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# Population-based estimates of survival and cost for metastatic melanoma

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## ABSTRACT

**Background** Fewer than half of all patients with metastatic melanoma survive more than 1 year. Standard treatments have had little success, but recent therapeutic advances offer the potential for an improved prognosis. In the present study, we used population-based administrative data to establish real-world baseline estimates of survival outcomes and costs against which new treatments can be compared.

**Methods** Data from administrative databases and patient registries were used to find a cohort of patients with metastatic melanoma in Ontario. To identify individuals most likely to receive new treatments, we focused on patients eligible for second-line treatment. The identified cohort had two characteristics: no surgical resection beyond primary skin excision, and receipt of first-line systemic therapy.

**Results** Patient characteristics, Kaplan–Meier survival curves, and mean costs are reported. Of the 33,585 patients diagnosed with melanoma in Ontario from 1 January 1991 to 31 December 2010, 278 met the study inclusion criteria. Average age was 63 years, and 62% of the patients were men. Overall survival was estimated to be 19%, 12%, and 6% at 12, 24, and 60 months respectively. Mean survival time was 11.5 months, and mean cost was $30,685.

**Conclusions** Our baseline estimates indicate that survival outcomes are poor and costs are high for patients receiving standard treatment. Understanding the relative improvement accruing from any new treatment requires a comparison with the existing standard of care.

**Key Words** Metastatic melanoma, population-based data, real-world, effectiveness, cost, comparative effectiveness research

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## BACKGROUND

The global incidence of malignant melanoma has increased, particularly in the Western world, and as a result, melanoma has become an important health policy issue[1]. Although melanoma is predicted to account for only approximately 3% of all new cancers diagnosed in Canada in 2014[2], it is the most aggressive form of skin cancer and generally fatal if it spreads beyond the primary site in the skin[1].

The Canadian Cancer Society estimated that approximately 6500 new cases of malignant melanoma and 1050 melanoma-related deaths would occur in Canada in 2014[2]. Primary melanoma usually presents as a changing lesion on the skin. If detected early, it can be cured with surgery alone[3]. Standard treatment options for metastatic melanoma have traditionally included chemotherapy, radiation therapy, and immunotherapy[4], which have been much less successful than the options for primary disease, resulting in median survival times of less than 1 year in patients with distant metastasis[5,6]. When an initial treatment for metastatic melanoma has not been successful, no standard second-line treatment has been available[7], although enrolment in a clinical trial remains a possibility.

Recent advances in immunotherapy and targeted drug therapies have demonstrated potential in terms of improved survival for metastatic patients[8,9]. For example, the immunotherapeutic agent ipilimumab has demonstrated an ability to augment the immune response against melanoma[10], thus helping to prolong the lives of people with advanced melanoma[11,12]. Targeted therapies such as vemurafenib and dabrafenib have also been shown to significantly increase overall survival[13]. Starting in 2011, these new therapies began to be approved and adopted for the treatment of patients with metastatic disease[9,14].

As new approaches for the treatment of metastatic melanoma are developed, health policy decisions can

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benefit from the establishment of a baseline against which new treatments can be compared and their relative improvement appraised. The objective of the present study was to estimate the effectiveness and cost of the standard of care at the time that new treatments are being introduced. Accordingly, we estimated overall survival (as a baseline measure for the real-world effectiveness of the existing standard of care) and costs for a cohort of metastatic melanoma patients. Using population-based administrative data, which reflect the real-world impact of existing treatments, we established baseline estimates. The analysis was focused on an Ontario cohort of patients with metastatic melanoma who would be eligible for second-line treatment and, consequently, likely candidates for newly developed therapies.

