Cost-Effectiveness Analysis of Screening for KRAS and BRAF Mutations in Metastatic Colorectal Cancer

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Background
In 2009, the American Society of Clinical Oncology recommended that patients with metastatic colorectal cancer (mCRC) who are candidates for anti-epidermal growth factor receptor (EGFR) therapy have their tumors tested for KRAS mutations because tumors with such mutations do not respond to anti-EGFR therapy. Limiting anti-EGFR therapy to those without KRAS mutations will reserve treatment for those likely to benefit while avoiding unnecessary costs and harm to those who would not. Similarly, tumors with BRAF genetic mutations may not respond to anti-EGFR therapy, though this is less clear. Economic analyses of mutation testing have not fully explored the roles of alternative therapies and resection of metastases.

Methods
This paper is based on a decision analytic framework that forms the basis of a cost-effectiveness analysis of screening for KRAS and BRAF mutations in mCRC in the context of treatment with cetuximab. A cohort of 50,000 patients with mCRC is simulated 10,000 times, with attributes randomly assigned on the basis of distributions from randomized controlled trials.

Results
Screening for both KRAS and BRAF mutations compared with the base strategy (of no anti-EGFR therapy) increases expected overall survival by 0.034 years at a cost of $22,033, yielding an incremental cost-effectiveness ratio of approximately $650,000 per additional year of life. Compared with anti-EGFR therapy without screening, adding KRAS testing saves approximately $7500 per patient; adding BRAF testing saves another $1023, with little reduction in expected survival.

Conclusions
Screening for KRAS and BRAF mutation improves the cost-effectiveness of anti-EGFR therapy, but the incremental cost effectiveness ratio remains above the generally accepted threshold for acceptable cost effectiveness ratio of $100,000/quality adjusted life year.

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against EGFR that was approved in 2006 (16). Bevacizumab, a monoclonal antibody that inhibits the function of vascular endothelial growth factor (VEGF), was approved by the FDA in 2004, for first-line treatment in patients with mCRC. In 2006, following a trial (E3200) demonstrating a statistically significant difference in overall survival (13.0 months vs. 10.8 months) between patients on 5-FU + folinic acid + oxaliplatin (FOLFOX4) and bevacizumab and those on FOLFOX4 only, the FDA extended approval for its use as second-line therapy with 5-fluorouracil-based chemotherapy (17). On the other hand, the effect on overall survival of genetic mutations in the serine/threonine-protein kinase B-Raf (BRAF-V600, or BRAF) is unclear (4,18,19). Patients with BRAF mutations appear to have a poorer prognosis. Retrospective subset analyses suggest that, regardless of BRAF status, patients might benefit from anti-EGFR therapies in the first-line setting. There appears to be no benefit after the patient has progressed after first-line therapy (4). KRAS and BRAF mutations are mutually exclusive in individuals. Both carry additional potential harms (16,20).

In 2009, the American Society of Clinical Oncology issued a provisional clinical opinion recommending that all patients with mCRC who are candidates for anti-EGFR treatments have their tumors tested for KRAS mutations (21). Screening for and then limiting anti-EGFR therapy to those without KRAS mutations is aimed at providing the treatment to those who are likely to benefit from it while avoiding unnecessary costs and harm to those who are not likely to benefit. Anti-EGFR treatments are provided to patients with both curative and palliative intent. In the case of treatments administered with a curative intent, the only potential cure is resection of the metastases. Such a successful cure carries additional costs. The monoclonal antibody treatments, especially anti-EGFR therapy, are considerably more expensive than other existing treatments (22,23). In addition, for many patients without a KRAS mutation who do receive anti-EGFR treatment, there may be no meaningful gain in terms of length of survival and only harmful side effects and expenses. In the case of BRAF screening, an economic analysis is warranted to understand the effect of poorer prognosis and lack of effect following progression after first-line treatment.

