Clinical Cancer Research

Predictive Biomarkers and Personalized Medicine

KRAS and *BRAF* Mutation Analysis in Metastatic Colorectal Cancer: A Cost-effectiveness Analysis from a Swiss Perspective

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Abstract

Purpose: Monoclonal antibodies against the epidermal growth factor receptor (EGFR), such as cetuximab, have led to significant clinical benefits for metastatic colorectal cancer (mCRC) patients but have also increased treatment costs considerably. Recent evidence associates *KRAS* and *BRAF* mutations with resistance to EGFR antibodies. We assessed the cost-effectiveness of predictive testing for *KRAS* and *BRAF* mutations, prior to cetuximab treatment of chemorefractory mCRC patients.

Experimental Design: A life-long Markov simulation model was used to estimate direct medical costs (€) and clinical effectiveness [quality-adjusted life-years (QALY)] of the following strategies: KRAS testing, KRAS testing with subsequent BRAF testing of KRAS wild-types (KRAS/BRAF), cetuximab treatment without testing. Comparison was against no cetuximab treatment (reference strategy). In the testing strategies, cetuximab treatment was initiated if no mutations were detected. Best supportive care was given to all patients. Survival times/utilities were derived from published randomized clinical trials. Costs were assessed from the perspective of the Swiss health system.

Results: Average remaining lifetime costs ranged from €3,983 (no cetuximab) to €38,662 (no testing). Cetuximab treatment guided by KRAS/BRAF achieved gains of 0.491 QALYs compared with the reference strategy. The KRAS testing strategy achieved an additional gain of 0.002 QALYs compared with KRAS/BRAF. KRAS/BRAF testing was the most cost-effective approach when compared with the reference strategy (incremental cost-effectiveness ratio: €62,653/QALY).

Conclusion: New predictive tests for KRAS and BRAF status are currently being introduced in pathology. Despite substantial costs of predictive testing, it is economically favorable to identify patients with KRAS and BRAF wild-type status. *Clin Cancer Res; 17(19); 6338–46. ©2011 AACR.*

Introduction

Despite substantial progress in surgery and chemotherapy treatments, patients with metastatic colorectal cancer (mCRC) generally have a poor prognosis. Monoclonal antibody (mAb) therapy targeted against the epidermal growth factor receptor (EGFR), for example, cetuximab (Erbitux; Merck KGaA) has led to significant clinical benefits in mCRC patients (1). Overexpression and activation of EGFR and transduction of activation signal play an important role in tumor progression (2, 3). Recent evidence suggests that genetic alteration of downstream regulator proteins such as KRAS and BRAF are associated with lack of response to antibody therapy (4–10). Prevalence of the KRAS proto-oncogene in mCRC is 30% to 45% (6, 11–14), whereas about 10% of wild-type KRAS tumors show BRAF-V600E (*BRAF*) mutation (13, 15). Mutations in *KRAS* and *BRAF* occur in a mutually exclusive manner in CRC cells (16).

KRAS and *BRAF* gene status can be assessed by formalin-fixed, paraffin-embedded tissue. Several methods are available to detect oncogenetic mutations of *KRAS* and *BRAF* such as, for example, direct dideoxy sequence analysis (sequencing method), pyrosequencing or allele-specific real-time PCR or others (17–21). However, the cycle sequence method is the "gold standard" for KRAS analysis (22). In Swiss laboratories, DNA sequencing after Sanger (dye terminator cycle sequencing) is generally used (23). Given high sensitivity and perfect specificity of these assays, false-negative or false-positive results are scarce, but cannot be ruled out entirely.

Recently, the American Society of Clinical Oncology issued a provisional clinical opinion on testing for *KRAS* mutation in mCRC patients, stating that *KRAS* mutation

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Translational Relevance

Markers with a high predictive value, such as *KRAS* and *BRAF* gene mutations, can help identifying patients who are likely or unlikely to benefit from antiepidermal growth factor receptor drugs such as cetuximab. Currently, no data is available on the health economic implications of testing for *KRAS* and/or *BRAF* gene mutations prior to cetuximab treatment of metastatic colorectal cancer patients. Using state-of-the-art health economic methodology, this study is dealing with the current lack of economic data on this topic which is of highest relevance for oncologists, pathologists, and health policy makers. The model can also be used for comparable decision problems arising with other predictive tests in pathology.

should be assessed in patients with mCRC who are candidates for EGFR antibody therapy (24). In case of a *KRAS* mutation, antibody treatment should not be administered (24). However, international guidelines for carrying out and assessing *KRAS* mutations are still being developed (25). Testing for *BRAF* mutation has just started in some laboratories. Recent clinical evidence supports *BRAF* mutation analysis, although the available testing procedures are fairly expensive.

