ORIGINAL ARTICLE EPEYNHTIKH EPΓΑΣΙΑ

The economic burden of cutaneous malignant melanoma in the Greek outpatient setting during the 3-year period, 2017–2019

OBJECTIVE To quantify direct medical outpatient costs incurred by cutaneous malignant melanoma (CMM) covered by the national health insurance system in Greece, for the period 2017-2019. METHOD This study is a prevalence-based, cost-of-illness study, conducted from the perspective of the third-party insurer in Greece. Using an electronic third-party payer database, examinations conducted on, and pharmaceuticals prescribed to Greek patients diagnosed with CMM were collected and converted to costs using local unit costs. Outpatient healthcare resource utilization (HCRU) data were extracted for CMM-related ICD10 codes. Unit costs were obtained from the pharmaceuticals reimbursement lists of the National Organization for the Provision of Health Services (EOPYY) and state tariffs. RESULTS The total outpatient costs of CMM between 2017 and 2019 amounted to €74,007,121 (€ 29,039,029 in 2019, € 24,093,994 and € 20,874,097 in 2018 and 2017, respectively). Pharmaceutical costs accounted for 92.6% and examination costs 8.4% of total outpatient expenditure. Male patients incurred slightly higher total outpatient costs than female patients. Radiological examinations, and protein kinase inhibitors and monoclonal antibodies accounted for the major proportion of outpatient examination and pharmaceutical treatment costs, respectively. CONCLUSIONS The currently available and emerging diagnostic procedures and the high-cost, innovative, but effective, pharmaceutical treatment for CMM create the need to generate evidence of costs and outcomes for patients receiving different levels care. The diagnosis and treatment of CMM incur a considerable and escalating cost to the healthcare system in Greece. This study was a real-world cost-of-illness study, conducted to provide information for the health policy decision-makers, at all stages, on the magnitude of CMM-attributable outpatient costs, to assist them in efficient health resource allocation.

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Οικονομικό φορτίο του δερματικού κακοήθους μελανώματος στο περιβάλλον των εξωτερικών ασθενών στην Ελλάδα κατά την τριετία 2017–2019

Περίληψη στο τέλος του άρθρου

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Cutaneous malignant melanoma (CMM) is a cause of considerable skin cancer-related morbidity and mortality in developed countries with predominantly fair-skinned residents. Despite the initially positive 5-year prognosis for patients in the earlier disease stages, prognosis severely worsens for patients diagnosed at advanced stages.⁷ It has been reported that only 15% of cases of CMM diagnosed at metastatic stages will survive 3 years after diagnosis.² CMM is a fairly common disease, with the global 2020, age-standardized incidence rate (ASR) estimated at 3.4 cases per 100,000 persons, with 324,635 (95% CI: 314,175.0–335,443.0) newly diagnosed cases and

57,043 (95% CI: 52,174.6–62,365.7) reported deaths per year. In Europe, it is estimated that the ASR is 11.4 cases per 100,000 persons, corresponding to 150,627 (95% CI: 147,394.0–153,931.0) newly diagnosed cases per year, and the annual mortality burden is estimated at 26,360 (95% CI: 25,190.9–27,583.4) deaths. In Greece, the corresponding 2020 ASR was 7.2 cases per 100,000 persons or 1,313 (95% CI: 926.6–1,860.5) newly diagnosed cases and 295 (95% CI: 224.5–387.7) annual deaths.³

The diagnosis and treatment of CMM has changed dramatically in the past decade. The development of innovative imaging techniques, such as dermoscopy, ultrasound

(US), computed tomography (CT), magnetic resonance imaging (MRI) and positron emission tomography (PET) scan has increased diagnostic precision and facilitated disease staging.⁴ Innovative forms of treatment, including monotherapies, combinations and sequential therapies with checkpoint inhibitors and inhibitors targeting the mitogen activated protein kinase (MAPK) pathway, have contributed to a decrease in mortality, although patients diagnosed with stage IV disease continue to experience poor survival.⁵

New diagnostic and treatment protocols have resulted in escalating costs for healthcare systems worldwide. As solar ultraviolet radiation (UVR) is the main environmental risk factor for CMM, the disease is deemed to be highly preventable and hence, the costs of CMM management could be avoided with effective prevention policies.

