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Systematic Literature Review

Cost-Effectiveness of *RAS* Genetic Testing Strategies in Patients With Metastatic Colorectal Cancer: A Systematic Review

Brigid Unim, MD, PhD,[1,*] Erica Pitini, MD,[1] Corrado De Vito, MD, PhD,[1] Elvira D'Andrea, MD, MPH,[1,2] Carolina Marzuillo, MSc,[1] Paolo Villari, MD, MPH[1]

[1]*Department of Public Health and Infectious Diseases, Sapienza University of Rome, Rome, Italy;* [2]*Brigham & Women's Hospital, Department of Medicine, Division of Pharmacoepidemiology & Pharmacoeconomics, Boston, MA, USA.*

ABSTRACT

Background: Monoclonal antibodies against epidermal growth factor receptor (EGFR) have proved beneficial for the treatment of metastatic colorectal cancer (mCRC), particularly when combined with predictive biomarkers of response. International guidelines recommend anti-EGFR therapy only for *RAS* (*NRAS, KRAS*) wild-type tumors because tumors with *RAS* mutations are unlikely to benefit.

Objectives: We aimed to review the cost-effectiveness of *RAS* testing in mCRC patients before anti-EGFR therapy and to assess how well economic evaluations adhere to guidelines.

Methods: A systematic review of full economic evaluations comparing *RAS* testing with no testing was performed for articles published in English between 2000 and 2018. Study quality was assessed using the Quality of Health Economic Studies scale, and the British Medical Journal and the Philips checklists.

Results: Six economic evaluations (2 cost-effectiveness analyses, 2 cost-utility analyses, and 2 combined cost-effectiveness and cost-utility analyses) were included. All studies were of good quality and adopted the perspective of the healthcare system/payer; accordingly, only direct medical costs were considered. Four studies presented testing strategies with a favorable incremental cost-effectiveness ratio under the National Institute for Clinical Excellence (£20 000-£30 000/QALY) and the US ($50 000-$100 000/QALY) thresholds.

Conclusions: Testing mCRC patients for RAS status and administering EGFR inhibitors only to patients with *RAS* wild-type tumors is a more cost-effective strategy than treating all patients without testing. The treatment of mCRC is becoming more personalized, which is essential to avoid inappropriate therapy and unnecessarily high healthcare costs. Future economic assessments should take into account other parameters that reflect the real world (eg, *NRAS* mutation analysis, toxicity of biological agents, genetic test sensitivity and specificity).

Keywords: anti-EGFR, colorectal cancer, cost-effectiveness, pharmacogenetic tests, RAS, systematic review.

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Introduction

Colorectal cancer (CRC) is a significant healthcare issue worldwide. According to the global cancer statistics, CRC is the third most commonly diagnosed cancer, with more than 1 million new cases in 2018, and the second most common cause of cancer-related mortality in both sexes combined.[1,2] It is expected that the incidence of CRC will increase in the Western world owing to aging populations and poor lifestyles.[3] At diagnosis, about 25% of patients have metastases that have already developed, and almost 50% of all CRC patients will form metastases as the disease progresses.[4]

Advances in the treatment of metastatic colorectal cancer (mCRC) have been made in recent years and mainly consist of the introduction of monoclonal antibodies against epidermal growth factor receptor (EGFR) or vascular endothelial growth factor (VEGF) in addition to chemotherapy. The mechanisms of action of monoclonal antibodies include interference with DNA replication and inhibition of EGFR activity (eg, cetuximab, panitumumab) or VEGF (eg, bevacizumab).[5] Nevertheless, treatment of mCRC patients with anti-EGFR antibodies is effective only for tumors lacking mutations in *RAS* genes (mainly *KRAS* and *NRAS*).[6-8] *KRAS* mutations are detected in about 40% of CRCs[4]; the frequency of *NRAS* mutations ranges between 1% and 7%, whereas almost no

* Address correspondence to: Brigid Unim, MD, PhD, Department of Public Health and Infectious Diseases, Sapienza University of Rome, Piazzale Aldo Moro 5, 00185 Rome, Italy. Email: brigid.unim@uniroma1.it

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HRAS mutations are seen in CRCs.[9] There are no validated predictive markers available for anti-VEGF therapy.[4]

International guidelines for CRC recommend testing the mutation status of both *KRAS* and *NRAS*. Anti-EGFR therapy should be given only when no mutations exist in these genes (ie, *KRAS* and *NRAS* are wild-type). Routine testing for other mutation profiles in clinical practice (eg, *BRAF, EGFR, PI3K and PTEN* status) is not recommended in these patients because it is not necessary for therapeutic decision making. Nevertheless, it provides information for identifying subgroups and stratifying patients in clinical trials.[5,10,11] In particular, *BRAF* testing is recommended in mCRC patients as a prognostic marker.[10] Given the importance of personalized treatment of CRC, the aims of the study are (1) to review and evaluate the evidence supporting the cost-effectiveness of genetic testing of mCRC patients for *RAS* mutations before targeted therapy with monoclonal antibodies in all treatment lines and (2) to evaluate how well economic evaluations adhere to guidelines on *RAS* testing in mCRC patients.

Methods

Literature Search and Study Selection

This systematic review of economic evaluations of *RAS* testing in patients with mCRC was conducted according to the guidelines from the Centre for Reviews and Dissemination, University of York, on undertaking systematic reviews of economic evaluations[12] and the Cochrane Handbook for systematic reviews.[13] Two investigators independently searched Medline, the Health Technology Assessment Database, the National Health Service Economic Evaluation Database, Scopus, and Web of Science. The search was limited to English-language records published between January 2000 and December 2018. The following search terms were used: genetic* OR pharmacogenetic* economic evaluation*, cost-effectiveness, cost-utility, cost-benefit, cost-minimization, OR QALY* OR LYG* AND colorectal cancer*. The search strings were adjusted for each database while maintaining a common overall architecture. Titles, abstracts, and full texts of the identified records were assessed, and discrepancies were resolved by consensus. We excluded studies that compared only the efficacy or effectiveness of various anti-EGFR treatments and those that focused on adverse events associated with anti-EGFR treatment (eg, treatment of neutropenia guided by UGT1A1 genetic testing; Appendix 1 in Supplemental Materials found at https://doi.org/10.1016/j.jval.2019.07.009). A manual review of references from eligible economic analyses was also performed to identify potentially relevant studies. The records were selected according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Statement.[14] We have applied the methodological approach used in this review in previous studies.[15-18]