Predictive testing helps selecting the treatments that patients will most benefit from. Additional costs of novel predictive tests such as KRAS and BRAF have to be balanced against cost savings associated with avoiding treatment of patients who will predictably not respond to antibody treatment. Markov models have already been used in the metastatic breast cancer setting to measure the cost-effectiveness of different testing strategies (26, 27). However, the economic consequences of testing for *KRAS* and/or *BRAF* mutations in mCRC patients have not yet been studied. The objective of this analysis is to assess the cost-effectiveness of testing for *KRAS/BRAF* mutations, prior to cetuximab treatment of chemorefractory mCRC patients, from a Swiss health care system perspective.

Methods

Overview of mCRC disease model

On the basis of a previously used modeling framework (28), we constructed a Markov state transition model with an 1-month cycle length to assess the economic consequences associated with each testing strategy. Effectiveness was assessed in terms of quality-adjusted life-years (QALY). On this basis, incremental cost-effectiveness ratios (ICER) were calculated. The time horizon of the analysis was life long.

Costs were assessed from the perspective of the Swiss health care system. Accordingly, nonmedical direct costs and indirect costs were not taken into account. Direct medical costs included drug costs, costs for predictive testing (where applicable), diagnostic procedures, and hospitalization. Costs and effects were discounted at an annual rate of 3% (29). Costs are expressed in Euros (€). An exchange rate of €1.00 = CHF1.50 was used (February 2010).

The Markov model was implemented in TreeAge Pro 2009 (TreeAge Software Inc.).

Patient population studied

The model followed a hypothetical cohort of chemorefractory, mCRC patients aged 50 years (45% female, 55% male; ref. 30). It was assumed that 70% of patients were wild-type KRAS and that 8% of this group (6% of the total) had a *BRAF* mutation status (8, 16, 31, 32). The eligibility criteria of our patient population were defined by the phase III National Cancer Institute of Canada Trial Group CO.17 (CO.17) study (33). In brief, patients had advanced CRC (Eastern Cooperative Oncology Group performance status 0–2) with immunohistochemically detectable EGFR expression. They were chemorefractory and no other anticancer therapy was available (33). The influence of all-cause mortality on the survival experience of the cohort was modeled using Swiss life tables (34).

Strategies compared

Following testing strategies were assessed: KRAS alone and a sequential approach with BRAF testing of all KRAS wild-type patients. Patients with KRAS wild-type (in the KRAS alone strategy), or with KRAS wild-type/BRAF wild-type status, received cetuximab. Best supportive care (BSC) was administered to patients with *KRAS* or *BRAF* mutation. Costs and effects of the no cetuximab treatment strategy served as reference values. Administering cetuximab to the entire patient population without prior predictive testing (no-testing strategy) was added to estimate the overall benefit of predictive testing.

The occurrence of false-positive and false-negative test results may have severe consequences for the affected patients. Information on sensitivity and specificity of mutation analyses (sequencing method) were derived from published literature (22). The probabilities of false-positive and false-negative test results were assumed to be the same for KRAS and BRAF, each taken by itself. Sensitivity and specificity of the KRAS and BRAF testing strategy were evaluated according to the "believe-the-positive" approach, that is, the combined result was positive if 1 test indicated a positive result (mutation). Both tests were regarded as conditionally independent (Table 1; ref. 35).

Disease stages and clinical data sources

The Markov model comprised 3 commonly exhaustive and mutually exclusive health states: stable/responsive disease, disease progression, and death. All patients entered the model in the stable state and they could remain stable or progress. Patients with progressive disease could remain in this state or die (Fig. 1).