A limited number of economic studies have assessed the impact of innovative imaging techniques, and of the application of immunotherapy and targeted therapy on healthcare resource utilization (HCRU) and the costs of CMM. Specifically for Greece, the economic costs of CMM have never yet been studied systematically. The objective of this study was to quantify and break down the direct outpatient costs of CMM in Greece, for the period 2017–2019 using an electronic third-party payer database, and including all examinations conducted on, and pharmaceuticals prescribed to Greek patients diagnosed with CMM.

MATERIAL AND METHOD

Material

Outpatient HCRU data were extracted from the electronic prescription records of the e-Government Center for Social Security

Services (IDIKA SA), the only population-based dataset in Greece that includes outpatient examinations and pharmaceuticals, classified by disease, from the time of diagnosis until death or the last follow-up. This dataset also includes demographic data (age, gender), ICD10 and ATC5 codes, barcodes and the commercial names of examinations and pharmaceuticals, and the number of prescriptions prescribed and executed. Unit costs were obtained from the pharmaceuticals reimbursement list of the National Organization for the Provision of Health Services (EOPYY), including the sub-list with high-cost pharmaceutical products. Unit costs for examinations were obtained from state tariffs reported by EOPYY. Rebates and clawbacks were not included in the analysis. Costs were reported at Euro 2020 prices.

Regarding diagnosis, the following ICD10 codes were extracted: C43 and C43.0–C43.9. These are billable/specific ICD10 codes that can be used to define diagnosis for reimbursement purposes.

Method

The study is a prevalence-based, cost-of-illness study conducted from the perspective of the local third-party payer, i.e., EOPYY. Annual costs were calculated by applying unit costs to individual HCRU. All calculations were performed using Microsoft Excel 2010.

RESULTS

The total outpatient costs of CMM in Greece, during 2017–2019 amounted to \in 74,007,121. Over the time of the study, the total outpatient costs increased, from \in 24,093,994 and \in 20,874,097 in 2018 and 2017, respectively, approaching \in 29,039,029, in 2019. Figure 1 presents the observed annual outpatient, third-party payer, costs, by cost component, of CMM. Examinations accounted for 8.4% of the total outpatient costs (\in 6,187,937). The annual examination costs did not substantially change over time

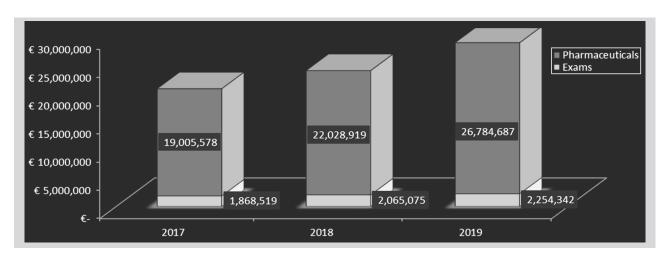


Figure 1. Annual total outpatient costs of diagnosis and treatment of cutaneous malignant melanoma in Greece by cost component (Euros, 2020).

(fig. 1). Pharmaceuticals accounted for a remarkably high proportion of the total cost, accounting for 91.6% of total outpatient costs (€ 67,819,184) for CMM, and the annual pharmaceutical costs increased noticeably over time (fig. 1).

Figure 2 shows the annual total outpatient costs by gender. Male patients incurred higher total outpatient costs than female patients, by \in 889,759 (\in 37,448,440 and \in 36,558,681 for males and females, respectively).

Figure 3 shows the annual costs for examinations and pharmaceuticals by gender. Male patients were responsible for higher examination costs, by \in 1,057,727 compared

with females (\in 3,622,832 and \in 2,565,105, for males and females, respectively). Total outpatient pharmaceutical costs did not vary significantly by gender (\in 33,825,608 and \in 33,993,576 for male and female patients, respectively).

In terms of cost by ICD10 code, the "Malignant melanoma of the trunk" (C43.5) incurred the highest examination costs (€ 211,897) among the ICD10 codes, during 2017–2019 (tab. 1).

The most frequently prescribed examinations, at considerable cost for social insurance (€ 2,601,291) were imaging (radiological) examinations (tab. 2). As expected, on patent

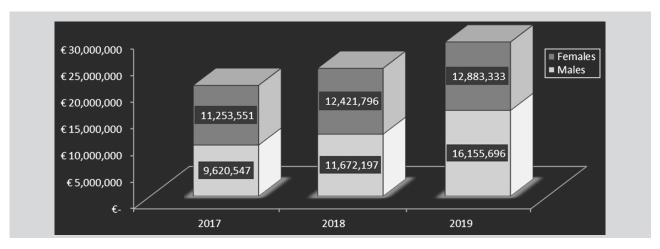


Figure 2. Annual total outpatient costs of diagnosis and treatment of cutaneous malignant melanoma in Greece by gender (Euros, 2020).