Blank et al. (24) reports cost-effectiveness analyses of screening for KRAS and BRAF mutations in mCRC in the Swiss health systems. They estimated anti-EGFR therapy combined with screening costs at $83 147 (€62 653) per quality-adjusted life year (QALY) saved. For the United States, it has been estimated that KRAS testing would save more than $700 million compared with providing anti-EGFR screening to all mCRC patients, excluding the costs of additional resections (25). Another study has also advocated the use of screening for KRAS mutations, with very accommodating break-even pricing of $3500 per screening (26). These studies lack transparency regarding how they analyze the treatments, resection of metastases, and survival for the different types of metastases. These aspects have major effects on the costs and effects in the analysis. This paper aims to evaluate the costs and effects of screening for KRAS and BRAF mutations in mCRC in the context of targeting the use of cetuximab to those without these mutations. The analysis uses the available evidence base, including the use of treatments, resection probabilities, and length of survival to create and calibrate a comprehensive analytical framework. Reported overall survival rates from different trials are used to develop best estimates to analyze the base case and conduct subsequent sensitivity analyses. The paper provides insight into the major costs in the treatment of mCRC, including resection costs, and clarifies the economic case for anti-EGFR therapy and associated screening in the United States.

Methods

This paper is based on a decision analytic framework. The framework forms the basis of a cost effectiveness analysis of undertaking screening for KRAS and BRAF mutations in mCRC in the context of treatment with cetuximab. The framework operates within a rich probability structure that “creates” individual patient profiles from probability distributions and passes them through treatment regimens to analyze costs and effects. The parameters in the analytical framework are based on the available evidence from clinical trials and other literature in clinical oncology. The framework is designed to provide answers to questions about the suitability of screening mCRC patients for KRAS and BRAF genetic mutations under varying circumstances.

Outcomes Evaluated

Our primary outcome of interest is overall survival, which, in a setting comparing a base strategy to alternatives, is measured in terms of life years saved (LYS) through the implementation of the alternatives. Average LYS and costs are calculated in 10 000 simulations, each with 50 000 mCRC patients. Separately, the two averages provide comparison of health impact and costs among strategies, and combined they provide the incremental cost-effectiveness ratio (ICER) in terms of US Dollars per LYS: ICER = (Cost of Strategy1 – Cost of Strategy2) / (Effect of Strategy1 – Effect of Strategy2).

Model Structure

We compared four strategies (Figure 1): No anti-EGFR therapy (best supportive care); anti-EGFR therapy without screening; screening for KRAS mutations only (before providing anti-EGFR therapy); and screening for KRAS and BRAF mutations (before providing anti-EGFR therapy). These strategies are evaluated in the context of two broad strategies of treatments: anti-EGFR and best supportive care, which can include all treatments other than anti-EGFR, such as chemotherapy, radiotherapy, anti-VEGF, and surgery. Anti-EGFR and anti-VEGF strategies or paths of treatment will include lines of treatment that might belong to the other types of strategies of treatments. None of these treatments by themselves can “cure” mCRC. Only complete resection may cure it. These treatments are aimed at either increasing the possibility of resecting the metastasis or providing palliative care. Although we include BRAF testing in the last strategy, evidence suggests that tumor BRAF mutation status does not predict response to treatment (like KRAS) but is simply a predictor of poor survival, independent of anti-EGFR therapy (4, 27). This strategy is included to test the potential contribution of BRAF testing if BRAF mutation proves to predict anti-EGFR therapy effectiveness.

A cohort of patients with mCRC is simulated with attributes randomly assigned based on distributions from available randomized controlled trials. The initial randomly assigned attributes include the nature of metastases (synchronous lung and liver, metachronous lung and liver, synchronous abdominal and peritoneal metastases,
and initial resectability), weekly transition probabilities for survival and treatment, and weekly costs. Along the treatment paths, a patient can enter the following states: anti-EGFR treatment, anti-VEGF treatment, oxaliplatin- or irinotecan-based treatments, surgery, surveillance, or death. As in a typical decision analysis, death is an “absorbing” state that forms the end of tracking a simulated patient. Patients can enter, leave, and reenter the other states based on conditional transition probabilities. Patients can transition on a weekly basis (ie, model cycle length = 1 week).

The values of parameters needed for the various lines of treatment are estimated using observations from randomized controlled trials. The model is calibrated such that the overall survival for different strategies built on the observations and probabilities for treatments and resections should not be statistically significantly different from findings in randomized controlled trials.

Chemorefractory patients are eligible for anti-EGFR therapy. We do not differentiate between the cumulative toxicities of non-cetuximab treatments, which can inhibit their repeated usage in different combinations. The model’s parameters and the values used in the analysis are provided in Table 1.