Clinical event rates for all patients under cetuximab or BSC were assessed from median times to progression and median times to death, as observed in the phase III

Table 1. Strategies and characteristics of predictive tests

Test strategy	Test result	Treatment	Sensitivity (95% CI)	Specificity (95% CI)	Ref.
KRAS	KRAS wt	CET	0.955 (0.917–0.979)	0.997 (0.982–1.0)	22
	KRAS mt	BSC			
KRAS and BRAF[a]	KRAS wt/BRAF wt	CET	0.998 (0.993–0.9996)	0.994 (0.964–1.0)	22, 35
	KRAS wt/BRAF mt	BSC	0.998 (0.993–0.9996)	0.994 (0.964–1.0)	
	KRAS mt	BSC	0.955 (0.917–0.979)	0.997 (0.982–1.0)	
No test	–	All CET	–	–	–
No CET (no test)[b]	–	All BSC	–	–	–

Abbreviations: CET, cetuximab; Mt, mutant; wt, wild-type.
[a]BTP: Believe the positive. One positive test result is sufficient for an overall positive result. The overall result is negative if both tests are negative.
[b]Reference strategy.

randomized CO.17 trial (32, 33), which compared BSC plus cetuximab with BSC. As an exception, event rates for patients with a *BRAF* mutation status under cetuximab treatment were extracted from a retrospective analysis of mCRC patients treated with cetuximab plus chemotherapy (36). We assumed that patients with *BRAF* mutation receiving BSC would have the same event rates as patients with a *KRAS* mutation in the CO.17 BSC arm (Table 2). The treatment effect, namely transition probabilities for patients with KRAS wild-type and *KRAS* mutation, was hence modeled dependent on mutation status and treatment given (4–6, 9, 32). HRs were assumed to be constant [HR $= -\ln(0.5)$/median survival time]. An exponential shape of the survival curves was assumed. Transition probabilities were estimated from these rates using the standard formula, that is, $1 - e^{(-\text{rate}*\text{time})}$.

Utilities

Preference-based measures of health-related quality of life were available from the CO.17 study. They were prospectively collected using the self-reported Health Utility Index Mark 3 questionnaire (37, 38). Mean utility in the wild-type cetuximab group (stable disease state, responding to treatment) was 0.72 (CI: 0.49–0.95) at baseline and increased over time (0.77; CI: 0.55–0.99 at week 24). Mean utility in the BSC group was 0.71 (CI: 0.47–0.95) at baseline and decreased over time (0.70 at week 24; CI: 0.56–0.94; ref. 38). In our model, the latter values were applied to both wild-type and mutant patients in the stable disease state without cetuximab treatment and to mutant patients with cetuximab. For patients in the progression state, a value of 0.5 (0.45–0.72) was assumed, as reported earlier in European studies (39, 40).

Medical resource use

Best supportive care. BSC was given to all patients. Given that patients were assumed to be chemorefractory, BSC therapy consisted mainly of palliation of symptoms and improvement of quality of life (33, 41). Concomitant therapy (antibiotics, opiates, steroids, antithrombotics, antidiarrheals, antiemetics, and blood formation products) and episodes of hospitalization were assumed to be the same for all patients during a given period of time (e.g., month of follow-up; ref. 38). Quantities of medical interventions such as diagnostic and therapeutic interventions were assessed on the basis of published literature (38). Length of average hospital stay for colorectal patients was based on data provided by the Swiss Federal Statistical Office (Supplementary Appendix S1).

The model considered differences in medical resource use between the treatment groups (reference and cetuximab group) which arose from different survival times.

Reference group. All patients in the reference strategy (no cetuximab) received BSC only (as described above). Concomitant therapy, diagnostic ultrasound, and palliative surgery including hospitalization were used in these patients. For the evaluation of disease status, all patients had a monthly medical consultation, chest radiologic imaging and cross-sectional imaging every 8 weeks, and a MRI at baseline (Supplementary Appendix S1; ref. 33).

Cetuximab group. Patients with wild-type KRAS/BRAF status received BSC (as described above) plus cetuximab; in the no-testing strategy all patients received BSC plus cetuximab. Cetuximab was given until disease progression or intolerable toxicity. For tumor evaluation, diagnostic tests were used as described above (Supplementary Appendix S1; ref. 33). The cetuximab treatment group was assumed to have physician outpatient assessments every week due to the infusion schedule of the drug. The dosing regimen of cetuximab matched the treatment schedule described elsewhere (32, 33). An intravenous loading dose of 400 mg/m^2 body surface area was followed by a weekly maintenance dose of 250 mg/m^2. Adjusting for the gender distribution in Swiss incident cases (30), the model assumed a loading dose and a maintenance dose of 706 and 441 mg, respectively. Administration costs for drug infusion were taken into account.

