A modelling study of the cost-effectiveness of a risk stratified surveillance programme for melanoma in the UK

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Highlights

What is already known about this topic?

- Population-wide screening for melanoma is unlikely to be cost-effective, but the cost-effectiveness of targeted surveillance in high-risk groups is unknown.

What this study adds

- A self-completed risk assessment tool yielding a summary score may be a viable approach to identifying high-risk groups.
- The decision model presented here synthesises all relevant, current evidence on the costs and consequences of various targeted surveillance strategies.
- In a UK setting, we estimate that those identified as 'moderate' risk should be offered a one-off full-body skin examination. Those at increasing risk should be enrolled into quinquennial monitoring, rising to annual monitoring for the highest risk. This strategy would cost £10,199 per QALY gained, but full uptake could cost £164m per year, and there is substantial uncertainty associated with the decision.

What insights does the paper provide?

- Risk-stratified surveillance is on average cost-effective but expensive.
- However, there is substantial decision uncertainty.

Abstract

Background: Population-wide screening for melanoma is unlikely to be cost-effective. However, targeted surveillance of high risk individuals may be.

Objective: To estimate the cost-effectiveness of various surveillance strategies in the UK population, stratified by risk using a simple self-assessment tool scoring between 0-67 (Williams et al. 2011).

Methods: Decision model comparing alternative surveillance policies from the perspective of the UK NHS over 30 years. The strategy with the highest expected net benefit for each risk score is identified, resulting in a compound risk-stratified policy describing the most cost-effective population-wide strategy. The overall expected cost and QALYs, the incremental cost-effectiveness ratio and associated uncertainty are reported.

Results: The most cost-effective strategy is for those with a Williams score of 15-21 (relative risk of 0.79 to 1.60 versus a mean score in the UK of 17) to be offered a one-off full-body skin examination, and for those with a score of 22 or more (RR 1.79+) to be enrolled into a quinquennial monitoring programme, rising to annual recall for those with a risk score above 43 (RR 20.95+). Expected incremental cost would be £164m per annum (~0.1% of NHS budget), gaining 15,947 additional QALYs, yielding an ICER of £10,199 per QALY gained (51.3% probability <£30,000).

Conclusions: The risk-stratified policy would be expensive to implement but cost-effective compared to typical UK thresholds (£20,000 - £30,000 per QALY gained), although decision uncertainty is high. Phased implementation, enrolling only higher risk individuals would be substantially less expensive, but with consequent foregone health gain.

Introduction

Approximately 14,500 new cases of malignant melanoma are diagnosed and approximately 2600 deaths occur in the UK each year.[1] Early detection is critical: 90% of patients survive for five or more years, but this falls to 25% of women and less than 10% of men with metastatic disease at diagnosis.[1] The cost of treating metastatic melanoma far outweighs the cost of treating primary melanoma and the relative increase has risen sharply with the recent introduction of several high cost drugs that palliate for the most part. For example, nivolumab costs approximately £70,000 per patient per year for an additional gain of 1.3 QALYs compared with dacarbazine.[2] Screening programmes are therefore of increasing relevance. The UK National Screening Committee has not formally reviewed whether a programme for melanoma would be an efficient use of public funds.[3] However, existing evidence suggests such a programme would have difficulty identifying the target population,[4] raises concerns about whether a comprehensive programme could be cost-effective[5] and cites lack of evidence on the cost-effectiveness of full-body skin examination (FBSE), except in those with a history of melanoma.[6]

Two recent systematic reviews[7 8] concluded that whilst skin cancer prevention initiatives are highly cost-effective,[7] there is a lack of evidence on the cost-effectiveness of early detection programmes,[7] and future research should focus on targeted screening/surveillance in high risk populations.[8] Based on this, the US Preventive Services Task Force (2016) reiterated its previous recommendation[9] that the "current evidence is insufficient to assess the balance of benefits and harms of visual skin examination… to screen for skin cancer in adults."[10]

Several tools have been developed to enable identification of higher risk individuals.[11] One of the better performing was developed from a case-control study in the USA by Williams *et al*.[12] It is a self-assessed clinical risk estimation model not requiring expert FBSE that, in a split-sample validation population, had an area under the receiver operator characteristic curve of 0.70 (95%C.I. 0.64 to 0.77) and was able to identify 15% of the population in whom 50% of melanomas would be expected to develop.[12] We have recently shown that it is both feasible and acceptable to collect data on risk of melanoma in the waiting rooms of UK family practices and that using the Williams model produces a distribution of risk in the attending population which allows identification of sub-groups at different levels of risk.[13]

The purpose of this study is to establish whether using the Williams model and resulting score to risk-stratify the population and guide future management is a cost-effective approach to reducing mortality and morbidity from melanoma in a UK setting. Key to this is determining the risk score at which it is most cost-effective to enrol patients into a surveillance programme. If the score is set too low, primary care capacity will be absorbed examining patients with an extremely low risk of melanoma at the expense of other patients with a greater capacity to benefit. If set too high, then patients will be falsely reassured and any benefits in terms of reduced melanoma morbidity and mortality will be foregone. Specifically therefore, this study aims to identify the optimal cut-off scores from the Williams self-assessment tool[12] at which users are recommended to either (a) visit their primary care practitioner for a one-off FBSE, or (b) be entered into a routine primary care-based monitoring programme, and if so, (c) the optimal frequency of visits, ranging from 5-yearly to annual.

Method

We substantially adapted and modified a decision model we previously developed for a novel diagnostic aid for melanoma.[14] The adapted model is a patient level simulation following a simulated cohort of participants (UK general public) one by one. Uncertainty is propagated through the model via Monte Carlo simulation (distributions of parameters are specified in Table 1). The code was written in R,[15-17] and run on the University of Cambridge High Power Cluster computing facility. Code is available on request from the corresponding author. Ethical approval was not required for this study.

The Williams Self-Assessment Tool

The scenarios we model focus on the Williams self-assessment tool (Appendix 1).[12] This is a rapid questionnaire comprising eight questions on sex, age, hair colour, density of freckles, history of severe sunburn in childhood and adolescence, number of raised moles on the arms and history of non-melanoma skin cancer yielding a summary score between 0 (lowest risk) and 67.

Model definition

The model comprises two modules: natural history and clinical (Figure 1). The link between the two is determined by the comparator policies, described below. Cohorts of a given age, gender and Williams score[12] are simulated. In year zero, the distribution of prevalent melanomas and their disease stages in each cohort is estimated based on UK prevalence data and stage at diagnosis,[18 19] adjusted for risk score. The natural history module is a Markov-like model and simulates patients' trajectories over a period of 30 years: each year patients are at risk of new melanomas developing according to UK incidence by age and gender[19] adjusted for risk score,[12] and undiagnosed (and hence untreated) melanomas progress according to estimated rates of progression.[20] When the model determines that contact is made with the health service, the simulated patient 'breaks out' of the natural history module into the clinical module, which has a decision tree structure. Once reaching a terminal node of the decision tree, the patient is returned to the natural history module.

Natural History Module

Cutaneous melanoma is categorised into four main types (superficial spreading, lentigo maligna, acral lentiginous and nodular)[21] each with nine stages of invasion (Stages 1a to 4) plus an *in situ* stage for all except nodular melanoma (which is by definition invasive).[22] We assumed that invasive disease would progress at the same rate irrespective of primary melanoma subtype, but allowed the rate of progression from *in situ* disease to vary by subtype, yielding a total of 12 discrete stages describing the disease. The model also included no melanoma and dead health states. The overall prevalence of undiagnosed melanoma in the community in year 0 was estimated at 0.162%, assumed the same as that observed in a population screening study in Northern Germany[18] (Review details Appendix 2). This was distributed according to risk score by combining with UK relevant epidemiological data.[12 19 23 24] The parameters of the resulting risk function are in Table 1. The annual incidence was estimated using an analogous approach. Full details are in Appendix 3.