## METHODS

### Data

The Ontario Cancer Data Linkage Project ("cd-link," http://www.ices.on.ca/Research/Research-programs/Cancer/cd-link) links administrative data about cancer patients in Ontario from multiple administrative databases and registries, including the Ontario Cancer Registry, the Canadian Institute for Health Information's Discharge Abstract Database (CIHI-DAD), the National Ambulatory Care Reporting System (NACRS) Database, the Ontario Health Insurance Plan (OHIP) Claims Database, the Ontario Drug Benefit claims database, the New Drug Funding Program database, and the Ontario Home Care Administrative System and Home Care Database. These administrative datasets provide information about physician services, hospitalizations, cancer clinic visits, prescription drugs, home care, basic demographics, tumour characteristics, and vital statistics.

We acquired risk-reduced coded data for all patients diagnosed with malignant melanoma in Ontario from 1 January 1991 to 31 December 2010. Table I describes the administrative sources and data used in the cohort selection and analysis.

### Cohort Identification

To identify patients most likely to be candidates for newly developed treatments, we screened patients based on two criteria (Figure 1):

- no surgical resection beyond primary skin excision, and
- receipt of first-line systemic chemotherapy during or after 2003.

The presence of both criteria indicated a patient with unresectable metastatic melanoma who had received what was considered standard first-line therapy in the period before 2011[3,9]. The use of 2003 as a starting point allowed for up to 8 years of follow-up.

Between 1 January 1991 and 31 December 2010, 33,585 people in Ontario were diagnosed with malignant melanoma. In step 1, we used the appropriate Canadian Classification of Health Interventions codes for a resection or excision to exclude patients whose records in the CIHI-DAD and NACRS datasets showed surgical resection for any site other than the primary skin resection. Such resections were deemed to have been related to the metastatic melanoma. This group consisted of patients who had undergone surgical resection for any site other than the skin from 6 months before diagnosis to any time after diagnosis, and those who had undergone skin resection more than 6 months after initial diagnosis.

In step 2, we investigated chemotherapy use in the remaining patients. Because systemic chemotherapy has traditionally been used to treat metastatic melanoma[5,6], chemotherapy use was taken to indicate the presence of both metastatic disease and first-line therapy. We relied on variables in the CIHI-DAD, NACRS, and OHIP datasets to

**TABLE I** Administrative sources and data used for cohort selection and analysis

| Source | Data |
|---|---|
| Ontario Cancer Registry | Site of origin of the malignant melanoma,[a] date of last contact with the patient, vital status, age, sex |
| CIHI Discharge Abstract Database | Date of hospital admission, intervention code,[b] resource utilization |
| National Ambulatory Care Reporting System Database | Date of care episode,[c] intervention code,[b] most responsible diagnosis,[d] resource utilization[e] |
| OHIP Claims Database | Physician services,[f] date provided, fee paid |
| Ontario Drug Benefit Claims Database | Total amount paid by the Ministry of Health and Long-Term Care, dispensing date |
| New Drug Funding Program Database | Disease, drug name, dispensing date |
| Ontario Home Care Administrative System and Home Care Database | Type of service, date provided, duration[g] |

[a] International Classification of Diseases, 9th revision.
[b] Canadian Classification of Health Interventions.
[c] Includes emergency room visits, day procedures, and cancer clinic visits.
[d] Canadian version of the International Classification of Diseases, 10th revision.
[e] Based on resource intensity weights.
[f] Ontario Health Insurance Plan Schedule of Benefits.
[g] For services delivered on an hourly basis.
CIHI = Canadian Institute for Health Information; OHIP = Ontario Health Insurance Plan.

