 2015, UK | 13.5 | New CRC patients | <50 | — | MSI+BRAF | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | — | — | 5,491 |
| Snowsill 2015, UK | 13.4 | New CRC patients | <50 | — | MSI | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | — | — | 5,610 |
| Snowsill 2015, UK | 13.6 | New CRC patients | <50 | — | MSI+BRAF+IHC | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | — | — | 5,774 |
| Snowsill 2015, UK | 13.3 | New CRC patients | <50 | — | IHC+BRAF | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | — | — | 5,831 |
| Snowsill 2015, UK | 13.1 | New CRC patients | <50 | Amst II | — | — | Y | Colonoscopy every 2 years | — | Vs NS | — | — | 6,021 |
| Snowsill 2015, UK | 13.2 | New CRC patients | <50 | — | IHC | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | — | — | 6,444 |
| Leenen 2016, Netherlands | 17.3 | New CRC patients | <70 | — | MSI+IHC +MLH1 Hyperm. | 4 MMR genes +EPCAM | Y | Colonoscopy every 2 years + transvaginal US and endometrial biopsy every year or TAHBSO at age 40 | 2 | Vs <60/MSI+IHC +MLH1 Hyperm. | 7,051 | — | — |
| Leenen 2016, Netherlands | 17.3 | New CRC patients | <70 | — | MSI +IHC +MLH1 Hyperm. | 4 MMR genes +EPCAM | Y | Colonoscopy every 2 years + transvaginal US and endometrial biopsy every year or TAHBSO at age 40 | 2 | Vs <70/RBG/MSI+IHC +MLH1 Hyperm. | 7,341 | — | — |
| Snowsill 2015, UK | 13.7 | New CRC patients | <50 | — | IHC (+MSI +BRAF) | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | — | — | 7,601 |
| Mvundura 2010, USA | 6.5 | New CRC patients | <50 | — | IHC+BRAF | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | 7,832 | — | — |

Table 2 Continued

| First author, year, country | N | Target population | Age cutoff criteria | Clinical criteria | Tumor testing | Gene sequencing | Relatives cascade testing | Preventive strategy | Tier | ICERs | | |
|---|------|-----------------------------|---------------------|-------------------|------------------------|-----------------|---------------------------|---|------|----------------------------------|----------|---------|
| | | | | | | | | | | Comparisons | LYG QALY | |
| Mvundura 2010, USA | 6.6 | New CRC patients | <50 | — | IHC | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | 7,944 | — |
| Snowsill 2015, UK | 13.8 | New CRC patients | <50 | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | — | 9,571 |
| Mvundura 2010, USA | 6.7 | New CRC patients | <50 | — | MSI | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | 11,680 | — |
| CADTH 2016, Canada | 19.8 | New CRC patients (age > 50) | <70 | — | IHC+MLH1 Hyperperm. | 4 MMR genes | Y | Colonoscopy every 2 years + TAHBSO at age 45 | — | Vs RBG/IHC + MLH1 Hyperperm.° | 19,455° | 20,757° |
| Mvundura 2010, USA | 6.8 | New CRC patients | <50 | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs NS | 44,902 | — |
| Mvundura 2010, USA | 6.6 | New CRC patients | <50 | — | IHC | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs <50/IHC+BRAF | 60,569 | — |
| Age-targeted CRC-based LS screening programs not accepted as cost-effective | | | | | | | | | | | | |
| Snowsill 2015, UK | 13.7 | New CRC patients | <50 | — | IHC (+MSI +BRAF) | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs <50/MSI+BRAF | — | 25,106 |
| Snowsill 2015, UK | 13.8 | New CRC patients | <50 | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs <50/IHC+MSI +BRAF | — | 82,962 |
| Mvundura 2010, USA | 6.7 | New CRC patients | <50 | — | MSI | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs <50/IHC | 168,905 | — |
| Mvundura 2010, USA | 6.8 | New CRC patients | <50 | — | — | 4 MMR genes | Y | Colonoscopy every 2 years | 2 | Vs <50/MSI | 252,643 | — |