Clinical Inputs

**Treatment sequence and curative vs palliative pathways.** The model does not differentiate between the effectiveness of the sequence in which the different treatments are administered, as exposure to chemotherapy itself appears to be more important than the sequence (28, 29). Nor does the model differentiate between curative and palliative care. In all intervention strategies, all patients are eligible for anti-VEGF therapy. We identified no data indicating whether testing for KRAS or BRAF mutations influences the choice between curative and palliative paths, which are not well-differentiated in guidelines or practice. The model allows patients to undergo both neo-adjuvant and adjuvant treatments. In the case of neo-adjuvant treatments, we assume that the primary role of the treatment is to convert unresectable metastases of the liver to resectable ones.

**Figure 1.** Markov model of disease progression and treatment in metastatic colorectal cancer. Clone 1, Clone 2 are clone copies of the master clone subtrees 1 and 2, indicated by the respectively numbered heavy lines. The clone copies have the same structure as but can have different calculations from the master clone subtrees. Legend: □ Terminal node (the outcome because of following a path); □ Logical node (logical decisions are made based on logical structure in the node); □ Markov node (indicates the presence of a hidden or shown Markov subtree at the node); □ Decision node (indicates the point of decision, which in our case is choosing between the four strategies); KRAS = V-Ki-ras2 Kirsten rat sarcoma viral oncogene homolog, BRAF = serine/threonine-protein kinase B-Raf, EGFR = epidermal growth factor receptor, VEGF = vascular endothelial growth factor.

**Metastases.** We incorporate three types of metastases: synchronous lung and liver, metachronous lung and liver, and synchronous abdominal and peritoneal metastases. Approximately 15% to 25% of patients with CRC present with synchronous liver cancer (4,5). Among those with mCRC, evidence supports the association of synchronous liver metastases with a worse prognosis than metachronous metastatic liver cancer (4). Nearly 50% of patients with metastatic CRC have either synchronous abdominal or peritoneal metastases, for which there is only palliative treatment. Chemotherapies. In the model, we also combine oxaliplatin-, irinotecan-, and capecitabine-based treatments into a single type of treatment. Combination treatments that use cetuximab with either oxaliplatin or irinotecan are considered anti-EGFR treatments. We include only cetuximab as an anti-EGFR treatment in the analysis because it is, by a wide margin, the most common anti-EGFR treatment used in the United States.
For patients following palliative treatment paths, the maximum survival is 28 months (30). For patients on curative treatment paths, the major factor driving survival rates is curative resection of the liver metastases. Studies providing an understanding of survival rates for patients under different types of treatments, independent of surgeries, are uncommon (9). Even with major advancements in treatment therapies for mCRC, the survival of patients in nonresected cases does not exceed 5 years. For patients who do not undergo any resection, nearly 2% survived for 3 years, but none were alive at 5 years (9,31). Of the patients who have undergone hepatic resection, 85%, 39%, 25%, and 11% are alive 1, 3, 5, or 10 years after the surgery, respectively (9,32–35).