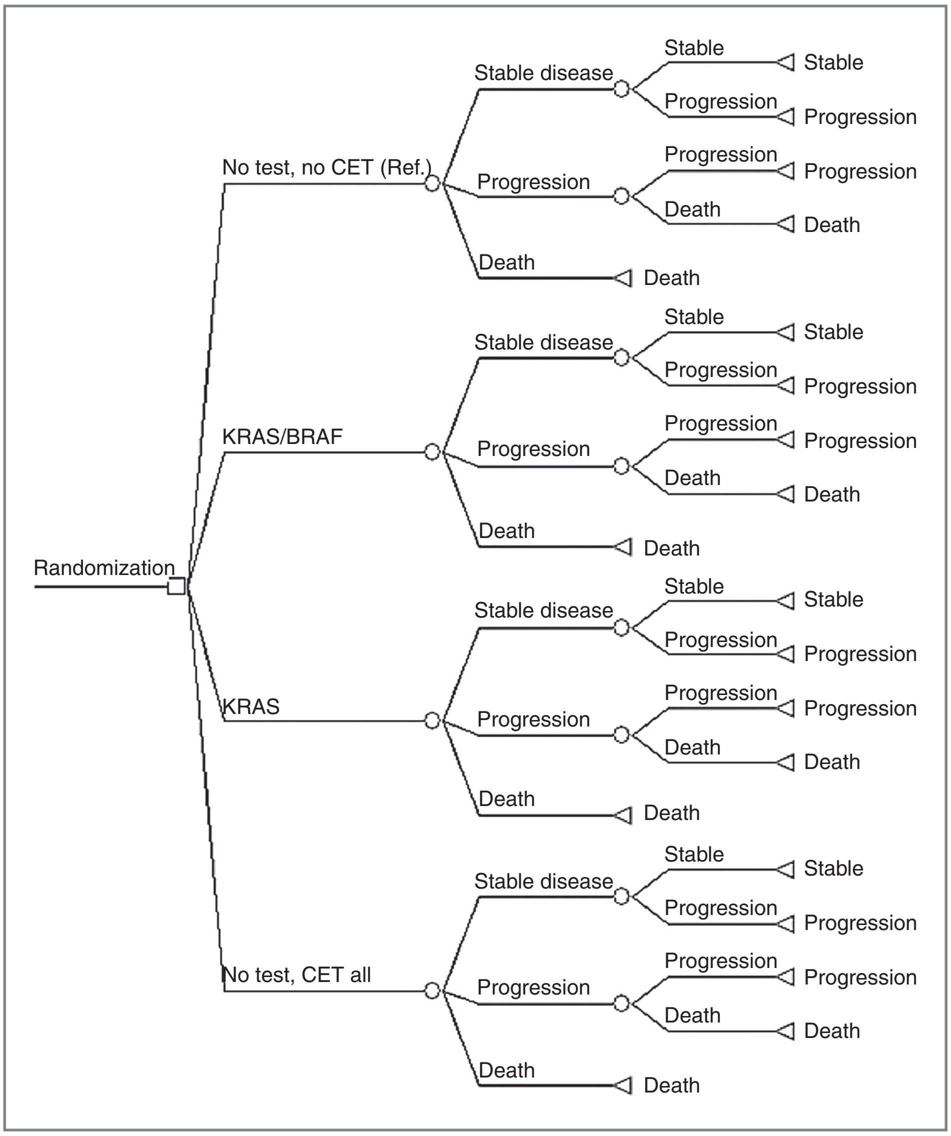

Figure 1. Overview of Markov model. CET, cetuximab; Ref, reference strategy.

Unit costs

Costs for laboratory tests, diagnostic interventions, and drug administration time were estimated on the basis of resource utilization and were multiplied by unit costs drawn from the official Swiss tariff list (Tarmed; ref. 42). Drug costs were based on official Swiss pharmacy prices (Supplementary Appendix S1; ref. 43). Average hospital length of stay was obtained from Swiss hospital statistics (44, 45). According to the Swiss Federal Office for Statistics, 50% of hospital per diem costs were paid by Statutory Health Insurance, the rest is covered by cantonal authorities (45, 46). Hence, the hospitalization costs were computed on this basis (case-based lump sum €1,127 plus daily rate of €152; ref. 44). Concomitant therapy was assumed to be the same for all patients, hence those costs were not included (38).