Data on the rate of progression of untreated melanoma do not exist and it would be most unethical to conduct a prospective cohort study to establish this empirically. Therefore data were elicited from a representative group of experts in melanoma,[20] (Table 1 and Appendix 4). Age and gender specific background and melanoma-specific mortality data are extracted from UK lifetables[25] (Appendix 5) adjusted for the odds ratio[22] (Appendix 6).

Clinical Module

The clinical module describes the patient pathway following health service contact (Figure 1). The model allows two ways for a patient to present in primary care: of their own initiative with a mole that they are concerned about, or because they have been advised to do so following a risk assessment. Any suspicious moles are inspected during a FBSE from a primary care practitioner, and the patient either referred to secondary care or discharged. Figure 1 (right hand side) illustrates the pathway; the natural history component of the model will have determined whether a patient is healthy ('D-') or has melanoma ('D+'). For a patient with a melanoma ('D+'), the probability of the primary care practitioner identifying it and referring a patient to secondary care is the sensitivity of the practitioner, denoted P(T+|D+), and is based on data from the control arm of a recently study of a diagnostic aid in primary care.[26] Likewise the probability of correctly discharging a patient without melanoma is the specificity (denoted (P(T-|D-) in Figure 1), extracted from the same source. Data are summarised in Table 1.

Patients with melanoma correctly referred (true positives, with probability P(T+|D+)) receive appropriate treatment according to disease stage ('D&T_{stage}' in Figure 1; see section 'costs' below for details). They are then flagged as having a history of melanoma and are at risk of mortality as described in the natural history module (data based on stage-specific prognosis post diagnosis[22]). Patients with melanoma who are not referred (false negatives, with probability 1 - P(T+|D+)) are discharged and return to the 'natural history' module where they are at risk of disease progression and mortality. Patients without melanoma (D-) who are referred incur the cost of referral followed by discharge to the community. Finally, patients without melanoma who are not referred are reassured and discharged back to the community direct from primary care.

Contact with health service: comparator policies

There are seven alternative policies.

The first is the status quo. This assumes an ad hoc presentation by a member of the public concerned about a skin lesion, the probability of which is estimated at 0.73% per annum[19 24 26-28] (Appendix 7). The second policy is to invite all at-risk persons to primary care for a one-off FBSE by a primary care practitioner in year 0; patients then present opportunistically (with lesions of concern) in the remaining years. Policies 3-7 represent enrolment into a primary care-based monitoring programme with increasing frequency of recall from five-yearly to annual. Thus, under policy 3 patients attend for a body examination in years 0, 5, 10, 15…, (with ad hoc presentation in the intervening years). Under policy 4, patients present in years 0, 4, 8, 12, and so forth.

In policies 2-7, we assume the Williams tool is used by members of the public to assess their own risk prior to contact with the health service. This could be administered, for example, via a leaflet in pharmacies, primary care waiting rooms or other public places, or electronically via a smartphone app. The objective of this analysis is to determine the optimal cut-off scores at which each of the seven policies is recommended.

Costs

The perspective and price year of the analysis is the UK NHS and 2015, with future costs discounted at a rate of 3.5%. Unit costs were extracted from standard NHS sources,[29 30] and care pathways and primary care consultation time from current guidelines[31] and a recent clinical trial[26] (Table 1 and Appendix 8).

Health state Utilities

A systematic review of health related quality of life in patients with melanoma identified three distinct periods of impact of the disease: at diagnosis, treatment and follow-up.[32] We assumed that patients who are unaware they have melanoma suffer no impairment in quality of life (assigned a utility of 1), whilst from the point of diagnosis, a health utility impairment was assigned as per the authors' previous model in a related area,[14] adapted from a study of health related quality of life measurement in melanoma patients[33] (Table 1).

Model Calculation and analysis

To determine the appropriate cohort size and number of iterations, one of the seven scenarios under one age/gender/risk score (baseline scenario, 35yo male, risk score 17) was run under a range of cohort sizes and iterations a total of 50 times. The coefficient of variation (CV) of the expected and standard errors of cost and QALYs were calculated from these, with a 'target' CV of 2% or below considered 'stable'. A cohort size of 1000 and 1000 iterations yielded coefficients of variation of 0.39%, 2.21%, 0.01% and 1.93% for mean cost, SE mean cost, mean QALYs and SE mean QALYs respectively (Appendix 9).

The model therefore generates 1,000 patients of a given age, gender and risk score group, and simulates their development, progression and treatment of melanoma over 30 years under each of the seven policies 1000 times. We estimated the expected cost, QALYs and net benefit (defined as the QALY gain multiplied by the thresholds of £20,000 and £30,000, less the cost) for each policy. The model was calculated for each of the seven policies at seven selected values for the Williams risk score (10, 17, 20, 25, 30, 50 and 60), males and females, and four starting ages (35, 45, 55 and 65). Results were weighted for the age/gender of the UK population to yield costs, outcomes and net benefit by risk score alone. The risk scores at which the model was evaluated were chosen to get a spread of scores, but included 17 as this is the mean risk score for the UK population.[13] Net benefits for intervening scores were estimated by linear interpolation.

The policy yielding the highest net benefit was noted for each risk score, and the cut-off scores at which the optimal policy changed identified. This risk-stratified policy describes the most cost-effective strategy given the epidemiology and demographics of the UK population. The overall expected cost and QALY gains of this risk-stratified policy are applied to the UK population, and compared with expected cost and QALYs of the status quo, thus estimating the overall incremental cost per QALY gained of the stratified policy versus status quo.

Results

Figures 2a&b show the expected net benefit and 95% credibility intervals from each policy as a function of selected risk scores at a willingness to pay (WTP) of £20,000 and £30,000 per QALY respectively (data in Appendix 10, additional figures Appendix 11). At lower risk scores, all options have a very similar expected net benefit. As the risk score increases, the expected net benefit of status quo (no screening) and the less intensive policies drops below that of the more intensive policies.

Given a WTP of £30,000 per QALY the optimal policy is for those with a risk score between 15 and 21 to be offered a one-off FBSE to check for melanoma. Those with a risk score of 22 and above should be enrolled into a monitoring programme with quinquennial recall, rising to annual for those with a score over 43.

If this 'compound' policy were to be enacted across the UK, the expected additional cost per person over 30 years would be £164.89, yielding an extra 0.016 QALYs per person. The incremental cost per QALY gained is thus £10,199. (Table 2; Appendix 10). The 95% credibility ellipse (Figure 3) and cost-effectiveness acceptability curve (Figure 4) illustrate the high decision uncertainty; at NICE's threshold of around £20,000 to £30,000, there is only a 51.0% to 51.3% probability that the policy is cost-effective. Thus, whilst the compound risk-adjusted policy yielding the highest expected net benefit can be identified (Table 2), there is a great deal of decision uncertainty. This is a function of both the small absolute difference in net benefit between policies at lower risk scores (Figure 2), and the substantial parameter uncertainty (Table 1). The probability of cost-effectiveness does not exceed 51-52% due to the proportion of the probability mass in the north-west quadrant of the cost-effectiveness plane, representing scenarios where the policy is both more expensive but less effective (i.e. yields fewer QALYs) than the status quo (Figure 3).

Discussion

Interpretation of results

The results in Table 2 and Figure 2 show how the recommended intensity of surveillance increases with risk score, from status quo (no screening programme), rising to enrolment in a monitoring programme of increasing frequency of recall for the highest risk individuals. This suggests the model has face validity. However, we are also able to identify the most efficient cut-off scores for these recommendations: all those with a Williams' risk score greater than 15 should have a one-off FBSE with a primary care practitioner. Those with a risk score greater than 22 should be enrolled into a primary care-based monitoring programme with 5-year recall, rising to annual monitoring for those with a score above 43.

