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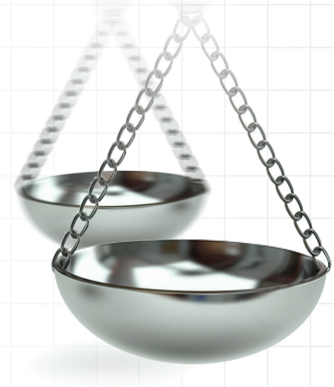

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Costs associated with adverse events for systemic therapies in metastatic melanoma

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Aim: To determine the costs of adverse events (AEs) associated with current metastatic melanoma (MM) therapies. **Materials & methods:** Two retrospective cohort studies were independently conducted using the PharMetrics and MarketScan databases. Included patients were aged ≥18 years, and had ≥1 MM diagnosis and ≥1 claim for systemic therapy from 2004 to 2015. **Results:** A total of 1654 and 1329 patients were identified in PharMetrics and MarketScan, respectively. The corresponding adjusted 30-day incremental costs of AEs by category were highest for CNS/psychiatric (US$21,277 and $18,739), gastrointestinal ($18,534 and $15,648), respiratory ($17,338 and $17,064), cardiovascular ($16,083 and $15,430), hematological/lymphatic ($14,997 and $15,538) and metabolic/nutritional AEs ($12,340 and $17,251). **Conclusion:** The costs of AEs associated with systemic therapies for MM are substantial.

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Keywords: adverse events • chemotherapy • cost • immunotherapy • metastatic melanoma • targeted therapy

Melanoma accounts for less than 1% of skin cancer cases in the USA [1]. However, it is responsible for the majority of skin cancer deaths. In 2018, an estimated 91,270 new cases of invasive melanoma will be diagnosed in the USA, and the disease will result in approximately 9320 deaths [2]. Melanoma that has spread to locations beyond the skin is referred to as metastatic melanoma (MM). In the USA, it is estimated that 4% of patients with melanoma initially present with distant metastatic disease [3]. The prognosis for these patients is poor, with an estimated 5-year survival rate of 17.9% [4] and a median overall survival of less than 1 year [5].

Melanoma entails substantial direct healthcare costs. In a recent large review, estimates of the annual cost of melanoma care in the USA, including all disease stages, ranged from $44.9 million for existing cases in Medicare patients, to $932.5 million for newly diagnosed cases across all age groups [6]. Annual per-patient costs ranged from $506 in prevalent cases of melanoma to $23,410 in newly diagnosed cases. The cost of melanoma increases significantly as the disease progresses. Using the Surveillance, Epidemiology, and End Results–Medicare-linked database, which contains data on incident cancer cases in the USA between 1991 and 2002, Davis *et al.* estimated that the adjusted all-cause healthcare cost per patient per month was $11,471 for stage IV melanoma (i.e., distant MM), compared with $2338, $3395 and $6885 for stages IIB/C, IIIA/B and IIIC, respectively [7]. The therapeutic landscape for MM is changing rapidly with the development of a range of new treatments. Novel targeted and immunotherapy agents (e.g., vemurafenib, dabrafenib, trametinib, ipilimumab, pembrolizumab and nivolumab), as well as combination regimens, have demonstrated significantly improved response rates and outcomes in the treatment of advanced unresectable melanoma and MM compared with conventional treatments such as chemotherapy [8,9]. The National Comprehensive Cancer Network recommends systemic therapies for the treatment of MM, including targeted therapy for patients with *BRAF* mutations, immunotherapies (irrespective of *BRAF* status), high-dose IL-2 and chemotherapies [10]. However, all systemic therapies are associated with adverse events (AEs) and the potential for considerable toxicity. For example, immunotherapy is associated with a number of severe AEs, the majority of which are immune-related, involving the gastrointestinal, liver, skin, endocrine,

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nervous, ocular and other organ systems [8,11]. BRAF inhibitors have been found to be associated with higher rates of cutaneous AEs, including squamous cell carcinoma (SCC) and keratoacanthoma, while MEK inhibitors have been associated with hypertension and rash [9,12–15].

Previous studies have demonstrated that the management of treatment-related AEs in patients with MM is associated with substantial healthcare resource utilization and costs [11,16–19]. However, few such studies have included the newer targeted immunotherapies. As new therapies for MM continue to become available, it is important to understand the healthcare expenditures associated with AEs related to both existing and new therapies. Such an understanding can inform treatment decisions for patients and healthcare providers, and pharmacoeconomic modeling for payers. The objective of this study was to estimate the real-world incremental healthcare costs of specific AEs among patients with MM treated with systemic therapies using the most recent data available.

Materials & methods

Data source

This was a retrospective cohort study utilizing two healthcare administrative claim databases. The first was the Truven Health Analytics' MarketScan Commercial Claims and Encounters plus the MarketScan Medicare Supplement and Coordination of Benefit database (hereafter referred to as MarketScan). MarketScan includes the patient-level paid and adjudicated medical and pharmacy claim histories of 110 million covered lives belonging to 12 national and regional health plans in the USA, and is representative of the national, commercially insured population as well as those who have both Medicare coverage and supplemental employer-sponsored coverage. Thus, MarketScan captures the full continuum of care in all settings, including physician office visits, hospital stays and outpatient pharmacy claims.

