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ORIGINAL REPORT

First- and Second-Line Bevacizumab in Addition to Chemotherapy for Metastatic Colorectal Cancer: A United States–Based Cost-Effectiveness Analysis

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ABSTRACT

Purpose
The addition of bevacizumab to fluorouracil-based chemotherapy is a standard of care for previously untreated metastatic colorectal cancer. Continuation of bevacizumab beyond progression is an accepted standard of care based on a 1.4-month increase in median overall survival observed in a randomized trial. No United States–based cost-effectiveness modeling analyses are currently available addressing the use of bevacizumab in metastatic colorectal cancer. Our objective was to determine the cost effectiveness of bevacizumab in the first-line setting and when continued beyond progression from the perspective of US payers.

Methods
We developed two Markov models to compare the cost and effectiveness of fluorouracil, leucovorin, and oxaliplatin with or without bevacizumab in the first-line treatment and subsequent fluorouracil, leucovorin, and irinotecan with or without bevacizumab in the second-line treatment of metastatic colorectal cancer. Model robustness was addressed by univariable and probabilistic sensitivity analyses. Health outcomes were measured in life-years and quality-adjusted life-years (QALYs).

Results
Using bevacizumab in first-line therapy provided an additional 0.10 QALYs (0.14 life-years) at a cost of $59,361. The incremental cost-effectiveness ratio was $571,240 per QALY. Continuing bevacizumab beyond progression provided an additional 0.11 QALYs (0.16 life-years) at a cost of $39,209. The incremental cost-effectiveness ratio was $364,083 per QALY. In univariable sensitivity analyses, the variables with the greatest influence on the incremental cost-effectiveness ratio were bevacizumab cost, overall survival, and utility.

Conclusion
Bevacizumab provides minimal incremental benefit at high incremental cost per QALY in both the first- and second-line settings of metastatic colorectal cancer treatment.

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INTRODUCTION

Colorectal cancer is the third most common cancer and the third leading cause of cancer death in men and women in the United States.[1] In 2010, $14 billion was spent in the United States on management of colorectal cancer.[2]

Fluorouracil (FU) combined with oxaliplatin (FOLFOX) is the most commonly used regimen in first-line therapy for metastatic colorectal cancer (mCRC).[3] This regimen is essentially equivalent in efficacy to capecitabine plus oxaliplatin (XELOX).[4] Bevacizumab, a monoclonal antibody against the vascular endothelial growth factor A, is commonly added to the regimen based on data from randomized clinical trials.[5-7] FU and irinotecan (FOLFIRI) is commonly administered as a second-line regimen for patients with mCRC.[8] Continuation of bevacizumab beyond first progression has an overall survival benefit,[9] and administration of bevacizumab in addition to chemotherapy in both first- and second-line settings is now a standard practice. The modest survival benefit and high cost of bevacizumab have raised concerns regarding the cost effectiveness of this approach.

Although some international studies have evaluated the cost effectiveness of bevacizumab in mCRC,[10-12] it has not been evaluated using a

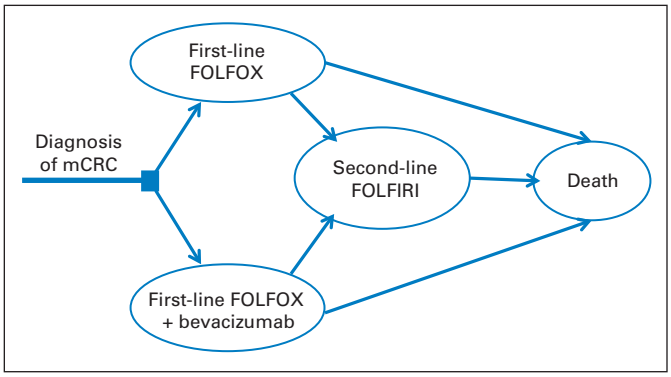

Fig 1. Markov model diagram for first-line model. FOLFIRI, fluorouracil plus irinotecan; FOLFOX, fluorouracil plus oxaliplatin; mCRC, metastatic colorectal cancer.

modeling approach in the United States. In this study, we estimate the cost effectiveness of bevacizumab from the perspective of the US payer.

METHODS

We developed two Markov models to evaluate the additional costs and effectiveness of bevacizumab as first- and second-line therapies. In the first-line model, we compared FOLFOX with or without bevacizumab in patients with newly diagnosed mCRC. On progression of disease, both groups received FOLFIRI without bevacizumab and subsequently experienced progression until death (Fig 1). In the second-line model, we compared FOLFIRI with or without bevacizumab, with subsequent progression to death, in patients who had experienced progression during first-line chemotherapy with bevacizumab (Fig 2).