Figure 3. Annual examination and pharmaceutical costs of diagnosis and treatment of cutaneous malignant melanoma in Greece by gender (Euros, 2020).

Table 1. Total examination costs for cutaneous malignant melanoma in Greece by ICD10 code (Euros, 2020).

ICD10 code	Clarification	Exams, n (%)		Costs (€)
C43	Malignant melanoma of skin	322,898	(87.1)	5,291,417
C43.0*	Malignant melanoma of lip	326	(0.1)	4,575
C43.1*	Malignant melanoma of eyelid, including canthus	2,523	(0.7)	46,051
C43.2*	Malignant melanoma of ear and external auricular canal	1,018	(0.3)	27,552
C43.3*	Malignant melanoma of other and unspecified parts of face	8,170	(2.2)	157,130
C43.4*	Malignant melanoma of scalp and neck	4,366	(1.2)	88,002
C43.5*	Malignant melanoma of trunk	11,289	(3.0)	211,897
C43.6*	Malignant melanoma of upper limb, including shoulder	3,595	(1.0)	73,660
C43.7*	Malignant melanoma of lower limb, including hip	8,178	(2.2)	155,177
C43.8*	Overlapping malignant melanoma of skin	205	(0.1)	3,784
C43.9*	Malignant melanoma of skin, unspecified	8,280	(2.2)	128,694
Total		370,848	(100.0)	6,187,937

^{*}C43.0-C43.9: Billable/specific ICD10 codes that can be used to indicate a diagnosis for reimbursement purposes

Table 2. Total examination costs for cutaneous malignant melanoma in Greece by costliest exam category code (Euros, 2020).

Examination category code	Examination categories	Examinations, n (%)	Costs (€)
04. Radiology	X-rays, computed tomography (CT), bone densitometry (radiology and nuclear medicine), ultrasound	50,211 (13.5)	2,601,291
24. Magnetic resonance imaging (MRI)	MRIs	6,438 (1.7)	1,293,917
13. Biochemical assays (ELISA)	Biological material exams 1 (Biopathology) (hematological, biochemical, microbiological exams)	228,790 (61.7)	813,433
49. Scintigraphy	Scintigraphies	2,352 (0.6)	624,543
16. Hormone assays (ELISA)	Biological material exams 2 (biopathology and nuclear medicine) (immunological, hormone exams)	18,161 (4.9)	207,860
56. Biomarkers	Biomarkers	1,683 (0.5)	172,423
50. Ultrasound	Vascular ultrasound (triplex), cardiac ultrasound, ultrasound	15,075 (4.1)	171,755
12. Immunological assays (ELISA)	Biological material exams 2 (biopathology and nuclear medicine) (immunological, hormone exams)	11,609 (3.1)	139,148

pharmaceuticals accounted for 99.5% of the total outpatient pharmaceutical costs of CMM (tab. 3). The costliest active substances, according to their chemical structure/subgroup (ATC4) are presented in table 4.

DISCUSSION

To the best of the authors' knowledge, this is the first study to project the real-life total outpatient cost of CMM in Greece. The study identified the main expenditure for CMM in outpatient practice in Greece for the period 2017–2019, with estimation of outpatient costs under real-life conditions, using prospective individual data. The total outpatient costs of CMM for the 3-year period amounted

Table 3. Annual pharmaceutical costs for treatment of cutaneous malignant melanoma in Greece by pharmaceutical category (Euros, 2020).

