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ORIGINAL REPORT

Cost-Effectiveness of Skin Surveillance Through a Specialized Clinic for Patients at High Risk of Melanoma

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A B S T R A C T

Purpose

Clinical guidelines recommend that people at high risk of melanoma receive regular surveillance to improve survival through early detection. A specialized High Risk Clinic in Sydney, Australia was found to be effective for this purpose; however, wider implementation of this clinical service requires evidence of cost-effectiveness and data addressing potential overtreatment of suspicious skin lesions.

Patients and Methods

A decision-analytic model was built to compare the costs and benefits of specialized surveillance compared with standard care over a 10-year period, from a health system perspective. A high-risk standard care cohort was obtained using linked population data, comprising the Sax Institute's 45 and Up cohort study, linked to Medicare Benefits Schedule claims data, the cancer registry, and hospital admissions data. Benefits were measured in quality-adjusted life-years gained. Sensitivity analyses were undertaken for all model parameters.

Results

Specialized surveillance through the High Risk Clinic was both less expensive and more effective than standard care. The mean saving was A$6,828 (95% CI, $5,564 to $8,092) per patient, and the mean quality-adjusted life-year gain was 0.31 (95% CI, 0.27 to 0.35). The main drivers of the differences were detection of melanoma at an earlier stage resulting in less extensive treatment and a lower annual mean excision rate for suspicious lesions in specialized surveillance (0.81; 95% CI, 0.72 to 0.91) compared with standard care (2.55; 95% CI, 2.34 to 2.76). The results were robust when tested in sensitivity analyses.

Conclusion

Specialized surveillance was a cost-effective strategy for the management of individuals at high risk of melanoma. There were also fewer invasive procedures in specialized surveillance compared with standard care in the community.

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INTRODUCTION

Melanoma and keratinocytic cancers are the most commonly diagnosed cancers in countries with individuals of predominantly European origin, and their diagnosis and treatment places a high burden on the health care system in terms of resource use and costs.[1-5] Melanoma is less common than keratinocytic cancers but accounts for most skin cancer deaths.[6] The thickness of a melanoma lesion at diagnosis is an important prognostic marker, and 5-year relative survival decreases as thickness increases.[7] Important risk factors for melanoma, in addition to solar and artificial UV radiation exposure,[8] include high melanocytic nevus count and dysplastic nevus syndrome,[9] a strong family history of melanoma,[10] or high-penetrance gene mutations.[11] Although there is variation in international guidelines about how best to identify and manage high-risk patients,[12] Australian guidelines recommend surveillance intervals that are based on assessment of the level of future risk of melanoma.[13] Surveillance of patients at high risk of melanoma has been shown to be effective in detecting subsequent melanomas at an early stage.[14-17]

A High Risk Clinic for patients at high risk of melanoma was established at the Sydney Melanoma Diagnostic Centre, Royal Prince Alfred Hospital, Sydney, Australia, in 2006, to examine the effectiveness of surveillance using digital dermoscopy

ASSOCIATED CONTENT

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and total body photography. Assessment of this clinic demonstrated effective surveillance in terms of early detection of melanoma and low excision rates; 91% of melanomas were detected with a lesion thickness < 1 mm, and the benign to malignant excision ratio for keratinocytic lesions and melanoma was 1.6:1.[18] Monitoring of lesions is time consuming and requires highly trained staff and specific resources. Evidence of cost-effectiveness and data addressing potential overtreatment of suspicious skin lesions is required for wider implementation. This study aimed to address these evidence gaps by conducting a cost-effectiveness analysis from an Australian health care system perspective, examining the costs and benefits of skin cancer monitoring using specialized surveillance compared

Table 1. Model Inputs for Specialized Surveillance and Standard Care Treatment Strategies

Item	Specialized Surveillance				Standard Care			
	Base Case	Low*	High*	Source or First Author	Base Case	Low*	High*	Source
Annual probabilities								
Melanoma by stage at diagnosis								
In situ melanoma	0.45	0.02	0.90	†	0.15	0.08	0.30	‡
Stage I melanoma	0.42	0.02	0.84	†	0.59	0.29	0.9	‡
Stage II melanoma	0.09	0.04	0.18	†	0.22	0.11	0.44	‡
Stage III melanoma	0.03	0.02	0.06	†	0.05	0.02	0.09	‡
Stage IV melanoma	0.000	NA	NA	†	0.005	0.003	0.01	‡
Excisions under surveillance§								
Probability of an excision	0.40	0.21	0.84	†	0.64	0.32	0.99	‖
Melanoma only	0.12	0.06	0.24	†	0.05	0.02	0.09	‖
Keratinocytic lesion only	0.18	0.09	0.36	†	0.13	0.07	0.26	‖
Benign lesions only	0.50	0.25	0.99	†	0.28	0.14	0.55	‖
Melanoma and keratinocytic lesion	0.02	0.01	0.04	†	0.03	0.01	0.06	‖
Melanoma and benign lesion	0.07	0.03	0.14	†	0.08	0.04	0.17	‖
Keratinocytic and benign lesion	0.09	0.04	0.18	†	0.33	0.15	0.66	‖
Melanoma and keratinocytic and benign lesion	0.01	0.008	0.04	†	0.10	0.04	0.20	‖
Event rates for hospital treatment by stage of disease								
Stage II								
Probability of receiving a sentinel lymph node biopsy procedure	0.72	0.36	0.99	Morton[25]	Same values as High Risk Clinic patients			
Probability of sentinel lymph node biopsy being positive	0.16	0.13	0.22	Morton[25]				
Stage III and stage IV					Same values as High Risk Clinic patients			
Disease-free 5-year survival stage III	0.62	0.47	0.78	Balch[7]				
Probability of progression to stage IV	0.28	0.14	0.51	Balch[7]				
Relapse in stage III	0.50	0.25	0.67	Coit[26]				
Probability of resectable disease (> 2 years)	0.48	0.25	0.71	Watts[21]				
5-year survival with stage III relapse and potentially resectable disease (early detection of metastases)	0.6	0.3	0.99	Romano,[27] Garbe[28]				
5-year survival with stage III relapse and potentially unresectable disease (late detection of metastases)	0.18	0.09	0.36	Watts,[21] Romano[27]				
Disease-free 5-year survival stage IV	0.18	0.7	0.19	Balch[7]				
Utilities					Same values as High Risk Clinic patients			
Full health	1.000							
In situ melanoma, treatment	0.687	0.642	0.733	Tromme[29]				
In situ melanoma, remission	0.809	0.773	0.844	Tromme[29]				
Stage I melanoma, treatment	0.579	0.642	0.733	Tromme[29]				
Stage I melanoma, remission	0.802	0.773	0.844	Tromme[29]				
Stage II melanoma, treatment	0.579	0.486	0.671	Tromme[29]				
Stage II melanoma, remission	0.802	0.764	0.839	Tromme[29]				
Stage III melanoma, treatment	0.535	0.395	0.676	Tromme[29]				
Stage III melanoma, remission	0.703	0.659	0.746	Tromme[29]				
Stage IV melanoma, treatment	0.583	0.524	0.642	Tromme[29]				
Stage IV melanoma, remission	0.796	0.708	0.883	Tromme[29]				
Keratinocytic lesion excision	0.976	0.924	1.000	Chen[30]				
Benign nevus excision	0.971	0.924	1.000	Chen [30]				

