Cost-effectiveness of a melanoma screening program: using whole disease modelling to inform resource allocation within a National Health Service

Running title: Cost-effectiveness of melanoma screening

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Abstract

Objectives: This study aims to assess the potential impact of a screening programme on direct costs and life expectancy, compared with usual care, in the era of targeted drugs and cancer immunotherapy.

Methods: Using a Whole Disease Model approach, a Markov simulation model with a time horizon of 25 years was devised to analyse the cost-effectiveness of a one-time, general practitioner-based melanoma screening strategy in the population older than 20 years compared to no screening. The study considered the most up-to-date drug therapy and was conducted from the perspective of the Veneto regional healthcare system within the Italian National Health Service, considering only the direct costs. Sensitivity analyses, both one-way and probabilistic, were performed to identify the parameters with the greatest impact on cost-effectiveness and to assess the robustness of our model.

Results: Over a 25-year time horizon, the screening intervention dominated usual care. The probabilistic sensitivity analyses confirmed the robustness of these findings. The key drivers of the model were the proportion of melanomas detected by the screening procedure and the adherence of the target population to the screening programme.

Conclusions: The screening programme proved to be a dominant option compared to usual care. These findings should prompt serious consideration of the design and implementation of a regional or national melanoma screening strategy within a National Health Service.

Keywords: Cost-effectiveness, Melanoma screening, Sensitivity analysis, Cancer prevention strategy

Introduction

The economic burden of cancer is increasing, not only because of its rising incidence and improved survival rates but also as a consequence of the increasing costs of patient care.[1-3] The incidence rates of malignant cutaneous melanoma both in Europe and in the U.S. have risen steadily in recent decades.[4-5] In Italy, the incidence rates have increased for both men (from 1.6/100,000 in 1970 to 21/100,000 in 2015) and women (from 2/100,000 in 1970 to 17/100,000 in 2015) .[6] Malignant cutaneous melanoma is thus an important public health issue as well as an economic concern, and the financial pressure on healthcare systems is inducing policy-makers to focus more on the appropriate allocation of resources.

Melanoma survival has a strong negative correlation with the extent of tumour invasion at diagnosis.[7] Advanced melanoma entails much higher costs than early stages of the disease.[8-9] The impact of early detection on extended survival and subsequent treatment costs has increased the interest in analysing the cost-effectiveness of melanoma screening strategies.[10-14] One of the first such analyses was performed by Girgis et al. more than 20 years ago in Australia. Their findings indicated that a melanoma screening programme could be cost-effective if conducted every five years, particularly for men: the incremental cost-effectiveness ratio (ICER) ranged from A$ 5,745 (€ 3,541) to A$ 25,214 (€ 15,543) per life-year saved.[10] Similarly, in the USA, Losina et al. developed a computer Markov simulation model in 2007 to compare various melanoma screening strategies (one-time screening *vs* every 2 years *vs* annually, as of 50 years of age) to usual care. In the general population, these three strategies coincided with an ICER of US $10,100/QALY (€ 7,370/QALY), US $80,700/QALY (€ 58,885/QALY) and US $586,800/QALY (€428,172/QALY), respectively.[13] More recently, Pil et al. designed a Markov model with a latent period of 20 years and a time horizon of 50 years to analyse the cost-effectiveness of two population-based skin cancer screening programmes in Belgium, comparing them with no screening. The total Belgian population aged 18 years or older was assumed to have been invited for the screening programme. The two strategies achieved a similar ICER of about US $36,500/QALY (€ 32,975/QALY) in men and US $20,500/QALY (€18,520/QALY) in women. The authors also predicted that the cost of treating stage III and IV melanoma will continue to rise due to new treatments, making screening an increasingly cost-effective strategy.[14]

To the best of our knowledge, evidence of the cost-effectiveness of melanoma screening considering the new target therapy is lacking. Hence, the aim of our study was to develop a cost-effectiveness model to assess the potential impact of a one-time general practitioner (GP)-based melanoma screening program in terms of direct costs and life expectancy over a 25-year time horizon, considering the most up-to-date drug therapies. For this purpose, we used a Whole Disease Model to simulate two counterfactual scenarios (with the target population receiving or not receiving the screening programme), adopting the perspective of the Veneto regional healthcare system within the Italian National Health Service.

Material and methods

Context

Italy's healthcare system is a decentralised National Health Service, which is organised at the national, regional and local levels and provides universal coverage free of charge at the point of service. The national level is responsible for ensuring the general objectives and fundamental principles of the National Health Care System. Regional governments, through regional health departments, are responsible for ensuring the delivery of the essential levels of health care (defined at national level) through a network of population-based health management organisations (local health authorities) and accredited public and private hospitals.