#### Table 1. Model parameters*

<table>
<thead>
<tr>
<th>Parameters</th>
<th>Estimates base case</th>
<th>Values (in 2010 US$)</th>
<th>Estimates range (%)</th>
<th>Sources</th>
</tr>
</thead>
<tbody>
<tr>
<td>Proportion of patients with KRAS mutations</td>
<td>28%</td>
<td>–</td>
<td>25–60</td>
<td>(49, 50)</td>
</tr>
<tr>
<td>Proportion of patients with BRAF mutations</td>
<td>4%</td>
<td>–</td>
<td>3–10</td>
<td>(49, 50)</td>
</tr>
<tr>
<td>Proportion of patients with initially resectable</td>
<td>20%</td>
<td>–</td>
<td>10–25</td>
<td>(4, 9)</td>
</tr>
<tr>
<td>metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Proportions of patients with metachronous/synchronous</td>
<td>30%/20%/50%</td>
<td>–</td>
<td>†</td>
<td>(4, 10, 33, 34, 51-54)</td>
</tr>
<tr>
<td>synchronous abdominal-peritoneal metastases</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Median number of cycles of conversion therapy</td>
<td>22 cycles</td>
<td>–</td>
<td>†</td>
<td>(13)</td>
</tr>
<tr>
<td>Gap between treatment with bevacizumab and resection</td>
<td>6 weeks</td>
<td>–</td>
<td>†</td>
<td>(4)</td>
</tr>
<tr>
<td>of metastases (because bevacizumab increases the risk</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>of bleeding and hinders wound healing)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Interaction of KRAS mutation on chemotherapies’</td>
<td>No effect‡</td>
<td>–</td>
<td>4–21 decrease</td>
<td>(22, 55)</td>
</tr>
<tr>
<td>effectiveness</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Effect of cetuximab when KRAS mutation is present</td>
<td>No effect</td>
<td>–</td>
<td>†</td>
<td>(41)</td>
</tr>
<tr>
<td>Probability of conversion (to resectable) with:</td>
<td>14%/25%</td>
<td>–</td>
<td>14-3020-30</td>
<td>(13, 45, 56, 57)</td>
</tr>
<tr>
<td>Chemotherapy</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab and chemotherapy</td>
<td>14%</td>
<td>–</td>
<td>20</td>
<td>Interpolation; (4)</td>
</tr>
<tr>
<td>Maximum overall survival under palliative care</td>
<td>28 months</td>
<td>–</td>
<td>†</td>
<td>(30)</td>
</tr>
<tr>
<td>Probability of 1-, 3-, 5-, 10-year survival following hepatic resection</td>
<td>85%, 39%, 25%, and 11%</td>
<td>–</td>
<td>†</td>
<td>(32-35)</td>
</tr>
<tr>
<td>Recurrence after hepatic resection</td>
<td>46% within 12 months</td>
<td>–</td>
<td>†</td>
<td>(36)</td>
</tr>
<tr>
<td>Repeat hepatic resection rates</td>
<td>13%–83%</td>
<td>–</td>
<td>†</td>
<td>(38)</td>
</tr>
<tr>
<td>Third hepatic resections</td>
<td>16% of the patients who experienced recurrence had third hepatectomy 3–32 mo between second and third hepatectomy with a median of 13–15 mo</td>
<td>–</td>
<td>†</td>
<td>(32, 37, 38)</td>
</tr>
<tr>
<td>Costs</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Chemotherapy Rx costs per week</td>
<td>–</td>
<td>451</td>
<td>+50</td>
<td>(46)</td>
</tr>
<tr>
<td>(Costs proportioned according to the usage of</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FOLFOX, FOLFIRI and CapeOX)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cetuximab Rx costs per week (regular)</td>
<td>–</td>
<td>4180‡</td>
<td>+50</td>
<td>(46)</td>
</tr>
<tr>
<td>Cetuximab Rx costs per week (initial)</td>
<td>–</td>
<td>6653‡</td>
<td>+50</td>
<td>(46)</td>
</tr>
<tr>
<td>Bevacizumab + 5-FU Rx average costs per week</td>
<td>–</td>
<td>1278</td>
<td>+50</td>
<td>(46)</td>
</tr>
<tr>
<td>Physician costs of administering treatment per cycle</td>
<td>–</td>
<td>189</td>
<td>+50</td>
<td>(58)</td>
</tr>
<tr>
<td>Monitoring costs</td>
<td>–</td>
<td>77</td>
<td>+50</td>
<td>(58, 59)</td>
</tr>
<tr>
<td>Carcinoembryonic antigen (every 3 mo or 2 y; 6 mo for 3-5 y)</td>
<td>–</td>
<td>77</td>
<td>+50</td>
<td>(58, 59)</td>
</tr>
<tr>
<td>Chest, abdominal, and/or pelvic CT scan (every 3–6 mo for 2 y; 6–12 mo up to a total of 5 y)</td>
<td>–</td>
<td>1160</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Colonoscopy at 1, 3, and then every 5 y</td>
<td>–</td>
<td>706</td>
<td></td>
<td></td>
</tr>
<tr>
<td>KRAS screening costs</td>
<td>–</td>
<td>224</td>
<td>±50</td>
<td>(58)</td>
</tr>
<tr>
<td>KRAS + BRAF screening costs</td>
<td>–</td>
<td>303</td>
<td>±50</td>
<td>(58)</td>
</tr>
<tr>
<td>Hepatic surgery costs</td>
<td>–</td>
<td></td>
<td>±50</td>
<td>(48)</td>
</tr>
<tr>
<td>Hospital and professional costs</td>
<td>–</td>
<td>40 300</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mortality costs (in 5% cases)</td>
<td>–</td>
<td>20 657</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Morbidity costs (in 30% cases)</td>
<td>–</td>
<td>12 394</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

* FOLFOX = Leucovorin Calcium, Fluorouracil and Oxaliplatin; FOLFIRI = Leucovorin Calcium, Fluorouracil and Irinotecan Hydrochloride; CapeOX = Capecitabine and Oxaliplatin; Rx = Treatment; CT = Computed Tomography; – = not applicable.

