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# A retrospective observational study to estimate the attrition of patients across lines of systemic treatment for metastatic colorectal cancer in Canada

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## ABSTRACT

**Background** Selection and sequencing of treatment regimens for individual patients with metastatic colorectal cancer (mCRC) is driven by maintaining reasonable quality of life and extending survival, as well as by access to and cost of therapies. The objectives of the present study were to describe, for patients with mCRC, attrition across lines of systemic therapy, patterns of therapy and their timing, and *KRAS* status.

**Methods** A retrospective chart review at 6 Canadian academic centres included sequential patients who were diagnosed with mCRC from 1 January 2009 onward and who initiated first-line systemic treatment for mCRC between 1 January and 31 December 2009. Death was included as a competing risk in the analysis.

**Results** The analysis included 200 patients who started first-line therapy. The proportions of patients who started second-, third-, and fourth-line systemic therapy were 70%, 30%, and 15% respectively. Chemotherapy plus bevacizumab was the most common first-line combination (66%). The most common first-line regimen was FOLFIRI plus bevacizumab. *KRAS* testing was performed in 103 patients (52%), and 38 of 68 patients (56%, 19% overall) with confirmed *KRAS* wild-type tumours received an epidermal growth factor receptor inhibitor (EGFRi), which was more common in later lines. Most *KRAS* testing occurred after initiation of second-line therapy.

**Conclusions** In the modern treatment era, a high proportion of patients receive at least two lines of therapy for mCRC, but only 19% receive EGFRi therapy. Earlier *KRAS* testing and therapy with an EGFRi might allow a greater proportion of patients to access all 5 active treatment agents.

**Key Words** Treatment patterns, epidermal growth factor inhibitor, *KRAS* testing, anti–vascular growth factor agents, chemotherapy

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## INTRODUCTION

Despite dramatic survival improvements after the introduction of new systemic chemotherapies and biologically targeted therapies in the early 2000s, colorectal cancer remains an area of high unmet medical need[1]. Patients with metastatic colorectal cancer (mCRC) are eligible for several lines of treatment, beginning with the regimen deemed most appropriate after an informed discussion between physician and patient[2]. Combination regimens with chemotherapy backbones consisting of either oxaliplatin or irinotecan in combination with a fluoropyrimidine—5-fluorouracil (5FU) or capecitabine—are the most common first- and second-line systemic chemotherapy regimens[2].

Treatment regimens for patients with mCRC have evolved as new agents have become available[3]. Evidence demonstrating the benefits of biologic agents has added to the therapeutic options for mCRC, with the anti–vascular

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growth factor biologic bevacizumab becoming available in Canada in 2005, followed in 2008 by the epidermal growth factor (EGFR) inhibitors panitumumab and cetuximab for third-line therapy in patients with mCRC[4–7].

The incorporation of routine genetic testing for patients with mCRC was recommended in 2010 by Canadian expert group consensus, based on evolving biomarker science at the time. Initially, EGFR inhibitors were marketed for use only in patients with *KRAS* wild-type tumours[4,7]. The prevalence and timing of *KRAS* testing and its relationship to the use of EGFR inhibitors is important in understanding treatment patterns in those patients[8].

Overall, the selection and sequencing of treatment regimens for individual patients with mCRC is governed by the overriding goals of maintaining a reasonable quality of life while extending survival. Data from American and two centre-specific Canadian analyses have provided some insight into practice patterns for the management of mCRC in North America[1,3,9–12]. Because a comprehensive national database was not readily available, the present study was undertaken to gain further insight into mCRC treatment practices across Canada.

The primary objectives of the study were to estimate, by line of treatment, the proportion of patients initially treated with first-line systemic therapy for mCRC who go on to receive subsequent systemic therapy ("patient attrition") and to analyze treatment patterns in multiple centres across Canada, including exposure to the 5 classes of agents currently approved for the treatment of mCRC.