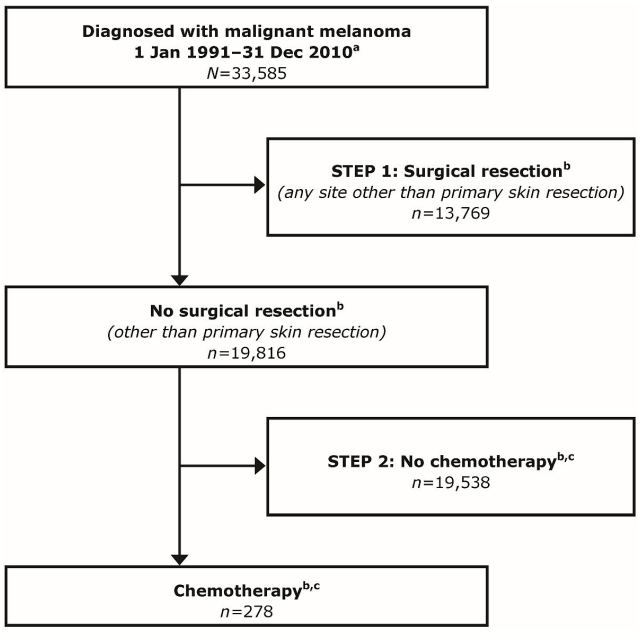


**FIGURE 1** Cohort selection. [a]Based on codes (International Classification of Diseases, 9th revision) in the Ontario Cancer Registry. [b]Based on codes (Canadian Classification of Health Interventions) in the Canadian Institute for Health Information's Discharge Abstract Database and National Ambulatory Care Reporting System Database. [c]Based on the Ontario Health Insurance Plan's Schedule of Benefits.

determine if a patient had received chemotherapy after being diagnosed with malignant melanoma and when the chemotherapy was given. More specifically, we used Canadian Classification of Health Interventions codes from the CIHI-DAD and NACRS datasets and fee codes from the OHIP dataset, plus variables indicating when the chemotherapy occurred, to identify the date that the patient first received chemotherapy as the date of progression to metastatic melanoma. We excluded patients who either did not receive chemotherapy during or after the year 2003 or for whom the chemotherapy received during that period was not a first instance of chemotherapy. We referred to the New Drug Funding Program dataset to ensure that the patients we thus identified as having metastatic disease did not subsequently receive interferon therapy, because such patients would be more appropriately identified as having stage III melanoma. Any patients found to have received subsequent interferon therapy were excluded from the cohort.

### Survival Estimates

We recorded time-to-event data for each patient in the cohort starting from the time of progression to metastatic melanoma to the date of last contact or death. Patients for whom a death was not recorded were treated as censored at the date of last contact. Overall survival and survival stratified by age at metastasis, presence of brain metastasis, and site of origin of the malignant melanoma were estimated using Kaplan–Meier curves. The comparison of survival for patients with and without brain metastasis was based on evidence indicating that brain metastases are an important prognostic factor for overall survival[15].

### Cost Estimates

We calculated patient costs for acute inpatient hospitalizations, ambulatory care, physician services, prescription drugs, and home care. Patient costs for hospitalizations (CIHI-DAD) and ambulatory care (NACRS) were calculated as the product of the resource weight, reflecting the intensity of service utilization for the specific episode, and the appropriate unit cost[16]. We calculated patient costs for physician services (OHIP), prescription drugs (Ontario Drug Benefit), and home care (Ontario Home Care Administrative System or Home Care Database) on a per-episode basis (for example, per prescription, per service)[16].

We estimated monthly mean costs for the various categories based on a phase-of-care approach[17,18]. Months of observation and costs of care for patients in the cohort were divided into three clinically relevant phases of care: Initial, Continuing, and Last Year of Life. We defined the Initial phase as the first 12 months after progression to metastatic melanoma. Among the patients who died, the Last Year of Life phase was defined as the final 12 months of life. The Continuing phase consisted of all months between the Initial and Last Year of Life phases. In keeping with the approach of Yabroff *et al.*[17], we first allocated costs to the Last Year of Life phase and then to the Initial phase; any remaining months were allocated to the Continuing phase. For patients who were not observed to have died after developing metastatic melanoma, we allocated costs to the Initial and Continuing phases of care. Costs were adjusted to reflect 2011 Canadian dollars based on the health care–specific Consumer Price Index.

### Statistical Analysis

Descriptive statistics, including sample sizes, means, and proportions, were calculated for the cohort. In the presence of censoring, we used a partitioned estimator[19] to estimate mean survival time and cost. This approach allowed us to account for the presence of censoring while also making use of the survival and cost histories for censored patients up to the month in which they were censored. All analyses were conducted in either the SAS (version 9.4: SAS Institute, Cary, NC, U.S.A.) or the R (version 2.15.2: The R Foundation, Vienna, Austria) software application.