4 MMR genes, all 4 mismatch repair genes (MLH1, MSH2, MSH6, and PMS2); Amst II, Amsterdam II criteria; BRAF, BRAF testing; CADTH, Canadian Agency for Drugs & Technologies in Health; CRC, colorectal cancer; EPCAM, EPCAM gene; ICERs, incremental cost-effectiveness ratios; IHC, immunohistochemistry testing; LS, Lynch syndrome; LYG, life-years gained; MLH1 Hyperperm., MLH1 hypermethylation testing; MSI, microsatellite instability testing; New CRC patients, newly diagnosed colorectal cancer patients; NS, no screening; QALY, quality-adjusted life-years; RBG, Revised Bethesda Guidelines criteria; TAHBSO, total abdominal hysterectomy and bilateral salpingo-oophorectomy; Tier, the Centers for Disease Control and Prevention (CDC) classification of genomic applications; transvaginal US, transvaginal ultrasonography; Y, yes.

sections, one for programs with accepted ICERs and another for programs where ICERs were not accepted.

Universal CRC-based LS screening programs accepted as cost-effective

Most cost-effective programs with an accepted ICER (**Table 1**) included, as a preliminary tumor test, either IHC testing alone or IHC testing in combination with a *BRAF* test.^{30,33,34,39,42} All programs included cascade screening of relatives.^{27,30,33,34,39,42,43} Colonoscopy surveillance was the most widely used preventive strategy.^{27,30,33,34,39,42,43} Several programs also included TAHBSO at age 40–45 years or after completion of childbearing.^{33,34,39,43} All but one⁴³ of the diagnostic strategies used were categorized as tier 1.

Universal programs based on IHC plus *BRAF* testing achieved accepted ICERs when compared with either no screening or with age-targeted CRC-based programs using an age cutoff of 50 years.^{30,33,34,39,42} Conversely, these programs did not achieve accepted ICERs when compared with selective CRC-based screening programs.^{38,39} Universal programs based on IHC testing resulted in accepted ICERs when compared with either no screening or with age-targeted CRC-based programs using an age cutoff of 50 years,^{30,42} but did not result in accepted ICERs when compared with universal programs based on IHC testing plus *BRAF* testing.^{30,42,43} One universal program based on IHC testing plus *MLH1* hypermethylation testing showed an accepted ICER when compared with an age-targeted CRC-based program using an age cutoff of 70 years.⁴³ Universal programs based on MSI testing showed accepted ICERs when compared with no screening and with age-targeted CRC-based programs using an age cutoff of 50 years,^{27,30,42} but conversely did not show accepted ICERs when compared with universal programs based on IHC testing.^{30,42} Universal programs based on up-front gene sequencing in all CRC patients never resulted in accepted ICERs.^{27,30,33,34,38,39,42}

Age-targeted CRC-based LS screening programs accepted as cost-effective

Most cost-effective programs with an accepted ICER (**Table 2**) used an age cutoff of 50 years and included different preliminary tumor tests as part of the diagnostic strategy.^{30,37} All programs included cascade screening of relatives and 2-year colonoscopy surveillance.^{30,36,37,41,43} Most diagnostic strategies were categorized as tier 2.^{30,36,37,41}

Programs based on an age cutoff of 50 years and preliminary tumor testing achieved accepted ICERs when compared with no screening.^{30,37} Programs based on an age cutoff of 70 years and preliminary tumor testing gave accepted ICERs when compared with age-targeted programs with lower age thresholds.^{36,41} Programs based on up-front gene sequencing in CRC patients <50 years old achieved accepted ICERs when compared with no screening,^{30,37} but conversely did not achieve accepted ICERs when compared with programs based on an age cutoff of 50 years and preliminary tumor testing.^{30,37}

Selective CRC-based LS screening programs accepted as cost-effective

Most selective programs with accepted ICERs used Bethesda guidelines or the MMRpro computational model to select CRC patients for genetic screening^{26,27,33,34,39,43} (**Supplementary Table S10**). IHC and MSI testing were most frequently used as preliminary tumor tests.^{26–28,33,34,39} Some older programs used diagnostic strategies based on outdated clinical criteria, such as the first edition of the Bethesda guidelines, and the sequencing of only two *MMR* genes.^{26–28} Most programs included cascade screening of relatives.^{26–28,33,34,39,43} Colonoscopy surveillance intervals included in the preventive strategies ranged from 1 to 3 years. None of the diagnostic strategies used in selective programs with accepted ICERs belonged to the tier 1 category.^{26–28,33,34,39,43}