† A blank cell in the “estimates range” column indicates that we used only the base case estimate of the variable in the analysis.

‡ Cetuximab is given in combination with chemotherapies, so there is at least the “standard” treatment effect of the chemotherapies given in combination. In this case, we used the cost of a cetuximab regimen, which includes irinotecan, every 2 weeks (4).

**Resection and Survival.** For patients following palliative treatment paths, the maximum survival is 28 months (30). For patients on curative treatment paths, the major factor driving survival rates is curative resection of the liver metastases. Studies providing an understanding of survival rates for patients under different types of treatments, independent of surgeries, are uncommon (9). Even with major advancements in treatment therapies for mCRC, the survival of patients in nonresected cases does not exceed 5 years. For patients who do not undergo any resection, nearly 2% survived for 3 years, but none were alive at 5 years (9,31). Of the patients who have undergone hepatic resection, 85%, 39%, 25%, and 11% are alive 1, 3, 5, or 10 years after the surgery, respectively (9,32–35).
In addition, these patients have nearly always experienced recurrence (13). From 10% to 25% of patients presenting with lung or liver cancer are initially resectable (4,9). For the remainder of the patients, depending on their suitability for potential conversion to becoming resectable, they undergo conversion therapies that can include the chemotherapies bevacizumab and cetuximab. A median of 22 cycles of treatments are needed for conversion to resectability. Conversion and resection are followed by recurrence in 46% of the patients within a year of the resection (36). In most cases, the first curative hepatic resection leaves the remainder of the liver unavailable for another resection. Still, a second resection and third resection are performed in 6% to 11% and 16% of the patients, respectively (32,37,38). Survival rates after the second hepatectomy are similar to the ones after the first hepatectomy (32). The estimates available for parameterizing a patient’s overall survival after having undergone treatments and monitoring vary considerably. Generally, randomized controlled trials report outcomes in two ways: the first is the proportion having that outcome (ie, alive or progression-free) at certain milestones (after 3, 5, or 10 years) or the median value of that outcome (ie, median survival time in months or years). We took advantage of the availability of two forms of survival data by parameterizing our model to the first set of expressions (proportion reaching a 3-, 5-, or 10-year milestone). We used the standard conversion technique of converting the percentage for a fixed period (say, 30% being alive at 3 years) to an annual rate, followed by a second conversion of the annual rate to a percentage for the desired period which, in our case, is a week (39). We used the second expression, median survival in months or years, as a calibration measure.

The overall survival rate varies considerably with trials. In non-cetuximab therapies, mean overall survival has been reported between 4.8 months and 20 months. In cetuximab-based therapies, mean overall survival varies between 8.1 months and 23.5 months (1,40-45). Such substantial variation is expected because patient profiles can vary considerably between trials. The primary source of variation, which appears to go unrecognized in such discussions, is likely to be the time of diagnosis of the metastases.

Cost Inputs

To approximate the market price of the chemotherapies, we used wholesale pricing estimated by the average selling price (46). To these we added the median Medicare average payment for physician services for administration of the chemotherapies (47). We test the sensitivity of the results to higher costs by increasing them by 50%. The costs are based on doses per 80 kg, 5 ft 11 in, body surface area 2.0 m2. Among chemotherapies, costs vary widely between therapies with and without capcitabine. Among HMO Research Network sites participating in the CERGEN study, we observed that nearly 15% of the patients with mCRC were given capcitabine-based therapies. Using this information and the treatment regimens recommended by the National Comprehensive Cancer Network, we created a weighted average of the cost of the treatments (4). Hepatic resection costs are prominent for being nearly a magnitude greater (48). Costs of postoperative morbidity, observed in 30% of the cases, and postoperative mortality, observed in less than 5% of the cases, were also included (48). All costs were inflation-adjusted to 2010 US dollars, and future costs and life years discounted at 3%.