## RESULTS

### Cohort Characteristics

The final study cohort consisted of 278 patients who had undergone no surgical resection beyond primary skin resection and who had received first-line systemic chemotherapy (Table II). Average age at progression to metastatic melanoma was 63 years, and 62% of the cohort were men. On average, progression to diagnosis and treatment of metastatic disease took approximately 4 years. The most common site of origin for the melanoma was the trunk area (31%). Approximately 20% of the patients were identified as having brain metastasis.

### Survival

Overall survival was approximately 19%, 12%, and 6% at 12, 24, and 60 months respectively [Figure 2(A)]. Estimated mean survival duration was 11.5 months, and estimated

median survival duration was 4.1 months. For patients more than 70 years of age at presentation with metastatic melanoma, survival was 18% and 10% at 12 and 24 months respectively. Survival at 12 and 24 months for patients 70 years of age or younger was 19% and 13% respectively [Figure 2(B)]. For patients who developed brain metastasis, survival was 17% and 9% at 12 and 18 months respectively; it was 19% and 13% at 12 and 24 months respectively for patients identified as not having brain metastasis [Figure 2(C)]. Survival also varied depending on the site of origin of the melanoma [Figure 2(D)]. Outcomes were especially poor when the site of origin was not specified (approximately 9% at about 12 months).

**Table II** Characteristics of the 278 patients with metastatic melanoma

| Characteristic | Value |
|---|---|
| Sex (%) | |
| Men | 62 |
| Women | 38 |
| Mean age (years) | |
| At 1st diagnosis of malignant melanoma | 59 |
| At progression to metastatic melanoma | 63 |
| Mean time from 1st diagnosis to progression to metastatic disease (years) | 4 |
| Brain metastasis[a] (%) | 20 |
| Site of origin (%) | |
| Head and neck[b] | 21 |
| Trunk | 31 |
| Arm | 16 |
| Leg | 15 |
| Not specified | 17 |

[a] Based on Canadian Classification of Health Interventions codes for brain radiation.
[b] Includes scalp, neck, face, lip, and ear.

## Costs

The estimated mean total cost for the cohort across all phases of care was approximately $30,685 (Table III). In conjunction with mean survival time, that total cost translates into a mean cost of $2668 per month of survival. Mean costs in the last year of life accounted for 84% of the total mean cost. Mean costs in the initial 12 months after progression and in the Continuing phase accounted for 9% and 7% of total mean costs respectively. Accordingly, all of the cost categories were highest in the Last Year of Life phase. For instance, the mean home care cost was higher by a factor of approximately 20 in the Last Year of Life phase than in the Initial phase. That cost comprised mainly nursing visits and homemaking or personal support, more than half of which was devoted to end-of-life care in the home. Of the various cost categories, acute inpatient hospitalizations represented the largest single expenditure. In contrast, the smallest amount was spent on prescription drugs. Some of the more commonly prescribed drugs were pain medications and drugs for treating or preventing the nausea and vomiting caused by chemotherapy drugs. Physician services represented approximately 20% of the total mean cost and included services such as subsequent visits after hospital inpatient services and palliative care.

Figure 3 depicts the mean monthly costs for the cohort by phase of care. Estimated mean costs were higher in the