Data Extraction and Quality Assessment

Two reviewers independently extracted data and assessed the quality of the studies using the Quality of Health Economic Studies (QHES) scale[19] and the British Medical Journal[20] and Philips checklists.[21] To compare monetary values expressed in different currencies and for different years, we used the national inflation rates provided by the World Bank[22] to express the costs of genetic testing in national currencies in 2017. These values were then converted to 2017 international USD (Int$) using purchasing power parity exchange rates.[23] We performed a descriptive analysis of the included studies to summarize their main characteristics and to compare study interventions, methods, results, and adherence to guidelines.

Results

The literature search yielded 163 records, of which 116 were excluded after screening by title and abstract. Twenty-five records were excluded after reviewing the full text, leaving 6 economic evaluations for inclusion in the review (Fig. 1).[24-29]

General Characteristics of the Studies

The 6 studies were published between 2010 and 2017 (Table 1) and conducted in the United States[1,25,26] Germany,[26] Switzerland,[27] Canada,[28] and Japan.[24,29] The types of economic evaluation used were cost-effectiveness analysis,[25,26] cost-utility analysis (CUA),[28,29] or both cost-effectiveness analysis and CUA.[24,29] In all studies, a comparison was made between testing for *RAS* mutation status before treatment and a no-testing strategy. The viewpoint in all studies was that of the healthcare system or healthcare payer, and therefore only direct medical costs were included in the analysis. All studies used a Markov model to estimate cost-effectiveness, which was reported as incremental cost-effectiveness ratio (ICER), life-year(s) gained (LYG), and quality-adjusted life-year(s) (QALY). The most frequently used discount rate for costs and benefits was 3%.[25,27,29] The ICER thresholds reported in the studies were in the range of $50 000 to $100 000,[25,27,29] ¥5 million to ¥6 million,[24,29] and £20 000 to £30 000.[27,29]

Basic Assumptions and Quality of the Studies

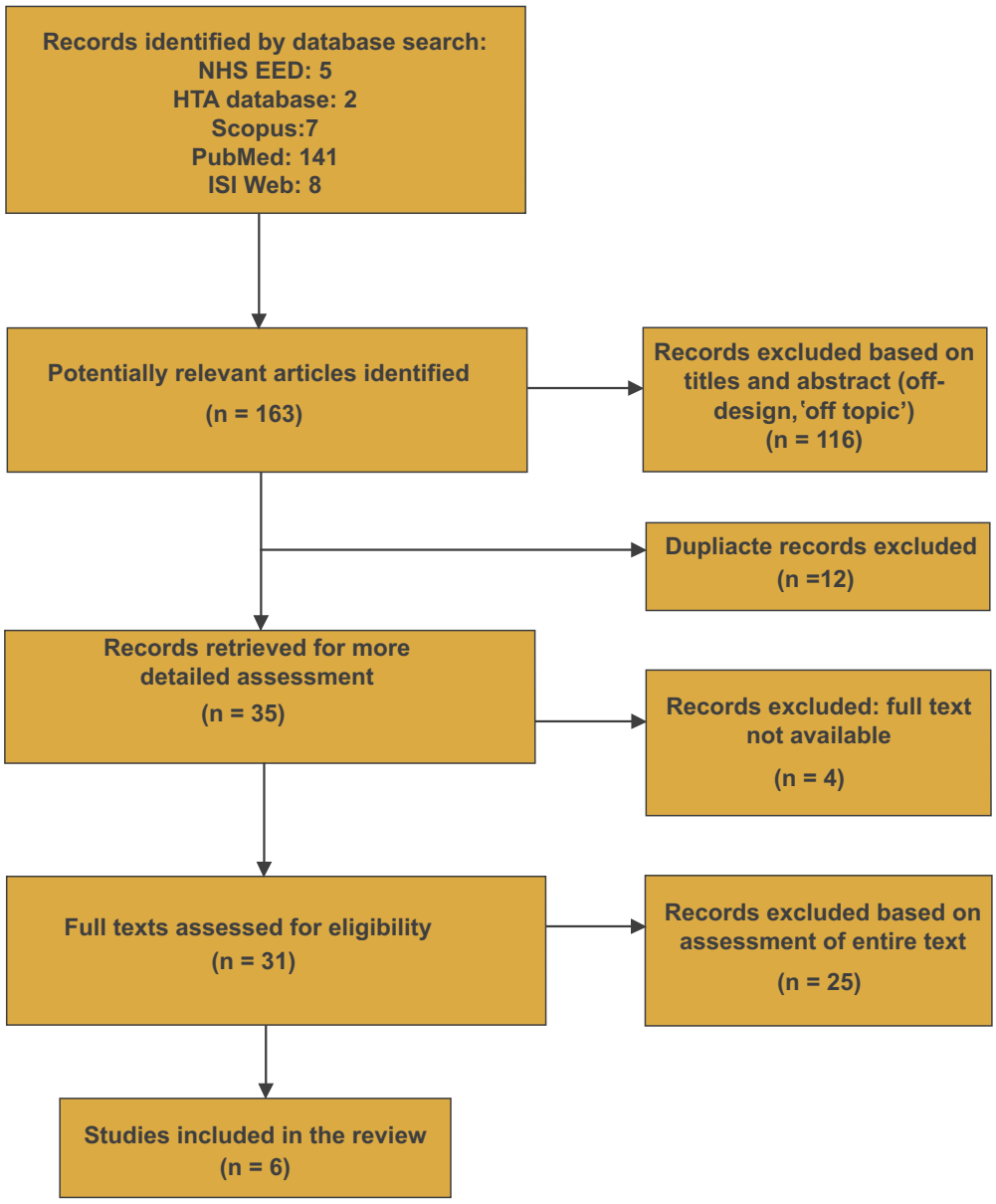
All studies specified the genotype prevalence, except one,[28] and the *KRAS* wild-type was more common. Two studies reported the genetic test sensitivity and specificity,[26,27] which ranged between 95% and 100%. All studies also reported the cost of genetic testing and the relative currency; the cost of *RAS* testing ranged from Int $177 to Int $317. Combined *KRAS* and *BRAF* testing cost approximately Int $323, whereas comprehensive next-generation sequencing (NGS) profiling cost Int $4016 (Table 1). Saito et al[24] and the Ontario Ministry of Health[28] also considered severe adverse events (grades 3 and 4) in the economic model.