Pharmaceutical category	Pharmaceuticals, n (%)	Costs (€)	
Generic pharmaceuticals	14,224 (13.2)	359,172	
2017	4,521 (4.2)	97,576	
2018	4,278 (4.0)	120,984	
2019	5,425 (5.0)	140,612	
On patent pharmaceuticals	93,884 (86.8)	67,460,012	
2017	31,738 (29.4)	18,908,002	
2018	29,387 (27.2)	21,907,935	
2019	32,759 (30.3)	26,644,076	
Total	108,108 (100.0)	67,819,184	

Table 4 Total pharmaceutica	al costs for treatment of cutaneou	is malignant melanoma in Greece	te by costliest ATC4 code (Euros, 2020).
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ATC4 code	Clarification	Pharmaceu	ticals, n (%)	Costs (€)
L01XE	Protein kinase inhibitors	25,637	(23.7)	46,287,830
L01XC	Monoclonal antibodies	11,178	(10.3)	19,245,684
B03XA	Other antianemic preparations	582	(0.5)	446,558
L03AB	Interferons	6,111	(5.7)	348,324
V08AB	Water-soluble, nephrotropic, low osmolar X-ray contrast media	8,978	(8.3)	243,489
N02AB	Phenylpiperidine derivatives	2,740	(2.5)	169,786
H02AB	Glucocorticoids	7,588	(7.0)	150,262
L03AA	Colony stimulating factors	567	(0.5)	145,475
V08CA	Paramagnetic contrast media	2,822	(2.6)	139,500
B01AB	Heparin group	4,720	(4.4)	136,454

to \in 74,007,121. Of the total outpatient costs, 8.4% was attributed to examinations (\in 6,187,937) and 91.6% to pharmaceuticals (\in 67,819,184). This finding is consistent to the findings of a Dutch⁷ and a French study,⁸ which also reported that the pharmaceutical cost was the main component in the overall cost of CMM outpatient care.

Over the 3-year period of analysis, € 1,08 billion were cumulatively spent on examinations,9-11 of which 0.6% (€ 6,187,937) was related to examinations for the diagnosis and monitoring of CMM. The main examination expense was on imaging (radiological) examinations which accounted for 42% of total examination costs. Patients appear to be increasingly undergoing imaging-based surveillance, in light of the availability of targeted therapies and immunotherapies. 12-19 The National Comprehensive Cancer Network (NCCN) recommends CT or PET scans every 3-12 months for patients with stage IIB-IV asymptomatic CMM.²⁰ The European Society of Medical Oncology (ESMO) recommends physical examination only, every 3 months.²¹ Dermoscopy continues to be the most widely used skin imaging tool for prediction of Breslow thickness⁷ and to determine the initial need for sentinel lymph node biopsy (SLNB).8 Dermoscopy is not prescribed separately by Greek dermatologists, and its cost is included in that for the physician's visit.

In Greece, the public outpatient pharmaceutical costs for CMM for 3 years amounted cumulatively to € 5,84 billion (€ 1,945 billion annually),^{22,23} of which 1.2% (€ 67,819,184) originated from pharmaceutical treatment for CMM. Since 2011, immunotherapy and targeted therapy have provided new promising options for advanced CMM.²⁴ These technologies are patent-protected and thus the penetration of generics appeared to be low (13.6%), as expected. The new therapies have been priced at high price premiums compared with chemotherapy. The total costs of protein

kinase inhibitors (ATC4: L01XE) for CMM management was \in 46,287,830 and the cost of monoclonal antibodies (ATC4: L01XC) \in 19,245,684. These therapies are the main cost drivers of outpatient pharmaceutical care.

The total management cost of CMM was estimated at € 1,634/patient in France, 25 € 3,456/patient in Italy, 26 € 10,269/patient in the US, 27 and € 20,578/patient in Canada 28 prior to the introduction of the new treatments. After ipilimumab became available, the costs increased to € 107,000/patient in France, 29 and € 81,484/patient in the Netherlands. 7 A study from Australia reported a cost of € 112,322/patient between 2012 and 2014 30 for all new pharmaceuticals, as the costs were restricted to the first three years of treatment. In 2018, the first study to evaluate the impact of immunotherapies and targeted therapies reported mean management cost of € 269,682/patient for the French setting. 8

Our study showed that the costs attributable to male patients are higher than to female patients. CMM is documented to be more prevalent among males between the ages of 25–50 years,^{3,31} mainly due to the higher rates of CMM of the trunk.²¹ Our findings appear in alignment with the literature, as CMM of trunk (C43.5) was the highest cause of examination costs (€ 211,897) among the ICD10 codes under study.

The clinical outcome of immunotherapy is not easy to predict and, in some cases, it is not positive for patients.³² Unlike targeted therapy, which has predictive response markers, validated biomarkers still need to be approved for the immunotherapeutic agents.^{33,34} Precision medicine has paved the way for increasingly personalized treatments, minimizing the proportion of non-responders while avoiding harmful, controversial and expensive treatments.