Programs that used MMRpro for the clinical criteria and an IHC test as the preliminary tumor test achieved accepted ICERs when compared with no screening,^{33,34,39} while one program based on RBG and IHC testing provided accepted ICERs when compared with a program based on MMRpro and IHC testing.^{33,34} One program based on RBG and IHC plus *BRAF* testing did not give accepted ICERs when compared with no screening.³⁸

Other LS screening programs accepted as cost-effective

One EC-based program with an age cutoff of 70 years showed accepted ICERs when compared both with programs with an age cutoff of 50 years and with programs with an age cutoff of 70 years and RGB as the clinical criteria used.⁴⁴ One EC-based program based on clinical criteria and IHC testing achieved an accepted ICER when compared with a program based on an age cutoff of 50 years and clinical criteria.³² General population-based programs, focused on individuals older than 20 years and with a mutation risk greater than 5% according to the PREMM₁₂₆ model, gave accepted ICERs when compared with a selective CRC-based program.³¹ A LS family registry-based program showed accepted ICERs in an outdated Danish study that evaluated the cost-effectiveness of LS surveillance in at-risk families.²⁹ A cascade testing-based program focused on FDRs of LS patients dominated an unselective surveillance program with no genetic testing.³⁵ Genetics clinic-based programs based on next-generation sequencing (NGS) panels, including genes associated both with highly penetrant CRCP syndromes and LS, achieved accepted ICERs when compared with a CRC-based program.⁴⁰

DISCUSSION

The increased use of economic evidence would facilitate the effective translation of research findings into medical practice.⁵² As for other genetic testing programs,¹¹ a systematic review of economic evaluations is the most useful way to identify all potentially cost-effective LS screening programs and to assess their suitability in health-care services.⁵³

LS screening programs were divided into six categories depending on the target population: thus, we identified

CRC-based, EC-based, general population-based, LS family registry-based, cascade testing-based, and genetics clinic-based LS screening programs. For CRC-based LS programs, three additional subcategories were identified: universal CRC-based, age-targeted CRC-based, and selective CRC-based LS screening programs. LS screening programs basically consist of three subunits: diagnostic strategy, cascade screening, and preventive strategy. In each screening category, programs differed from each other according to the components included in their subunits. In this regard, diagnostic strategies showed the highest variability, and thus represented the hallmark of each program. Cascade screening of relatives was included in almost all programs. Because it allowed identification and surveillance of additional mutation carriers, cascade screening was a key component in improving cost-effectiveness.^{26–28,30,31,33,34,36–44} All preventive strategies included colonoscopy surveillance. TAHBSO was included in several programs, but it did not affect cost-effectiveness because its adherence estimates were generally conservative.^{33,34,39,41,43,44} When included, EC surveillance resulted in additional costs without any health benefits,^{31,33,34,41,44} in accord with the lack of proven benefit for gynecologic surveillance.⁵⁴ Aspirin chemoprevention as a preventive strategy in addition to colonoscopy was modeled in one study, but it had little influence on the cost-effectiveness of LS screening.³⁸

CRC-based screening programs were the most investigated category in the included studies.^{26–28,30,33,34,36–39,41–43} All three subcategories covered programs with accepted ICERs, but only universal programs included diagnostic strategies that belong to tier 1, namely those that may have a significant positive impact on public health according to the CDC's Office of Public Health Genomics classification of genomic applications.^{19,20} An additional concern is that the clinical criteria included in selective programs might be insufficiently sensitive or specific to identify patients who need further investigation and might also be difficult and costly to introduce into routine practice.^{39,55,56} Furthermore, it is likely to be challenging to identify the most cost-effective tumor testing approach for the selection of CRC patients for gene sequencing. Therefore, the choice between IHC and MSI testing as initial screen and the choice between *BRAF* and *MLH1* hypermethylation testing as additional tumor testing for each screening program should depend on context-specific factors such as the available technologies, the staffing expertise, the physician preferences, the availability of specific screening protocols for colon cancer patients, and billing and reimbursement constraints. However, the continuing decrease in the cost of genetic testing will lead to a streamlining of the diagnostic strategies and an improvement of cost-effectiveness for the CRC-based screening.