Each health state was assigned a health utility score based on published studies. Only direct medical costs were considered and are stated in 2013 US dollars. All costs and outcomes were discounted by 3% annually. Each model cycle represents 2 weeks, because patients receive chemotherapy biweekly in clinical practice. The primary outputs of the models included total cost, life-years (LYs), quality-adjusted LYs (QALYs), and incremental cost-effectiveness ratios (ICERs). The Markov models were implemented in C++ language, and statistical analyses were performed in R software (http://www.r-project.org).

Patients and Treatment Regimens

We based our assumption describing the survival benefits associated with first-line FOLFOX plus bevacizumab versus FOLFOX on the results from the N01966 trial, which demonstrated an improved median overall survival (OS) of 1.4 months when bevacizumab was added to FOLFOX and XELOX.[6] Patient characteristics, regimen information, and treatment outcomes for trials used in the models are summarized in Appendix Table A1 (online only). We based our assumption about the benefit of second-line bevacizumab on the ML18147 trial, which demonstrated a median OS benefit of 1.4 months when bevacizumab was continued beyond progression in combination with second-line FU-based chemotherapy.[9]

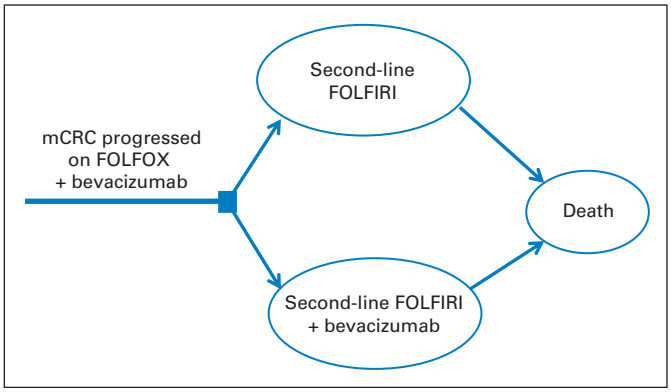

Fig 2. Markov model diagram for second-line model. FOLFIRI, fluorouracil plus irinotecan; FOLFOX, fluorouracil plus oxaliplatin; mCRC, metastatic colorectal cancer.

Mortality Estimates

The overall mortality rate corresponded to the probability of transition from any state to the death state, which was estimated as the cause-specific mortality from mCRC and background mortality resulting from other causes. The cause-specific mortalities of each treatment strategy were derived from the OS curves in the studies associated with each treatment regimen. Engauge Digitizer software (http://digitizer.sourceforge.net) was used to extract the data points from each OS plot, and these data points were then used to fit parametric survival models. We found that Weibull and log-logistic models provided a good fit for all curves according to the Akaike information criterion and the Schwarz Bayesian criterion.[13] Between the Weibull and log-logistic models, we selected the Weibull distribution because it can have an increasing hazard rate and is suitable for modeling the events occurring early during follow-up periods. On the basis of the fitted Weibull OS model, denoted as $OS(t)$, we computed the cause-specific mortality $\mathrm{m}(t)$ at cycle t as follows:

$$\mathrm{m}(t) = \frac{p(t \le T \le t+1)}{p(T \ge t)} = \frac{(OS(t) - OS(t-1))}{OS(t)}$$

We estimated the background mortality for each age group based on US life-tables.[14] The models sampled the initial age at diagnosis of mCRC in each simulation run using the age distribution for mCRC from SEER data.[15]

Progression Risk

In the first-line model, the transitions from first- to second-line therapy in each cycle were determined by the estimates of the progression risks based on N01966. Estimates of mortality and progression risk beyond the follow-up time in the clinical trials were extrapolated based on the fitted survival models.

Utility Estimates

To compute the total QALYs in the Markov models, survival time was adjusted by health-related quality of life. We used previously published mean utilities of 0.85 and 0.65 for patients in first- and second-line settings, respectively.[16,17]

Cost Estimates

Direct costs included drug, administration, and adverse event (AE) costs. In the first-line setting, the intravenous drug costs for each 2-week cycle of FOLFOX were based on the following doses: oxaliplatin 85 mg/m^2, leucovorin 200 mg/m^2, and FU 400 mg/m^2 bolus and 600 mg/m^2 continuously over 46 hours. In the second-line setting, the costs for each 2-week cycle of FOLFIRI were based on the following doses: irinotecan 180 mg/m^2, leucovorin 400 mg/m^2, and FU 400 mg/m^2 bolus and 2,400 mg/m^2 continuously over 46 hours. When bevacizumab was added, the cost was based on dosing at 5 mg/kg. We used a body-surface area of 1.86 m^2 and body weight of 82 kg, based on mean US values.[18] We did not round up drugs to the full vial size. To estimate the unit price of each drug, we used the 2013 average sales price from the Centers for Medicare and Medicaid Services.[19]

Administration and AE costs were calculated according to the Medicare physician fee schedule for 2013. Each chemotherapy infusion was assumed to last 4 hours. The fees for outpatient physician visits were based on Current Procedure Terminology codes.[20] The methods used for these cost calculations were previously described by Tumeh et al.[21] The fees for physician visits and chemotherapy administration are listed in Appendix Table A2 (online only).