The outpatient costs of CMM estimated in this study

could be avoided to a large extent, resulting in meaningful savings for the healthcare system. More than 90% of skin cancers can be prevented through primary and secondary prevention.35 It is estimated that 60-80% of cases of CMM are caused by exposure to UVR, from either natural or artificial sources.^{36–38} Avoiding exposure to UVR (i.e., avoiding the sun at peak hours, wearing protective clothing, using sunscreen, etc.) helps to reduce the incidence of primary CMM.³⁹ In northern Germany, systematic skin cancer screening has reduced mortality from 1.7 deaths per 100,000 CMM cases to 0.9 deaths per 100,000 CMM cases. 40 It has been reported that 55% of the annual direct cost of CMM treatment is for stage IV patients, and about 1/3 of the total cost is related to end-of-life CMM treatment. 41 The net CMM management cost in the last year of the life of patients with metastatic disease is about twice that of patients with local CMM.42 Hence, if all patients with CMM were diagnosed at stage 0 or I, the annual direct treatment cost of patients aged 65 and older would be 40-65% lower than the current cost, saving significant resources for the healthcare system.⁴³

In Greece, a closed budget has been recently implemented between 2018–2020, with the aim of capping pharmaceutical expenditure for CMM, based on the disease stage. This measure has been partially effective in containing costs for the period 2018–2020.⁴⁴ Typically, a closed budget groups products by ATC4 therapeutic category, and is used as a means of limiting the total spending for the specific pharmaceutical class, while encouraging compliance with evidence-based clinical protocols. The annual revision of a closed budget may allow the inclusion of new therapies that could fulfil currently unmet medical needs. The implementation of a closed budget may also facilitate the assessment of the budget impact and the cost-benefit of reimbursing new treatments.⁴⁵

This study has some limitations. Firstly, the economic burden of CMM is estimated only in the outpatient setting, in the absence of consistent electronic prescribing databases in Greek public hospitals. Useful information regarding HCRU, such as number of admissions and readmissions, duration of hospitalization, management of treatment emergent adverse events (TEAEs), palliative care, etc., for patients with CMM are not available to IDIKA SA. Hence, the present study represents a partial estimation of the economic burden of CMM in Greece. Secondly, IDIKA SA, in accordance with local privacy regulations, provides data per examination and pharmaceutical, and not according

to the patient's social security number (AMKA), making it overwhelmingly difficult to estimate the per-patient cost of CMM. Thirdly, the patients' age, in most cases, was incorrectly entered to the database by physicians. Consequently, analysis by age or by age group was extremely difficult. Fourthly, as IDIKA SA does not provide data by disease stage, it was impossible to estimate costs per disease stage. Furthermore, some pharmaceutical categories were excluded from the analysis: e.g., pharmaceuticals that had been imported on a patient basis by the Pharmaceutical Research and Technology Company (IFET SA); those that had been withdrawn from the Greek market or had changed brand name at the time of analysis; those that are not legally included in public pharmaceutical expenditure (e.g., vaccines), and pharmaceuticals included in the negative (non-reimbursed) list. Finally, another limitation stems from the difference between the acquisition cost and net cost of pharmaceuticals in Greece. Based on the current legislation, recent agreements are in place between the Ministry of Health and pharmaceutical companies regarding the reimbursement of pharmaceuticals. The details of these agreements, however, remain confidential. Consequently, list prices for pharmaceuticals may not reflect the actual costs for EOPYY.

In conclusion, in an era of effective current and emerging innovative imaging techniques and pharmaceutical therapies for patients with CMM, it is critical to generate real-world evidence showing the costs and outcomes associated with patients undergoing treatment. As the healthcare system moves towards a value-based approach to the provision and reimbursement of care, the possibility of utilization of administrative data through registries provides information necessary to establishing the value of current and new prevention policies and treatments. This study showed that outpatient CMM diagnosis and treatment are provided at a considerable cost to the healthcare service in Greece. The study quantified these costs, with a view to providing relevant information for the health policy decision-makers at all stages of decision-making, on the magnitude of CMM-attributable outpatient costs and to assisting them in more efficient health resource allocation.