Sensitivity analysis

Deterministic sensitivity analysis. One-way sensitivity analyses assessed the robustness of the base-case results. Parameters subject to statistical uncertainty (utility values, sensitivity, and specificity of mutation analyses) were varied within their 95% CIs (47). The prevalence of *KRAS* and *BRAF* mutations was varied between 0.25 to 0.40 (17, 48) and 0.05 to 0.22 (15, 49), respectively. Parameters representing overall survival and progression-free survival were assessed by varying the underlying median times to event by ±25% or within their 95% CIs if available. Where 95% CIs were available, we checked whether such variation by ±25% would have been adequate. It was found to be a slightly conservative approach that rather overestimated the uncertainty in the survival time parameters.

Variables not subject to statistical uncertainty were considered in scenario analyses. Variables with direct impact

Table 2. Clinical input parameters: survival according to mutation status and treatment strategy

Mutation status				Ref.			Ref.
	KRAS	wt			wt	mt	
	BRAF	wt	mt		-	-	
Median OS (mo)	CET	13.0	6.5	36	9.5	4.5	32
	BSC	4.8	4.6	32	4.8	4.6	32
Median PFS (mo)	CET	7.0	2.0	36	3.7	1.8	32
	BSC	1.9	1.8	32	1.9	1.8	32

Abbreviations: CET, cetuximab; Mt, mutation; wt, wild-type; PFS, progression-free survival; OS, overall survival.

on the ICER were varied by ±30%: costs of cetuximab, of mutation analyses, and of palliative care of metastatic disease. Medical resource use (diagnostic interventions) was varied in the BSC group only. Discount rates of 0% and 6% were additionally assessed.

Probabilistic sensitivity analysis. Probabilistic sensitivity analysis (PSA; second-order Monte Carlo simulation) estimated overall parameter uncertainty around the base case by using 10,000 sets of parameter values, which were randomly sampled from statistical distributions reflecting the ranges of variation used in deterministic sensitivity analysis (50). Beta distributions were used for *KRAS/BRAF* mutation prevalence, and test sensitivity and specificity and utility during stable disease and after progression. Gamma distributions were used for median survival times and median time to progression. Unit costs were not subject to uncertainty and not included in the PSA (42).

Results

Base-case analysis

Cost. In the base-case analysis, the addition of cetuximab to BSC increased costs considerably. As cetuximab use was restricted to patients who benefited most from therapy, the increase in costs in the testing strategies was distinctly lower than in the no-testing strategy. The costs of mutation analysis (€394 per analysis) were overcompensated by savings associated with the restriction of cetuximab administration to expected responders. Average lifetime per-patient costs were €34,771, €35,361 and €38,662 in the KRAS/BRAF, KRAS, and no-testing strategies, respectively. If KRAS/BRAF testing was used, per-patient savings would be €590 and €3,301 compared with KRAS testing and the no-testing strategy (Table 3).

Effect. Given imperfect sensitivity and specificity of the mutation analyses, different testing strategies led to different clinical outcomes (Table 1). Some patients had false-negative or false-positive results and hence, received cetuximab or BSC treatment inappropriately, translating into QALY loss. Accordingly, the no-testing strategy led to the highest QALY result (0.947 QALYs per patient). The KRAS/BRAF and KRAS testing strategies accrued 0.934 and 0.936 QALYs, respectively. The lowest result was observed in the reference strategy with no cetuximab use (0.443 QALYs; Table 3).