The mean risk score in the UK population is 17.[13] Implementing this policy in the UK would involve inviting an estimated 61% of the adult population to at least one examination (approximately 29.9m people), at an extra cost of £4.9bn over 30 years, or approximately £164m per year (0.1% of the 2016 NHS budget). This cost is the present value discounted at 3.5% per annum and includes the cost of monitoring as well as subsequent referrals and surgery. However, this would yield approximately 15,947 additional QALYs per year: an incremental cost per QALY of £10,199, well within what is usually considered cost-effective in the UK (£20,000 to £30,000 per QALY).[34] By way of comparison the existing breast screening programme in the UK adds approximately £42.5m to NHS expenditure, but generates around 2,040 extra QALYs (£20,800 per QALY gained).[35] A phased implementation involving only higher risk individuals would be substantially less expensive, but with consequent foregone health gain.

These recommendations are based on expected values, rather than on the results of hypothesis tests. This approach is consistent with statistical decision theory,[36] a key assumption of which is that decision makers are risk neutral[37] and thus interested in maximising expected outcomes subject to budgetary constraints. Uncertainty in decisions therefore should not be a factor in whether to adopt one particular strategy or another, but is critical to guide future research, ideally via value of information analysis.[38 39] Our analysis suggests that there is a great deal of decision uncertainty, with only a 51%-52% probability that such a surveillance programme is cost-effective (Figure 3).[40] A phased implementation as suggested above must provide the opportunity to reduce decision uncertainty, for example through a cluster or stepped-wedge randomised controlled trial. This would inform the decision to either expand the scheme to lower risk individuals, limit to higher risk, or disinvest entirely. Additional preparatory research to establish the feasibility, sensitivity and specificity of nurses in conducting a FBSE as part of a screening programme is also critical.

Strengths & Weaknesses

As with any decision model, the robustness of the policy recommendations is contingent on the quality of the modelling and availability of source data. Our model is a patient level simulation of a complex decision framework with a total of 476 possible compound policies (seven strategies at 68 risk scores). The model development process was methodical and rigorous, gathering the most appropriate evidence on all input parameters.

The major limitations in the model were due to lack of relevant data. Specifically, the risk of progression in undiagnosed melanoma was based on expert opinion.[20] This limitation is common to many decision analyses, particularly of screening studies: in order to quantify the added health benefit of screening, it is necessary to know the disease course of those who would otherwise not be identified and treated. Prospectively withholding treatment from melanoma patients to observe this would clearly be deeply unethical therefore the only alternative is to seek expert opinion. A number of techniques exist (e.g.[41]), a key feature of which is that they focus on eliciting experts' uncertainty (in terms of a range of plausible values, weighted according to strength of belief) rather than a single 'best guess' for a particular parameter. We conducted an elicitation exercise in a transparent and replicable manner to address this issue.[20] Due to a lack of evidence,[10] we were also unable to include potential screening-related harms in the model. These include risk of overdiagnosis,[42] side effects of treatment, or psychological harms[43] and are important when considering any future screening programme.

Treatment of late stage disease in the model is based on 2010 guidelines which do not include newer, expensive treatments of varying cost-effectiveness.[44-46] If these add substantial cost with limited health gain, it becomes even more cost-effective to detect (and thus treat) earlier in the disease process.

Further limitations include the costs and practicalities of introducing such surveillance. We assumed all patients initially receive a FBSE by a GP. Not offering a full body examination may reduce the cost of the consultation, but at risk of lower sensitivity. A community nurse conducting the examinations would be less expensive than a GP, but since the current gold standard is examination in secondary care, costs of providing and training for both GP and nurse would need consideration.[47] Surveillance could be offered in other locations such as community clinics and via telemedicine.[48]

We assumed perfect adherence and did not explicitly account for recurrent or multiple lesions. Lower adherence will reduce both costs and health gain from the programme. Recurrent skin cancers were indirectly accounted for in the post-treatment survival functions.[22] Patients with multiple lesions will have increased surgical costs, but the marginal cost is likely to be small compared with the cost of non-surgical treatment at later stages of the disease and so is unlikely to alter our conclusions substantially.

The baseline utility for patients was assumed equal to perfect health (i.e. 1). Population norms suggest a declining utility with age.[49] However, the model applies an absolute reduction in utility (and hence QALYs) with various health states, thus the incremental QALY gain is insensitive to this.

A final limitation was that we only considered a maximum recall interval of 5 years. It may be more efficient for recall to be less frequent for medium risk individuals, for example, decennially. However, this was out of scope of this analysis.

Despite these caveats, the model is based on the best evidence available to the authors at the time of writing: no decision model is perfect and can always be improved. Decisions as to what concepts to include in a decision model must be balanced against the resources available to conduct it, and the need for a timely policy recommendation. Acknowledged limitations of a decision model, both in terms of structure and data inputs, provide an agenda for future research in the area.

Conclusion

Current evidence is highly uncertain but suggests that, on balance, a UK-wide programme to identify patients at risk of melanoma using the Williams self-assessment tool is potentially cost-effective. Nevertheless, a programme would be expensive to implement due to its scale. Additional research into the feasibility, sensitivity and specificity of nurses in conducting FBSE as part of a programme is required. Ultimately a phased implementation, targeting only the highest risk groups may be practical to implement, but must be embedded within a rigorous randomised trial to reduce decision uncertainty and hence inform further rollout.

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Table 1: Input parameters

Parameter	Dbn	Hyperparameters	mean	median	SE	95% CrI	
Probability of prevalent melanoma in year 0 by risk score*							
α	N	(-8.454, 0.119)	-8.454		0.119		
β	N	(0.100, 0.008)	0.100		0.008		
Annual probability of incident melanoma by risk score*							
α	N	(-10.270, 0.186)	-10.270		0.186		
β	N	(0.117, 0.008)	0.117		0.008		
Transition Probabilities (From state > To state)**							
ISLM>ISLM	mCM	$\begin{pmatrix} 0.167 & 0.102 & 0.023 & 0.999 \\ 9.624 & 2.133 & 0.073 & 0.956 \\ 9.885 & 9.988 & 0.039 & 0.604 \\ 2.412 & 9.960 & 0.101 & 0.994 \\ 9.964 & 3.223 & 0.019 & 0.665 \\ 9.810 & 9.970 & 0.649 & 0.964 \end{pmatrix}$		0.92		(0.02, 1.00)	20
ISLM>1A				0.06		(0.00, 0.88)	
ISLM>1B				0.00		(0.00, 0.11)	
ISLM>2A				0.00		(0.00, 0.07)	
ISLM>2B				0.00		(0.00, 0.09)	
ISLM>2C				0.00		(0.00, 0.07)	
ISLM>3A				0.00		(0.00, 0.02)	
ISSS>ISSS	mCM	$\begin{pmatrix} 0.739 & 0.319 & 0.003 & 0.996 \\ 2.069 & 2.033 & 0.610 & 1.000 \\ 9.055 & 6.031 & 0.012 & 0.973 \\ 9.687 & 2.788 & 0.034 & 0.903 \\ 7.133 & 9.546 & 0.264 & 0.990 \\ 0.450 & 0.137 & 0.038 & 0.621 \end{pmatrix}$		0.83		(0.03, 1.00)	
ISSS>1A				0.14		(0.00, 0.82)	
ISSS>1B				0.02		(0.00, 0.15)	
ISSS>2A				0.01		(0.00, 0.08)	
ISSS>2B				0.00		(0.00, 0.02)	
ISSS>2C				0.00		(0.00, 0.01)	
ISSS>3A				0.00		(0.00, 0.01)	
ISAL>ISAL	mCM	$\begin{pmatrix} 0.839 & 0.386 & 0.000 & 0.999 \\ 1.492 & 0.248 & 0.000 & 0.759 \\ 10.000 & 10.000 & 0.000 & 0.969 \\ 6.603 & 8.078 & 0.000 & 0.777 \\ 8.718 & 9.295 & 0.000 & 0.671 \\ 9.634 & 10.000 & 0.247 & 0.810 \\ 8.705 & 9.196 & 0.000 & 0.973 \end{pmatrix}$		0.79		(0.03, 1.00)	
ISAL>1A				0.13		(0.00, 0.70)	
ISAL>1B				0.03		(0.00, 0.23)	
ISAL>2A				0.01		(0.00, 0.09)	
ISAL>2B				0.01		(0.00, 0.05)	
ISAL>2C				0.01		(0.00, 0.06)	
ISAL>3A				0.00		(0.00, 0.02)	
ISAL>3B				0.00		(0.00, 0.00)	
1A>1A	mCM	$\begin{pmatrix} 1.034 & 0.568 & 0.000 & 0.999 \\ 9.734 & 9.973 & 0.004 & 1.000 \\ 2.932 & 9.951 & 0.002 & 1.000 \\ 0.052 & 0.233 & 0.009 & 0.985 \\ 9.865 & 9.992 & 0.000 & 0.365 \\ 0.011 & 0.126 & 0.031 & 0.989 \\ 9.867 & 9.903 & 0.021 & 0.993 \\ 0.000 & 9.995 & 0.014 & 0.962 \\ 0.000 & 9.971 & 0.009 & 0.999 \end{pmatrix}$		0.72		(0.05, 1.00)	
1A>1B				0.14		(0.00, 0.53)	
1A>2A				0.03		(0.00, 0.16)	
1A>2B				0.00		(0.00, 0.26)	
1A>3A				0.01		(0.00, 0.08)	
1A>2C				0.00		(0.00, 0.10)	
1A>3B				0.02		(0.00, 0.17)	
1A>3C				0.00		(0.00, 0.00)	
1A>4				0.00		(0.00, 0.00)	
1A>ISSS				0.02		(0.00, 0.16)	
1B>1B	mCM			0.69		(0.10, 0.92)	
1B>2A				0.14		(0.03, 0.52)	
1B>2B				0.03		(0.00, 0.33)	
1B>2C				0.03		(0.00, 0.18)	