Regarding methodological quality, the results of the QHES scale (Table 2) were consistent with the BMJ findings. The studies are of high quality, with the lowest score of 84 awarded to Vijayaraghavan et al.[26] The studies, except one,[25] reported the perspective of the analysis (item 1). Uncertainty in the economic models was correctly handled by probabilistic sensitivity analysis (PSA)[27-29] and multiple 1-way[24,25] and 2-way sensitivity analyses[24] (item 5). Vijayaraghavan et al[26] conducted only a 1-way sensitivity analysis; in addition, benefits and costs were not discounted (item 8). Blank et al[27] did not report the price data (item 9). The Ontario Ministry of Health[28] study did not discuss its results (item 13), whereas Saito et al[24] did not disclose the source of funding for the study (item 16).[21] Most structural issues (Table 3) were observed in sections S1[25-27,29] and S7[25-29] of the Philips checklist.[21] Most data issues regarded sections D1,[24-29] D2,[25,26,28,29] and D4.[24-29] The model was calibrated (C1) in one study.[25]

Adherence to Guidelines

International guidelines[5,10,11,30] recommend that *RAS* screening should include *KRAS* and *NRAS* analysis as predictors of response to anti-EGFR antibodies, but none of the economic evaluations

Figure 1. The Preferred Reporting Items for Systematic Reviews and Meta-Analyses flow diagram of study selection process.



included in this review took *NRAS* mutation status into consideration. In the study by Saito et al,[24] *KRAS* testing correctly guided the first-line treatment regimen with panitumumab, but the comprehensive screening strategy included not recommended genes as predictors of anti-EGFR response (ie, *PTEN*, *ERBB2*, *SRC*, *BRAF*, and *RNF43*).[5,10,11,30] Furthermore, Behl et al[25] and Blank et al[27] used *BRAF* genetic testing to guide the therapy of mCRC patients with cetuximab, which is not recommended because the *BRAF* test is a prognostic marker and thus cannot predict the response to anti-EGFR antibodies.[5,10,11,30]

Anti-EGFR therapy as the first-line treatment of *RAS* wild-type mCRC patients is recommended unless contraindicated (by, for example, reduced organ function or cardiovascular insufficiency).[10,11,31] Nonetheless, only Saito et al[24] included first-line therapy in the economic model. The Ontario Ministry of Health study[28] adhered to the use of anti-EGFR agents specifically in third-line treatment as recommended by the Canadian Expert Group.[32]

Cost-Effective Strategies

In all 6 studies, the comparative cost-effectiveness analyses focused on the benefit of anti-EGFR therapy guided by genetic testing rather than on the benefit of anti-EGFR antibodies alone. Anti-EGFR antibodies were provided to mCRC patients in first-line[24] or subsequent lines[25-29] as monotherapy[25,27-29] or combination therapies.[24,26,28] The latter consisted of monoclonal antibodies together with irinotecan,[28] FOLFIRI (irinotecan, 5-fluorouracil, and leucovorin),[24,26] or FOLFOX (leucovorin, 5-fluorouracil, and oxaliplatin)[24]; the chemotherapy components were administered by infusion (irinotecan, leucovorin, oxaliplatin, 5-fluorouracil) or bolus (5-fluorouracil).

Table 1. General characteristics of full economic evaluations of *RAS* genetic testing.

First author, country, year	Type of economic evaluation	Time horizon	Perspective	Model of analysis	Sensitivity analysis	Discount rate, %	Source of effectiveness data	Source of cost	Cost of testing	Cost of testing in Int $ (2017)	Source of funding
Saito, Japan, 2017[24]	CEA, CUA	5 years	Healthcare payer	Markov model	One way; multivariate	2 (cost and benefits)	RCT; retrospective analysis; meta-analysis	Official tariff	RAS testing: ¥25.000; comprehensive screening: ¥400.000	RAS testing: 251; comprehensive screening: 4016	Missing
Behl, USA, 2012[25]	CEA	10 years	Missing	Markov model	One way	3 (cost and benefits)	RCT	Health insurance plan	KRAS testing: US $224; KRAS + BRAF testing: US $303	KRAS testing: 239; KRAS + BRAF testing: 323	National Cancer Institute at the National Institutes of Health, USA
Vijayaraghavan, Germany and USA, 2012[26]	CEA	Lifetime	Healthcare payer	Markov model	One way	Missing	RCT; retrospective analysis	USA: health insurance plan; Germany: literature, expert opinion	KRAS test: US $243	259	Roche Molecular Systems, Inc, Pleasanton, CA, USA
Blank, Switzerland, 2011[27]	CUA	Lifetime	Healthcare system	Markov model	One way; scenario; probabilistic	3 (cost and benefits)	RCT	Official tariff	€394 per analysis	317	Educational grant of the ETH, Zurich Foundation, and the Competence Center for Systems Physiology and Metabolic Diseases, Zurich, Switzerland
The Ontario Ministry of Health and Long-Term Care, Canada, 2010[28]	CUA	Lifetime	Ontario Ministry of Health and Long-Term Care	Markov model	Probabilistic	5 (cost and benefits)	RCT	Literature; health insurance plan; public database	KRAS testing: Can $500	448	Ontario Ministry of Health and Long-Term Care, Toronto, Ontario, Canada
Shiroiwa, Japan, 2010[29]	CEA, CUA	2.5 years	Healthcare payer	Markov model	One way; probabilistic	3 (cost and benefits)	RCT	Social insurance plan; official drug tariff	KRAS test: ¥20.000 (US $220)	247	Roche Diagnostics K.K., Tokyo, Japan

CEA indicates cost-effectiveness analysis; CUA, cost-utility analysis; RCT, randomized clinical trial; Int$ 2017, international US dollars; ¥, Japanese yen.