The second database was the IMS LifeLink PharMetrics Plus database (hereafter referred to as PharMetrics), which includes a diverse geographic representation of employers, payers, providers, diseases and therapy areas. The database is derived from 90% of US hospitals and 80% of US doctors, and is representative of 85% of the Fortune 100 companies. Data elements include inpatient and outpatient diagnoses and procedures, retail and mail order prescription records, detailed information on pharmacy and medical benefits (copayment, deductible), inpatient stay (admission type and source, discharge status) and provider details (specialty, provider ID) for 150 million lives in the USA from 2006 onward.

The study period was 1 July 2004 to 30 September 2015 for the MarketScan database, and 1 July 2004 to 30 November 2014 for the PharMetrics database, which reflects the most recent data available for each database at the time of the study. All patient records were deidentified and fully compliant with US patient confidentiality requirements (the Health Insurance Portability and Accountability Act). The purpose of examining our study objectives in two different databases, which vary with regard to the patients and data they include, was to validate the results and increase the robustness of the study. It is possible that some patients are included in both databases, but because the patient records are deidentified it is not possible to determine this. Therefore, the databases were separately analyzed.

Patient selection

All patients with MM who received one of the three following types of therapy were eligible for inclusion:

- Targeted therapy: trametinib, dabrafenib, dabrafenib/trametinib combination or vemurafenib
- Immunotherapy: pembrolizumab, nivolumab or ipilimumab
- Other therapy: dacarbazine, temozolomide, albumin-bound paclitaxel or high-dose IL-2

Patients were included in the study if they had at least one diagnosis of malignant melanoma (*International Classification of Diseases 9* [ICD-9] 172.0–9) during the study period, and a diagnosis of metastasis (ICD-9 196.xx, 197.xx, 198.xx, 199.xx) within 30 days before or 60 days after their malignant melanoma diagnosis. The index diagnosis date was defined as the date of the first diagnosis of malignant melanoma accompanied by metastasis. Included patients had at least one pharmacy or medical claim for a study drug within 1 year of the index diagnosis date. The index date was defined as the date of the first prescription for a study drug (the index treatment). All included patients were aged ≥18 years as of the index date, and had to be continuously enrolled in the database during the 6-month preindex. Patients were excluded if they had a diagnosis of nonmelanoma primary malignancy (ICD-9 140.xx–165.xx, 170.xx–171.xx, 173.xx–195.xx, 200.xx–208.xx) during the 6-month preindex, if they were

pregnant (ICD-9 630.xx–679.xx, V22.xx–V24.xx, V27.xx–V28.xx) at any point during the study period, or if they had more than one index drug.

Each selected patient was assigned to one of 11 mutually exclusive treatment groups based on their index drug. The index drug was assigned in the following hierarchical order using an algorithm based on that of Arondekar *et al.*, which was designed to maximize the sample size of patients receiving the most recently approved drugs [16]:

Nivolumab > pembrolizumab > dabrafenib/trametinib combo > dabrafenib > trametinib > vemurafenib > ipilimumab > dacarbazine > temozolomide > high-dose IL-2 > paclitaxel

Outcomes & measures

The main outcomes of the study were the occurrence of treatment-related AEs and the total incremental costs associated with these AEs. Outcomes were measured during the postindex (follow-up) period, which began on the index date and continued until the patient stopped receiving the index treatment, the end of the study period, loss to follow-up or death, and thus varied between patients. Treatment-related AEs were defined as those known to be associated with the 11 study drugs, and were established from product package inserts and/or published clinical trials. AEs were identified by a primary or secondary diagnosis on any nondiagnostic inpatient or outpatient claim within the postindex period.

Outcomes were assessed for ten specific categories of AEs and were compared between pairs of cohorts: an AE cohort, which included patients who experienced the treatment-related AE in question, and a control cohort, which included patients on the same treatment who did not experience that AE during follow-up. Comparisons were made separately for each AE category, so it was possible for patients to be included in more than one AE–control comparison. AEs were grouped as follows (the full list and ICD-9 codes can be found in Appendix 1).

