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## Metastatic Colorectal Cancer: A systematic review of the value of current therapies

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### Abstract

**Aim**—To evaluate, from a US payer perspective, the cost-effectiveness of treatment strategies for metastatic colorectal cancer (mCRC).

**Methods**—We performed a systematic review of published cost-effectiveness analyses of treatment strategies for mCRC with pre-specified search criteria.

**Results**—We identified 14 papers that fulfilled our search criteria and revealed varying levels of value amongst current treatment strategies. Older agents such as 5FU, irinotecan, and oxaliplatin provide high value treatments. More modern agents targeting the *EGFR* or *VEGF* pathways, such as bevacizumab, cetuximab and panitumumab do not appear to be cost effective treatments at their current costs. The analytical methods used within the papers varied widely, and likely plays a significant role in the heterogeneity in incremental cost effectiveness ratios.

**Conclusions**—The cost-effectiveness of current treatment strategies for mCRC is highly variable. Drugs recently approved by the Federal Drug Administration (FDA) for mCRC are not cost-effective, and this is primarily driven by high drug costs.

### 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 (US).<sup>1</sup> In 2010, the US spent \$14 billion for

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the management of colorectal cancer.<sup>2</sup> While multidisciplinary care is employed in the treatment of localized colon cancer, systemic chemotherapy is the mainstay of treatment in metastatic colorectal cancer (mCRC). There are currently 10 Food and Drug Administration (FDA) approved drugs for the management of mCRC, which include 5-fluorouracil (5FU), oxaliplatin, irinotecan, capecitabine, bevacizumab, cetuximab, panitumumab, ziv-aflibercept, regorafenib and ramucirumab. There are a variety of regimens with different combinations of these drugs, for use in the first, second and third line settings of treatment. For example, 5FU, oxaliplatin (FOLFOX) and bevacizumab are commonly used as a first line therapy.<sup>3</sup> The Rat Sarcoma Viral Oncogene Homolog (*RAS*) is a family of genes including *KRAS* and *NRAS* that are often found to be mutated in colorectal cancer. When a tumor is *RAS* wild-type (WT), patients derive a benefit from monoclonal antibodies, such as cetuximab or panitumumab, which target the epidermal growth factor receptor (*EGFR*). Thus, *EGFR* targeted therapy, in addition to chemotherapy, is a common second line strategy for patients with *RAS* WT disease.<sup>4</sup> The chemotherapy backbone in second-line is often 5FU and irinotecan (FOLFIRI), with regorafenib monotherapy commonly used as a third line option.<sup>5</sup>

There are multiple different combinations and sequencing strategies available, and this is often dependent on patient and tumor specific factors. Individual patients typically experience different toxicities to individual drugs and the results of *RAS* testing dictate certain treatment choices. Other strategies include using genetic and pharmacokinetic testing to identify patients that are at a greater risk of developing toxicity from certain systemic agents.<sup>6,7</sup> Furthermore, specific liver directed therapies are available to treat hepatic metastases.<sup>8,9</sup>

In the current economic climate with increasing healthcare costs, policy makers have begun to place greater emphasis on the value, or cost-effectiveness (CE), of management strategies. CE studies can be performed using three different methods: 1) analyzing cost and efficacy data collected prospectively alongside a clinical trial; 2) using large databases such as the Surveillance, Epidemiology and End Results (SEER)-Medicare linked database to evaluate cost-effectiveness retrospectively; 3) developing a Markov model to merge data from clinical trials with financial data, commonly from Medicare sources.<sup>10</sup> Efficacy data is often adjusted for quality of life, in order to calculate quality adjusted life years (QALYS) gained. The financial costs of toxicities are incorporated with the final results of the analysis, which then produces an incremental cost effectiveness ratio (ICER) for a specific treatment that is expressed as a dollar amount for each QALY gained.

The objective of this study was to systematically review the value of treatment strategies for mCRC from a US perspective.