RAS testing followed by cetuximab mono- or combination therapy

In the article by Vijayaraghavan et al[26] (Table 4), using *KRAS* testing to select patients for cetuximab monotherapy is a dominant strategy with equal effectiveness and lower costs; it can save $8040/patient in the United States and €3856/patient in Germany. Administering cetuximab together with irinotecan to *KRAS* wild-type patients and irinotecan alone to patients with *KRAS* mutations increased life expectancy at an additional cost of $35 539/LYG. In Switzerland,[27] testing for *KRAS* and *BRAF* status followed by cetuximab treatment if no mutations were detected was the most cost-effective approach, with an ICER of €62 653/QALY when compared with the reference strategy (best supportive care [BSC] for all, no testing, no cetuximab). The utilities were derived from the CO.17 trial in which the Health Utility Index Mark 3 scores were prospectively collected. A value of 0.71 was applied[33] to wild-type and mutant patients in the stable state without cetuximab treatment and to mutant patients receiving cetuximab; a value of 0.5 was applied[34,35] to patients in the progression state. In the Canadian setting,[28] *KRAS* testing was cost-effective for cetuximab monotherapy at a willingness-to-pay (WTP) value of $54 802 and for cetuximab with irinotecan combination therapy at a WTP value of $42 701. The latter was the preferred cost-effective option when all treatment strategies were considered simultaneously in the analysis. The utility value of 0.71 was applied to all patients; an increase of 0.07 for cetuximab, panitumumab, or cetuximab with irinotecan treatments was assigned to patients for all strategies except BSC.[33] In a sensitivity analysis,[36] the utility increase for panitumumab was estimated at 0.12

Two studies found high ICERs for *RAS* testing followed by anti-EGFR therapy (Table 4).[25,29] According to Behl et al,[25] screening for *KRAS* and *BRAF* improves the cost-effectiveness of anti-EGFR therapy in the United States, although the ICER, compared with the reference strategy (no anti-EGFR therapy), remains above the US threshold of $100 000/QALY. In the analysis by Shiroiwa et al,[29] the *KRAS*-testing strategy (*KRAS* testing plus cetuximab for patients with wild-type *KRAS*) was dominant compared with the no–*KRAS*-testing strategy (cetuximab to all patients without *KRAS* testing) with a cost reduction of ¥0.5 million/patient. Nevertheless, the ICER of cetuximab (with or without a *KRAS* test) fell above the Japanese, American, and British thresholds, even if treatment was limited to patients with wild-type *KRAS*. The utilities for wild-

Table 2. Quality of full economic evaluations of *RAS* genetic testing.

Item	Points	Saito, 2017[24]	Behl 2012[25]	Vijayaraghavan, 2012[26]	Blank, 2011[27]	The Ontario Ministry of Health, 2010[28]	Shiroiwa, 2010[29]
1. Was the study objective presented in a clear, specific, and measurable manner?	7	x	x	x	x	x	x
2. Were the perspective of the analysis (societal, third-party payer, etc) and reasons for its selection stated?	4	x	—	x	x	x	x
3. Were variable estimates, from the best available source, used in the analysis (ie, randomized control trial; best, expert opinion; worst)?	8	x	x	x	x	x	x
4. If estimates came from a subgroup analysis, were the groups prespecified at the beginning of the study?	1	x	x	x	x	x	x
5. Was uncertainty handled by (1) statistical analysis to address random events or (2) sensitivity analysis to cover a range of assumptions?	9	x	x	—	x	x	x
6. Was incremental analysis performed between alternatives for resources and costs?	6	x	x	x	x	x	x
7. Was the methodology for data abstraction (including the value of health states and other benefits) stated?	5	x	x	x	x	x	x
8. Did the analytic horizon allow time for all relevant and important outcomes? Were benefits and costs that went beyond 1 year discounted (3% to 5%) and justification given for the discount rate?	7	x	x	—	x	x	x
9. Was the measurement of costs appropriate and the methodology for the estimation of quantities and unit costs clearly described?	8	x	x	x	—	x	x
10. Were the primary outcome measure(s) for the economic evaluation clearly stated, and did they include the major short-term, long-term, and negative outcomes?	6	x	x	x	x	x	x
11. Were the health outcome measures/scales valid and reliable? If previously tested, valid and reliable measures were not available, was justification given for the measures/scales used?	7	x	x	x	x	x	x
12. Were the economic model (including structure), study methods and analysis, and the components of the numerator and denominator displayed in a clear, transparent manner?	8	x	x	x	x	x	x
13. Were the choice of economic model, main assumptions, and limitations of the study stated and justified?	7	x	x	x	x	—	x
14. Did the author(s) explicitly discuss direction and magnitude of potential biases?	6	x	x	x	x	x	x
15. Were the conclusions/recommendations of the study justified and based on the study results?	8	x	x	x	x	x	x
16. Was there a statement disclosing the source of funding for the study?	3	—	x	x	x	x	x
Total	100	97	96	84	92	93	100

type *KRAS* patients receiving cetuximab and the ineffective/no cetuximab group were assumed to be 0.7 for progression-free survival (PFS).[33] Disutility scores were altered by gamma distribution in the PSA.

RAS testing followed by panitumumab mono- or combination therapy

Saito et al[24] (Table 4) considered the administration of panitumumab together with FOLFOX without genetic testing as

Table 3. Risk of bias assessment using the Philips checklist for economic modeling studies.