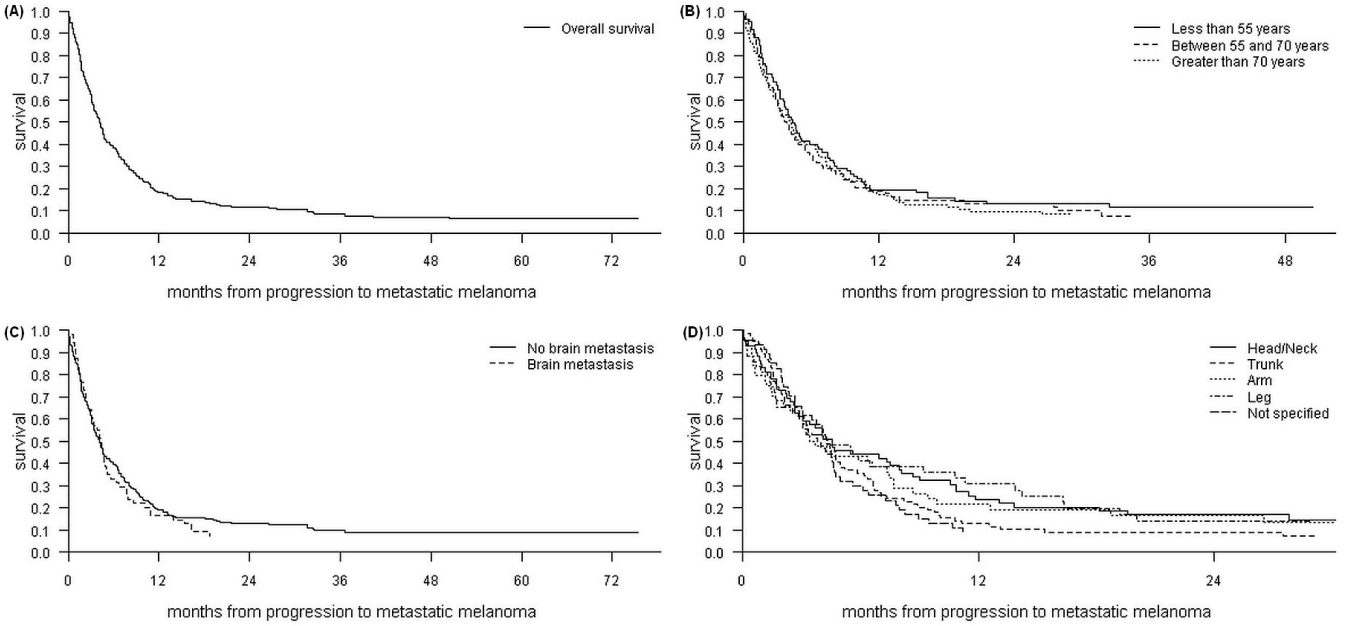


**FIGURE 2** Kaplan–Meier survival curves (A) for the cohort overall, and for the cohort stratified (B) by age at metastasis, (C) by brain metastasis (measures survival from progression to metastatic melanoma for patients who eventually develop brain metastasis rather than survival from diagnosis with brain metastasis), and (D) by site of melanoma. In each case, the analysis was stopped when the number at risk was less than 5. Because patients develop brain metastasis at various times, not all patients have brain metastasis at time 0.

initial months after progression and in the last months of life and lower in the Continuing phase, resulting in an approximately U-shaped curve (Figure 3). Starting in the second month after progression, mean costs gradually declined, remaining fairly constant during the continuing phase. Mean costs increased in the Last Year of Life phase, peaking at approximately $7500 in the month preceding the last month of life.

## DISCUSSION

Our study describes the characteristics, survival prognosis, and costs for a cohort of patients in Ontario with metastatic melanoma. We identified patients with unresectable metastatic melanoma who had received prior systemic therapy and would be candidates for newly developed therapies. Outcomes for the patients were poor, with 1-year survival being less than 20%.

Our results represent baseline estimates of mean survival time and cost reflecting the real-world standard of care in the period before new treatments began to emerge in 2011. Although the new therapies are not curative, they do represent important advances in the treatment of metastatic melanoma[9]. Assessing the potential improvement that those therapies might represent requires establishment of a baseline against which their relative performance can be measured. Being able to gauge whether a new treatment is in fact producing better results requires reference to a starting point (for example, in terms of survival). Patient-level administrative data offer a valuable source of evidence for estimating the real-world effectiveness and cost of existing treatments and thus providing a baseline