- Cardiovascular: secondary hypertension, hypertension complications, hypotension, tachycardia (including supraventricular)
- CNS and psychiatric: anxiety/depression, confusion, convulsions, hemiparesis, somnolence, encephalopathy
- Gastrointestinal: abdominal pain, colitis, constipation, diarrhea, mucositis and stomatitis, nausea/vomiting
- Hematological and lymphatic: anemia, leukopenia, lymphopenia, neutropenia, pulmonary embolism, thrombocytopenia
- Metabolic and nutritional: acute renal failure; abnormal renal or liver function test; bilirubinemia; elevation of transaminase, lactate dehydrogenase, phosphatase, amylase or lipase; hyponatremia; hypophysitis; edema
- Pain: headache, myalgia/arthralgia/musculoskeletal/back/other pain, peripheral neuropathy
- Skin and subcutaneous tissue: alopecia, diaphoresis (sweating), hyperkeratosis, benign neoplasms of the skin (including papilloma), photosensitivity reaction, pruritus (itching), rash, SCC, keratoacanthoma
- Respiratory: dyspnea, pneumonitis
- General disorder and administration site conditions: fever (pyrexia) and/or chills
- Other: anaphylaxis, anuria/oliguria, asthenia/fatigue, decreased appetite/anorexia, infections (including folliculitis), decreased ejection fraction, muscular weakness, retinal detachment

Incremental AE costs were calculated as the difference in 30-day healthcare costs between patients with the specific AE and those without the AE. The date of the first specific AE claim served as the beginning of the 30-day cost period. For patients without the specific AE, a shadow AE date was assigned by randomly sampling from the distribution of the number of days from the index date to the event for patients with the AE, and then adding that number of days to the control's index date. This ensured that controls used the study drug for a comparable amount of time as patients who developed the AE. Healthcare costs included the total adjudicated amount paid to all providers for inpatient and outpatient services and drugs, with the exception of the study drugs and other cancer therapies. This amount included payments made by the insurer, patient (deductible, copayment, coinsurance), and any coordination of benefits as indicated on the claim. All costs were inflation-adjusted to 2015 US dollars using the medical component of the Consumer Price Index.

Statistical analysis

Baseline demographic and clinical characteristics were analyzed descriptively for all patients. The 6-month period prior to the index date was defined as the baseline period. The baseline demographic characteristics assessed included age, gender, region, and place and year of index treatment. The baseline clinical characteristics assessed

Table 1. Sample selection flow chart.

Eligibility criterion	PharMetrics (n)	MarketScan (n)
Patients with at least one diagnosis of malignant melanoma during the study period	456,912	438,292
Diagnosis of metastasis within 30 days before or 60 days after the malignant melanoma diagnosis	41,797	39,655
At least one pharmacy or medical claim for a study drug within 1 year of the index diagnosis date	6914	6639
No more than one index drug	6911	6590
No diagnosis of nonmelanoma primary malignancy during the 6-month baseline period	2042	1876
No pregnancy during the study period	2003	1853
Aged ≥18 years as of the index date and with continuous enrolment for the 6-month baseline period	1456	1329

included National Council on Compensation Insurance score, Charlson Comorbidity Index (CCI) score, baseline cancer therapy, presence of baseline hospitalization or emergency room (ER) visit and a selected list of co-morbid conditions. Descriptive analysis also included the assessment of unadjusted AE costs. For binary and categorical variables, between-group differences were assessed using c^2 tests. For continuous variables, between-group differences were assessed using Kruskal–Wallis tests. A p-value less than 5% was considered statistically significant throughout the analyses.

Multivariate analysis included assessment of the adjusted incremental cost of each category of AE, which was computed by using multivariate regressions to estimate the costs during the 30 days following the AE. Costs were modeled using Blough and Ramsey's formulation of a two-part cost model to address the skewness of cost data and the large number of $0 costs [20]. Logistic regression was first estimated to examine determinants, and predict the probability of any healthcare expenditures during the 30 days following the AE. Costs for subjects with positive (>$0) healthcare expenditures were then modeled using a generalized linear model with a log link and gamma distribution of variance to account for the skewed distribution of costs. Propensity score method with inverse probability of treatment weighting was used to adjust for patient characteristics including age, sex, rural/urban, geographic location, health insurance, index treatment, physician specialty, place and year of index treatment, payer, CCI, baseline cancer therapy, baseline hospitalization, baseline ER visit, baseline co-morbidities and baseline AEs.

Predicted costs were estimated by using the generalized linear model coefficients for both the AE and control cohorts, adopting recycled predictions. In this way, the regression model was used to calculate a predicted 30-day cost for every patient based on the covariate values assuming the patient experienced an AE (case) and again assuming the patient did not (control). The estimated incremental cost was assessed by calculating the difference at the patient level, followed by averaging the incremental cost across patients.