## METHODS

### Study Design

This retrospective medical chart review was conducted at 6 major cancer centres across Canada. Data were collected through chart reviews of patients who had been diagnosed with mCRC and who had received at least 1 systemic treatment (any one or a combination of chemotherapy, biologic therapy, and investigational therapy).

### Eligibility Criteria and Data Collection

Eligible patients with mCRC were identified from medical records (paper and electronic) at participating Canadian oncology treatment centres in the provinces of British Columbia, Ontario, and Quebec. The analysis included sequential adult patients who were diagnosed with mCRC on or after 1 January 2009 and who initiated first-line systemic treatment between 1 January 2009 and 31 December 2009. The index year 2009 was chosen because of the availability of EGFR inhibitors in mid- to late 2008; thus, all patients should have had access to those agents in third-line therapy. All patients had metastatic disease in 2009, but might not have had metastatic disease at the time of the original diagnosis. Patients for whom the start date of any line of systemic treatment for mCRC was unknown or who received chemotherapy for diseases other than mCRC in the 3 years preceding the index date were excluded. The index date for each patient was defined as the date of initiation of first-line systemic treatment for mCRC. In each patient chart, a window of 6 months before the index date was examined to confirm the dates of the mCRC diagnosis and the start of first-line systemic treatment. A 3-year window before the index date was also examined to obtain details concerning any adjuvant treatment; thus, the entire study period ran from 1 January 2006 (3 years before 1 January 2009) to the end of the chart review process, which was approximately July–December 2014.

### Endpoints

The primary endpoint was the proportion of patients who received first-line therapy and who went on to receive subsequent lines of systemic therapy for mCRC, by line of therapy. A new line of therapy was defined as the initiation of a new regimen after the end of the previous line of therapy or a break in treatment of more than 120 days followed by subsequent treatment (whether the same systemic agents from the prior line or new systemic agents were administered after that time point). The following scenarios did not constitute a new line of therapy: a change in regimen after the first cycle because of intolerance; discontinuation of a single drug in a multi-drug regimen; addition or discontinuation of a biologic agent being used in combination with other systemic treatments; a break in treatment of 120 days or less, with re-initiation of the prior treatment regimen. Secondary endpoints were the proportions of patients who received various types of systemic agents, duration of each line of therapy, time between the lines of therapy, the proportion of patients who underwent *KRAS* testing, and the timing and geographic variation of that testing and its relationship with EGFR inhibitor treatment.

### Statistical Analysis

Proportions and 95% confidence intervals (CIs) for patients receiving various lines of treatment were calculated for all registered patients. Patients were categorized into subgroups based on *KRAS* testing, *KRAS* status, use of an EGFR inhibitor, and use of an EGFR inhibitor in patients with *KRAS* wild-type disease. Patients were considered evaluable for timing of *KRAS* status if the date of testing was available in the chart. Subgroup analyses by province were also performed. Kaplan–Meier estimates for proportions were also computed, censoring patients without the event of interest at their last date of contact or death. Cumulative incidence rates were calculated, with death as a competing risk[13]. A sensitivity analysis was conducted using an alternative definition of a new line of therapy as only the initiation of a new regimen after the end of the previous line of therapy regardless of any break in treatment.

## RESULTS

### Patients

Table I presents patient demographics and baseline characteristics for the patients with mCRC who initiated first-line systemic therapy in 2009. Median age at initiation of first-line therapy was 62 years. Most patients presented with stage IV mCRC at diagnosis. In this cohort of patients, 94% had colon cancer; the remaining 6% had rectal cancer. Over the course of the analysis, 142 patients (71%) died; the Kaplan–Meier estimate for median time to death for all patients registered to the study was 24.7 months (95% CI: 22.2 months to 29.6 months).