**TABLE III** Mean costs for the cohort in 2011 Canadian dollars, by cost category and phase of care

| Phase of care | Cost category[a] | | | | | |
|---|---|---|---|---|---|---|
| | Acute inpatient hospitalization[b] | Ambulatory care[c] | Physician services[d] | Prescription drugs[e] | Home care[f] | TOTAL |
| Initial[g] | 1,113 | 729 | 536 | 271 | 177 | 2,826 |
| Continuing[h] | 551 | 270 | 683 | 506 | 46 | 2,056[i] |
| Last year of life[j] | 12,390 | 3,815 | 4,462 | 1,827 | 3,309 | 25,803 |
| TOTAL | 14,054 | 4,814 | 5,681 | 2,604 | 3,532 | 30,685 |

[a] As accrued by patients over the entire time spent in the associated phase of care. The categories are mutually exclusive.
[b] From the Canadian Institute for Health Information Discharge Abstract Database.
[c] From the National Ambulatory Care Reporting System Database.
[d] From the Ontario Health Insurance Plan Claims Database.
[e] From the Ontario Drug Benefit Claims Database.
[f] From the Ontario Home Care Administrative System and Home Care Database.
[g] The first 12 months after progression.
[h] The months between the Initial and Last Year of Life phases.
[i] Estimated annual mean costs in the Continuing phase are $358.
[j] The final 12 months of life. For patients who die within 1 year, costs for the first 12 months after progression are allocated to the Last Year of Life phase.

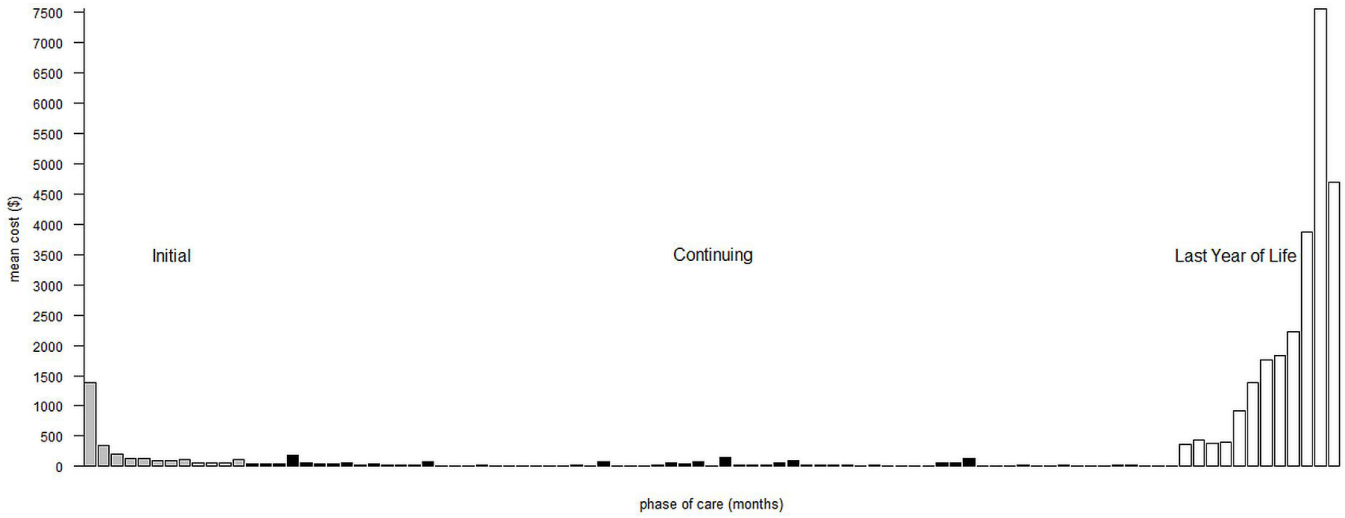


**FIGURE 3** Cost curve for the cohort, depicting monthly mean cost by phase of care. Each bar represents 1 month. The Initial phase was defined as the first 12 months after progression to metastatic melanoma; the Last Year of Life phase was defined as the final 12 months of life; and the Continuing phase was defined as all the months between the Initial and the Last Year of Life phases of care. All costs are given in 2011 Canadian dollars.

for comparison with new treatments. Had such baseline values been established in 2011, they could have helped to inform adoption and funding decisions involving the new therapies.