Incremental cost-effectiveness. The least costly and least effective approach was the reference strategy (no cetuximab) (Table 3). Testing for *KRAS* and *BRAF* mutations led to average per-patient costs of €30,788 and a quality-adjusted survival time of 0.491 QALYs, translating into an ICER of €62,653 per QALY gained, compared with no cetuximab. Testing for KRAS only led to an ICER of

Table 3. Base-case cost-effectiveness analysis of different testing strategies

Test strategy	Lifetime cost per person	Lifetime efficacy	Incremental costs[a]	Incremental efficacy[a]	ICER
Unit	€	QALY	€	QALY	€/QALY
Reference (No CET, no test)	3,983	0.4430	–	–	–
KRAS and BRAF	34,771	0.934	300,788[b]	0.491[b]	62,653[b]
KRAS	35,361	0.936	590[c]	0.002[c]	313,537[c]
No test	38,662	0.947	3,301[d]	0.010[d]	314,588[d]

Abbreviations: CET, cetuximab; ICER, incremental cost-effectiveness ratio.
[a]Relative to the strategy with the next lower cost.
[b]Compared with the reference strategy (no CET).
[c]Compared with KRAS/BRAF.
[d]Compared with KRAS.

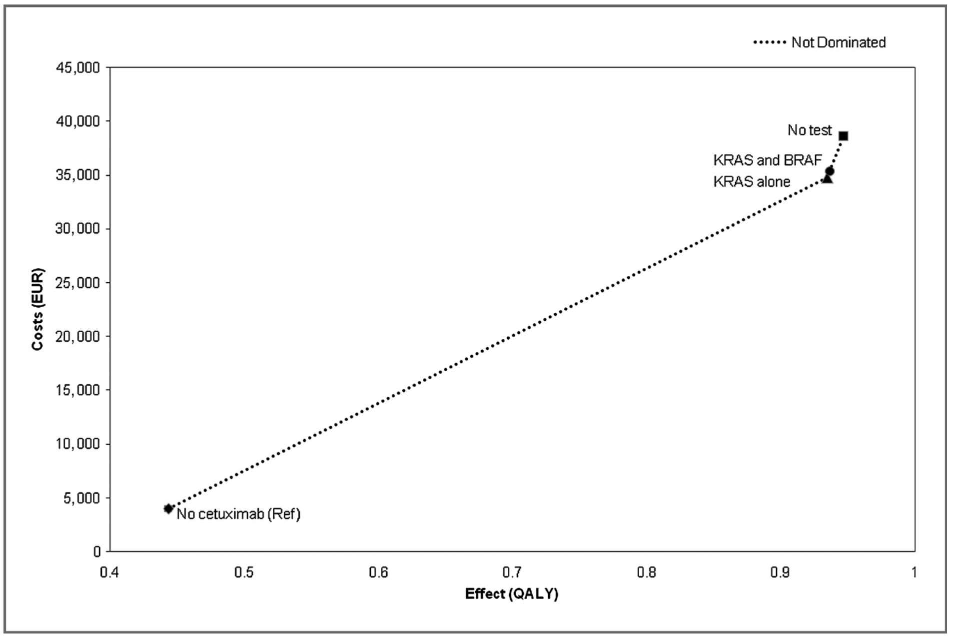

Figure 2. Base-case cost-effectiveness analysis. CET, cetuximab; Ref, reference strategy.

€313,537 per QALY versus KRAS and BRAF testing. The regimen with no predictive testing showed an even less favorable ICER (€314,588 per QALY vs. KRAS; Fig. 2).

In Switzerland, about 4,011 new CRC patients are registered annually (average 2,003–2,006; ref. 30). If 25% (1,003) of these patients developed metastatic disease (51, 52), KRAS and BRAF testing would lead to annual direct cost savings of €591,170 and a loss of 1.89 QALYs compared with KRAS. In comparison with no testing, KRAS and BRAF testing would save €3,902,673 and imply a loss of 12.41 QALYs, per year. Compared with the no cetuximab strategy, the usage of *KRAS* and *BRAF* mutation analysis, with subsequent cetuximab administration where indicated, would require an annual net investment of about €30.9 million to acquire a gain of 493 QALYs.

Sensitivity analysis

The results of the deterministic sensitivity analyses indicated that varying the overall survival of wild-type KRAS patients with BSC or the utility value for progressive disease had the strongest impact on the ICER (Supplementary Appendix S2a and b). The rank order of strategies was sustained in all situations assessed. The impact of the scenario analyses on ICER results was minor (Supplementary Appendix S3).

In PSA, KRAS and BRAF testing was the dominant strategy over a willingness to pay range of €10,000 to €40,000 per QALY gained. Beyond €40,000 per QALY, KRAS became the preferred strategy (Fig. 3). Further PSA results are presented in Supplementary Appendix S4.