A Whole Disease Model was developed in a previous study [8], based on the patient care pathway for malignant cutaneous melanoma that was implemented in the Veneto Region in Northeast Italy on the grounds of international evidence and guidelines.[15-17] Whole Disease Modelling represents a methodological framework for developing economic models of whole health systems, including disease and treatment pathways, to inform resource allocation decisions.[15]

Briefly, the Whole Disease Model contained clinical and process probabilities. The clinical probabilities were estimated from the literature or, failing this, from a clinical database of patients followed-up by the Veneto Institute of Oncology (IOV). The deterministic chance (100%) of a process was established when the clinical pathway indicated a procedure for all patients with a given clinical condition. [17] Where the clinical pathway left decisions regarding particular diagnostic or therapeutic procedures to the physician's discretion, process probabilities were identified using other guidelines, such as those of the National Comprehensive Cancer Network (NCCN).[16] If these other international guidelines were not sufficiently explanatory, several national melanoma experts were asked to indicate (based on their professional experience) the probability of patients with a given condition undergoing certain procedures, using the Delphi technique to obtain a consensus.[18]

The findings of this previous study, in terms of annual direct costs for each disease stage, were used as input cost data for the present study.

On this basis, we consider two alternative scenarios for the Veneto regional healthcare system: a strategy including GP-based melanoma screening strategy of the population over the age of 20 years and one without any melanoma screening (usual care or status quo).

Screening strategy

The GP-based melanoma screening strategy was devised largely on the strength of the SCREEN project conducted in Northern Germany,[19-23] adapting some aspects of the model to make it more compliant with the Veneto healthcare system.

The main characteristics of the screening strategy are detailed below.

Target population: people aged >20 years, resident in the Veneto Region.

Recruitment strategy: according to the screening strategy, an invitation is mailed to all residents in the Veneto Region 20 years of age or older. This method was chosen because it is the recruitment scheme already in use for other regional cancer screening programs. The mail invitation includes a letter and a leaflet with explanatory photos to help people identify a mole as suspicious and to self-refer for a screening visit.

Primary screening test: participants can refer to their own GPs if he/she took part in the project or otherwise to another available GP working in the same Integrated Primary Care Team. Participants undergo a total-body skin examination (TBSE) by a trained GP, who refers them to a dermatologist if any genuinely suspicious lesions are found.

Secondary screening test: dermatologists examine patients referred by GPs and may take a biopsy to reach a tentative clinical diagnosis.

Organisation of the screening process: Regional authorities decide the number of GPs to involve in the screening process. GPs are invited to participate in the project and authorised to conduct the primary screening test after completing a one-day (eight-hour) mandatory training course. Twelve-hour shifts of out-of-hours medical service are planned to enable GPs to attend the course. The number of GPs participating is assumed so that each of them would spend, on average, about 30 minutes of each working day on screening the participating population over the course of one year (assuming that a TBSE takes 12 minutes on average and 220 working days). This means that every GP can screen about 550 people in a year (2.5 visits each days x 220 working days). Basing on Breitbart [19], we set the percentage of target population participating to the screening program equal to 19%; thus we estimated that one GP is needed every 2895 citizens (calculated as 550/0.19). Thus, over an hypothetical target population of 100,000 citizens, this means that 34.5 GPs have to be involved. The number of courses organised is estimated as one for every 30 GPs receiving the training, resulting in 1.15 courses per 100,000 target people. In order to cover the GPs' absence due to the training course, we considered the involvement of out-of-hours doctors: we estimated one out-of-hours shift for every 4.3 GPs (as out-of-hours doctors and GPs take care of 6,500 and 1,500 people, on average, respectively [24]).

Table 1 shows the screening-related variables, which were derived from the SCREEN pilot project.[19-23]

Model structure

We developed a Markov model using TreeAge Pro 2011 over a time horizon of 25 years to compare costs and outcomes with and without (usual care) screening (Figs. 1a-c). In this study, we focused only on cases of melanoma detectable during the one-time screening campaign and followed them over a time horizon of 25 years. Thus, future cases of melanoma have not been considered in our analyses assuming that these cases will have equal costs and life expectancy in both scenarios.

The model shows four mutually-exclusive health states for patients with melanoma in stages I, II, III and in regression: stable; locoregional relapse; distant relapse; and death (melanoma-related or due to natural

causes). It shows only two health states – stable or natural death – for the melanoma-free and stage 0 (melanoma in situ) population. Finally, the model for stage IV melanoma patients presents three mutually-exclusive health states: stable; relapse; and death.

The clinical probabilities governing the transition through each state of the Markov model [25-27] are reported in Tables 1S-4S (see Supplementary material). To separately obtain the probabilities of locoregional and distant relapse, the above likelihoods must be multiplied by those given in Table 2S.