The costs for grade 3 to 4 AEs were based on diagnosis-related group codes.[21] The N01966 trial reported only toxicities related to bevacizumab that had a significant difference between arms.[6] The model projected that patients

Table 1. Model Parameters: Baseline Values, Ranges, and Distributions for Sensitivity Analysis

Variable	Value	Minimum	Maximum	Study	Distribution
AE incidence					
First-line FOLFOX					
Hypertension	0.010	0.001	0.090	N01966	0.49 to 48.51*
Venous thromboembolic event	0.050	0.036	0.069	N01966	35.050 to 665.950*
First-line FOLFOX plus bevacizumab					
Hypertension	0.040	0.013	0.114	N01966	2.84 to 68.16*
Venous thromboembolic event	0.080	0.062	0.102	N01966	55.92 to 643.08*
Second-line FOLFIRI					
Previously treated with bevacizumab					
Hypertension	0.010	0.004	0.025	ML18147	4.09 to 404.91*
Venous thromboembolic event	0.030	0.017	0.051	ML18147	12.270 to 396.730*
No previous treatment with bevacizumab					
Hypertension	0.018	0.008	0.041	E3200	5.130 to 279.870*
Venous thromboembolic event	0.025	0.012	0.050	E3200	7.125 to 277.875*
Second-line FOLFIRI plus bevacizumab†					
Hypertension	0.020	0.01	0.039	ML18147	8.02 to 392.98*
Venous thromboembolic event	0.050	0.0323	0.076	ML18147	20.05 to 380.95*
Costs per cycle, $					
Administration‡	284.77	177.70	375.44		28.295 to 10.06§
FOLFOX	435.05	348.04	522.06		100 to 4.351§
Bevacizumab	2,649.42	2,119.54	3,179.30		64 to 6.25§
FOLFIRI	392.60	314.08	471.12		100 to 3.926§
AE costs, $					
Hypertension	51.89	41.51	62.27		100 to 0.519§
Venous thromboembolic event	5,567.00	4,453.60	6,680.40		100 to 55.670§
Utility					
Before progression	0.85	0.68	1	Ramsey et al[16]	14.15 to 2.497*
Beyond progression	0.65	0.52	0.78	Ramsey et al[16,17]	34.35 to 18.496*
Discount factor	0.03	0	0.05		0 to 0.05‖

Abbreviations: AE, adverse event; FOLFIRI, fluorouracil plus irinotecan; FOLFOX, fluorouracil plus oxaliplatin.
*Beta.
†Assuming previous treatment with bevacizumab.
‡Clinical visit plus chemotherapy.
§Gamma.
‖Uniform.

with venous thromboembolic events would be treated with enoxaparin (1 mg/kg twice daily) for 6 months according to American Society of Clinical Oncology guidelines.[22] Hypertension was assumed to be managed with amlodipine in the outpatient setting (Table 1).

Model Validation

We performed external and internal model validations. In the external validation, we compared the survival curves used in this study with those for the same treatment in other published studies. N01966 OS curves were compared with those from studies by Schmoll et al[23] and Tournigand et al.[8] The internal validation showed that the progression-free survival and OS curves generated by the Markov model simulation closely approximated those presented in the clinical trials (Appendix Fig A1, online only).

Sensitivity Analysis

A series of sensitivity analyses were performed to evaluate the robustness of the model and address uncertainty in the estimation of variables. Utilities were varied over their 95% CIs. Drug costs were varied within ± 20% of their baseline values as in a similar study.[24] Physician fees were varied across the range for all provider sites in the Centers for Medicare and Medicaid Services database as previously described.[25] All ranges and distributions used in sensitivity analyses are summarized in Table 1.

We addressed the uncertainty of survival probabilities in the models. First, we identified the range for each survival curve based on the CI for the corresponding median survival. We adjusted the curve $S(t)$ by a hazard ratio γ such that the adjusted survival $[S(t)]^{\gamma}$ had a median survival within the reported CI. We then re-estimated the risk of progression or death in each model cycle based on the adjusted survival curves $[S(t)]^{\gamma}$ with the lowest and highest values of hazard ratio γ.