## Lines of Therapy Received

Of the 200 patients who received first-line therapy, 139 (70%; 95% CI: 63% to 76%) started second-line therapy, 60 (30%; 95% CI: 24% to 37%) started third-line therapy, and 29 (15%; 95% CI: 10% to 20%) started fourth-line therapy. Median lines of therapy was 2, with a maximum of 9 (1 patient). Median weeks of treatment were 26 (range: 1–228 weeks), 16 (range: 1–168 weeks), 16 (range: 2–101 weeks), and 14 (range: 4–42 weeks) for the first, second, third, and fourth lines of systemic therapy respectively. Because death was a competing risk for proceeding to a subsequent line of therapy, we examined the proportions of patients who died before proceeding to the next line of therapy. Of the patients who had initiated a prior line of therapy, 40 of 200 (20%), 58 of 139 (42%), and 21 of 60 (35%) died before proceeding to a second, third, and fourth line of therapy respectively.

## Regimens Used

We examined the proportions of patients who received chemotherapy alone, chemotherapy plus a biologic, and biologic agents alone. Of all 200 patients, most ($n$ = 164, 82%) received chemotherapy plus a biologic at some point in their treatment. The use of chemotherapy plus a biologic was most common during first-line therapy (69%; 95% CI: 62% to 75%). Chemotherapy alone was used most frequently in second-line therapy (42%; 95% CI: 35% to 48%), and biologic therapy alone was most common in third- and fourth-line therapy [7% (95% CI: 4% to 11%) in each line].

**TABLE I** Demographics and baseline characteristics for the 200 study patients

| Characteristic | Value |
|---|---|
| Age at index date (years) | |
| Median | 61.5 |
| Range | 20–86 |
| Age group [*n* (%)] | |
| <65 Years | 119 (60) |
| ≥65 Years | 81 (40) |
| Type of CRC [*n* (%)] | |
| Colon | 188 (94) |
| Rectum | 12 (6) |
| Stage at initial diagnosis [*n* (%)] | |
| I | 3 (2) |
| II | 17 (9) |
| III | 25 (13) |
| IV | 155 (78) |
| Time from mCRC diagnosis to first-line therapy (days) | |
| Median | 49 |
| Range | 1–485 |
| Prior adjuvant therapy [*n* (%)] | 10 (5) |

(m)CRC = (metastatic) colorectal cancer.

Table II shows the top 3 regimens for each line of therapy and their durations. The most common first-line regimen was FOLFIRI (leucovorin–fluorouracil–irinotecan) plus bevacizumab. In second line, mFOLFOX6 (leucovorin–fluorouracil–oxaliplatin, modified) was the most common regimen. The most common third-line regimen was EGFR inhibitor combination therapy. In the fourth line, the most common regimen was EGFR inhibitor monotherapy.

We also examined the use of biologics across all lines of therapy: biologic combinations or monotherapy were used in all four lines (Table II). Bevacizumab-containing therapies were the most frequent in the first three lines of therapy, being used in 132 (66%), 50 (36%), 16 (27%), and 2 (7%) patients in the first, second, third, and fourth line respectively. No patients received an EGFR inhibitor

**TABLE II** Frequency and duration of use of the top 3 regimens and biologics

| Therapy line and regimen | Patients | | Duration (weeks) | |
|---|---|---|---|---|
| | *(n)* | (%) | Median | Range |
| *First line* | 200 | | | |
| FOLFIRI–bevacizumab | 104 | 52 | 33 | 2–228 |
| mFOLFOX6 | 24 | 12 | 25 | 2–48 |
| mFOLFOX6–bevacizumab | 15 | 8 | 28 | 6–67 |
| *Second line* | 139 | | | |
| mFOLFOX6 | 51 | 37 | 16 | 2–50 |
| FOLFIRI–bevacizumab | 28 | 20 | 18 | 4–168 |
| FOLFIRI | 12 | 9 | 17 | 2–95 |
| EGFRi combination therapy[a] | 5 | 4 | 15 | 10–97 |
| EGFRi monotherapy | 1 | 1 | 40 | 40–40 |
| *Third line* | 60 | | | |
| EGFRi combination therapy[a] | 12 | 20 | 20 | 4–101 |
| EGFRi monotherapy | 10 | 17 | 20 | 2–42 |
| mFOLFOX6 | 10 | 17 | 17 | 9–42 |
| FOLFIRI–bevacizumab | 9 | 15 | 15 | 4–93 |
| *Fourth line* | 29 | | | |
| EGFRi monotherapy | 7 | 24 | 12 | 4–42 |
| FOLFIRI | 5 | 17 | 16 | 6–37 |
| mFOLFOX6 | 3 | 10 | 16 | 12–22 |
| EGFRi combination therapy[a] | 2 | 7 | 26 | 21–31 |