Discussion

This work is the first study addressing the cost-effectiveness of predictive KRAS and BRAF testing, prior to cetuximab administration to mCRC patients. Testing for KRAS and BRAF status with subsequent cetuximab treatment of patients with confirmed wild-type showed the most favorable ICER, of €62,653 per QALY gained compared with no cetuximab use. Robustness of results was ascertained in a wide range of sensitivity analyses.

According to the revised prescribing information, mCRC patients with *KRAS* mutations are not recommended to receive cetuximab, as they are unlikely to benefit from anti-EGFR drugs (53). Given this, KRAS assessment is routine practice in Swiss pathology laboratories. Recently, testing for *BRAF* mutations has been introduced as a result of growing evidence of predictive and prognostic value in mCRC patients considered for antibody treatment (8, 16, 54, 55). Our results add to the rationale for these approaches.

Predictive tests need to have appropriate sensitivity and specificity. For KRAS and BRAF, sequencing analysis is frequently used, as was assumed in our model (56). Direct sequencing analysis is characterized by its potential to detect all mutations, leading to very high specificity (23). On the other hand, this method may feature a lack in sensitivity compared with other techniques (56). In consequence, some patients with *KRAS* or *BRAS* mutations may still receive anti-EGFR treatment.

Further EGFR downstream regulators have been associated with lack of response to mAbs in mCRC, for example, loss in PTEN expression (3) or *PIK3CA* mutation (57). However, the evaluation of PTEN requires more standardization and is not yet ready for the clinical setting (57, 58). Furthermore, the real predictive value of *PIK3CA* mutations is not firmly established (36). Due to the complexity of the signaling pattern, it is likely that future predictive test assays will include several molecular biomarkers before antibody treatment. The appraisal of costs and effectiveness of new test assays is a pending task.

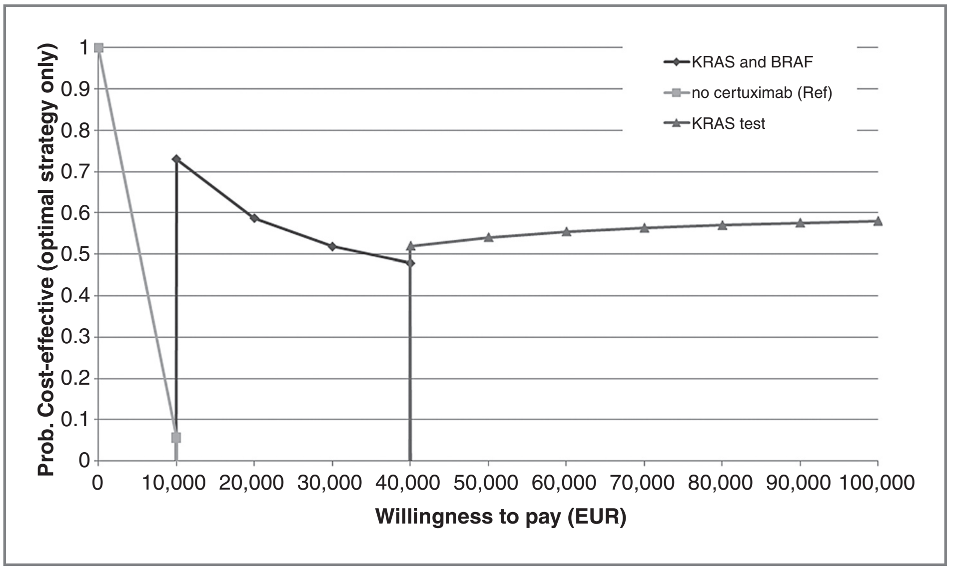

Figure 3. Probabilistic sensitivity analysis (acceptability frontier). The cost-effectiveness acceptability frontier shows the PSA-based probability of strategies being cost-effective. For different willingness to pay thresholds, different strategies are optimal. For each threshold, only the probability for the optimal strategy is shown. The no-testing strategy is not displayed in the figure. Ref, reference strategy; prob, probability.