1B>3A		$\begin{pmatrix} 0.448 & 0.294 & 0.098 & 0.924 \\ 10.000 & 9.915 & 0.000 & 0.957 \\ 0.893 & 1.659 & 0.000 & 0.963 \\ 0.000 & 9.696 & 0.393 & 0.910 \\ 0.232 & 0.398 & 0.000 & 0.939 \\ 9.841 & 9.398 & 0.000 & 0.934 \\ 9.526 & 9.769 & 0.065 & 0.968 \\ 9.809 & 0.845 & 0.081 & 0.931 \end{pmatrix}$	0.01		(0.00, 0.18)
1B>3B			0.01		(0.00, 0.12)
1B>3C			0.01		(0.00, 0.07)
1B>4			0.01		(0.00, 0.06)
1B>1A			0.00		(0.00, 0.00)
2A>2A	mCM	$\begin{pmatrix} 1.688 & 1.004 & 0.000 & 0.918 \\ 2.725 & 2.357 & 0.023 & 0.962 \\ 8.995 & 9.106 & 0.000 & 0.629 \\ 0.524 & 0.623 & 0.220 & 0.884 \\ 5.262 & 8.588 & 0.266 & 0.691 \\ 0.078 & 1.900 & 0.470 & 0.818 \end{pmatrix}$	0.61		(0.11, 0.91)
2A>2B			0.18		(0.03, 0.60)
2A>3A			0.05		(0.01, 0.19)
2A>2C			0.05		(0.01, 0.25)
2A>3B			0.02		(0.00, 0.10)
2A>4			0.01		(0.00, 0.07)
2A>3C			0.01		(0.00, 0.05)
2B>2B	mCM	$\begin{pmatrix} 0.260 & 0.257 & 0.009 & 0.994 \\ 4.960 & 10.000 & 0.008 & 0.987 \\ 2.069 & 2.495 & 0.028 & 0.977 \\ 4.565 & 5.173 & 0.019 & 0.991 \\ 0.140 & 0.230 & 0.010 & 0.991 \\ 0.387 & 0.262 & 0.010 & 0.984 \end{pmatrix}$	0.52		(0.01, 0.99)
2B>2C			0.14		(0.00, 0.49)
2B>3A			0.11		(0.00, 0.52)
2B>3B			0.06		(0.00, 0.31)
2B>3C			0.00		(0.00, 0.24)
2B>4			0.00		(0.00, 0.21)
2B>2A			0.00		(0.00, 0.11)
2C>2C	mCM	$\begin{pmatrix} 1.977 & 2.396 & 0.014 & 0.954 \\ 0.129 & 0.174 & 0.058 & 0.986 \\ 1.036 & 1.319 & 0.000 & 0.943 \\ 1.813 & 1.456 & 0.030 & 0.932 \\ 4.446 & 1.759 & 0.061 & 0.927 \end{pmatrix}$	0.44		(0.09, 0.83)
2C>3A			0.14		(0.01, 0.82)
2C>3B			0.07		(0.00, 0.52)
2C>3C			0.05		(0.00, 0.41)
2C>4			0.03		(0.00, 0.26)
2C>2B			0.00		(0.00, 0.04)
3A>3A	mCM	$\begin{pmatrix} 1.393 & 0.993 & 0.013 & 0.977 \\ 1.360 & 1.643 & 0.015 & 0.987 \\ 0.983 & 0.587 & 0.011 & 1.000 \\ 1.691 & 0.340 & 0.012 & 0.991 \\ 0.437 & 0.072 & 0.027 & 0.993 \\ 0.035 & 0.218 & 0.022 & 0.993 \\ 4.673 & 0.697 & 0.021 & 0.969 \\ 0.033 & 0.327 & 0.007 & 0.990 \end{pmatrix}$	0.61		(0.08, 0.96)
3A>3B			0.15		(0.01, 0.63)
3A>3C			0.09		(0.00, 0.54)
3A>4			0.03		(0.00, 0.35)
3A>1A			0.00		(0.00, 0.00)
3A>1B			0.00		(0.00, 0.01)
3A>2A			0.00		(0.00, 0.00)
3A>2B			0.00		(0.00, 0.00)
3A>2C			0.00		(0.00, 0.00)
3B>3B	mCM	$\begin{pmatrix} 1.253 & 2.103 & 0.126 & 0.995 \\ 2.722 & 1.932 & 0.003 & 0.997 \end{pmatrix}$	0.43		(0.15, 0.87)
3B>3C			0.30		(0.05, 0.68)
3B>4			0.14		(0.02, 0.44)
3C>3C	mCM	$\begin{pmatrix} 3.785 & 2.926 & 0.008 & 0.988 \end{pmatrix}$	0.57		(0.21, 0.87)
3C>4			0.31		(0.08, 0.66)
Odds ratio of death by disease stage (vs 1A)***					
1A	-	-	1	0	22
1B	LN	(1.449, 0.007)	4.261	0.007	
2A	LN	(2.506, 0.007)	12.250	0.007	
2B	LN	(3.045, 0.007)	21.000	0.007	