[a] Includes panitumumab, panitumumab–irinotecan, panitumumab–FOLFIRI, panitumumab–bevacizumab, cetuximab, cetuximab–irinotecan, cetuximab–FOLFIRI, cetuximab–XELIRI–bevacizumab, cetuximab–XELOX, cetuximab.

FOLFIRI = leucovorin–5-fluorouracil–irinotecan; mFOLFOX6 = leucovorin–5-fluorouracil–oxaliplatin, modified; EGFRi = inhibitor of the epidermal growth factor receptor; XELIRI = irinotecan–capecitabine; XELOX = oxaliplatin–capecitabine.

(cetuximab or panitumumab) during first-line therapy. In the second line, 1% of patients received an EGFR inhibitor as monotherapy, and 4% received one as part of combination therapy. In the third line, 17% of patients received an EGFR inhibitor as monotherapy, and 20% received one as part of combination therapy. In the fourth line, 24% of patients received an EGFR inhibitor as monotherapy, and 7% received one as part of combination therapy. Overall, 7% of patients received cetuximab and 2% received panitumumab as part of combination therapy, and 3% of patients received cetuximab and 9% received panitumumab as monotherapy.

All patients registered to the study received at least 1 of the 5 therapeutic drug classes available for mCRC [5FU (or capecitabine), bevacizumab, an EGFR inhibitor, irinotecan, and oxaliplatin] either alone or in various combinations (Figure 1). Almost all patients (88%) received at least 3 of the 5 agents, and 39% received 4 agents.

### *KRAS* Testing

Of the 200 patients registered to the study, only 103 (52%) underwent testing for *KRAS* status. Of those 103 patients, 32 (31%) had *KRAS*-mutant tumours, 68 (66%) had *KRAS* wild-type tumours, and 3 patients had an unknown status.

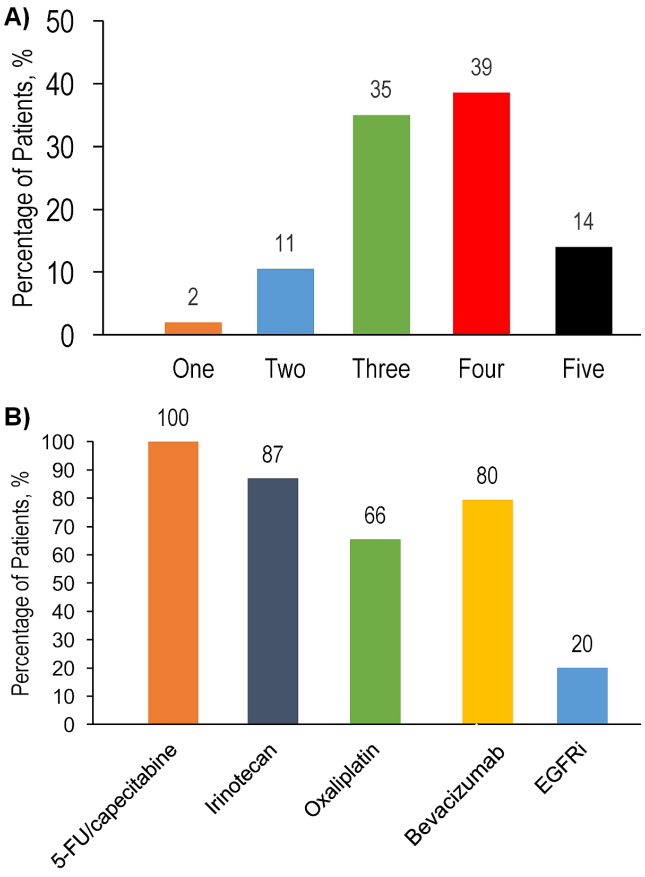


**FIGURE 1** (A) Percentage of patients who received 1, 2, 3, 4, or all 5 of the agents available for metastatic colorectal cancer at some point during therapy. (B) Percentage of patients who received each agent during therapy, either alone or in combination with another therapy. 5-FU = 5-fluorouracil; EGFRi = epidermal growth factor receptor inhibitor.