Results

Patient characteristics

A total of 1654 patients from PharMetrics and 1329 patients from MarketScan met all inclusion and exclusion criteria. Table 1 depicts the sample selection steps. Using the aforementioned hierarchical treatment selection method, in the PharMetrics sample 23.2% of patients (n = 384) initiated targeted therapies, 31.4% (n = 519) initiated immunotherapies and 45.4% (n = 751) initiated other therapies. A similar treatment distribution was seen in the MarketScan sample (Table 2). The mean age (± standard deviation) was 61 years (±10 years) in PharMetrics and 60 years (±13 years) in MarketScan, and 63 and 59% of patients were male, respectively. The majority of patients (64%) in PharMetrics had a preferred provider organization health insurance plan, while the majority of patients (57%) in MarketScan had a health maintenance organization plan. Approximately 70% of both samples had a commercial insurance payer, while 30% were covered by Medicare. Patients in the newer targeted therapy and immunotherapy cohorts had index dates in 2011 onward. The majority of those assigned to other therapies had their index years in 2005–2010, with steep declines seen from 2012 onward, due in part to the hierarchical selection strategy. In PharMetrics, 48% of patients had claims for excision surgery, 28% had hospitalizations and 38% had ER visits in the preindex period. Similar proportions were seen in MarketScan. The mean CCI score was 8.0 in patients from both databases, and cardiovascular disease was the most common co-morbidity (38% of patients in PharMetrics and 44% in MarketScan). Detailed baseline characteristics can be seen in Table 3A and B.

AE cost analysis

Table 4 depicts the unadjusted healthcare costs observed for patients with and without each category of AE. The

Table 2. Patient distribution by treatment cohorts.

Treatment		PharMetrics		MarketScan	
		n	%	n	%
Total sample		1654		1329	
Targeted therapy	Overall	384	23.2	276	20.8
	Trametinib	3	0.2	4	0.3
	Dabrafenib	51	3.1	34	2.6
	Dabrafenib/trametinib combination	87	5.3	84	6.3
	Vemurafenib	243	14.7	154	11.6
Immunotherapy	Overall	519	31.4	390	29.4
	Pembrolizumab†	N/A	N/A	1	0.1
	Nivolumab†	N/A	N/A	N/A	N/A
	Ipilimumab	519	31.4	389	29.3
Other therapy	Overall	751	45.4	663	49.9
	Dacarbazine	189	11.4	126	9.5
	Temozolomide	470	28.4	426	32.1
	Albumin-bound paclitaxel	74	4.5	87	6.6
	High-dose IL-2	18	1.1	24	1.8

†Nivolumab (approved on 22 December 2014) and pembrolizumab (approved on 4 September 2014) were not available at the time of analysis due to database cutoff limitation.
N/A: Not applicable.

mean cost was higher for all AEs, ranging from $15,927 to $24,156, compared with $4338–7667 in patients without the AEs. Similar mean costs were seen in the two databases. Multivariate analysis showed that after controlling for baseline demographic and clinical characteristics, the adjusted incremental costs were significantly higher for patients with all categories of AEs compared with patients without the AE (Table 5). In the PharMetrics and MarketScan databases, the respective adjusted 30-day incremental costs of AEs by category were as follows: CNS and psychiatric disorders: $21,277 (95% CI: $20,748–21,806) and $18,739 (95% CI: $18,255–19,222); gastrointestinal: $18,534 (95% CI: $18,061–19,007) and $15,648 (95% CI: $15,173–16,122); respiratory: $17,338 (95% CI: $16,850–17,826) and $17,064 (95% CI: $16,620–17,508); cardiovascular: $16,083 (95% CI: $15,640–16,526) and $15,430 (95% CI: $15,052–15,809); hematological/lymphatic: $14,997 (95% CI: $14,652–15,342) and $15,538 (95% CI: $15,134–15,941); general/administration site: $14,227 (95% CI: $13,829–14,625) and $13,371 (95% CI: $13,018–13,724); metabolic/nutritional: $12,340 (95% CI: $11,851–12,829) and $17,251 (95% CI: $16,825–17,677); pain: $12,928 (95% CI: $12,553–13,303) and $16,104 (95% CI: $15,691–16,518); skin/subcutaneous tissue: $11,016 (95% CI: $10,717–11,315) and $10,597 (95% CI: $10,319–10,875); and other $15,065 (95% CI: $14,643–15,487) and $15,381 (95% CI: $14,950–15,812).

Discussion

In this large, retrospective cohort study, we found that treatment-related AEs were associated with significant and substantial increases in healthcare costs in patients receiving current therapies for MM. The most expensive AE category in both databases was CNS and psychiatric disorders, but the 30-day adjusted incremental cost was over $10,000 for every AE category analyzed. Given the increasing availability of newer systemic treatment options and escalating expenditures on cancer management, these findings represent valuable information that may be used to better understand the economic burden of AEs and their impact on MM patients and healthcare systems.

Our findings are consistent with the results of previous studies, which have indicated that systemic MM therapies are associated with treatment-related AEs that lead to increased healthcare resource utilization and expenditures [11,16–19]. However, previous studies have largely focused on AEs related to older treatments, such as chemotherapies. Only a few studies have included patients who received targeted or immunotherapies, or assessed the costs of AEs related to these novel treatments. One recent US retrospective claims database analysis investigated the overall costs of AEs associated with melanoma therapies (including vemurafenib, ipilimumab, dacarbazine, paclitaxel and temozolomide), and found that hematological and lymphatic disorders incurred the highest costs across therapies [18]. Arondekar *et al.* recently published a retrospective claims-based analysis of the healthcare costs associated with AEs in patients with MM in the MarketScan commercial and Medicare supplemental databases

Table 3A. Baseline demographic and clinical characteristics (PharMetrics).