## Methods

We performed a systematic literature search to identify published cost-effectiveness studies in the MEDLINE database through a series of searches using combinations of the medical subject heading (MeSH) and free text terms “cost, effectiveness and metastatic colorectal cancer” generating an initial pool of 124 articles that were assessed for suitability as shown

in Figure 1. Two reviewers (EN and DG) independently performed a study selection and quality assessment using a predefined format. Any disagreement was resolved by another reviewer (CF). Studies were carefully screened for possible duplication of study population based on the author list, participating institutions, and period of patients' diagnosis and accrual. Criteria for inclusion in the systematic review were: 1) articles published in English between January 1st, 2005 and April 1, 2015, with a full set of experimental details; 2) evaluated patients with metastatic colorectal cancer undergoing treatment; 3) involved a direct comparison between two interventions with measurement of costs and effectiveness allowing calculation of an incremental cost-effectiveness ratio (ICER); 4) data included in analysis was not duplicated in any other article included in our systematic review; and 5) studies were performed from a US perspective, with results presented in US dollars.

## Results

The search strategy generated an initial pool of 124 articles, which was narrowed to 14 using the exclusion criteria depicted in figure 1. These 14 studies are described in table 1.

### Conventional chemotherapy strategies

Although generic versions are now currently available within the United States (irinotecan, 2008; oxaliplatin, 2012), several studies previously evaluated the cost-effectiveness of first line systemic chemotherapy in mCRC. Based upon the clinical data from the N9741 randomized clinical trial, Hillner et al. compared infusional and bolus 5-fluorouracil (5FU) in addition to oxaliplatin (FOLFOX) versus irinotecan and bolus 5FU (IFL).<sup>11,12</sup> FOLFOX had an ICER of \$80,410 per LY, \$111,890 per QALY. When the model incorporated a revised IFL with lower rates of AEs, the ICER was \$84,780/LY. Due to chemotherapy toxicity among patients, dose delays and skipped doses were as high as 77% and 85%, in the FOLFOX and IFL treatment arms, respectively. Hypothetically, if patients had received treatment without delays or interruptions, the ICER of FOLFOX would increase to \$117,910/LY and \$220,200/QALY. Thus, the primary driver of the model was the cost of oxaliplatin and the disutility of oxaliplatin induced peripheral neuropathy and its associated treatment costs.

Using clinical data from a large randomized phase III study of mCRC patients receiving chemotherapy in the first line setting,<sup>13</sup> Tumeq et al. developed a Markov model comparing the cost-effectiveness of FOLFOX versus infusional and bolus 5FU with irinotecan (FOLFIRI).<sup>14</sup> FOLFOX was associated with an ICER of \$65,170/QALY, but ranged from \$34,772-\$91,968/QALY depending on the number of cycles received (between 4-12 cycles). The primary drivers of this model were the similarity in median OS associated with the two chemotherapy regimens, the probability of death associated with FOLFOX, and the relatively higher cost of oxaliplatin compared with irinotecan. A SEER database study analyzed the cost of mCRC from 1995-2005 among Medicare patients who received chemotherapy and who were not candidates for liver directed therapy or surgical metastectomy.<sup>15</sup> The 6.8-month OS improvement among mCRC patients during this timeframe offset the rising treatment-related costs, which was calculated to be \$66,200/LY and \$99,1000/QALY.

## Bevacizumab

Two studies evaluated the incremental benefit of adding bevacizumab to a 5FU based chemotherapy backbone. A Markov model evaluated bevacizumab in the first-line setting, and then when continued beyond progression in the second-line setting.<sup>16</sup> The authors found ICERs of \$571,240/QALY and \$364,083/QALY in the first- and second-line settings, respectively. A retrospective database analysis found that adding bevacizumab to chemotherapy in the first-line setting cost \$75,303/LY.<sup>17</sup> The lower ICER in the retrospective study, compared to the Markov model, may be due to the greater bevacizumab efficacy seen in the retrospective study.<sup>3</sup>

## RAS testing and cetuximab/panitumumab

The prognosis for patients with *BRAF* and *KRAS* mutated mCRC is worse compared to those not harboring these mutations.<sup>18</sup> Two studies were identified that assessed the cost-effectiveness of testing for either *KRAS* and/or *BRAF* mutations in the context of treatment regimens including anti-*EGFR* agents. Behl *et al.* utilized a Markov model of disease progression to assess best supportive care versus anti-*EGFR* therapy with and without screening for *KRAS* alone and with *BRAF* testing. The authors found that screening for both mutations, compared with best supportive care alone, marginally improved the CE of anti-*EGFR* therapies, with an ICER of \$648,396/LY and a cost savings of approximately \$7,500 per patient.<sup>19</sup>

Another Markov model was constructed to determine the value of testing for the *KRAS* gene mutation in mCRC patients prior to treatment with an *EGFR*-inhibitor-containing regimen. This group reported cost-savings between \$7,500-12,400 per/patient in the US and between €3,900-9,600 per/patient in Germany. Combination therapy (cetuximab + irinotecan in the US / cetuximab + FOLFIRI in Germany) with *KRAS* testing yielded an ICER of \$35,539/LY.<sup>20</sup> The lower ICER in the study by Vijayaraghavan *et al.* may be due to their failure to account for the costs of tumor resection and of second-line therapy.