Long-term survival was estimated by interpolating the probability of death in the second year with survival in the tenth year, as reported by Balch [25], and plotting Kaplan–Meier curves for stage IV, imposing the condition assumption that all stage IV patients must be dead within ten years.

For the patients in stages II and III undergoing adjuvant interferon therapy, we applied a 17% relative reduction in the probability of occurrence of a first relapse and a 9% relative reduction in the probability of death in the first year, as reported in the meta-analysis by Mocellin et al.[28]

Since our Whole Disease Model considered the most up-to-date drug therapies for the advanced stages (namely III inoperable and IV), in Tables 3S and 4S on Supplementary material the melanoma-related death risk was updated in line with the results of trials whenever data were available,[29-32] and then the likelihoods were gradually aligned over a period of 10 years with those of the period before the latest drugs were introduced.[25] A proportion of patients was assumed to have permanently discontinued their therapy due to treatment-related adverse events during their second-line treatment. This likelihood was set at 11% during the first year and at 15% lifelong.[29-32]

An annual risk of natural death (ranging from 0.9% in the first year to 1.6% in the 25th year) was also applied to all individuals in the model, based on the life tables for the Veneto Region.[33]

Effects

The incidence rate of melanoma for adults over 20 years of age in the Veneto Region for 2016 was calculated using the incidence rate in the same region in 2013 and the compound annual growth rate (3.6% in men, 2.4% in women) calculated from 1987 to 2013.[34] The same overall incidence was set for both the screening and the no-screening branches of the model, based on the assumption that the incidence of melanoma is not influenced by the screening strategy during a steady-state period, as seen in the SCREEN project in Northern Germany.[22]

Table 5S (see Supplementary material) shows the distribution by stage of melanoma at diagnosis in the Veneto Region. These stage frequencies at diagnosis corresponded to the current incidence of melanoma, and they were assigned to patients in the non-screening branch as well as to patients in the screening branch who failed to attend or were false negative cases. Data were obtained from the Veneto Cancer Register (personal communication). To obtain the distribution by melanoma stage at diagnosis of the true positive

screened patients, we applied the percentage of relative variation observed before and after implementing the SCREEN project in Northern Germany to the distribution described above.[23] We chose to adopt this approach since the population of the Veneto Region and that of Germany have a similar pre-screening stage at diagnosis distribution; thus, similar variations are expected after screening.

The health effect of the screening was represented as the variation in life expectancy as a result of the melanoma stage shift. A score of 0 (death) or 1 (alive) was assigned to each person in the model for each year and was discounted at a 3% annual rate.

Costs

The study was conducted from the perspective of the Veneto regional healthcare system within the Italian National Health Service, considering only the direct costs borne by a regional government while excluding direct and indirect patient costs. Costs (in Euros) are drawn from official reimbursement tariffs in effect in 2017. Further, the costs (and outcomes) after the first year have been discounted at a 3% annual rate. The costs for a healthcare system of implementing the screening campaign per 100,000 target population are presented in Table 6S (See Supplementary material).

As stated above, the annual direct costs for each stage of disease reported in Table 8 are drawn from a previous study.[8] The same stage specific clinical pathways were modelled after diagnosis in both scenarios. We assumed that each transition from a Markov state to another one happens in the sixth month. In the year when a transition towards locoregional or distant relapse occurred, we stopped the follow-up costs after six months and applied a cost that included re-staging and surgical/medical treatments for the remaining six months (see Table 7S, Supplementary material). In the case of death due to natural causes, we stopped the follow-up and any possible medical treatments at six months, while in the case of melanoma-related death we stopped the costs of medical therapy six months beforehand (no treatment costs were applied because the patients were expected to die by the end of the sixth month), and we applied the cost of three months of palliative care.[35]

The costs associated with the occurrence of a locoregional lesion include surgery and the introduction of medical therapy, amounting to € 10,560. For every melanoma stage, the cost associated with the occurrence of distant relapse was € 40,929, taking into account the weighted probability of different metastasis sites and the probability of surgical therapy for each site as well as the related costs.[8] Finally, the cost associated with palliative care was € 2,199 and includes hospitalisation, hospice and outpatient care.[35]

Cost-effectiveness analysis

The National Institute for Health and Clinical Excellence (NICE) established a willingness-to-pay (WTP) threshold between £20,000 and £30,000 per QALY.[36] We considered a (WTP) threshold of € 25,000 per life-year gained to ascertain the cost-effectiveness of one-time screening compared to the usual care option. This

threshold should be appropriate even if we considered life-years gained instead of quality of life, as any adjustment would lower this threshold.