Patient characteristics	Overall (n = 1654)		Targeted therapy (n = 384)		Immunotherapy (n = 519)		Other therapy (n = 751)		p-value†
	n	%	n	%	n	%	n	%	
Age group, years									< 0.01
18–24	2	0	–	–	–	–	2	0	
25–34	63	4	13	3	18	3	33	4	
35–44	174	11	64	17	39	8	71	9	
45–54	417	25	85	22	112	22	220	29	
55–64+	998	60	222	58	350	67	426	57	
Distribution of 65 and above									
65–74	700	42	156	41	211	41	333	44	
75–84	113	7	45	12	45	9	23	3	
85+	185	11	21	6	94	18	70	9	
Male	973	59	214	56	299	58	460	61	0.06
Rural (vs urban)	225	14	47	12	74	14	104	14	0.44
Geographical region									0.15
Northeast	294	18	55	14	114	22	125	17	
Midwest	356	22	51	13	120	23	185	25	
South	607	37	171	45	132	26	304	41	
West	340	21	81	21	127	25	132	18	
Unknown	56	3	25	7	25	5	5	1	
Health insurance									< 0.01
PPO	1051	64	269	70	357	69	425	57	
HMO	171	10	21	6	26	5	124	17	
Directed healthcare/health savings account	202	12	36	9	66	13	100	13	
Point-of-service	92	6	13	3	38	7	41	6	
Other	137	8	45	12	31	6	61	8	
Prescribing physician specialty									< 0.01
Oncologist/hematologist	336	20	38	10	130	25	168	22	
Primary care	66	4	9	2	39	8	17	2	
Radiologist/nuclear medicine	57	3	4	1	11	2	41	6	
Other specialist	261	16	81	21	59	11	120	16	
Facility	391	24	23	6	277	53	92	12	
Unknown	544	33	229	60	3	1	312	42	
Place of index treatment									< 0.01
Inpatient hospital	27	2	5	1	5	1	17	2	
Outpatient hospital	465	28	43	11	174	34	248	33	
Physician office	598	36	216	56	282	54	101	13	
Other	28	2	10	3	2	0	17	2	
Unknown	536	32	111	29	57	11	369	49	
Payer									< 0.01
Commercial	1153	70	294	77	318	61	541	72	
Medicare	501	30	90	24	201	39	210	28	
Year of index treatment									< 0.01
2005	131	8	–	–	–	–	131	18	
2006	92	6	–	–	–	–	92	12	
2007	83	5	–	–	–	–	83	11	
2008	74	4	–	–	–	–	74	10	
2009	100	6	–	–	–	–	100	13	

†For binary and categorical variables, between-group differences were assessed using χ^2 tests. For continuous variables, between-group differences were assessed using Kruskal–Wallis tests. A p-value less than 5% was considered statistically significant.
CCI: Charlson comorbidity index; COPD: Chronic obstructive pulmonary disease; ER: Emergency room; HMO: Health maintenance organization; PPO: Preferred provider organization; SD: Standard deviation.

Table 3A. Baseline demographic and clinical characteristics (PharMetrics) (cont.).

Patient characteristics	Overall (n = 1654)		Targeted therapy (n = 384)		Immunotherapy (n = 519)		Other therapy (n = 751)		p-value†
	n	%	n	%	n	%	n	%	
2010	97	6	–	–	–	–	97	13	
2011	158	10	55	14	23	4	80	11	
2012	277	17	91	24	145	28	41	6	
2013	174	10	85	22	75	14	14	2	
2014	271	16	89	23	172	33	9	1	
2015	196	12	63	17	104	20	29	4	
CCI (mean, SD)	8.0	2.3	7.2	2.3	8.3	2.1	8.3	2.4	0.22
Baseline cancer therapy									
Excision surgery	791	48	174	45	240	46	377	50	0.22
Chemotherapy or biological therapy	266	16	114	30	58	11	94	13	< 0.01
IFN-α	76	5	16	4	23	4	37	5	0.56
Preindex hospitalization	465	28	127	33	162	31	176	23	0.04
Preindex ER visit	623	38	137	36	189	37	297	40	0.44
Co-morbidities									
Anxiety	141	9	20	5	64	12	58	8	< 0.01
Cardiovascular disease	634	38	144	38	197	38	293	39	0.34
Cerebrovascular disease	–	–	–	–	–	–	–	–	–
COPD	103	6	17	5	29	6	57	8	0.04
Diabetes	207	13	43	11	64	12	101	13	0.23
Depression	93	6	12	3	46	9	35	5	0.03

†For binary and categorical variables, between-group differences were assessed using χ^2 tests. For continuous variables, between-group differences were assessed using Kruskal–Wallis tests. A p-value less than 5% was considered statistically significant.
CCI: Charlson comorbidity index; COPD: Chronic obstructive pulmonary disease; ER: Emergency room; HMO: Health maintenance organization; PPO: Preferred provider organization; SD: Standard deviation.

from 2004 to 2012 (n = 2621), demonstrating significant incremental costs for all AE categories except skin and subcutaneous tissue disorders [16]. The most expensive AE categories in that study were metabolic and nutritional disorders, followed by hematological and lymphatic disorders/effects.