All but 1 of the patients who underwent *KRAS* testing were tested after their metastatic diagnosis. The *KRAS* testing was most commonly done after initiation of second-line therapy: 6 of 103 (6%) were tested before initiating any therapy; 18 (17%) were tested after initiating first-line therapy; 58 (56%), after initiating second-line therapy; 15 (15%), after initiating third-line therapy; 2 (2%), after initiating fourth-line therapy; and 1 (1%), after initiating fifth-line therapy. For the other 3 patients, date information was missing. For all evaluable patients, median time to *KRAS* testing was 160.6 weeks.

Of the 68 patients with *KRAS* wild-type tumours, 38 (56%) received an EGFR inhibitor at some point after testing. Another 2 patients (1 with unknown *KRAS* status and 1 who was not tested) also received an EGFR inhibitor. Table III presents the event that followed *KRAS* testing. Of the 68 patients with *KRAS* wild-type tumours, 31 (46%) received an EGFR inhibitor as the next event after *KRAS* testing, and 19 (28%) died within 120 days of testing without receiving subsequent therapy. The cumulative incidence of *KRAS* testing with death as a competing risk after 3 years was 55%, 40%, and 51% of patients in British Columbia, Ontario, and Quebec respectively (34%, 31%, and 35% of patients died without any *KRAS* testing). In the Kaplan–Meier analysis, median weeks from *KRAS* testing to the start of an EGFR inhibitor was 13 (95% CI: 3 weeks to 170 weeks) in Ontario, 28 (95% CI: 15 weeks to 92 weeks) in British Columbia, and 35 (95% CI: 17 weeks to 45 weeks) in Quebec. Relative to line of treatment, most patients were tested after initiating second-line therapy: 70% in British Columbia, 60% in Ontario, and 90% in Quebec. The frequency of testing for all lines of therapy and for all patients ranged from 30% to 70% across the study sites.

### Sensitivity Analysis

The sensitivity analysis produced results similar to those in the main analysis, demonstrating the robustness of the definition of a new line of therapy: of the 200 patients who received first-line therapy, 139 (70%), 59 (30%), and 27 (14%) proceeded to second, third, and fourth lines of therapy respectively. Of the 103 patients who underwent *KRAS* testing, 6% were tested before initiating any therapy; 12%, after initiating first-line therapy; 62%, after initiating second-line therapy; 17%, after initiating third-line therapy; 2%, after initiating fourth-line therapy; and 1%, after initiating fifth-line therapy.

## DISCUSSION

This retrospective observational study summarizes treatment patterns in 200 patients with mCRC receiving systemic therapy at 6 major cancer centres across Canada. Although systemic treatment was common for patients with mCRC, our analysis of the number of patients proceeding to subsequent lines of therapy with death as a competing risk showed a progressive decline in the proportion of patients receiving subsequent therapy, with 70%, 30%, and 15% receiving second-, third-, and fourth-line therapy respectively. Chemotherapy plus bevacizumab was the most common combination used in first-line therapy. The regimens most commonly used in the second, third, and fourth lines