Sensitivity analyses

We conducted a series of sensitivity analyses, varying some parameters to assess the robustness of our model and identify the parameters with the greatest impact on cost-effectiveness. We focused particularly on screening-related variables, such as the participation rate and sensitivity/specificity of the screening procedure (Table 1), as well as on the discount rate (using a range from 0% to 5%).

We performed a probabilistic sensitivity analysis to determine the impact of the uncertainty surrounding the model input parameters. Beta distributions were assigned to the screening-related probabilities, such as the participation rate and the proportion of participants referred to a dermatologist (Table 1). In addition to the above-mentioned variables, we chose to assign a Dirichlet distribution to the stage-at-diagnosis probabilities shown in Table 5S (see Supplementary material) to embed the uncertainty of these percentages in our analysis. Since costs were assigned on the basis of guidelines and defined according to official reimbursement tariffs, we chose not to include them in our sensitivity analyses. A random value from the corresponding distribution was selected. This generated an estimate of the mean cost and outcomes associated with each scenario. This was repeated 10,000 times, and the results for each simulation were noted. An estimate of the average costs and outcomes can thus be obtained, along with the 95% credibility intervals. A sensitivity analysis was conducted for the tornado diagram by holding the target variable at its lowest and highest values and running a 10,000 PSA simulation.

Cost–consequence analysis

Furthermore, we investigated the impact of the screening intervention on expected costs and health outcomes in the Veneto Region via cost–consequence analysis.[37] The total budgetary impact of the screening programme and the overall improvement in terms of survival over the 25-year time horizon were estimated.

Table 1: Screening-related variables.

	%	Point estimate for a hypothetical 100,000 target population	Range of values considered in the deterministic sensitivity analysis	Distribution	Source
(A) Participants (people seen by a GP) among target population	19	19,000	[5% - 50%]	Beta (19, 81)	Breitbart[19]
(B) Proportion of participants referred to a dermatologist	16.71[a]	3,175	[5% - 50%]	Beta (16.71, 83.29)	Waldmann [21]
(C) Proportion of participants undergoing biopsy	2.11[b]	401	N/A	N/A	Calculated from SCREEN project data
(D) Proportion of melanomas detected by the screening procedure among all melanomas in the year	52	22	[15% - 65%]	Beta (52, 48)	Waldmann[20]
(E) Incidence of melanoma per 100,000 population (including melanoma in situ)	42	42	[20 – 65]	Poisson (42)	Veneto Cancer Registry [34]
Sensitivity of screening	69[c]		[55% - 95%]	Beta (69, 31)	Waldmann[20] and Hübner[22]
Specificity of screening	98[d]		[85% - 99.9%]	Beta (98, 2)	Waldmann[20] and Hübner[22]
(F) Positive predictive value (PPV) of screening (melanoma cases among patients undergoing biopsy)	5.50	22 / 401	N/A	N/A	Calculated from SCREEN project data

(G) Negative predictive value (NPV) of screening (true negative cases among patients not undergoing biopsy)	99.95	18,779 / 18,788	N/A	N/A	Calculated from SCREEN project data

[a] Estimated as the number of individuals seen by a dermatologist (46,578) out of the number of individuals screened by GPs (278,741) based on Waldmann.[21]

[b] The proportion of dermatologist patients undergoing biopsy was 12.64% (2.11/16.71).

[c] Sensitivity of screening was estimated as the ratio between the number of cases detected as part of the SCREEN project (585 true positive, according to Waldmann[20]) and the total number of cases of melanoma among participants (585 true positive and 258 false negative, according to Hübner [22]).

[d] Specificity of screening has been estimated as the ratio between true negatives and the total number of healthy subjects. The latter has been calculated as the difference between the total number of participants and the sum of true positives and false negatives, according to Hübner[22], while the former has been calculated taking into account that of 7408 positive to screening only 452 were true positive, according to Waldmann.[20]