Our study expands on the work of Arondekar *et al.* by looking at more recent data, a longer time period and the additional PharMetrics database. Thus, we were able to include more patients and thereby increase the robustness and generalizability of the results. We were also able to include more patients who received targeted therapy and immunotherapy, particularly the recently approved (2013) targeted therapies trametinib and dabrafenib. As a result, we found higher incremental costs between patients with and without all categories of AE, and all of these were statistically significant. The fact that we yielded similar results from two separate databases further strengthens our findings.

Although effective in the treatment of MM, newer targeted and immunotherapy agents are associated with a wide spectrum of AEs. The complexity of management and resultant cost varies both between and within AE categories. In a recent literature review, Vouk *et al.* attempted to estimate the economic burden of treatment-related AEs in MM patients (including dacarbazine, paclitaxel, fotemustine, ipilimumab and vemurafenib) and found that the most costly were grade 3/4 AEs related to immunotherapy (colitis, diarrhea) and chemotherapy (neutropenia, leukopenia) [17]. The treatment of neutropenia and leukopenia associated with chemotherapy and the treatment of SCC associated with targeted therapy contributed substantially to country-specific economic burdens. In another literature review (including dacarbazine, temozolomide, fotemustine, IL-2, ipilimumab, vemurafenib, dabrafenib and trametinib), Wehler *et al.* found that in outpatient settings, the most expensive AEs included SCC, anemia, peripheral neuropathy and diarrhea, while in inpatient settings, the most expensive AEs included hypophysitis, dyspnea, elevated liver enzymes, SCC, peripheral neuropathy and diarrhea [19]. Trametinib, dabrafenib and trametinib–dabrafenib combination therapy have been associated with an increased rate of cardiovascular AEs, which provide a possible reason for the higher cardiovascular AE costs seen in our study [12,13]. In addition, *BRAF* inhibitor therapy is known to be associated with increased rates of skin toxicity, including SCC [14,15], which may

Table 3B. Baseline demographic and clinical characteristics (MarketScan).

Patient characteristic	Overall (n = 1329)		Targeted therapy (n = 276)		Immunotherapy (n = 390)		Other therapy (n = 663)		p-value[†]
	n	%	n	%	n	%	n	%	
Age (mean, SD), years	60	13	57	13	61	13	60	13	0.03
Age group, years									0.01
18–24	4	0	–	–	3	1	1	0	
25–34	37	3	12	4	10	3	15	2	
35–44	121	9	38	14	24	6	59	9	
45–54	286	22	68	25	76	20	142	21	
55–64+	452	34	87	32	134	34	231	35	
Distribution of 65 and above									
65–74	240	18	44	16	78	20	118	35	
75–84	148	11.1	20	7	49	13	79	12	
85+	41	3	7	3	16	4	18	3	
Male	837	63	159	58	245	63	433	65	0.08
Rural (vs urban)	242	18	49	18	63	16	130	20	0.37
Geographical region									0.09
Northeast	208	16	53	19	70	18	85	13	
Midwest	309	23	63	23	94	24	152	23	
South	483	36	88	32	129	33	266	40	
West	306	23	66	24	89	23	151	23	
Unknown	23	2	6	2	8	2	9	1	
Health insurance									< 0.01
PPO	185	14	25	9	57	15	103	16	
HMO	760	57	180	65	236	61	344	52	
Directed healthcare/health savings account	159	12	20	7	35	9	104	16	
Point-of-service	80	6	8	3	20	5	52	8	
Other	145	11	43	16	42	11	60	9	
Physician specialty									< 0.01
Oncologist/hematologist	296	22	29	11	117	30	150	23	
Primary care	100	8	9	3	27	7	64	10	
Radiologist/nuclear medicine	28	2	4	2	3	1	21	3	
Other specialist	184	14	50	18	41	11	93	14	
Facility	291	22	11	4	192	49	88	13	
Unknown	430	32	173	63	10	3	247	37	
Place of index treatment									< 0.01
Inpatient hospital	19	1	8	3	1	0	10	2	
Outpatient hospital	424	32	49	18	209	54	166	25	
Physician office	424	32	31	11	173	44	220	33	
Other	61	5	15	5	3	1	43	7	
Unknown	401	30	173	63	4	1	224	34	
Payer									0.01
Commercial	915	69	209	76	255	65	451	68	
Medicare	414	31	67	24	135	35	212	32	
Year of index treatment									< 0.01
2005	99	8	–	–	–	–	99	15	
2006	84	6	–	–	–	–	84	13	
2007	54	4	–	–	–	–	54	8	
2008	85	6	–	–	–	–	85	13	

[†]For binary and categorical variables, between-group differences were assessed using χ^2 tests. For continuous variables, between-group differences were assessed using Kruskal–Wallis tests. A p-value less than 5% was considered statistically significant.
CCI: Charlson comorbidity index; COPD: Chronic obstructive pulmonary disease; ER: Emergency room; HMO: Health maintenance organization; PPO: Preferred provider organization; SD: Standard deviation.