In univariable sensitivity analyses, we varied the value of one parameter at a time over its defined range and examined the effect on the ICER. In probabilistic sensitivity analyses (PSAs), we ran the model 10,000 times, each time randomly varying all parameters simultaneously. We used gamma distribution for cost parameters, beta distribution for parameters bounded between 0 and 1, and uniform distribution for the discount factor. The baseline values, ranges, and distributions of model parameters are listed in Table 1.

We performed an additional analysis to evaluate the robustness of the model by altering the data sources for the first-line model (using sequential nonrandomized results of TREE1 [Three Regimens of Eloxatin Evaluation] and TREE2 [Three Regimens of Eloxatin Evaluation with bevacizumab]) studies.[5] Furthermore, we compared the costs and effectiveness for patients who received bevacizumab in the first- and second-line settings versus those who did not receive bevacizumab in either setting. We used the control arm of the E3200 study to define the outcomes of second-line therapy without receipt of prior bevacizumab.[26] Although the E3200 study used second-line FOLFOX, we felt that it was acceptable to use these data to model second-line outcomes, because FOLFOX and FOLFIRI have similar efficacy in this setting.[27] For patients who had received first-line bevacizumab, we used the ML18147 trial to define the outcomes of second-line FOLFIRI plus bevacizumab.[9] Although the reliability of these results is limited by the data being derived from different

Table 2. Base Case Results

Result	First-Line Model			Second-Line Model		
	FOLFOX	FOLFOX Plus Bevacizumab	Incremental	FOLFIRI	FOLFIRI Plus Bevacizumab	Incremental
LYs	1.78	1.92	0.14	0.99	1.15	0.16
QALYs	1.31	1.41	0.10	0.64	0.75	0.11
Total cost of regimen, $*	32,561	93,112	60,551	7,443	46,764	39,321
ICER, $						
Per LY			438,779			235,455
Per QALY			571,240			364,083

Abbreviations: FOLFIRI, fluorouracil plus irinotecan; FOLFOX, fluorouracil plus oxaliplatin; ICER, incremental cost-effectiveness ratio; LY, life-year; QALY, quality-adjusted life-year.
*Total cost of regimen in first-line model = first-line chemotherapy + second-line chemotherapy + adverse events. Total cost of regimen in second-line model = second-line chemotherapy + adverse events.

trials, these analyses were used only to assess whether the direction and magnitude of the differences in cost effectiveness of bevacizumab use in mCRC were similar to our primary analyses.

RESULTS

Base Case Results

As shown in Appendix Table A3 (online only), drug costs for FOLFOX, FOLFIRI, and bevacizumab were estimated at $435, $393, and $2,649, respectively, per 2-week cycle. In the primary analysis, the effectiveness and costs were compared in the first-line model for the FOLFOX and FOLFOX-plus-bevacizumab groups. FOLFOX provided 1.31 QALYs (1.78 LYs) at a cost of $32,561. FOLFOX plus bevacizumab provided 1.41 QALYs (1.92 LYs) at a cost of $92,112 (Table 2). The ICER for FOLFOX plus bevacizumab was $571,240 per QALY. In the second-line model, FOLFIRI provided 0.64 QALYs (0.99 LYs) at a cost of $7,443. FOLFIRI plus bevacizumab provided 0.75 QALYs (1.15 LYs) at a cost of $46,764. The ICER for FOLFIRI plus bevacizumab was $364,083 per QALY.

Sensitivity Analyses

The results of univariable sensitivity analyses are shown in the tornado diagrams (Fig 3). The parameters with the greatest influence on the ICERs were similar in both models: median OS for each regimen, drug cost of bevacizumab, and utility values for living with mCRC. Across broad variation in the ranges for each parameter, the ICER remained > $200,000 per QALY. The median PFS and the discount factor had a minor influence on the ICER in the first-line model. The effects of other parameters were negligible.

The ICERs for 10,000 samples in the PSA are shown in the scatterplot (Fig 4), with quadrants indicating the differences in costs and effectiveness and a line indicating the level of $100,000 per QALY. For each model, all the points were above the $100,000-per-QALY line. The cost-effectiveness acceptability curve is shown in Appendix Figure A2 (online only) for varying values of willingness to pay per QALY. In the structural sensitivity analysis using data from other studies to compare ICERs with the base case analyses, our alternative first-line model demonstrated an ICER of $240,810 per QALY. In the analysis comparing bevacizumab in the first- and second-line settings