Figure 1a: Structure of the model – screening and no screening branches

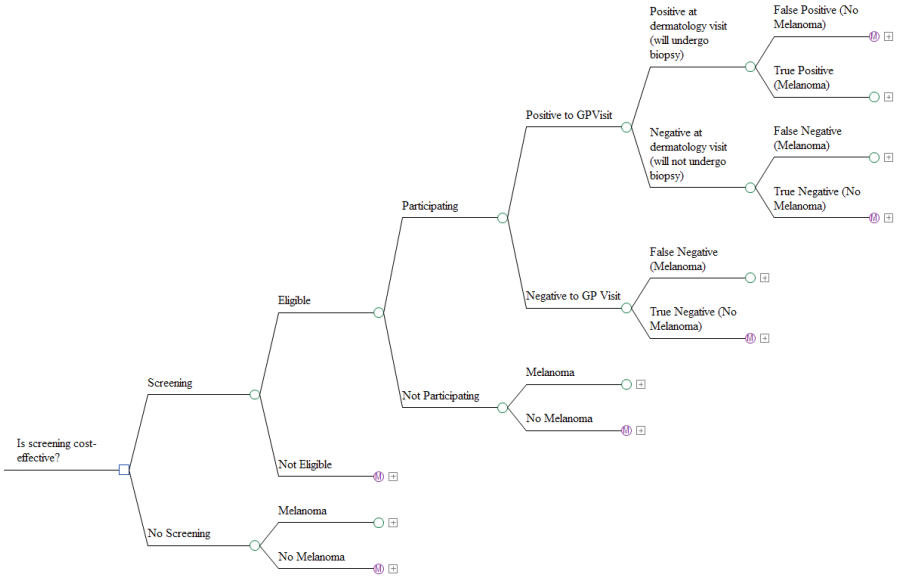
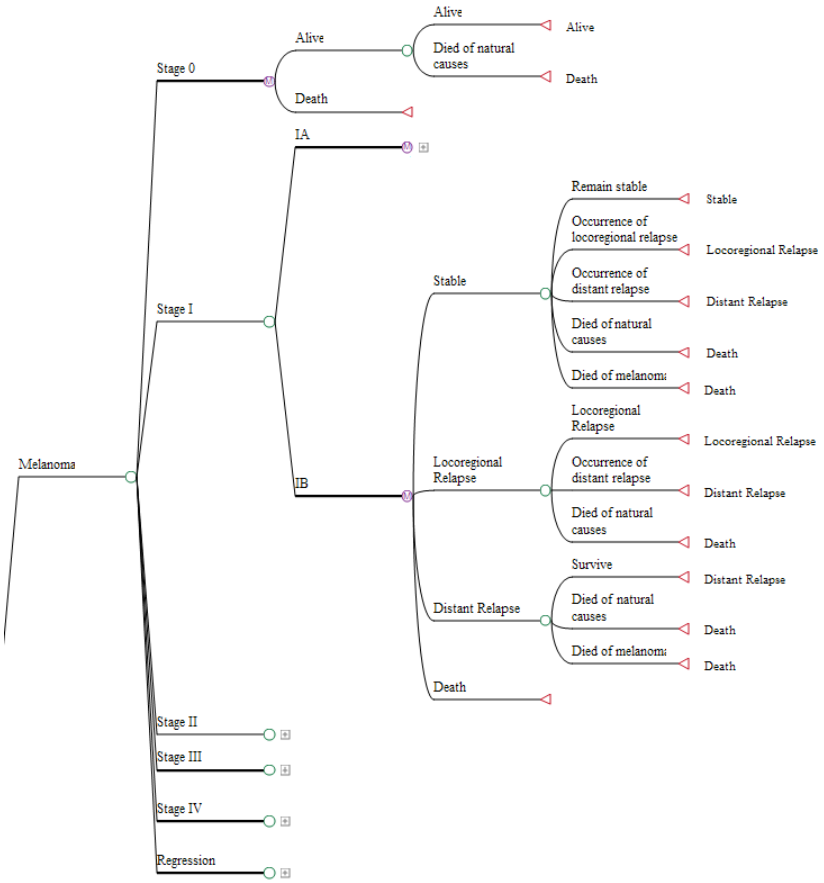
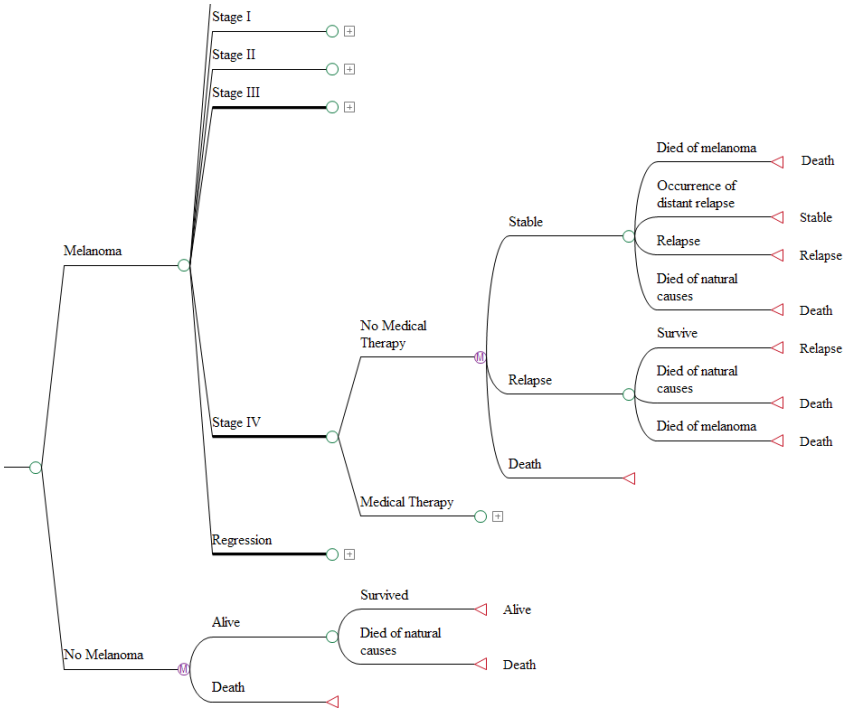