Abbreviations: MBS, Medicare Benefits Schedule; NA, not applicable.
*Calculation for sensitivity analyses on the basis of multiplier equation (0.5 and 2) for excision probabilities and from published literature for other values.
†Pseudo-stage on the basis of Breslow thickness (see Methods), on the basis of data used for the High Risk Clinic study.[18]
‡Pseudo-stage on the basis of Breslow thickness if degree of spread not provided, using linked data from the Sax Institute's 45 and Up Study, with MBS and New South Wales Cancer Registry 2006 to 2008 data.
§Calculations for probabilities by lesion type as determined by the model structure (Data Supplement, Table S5). Probabilities exclude excisions for melanoma recurrence and MBS item no 30071 (diagnostic incision/shave biopsy of skin or mucous membrane).
‖Linked data from the Sax Institute's 45 and Up Study with MBS 2006 to 2010 and New South Wales Cancer Registry data.

Table 2. Summary of Annual Costs in Specialized Surveillance and in Standard Care

Description	Annual Base Case (A$)	Range[a] (A$)		Medicare Benefits Schedule/Source
		Low	High	
Specialized surveillance[b]	884	884	1,022	Watts[21] MBS item 23, High Risk Clinic surveillance costs $744
Specialized surveillance excisions[c,d]				
Melanoma excision biopsy[e]	453	227	906	MBS items 72830, 23, 110, 73924, weighted cost for excision MBS item 31205 and 31210
Keratinocytic lesion[f]	268	128	511	MBS items 72816, 23, 73924, weighted cost for keratinocytic lesion excision $171
Benign lesion[f]	204	96	383	MBS items 72816, 23, 73924, weighted cost for benign lesion excision $94
Melanoma excision biopsy[e] and keratinocytic lesion	563	293	1,173	As above; multiple service rule applied to excisions, pathology MBS item 72830
Melanoma excision biopsy[e] and benign lesion	484	261	1,045	As above; multiple service rule applied to excisions, pathology MBS item 72830
Keratinocytic and benign lesion	308	173	691	As above; multiple service rule applied to excisions, pathology MBS item 72817 or 72818
Melanoma excision biopsy[e] and keratinocytic and benign lesion	579	334	1,336	As above; multiple service rule applied to excisions, pathology MBS item 72830
Incision/shave biopsy[g]	44	22	89	MBS item 30071
Standard care surveillance[h]	70	70	140	MBS item 23
Standard care excisions[d,i]				
Melanoma excision biopsy[e,i]	463	232	926	MBS items 72830, 110, 73927, weighted cost for excision MBS item 31205 and 31210
Keratinocytic lesion[j]	260	129	514	MBS items 72816, 73927, weighted cost for keratinocytic lesion excision $171
Benign lesion[j]	151	74	298	MBS items 72816, 73927, weighted cost for benign lesion excision $63
Melanoma excision biopsy[e] and keratinocytic lesion	583	316	1,263	As above; multiple service rule applied to excisions, pathology MBS item 72830
Melanoma excision biopsy[e] and benign lesion	494	262	1,046	As above; multiple service rule applied to excisions, pathology MBS item 72830
Keratinocytic and benign lesion	301	165	660	As above; multiple service rule applied to excisions, pathology MBS item 72817 or 72818
Melanoma excision biopsy[e] and keratinocytic and benign lesion	599	347	1,388	As above; multiple service rule applied to excisions, pathology MBS item 72830
Incision/shave biopsy[g]	52	26	104	MBS items 30071
Hospital costs[k]				
Wide excision	2,974	2,416	3,533	
Sentinel lymph node biopsy	2,686	1,167	4,205	
Complete lymph node dissection	11,492	8,450	14,797	
Treatment of recurrent stage III or stage IV	125,239	94,480	156,120	Medical Services Advisory Committee[31] includes PET, surgery, chemotherapy or radiotherapy or combination
Stage III monitoring costs[l]				
Stage III year 2	2,127			MBS items 116, 55808, 61553
Stage III year 3	1,813			MBS items 116, 55808, 61553
Stage III year 4	1,813			MBS items 116, 55808, 61553
Stage III year 5	157			MBS items 116, 55808
Stage III years 6 to 10	157			MBS items 116, 55808
Other costs				
Palliative care	22,092	11,046	44,184	Kardamanidis[32] Average hospital cost in the last year of life for a patient with cancer
End-of-life care	17,714			Kardamanidis,[32] Swerisson[33] Average hospital cost in last year of life; 50% of Australians die in hospital

Abbreviations: MBS, Medicare Benefits Schedule; PET, positron emission tomography.

[a]Calculation for sensitivity analyses based on multiplier equation (0.5 and 2) for excision probabilities and from published literature for other values.

[b]Based on mean annual cost from microcosting study[21]: total body photography ($34), sequential digital dermoscopy ($65), and two extended appointments for skin surveillance ($140), and mean annual salary and overheads of High Risk Clinic ($645). The total body photography costs were based on a new set of photographs every 5 years.

[c]High Risk clinic excision data were based on results from a 5-year review of the High Risk Clinic.[18] All excisions were classified by lesion type.