Quality criteria	Questions for critical appraisal	Saito, 2017[24]	Behl 2012[25]	Vijayaraghavan 2012[26]	Blank, 2011[27]	The Ontario Ministry of Health 2010[28]	Shiroiwa, 2010[29]
Structure (S)							
S1: Statement of decision problem/objective	Is there a clear statement of the decision problem?	✓	✓	✓	✓	✓	✓
	Is the objective of the evaluation and model specified and consistent with the stated decision problem?	✓	✓	✓	✓	✓	✓
	Is the primary decision maker specified?	✓	—	—	—	✓	—
S2: Statement of scope/ perspective	Is the perspective of the model stated clearly?	✓	—	✓	✓	✓	✓
	Are the model inputs consistent with the stated perspective?	✓	NA	✓	✓	✓	✓
	Has the scope of the model been stated and justified?	✓	✓	✓	✓	✓	✓
	Are the outcomes of the model consistent with the perspective, scope and overall objective of the model?	✓	✓	✓	✓	✓	✓
S3: Rationale for structure	Has the evidence regarding the model structure been described?	✓	✓	✓	✓	✓	✓
	Is the structure of the model consistent with a coherent theory of the health condition under evaluation?	✓	✓	✓	✓	✓	✓
	Are the sources of data used to develop the structure of the model specified?	✓	✓	✓	✓	✓	✓
	Are the causal relationships described by the model structure justified appropriately?	✓	—	—	✓	✓	✓
S4: Structural assumptions	Are the structural assumptions transparent and justified?	✓	—	—	✓	✓	✓
	Are the structural assumptions reasonable given the overall objective, perspective and scope of the model?	✓	✓	✓	✓	✓	✓
S5: Strategies/ comparators	Is there a clear definition of the options under evaluation?	✓	✓	✓	✓	✓	✓
	Have all feasible and practical options been evaluated?	✓	✓	✓	✓	✓	✓
	Is there justification for the exclusion of feasible options?	NA	NA	NA	NA	NA	NA
S6: Model type	Is the chosen model type appropriate given the decision problem and specified causal relationships within the model?	✓	✓	✓	✓	✓	✓
S7: Time horizon	Is the time horizon of the model sufficient to reflect all important differences between options?	✓	✓	✓	✓	✓	✓
	Is the time horizon of the model, the duration of treatment and the duration of treatment effect described and justified?	✓	—	—	—	—	—
S8: Disease states/ pathways	Do the disease states (state transition model) or the pathways (decision tree model) reflect the underlying biological process of the disease in question and the impact of interventions?	✓	✓	✓	✓	✓	✓
S9: Cycle length	Is the cycle length defined and justified in terms of the natural history of disease?	✓	✓	—	✓	✓	✓
Data (D)							
D1: Data identification	Are the data identification methods transparent and appropriate given the objectives of the model?	✓	✓	✓	✓	✓	✓

continued on next page

Table 3. Continued

Quality criteria	Questions for critical appraisal	Saito, 2017[24]	Behl 2012[25]	Vijayaraghavan 2012[26]	Blank, 2011[27]	The Ontario Ministry of Health 2010[28]	Shiroiwa, 2010[29]
	Where choices have been made between data sources, are these justified appropriately?	✓	NA	NA	—	—	NA
	Has particular attention been paid to identifying data for the important parameters in the model?	✓	✓	✓	✓	✓	✓
	Has the process of selecting key parameters been justified and systematic methods used to identify the most appropriate data?	—	✓	—	✓	✓	—
	Has the quality of the data been assessed appropriately?	—	—	—	—	—	—
	Where expert opinion has been used, are the methods described and justified?	—	NA	—	NA	—	NA
D2: Pre-model data analysis	Are the pre-model data analysis methodology based on justifiable statistical and epidemiological techniques?	✓	—	—	✓	—	—
D2a: Baseline data	Is the choice of baseline data described and justified?	✓	✓	✓	✓	✓	✓
	Are transition probabilities calculated appropriately?	✓	—	—	✓	—	—
	Has a half cycle correction been applied to both cost and outcome?	—	—	—	—	—	—
	If not, has this omission been justified?	—	—	—	—	—	—
D2b: Treatment effects	If relative treatment effects have been derived from trial data, have they been synthesized using appropriate techniques?	—	—	—	—	—	—
	Have the methods and assumptions used to extrapolate short-term results to final outcomes been documented and justified?	—	✓	—	—	—	—
	Have alternative assumptions been explored through sensitivity analysis?	✓	✓	✓	✓	✓	✓
D2c: Quality-of-life weights/ utilities	Are the utilities incorporated into the model appropriate?	✓	NA	NA	✓	✓	✓
	Is the source for the utility weights referenced?	✓	NA	NA	✓	✓	✓
	Are the methods of derivation for the utility weights justified?	—	NA	NA	✓	✓	✓
D3: Data incorporation	Have all data incorporated into the model been described and referenced in sufficient detail?	✓	✓	✓	✓	✓	✓
	Has the use of mutually inconsistent data been justified (i.e. are assumptions and choices appropriate)?	✓	NA	—	✓	NA	✓
	Is the process of data incorporation transparent?	✓	✓	✓	✓	✓	✓
	If data have been incorporated as distributions, has the choice of distribution for each parameter been described and justified?	NA	NA	NA	NA	NA	NA
	If data have been incorporated as distributions, is it clear that second order uncertainty is reflected?	NA	NA	NA	NA	NA	NA
D4: Assessment of uncertainity	Have the four principal types of uncertainty been addressed?	—	—	—	—	—	—
	If not, has the omission of particular forms of uncertainty been justified?	—	—	—	—	—	—
D4a: Methodological uncertainity	Have methodological uncertainties been addressed by running alternative versions of the model with different methodological assumptions?	—	—	—	✓	—	✓

continued on next page

Table 3. Continued

Quality criteria	Questions for critical appraisal	Saito, 2017[24]	Behl 2012[25]	Vijayaraghavan 2012[26]	Blank, 2011[27]	The Ontario Ministry of Health 2010[28]	Shiroiwa, 2010[29]
D4b: structural uncertainty	Is there evidence that structural uncertainties have been addressed via sensitivity analysis?	—	—	—	—	—	—
D4c: Heterogeneity	Has heterogeneity been dealt with by running the model separately for different sub-groups?	—	—	—	—	—	—
D4d: Parameter	Are the methods of assessment of parameter uncertainty appropriate?	✓	✓	_	✓	✓	✓
	Has probabilistic sensitivity analysis been done, if not has this been justified?	—	—	—	✓	✓	✓
	If data are incorporated as point estimates, are the ranges used for sensitivity analysis stated clearly and justified?	✓	✓	_	✓	✓	✓
CONSISTENCY (C)							
C1: Internal consistency	Is there evidence that the mathematical logic of the model has been tested thoroughly before use?	—	✓	—	—	—	—
C2: External consistency	Are the conclusions valid given the data presented?	✓	✓	✓	✓	✓	✓
	Are any counterintuitive results from the model explained and justified?	NA	NA	NA	NA	NA	NA
	If the model has been calibrated against independent data, have any differences been explained and justified?	NA	✓	NA	NA	NA	NA
	Have the results of the model been compared with those of previous models and any differences in results explained?	✓	✓	✓	✓	_	✓