**TABLE III** Next event after *KRAS* testing in the study patients

| Event | *KRAS* wild-type[a] | | | | *KRAS* mutated[b] | | | |
|---|---|---|---|---|---|---|---|---|
| | Patients | | Time to event (weeks) | | Patients | | Time to event (weeks) | |
| | *(n)* | (%) | Median | 95% CI | *(n)* | (%) | Median | 95% CI |
| EGFRi treatment[c] | 31 | 46 | 13.1 | 5.9 to 23.0 | 0 | NA | NA | NA |
| Non-EGFRi treatment | 14 | 21 | 10.9 | 0 to 47.0 | 11 | 34 | 9.9 | 4.3 to 30.1 |
| Death | 19 | 28 | 8.6 | 5.6 to 12.7 | 17 | 53 | 18.3 | 12.7 to 37.9 |
| End of study | 4 | 2 | 16.6 | 6.4 to 26.0 | 4 | 13 | 19.6 | 6.9 to 51.1 |

[a] For 68 evaluable patients. Time to event considers 66 patients because of missing dates for 2 patients testing as *KRAS* wild-type.
[b] For 32 evaluable patients.
[c] Monotherapy or combination therapy. Includes panitumumab, panitumumab–irinotecan, panitumumab–FOLFIRI, panitumumab–bevacizumab, cetuximab, cetuximab–irinotecan, cetuximab–FOLFIRI, cetuximab–XELIRI–bevacizumab, cetuximab–XELOX, cetuximab.
CI = confidence interval; EGFRi = inhibitor of the epidermal growth factor receptor; NA = not applicable; FOLFIRI = leucovorin–5-fluorouracil–irinotecan; XELIRI = irinotecan–capecitabine; XELOX = oxaliplatin–capecitabine.

were, respectively, mFOLFOX6, combination therapy with an EGFR inhibitor, and EGFR inhibitor monotherapy. The EGFR inhibitors or chemotherapy alone were more common in later than in earlier lines of therapy. Most patients received at least 3 of the 5 classes of therapy (5FU or capecitabine, irinotecan, oxaliplatin, bevacizumab, and EGFR inhibitor), and many received at least 4 of the 5 classes. Overall, those results provide a snapshot of treatment patterns in patients with mCRC from 2009 to 2014 in Canada and demonstrate that, overall, treatment accorded with published guidelines at that time[5].

Several studies have examined treatment patterns in patients with mCRC in the United States. In those studies, 45%–53% of patients received second-line treatment, 19%–28% received third-line treatment, and 13%–14% received fourth-line treatment[1,3,10,11]. The proportions of patients who proceeded to second-line treatment were lower than those observed in our study, which might reflect differences between the studies such as drug availability, system or access differences, or differences in study methods (for example, claims database vs. retrospective observational study). For example, the study by Song *et al.*[3] might have underestimated the proportion of patients proceeding to subsequent lines, because the follow-up time might have been insufficient for some patients. Each of the studies also showed some variation in the definition of a new line of therapy; however, our sensitivity analysis defining a new line of therapy as the initiation of a new regimen regardless of any break in treatment demonstrated results consistent with those in the primary analysis, suggesting that such differences in definition are unlikely to be the main contributor to the observed differences. Importantly, however, previous studies examined time ranges earlier than that examined in our study (2001–2005[3], 2003–2006[11], 2004–2008[1], and 2004–2011[10] compared with 2009–2014 in the present study). The effect of improvements in survival rates since 2001 must therefore be taken into account when considering the differences. Indeed, the rate of deaths attributable to mCRC in the United States fell an average of 2.7% per year between 2004 and 2013[14].

Previous studies of patients with mCRC at single Canadian centres have reported results similar to those in the present study: McLean *et al.*[9] reported that 74%, 36%, and 16% of 215 patients treated between 2002 and 2013 received second-, third-, and fourth-line treatment respectively. Ho *et al.*[15] reported that 36% of patients received third-line therapy in a study of 321 patients treated in 2009.

Our analysis found that the most common combination treatment was chemotherapy plus bevacizumab, which is consistent with previous analyses[1,9–11]. The most common chemotherapy backbone used for first-line treatment in our study was FOLFIRI; in contrast, previous studies found FOLFOX to be the most common first-line chemotherapy regimen[1,9,11]. Because FOLFOX and FOLFIRI are associated with similar outcomes[16], that difference in the choice of first-line chemotherapy is not surprising and is likely to be a reflection of physician or patient preference, or provincial or national reimbursement restrictions.