Table 3B. Baseline demographic and clinical characteristics (MarketScan) (cont.).

Patient characteristic	Overall (n = 1329)		Targeted therapy (n = 276)		Immunotherapy (n = 390)		Other therapy (n = 663)		p-value†
	n	%	n	%	n	%	n	%	
2009	123	9	–	–	–	–	123	19	
2010	92	7	–	–	–	–	92	14	
2011	133	10	42	15	22	6	69	10	
2012	209	16	63	23	117	30	29	4	
2013	149	11	52	19	81	21	16	2	
2014	205	15	81	29	114	29	10	2	
2015	96	7	38	14	56	14	2	0	
CCI (mean, SD)	8.0	2.1	8.1	2.1	8.2	2.0	7.9	2.2	0.14
Baseline cancer therapy									
Excision surgery	686	52	157	57	195	50	334	50	0.14
Chemotherapy or biological therapy	220	17	83	30	38	10	99	15	< 0.01
IFN-α	53	4	10	4	14	4	29	4	0.77
Preindex hospitalization	433	33	86	31	103	26	244	37	< 0.01
Preindex ER visit	402	30	90	33	103	26	209	32	0.14
Co-morbidities									
Anxiety	99	8	18	7	44	11	37	6	< 0.01
Cardiovascular disease	578	44	118	43	187	48	273	41	0.10
Cerebrovascular disease	–	–	–	–	–	–	–	–	
COPD	86	7	18	7	22	6	46	7	0.71
Diabetes	177	13	27	10	52	13	98	15	0.12
Depression	66	5	12	4	29	7	25	4	0.03

†For binary and categorical variables, between-group differences were assessed using χ^2 tests. For continuous variables, between-group differences were assessed using Kruskal–Wallis tests. A p-value less than 5% was considered statistically significant.
CCI: Charlson comorbidity index; COPD: Chronic obstructive pulmonary disease; ER: Emergency room; HMO: Health maintenance organization; PPO: Preferred provider organization; SD: Standard deviation.

explain why the incremental cost of skin and subcutaneous disorders was significant in our study but not in that of Arondekar *et al*.

This study has several limitations, mostly owing to the data source. First, despite using the most recently available data, the proportion of patients who received second-generation targeted therapy, immunotherapy or combination therapy was still relatively small. Second, although we imposed a time requirement to identify treatment-related AEs, it is possible that the AEs included may not have been caused by the specific treatment but by chronic conditions or treatments received prior to the study period. Third, ICD-9 codes were used to identify AEs, and therefore the AEs assessed in the study may not directly correspond to those used in trials. Furthermore, measurement bias may have been introduced if AEs were undercoded or miscoded on administrative claims, and mild AEs may have been under-reported. Therefore, the costs of AEs may have been underestimated. Fourth, despite using advanced multivariate analysis with propensity score to adjust for baseline characteristics, residual confounding – for example, disease severity – may have influenced the difference in costs between patients with and without AEs. Fifth, we measured all-cause costs and thus, despite careful matching between patients with and without each AE, the costs captured may not solely represent costs incurred by the AEs. Sixth, although we included a large number of patients from two different databases, these patients are representative of the commercially insured US population and thus the results may not be generalizable to individuals on Medicare or Medicaid. Seventh, owing to the nature of claims data, we cannot be sure that the AEs observed were directly attributable to the study treatments. Lastly, some AEs, especially immune-mediated AEs such as hypophysitis and hypothyroidism, have a prolonged impact on patients, and thus the 30-day cost difference used may have underestimated the true cost of treatment-related AEs.

Conclusion

The incremental costs of AEs associated with systemic therapies for MM are substantial. The wide spectrum of AEs related to therapies for MM and their associated costs calls for greater awareness and prevention of these AEs to reduce morbidity among patients, as well as to decrease the financial burden on both payers and patients.

Table 4. Unadjusted costs by adverse event category.