## Regorafenib

Regorafenib is a tyrosine kinase inhibitor that is approved for patients whose disease has progressed on multiple prior lines of systemic therapy. It provides an additional 6 weeks of life for these patients with advanced disease and was recently shown to cost \$900,000/QALY.<sup>21</sup>

## Genetic and pharmacokinetic testing

A significant amount of research has been performed analyzing the *UGT1A1* gene as a biomarker for potential irinotecan toxicity.<sup>22</sup> Patients with genetic mutations received a 25% irinotecan dose reduction and the study found that 11% of patients would be dose reduced to avoid 84.5/10,000 cases of severe neutropenia and save a total of \$2.7 million in treatment costs or an average saving of \$272 per patient.

Another technique to personalize the dosing of 5FU is through pharmacokinetically (PK) guided dosing. This strategy has been shown to improve response rates, decrease toxicity,<sup>7</sup>

and although limited by its reliance on a non-randomized study, was shown to be cost-effective with an ICER of \$23,000/QALY.<sup>23,24</sup>

### Liver directed therapies

Other studies have evaluated the cost-effectiveness of liver directed therapies and surgery in metastatic CRC. One group looked at multi-site cryoablation (MCA) of oligo-metastatic CRC (sites: liver, lung, soft tissue, retroperitoneal, intraperitoneal, bone), and with a median OS of 24 months, MCA was calculated to cost \$39,661-\$85,580/LY.<sup>25</sup> Similarly, Abbott et al. looked at the cost-effectiveness of simultaneous resection and radiofrequency ablation (RFA) versus two-stage hepatectomy among highly selected patients with bilobar colorectal liver metastasis.<sup>26</sup> The total cost of resection with RFA was estimated to be \$37,120 and was associated with a 46.2 month OS, while the cost of a two-stage resection was estimated to be \$62,198 and was associated with a 35.9 month OS. In addition to health utility values and associated QALYs, the cost of office visits, laboratory evaluation, and treatment related complications were not incorporated into this model. Based upon the clinical data from five prior cohort studies, another group reported on the cost-effectiveness of laparoscopy preceding laparotomy versus laparotomy alone for the initial surgical evaluation and treatment of potentially resectable hepatic metastasis.<sup>27</sup> Due to the high rate of patients found to have intra-abdominal metastases intra-operatively despite the use of advanced imaging modalities (~10%),<sup>28</sup> laparoscopy followed by laparotomy was found to be cost-effective when compared to laparotomy alone, with an ICER of \$40,000/QALY.

**Different Sequences of therapy**—Wong et al. obtained clinical data from previous multicenter phase II and randomized phase III trials and devised a Markov model that incorporated nine possible mCRC treatment strategies and sequences.<sup>29</sup> The following outcomes were observed: FOLFOX, when compared to 5FU in the first-line setting, had an ICER of \$102,347; FOLFOX with bevacizumab, when compared to FOLFOX in the first-line setting, had an ICER of \$170,896; Cetuximab and irinotecan when compared to cetuximab alone in the third-line setting, had an ICER of \$243,096. The cost of targeted agents and their associated efficacy, rather than the sequence of first-line therapy, were found to be the primary drivers of the model. Although not likely to have had a substantial impact on the results, the model was limited by the failure to incorporate significant adverse effects, health utilities, and QALYs.

### Discussion

With the rising drug costs in the US, cost-effective treatment strategies for mCRC are becoming increasingly important. Our analysis revealed varying levels of value amongst current treatment strategies. Older agents that are now available in generic form such as 5FU, irinotecan, and oxaliplatin appear to be high value, cost-effective treatments. More modern agents, targeting the *EGFR* or *VEGF* pathways such as bevacizumab, cetuximab and panitumumab appear to not be cost-effective treatments and are deemed to be of low value at their current cost. However, with the use of biomarkers such as *RAS* mutational analysis, *EGFR* targeted agents can potentially be more cost-effective.