[d]Mean cost for an excision. Patients may have more than one excision in a year. The base case assumes all excisions take place at the time of a skin examination. Procedures within a hospital were costed at 85%, or if outside a hospital at 100%. The multiple service rule was applied for multiple excision types on the same day. Pathology costs were valued as level 5 (Medicare Benefits Schedule item 30195) for melanoma reports or level 3 (Medicare Benefits Schedule item 72823) for keratinocytic and benign nevus reports, on the basis of personal communication with pathology staff at Royal Prince Alfred Hospital. One annual pathology cost was levied if a patient had an excision. If melanoma was reported, MBS item no 72830 was used; otherwise, MBS item 72816, 72817, or 72818 was used depending on number of annual excisions. One pathology handling fee per patient was included; MBS item 73924 for High Risk Clinic patients and 73927 for standard care patients. For the purposes of this analysis, a wide excision was assumed to be performed in hospital and was included under hospital costs.

[e]Weighted mean cost for melanoma excision biopsy from the linked data set using MBS item numbers 31205 to 31210. Contains additional costs for suture removal outside the hospital and referral to a specialist surgeon for a wide excision.

[f]Weighted mean cost based on medical records of keratinocytic and benign lesion excisions for 87 High Risk Clinic patients over a 12-month period.

[g]Incision biopsy pathology cost was bundled under the pathology item number for excisions done at the same time.

[h]Based on costs for a clinical appointment for a skin examination from a primary care physician, on the basis of a telephone survey of skin cancer clinics and mixed practice clinics in New South Wales.

[i]Standard care group excision data were calculated from a linked data using the Sax Institute's 45 and Up Study with data from the Medicare Benefits Schedule, New South Wales Cancer Registry, and New South Wales Admitted Patient Data Collection 2006 to 2010.

[j]Weighted mean cost for keratinocytic and benign lesions excisions from MBS item numbers used by the standard care group (Data Supplement, Table S2).

[k]Hospital costs have been calculated using linked data from the New South Wales Cancer Registry and the Admitted Patient Data Collection (Data Supplement, Tables S3 and S4).

[l]Based on a follow-up schedule of four patient review appointments in year 2, two reviews in years 3 and 4, and one review thereafter using ultrasound and PET. PET is not continued after 4 years.

with standard care in the community. Ethical approval was granted by New South Wales Population and Health Services Research Ethics Committee.

PATIENTS AND METHODS

Study Population of High-Risk Patients

Intervention: High Risk Clinic Specialized Surveillance. High Risk Clinic participants were selected on the basis of having a confirmed family history of three or more first- or second-degree relatives with melanoma and a confirmed personal history of invasive melanoma; or dysplastic nevus syndrome and a confirmed personal history of invasive melanoma; or a personal history of at least two confirmed invasive melanomas, one diagnosed in the past 10 years; or a confirmed high-penetrance mutation affecting melanoma risk.[18] Over a 5-year period, 311 patients underwent specialized surveillance (Data Supplement, Table S1).[18]

Standard Care. A cohort of high-risk patients receiving standard (routine) care in the community was identified from the Sax Institute's 45 and Up cohort study, Australia,[19] linked to population health data from the Medicare Benefits Schedule claims data,[20] New South Wales Cancer Registry, and hospital admissions data from the Admitted Patient Data Collection (Data Supplement, Methods, and Fig S1). Patients were selected on the basis of a reported family history of two first-degree relatives with melanoma and a confirmed personal history of invasive melanoma, or a personal history of at least two confirmed invasive melanomas, one in the past 10 years (Data Supplement, Table S1). Data were linked using a linkage key provided by the New South Wales government's Centre for Health Record Linkage in accordance with ethical, legal, and confidentiality requirements (Data Supplement, Fig S1). Deterministic matching using month and year of melanoma diagnosis, morphology, topography, and sex was used to identify and remove 30 patients who were in both standard care and specialized surveillance groups. The standard care group consisted of 607 patients, with data from a similar time period.

Surveillance-Treatment Pathway

Surveillance. Specialized surveillance consisted of two clinic visits per year.[18,21] If a suspicious lesion was identified, the lesion was excised or the patient was reviewed after 3 months. The histopathology and classification of all excisions were documented.[18]

Given their history of invasive melanoma, patients treated with standard care were assumed to undergo an annual skin examination conducted by their usual doctor or dermatologist. Australian guidelines[13] recommend that patients with American Joint Cancer Committee (AJCC)[7] stage I melanoma be reviewed at 6-month intervals for the first 5 years and then annually.[13] Clinical pathways for standard care were obtained through a telephone survey of 10 primary care practices in Sydney and major towns in New South Wales.

Classification and staging of suspicious lesions. Suspicious lesions were categorized into four categories: histopathologically confirmed melanoma; histopathologically confirmed keratinocytic cancers, including basal cell carcinoma, squamous cell carcinoma, and squamous cell carcinoma in situ; histopathologically confirmed benign lesions; and biopsy of skin or mucous membrane for diagnostic purposes. Excisions were defined on the basis of Medicare Benefit Schedule item numbers pertaining to treatment of suspicious lesions and included the following procedures: excision, serial curettage, and CO_2 laser or erbium laser excision-ablation, including any associated cryotherapy or diathermy (Data Supplement, Table S2).

AJCC melanoma staging is based on tumor thickness, ulceration, the number of lymph nodes, nodal metastatic mass, and metastatic spread[7]; however, we used a simplified staging classification for both groups, because ulceration and mitotic rate were not available from the cancer registry. If spread of disease was not documented, lesion thickness was used to determine stage, defined as in situ (no invasion), pseudo-stage I (0 to 1.0 mm), pseudo-stage II (1.01 to $\leq$ 4.00 mm), pseudo-stage III ($\geq$ 4.01 mm or lymph node involvement), and pseudo-stage IV (distant metastatic disease). We validated the pseudo-stage against AJCC stage in all 77 primary melanoma reports from the specialized surveillance group and found 92% agreement (and weighted κ statistic 0.93, 95% CI, 0.87 to 0.99). Identification of new primary melanoma and recurrence of melanoma was by histopathology reports in the patients' medical records (High Risk Clinic) or using cancer registry data (standard care).