Cost-effectiveness thresholds for clinical interventions vary between countries. Threshold values of $50,000 to $100,000 (€38,500–€77,000) per QALY gained (United States) or £20,000 to £30,000 (€23,000–€35,000) per QALY gained (United Kingdom) are regarded as realistic in the literature (59). However, Braithwaite and colleagues revealed that current resource allocation preferences among the population of the United States are not consistent with these thresholds (60). They estimated a social willingness to pay between $109,000 per QALY (€86,500 per QALY) and $297,000 per QALY (€235,600 per QALY) when considering the impact of health care on quality as well as quantity of life. Also, it can be assumed that the U.K. thresholds (National Institute for Health and Clinical Excellence) are stricter than the limits usually accepted in Switzerland.

Mittmann and colleagues conducted an economic evaluation of cetuximab therapy for mCRC patients (38). In a subanalysis, they assessed cetuximab versus BSC in KRAS wild-type patients. The resulting ICER of €144,360 (CI: €100,737–€258,896) per QALY gained is unfavorable compared with our result. The authors found a QALY difference of 0.18, which is about half of our estimated QALY gain. A likely reason for this apparent discrepancy is that Mittmann and colleagues restricted the time horizon of their analysis to the observation period of the CO.17 trial (18–19 months, during which 77% and 82% patients in the cetuximab and BSC arms died, respectively; refs. 33, 38). In contrast, our model used a life-long time horizon, in line with good health economic practice for the assessment of interventions with life-long consequences or an impact on survival (61). Taking into account the full survival experience of all patients inclusive of longer-term survivors, using appropriate modeling techniques, lead to a higher accumulation of QALYs gained and is likely to explain our more favorable ICER results. A further health economic analysis found an ICER of about €70,000 per QALY for cetuximab in combination with chemotherapy (41). This analysis did not differentiate between *KRAS* mutant and wild-type patients, although it was mentioned by the authors that factors specific to the patient population should be considered.

Some limitations of our study are related to data availability. Starting with a clearly defined patient population, we tried to identify the most appropriate model inputs currently available from the literature. However, clinical evidence from biomarker-based randomized trials is scarce in the CRC setting. Hence, clinical and utility data originated from few studies conducted outside Switzerland (8, 32, 33, 38). It is our understanding that the clinical data sources used in the model are the most appropriate ones that are available from the published literature. Evidence on clinical effectiveness stems from a subgroup analysis of patients recruited to the prospective randomized clinical trial by Karapetis and colleagues (32), as well as from a retrospective analysis (De Roock) (36). The event rates (median overall and progression-free survival) for BRAF wild-type/mutation seen in the latter study are consistent with other, smaller studies (8, 62). All of these studies enrolled chemorefractory advanced CRC patients that were treated with BSC or cetuximab plus BSC. On the basis of the baseline characteristics of these studies, the patient collectives can be assumed to be comparable. Given the uncertainty present in the trial data, and potentially limited transferability to routine clinical practice populations, extensive sensitivity analyses have been carried out.

Available quality of life and utility data allowed to differentiate on the basis of cetuximab treatment versus BSC but not on the basis of mutation status. Given that both *BRAF* and *KRAS* mutation is associated with a similar lack of response to cetuximab, similar quality of life was assumed in nonresponders as in BCS-treated patients. Furthermore, differences in QALY results originated mainly from differences in survival time due to mutation status and treatment given. This instance has been fully incorporated into our analysis. Utility values had to be drawn from non-Swiss sources, although there might be some differences in clinical treatment schedules or perception of quality of life. In particular, the utility value for progressive disease had a substantial influence on the main ICER result, although it did not change the final conclusion. While being aware of this limitation, we included the foreign data as the best available source of clinical evidence. Information on clinical resource use was primarily clinical trial based, and deviations from routine practice patterns may have occured. However, varying the use of diagnostic procedures in the BSC group did not impact the main result.

Of note, this economic analysis is focusing on patients with late-stage, chemorefractory cancer. Latest evidence implies that cetuximab first-line treatment of mCRC leads to significant response in KRAS/BRAF wild-type patients (63). However, *BRAF* mutation seemed to have no impact on response to the antibody, suggesting that *BRAF* mutation may not have the same predictive value in first-line and chemorefractory tumors.

In conclusion, testing for *KRAS* and *BRAF* mutations prior to cetuximab treatment of chemorefractory mCRC patients is clinically appropriate and economically favorable, despite high costs for predictive testing.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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