Our analysis also revealed the difficulties in making comparisons between different cost-effectiveness studies. We attempted to reduce these limitations by excluding international data that were not presented in US\$.<sup>30</sup> However, even with this simplification, the scope of costs considered in different studies was highly variable, which makes comparisons exceedingly difficult.

Furthermore, the “threshold” for the definition for a cost-effective healthcare intervention remains undefined. Previous analyses suggested that the threshold was \$50,000/QALY based on the cost-effectiveness of dialysis.<sup>31</sup> More recent analysis revealed that this value should be updated to approximately \$130,000/QALY.<sup>32</sup> In other fields of medicine we note some excellent examples of treatments that are highly cost-effective. For example, hip or knee replacement surgery is estimated to cost less than \$20,000 per QALY.<sup>33</sup> Cataract surgery has also been found to cost less than \$20,000/QALY.<sup>34</sup> In the field of global health, the distribution of mosquito nets is frequently mentioned as a highly cost-effective health intervention at a cost of just \$34 per life year gained.<sup>35</sup>

The question of how to make new cancer drugs more cost-effective is multifactorial. More impressive survival benefits as recently proposed by the American Society of Clinical Oncology would improve the cost-effectiveness profile.<sup>36</sup> Using biomarkers to treat only the patients likely to get a significant survival benefit would also improve cost-effectiveness. Furthermore, reduced prices would of course improve the value of such therapies. Variable dosing strategies, including the duration of therapy also impact the overall cost of care, and thus the cost-effectiveness. Attention should be paid to these important factors in the design and development of clinical trials.

Ultimately however, currently in the US, neither clinicians nor policy-makers make decisions based on the cost-effectiveness of a certain therapy. A recent editorial in the *Journal of Clinical Oncology* noted that “...cost effectiveness research has become an academic exercise of no meaningful consequence...”.<sup>37</sup> While the findings of cost-effectiveness analyses regarding patients with mCRC provide variable findings regarding the value of these interventions, the approaches utilized offer benchmarks for assessing and comparing the merits of therapy using common terminology. Future approaches should use a standardized method to evaluate the cost-effectiveness of new drugs and technologies prior to their arrival in the US market-place. This will help to provide an appropriate cost for the benefit that new treatments provide.

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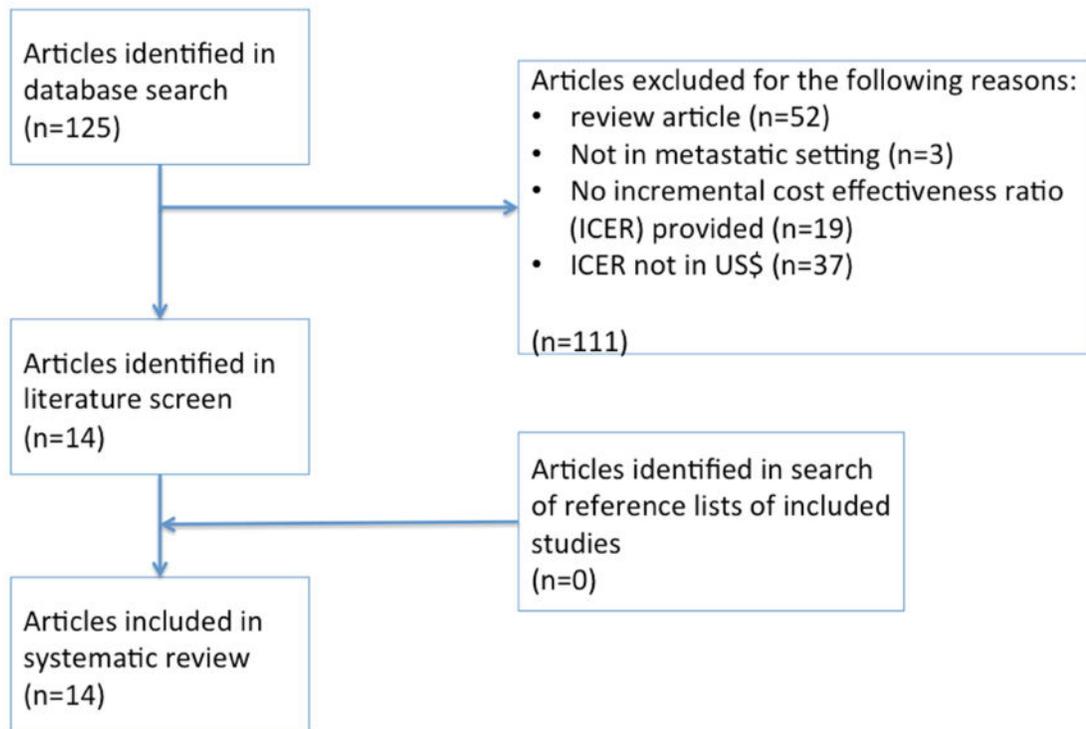