Cost-Effectiveness Analysis

The analysis was conducted as a two-level simulation using TreeAge Pro 2009 Suite, TreeAge Software, Inc, Williamstown, MA (Figure 1). A cohort of 50 000 patients is analyzed 10 000 times. Each time the cohort is analyzed, the system records the mean values of several variables, including cost and overall survival. The 10 000 mean values of each variable are sufficient to derive statistical inference for the population (49). The model follows each patient for a maximum of 10 years. In addition to showing the broad Markov structure, Figure 1 also shows that the basic algorithm is the same for the screening strategies compared in the model. Sensitivity analyses are described in Supplementary Material (available online).

Results

Table 2 shows the details of costs and effects of three anti-EGFR interventions and no anti-EGFR. The interventions are listed in order of increasing effect, as is standard in cost-effectiveness league tables. Compared with testing only for KRAS, providing anti-EGFR therapy to all mCRC patients without testing increases survival by 0.0026 years and costs $7493 more, with an ICER of approximately $2.8 million/LYS. Screening for both KRAS and BRAF mutations prior to administering anti-EGFR therapy compared with the base strategy (of no anti-EGFR therapy), increases OS by 0.034 years and costs $650 000 per LYS. Looking at the results from a slightly different perspective, compared with providing anti-EGFR therapy without screening, adding KRAS testing alone saves $7493 per patient, and adding BRAF testing saves an additional $1023 with little reduction in expected survival.

Underlying the results in Table 2 are several processes and, therefore, costs associated with undertaking any strategy. To better understand these costs, we also analyzed how the different processes contribute to the costs when implemented across populations of patients in the model. When we do not provide any anti-EGFR treatment, the average resection cost is $8600, whereas the total

<table>
<thead>
<tr>
<th>Strategy</th>
<th>Cost over 10 years ($)</th>
<th>Incremental cost ($)</th>
<th>Effect (overall survival in years)</th>
<th>Incremental effect</th>
<th>ICER: $ per life year saved</th>
</tr>
</thead>
<tbody>
<tr>
<td>No anti-EGFR therapy</td>
<td>34 291</td>
<td>NA</td>
<td>0.6686</td>
<td>NA</td>
<td>NA</td>
</tr>
<tr>
<td>KRAS and BRAF screening with anti-EGFR therapy</td>
<td>56 324</td>
<td>22 033</td>
<td>0.7025</td>
<td>0.0340</td>
<td>648 396</td>
</tr>
<tr>
<td>KRAS screening with anti-EGFR therapy</td>
<td>57 348</td>
<td>1023</td>
<td>0.7029</td>
<td>0.0004</td>
<td>2 814 338</td>
</tr>
<tr>
<td>Anti-EGFR therapy without screening</td>
<td>64 841</td>
<td>7493</td>
<td>0.7055</td>
<td>0.0026</td>
<td>2 932 767</td>
</tr>
</tbody>
</table>
average costs are $34,291. When we screen for both KRAS and BRAF mutations, average resection costs are $11,500 out of total average costs of $56,234. When anti-EGFR therapy is provided without screening, average resection costs are $11,500 out of total average costs of $64,841, accounting for 2% of the increase in average costs (compared with the screening scenario). The vast majority of additional treatment costs associated with anti-EGFR therapy is attributable to chemotherapy, with comparatively little increase in resection costs and subsequent improvement in overall survival.

A comparison of all four strategies’ costs and effects is pictured in Figure 2. The largest gain in survival and the largest increase in costs occurs from introducing anti-EGFR with screening for KRAS and BRAF mutations; however, the ICER for forgoing screening is extremely high (as shown by the steep slope of the line), because the increment in survival is less than a day. Figure 2 gives the impression that the estimates are deterministic in nature. Figure 3 provides a visual representation of the spread in costs and effects of the different strategies. In Figure 3, the scatter of average costs and effects under different strategies highlights that the major differences are in costs of the strategies with major overlap in effectiveness. Estimated standard errors for the treatment effects are: no anti-EGFR therapy: 0.0476; KRAS and BRAF screening with anti-EGFR therapy: 0.0495; KRAS screening with anti-EGFR therapy: 0.0496; anti-EGFR therapy without screening: 0.0500.