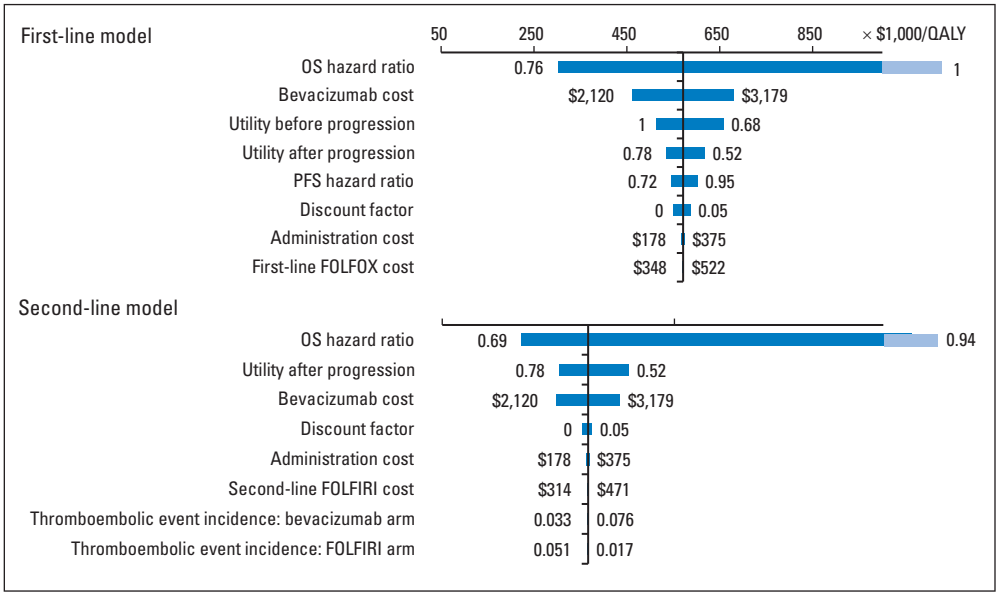

Fig 3. Univariable sensitivity analyses of variables with greatest influence on model. Bar shaded lighter blue indicates that actual value is beyond range of axis. FOLFIRI, fluorouracil plus irinotecan; FOLFOX, fluorouracil plus oxaliplatin; OS, overall survival; PFS, progression-free survival; QALY, quality-adjusted life-year.

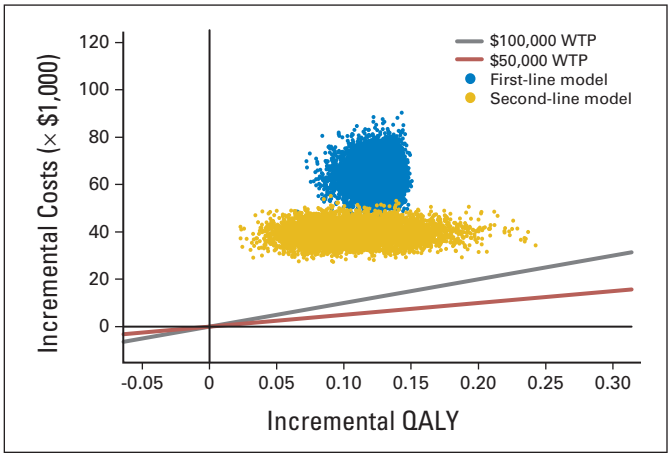

Fig 4. Scatter plot of probabilistic sensitivity analysis. Red and gray lines indicate threshold of willingness to pay (WTP) of $50,000 and $100,000 per quality-adjusted life-year (QALY), respectively. Each point in scatterplot corresponds to one sample of parameter values. Points above reference line indicate higher incremental cost-effectiveness ratio than threshold value.

versus bevacizumab in neither line of therapy, the ICER for the addition of bevacizumab was $1.2 million per QALY.

DISCUSSION

We performed a cost-effectiveness analysis of bevacizumab in addition to chemotherapy in mCRC. In both the first- and second-line settings, bevacizumab provided modest incremental benefit at high incremental cost per QALY. In both the first- and second-line models, adding bevacizumab prolonged the median OS by 6 weeks and increased costs by $60,000 and $40,000, respectively. Bevacizumab is more cost effective in the second line than in the first line because of a decreased period of treatment. In the best-case scenario for the most sensitive variables in the univariable sensitivity analysis, the ICER remained > $200,000 per QALY. The PSA revealed that the probability of bevacizumab being cost effective was 0% in the first- and second-line settings for a willingness-to-pay threshold of $100,000 per QALY. This uncertainty analysis suggests a high likelihood that bevacizumab exceeds the usually accepted values for cost-effective incremental costs of care.