Economic Evaluation

Economic methods. A decision-analytic Markov model was developed to simulate the observed management and potential progression of melanoma, starting with the identification of a suspicious lesion, observation or treatment, and return to surveillance, or, if melanoma, various treatment options on the basis of melanoma stage at diagnosis (Data Supplement, Figs S2 and S3). The model cycle length was 12 months, with a 10-year time frame and 6 health states, to represent observed long-term follow-up, informed by comprehensive prognostic and survival data.[7] The economic outcomes were resource use, costs, and cost-effectiveness, with the model result reported as the incremental cost per quality-adjusted life-year (QALY) gained of specialized surveillance compared with standard care. The Australian standard discount rate of 5%[22] was applied to all future costs and benefits. All costs were adjusted to 2013 dollars using published deflators.[23] The Markov model was constructed using TreeAge Pro 2015, and statistical analysis was performed using SAS 9.4 (SAS Institute, Cary, NC). The analysis was reported according to the Consolidated Health Economic Evaluation Reporting Standards Statement[24] checklist.

Resource use and costs: High Risk Clinic. Resource use, costs, and clinical pathways for specialized care were estimated using published data from the High Risk Clinic[18,21] (Table 1).[25-30] Unit costs for melanoma, keratinocytic, and benign lesion excisions were obtained from the appropriate Medicare Benefits Schedule[20] item numbers and our micro-costing study[21] (Table 2).[31-33] Cryotherapy rates were estimated from High Risk Clinic billing records from June 2013 to June 2015 and re-excision of keratinocytic lesions from standard care data. Because the High Risk Clinic operates within a public hospital, the standard fee for service is 85% of the scheduled fee.[34]

Standard care. The standard care linked data set (2006 to 2010) was used to calculate the frequency of procedures by lesion type. We used Medicare Benefits Schedule item numbers to calculate the cost of excisions, using a weighted average on the basis of the size and anatomic location of the lesion and procedure (Tables 1 and 2). For services provided outside a hospital, costs were calculated at 100% of the schedule fee. The multiple service rule[20] was applied when multiple excision types resulted in a reduced cost for second and subsequent excisions (50% and 25%, respectively) and pathology costs (Table 2).

Hospital costs. Costs for hospital treatment (Table 2) were obtained from Admitted Patient Data Collection hospital admission International Classification of Diseases, 10th revision diagnosis codes for melanoma linked to the cancer registry using stage and year at diagnosis. Mean costs by stage at diagnosis were calculated using Australian Refined Diagnosis-Related Group[35a] classifications (Data Supplement, Table S3) and length of stay in the hospital. The cost of a wide excision was calculated as the mean hospital cost, on the basis of patients with in situ or stage I melanoma. The

Table 3. Mean Total Costs (A$) and Quality-Adjusted Life-Years per Patient Over 10 Years for Each Strategy

Measure	Specialized Surveillance	Standard Care	Difference (95% CI)
Mean cost per patient	$13,468	$20,296	$6,828 ($5,564 to $8,092)
QALYs	7.87	7.56	0.31 (0.27 to 0.35)

Abbreviation: QALY, quality-adjusted life years.

cost of a sentinel lymph node biopsy was calculated as the mean cost of stage II admissions minus the mean cost of a wide excision (Data Supplement, Table S4). Stage III costs were estimated from International Classification of Diseases, 10th revision admission and treatment codes for lymph node dissection and Medicare Benefits Schedule data for relevant treatment and follow-up (Data Supplement, Fig S4). Costs for ongoing surveillance were based on the predicted frequency of specialist consultations[13] (Data Supplement). Costs related to death in hospital,[32] palliative care,[35,36] and treatment of metastatic disease[31,37] were obtained from published sources.

Model transitions. For specialized care, the probability of melanoma by stage at diagnosis and the annual frequency of excisions by lesion type was obtained from the High Risk Clinic 5-year follow-up study[18] (Table 1; Data Supplement, Table S5). High Risk Clinic participants joined the study at different time points. For our analysis, all patients started the model in their first year of surveillance. Data for all 311 participants were included.

Cancer registry data from 2004 to 2008 were used to calculate the probability of melanoma by stage at diagnosis and linked with the Medicare Benefits Schedule (years 2006 to 2008) to calculate the probability of excision by lesion type and to exclude excisions due to recurrence (Table 1; Data Supplement, Table S5). Survival estimates for the general population were obtained from life tables of the Australian Bureau of Statistics[38] and for melanoma-specific deaths from AJCC staging estimates[7] (Table 1).

Quality-of-life scores. Utility scores were assigned to health states. These scores reflect society's valuation of health outcomes ranging from 1.0 for full health to zero for death.[39] Utility scores for melanoma were obtained from a prospective study of patients with melanoma that measured health states longitudinally by stage at diagnosis and at remission.[29] Utility scores for excisions of nonmelanoma skin cancer,[40] benign nevus, and keratinocytic lesions were sourced from published literature (Table 2).[30] Individuals without an excision were assumed to be in full health.

Sensitivity analyses. A series of one-way and two-way sensitivity analyses were performed to evaluate the robustness of the model and to test the model parameters. Where high and low estimates could not be obtained from the literature, we used a standard multiplier equation (0.5 to 2.0) to address sensitivity around our model parameters. Quality-of-life measures were tested using 95% CIs. For two-way sensitivity analyses, we examined each parameter separately for an effect on the ratio of costs and outcomes. For probabilistic sensitivity analysis, we performed a Monte Carlo simulation, sampling 1,500 times from randomly assigned distributions of key variables identified from our one-way sensitivity analysis. We used β distributions for all probabilities and utility values and γ distributions for cost parameters.[41] The baseline values, ranges, and distributions are shown in Tables 1 and 2.

RESULTS

Specialized surveillance was both less expensive and more effective than standard care. The mean saving was A$6,828 (95% CI, $5,564 to $9,029) per patient and the mean QALY gain was 0.31 (95% CI, 0.27 to 0.35) for patients in specialized surveillance compared with standard care. The results for the base case are shown in Table 3. The mean cost per patient over 10 years in specialized surveillance was A$13,468 and in standard care was A$20,296; the QALYs were 7.87 and 7.56, respectively. The main drivers for these differences were detection of melanoma at an earlier stage resulting in lower treatment costs and fewer excisions for suspicious lesions in specialized surveillance compared with standard care. The annual probability of an excision was lower in specialized surveillance (0.40; 95% CI, 0.33 to 0.46) compared with standard care (0.64; 95% CI, 0.61 to 0.68). This corresponded to an annual mean number of excisions for suspicious lesions of 0.81 (95% CI, 0.72 to 0.91) in specialized surveillance and 2.55 (95% CI, 2.34 to 2.76) in standard care. Among patients who had at least one excision, the mean number of excisions over a 12-month period remained lower in specialized surveillance (2.05; 95% CI, 1.93 to 2.219) than in standard care (3.98; 95% CI, 3.82 to 4.14; Table 4).