Figure 1. selection of articles for review

Table 1

## summary of studies evaluating value of treatment strategies

Study First author	Pharma funded?	Description	Cost (\$)	LYs	QALYs	\$/LY	\$/QALY
<b>Conventional Chemotherapy</b>							
Howard <sup>15</sup>	no	Value of Irinotecan, capecitabine, oxaliplatin, bevacizumab, and cetuximab.	37,100	0.57		66,200	99,100
Tuneh <sup>14</sup>	no	FOLFIRI vs FOLFOX	5,314	0.10	0.082	53,140	65,170
Hillner <sup>11</sup>	yes	IFL vs FOLFOX	29,523	0.37		80,407	
Wong <sup>29</sup>	yes	5FU/LV vs FOLFIRI followed by FOLFOX	57,689	0.70		102,347	
Wong	Yes	FOLFIRI=>FOLFOX vs FOLFIRI/bevacizumab => FOLFOX => Cetuximab	67,313	0.41		170,896	
Wong	yes	FOLFIRI/bevacizumab => FOLFOX => Cetuximab vs FOLFOX/bevacizumab => irinotecan => cetuximab/irinotecan	44,388	0.16		243,096	
<b>Bevacizumab</b>							
Goldstein <sup>16</sup>	No	First-line bevacizumab	60,551	0.14	0.10	438,779	571,240
		Bevacizumab beyond progression	39,321	0.16	0.11	235,455	364,083
Shankaran <sup>17</sup>	yes	First-line chemotherapy	58,776	0.78		75,354	
Shankaran	yes	First-line bevacizumab	32,004	0.36		88,900	
<b>KRAS / EGFR inhibitors</b>							
Behl <sup>19</sup>	no	KRAS/BRAF screening with anti-EGFR therapy	22,033	0.034		650,000	
Vijayaraghavan <sup>20</sup>	yes	Irinotecan/cetuximab for KRAS WT and FOLFIRI for KRAS mutated, compared to Irinotecan/cetuximab for KRAS WT and no chemotherapy for KRAS mutated.	36,148	-		35,539	
<b>Regorafenib</b>							
regorafenib	no	Third-line regorafenib	40,000	0.13	0.04	310,000	897,000
<b>Genetic / Pharmacokinetic</b>							
Goldstein <sup>23</sup>	no	Pharmacokinetically guided FOLFOX	13,004	0.61	0.57	21,423	22,695
Gold <sup>22</sup>	no	UGT1A1 screening prior to irinotecan therapy.	272		0.0016		Dominated <sup>a</sup>
<b>Hepatic resections</b>							
Abbott <sup>26</sup>	no	Resection/REFA vs 2-stage hepatectomy for bilobar liver metastases					Dominated <sup>b</sup>
Karuna <sup>27</sup>	no	Laparoscopy vs Laparotomy prior to resection of hepatic metastases	500		0.02		Dominated <sup>c</sup>
Bang <sup>25</sup>	no	Multi-site cryoablations	73,900	1.97		37,513	

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<sup>a</sup>UGT1A1 testing dominated no testing ie - costs were reduced while also improving quality of life.

<sup>b</sup>Resection/RFA was better both in terms of cost and efficacy. It cost total of \$37,120 for 46.2 months survival. 2-stage hepatectomy cost \$62,198 for 35.9 months.

<sup>c</sup>Laparoscopy prior to laparotomy dominates the strategy of proceeding directly to laparotomy. I.e. it is less expensive and yields more QALYs to perform laparoscopy before planned laparotomy in these patients.