Other studies have analyzed the cost effectiveness of bevacizumab in mCRC in different settings.[10-12] A British study found that adding bevacizumab to FOLFIRI in first-line management cost £62,857 (US$102,000) per QALY.[12] A Canadian study found that the addition of bevacizumab had an ICER of Canadian $131,600 (US$120,000) per QALY,[10] whereas in Japan, it was ¥13.5 million ($113,000) per QALY.[11] A United States–based retrospective analysis found that adding bevacizumab to chemotherapy cost $75,303 per LY.[28] Were quality of life to be incorporated, this ICER would be expected to increase. Because of the differences in the modeling approaches, costs, and health care systems among countries, conclusions drawn from one country cannot be applied to another.[29] In addition, these analyses provided information in the first-line setting only. To our knowledge, our study is the first modeling study from a US payer perspective and the first worldwide to examine bevacizumab when continued beyond progression.

In advanced non–small-cell lung cancer, bevacizumab is approved in addition to chemotherapy based on the ECOG 4599 trial.[30] A United States–based analysis demonstrated an ICER of $560,000 per QALY.[24] Although informative, these results in lung cancer cannot be extrapolated to colon cancer.

When irinotecan was approved for mCRC, it was found to have an ICER of $49,000 per LY when added to FU.[31] When FOLFOX demonstrated a survival benefit over irinotecan and bolus FU, the ICER was $112,000 per QALY.[32] Anti–epidermal growth factor receptor therapies such as cetuximab can also be added to chemotherapy, with an ICER of $2.9 million per LY.[33] When using *KRAS* testing as a biomarker to select patients most likely to benefit, the ICER was reduced to $2.8 million per LY.[33] The magnitude of ICERs when new drugs gained approval more than a decade ago is significantly less than the ICERs for more modern monoclonal antibodies, such as bevacizumab and cetuximab. Although inflation in the costs of health care services accounts for some of this increase in cost, it should not substantially influence the incremental costs of these interventions over contemporary alternatives.

The threshold of $50,000 to $100,000 per QALY is frequently justified as a definition for a cost-effective health care intervention based on the cost effectiveness of dialysis.[34] A more recent analysis revealed that the ICER for dialysis is $130,000 per QALY.[35] Ultimately, the willingness of payers, patients, and other stakeholders to cover the costs of expensive cancer therapies will establish a new benchmark for cost-effective care.

As with any model, our analysis has limitations, which are governed by data availability and our assumptions.[36] We used reimbursement rates provided by Medicare, the largest public payer in the United States, which are generally lower than reimbursement rates for private insurers.[37] We are unaware of research comparing physician-administered drug reimbursement rates between Medicare and private payers. Our model was static and assumed no differences in drug acquisition costs over time. This may have resulted in overestimation of the cost of bevacizumab when it goes off patent. Our model provides a framework that can be used to assess the cost effectiveness of bevacizumab for any value of the drug price; the sensitivity analyses included wide variability in the cost of bevacizumab.

As with most modeling studies, these results are limited by the fact that the models were based on data from previously published trials and not collected prospectively. However, a benefit of this approach is that we were able to use national averages for costs, thus accounting for regional variations.

Patients recruited to the ML18147 trial received standard first-line FU-based chemotherapy with either oxaliplatin or irinotecan.[9] On progression, patients were switched between oxaliplatin and irinotecan. Given the similar efficacy and AE profile of these regimens,[8] we felt it was justified to simplify the model to FOLFOX followed by FOLFIRI. Our model was based on the use of FOLFOX4, as in the N01966 study; however, it has become more standard to use the modified FOLFOX6 regimen, which contains a higher dose of bolus FU.[5] There is only a $9 difference in cost per cycle for these regimens, and with similar outcomes, these differences would be well accounted for in the sensitivity analyses. We included in the model only those AEs that commonly affect cost or health utility. For example, peripheral neuropathy, proteinuria, and intestinal perforation were excluded from the model. Moreover, although our model provides a good framework for the management of mCRC, recently approved agents

have slightly changed the treatment paradigm. Notably, regorafenib is now commonly used as monotherapy in the third-line setting.[38] Cetuximab and panitumumab are also approved in patients without *KRAS*-mutated disease and represent alternative options to bevacizumab.[39,40]

The ICER of bevacizumab potentially could be improved with the use of an effective biomarker to select patients most likely to benefit. This has been demonstrated previously with other therapies. For example, in mCRC, testing the tumor for *KRAS* gene mutation status indicates which patients are more likely to benefit from therapy such as cetuximab or panitumumab, and *KRAS* testing improves the cost effectiveness of these interventions.[33] Several attempts have been made to find a biomarker that predicts response to bevacizumab; however, no predictive biomarker has been validated.[41]

Our study demonstrates the high incremental cost with low incremental benefit of bevacizumab in mCRC over wide variations in the assumptions incorporated into the models. In the era of personalized medicine, the needs of patients with mCRC or other malignancies warrant the development of new therapeutic technologies, but with the dramatic rises in drug prices over the last decades, the use of new treatments should be tailored to the patients who are most likely to benefit. In the current environment, costly drugs face few barriers to coverage and adoption by physicians. However, the process for new drug approval and the incorporation of drugs into treatment formularies and guidelines may eventually force physicians and policymakers to confront tradeoffs between cost and benefit more explicitly. Data from this study and others like it provide a starting point for such discussions.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at www.jco.org.