2C	LN	(3.731, 0.008)	41.741	0.008		
3A	LN	(2.626, 0.010)	13.821	0.010		
3B	LN	(3.486, 0.008)	32.667	0.008		
3C	LN	(4.215, 0.011)	67.667	0.011		
4	LN	(5.743, 0.006)	312.104	0.006		
Sensitivity and Specificity of primary care practitioner at detecting melanoma						
Sensitivity (P(T+|D+))	β	(29, 7)	80.1%		(66.3%, 91.6%)	26
Specificity (P(T-|D-))	β	(864, 536)	61.7%		(59.2%, 64.2%)	26
Costs						
GP consultation (per minute)		Constant	£3.80			29
GP consultation time (minutes)	N	(22.1,3.2)	22.1			26
Initial referral	Γ	(20.408, 5.439)	£111			30
Biopsy excision	Γ	(10.443, 13.694)	£143			30
Definitive surgery	Γ	(3.762, 41.468)	£156			30
CXR	Γ	(12.430, 2.414)	£30			30
CT Scan	Γ	(13.616, 9.695)	£132			30
Liver function test	Γ	(4.041, 0.742)	£3			30
FBC	Γ	(4.041, 0.742)	£3			30
Sentinel node biopsy	Γ	(1.165, 24.887)	£29			30
Radical lymph node dissection	Γ	(1.808, 547.925)	£991			30
Surgical removal of localised metastases	Γ	(1.256, 577.101)	£725			30
Radiotherapy (planning)	Γ	(8.890, 82.673)	£735			30
Radiotherapy (per fraction)	Γ	(17.014, 7.758)	£132			30
Chemotherapy (dacarbazine, procurement)	Γ	(1.330, 209.827)	£279			30
Chemotherapy (dacarbazine, delivery first attendance)	Γ	(6.934, 26.823)	£186			30
Chemotherapy (dacarbazine, delivery subsequent)	Γ	(3.239, 62.988)	£204			30
Dermatology follow-up	Γ	(12.183, 7.962)	£97			30
Summary Costs						
GP consultation			£83.98			
Chemotherapy, cycle			£1485			

Radiotherapy, 10 fraction cycle			£2055			
By disease stage						
D&T In situ (SS, LM, AL)			£396			
D&T stage 1a, 1b			£1463			
D&T stage 2a			£1880			
D&T stage 2b, 2c			£2048			
D&T stage 3a, 3b, 3c			£3171			
D&T stage 4			£4761			
Final year of life in situ, 1a (i.e. states ‘dead IS’, ‘dead 1a’)			£0			
Final year of life stage 1b-4			£4265			
Health State Utilities						
No melanoma	C	-	1.00	-	-	
Undetected disease	C	-	1.00	-	-	
Detected & treated, and post D&T:						
Stage 0	N	(0.93, 0.013)	0.93			33
Stage 1	N	(0.93, 0.013)	0.93			33
Stage 2	N	(0.87, 0.057)	0.87			33
Stage 3	N	(0.89, 0.046)	0.89			33
Stage 4	N	(0.52, 0.117)	0.52			****
Last year of life with IS or 1a disease (states ‘dead 0’ and ‘dead 1a’	N	(0.93, 0.013)	0.93			33
Last year of life with Stage 1b – 4 disease	N	(0.52, 0.117)	0.52			33
Dead	C	-	0			

So: Source.

* $P(prevalent\ or\ incident\ melanoma\ in\ year\ zero) = e^{(\alpha+\beta W)}$,*where W is risk score. mCM: modified Connor-Mosimann distribution. Parameters are presented as a (k-1)*4 matrix. Parameters relate to six-month transition probabilities (elicited probabilities were over a 6 not 12-month time horizon), which form the inputs to the modified Connor-Mosimann distribution. Columns mean, median, 95%CrI represent the respective moments of the twelve-month transition marginal probability distribution. Please see Appendix 4 for further details. ISLM: In situ lentigo maligna melanoma; ISSS: In situ superficial spreading melanoma; ISAL: in situ acral lentiginous melanoma; 1A, 1B etc: invasive melanoma of stage 1A, 1B etc. SE: Standard Error. CrI: Credibility Interval. LN: Log Normal. N: Normal. C: Constant. Dbn: Distribution. D&T: Diagnosed and Treated. GP: General Practitioner. CXR: Chest X-ray. FBC: Full Blood Count.*

***Note medians are aggregated from individual summaries so do not total 100%*

****Parameters of log-normal distribution are the natural log of the mean and the standard error of the natural log of the mean. C= Constant.*

***** Assumption based on reference* [33]

Table 2: Recommendations by risk score.

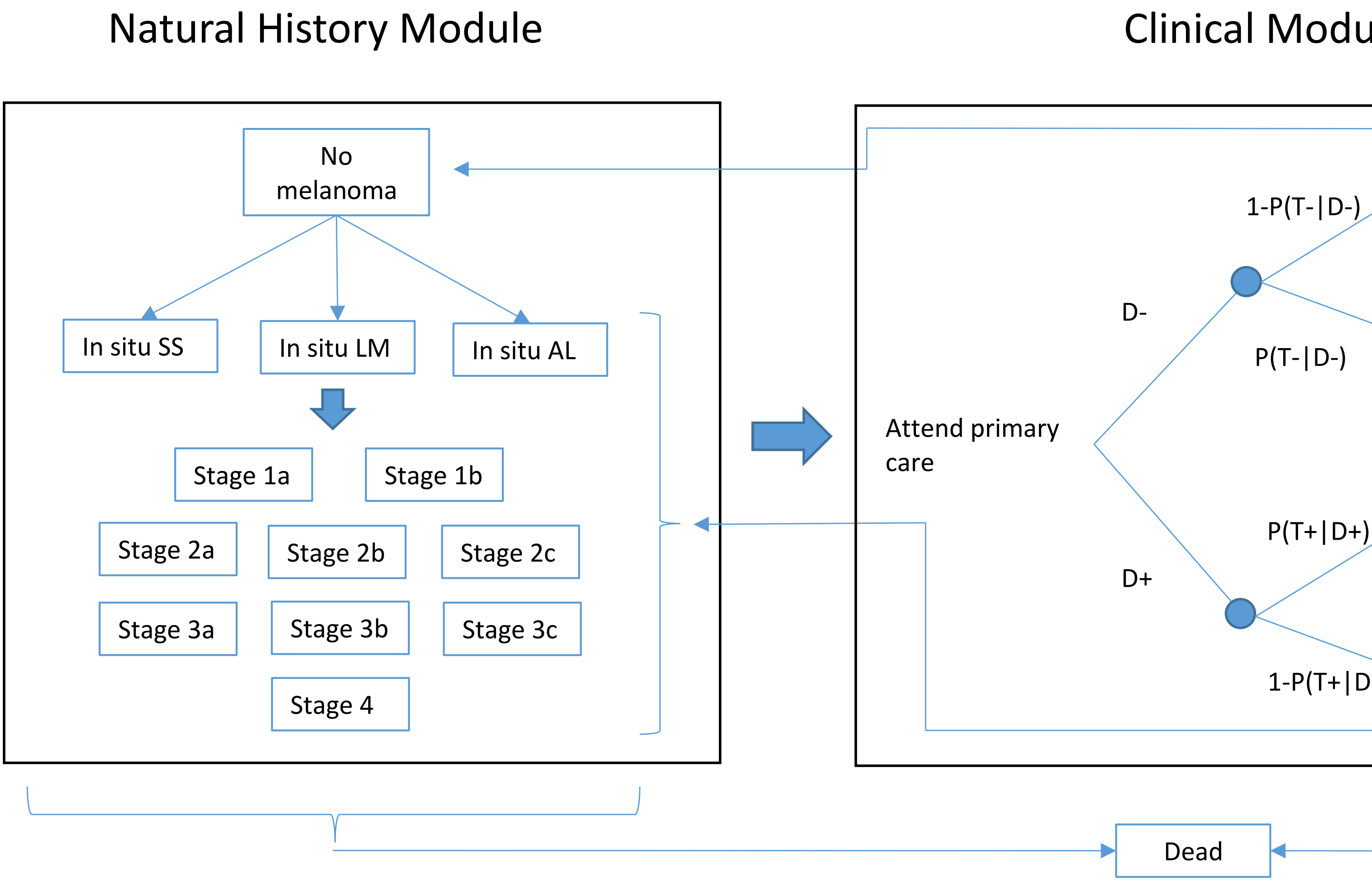
Risk score	Equiv. RR	Optimal policy	% of popn	Status Quo £ (SE)	QALYs (SE)	Cov(£, Q)	Monitoring programme £ (SE)	QALYs (SE)	Cov(£,Q)
0-14	0.14 – 0.70	Do nothing	38.6%	£34.99 (£6.79)	28.388 (0.346)	-0.449	£34.99 (£6.79)	28.388 (0.346)	-0.449
15-21	0.79 – 1.60	One-off exam	33.9%	£24.99 (£7.47)	16.347 (0.107)	-0.113	£141.3 (£18.01)	16.352 (0.107)	-0.072
22-28	1.79 – 3.62	5-yearly monitoring	19.4%	£40.87 (£15.48)	16.705 (0.094)	-0.476	£402.09 (£49.34)	16.727 (0.09)	-0.100
29-32	4.07 – 5.78	3-yearly monitoring	4.6%	£57.61 (£27.27)	14.638 (0.103)	-3.135	£573.01 (£75.42)	14.684 (0.086)	-0.567
33-42	6.50 – 18.63	2-yearly monitoring	3.2%	£219.62 (£109.45)	19.354 (0.256)	-40.098	£1128.51 (£129.7)	19.592 (0.121)	-4.259
43+	20.95+	Annual monitoring	0.2%	£170.45 (£123.05)	8.909 (0.263)	-35.990	£1105.36 (£176.67)	9.124 (0.085)	1.184
		Weighted average		£40.05 (£23.22)	21.066 (0.234)	-1.824	£204.93 (£38.47)	21.082 (0.229)	-0.377
		ICER					£10,198.57		