The results of one-way sensitivity analyses indicated that the variables most likely to influence the incremental cost-effectiveness ratio were the probability of an excision in standard care and specialized surveillance, the annual cost of specialized surveillance, and the cost of treating metastatic disease. A tornado diagram (Data Supplement, Fig S5) shows the variables with the greatest influence on the results stacked at the top of the graph. A low probability of excision in the standard care arm was the only

Table 4. Mean Excisions per Person in Specialized Surveillance and Standard Care From 2006 to 2010

	Specialized Surveillance (High Risk Clinic)						Standard Care					
No. of years of surveillance*	Patients	Total Patients Who Had an Excision†	Probability of an Excision	All Excisions‡	Mean No. Excisions per Person	Mean No. Excisions per Person With an Excision	Patients	Total Patients Who Had an Excision†	Probability of an Excision	All Excisions‡	Mean No. Excisions per Person	Mean No. Excisions per Person With an Excision
	a	*b*	*b/a*	*c*	*c/a*	*c/b*	*a*	*b*	*b/a*	*c*	*c/a*	*c/b*
1	311	133	0.43	275	0.88	2.07	586	384	0.66	1,507	2.57	3.92
2	280	127	0.45	256	0.91	2.02	580	391	0.67	1,589	2.74	4.06
3	257	98	0.38	189	0.74	1.93	584	389	0.67	1,647	2.82	4.23
4	197	56	0.28	130	0.66	2.32	573	340	0.59	1,314	2.29	3.86
5	97	40	0.41	84	0.87	2.10	548	335	0.61	1,262	2.30	3.77
Weighted over 5 years			0.40		0.81	2.05			0.64		2.55	3.98

*Surveillance years based on calendar year for standard care patients and years under surveillance for High Risk Clinic patients where all patients start surveillance at day 1. However, because High Risk Clinic patients joined the study at different time points, patients will have < 5 years of surveillance if they commenced in the clinic after 2006.
†Includes patients who had an excision biopsy, pathology-confirmed melanoma, keratinocytic, or benign lesion during study period.
‡Total excisions include excision biopsy and pathology-confirmed melanoma, keratinocytic, or benign lesion.

variable observed to increase the incremental cost-effectiveness ratio above a willingness to pay of $50,000 per QALY; and would need to be < 0.32 to be the cost-effective strategy (Fig 1). Probabilistic sensitivity analysis showed the incremental costs and quality-adjusted survival points predominantly in the bottom right quadrant of the cost-effectiveness plane (Fig 2), indicating that specialized surveillance is a less costly and more effective strategy.

DISCUSSION

This cost-effectiveness study addresses a key gap in knowledge about skin cancer screening identified by the US Preventive Services Task Force.[42] Specialized surveillance was less expensive and more effective compared with standard care, primarily because melanoma was detected at an earlier stage and there were fewer excisions performed. These results are relevant for other countries with populations of European origin, including the United States, where specialized monitoring of high-risk populations may be considered.

Data were only included in our study if available for both specialized surveillance and standard care groups. Access to linked population data sets, including Medicare claims, cancer registry, and hospital data, allowed us to accurately measure health system expenditure for a standard care comparator group over a similar time period to the specialized surveillance group. Complete data were available for melanoma excisions and hospitalizations and for keratinocytic lesion excisions. However, a limitation of our study is that hospitalization costs were not able to be included for keratinocytic lesions because these data were not available for the specialized surveillance group. We estimated keratinocytic lesion re-excisions for the specialized surveillance group on the basis of Medicare Benefits Schedule data, where they represented < 2% of excisions. In 2008, 61% of total expenditure on keratinocytic lesions was for out-of-hospital care, and 36% was for admitted care.[43] In our Markov model, we assumed that skin examinations