The cost-effectiveness of EC-based screening was assessed in only two of the included studies.^{32,44} Although both economic evaluations identified programs with accepted ICERs, it was problematic to directly compare and sum up the results because of the heterogeneity of their components.

We found that an age cutoff of 70 years is probably better than a lower age cutoff in terms of cost-effectiveness. However, as current guidelines do not recommend a single age cutoff for EC-based LS screening,^{1,54,57,58} further investigation would be needed to shed light on this.

The cost-effectiveness of general population-based screening using criteria determined by the PREMM₁₂₆ model to select people for referral for gene sequencing should be interpreted with care.³¹ Because PREMM₁₂₆ was not validated in the general population,⁵⁹ its use in this context may not be appropriate.⁶⁰

The cost-effectiveness of LS screening where NGS panels were used to test patients referred to cancer genetics clinics has both positive and negative aspects.⁴⁰ Thus, on the plus side, although we recognize that NGS panels provide a more comprehensive evaluation of the genetics of hereditary colorectal cancers, the lack of information on the criteria by which patients were referred to genetics clinics made it impossible for us to perform a full assessment of the program. Therefore, additional studies are required to determine whether these technologies can be successfully employed within LS screening programs.

As cascade screening of relatives was included in almost all programs with accepted ICERs, the number of relatives tested per proband was generally a key factor for cost-effectiveness. Several authors have recognized that LS screening programs are progressively more cost-effective as more relatives are tested.^{30,33,38,39,43} However, the number of relatives tested per proband varied widely across the studies, ranging from one to eight.^{30,33,34,36–40,42,43} In some models, the number of relatives tested was also influenced by other parameters, such as the uptake of genetic counseling (ranging from 45 to 52%)^{30,37,40,42} and the uptake of genetic testing (ranging from 29 to 100%)^{30,33,34,36–40,42,43} among relatives. The broad variability of these parameters results from a lack of data on the implementation of each activity in specific clinical contexts.^{10,61} Indeed, several factors, such as the specific features of the health-care system, differences in the genetic testing delivery model and the approaches used to contact and test relatives at risk of LS, cost limitations, and ethical considerations, may impact screening rates.⁶² Furthermore, several patient-related aspects could also affect the uptake of genetic testing: for example, socioeconomic status, family communication barriers and psychosocial inhibitions involved in informing relatives, and the family history of cancer.⁶² Sharing genetic test results with family members and caregivers can be of paramount importance in increasing screening rates of relatives and in improving the effectiveness and cost-effectiveness of LS screening.^{62,63}

Our systematic review can help inform health decision makers of the opportunities and challenges involved in integrating LS screening in public health policies.^{10,64} Compared with previous reviews,^{12,13} ours is a more comprehensive classification of all cost-effective LS screening programs and we assessed their feasibility within the related health-care contexts. We considered all target populations examined in the economic studies to provide a broad overview of the various

available LS screening programs. We analyzed full-service programs so that we could take into account both the health benefits and the costs of the cascade effect generated by genetic screening. On the other hand, we did not provide a definite evaluation of cost-effectiveness of different tumor testing approaches because we consider this an extremely context-sensitive issue. Another limitation of our study is that we did not assess other factors that could have an impact on the final implementation of the programs, other than cost-effectiveness, such as patient needs and resources, external policy and incentives, or structural characteristics of genetic services. An analysis of these factors should be performed and adjusted according to the specific contexts and settings where the program is going to be adopted. We did not assess the cost-effectiveness of integrating innovative testing technologies, such as the NGS panels or the tumor testing for somatic mutations, in CRC-based screening programs because no relevant economic evaluations have been identified.

In conclusion, from a health-care perspective, the cost-effectiveness of both universal and age-targeted CRC-based LS screening is acceptable in terms of willingness-to-pay for health gains. Therefore, as recommended by most US and European guidelines,^{1,54,57,58} universal or <70 years age-targeted CRC-based LS screening programs should be implemented in health practice. However, both the design of the screening program and the implementation process will need to be tailored to the characteristics of target populations and health-care systems to ensure the translation of cost-effectiveness evidence into the “real-world.”

SUPPLEMENTARY MATERIAL

Supplementary material is linked to the version of the paper at <http://www.nature.com/gjm>

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DISCLOSURE

The authors declare no conflict of interest.

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