'Status Quo' costs and QALYs represent the current expected costs and QALYs accrued by members of the population with various risk scores over a period of 30 years (figures discounted at 3.5%pa). 'Monitoring programme' shows the expected cost and QALYs accrued by those same patients under the 'optimal policy' option. Thus there is no change in cost or outcomes for those with a risk score under 14. The extra cost for those with a score of 15-21 represents the expected cost of the one-off exam and subsequent referral and treatment where incurred. The added benefit in these patients is 0.005 QALYs.

RR- relative risk of incident melanoma vs mean risk score in UK of 17[13] (calculations based on ratio of expected incidences at respective risk scores as per equation described in Appendix 2); Popn- population; £ - GB Pound; SE – Standard Error; Cov- Covariance; Q- QALYs; ICER- Incremental Cost Effectiveness Ratio.

1. Usher-Smith JA, Kassianos AP, Emery JD, et al. Identifying people at higher risk of melanoma across the U.K.: a primary-care-based electronic survey. Br J Dermatol 2017;**176**(4):939-48 doi: 10.1111/bjd.15181.

Figure 1: Model schematic



D+/D-: patient with or without melanoma. P(T+|D+): probability of a positive diagnosis given the patient has melanoma negative diagnosis given the patient does not have melanoma (specificity). D&T$_{stage}$: diagnosis and treatment in second Patient with history of treated disease of a given stage.

Figure 2a: Expected net benefit +/- 95% credibility interval, threshold = £20,000 per QALY.

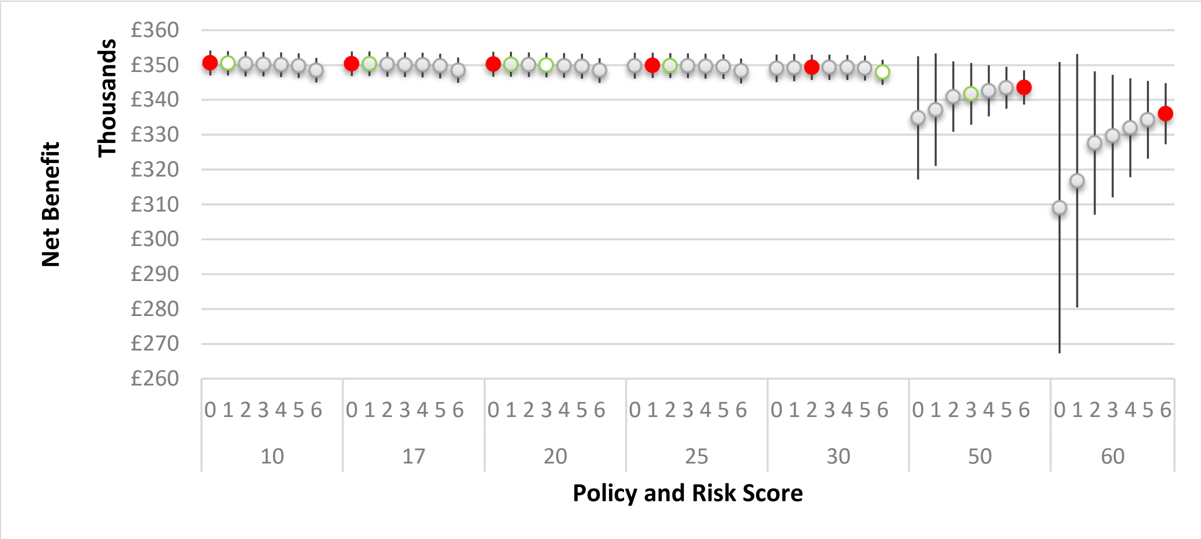
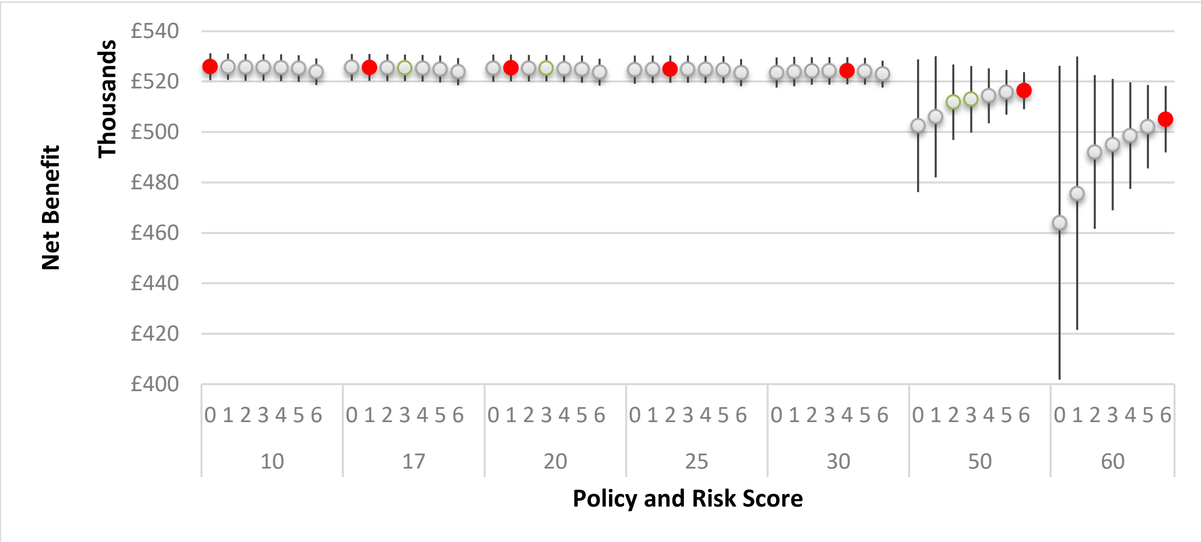
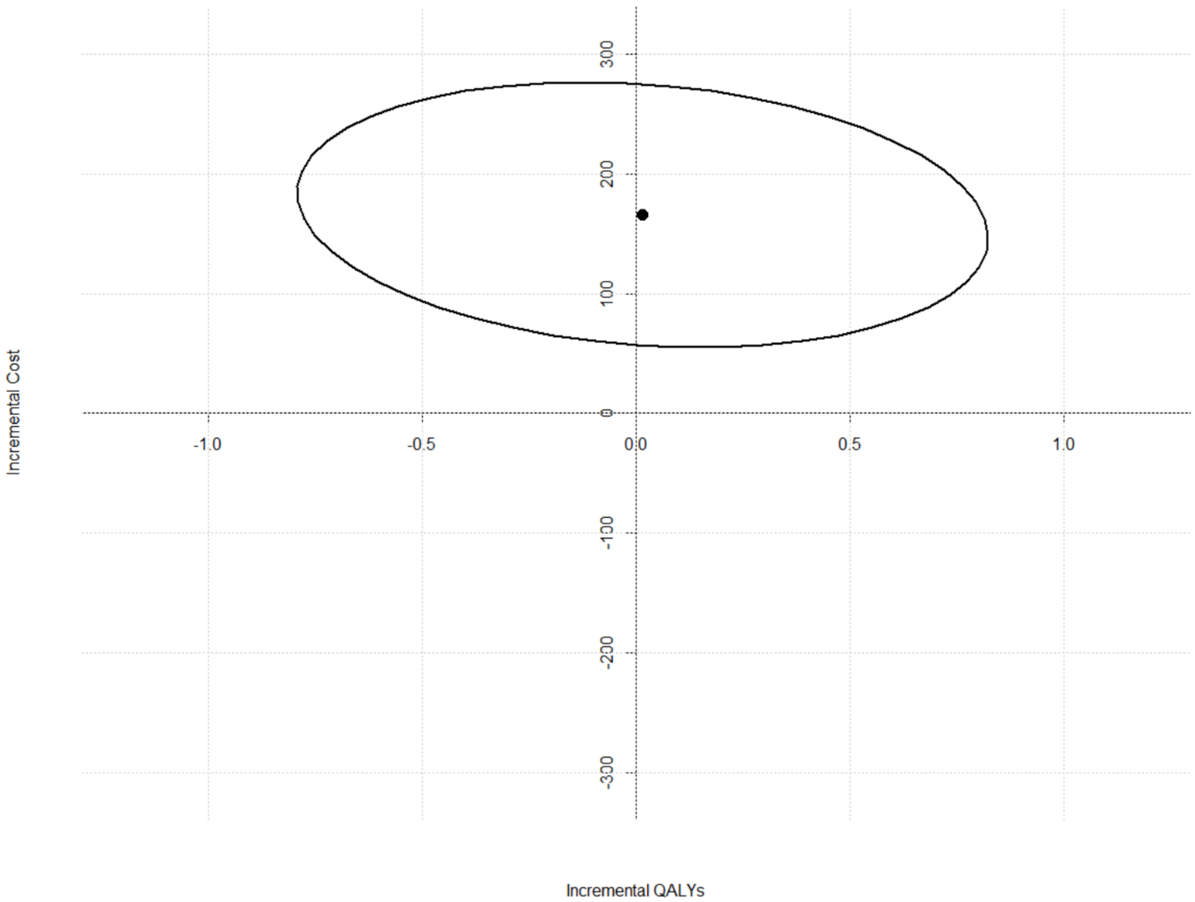