The difference in costs of the strategy with no anti-EGFR therapy and therapies with anti-EGFR therapy, with much overlap in effectiveness, stands out. In most cases, we expend considerably more by adopting an anti-EGFR therapy strategy, with a highly uncertain small gain in overall survival. To understand the simultaneous uncertainty in both costs and effects, we generated cost-effectiveness acceptability curves (CEACs). Net benefit CEACs in Figure 4 show the probability that an intervention is cost-effective compared with all other interventions for a range of threshold values of willingness to pay, which is an elicited maximum amount a potential payer would pay for an increment in health improvement (50,51). At willingness to pay thresholds at less than $1 million per life-year saved, providing anti-EGFR therapy with screening is definitely preferable. The probability that either screening strategy (only KRAS or both KRAS and BRAF) will be cost-effective decreases considerably at higher willingness-to-pay thresholds. Anti-EGFR therapy without screening has the highest probability of being considered cost-effective only for willing to pay thresholds of $3 million or more per additional year of survival. This aligns with the baseline ICERs in Table 2.

Figure 5 shows an acceptability frontier formed by the envelope of strategies that would be favored at specific willingness-to-pay thresholds. The acceptability frontier is derived from Figure 4, which excludes no anti-EGFR therapy for clarity but is based on the same information. Figure 5 simplifies the depiction of the selection from among the different strategies at specific willingness-to-pay thresholds by displaying only the optimal strategy at each threshold. At the lowest levels of willingness to pay, not using anti-EGFR therapy is preferred with certainty. With an increase in willingness to pay, the screening strategies are preferred. After about $3 million per year willingness to pay, providing anti-EGFR treatment to everyone is most preferred.

As we move right toward anti-EGFR therapy without screening, we can see that starting at a willingness to pay equal to the ICER of strategy of screening for KRAS and BRAF, the willingness-to-pay thresholds that would support more widespread use of anti-EGFRs are magnitudes higher than the oft-cited $50,000/QALY figure, which is considered a reasonable threshold (52).

We conducted the following sensitivity analyses, which are described and presented in the Supplementary Material (available online): 1) Conversion probability for chemotherapy is 30% [bevacizumab=30%, cetuximab=50%]; 2) conversion probability for bevacizumab is +10%; cetuximab is +20%; 3) cost of surgery is +50%; 4) cost of screening (a) +50% and (b) -50%; and

![Figure 2. Cost-effectiveness analysis of four strategies with no anti-EGFR therapy as the base strategy.](image-url)
5) prognostic decrease in overall survival with BRAF (regardless of treatment).

The sensitivity analyses provide insight into the responsiveness of the results to changes in the parameters. From among all sensitivity analyses, increasing the probabilities of conversion in sensitivity analysis 1 results in the highest response (increase) in overall survival. Nevertheless, the increment in survival is not proportionate to the change in the parameter values. In sensitivity analysis 1, increasing the probability of conversion using cetuximab regimens by 100% increases the mean overall survival only by 17%. This can be attributed to the successive Markov decision paths through which a patient must pass, which tend to reduce the net overall effect.

**Discussion**

Anti-EGFR treatment is costly. In mCRC, when the treatment is provided without screening for genetic mutations, it is the most...
costly strategy and carries a very small improvement in mean survival. We estimate that screening for \textit{KRAS} and/or \textit{BRAF} mutations can reduce the cost of anti-EGFR treatment but with a very small reduction in overall survival. The screening interventions are cost saving compared with providing anti-EGFR therapy to all mCRC patients.

At the lowest WTP levels, the preference is to forgo anti-EGFR therapy altogether. This is because, even with the cost savings resulting from the use of screening, the higher net cost of treatment, which allows anti-EGFR treatments for patients without genetic mutations, is unacceptably high if WTP is less than $350 000/LYS. These “lower” levels of willingness to pay for increased survival are quite high relative to commonly cited thresholds, such as $50 000/LYS or less for reasonable value and $100 000/LYS or more for questionable value.

Our results are considerably different from Blank et al. (24). The cost of base case (€3983) in their cost-effectiveness table is very low, which could be because of the exclusion of resection costs. Similarly, costs for other strategies are about half of ours. They appear to have excluded repeated surgeries, associated costs in all cases, and repeated application of treatments, including anti-EGFR (53). However, the major difference between their results and those presented here appears to be in the effect of anti-EGFR treatments. Blank et al. estimated nearly double the increase in lifetime overall survival with use of anti-EGFR therapy compared with no anti-EGFR therapy. Blank et al.’s estimates of overall survival match the randomized controlled trial findings for a subset of patients with wild-type \textit{KRAS} being evaluated for cetuximab and basic supportive care treatment versus BSC treatment only (22).