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GLOSSARY TERMS

overall survival: the duration between random assignment and death.

quality-adjusted life-year (QALY): a common measure of health improvement used in economic evaluation that measures life expectancy adjusted for quality of life.

utility: a measure of the preference for, or desirability of, a specific level of health status or specific health outcome.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

First- and Second-Line Bevacizumab in Addition to Chemotherapy for Metastatic Colorectal Cancer: A United States–Based Cost-Effectiveness Analysis

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Appendix

Table A1. Patient Demographic and Clinical Characteristics by Treatment Regimen

Characteristic	First-Line Treatment				Second-Line Treatment		
	FOLFOX/XELOX (n = 701)	FOLFOX/XELOX Plus Bevacizumab (n = 699)	FOLFOX (n = 111)	FOLFOX Plus Bevacizumab (n = 713)	FOLFIRI (n = 411)	FOLFIRI (n = 291)	FOLFIRI Plus Bevacizumab (n = 409)
Study	N01966 (2008)	N01966 (2008)	Tournigand et al[8] (2004)	Schmoll et al[23](2012)	ML18147 (2013)	E3200 (2007)	ML18147 (2013)
Age, years							
Median	60	60	65	60	63	61	63
Range	18-83	18-86	40-75	22-88	21-84	25-84	27-84
Male sex, %	56	60	72	58	63	61	65
Performance status 0 to 1, %	100	100	94	100	95	94	95
OS, months							
Median	19.9	21.3	20.6	21.3	9.8	10.8	11.2
Range			17.7-24.6		8.9-10.7		10.4-12.2
PFS, months							
Median	8.0	9.4	8.0	10.3	4.1	4.7	5.7
Range			6.2-9.4		3.7-4.4		5.2-6.2

Abbreviations: FOLFIRI, fluorouracil plus irinotecan; FOLFOX, fluorouracil plus oxaliplatin; OS, overall survival; PFS, progression-free survival; XELOX, capecitabine plus oxaliplatin.

Table A2. Costs of Drug Administration and Routine Management

Description	CPT Code	Cost ($)	Range ($)
Outpatient follow-up visit	99213	49.67	43.28-66.32
Inpatient first visit	99222	134.73	116.73-179.17
Inpatient follow-up visit	99232	70.09	61.58-94.16
Inpatient discharge visit	99238	70.77	60.98-93.4
Chemotherapy administration			
IV, first hour	96413	143.24	99.45-190.62
IV, additional hours	96415	30.62	22.7-39.5

NOTE. Assumptions were as follows: national payment amount (ie, GPCI), 1; conversion factor (for 2013), 34.023; data from year 2013.
Abbreviations: CPT, Common Procedure Terminology; GPCI, geographic practice cost index; IV, intravenous.

Table A3. Drug Costs for 2-Week Cycle

Drug and Dose	Cost ($)	Total Cost ($)
First-line FOLFOX		
Oxaliplatin 85 mg/m^2	0.535 per 0.5 mg	169.16
Leucovorin 200 mg/m^2	4.501 per 50 mg	36.01
FU 400 mg/m^2 bolus	1.995 per 500 mg	2.97
FU 600 mg/m^2 continuous infusion	1.995 per 500 mg	4.45
Palonosetron 250 mcg IV	19.384 per 25 mcg	193.84
Dexamethasone 12 mg orally	0.64 per 4 mg	1.92
Prochlorperazine 30 × 10 mg tablets	0.89 per 10 mg	26.70
First-line bevacizumab		
Bevacizumab 5 mg/kg	64.62 per 10 mg	2649.42
Second-line FOLFIRI		
Irinotecan 180 mg/m^2	4.46 per 20 mg	74.66
Leucovorin 400 mg/m^2	4.501 per 50 mg	66.97
FU 400 mg/m^2 bolus	1.995 per 500 mg	2.97
FU 2,400 mg/m^2 continuous infusion	1.995 per 500 mg	17.81
Palonosetron 250 mcg IV	19.384 per 25 mcg	193.84
Dexamethasone 12 mg orally	0.64 per 4 mg	1.92
Prochlorperazine 30 × 10 mg tablets	0.89 per 10 mg	26.70
Atropine 0.4 mg IV	1.73	1.73
Loperamide 2 to 4 mg once every 4 hours (30 tablets)	0.20 × 30	6.00
Total		392.60

Abbreviations: FOLFIRI, fluorouracil plus irinotecan; FOLFOX, fluorouracil plus oxaliplatin; FU, fluorouracil; IV, intravenous.