Figure 2b: Expected net benefit +/- 95% credibility interval, threshold = £30,000 per QALY



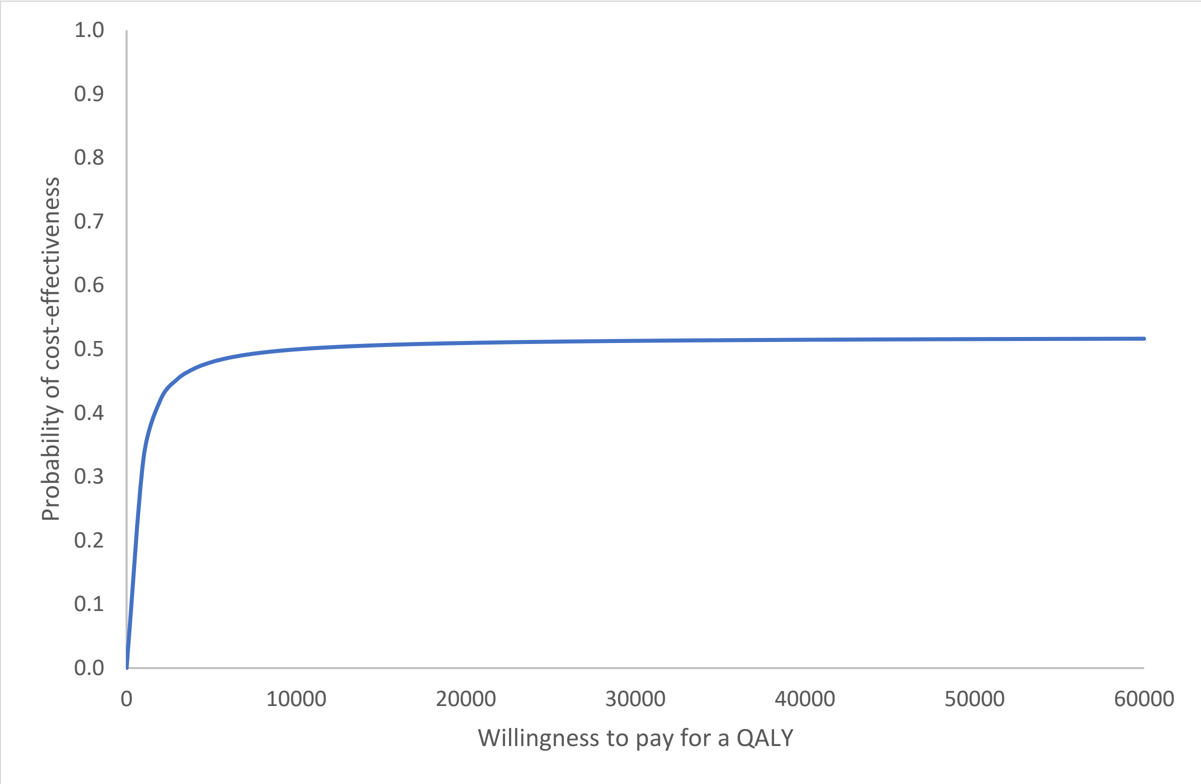
Policies are ranked in order of intensity: 0=status quo, 1=One-off exam, 2-6: enrolment in monitoring programme with examination every 5-1 years respectively. Expected net benefit and 95% credibility intervals are shown for each policy for each of 7 example risk scores. The option with the highest expected net benefit at each risk score is identified in red. For example, given a willingness to pay of £30,000 per QALY, the most cost-effective strategy for those with a risk score of 20 is a one-off FBSE, whilst those with a risk score of 30 should be enrolled in a monitoring programme with 3-yearly recall.

Figure 3: 95% credibility ellipse



Central locus is the expected incremental cost and QALYs gained per person enrolled into the 'compound' strategy in the UK. Uncertainty in the point estimates is illustrated with the 95% credibility ellipse. It is almost certain that the strategy will be cost increasing, but there is a great deal of uncertainty as to whether it will yield a health benefit.

Figure 4: Cost Effectiveness Acceptability Curve of Compound Risk-stratified policy vs Status Quo



Appendix 1: The Williams Self-Assessment Tool

Box A1.1 Questions in the electronic self-assessed questionnaire

Severe sunburns

- As a child between the ages of 2 and 10, how many sunburns did you have that were so severe they produced blisters or pain lasting two or more days? (none, 1-4, 5-9, 10 or more)
- As a child between the ages of 11 and 18, how many sunburns did you have that were so severe they produced blisters or pain lasting two or more days? (none, 1-4, 5-9, 10 or more)

Natural hair colour at age 15

- What was your natural hair colour at age 15? (red, blond, light brown, dark brown, black)

Freckles

- Before the age of 20, which of the following best describes how many freckles you hand on your arms? Freckles are different from moles, usually found on the face and shoulders and more common in children and those with red hair and fair skin. They fade in the winter months and are more numerous in individuals living closer to the equator. (none, few, several, a lot)

Moles on the arms

- Look at the skin on your left arm. To do this you may need to remove a sweater or roll up your sleeves. Starting with your shoulder and moving down to the wrist, please look at the moles on your left arm. Of those moles, I would like you to determine how many are raised. A raised mole is a brown or black spot or beauty mark, which may be large or small, which you can feel with your fingertips. Now run your fingertips over your left arm, and count any raised moles. Now do the same for your right arm. (none, 1, 2, 3 or more