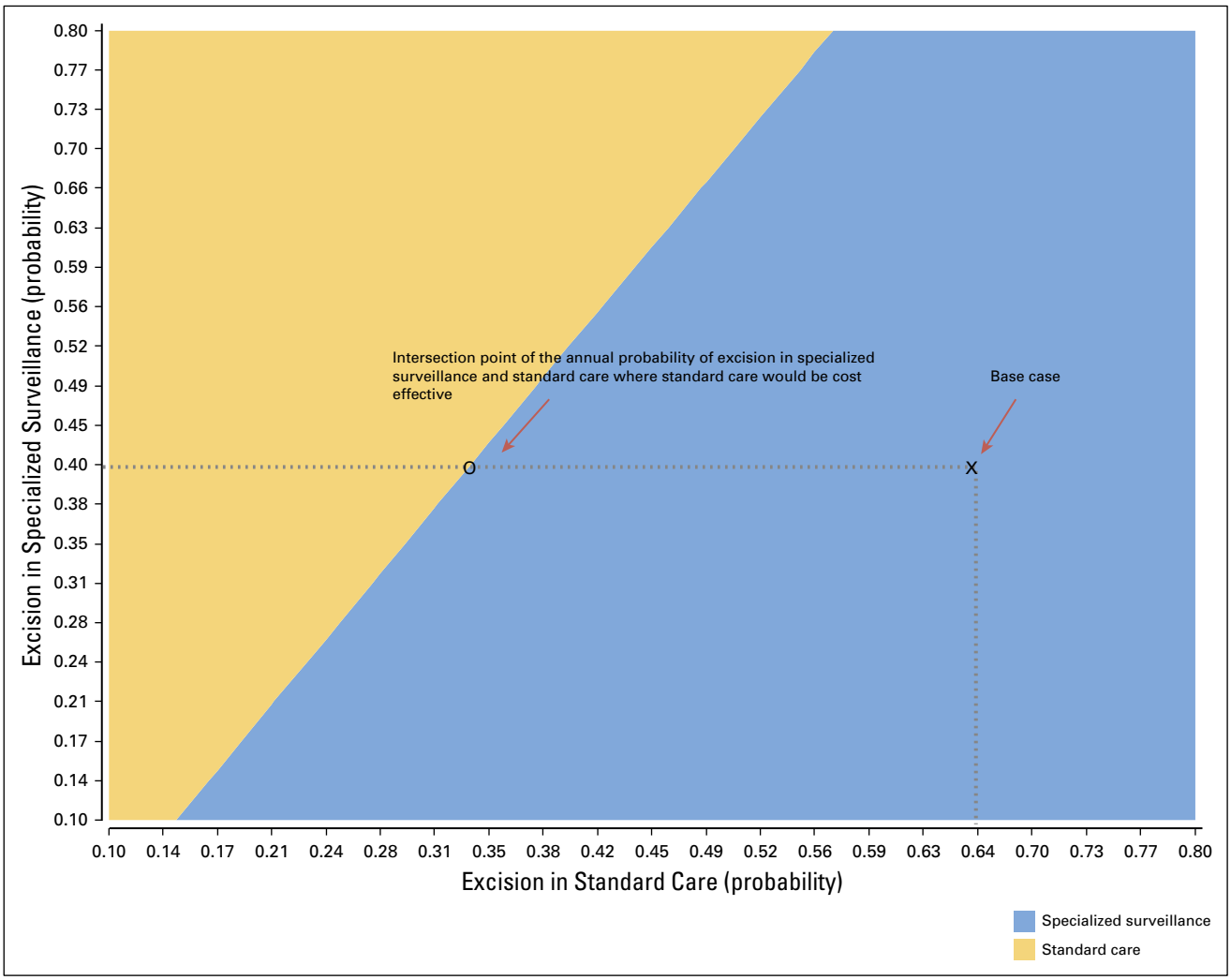

Fig 1. Two-way sensitivity analysis for the probability of an excision in specialized surveillance compared with probability of excision in standard care. At a willingness to pay of A$50,000 per quality-adjusted life-year, specialized surveillance is cost effective compared with standard care. X indicates the base case intersection point of the probability of excision in specialized surveillance of 0.40 and the probability of excision in standard care of 0.64 (see Table 1). The probability of an excision in standard care would need to be below 0.32 (shown as O) for standard care to be the cost-effective surveillance option.

were conducted annually in standard care and biannually in specialized surveillance. Because patients in standard care had more excisions, it is possible that we have underestimated the number of clinician appointments and therefore underestimated the cost of surveillance in standard care.

Although the standard care group was not a randomized control arm, we aimed to match the risk factor profile for the standard care group to that for the specialized surveillance group. As a result, there were some differences in baseline characteristics because the groups could not be matched perfectly. On the one hand, the specialized surveillance group may have had higher-risk characteristics because their family history data were confirmed, whereas the data set for standard care was based on self-reported family history. On the other hand, the standard care group had a higher proportion of men and on average were slightly older and of lower socioeconomic status than the specialized surveillance group. These are considered higher-risk characteristics, because lower educational attainment, male sex, and older age have been linked to more advanced melanoma in Australia,[44] and risk of melanoma and keratinocytic cancer increases with age.[1] Data for dysplastic nevus syndrome were not available for the linked data set, so that risk factor could not be compared. Although the cancer registry data did not contain AJCC staging information, the pseudo-stage used to classify all melanoma reports was found to have high agreement when validated against the AJCC stage classifications for primary melanomas detected in the High Risk Clinic.

Our study highlights several areas for further research. Our data indicate that there were fewer excisions for high-risk patients managed with specialized surveillance compared with standard care. This may be due to the high level of expertise and the assistance of technology in specialized surveillance and a protocol to return in 3 months for review of a suspicious lesion. Several factors may influence treatment in the community about whether a doctor would excise a suspicious lesion or take a watch-and-wait approach. These include level of training, the desire not to misdiagnose, patient pressure, time and work constraints for both the doctor and patient, and a fee-for-service payment system.[45-47] Other aspects of specialized surveillance that should be examined include assessment of societal costs (eg, patient out-of-pocket costs for travel, specialist visits, or treatment; productivity losses), patient satisfaction, and adherence to a surveillance regimen. Our