Our analysis is based on a general population of mCRC patients, of whom roughly 50% have synchronous abdominal and peritoneal metastases with a maximum overall survival of 6.5 months (54). It is difficult to compare findings from such a patient base to those from randomized controlled trials and other literature because of the variation in inclusion criteria for patients. Excluding those with abdominal/peritoneal metastases from anti-EGFR therapy might bring the cost effectiveness ratio closer to those in other studies. Including this exclusion in the model is not possible because of insufficient data. Ideally, to compare our estimates with the available evidence, we should compare our findings to the overall randomized patient base being treated and not differentiate overall survival based on mutation status.

In order to compare our findings and those of other researchers, we can see that only NCIC CO.17 reported a statistically significant difference in the effect of cetuximab on overall survival. Statistically insignificant gains in overall survival resulting from treatment with cetuximab align with our estimates. Vijayaraghavan et al. (55) provide a cost-effectiveness analysis of using anti-EGFR treatments in combination therapies compared with anti-EGFR treatments alone. Their cost structures also reflect a lack of retreatment with earlier treatments and inclusion of costs of resections (55). Compared with Vijayaraghavan et al. and Blank et al., our analytical structure assumes the adoption of multiple chemotherapies in basic supportive care to optimally improve overall survival (28,29).

Our analysis points to two types of potential cost savings that a policymaker or payer could obtain depending on their willingness to pay. At the lowest willingness to pay, the payer who decides against the use of anti-EGFR therapy can save about $20 000 per patient. A willingness to adopt anti-EGFR testing for both \textit{KRAS} and \textit{BRAF} could together save roughly $8000 compared with providing anti-EGFR treatment without any screening.

In a conference abstract, Shankaran et al. (25) estimated that $740 million in annual savings would be realized in the United States by providing \textit{KRAS} testing to all 29 762 mCRC patients. Using the same number of cases and their rate of prevalence of \textit{KRAS} mutation, we estimate that savings would be closer to $103 million.
million annually. The amount of detail available in their abstract prevents assessment of the reasons for the difference between the estimates.

This study has several limitations. First, we did not provide progression-free survival outcomes for the different strategies. In the case of mCRC patients, progression-free survival does not play a major role in deciding the course of treatment. Second, we did not incorporate differences among the treatment options in quality of life. There is an insufficient evidence base to undertake such an analysis. Mittmann et al. (22) and other papers based on the CO.17 trial have provided direct information regarding the quality of life for the patients, but it is for a much shorter duration: 24 weeks. Mittmann et al. report QALYs for two cases: patients without KRAS mutation who are subjected to cetuximab and those on non-anti-EGFR therapy. Without separate utility values for those administered cetuximab and having KRAS mutation, there is no way to incorporate the quality-of-life impact of side effects from cetuximab and basic supportive care. Our results show a small incremental gain in overall survival when forgoing KRAS testing before treatment. These gains may not have been seen if the health impact of treatment were expressed in quality-adjusted survival. Differences in quality of life among patients receiving alternate treatments have not been quantified in a way that allows quality-adjusted survival to be modeled.

This analysis did not consider patient preferences regarding discontinuation of cetuximab treatment because of the reduced quality of life from adverse reactions, which has been observed in 3% to 10% of patients (16). Dermatologic toxicities with treatment include an acneiform rash in 76% to 88% of the patients, with severe rash in 1% to 17% of the patients (16). Other common adverse reactions include headache, diarrhea, and infection (16).

Our analysis for BRAF testing assumes that 100% of the difference in survival between cetuximab users with BRAF mutations, similar to those with KRAS mutations, is because of a lack of response to cetuximab. However, evidence from randomized controlled trials suggests that BRAF mutations may independently predict prognosis (56–58). Our estimated savings from BRAF testing are overstated if any part of the survival difference is because of BRAF predicting of survival independent of therapy choice.

In general, our results are less supportive of the use of anti-EGFR therapy than previous analyses, and they indicate lower cost savings from KRAS testing than previously reported. Although we cannot confirm that anti-EGFR therapy is a cost-effective use of health care resources, we can affirm that KRAS testing is cost-saving. BRAF testing may offer additional savings.

References

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