first-line therapy, demonstrating that the no-testing strategy was less effective because it saved fewer lives than comprehensive screening (1.504 vs 1.706 LYG) or *RAS* testing (1.504 vs 1.631 LYG); comprehensive screening was the costliest of the 3 strategies.

The utilities were measured with the EQ-5D instrument in a previous study.[37] The values of 0.821, 0.782, and 0.681 were applied to patients receiving first-line therapy, second-line therapy, and BSC, respectively. Disutilities related to adverse events (0.02) were based on expert opinions.

Vijayaraghavan et al[26] demonstrated that *KRAS* testing before panitumumab monotherapy in subsequent lines of treatment saved $7546/patient in the United States and €4612/patient in Germany compared with administering panitumumab to all patients. In the Canadian setting,[28] *KRAS* testing before panitumumab monotherapy as third-line treatment was cost-effective at a WTP value of Can $47 795.

Genome sequencing and *RAS* testing followed by anti-VEGF combination therapy

According to Saito et al[24] (Table 4), comprehensive molecular profiling, using NGS technology, followed by the combination of bevacizumab with FOLFOX in first-line or with FOLFIRI in second-line treatment is a cost-effective strategy with an ICER of ¥4 260 187/QALY compared with *RAS* testing at the Japanese WTP value of ¥6 million/QALY.

Discussion

The importance of predictive genetic testing using *RAS* gene mutation status before therapy with monoclonal antibodies has been unequivocally demonstrated: clinical trials show that mCRC patients with *KRAS* mutations do not respond to anti-EGFR therapy,[6,7] and the therapy may negatively affect PFS and overall survival (OS).[8,11] The present systematic review of full economic evaluations highlights the cost-effectiveness of *RAS* testing before anti-EGFR therapy for all lines of treatment. It also indicates that *RAS* genetic testing before anti-EGFR therapy increases treatment costs and has a considerable effect on the healthcare system from the payer's perspective; nonetheless, it is a cost-effective strategy compared with anti-EGFR therapy without testing. With respect to the National Institute for Clinical Excellence WTP threshold (£20 000-£30 000/QALY or LYG)[38] and the US thresholds ($50 000-$100 000/QALY or LYG),[39] 4 studies adopted strategies with a favorable ICER for *KRAS* or *BRAF* testing before anti-EGFR therapy.[24,26-28] Behl et al[25] and Shiroiwa et al[29] reported ICERs that exceeded these thresholds. The findings of Behl et al[25] are less supportive of the use of anti-EGFR therapy and indicate lower cost savings from *KRAS* testing than other analyses. This could be due to the inclusion of costs for the resection of metastases, recurrence after resection, and conversion therapies in their study. The impact of resection costs and subsequent therapies on the analysis is indisputable, considering that almost 50% of patients in their model have recurrence within a year of resection. Nevertheless, accounting for these issues makes the model much closer to the real world, even if the overall cost-effectiveness is less favorable. The high ICERs found in the analysis by Shiroiwa et al[29] were mainly related to the cost of cetuximab in the Japanese setting; none of the other parameters varied in the sensitivity analysis (eg, cost of *KRAS* testing, *KRAS* mutation, cost of BSC) affected their results substantially. In general, the sensitivity analyses of the economic evaluations showed that ICERs were influenced by

Table 4. Treatment strategies and results of the cost-effectiveness analysis of *RAS* genetic testing in patients with metastatic colorectal cancer.

First author, country, year	Genes	Treatment lines/drugs	Reference strategy	Testing and treatment strategies	ICER	Threshold/ conclusion
Saito, Japan, 2017[24]	KRAS, BRAF, PTEN, SRC, ERBB2, RNF43	First line: panitumumab + FOLFOX Second-line: bevacizumab + FOLFIRI Third-line: BSC	Missing	(1) Anti-EGFR therapy without screening (no testing) (2) RAS mutation screening before anti-EGFR therapy (RAS screening) (3) Comprehensive molecular profiling before anti-EGFR therapy (comprehensive screening)	(2) vs (1): ¥3 049 132/QALY (3) vs (2): ¥4 260 187/QALY	¥6 million/ QALY Comprehensive screening was more cost-effective compared with RAS screening
Behl, USA, 2012[25]	KRAS, BRAF	All lines cetuximab + irinotecan	(1) No cetuximab therapy (BSC)	(2) Screening for KRAS and BRAF mutations + cetuximab (after first-line chemotherapy) (3) Screening for KRAS mutations only + cetuximab (after first-line chemotherapy) (4) Anti-EGFR therapy without testing (after first-line chemotherapy)	(2) vs (1): $648 396/LYG (3) vs (2): $2814 338/LYG (4) vs (3): $2932 767/LYG	US $50 000 to $100 000/QALY Screening for KRAS and BRAF mutation improves cost-effectiveness but the ICER remains above the threshold
Vijayaraghavan, Germany and USA, 2012[26]	KRAS	After first line, cetuximab alone or combined (irinotecan/ FOLFIRI); panitumumab	Missing	(1.1) KRAS testing + combination therapy: cetuximab + irinotecan/FOLFIRI if KRAS wt + BSC if chemotherapy fail AND cetuximab + BSC OR panitumumab + BSC if KRAS mutation (1.2) KRAS testing + combination therapy: cetuximab + irinotecan/FOLFIRI if KRAS wt AND chemotherapy without EGFR inhibitors/BSC if KRAS mutation (2) No KRAS testing + combination therapy (3) KRAS testing + cetuximab alone (4) No KRAS testing + cetuximab alone (5) KRAS testing + panitumumab alone (6) No KRAS testing + panitumumab alone (prior therapy includes first-line FOLFOX or FOLFIRI ± bevacizumab and/or second-line therapy with FOLFIRI/FOLFOX)	(1.2) vs (1.1): $35 539/LYG (1.1) vs (2): Less expensive, less effective (2) vs (1.2): Higher cost, same effectiveness (4) vs (3): Higher cost, same effectiveness (6) vs (5): Higher cost, same effectiveness	Threshold not reported. Under most scenarios, KRAS testing saved money with equivalent clinical outcomes
Blank, Switzerland, 2011[27]	KRAS, BRAF	Last line, cetuximab	(1) BSC for all (no testing, no cetuximab)	(2) KRAS only: BRAF testing if KRAS wt + cetuximab and BSC if KRAS/BRAF wt; BSC if KRAS/BRAF mutation; BSC if KRAS wt/BRAF mutation (3) KRAS + cetuximab and BSC if KRAS wt; BSC if KRAS mutation (4) No testing strategy + cetuximab and BSC to the entire patient population (cetuximab is provided as last-line therapy)	(2) vs (1): €62 653/QALY (3) vs (2): €313 537/QALY (4) vs (3): €314 588/QALY	€38 500–€77 000/ QALY (US $50 000 to $100 000) Testing for KRAS and BRAF is the most cost-effective approach, despite high costs for predictive testing