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ΠΕΡΙΛΗΨΗ

Οικονομικό φορτίο του δερματικού κακοήθους μελανώματος στο περιβάλλον των εξωτερικών ασθενών στην Ελλάδα κατά την τριετία 2017–2019

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Αρχεία Ελληνικής Ιατρικής 2023, 40(2):245-253

ΣΚΟΠΟΣ Ποσοτικός προσδιορισμός του άμεσου ιατρικού κόστους των εξωτερικών ασθενών με δερματικό κακόηθες μελάνωμα (ΔΚΜ), που καλύπτεται από το εθνικό σύστημα ασφάλισης της υγείας, στην Ελλάδα την περίοδο 2017– 2019. ΥΛΙΚΟ-ΜΕΘΟΔΟΣ Διεξήχθη μια μελέτη κόστους-ασθένειας βάσει του επιπολασμού της νόσου από την οπτική του τρίτου πληρωτή στην Ελλάδα. Χρησιμοποιώντας μια ηλεκτρονική βάση δεδομένων του τρίτου πληρωτή, συλλέχθηκαν δεδομένα για εξετάσεις και φαρμακευτικά προϊόντα που συνταγογραφήθηκαν σε Έλληνες ασθενείς με διάγνωση ΔΚΜ και μετατράπηκαν σε κόστος, χρησιμοποιώντας το ισχύον μοναδιαίο κόστος στην Ελλάδα. Τα δεδομένα χρήσης υγειονομικών πόρων (ΧΥΠ) για τους εξωτερικούς ασθενείς προήλθαν από τους κωδικούς ICD10 του ΔΚΜ. Το μοναδιαίο κόστος προήλθε από τους καταλόγους αποζημιούμενων φαρμάκων του Εθνικού Οργανισμού Παροχής Υπηρεσιών Υγείας (ΕΟΠΥΥ) και τα κρατικά τιμολόγια για τις διαγνωστικές εξετάσεις. ΑΠΟΤΕΛΕΣΜΑΤΑ Το συνολικό κόστος των εξωτερικών ασθενών με ΔΚΜ κατά την περίοδο 2017–2019 ανήλθε σε 74.007.121 € (29.039.029 € το 2019, 24.093.994 € και 20.874.097 € το 2018 και το 2017, αντίστοιχα). Το φαρμακευτικό κόστος αντιπροσώπευε το 92,6%, ενώ το κόστος των εξετάσεων αντιπροσώπευε το 8,4% του συνολικού κόστους των εξωτερικών ασθενών. Οι άνδρες ασθενείς παρουσίασαν ελαφρώς υψηλότερο συνολικό κόστος σε σύγκριση με τις γυναίκες ασθενείς. Οι ακτινολογικές εξετάσεις, οι αναστολείς της πρωτεϊνικής κινάσης και τα μονοκλωνικά αντισώματα ήταν οι κύριοι παράγοντες κόστους, στο διαγνωστικό και στο φαρμακευτικό κόστος, αντίστοιχα. ΣΥΜΠΕΡΑΣΜΑΤΑ Οι τρέχουσες διαθέσιμες και καινοτόμες διαγνωστικές μέθοδοι και οι υψηλού κόστους, αν και καινοτόμες και αποτελεσματικές φαρμακευτικές θεραπείες, υπογραμμίζουν την ανάγκη καταγραφής δεδομένων πραγματικού κόσμου που δείχνουν τόσο το κόστος όσο και τα αποτελέσματα για τους ασθενείς οι οποίοι λαμβάνουν διαφορετικά επίπεδα φροντίδας. Η διάγνωση και η θεραπεία του ΔΚΜ συνιστούν σημαντικό και κλιμακούμενο κόστος για τις υπηρεσίες υγείας στην Ελλάδα. Η παρούσα μελέτη ήταν μια μελέτη κόστους-ασθένειας με δεδομένα πραγματικού κόσμου που φιλοδοξεί να ενημερώσει τους υπεύθυνους λήψης αποφάσεων σε όλα τα στάδια, στην πολιτική υγείας, σχετικά με το μέγεθος του κόστους διαχείρισης των εξωτερικών ασθενών με ΔΚΜ και να συμβάλλει στην αποτελεσματική κατανομή των πόρων στην υγεία.

Λέξεις ευρετηρίου: Δεδομένα πραγματικού κόσμου, Δερματικό κακόηθες μελάνωμα, Μελέτη κόστους-ασθένειας, Περιβάλλον εξωτερικών ασθενών

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