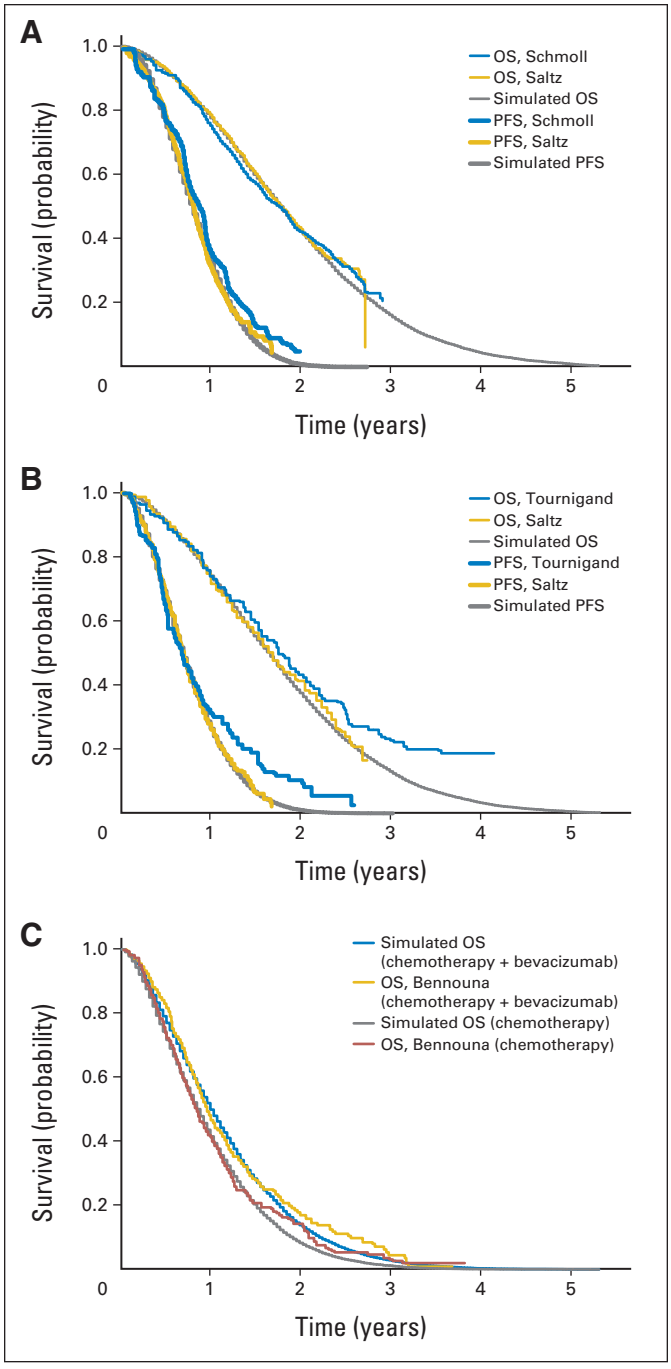

Fig A1. (A) Progression-free survival (PFS) inference and external validation for arm treated with fluorouracil plus oxaliplatin (FOLFOX) or capecitabine plus oxaliplatin (XELOX), with addition of bevacizumab (data adapted[6,23]), and (B) internal validation with simulation results for arm treated with FOLFOX or XELOX in first-line model (data adapted[6,8]). (C) Internal validation of overall survival (OS) in second-line model (data adapted[9]).

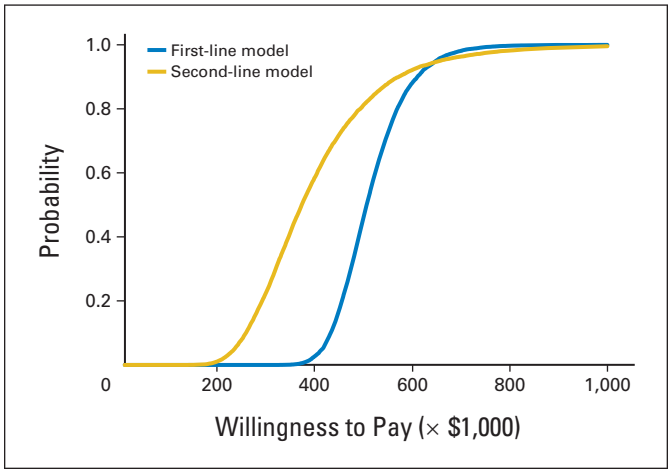

Fig A2. Cost-effectiveness acceptability curve.