continued on next page

Table 4. Continued

First author, country, year	Genes	Treatment lines/drugs	Reference strategy	Testing and treatment strategies	ICER	Threshold/ conclusion
The Ontario Ministry of Health and Long-Term Care, Canada, 2010[28]	KRAS	Third line cetuximab alone or combination (irinotecan)/ panitumumab	Missing	(0) BSC for all (no KRAS test; no treatment) (1a) KRAS test + cetuximab and BSC for patients with KRAS wt and BSC in patients with KRAS mutations (1b) No KRAS test + cetuximab and BSC for all (2a) KRAS test + panitumumab and BSC for patients with KRAS wt and BSC in patients with KRAS mutations (2b) No KRAS test + panitumumab and BSC for all (3a) KRAS test + cetuximab and irinotecan and BSC for patients with KRAS wt and BSC in patients with KRAS mutations (3b) No KRAS test + cetuximab and irinotecan and BSC for all (cetuximab, panitumumab, cetuximab + irinotecan, or BSC are provided as third-line therapy)	(1a) vs (0): $54 802/QALY (1b) vs (1a): dominated (2a) vs (0): $47 795/QALY (2b) vs (2a): $308 236/ QALY (3a) vs (0): $42 710/QALY (3b) vs (3a): $163 396/ QALY	Can $50 000/QALY Strategies considering KRAS testing were found to be cost-effective when compared with the corresponding strategies of no KRAS testing
Shiroiwa, Japan, 2010[29]	KRAS	Last line, cetuximab	Missing	(1) KRAS testing strategy: KRAS test + cetuximab as last line-therapy if KRAS wt OR BSC if KRAS mutation (2) No-KRAS-testing strategy: no test + cetuximab as last-line therapy for all patients (3) No-cetuximab strategy: no test + BSC for all patients	(1) vs (2): dominant (1) vs (3): ¥16 million/QALY (2) vs (3): ¥21 million/QALY	Japan: ¥6 million/ QALY; UK: £20 000–£30 000/QALY; US: $50 000–$100 000/QALY KRAS-testing strategy dominates no-KRAS-testing strategy (cost reduction 0.5 million per patient); however, the ICER of cetuximab (with or without KRAS test) falls above the thresholds

BSC indicates best supportive care; Can$, Canadian dollars; EGFR, epidermal growth factor receptor; FOLFOX, leucovorin, 5-fluorouracil, and oxaliplatin; FOLFIRI, irinotecan, 5-fluorouracil, and leucovorin; ICER, incremental cost-effectiveness ratio; LYG, life per year gained; QALY, quality-adjusted life-year; wt, wild-type; ¥, Japanese yen.

various parameters, such as utility value for progressive disease,[27] cost of therapeutic regimens with anti-EGFR agents,[26,28,29] cost of BSC and *KRAS* wild-type prevalence,[26] OS,[28,29] PFS,[24] and cost of NGS sequencing.[24]

The evaluation of adherence of economic models to international clinical guidelines highlighted different issues. First, Saito et al[24] included in their model other genes not recommended in clinical guidelines as predictors of anti-EGFR response and did not consider *NRAS* mutation status as required. They erroneously concluded that comprehensive screening of these genes in mCRC patients should be considered before monoclonal antibody therapy. Nevertheless, this approach cannot be recommended for introduction into clinical practice given that it is unnecessary and incurs the high cost of NGS technologies (Int $4016; 13- to 23-fold higher than *KRAS* testing). This conclusion does not imply that NGS approaches have no place in clinical practice. NGS has many advantages over Sanger sequencing, including its high speed and improved accuracy and cost-effectiveness for the detection of multiple genetic alterations with a minimum amount of DNA. Indeed, one clinical practice guideline recommends using NGS to obtain comprehensive information on mutations in multiple genes in metastatic tumors.[5] Nevertheless, NGS technologies are underused in developed and predominantly in developing countries because of, for example, the high cost of establishing and maintaining NGS facilities, lack of skilled staff, lack of educational programs, and lack of a regulatory framework. Although the cost of sequencing has decreased in recent years, other challenges for the adoption of NGS into clinical practice still persist.[40,41] More funds for genomic research, centralized NGS facilities at the regional or national level, training programs, and international collaborations may enhance the application of NGS technologies worldwide.[42,43]

Second, although the evidence was already available in 2013 that *KRAS* and *NRAS* status should be wild-type before treatment with anti-EGFR agents (panitumumab),[44,45] the recommendations on *NRAS* mutation status are reported only in guidelines

published from 2015.[5,10,11,30] Before 2015, *NRAS* was not reported among biomarkers for the treatment of advanced CRC[46-49] and was not recommended for inclusion in clinical routine.[50] Given the above, studies published before 2013 cannot be expected to have taken *NRAS* mutation status into account in their economic models. Nevertheless, clinical guidelines should be updated in a timely fashion when relevant new evidence becomes available.