Figure 1b: Structure of the model – Markov models



The model shows four mutually-exclusive health states for patients with melanoma in stage I, II, III, and in regression: stable; locoregional relapse; distant relapse; and death (melanoma-related or due to natural causes). It shows only two health states – stable or death due to natural causes – for the melanoma-free and stage 0 (melanoma in situ) population. The model for melanoma stage IV patients comprises three health states: stable; relapse; and death.

Figure 1c: Structure of the model – Markov models



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Results

The incremental discounted average life expectancy and costs in the two alternative scenarios (screening strategy *vs* usual care) over a 25-year period are shown in Table 2. Over a 25-year period, the average cost per citizen (over 20 years of age) to diagnose and treat melanoma was estimated to be € 70.06 (95% credibility interval: € 65.60 – 74.84) for the screening strategy and € 72.65 (95% credibility interval: € 67.87 – 77.94) for the usual care option (Table 2). Considering only the patients with melanoma, we observed an average cost of € 156,045 and € 170,943 with the screening campaign and the status quo, respectively. Compared to treatment as usual, the screening strategy would result in an average increase of four months of life for each patient (from 13.27 to 13.60 years), resulting in an overall gain of 13.90 years of life in the 100,000 target population.

Since the screening strategy was associated with lower mean costs and a higher survival rates than usual care, the screening intervention was therefore dominant. The screening strategy led to savings in both money and life-years, namely, -€ 18,551 per year of life gained, considering the entire target population.

The one-way sensitivity analyses show that the proportion of melanomas detected as part of the screening program and the screening adherence rate are the variables that contribute most to the variability of the ICER (Fig. 2).

The results of the probabilistic sensitivity analysis shows that almost all the 10,000 simulations are cost-effective, if not cost saving (Fig. 3), and that the screening option has a 97.38% probability of being dominant. Finally, Figure 4 shows the different ICER values over a period of 5, 10, 15, 20, and 25 years. Once again, these estimates and their credibility intervals were obtained using a probabilistic sensitivity analysis, with 10,000 simulations.

Cost–consequence analysis

According to our Whole Disease Model, from the perspective of the Veneto regional healthcare system (with a target population of 4,004,266 citizens aged over 20 years), a one-time screening programme could save 557 life-years and reduce the economic burden of melanoma by € 10.2 million (€ 280.4 million in the screening scenario *vs* € 290.6 million Euros in the usual care scenario).

Table 2: Average costs and life-years estimated with 10,000 simulations. 95% credibility intervals are given in brackets.

(I) Average costs and survival for all citizens over 20 years of age (target population)				
	Melanoma screening	Usual care (status quo)	Difference	
Average cost (€)	70.06 (65.60– 74.84)	72.65 (67.87 – 77.94)	-2.59 (-5.27 – -0.04)	Dominance of screening
Average survival (years)	15.57507 (15.5749 – 15.5751)	15.57493 (15.5747 – 15.5750)	0.00014 (0.00009 – 0.00019)	
(II) Average costs and survival for melanoma patients				
Average cost (€)	156,044.53 (152,262.23 – 160,116. 07)	170,942.65 (165,161.66 – 176,462.38)	-14,898.12 (-18550.01 – -11,013.35)	Dominance of screening
Average survival (years)	13.59975 (13.50370 – 13.68655)	13.27273 (13.12735 – 13.41103)	0.32702 (0.23340 – 0.42235)	

Figure 2: Tornado diagram showing the most influential screening variables for ICER. White bars show the maximum values of the variable while black bars show the minimum value. For instance, lower values for the percentage of melanomas detected by screening procedures lead to higher ICER.