All patients in our study received at least 1 of the 5 therapeutic drug classes available to treat mCRC (5FU or capecitabine, irinotecan, oxaliplatin, EGFR inhibitor, bevacizumab), 88% received at least 3, and many received 4 or more. In comparison, in the McLean *et al.*[9] study in Canada, 89% of patients received at least 3 of the 5 agents. The other single-centre Canadian study by Ho *et al.*[15] reported that 36% of patients received 5FU (or capecitabine), irinotecan, and oxaliplatin (3 of the 5 agents). A separate U.S. study reported that 19% of patients received 3 of the 5 agents, and 11% received all 5—rates lower than those observed in our study, possibly reflecting the present study's more current treatment era, with its improved survival rates[1].

Approximately half the patients in our study underwent *KRAS* testing, which occurred after initiation of second-line therapy in 80% of those patients. The frequency of *KRAS* testing was similar in all the participating provinces. Most patients with *KRAS* wild-type tumours received an EGFR inhibitor, most frequently during the third line of treatment; however, after testing, a significant proportion of patients with wild-type *KRAS* died without receiving an EGFR inhibitor. The pattern of *KRAS* testing and the low proportion of patients treated with EGFR inhibitors is

explained primarily by the use of those agents in patients with chemotherapy-refractory disease, which in turn was likely driven by differences in funding for EGFR inhibitors in that setting[17]. Given recent studies that have demonstrated a benefit for the earlier use of EGFR inhibitors, particularly for patients with left-sided malignancies in the first-line setting[18–22], resources to allow for earlier *KRAS* testing and use of those agents will be required to translate the observed benefit to patients.

The present multicentre study examined real-world treatment patterns in patients with MCRC in an era in which all 5 active agents were available; however, some limitations apply. We examined treatment patterns in the most populous provinces—Ontario, Quebec, and British Columbia—and so our results might be specific to those regions. The use of data from sequentially registered patients reduced the potential for selection bias. However, the study was limited by the use of academic sites only, which could have had patient populations not reflective of broader practice settings. Indeed, the rate of rectal cancer observed in our study was considerably lower than the expected rate of 30%[23]. Because of the retrospective nature of the study, which relied on patient records, the proportion of rectal cancers might have been underestimated because of misclassification, which has been reported for up to 39% of patients with rectal cancer[24]. Furthermore, access to *KRAS* testing and EGFR inhibitors might have been delayed in some centres during the study period—a factor that would not apply today[8,25].

## CONCLUSIONS

In this study, we reviewed treatment patterns in the modern era of MCRC therapy and cancer genotyping at 6 large Canadian centres. A higher-than-previously-reported proportion of patients proceeded to second-line therapy. Most patients received biologics as part of their therapy and had access to 3 of the 5 classes of therapy. Given the emerging evidence of the benefit from EGFR inhibitors in earlier lines of therapy, changes in policies to permit earlier testing for predictive biomarkers and earlier access to those inhibitors are warranted.

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### CONFLICT OF INTEREST DISCLOSURES

We have read and understood *Current Oncology*'s policy on disclosing conflicts of interest, and we declare the following interests: This study was funded by Amgen. HK has participated in clinical trials and advisory boards for Hoffman–La Roche, Sanofi, and Amgen. SB has participated in advisory boards sponsored by Amgen and Lilly, and has received speaking honoraria from Amgen. JM has participated in clinical trials, advisory boards, and educational events for Amgen. PK has received educational grants from Amgen, Novartis, Ipsen Biopharmaceuticals, Celgene, and Taiho Pharma Canada, and has participated in advisory boards with Amgen, Novartis, Ipsen Biopharmaceuticals, Celgene, Taiho Pharma Canada, Pfizer, and AstraZeneca. NA has participated in clinical trials and advisory boards with Amgen and Roche. FC has no conflicts of interest to disclose. MPC and BG are former employees of Amgen Canada and have stock or stock options in the company.

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