Third, two studies[25,27] inappropriately used *BRAF* genetic testing to guide the therapy of mCRC patients with cetuximab. *BRAF* testing is recommended for prognostic assessment or selection for clinical trials[10,11] but not for routine testing. Nevertheless, clinical trials of *BRAF*-targeted therapies (eg, encorafenib, binimetinib) are currently under investigation, suggesting new treatment strategies for *BRAF*-mutant CRC that could justify *BRAF* routine testing.[51,52] Economic evaluations should adhere strictly to guideline recommendations when selecting genes for assessment in mCRC patients. This would refine patient selection for the economic models and therefore could lead to more accurate results.

Finally, economic evaluations were not cited in recent guidelines.[5,10,11] Economic evaluations of available treatment options are a valuable support to clinical practice, because financial outcomes of healthcare services cannot be disregarded, especially in times of economic contraction. They facilitate the awareness of healthcare costs and thus should be considered in clinical guidelines.

The basic assumptions used to build the various economic models we reviewed here showed both differences and similarities. For instance, the sensitivity and specificity of *KRAS* and *BRAF* genetic testing, derived from literature studies, were included in only 2 economic evaluations.[26,27] The values reported were similar in the 2 studies, but Vijayaraghavan et al[26] varied the sensitivity and specificity of the *KRAS* test from 75% to 100% for the cetuximab-only strategy. The study demonstrated that even with a lower specificity of *KRAS* testing, not performing the test before chemotherapy was still not cost-effective. It should be kept in mind that sensitivity and specificity values for *RAS* genetic testing are surrounded by uncertainty. A recent clinical guideline reported assay sensitivity for *KRAS* mutation testing in the range of 84% to 100% across different testing methods, with Sanger sequencing at the lower end of the range. Specificity ranged from 98% to 100% for most assays, but some studies have reported lower values.[5] Specificity and sensitivity values for *RAS* testing should be investigated in future economic evaluations to enhance the understanding of their influence on outcomes. Another inconsistency across the studies was the inclusion of adverse events. Most studies[25-27,29] did not consider these events at all. Saito et al[24] did not include adverse events associated with panitumumab treatment because their rates are extremely low and the 2 parameters reported (skin toxicity, hypertension) did not affect the model. The study by Behl et al[25] confirmed these conclusions. In contrast, the Ontario Ministry of Health[28] incorporated adverse events with associated costs for all therapeutic regimens reported. The highest cost was associated with neutropenia ($4645), which occurred in more than 20% of patients treated with combination therapy, the preferred cost-effective option in Ontario. Adverse events, which particularly relate to the toxicity of biological agents, should be routinely included in economic evaluations for a comprehensive assessment of the available therapeutic options and for a more accurate cost-effectiveness analysis.

The included studies present other methodological limitations that may have biased the results. The perspectives adopted in all studies are from the point of view of the payer or provider. By excluding the societal level, the studies do not account for all effects on patients, their families, and the public. Furthermore, price adjustments for inflation or currency conversion were not given in 2 studies[26,28]; of the 4 studies that performed a CUA, methods to value benefits were not stated in 2 of them[28,29]; OS and PFS were reported differently across the studies, limiting direct comparisons of the estimates, and PFS outcomes were not provided for the different strategies in one study.[25] The analysis covers a limited number of countries, and none of the studies discussed the applicability of their outcomes to other settings.[24-29] Some clinical and utility data were not available for the specific settings of the studies and were derived from other countries[24,27,29] or not included in the model.[26] The source of funding (Table 1) was not declared in one study,[24] whereas Roche, a leading provider of genetic tests, funded 2 studies.[26,29] The Philips checklist[21] highlighted other sources of bias, especially in the data section. Although data for most parameters were derived from trials, systematic methods were not used to identify the most appropriate data.[24,26,29] None of the studies assessed the quality of the data or used meta-analysis to synthesize treatment effects. All 4 types of uncertainty were not considered. There is a need for a rigorous methodological approach and more transparency in reporting modeling studies. These issues should be addressed in future studies for the appropriate development of economic models.

The present review has some limitations that should be pointed out. The review included only 6 studies on *RAS* mutation analysis in mCRC patients. Nevertheless, the studies are of good quality, as underlined by the QHES assessment. The detailed therapeutic regimens and model parameters varied among studies, contributing to the heterogeneity of the results; thus, a meta-analysis was not performed. Consequently, publication bias could not be investigated; this is also due to the lack of a registry of model-based economic evaluations reporting on previous studies or those currently underway.[53]

Conclusions

The treatment pattern for mCRC is rapidly shifting to a more personalized approach, which is essential if the use of inappropriate therapy, with its associated undesirable effects and high costs, is to be avoided. Although the strategies involving *RAS* testing and the use of monoclonal antibodies are expensive, the benefit is high because *RAS* mutational status is a negative predictive biomarker for anti-EGFR therapies in mCRC patients. In recent years, newer targeted therapies with better outcomes for mCRC patients have been approved (eg, trifluridine-tipiracil, pembrolizumab),[54] but their application can increase treatment costs substantially; thus, the cost of targeted therapies needs to be significantly reduced for their integration into routine clinical practice.[55,56]

The economic evaluations, although of good quality, do not fully adhere to international recommendations regarding the assessment of mutational status before therapy with biological agents. Future economic assessments should consider *NRAS* mutation analysis and other parameters that reflect the real world, such as toxicity of biological agents, the sensitivity and specificity of genetic tests, and ethical, legal, and social issues relating to genome sequencing. International guidelines should consider the economic aspects of treatment strategies because the financial outcomes of healthcare services should not be disregarded. Adherence to guidelines for modeling studies and to clinical guidelines for the management of mCRC patients could enhance the accuracy of economic evaluations, which are essential for

guiding policy makers and clinicians in the selection of appropriate genomic applications.

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Supplemental Materials

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