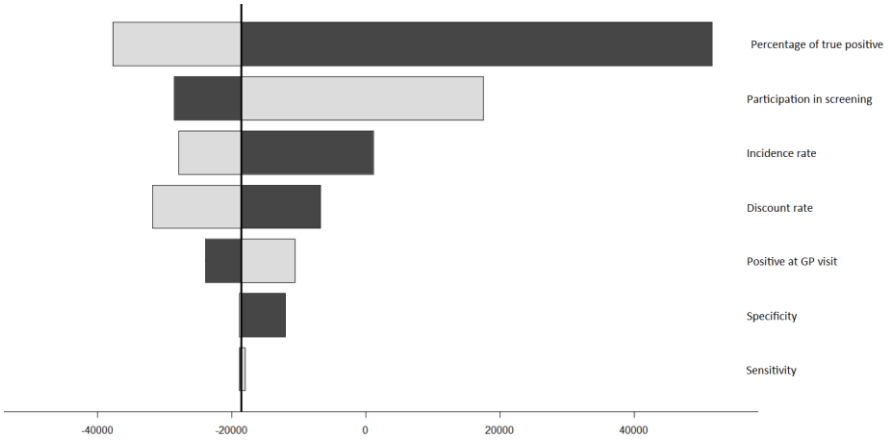


Figure 3: Results of probabilistic sensitivity analysis with 10,000 simulations. The ellipse represents the 95% confidence interval. WTP=Willingness to Pay

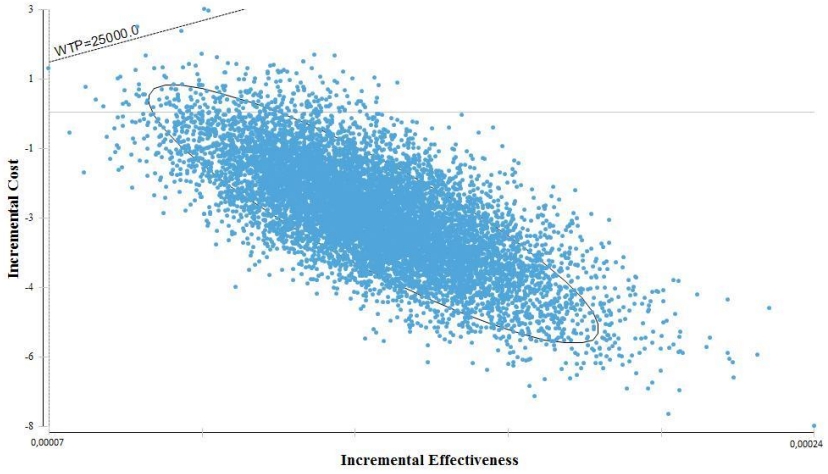
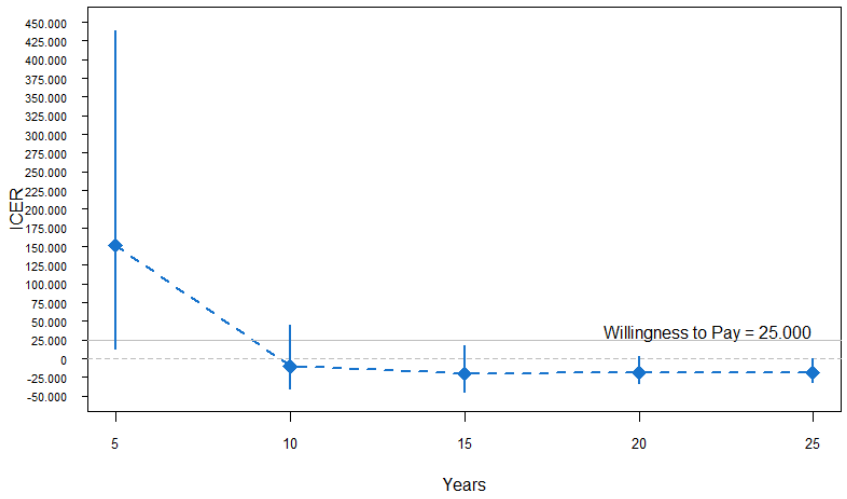


Figure 4: ICER by years, with 95% credibility intervals.



Discussion

The melanoma screening strategy proved to be dominant compared to usual care (status quo).