The characteristics of our cohort were similar to those reported elsewhere. Our survival estimates are comparable to results from a previous meta-analysis of phase II trials: 25.5% for 1-year survival and 10% for 2-year survival, with a median survival duration of 6.2 months[15]. Furthermore, a recent longitudinal study of metastatic patients conducted in Europe showed patient and tumour characteristics[20,21] that were similar to those in our cohort. At an estimated annual mean cost of approximately $30,000 per patient, our cost estimate resembles those at the lower end of the interval of estimates for metastatic melanoma from a systematic literature review of melanoma treatment costs[22]. It should be noted that the cost estimates from that systematic literature review were presented in 2010 U.S. dollars and primarily reflected U.S. studies, which would likely account for our estimates being lower. Consequently, the costs estimated in the present study represent the first good Canadian data on the cost of metastatic melanoma. The U-shaped cost pattern found in our study has also been observed for other cancers[17]. Those results—and the results for survival—reinforce the idea that administrative data can be used as a source of real-world evidence.

Future research should continue to investigate the use of population-based administrative data to inform decision-making in health policy, including its use in economic evaluations of alternative interventions[23]. Such use would mean that the administrative datasets should include data related to patient outcomes. The synthesis of information from both population-based observational studies and randomized studies has the potential to strengthen evidence-based decision-making by providing a thorough body of evidence on which to base decisions[24,25]. Specifically, future work could address the issue of how to reconcile data from randomized controlled trials of a new treatment with the importance of considering how the treatment will work in practice.

If decisions must be made before observational data on new treatments are available, then identifying population-based cohorts representing the current standard of care could provide useful benchmarks against which to compare trial-based evidence. Ideally, the process would be iterative, with baseline measures being updated as existing treatments are replaced by new treatments. In addition to helping to inform decision-making for health policy, an iterative approach to establishing baseline measures for mean effectiveness and mean cost could also provide guidance to pharmaceutical companies and others involved in developing new treatments. From a cost-effectiveness perspective, the baseline measures would represent the values that new treatments would have to improve upon if they were to be adopted and included on formularies. An iterative approach could also contribute to the ongoing assessment of health technologies by providing real-world evidence about performance throughout their life cycle.

Our study has several limitations that stem from the challenges of extracting the appropriate patient-level data from administrative databases. In particular, such databases are not designed for a particular study, but rather as repositories for a wide range of information, including resource use, costs, and patient characteristics. In the absence of exact fields in the datasets that would indicate who met the inclusion criteria for the study, we had to find alternative indicators. We chose use of chemotherapy as a broader indicator of metastatic disease that incorporated patients who progressed to metastatic disease from an earlier stage. To the extent that certain indicators depended on variables in the databases that are vague (for example, OHIP fee codes for physician services), we might have missed patients that should have been included in the cohort. We accounted for that possibility by selecting indicators as broadly as possible, so as to minimize the chance of excluding patients who should be in the cohort.

Another challenge to data extraction was the potentially limited availability of data for certain prognostic factors such as mitotic count, Breslow depth, and ulceration. Consequently, it might be necessary either to expand on the Ontario Cancer Registry or to create a new melanoma-specific registry to analyze such information at a population level.

In terms of the methods used for the analysis, a possible limitation is that we did not take into consideration the effect of covariates on survival when adjusting for censoring[26]. Given the shortness of the observed survival times relative to the amount of censoring, we felt that our approach was reasonable. Despite potential limitations, registries and other administrative records represent a valuable source of information for constructing population-based cohorts, and data of this type are widely used, including in cancer studies[27–30].

## CONCLUSIONS

As the treatment paradigm for metastatic melanoma changes, policymakers face a challenging environment in which new treatments compete for approval and inclusion on formularies. The present study demonstrates the use of population-based administrative data in establishing baseline estimates of the effectiveness and cost of standard treatment, against which the potential improvement of new treatments can be appraised.

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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 that we have none.

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