AE category	PharMetrics							MarketScan						
	With AE			Without AE			p-value†	With AE			Without AE			p-value†
	n	Mean ($)	SD	n	Mean ($)	SD		n	Mean ($)	SD	n	Mean ($)	SD	
Cardiovascular	696	20,010	32,639	958	6626	15,834	< 0.0001	773	19,343	31,551	556	6337	15,194	< 0.0001
CNS and psychiatric	617	24,156	38,140	1037	5632	15,642	< 0.0001	411	21,696	30,038	918	5639	15,635	< 0.0001
Gastrointestinal	812	20,807	31,339	842	6276	16,329	< 0.0001	566	19,348	29,141	763	6014	15,378	< 0.0001
Hematological and lymphatic	350	20,534	25,643	1305	4724	13,549	< 0.0001	466	20,868	25,842	863	6006	17,227	< 0.0001
Metabolic and nutritional	588	15,971	24,536	1066	5188	13,382	< 0.0001	594	21,114	32,994	735	5845	15,077	< 0.0001
Pain	600	17,506	27,683	1054	5170	11,869	< 0.0001	603	20,180	31,980	726	5247	12,045	< 0.0001
Skin and subcutaneous tissue	725	16,405	32,843	929	6796	14,704	< 0.0001	704	15,927	30,761	625	6503	14,076	< 0.0001
Respiratory	515	19,806	31,286	1139	5513	17,043	< 0.0001	464	21,003	31,842	865	5646	17,477	< 0.0001
General disorder and administration site conditions	313	17,954	31,953	1341	4338	11,524	< 0.0001	314	20,232	35,264	1015	5523	14,671	< 0.0001
Other	649	19,615	30,879	1005	7667	21,583	< 0.0001	621	18,370	29,002	708	5754	16,202	< 0.0001

†Between-group differences were assessed using Kruskal–Wallis tests. A p-value less than 5% was considered statistically significant.
AE: Adverse event; SD: Standard deviation.

Table 5. Adjusted incremental costs by adverse event category.

AE category	PharMetrics						MarketScan					
	Adjusted mean ($)†		Incremental cost ($)		95% CI for adjusted incremental cost ($)		Adjusted mean ($)†		Incremental cost ($)		95% CI for adjusted incremental cost ($)	
	With AE	Without AE	Observed	Adjusted	Lower CI	Upper CI	With AE	Without AE	Observed	Adjusted	Lower CI	Upper CI
Cardiovascular	22,283	6200	13,384	16,083	15,640	16,526	21,346	5916	13,006	15,430	15,052	15,809
CNS and psychiatric	26,631	5355	18,525	21,277	20,748	21,806	24,136	5397	16,057	18,739	18,255	19,222
Gastrointestinal	24,439	5905	14,532	18,534	18,061	19,007	21,427	5779	13,334	15,648	15,173	16,122
Hematological and lymphatic	19,878	4881	15,810	14,997	14,652	15,342	21,352	5814	14,862	15,538	15,134	15,941
Metabolic and nutritional	17,137	4797	10,783	12,340	11,851	12,829	22,656	5405	15,269	17,251	16,825	17,677
Pain	17,948	5020	12,336	12,928	12,553	13,303	21,093	4989	14,933	16,104	15,691	16,518
Skin and subcutaneous tissue	17,520	6504	9609	11,016	10,717	11,315	16,691	6094	9424	10,597	10,319	10,875
Respiratory	23,201	5863	14,293	17,338	16,850	17,826	22,503	5439	15,357	17,064	16,620	17,508
General disorder and administration site conditions	18,302	4074	13,616	14,227	13,829	14,625	19,001	5630	14,709	13,371	13,018	13,724
Other	21,907	6842	11,949	15,065	14,643	15,487	20,516	5135	12,616	15,381	14,950	15,812

†Propensity score with inverse probability of treatment weighting was used to adjust for age, sex, rural/urban, geographic location, health insurance, index treatment, physician specialty, place and year of index treatment, payer, CCI, baseline cancer therapy, baseline hospitalization, baseline ER visit, baseline co-morbidities and baseline AEs. Predicted costs were estimated by using the generalized linear model coefficients for both the AE and control cohorts, adopting recycled predictions.

AE: Adverse event; CCI: Charlson comorbidity index; ER: Emergency room.

Summary points

- Melanoma entails substantial direct healthcare costs.
- These costs are increased when patients experience adverse events (AEs).
- Novel targeted and immunotherapies have revolutionized the prognosis for metastatic melanoma (MM) patients, but are associated with the potential for significant toxicity and AEs.
- Few studies have examined the costs of AEs in MM patients undergoing novel therapies; understanding these costs is important for treatment decision-making and pharmacoeconomic modeling.
- We performed two large retrospective cohort studies to examine this in two commercial insurance databases: PharMetrics and MarketScan.
- Among 1654 and 1329 patients identified in PharMetrics and MarketScan, respectively, the adjusted 30-day incremental costs of AEs were over $10,000 for every AE category analyzed.
- Costs were highest for CNS/psychiatric, gastrointestinal, respiratory, cardiovascular and hematological/lymphatic AEs.
- We conclude that the costs of AEs associated with systemic therapies for MM are substantial.

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Authors' contributions

AZ Fu, S Mahmood, Z Li, Y Qiu, T Whisman and J Tang were involved in the study conception and design; analysis and interpretation of the data; drafting of the manuscript and final approval of the version to be published. All the authors agree to be accountable for all aspects of the work.

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Supplementary data

To view the supplementary data that accompany this paper please visit the journal website at: www.futuremedicine.com/doi/full/10.2217/cer-2018-0022

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