Our results differ to some degree from those of previous studies. Although it is difficult to draw comparisons because of differences in the screening methods, the composition of the screening team, the model designs and epidemiological factors related to the involved populations, all previous cost-effectiveness analyses show that a screening option would be more effective than usual care, but also more expensive.[10-14] Our results, although they are dissimilar, are hardly surprising, considering that – as Pil et al. observed in their recent cost-effective analysis of melanoma screening – the cost of treating stage III and IV melanoma will keep increasing as a result of new more expensive treatments, making screening an increasingly more cost-effective strategy.[14] Another reason our results are positive is the high incidence of melanoma in Italy, which is even higher in the Veneto Region.[34] In fact, a screening program is more effective and more cost-effective when the prevalence of the undiagnosed disease is high enough to justify the effort and costs of screening. For example, in 1992, in high-incidence countries such as Australia, economic evaluations for melanoma screening programmes suggested the potential cost-effectiveness of such interventions, with discounted ICER ranging from € 8,483 to € 25,843 per years of life gained, based on different assumptions (i.e. in many cases below the current NICE threshold of acceptability for cancer care).[10] Although the incidence of melanoma in Italy and in the Veneto Region has yet to reach the levels seen in Australia when Girgis et al. conducted their cost-effectiveness analysis, it has been rapidly and constantly increasing in recent decades [34] and is moving towards levels that would justify a screening campaign.

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The results of the sensitivity analysis in our model have highlighted the crucial impact of the adherence rate on life expectancy and the ICER. In other words, a high participation rate is obviously desirable, as it increases the proportion of melanomas diagnosed in the early stages and, consequently, the years of life saved by screening and early treatment. However, a high participation rate also reduces the cost-effectiveness of the screening because larger numbers of visits and biopsies add to the costs.

Importantly, the sensitivity and specificity of the screening did not result in marked changes in the baseline ICER value.

It underscores the importance of pairing public education in the sign of skin cancer with easy access to the assessment of concerning lesion.

Several studies have highlighted the importance of implementing policies that involve enrolling only higher-risk individuals. When a screening program was simulated by Wilson and colleagues, they found that a campaign targeting people at higher risk of developing melanoma was more cost-effective than population-wide screening.[38] It should be noted, however, that their model was built on the basis of the 2010 guidelines, which do not include the newer, expensive treatments for advanced stages of the disease. As Hübner et al. pointed out , focusing on individuals at high risk for melanoma may also improve the benefit-to-harm balance

of melanoma screening programs.[39] The screening program examined, in accordance with the SCREEN project conducted in Northern Germany, includes a recruitment scheme based on explanatory images that should help people identify a suspect lesion, so the invitation for screening tends to recruit potentially higher-risk individuals.

There are some limitations to this study that should be addressed in future work. First, melanoma screening programmes are likely to increase the number of other skin cancers that would be detected during skin examinations. Our model did not consider the costs and health outcomes related to this surplus diagnosis of keratin cell cancers that might otherwise go undetected without screening. Hence, it remains to be seen whether the costs of detecting a greater proportion of melanomas in the early stage of the disease will outweigh the unavoidable costs of finding and treating more keratinocyte cancers as well. Moreover, we did not consider the number of melanomas that would never develop clinical signs (overdiagnoses) but which, once diagnosed, inevitably expose patients to psychological harms [40] and treatments, which are not free of adverse effects. In addition, overdiagnoses increase the real costs of screening.

Second, other costs and measures of effectiveness were omitted, such as indirect costs (which are known to be high for this kind of tumour, especially in its advanced stages).[41] Any toxicity-related healthcare costs were also disregarded because evidence regarding the toxicity of the new therapies is still too recent and often controversial. Third, quality of life was not considered (although melanoma may well affect it, particularly in the advanced stages). Had it been taken into account, this would have presumably made the screening branch of the model even more cost-effective because screening prompted a shift towards less-advanced cancers, which should have a smaller effect on indirect costs and quality of life. Reducing the number of advanced melanomas and consequently using less medical therapy should also mean less toxicity and lower toxicity-related healthcare costs. However, the only costs that were not considered that might lower the cost-effectiveness of the screening were the indirect costs of the screening programme, and particularly its intangible costs due to worries over unnecessary visits and biopsies.

Finally, it has to be said that we did not take into account the uncertainty in the survival probabilities, so we may have failed to consider a further source of variation in the cost-effectiveness of the screening strategy. In the case of the curves drawn from Balch [25], however, the standard errors are relatively small because they are based on a large dataset and would therefore not be significant.

Conclusions

Adopting a Whole Disease Model approach, we have shown that a one-time GP-based melanoma screening programme proved to be dominant to usual care. Although it is acknowledged that some of the assumptions we made in calculating the cost-effectiveness estimates may not be precise and subject to variability, sensitivity analysis confirmed the robustness of our screening strategy. These findings could prompt

policymakers to consider the design and implementation of a melanoma screening strategy within public health care systems.

This study focused on a one-time screening intervention because we simulated a new scenario based on the SCREEN project conducted in Northern Germany. Further studies are warrantedto demonstrate the cost-effectiveness of repeated melanoma screening programs.

We hope this study will assist health care commissioners in melanoma cancer control, taking into account the latest evidence on epidemiological changes and health technology assessment evaluation.

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