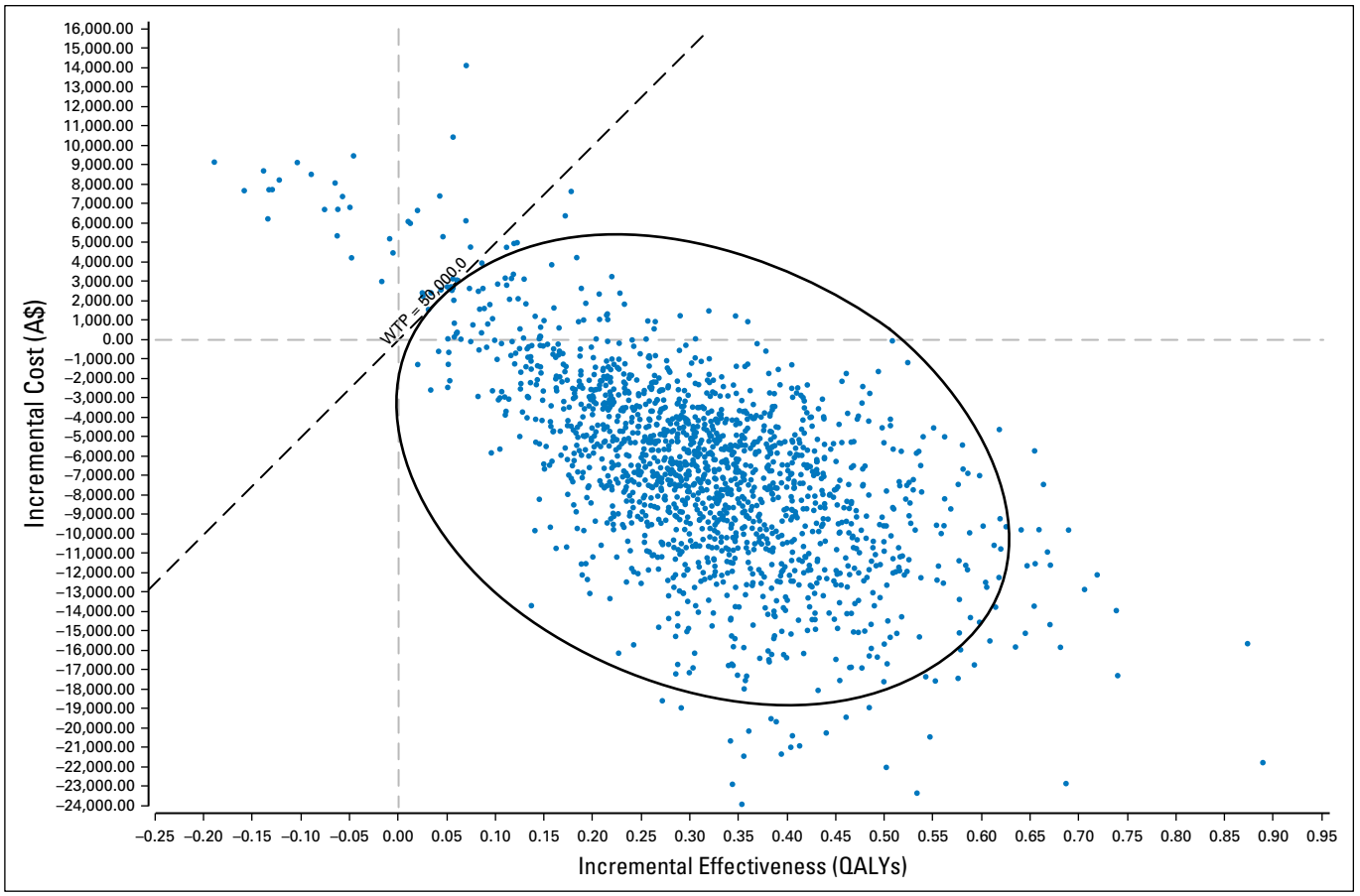

Fig 2. Incremental cost-effectiveness, specialized surveillance versus standard care. Estimated joint cost-effectiveness density for the specialized surveillance model presented on a cost-effectiveness plane. The ellipse represents the 95% CI of joint cost and effect pairs from Monte Carlo simulation. The majority of cost and effect pairs fall below the willingness to pay (WTP) line of $50,000 per quality-adjusted life-year and within the bottom right quadrant of the cost-effectiveness plane, indicating with reasonable certainty that the specialized surveillance strategy is both more effective and less expensive than standard care.

microcosting study reported societal costs of specialized surveillance were similar to health system costs, largely because of the considerable time commitment of patients to attend the High Risk Clinic. The High Risk Clinic in this study was located at a major, city-based hospital. It would be useful to model the costs and benefits of specialized surveillance in alternative settings, for example in primary care settings (eg, skin cancer clinics) or specialist dermatology practices.

Further exploration of risk factors may help to identify patients who require less intensive surveillance, because not all patients had a lesion excised over the study period. For some cancers, a less-intensive follow-up program has been shown to be the most cost-effective approach.[48] However, our findings indicate that for high-risk patients managed with specialized surveillance, rather than contributing to overtreatment, surveillance with a careful watch-and-wait approach to suspicious skin lesions resulted in fewer excisions and lower costs overall compared with surveillance in the community.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

Disclosures provided by the authors are available with this article at ascopubs.org/journal/jco.

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REFERENCES

1. Fransen M, Karahalios A, Sharma N, et al: Non-melanoma skin cancer in Australia. Med J Aust 197: 565-568, 2012
2. Doran CM, Ling R, Byrnes J, et al: Estimating the economic costs of skin cancer in New South Wales, Australia. BMC Public Health 15:952, 2015
3. Guy GP Jr, Machlin SR, Ekwueme DU, et al: Prevalence and costs of skin cancer treatment in the U.S., 2002-2006 and 2007-2011. Am J Prev Med 48: 183-187, 2015
4. Guy GP Jr, Ekwueme DU, Tangka FK, et al: Melanoma treatment costs: A systematic review of the literature, 1990-2011. Am J Prev Med 43: 537-545, 2012
5. Lomas A, Leonardi-Bee J, Bath-Hextall F: A systematic review of worldwide incidence of non-melanoma skin cancer. Br J Dermatol 166:1069-1080, 2012
6. Centers for Disease Control and Prevention's National Center for Health Statistics: SEER Cancer Statistics Factsheets: Melanoma of the Skin. National Cancer Institute, Bethesda, MD. 2015
7. Balch CM, Gershenwald JE, Soong SJ, et al: Final version of 2009 AJCC melanoma staging and classification. J Clin Oncol 27:6199-6206, 2009
8. Gandini S, Sera F, Cattaruzza MS, et al: Meta-analysis of risk factors for cutaneous melanoma: II. Sun exposure. Eur J Cancer 41:45-60, 2005
9. Gandini S, Sera F, Cattaruzza MS, et al: Meta-analysis of risk factors for cutaneous melanoma: I. Common and atypical naevi. Eur J Cancer 41:28-44, 2005
10. Gandini S, Sera F, Cattaruzza MS, et al: Meta-analysis of risk factors for cutaneous melanoma: III. Family history, actinic damage and phenotypic factors. Eur J Cancer 41:2040-2059, 2005
11. Cust AE, Harland M, Makalic E, et al: Melanoma risk for CDKN2A mutation carriers who are relatives of population-based case carriers in Australia and the UK. J Med Genet 48:266-272, 2011
12. Watts CG, Dieng M, Morton RL, et al: Clinical practice guidelines for identification, screening and follow-up of individuals at high risk of primary cutaneous melanoma: A systematic review. Br J Dermatol 172:33-47, 2015
13. Australian Cancer Network Melanoma Guidelines Revision Working Party: Clinical practice guidelines for the management of melanoma in Australia and New Zealand. Wellington, Australia, Cancer Council Australia and Australia Cancer Network, Sydney and New Zealand Guidelines Group, 2008
14. Haenssle HA, Vente C, Bertsch HP, et al: Results of a surveillance programme for patients at high risk of malignant melanoma using digital and conventional dermoscopy. Eur J Cancer Prev 13: 133-138, 2004
15. Salerni G, Carrera C, Lovatto L, et al: Benefits of total body photography and digital dermatoscopy ("two-step method of digital follow-up") in the early diagnosis of melanoma in patients at high risk for melanoma. J Am Acad Dermatol 67:e17-e27, 2012
16. Haenssle HA, Korpas B, Hansen-Hagge C, et al: Selection of patients for long-term surveillance with digital dermoscopy by assessment of melanoma risk factors. Arch Derm 146:257-264, 2010
17. Salerni G, Carrera C, Lovatto L, et al: Characterization of 1152 lesions excised over 10 years using total-body photography and digital dermatoscopy in the surveillance of patients at high risk for melanoma. J Am Acad Dermatol 67:836-845, 2012
18. Moloney FJ, Guitera P, Coates E, et al: Detection of primary melanoma in individuals at extreme high risk: A prospective 5-year follow-up study. JAMA Dermatol 150:819-827, 2014
19. 45 and Up Study Collaborators, Banks E, Redman S, et al: Cohort profile: The 45 and up study. Int J Epidemiol 37:941-947, 2008
20. Australian Government Department of Health: MBS Online: Medicare Benefits Schedule. http://www.mbsonline.gov.au
21. Watts CG, Cust AE, Menzies SW, et al: Specialized surveillance for individuals at high risk for melanoma: A cost analysis of a high-risk clinic. JAMA Dermatol 151:178-186, 2015
22. Department of Health Australian Government: Technical Guidelines for preparing assessment reports for the Medical Services Advisory Committee—Service Type:Investigative (Version 1.3), 2015. https://consultations.health.gov.au/mbd/msac-investigative-technical-guidelines/supporting_documents/MSAC_Investigative_Guidelines2015%20final%20for%20consultationaccessible%20150415.docx
23. Australian Institute of Health and Welfare: Health expenditure Australia: 2013–14. Canberra, Australia, AIHW, 2015
24. Husereau D, Drummond M, Petrou S, et al: Consolidated health economic evaluation reporting standards (CHEERS) statement. Value Health 16: e1-e5, 2013
25. Morton DL, Thompson JF, Cochran AJ, et al: Final trial report of sentinel-node biopsy versus nodal observation in melanoma. N Engl J Med 370: 599-609, 2014
26. Coit DG RA, Rogatko A, Brennan MF: Prognostic factors in patients with melanoma metastatic to axillary or inguinal lymph nodes. A multivariate analysis. Ann Surg 214:627-636, 1991
27. Romano E, Scordo M, Dusza SW, et al: Site and timing of first relapse in stage III melanoma patients: Implications for follow-up guidelines. J Clin Oncol 28:3042-3047, 2010
28. Garbe C, Paul A, Kohler-Späth H, et al: Prospective evaluation of a follow-up schedule in cutaneous melanoma patients: Recommendations for an effective follow-up strategy. J Clin Oncol 21:520-529, 2003
29. Tromme I, Devleesschauwer B, Beutels P, et al: Health-related quality of life in patients with melanoma expressed as utilities and disability weights. Br J Dermatol 171:1443-1450, 2014
30. Chen SC, Bayoumi AM, Soon SL, et al: A catalog of dermatology utilities: A measure of the burden of skin diseases. J Investig Dermatol Symp Proc 9:160-168, 2004
31. Medical Services Advisory Committee: Positron Emission Tomography for Recurrent Melanoma: Assessment Report. Canberra, Australia, Medical Services Advisory Committee, 2008
32. Kardamanidis K, Lim K, Da Cunha C, et al: Hospital costs of older people in New South Wales in the last year of life. Med J Aust 187:383-386, 2007
33. Swerissen H, Duckett S: Dying Well. Melbourne, Australia, Grattan Institute, 2014
34. Australian Government Department of Health: Medicare Benefits Schedule Book Category 2:

Diagnostic procedures. Canberra, Australia, Australian Government, 2013

35. Queensland, Legislative Assembly, Health and Community Services Committee: Palliative and Community Care in Queensland: Towards Person-Centred Care. Brisbane, Australia, Health and Community Services Committee, 2013

35a. Department of Health Australian Government: National Hospital Cost Data Collection Australian Public Hospital Cost weights for AR-DRG version 5.0, Round 14 (2009-10), version 6. https://www.ihpa.gov.au/sites/g/files/net636/f/publications/nhcdc-round18.pdf.

36. Palliative Care Australia: Palliative Care Service Provision in Australia: A Planning Guide. Canberra, PCA, 2003

37. KPMG: Advanced Melanoma: The Real Cost of Australia's National Cancer. Sydney, Australia 2014

38. Australian Bureau of Statistics: 3302.0.55.001: Life Tables, States, Territories and Australia, 2011-2013. http://www.abs.gov.au/AUSSTATS/abs@.nsf/Lookup/3302.0.55.001Explanatory%20Notes12011-2013?OpenDocument

39. Drummond MF, Sculpher MJ, Torrance GW, et al: Methods for the Economic Evaluation of Health Care Programmes (ed 3). Oxford, United Kingdom, Oxford University Press, 2005

40. Sebaratnam D, Penas PF, Morton R, et al: Cost effectiveness analysis of Mohs micrographic surgery versus traditional surgical excision for head and neck basal cell carcinoma. J Am Acad Dermatol 68:AB159, 2013 (abstr)

41. Briggs AH, Weinstein MC, Fenwick EA, et al: Model parameter estimation and uncertainty: A report of the ISPOR-SMDM Modeling Good Research Practices Task Force–6. Value Health 15:835-842, 2012

42. Wernli KJ, Henrikson NB, Morrison CC, et al: Screening for skin cancer in adults: Updated systematic evidence review for the US preventive services task force. JAMA 316:436–447, 2016

43. Australian Institute of Health and Welfare: Health System Expenditure on Cancer and Other Neoplasms in Australia: 2008–09. Canberra, Australia, AIHW, 2013

44. Youl PH, Baade PD, Parekh S, et al: Association between melanoma thickness, clinical skin examination and socioeconomic status: Results of a large population-based study. Int J Cancer 128: 2158-2165, 2011

45. Baade PD, Youl PH, Janda M, et al: Factors associated with the number of lesions excised for each skin cancer: A study of primary care physicians in Queensland, Australia. Arch Dermatol 144:1468-1476, 2008

46. Carli P, Nardini P, Crocetti E, et al: Frequency and characteristics of melanomas missed at a pigmented lesion clinic: A registry-based study. Melanoma Res 14:403-407, 2004

47. Morton RL, Rychetnik L, McCaffery K, et al: Patients' perspectives of long-term follow-up for localised cutaneous melanoma. Eur J Surg Oncol 39: 297-303, 2013

48. Meregaglia M, Cairns J: Economic evaluations of follow-up strategies for cancer survivors: A systematic review and quality appraisal of the literature. Expert Rev Pharmacoecon Outcomes Res 15: 913-929, 2015

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Cost-Effectiveness of Skin Surveillance Through a Specialized Clinic for Patients at High Risk of Melanoma

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