Prior non-melanoma skin cancer

- Have you ever been told by a doctor that you have skin cancer other than melanoma? If yes, what type of skin cancer have you had? Squamous cell cancer (yes or no); basal cell (also known as rodent ulcer) (yes or no); melanoma (yes or no); other skin cancer (yes or no)

Box A1.2: Williams *et al.* (2011)[12] melanoma risk score calculation (range 0-67)

Risk factor	Points			
Sex	Female	Male		
	0	7		
Age in years	35-44	45-54	55-64	65-74
	0	5	8	11
Number of severe sunburns ages 2-18	None	1-4	5-9	10 or more
	0	1	4	7
Natural hair colour at age 15	Dark brown/black	Light brown	Blond	Red
	0	4	5	8
Density of freckles on arms before age 20	None	A few	Several	A lot
	0	4	6	10
Number of raised moles on both arms	None	1	2	3 or more
	0	3	5	11
Prior non-melanoma skin cancer	No	Yes		
	0	13		

Appendix 2: Literature Review

A review of the literature was conducted to estimate the prevalence of undiagnosed melanoma in the community. The only study type able to provide an estimate (and hence inclusion criterion) is a population level screening programme.

We conducted a review (September 2017) of PubMed with the search terms “population prevalence melanoma screen”, limited to studies published 2007-2017. This identified 164 potentially relevant articles. Review by title yielded 7 studies. Review of abstract yielded one relevant study.[18] This was a population screening study in Germany.

Appendix 3: Calculation of annual incidence and prevalence of melanoma as a function of Williams Self-Assessment Risk Score

Data on age and gender specific incidence of malignant melanoma[19] were weighted according to UK population statistics[50] and re-categorised into age bands to match the risk score calculations (Table A3.1).[12]

Table A3.1: Incidence of melanoma (per 100,000 per year)

	Male	Female
<45	6.76	12.24
45-54	30.17	38.81
55-64	53.05	48.90
65+	110.72	74.06

Data from the Melatools Q study,[24] a cross-sectional study of 4040 members of the UK general population were combined with this to generate an annual probability of developing melanoma as a function of risk score. Within each age/gender group, the odds ratio of melanoma was calculated as the sum of the log-odds-ratios for the scores on all questions except age and gender (e.g. as per Tables A3.2 – A3.4). For example, the male in the first row of the sample data (risk score 24) has an odds ratio that is 10.07 times the lifetime odds of the lowest risk group (female, 35-44yo, no history of adolescent sunburn, dark brown/black hair, no freckles, no moles, no history of non-melanoma skin cancer), but 5.10 times the lifetime odds of the lowest risk within his age/gender group (male, 35-44yo, no history of adolescent sunburn, dark brown/black hair, no freckles, no moles, no history of non-melanoma skin cancer).

Table A3.2: Example Melatools-Q raw data

gender_desc	age_desc	gender	age	hair	moles	freckles	sunburns	hx_scc
Male	<45	1	1	2	2	4	1	2
Male	<45	1	1	2	1	1	2	2
Male	<45	1	1	3	1	3	1	2
Male	<45	1	1	2	1	1	1	2
Male	<45	1	1	2	1	2	2	2

Table A3.3: Associated Williams risk score

gender_desc	age_desc	gender	age	hair	moles	freckles	sunburns	hx_scc	Total
Male	<45	7	0	4	3	10	0	0	24
Male	<45	7	0	4	0	0	1	0	12
Male	<45	7	0	5	0	6	0	0	18
Male	<45	7	0	4	0	0	0	0	11
Male	<45	7	0	4	0	4	1	0	16

Table A3.4: Associated log-ORs

									Vs lowest possible risk		Vs lowest risk within age/gender group	
gender_desc	age_desc	gender	age	hair	moles	freckles	sunburns	hx_scc	Ln(OR)	OR	Ln(OR)	OR
Male	<45	0.68	0	0.39	0.25	0.99	0	0	2.31	10.07	1.63	5.10
Male	<45	0.68	0	0.39	0	0	0.09	0	1.16	3.19	0.48	1.62
Male	<45	0.68	0	0.45	0	0.63	0	0	1.76	5.81	1.08	2.94
Male	<45	0.68	0	0.39	0	0	0	0	1.07	2.92	0.39	1.48
Male	<45	0.68	0	0.39	0	0.44	0.09	0	1.6	4.95	0.92	2.51

Given the annual incidence of melanoma in each age/gender group, and the distribution of risk amongst that age group, it is possible to calculate the annual incidence by risk score. This is because the weighted sum of the odds ratios for all individuals relative to the lowest risk, divided by the odds of melanoma for that lowest risk individual equals the odds for the group as a whole (equation A3.1). Rearranging the formula, the odds of the lowest risk individual is equal to the sum of the odds ratios divided by the mean odds for the group (equation A3.2). The calculation with the five sample observations is shown in Table A3.4.

Equation A3.1

$$\frac{\sum_i w_i OR_i}{O_l} = \bar{O}$$

Equation A3.2

$$O_l = \frac{\sum_i w_i OR_i}{\bar{O}}$$

Table A3.5:

gender_desc	age_desc	OR	w_i	OR/n
Male	<45	5.10	0.2	0.012
Male	<45	1.62	0.2	0.0039
Male	<45	2.94	0.2	0.0070
Male	<45	1.48	0.2	0.0035
Male	<45	2.51	0.2	0.0060
	$\bar{O}$:	2.73	$\sum_i w_i OR_i$:	0.0324
			$\frac{\sum_i w_i OR_i}{\bar{O}}$:	0.0119

The odds of melanoma in <45yo males (Table A3.1) = P/(1-P) = 0.000068/(1+0.000068) = 0.000068
Odds of melanoma in lowest risk members of group = Odds * 0.0119 = 0.000068 + 0.0119 = 0.000000809

This means that a 35-44yo male with no history of adolescent sunburn, dark brown/black hair, no freckles, no moles, no history of non-melanoma skin cancer (equating to a Williams risk score of 7) has an odds of 0.000000809 of melanoma per annum. The log-odds is -14.027.

We know the odds ratio of melanoma for every individual relative to someone with a risk score of 7, so it is simply a matter of calculating the probabilities from the odds ratios (Table A3.6).

Table A3.6

gender_desc	age_desc	Williams Score	OR	Ln(OR)	Ln(Odds|score=7)	Ln(OR)+ Ln(Odds|score=7)	Odds	Probability
Male	<45	24	5.10	1.629	-14.027	-12.398	0.00000412	0.000412%
Male	<45	12	1.62	0.482	-14.027	-13.545	0.00000131	0.000131%
Male	<45	18	2.94	1.078	-14.027	-12.949	0.00000238	0.000238%
Male	<45	11	1.48	0.392	-14.027	-13.635	0.00000120	0.000120%
Male	<45	16	2.51	0.920	-14.027	-13.107	0.00000203	0.000203%

The probability of melanoma in lowest risk members of group (i.e. risk score 7) = O/(1+O) = 0.000000809/(1+0.000000809) = 0.000000809 = 0.0000809%. Note the probabilities in this example are artificially small due to only including 5 observations.

This was repeated for all age/gender groups in the MelatoolsQ data, and included participants with a range of risk scores between 0 and 49 (out of a theoretical maximum score of 67). The mean probability by risk score was calculated and a log-linear model fit to the data. This was repeated 50,000 times in a Monte Carlo simulation, each time sampling from the distributions of coefficients on the Williams OR model (see Table 2, Williams et al. 2011[12]). The coefficients of the log-linear model were recorded each iteration, and the mean and standard deviation of these samples interpreted as the mean and standard error of the coefficients. This yielded the parameters reported in Figure 1 (repeated here):

$P(incident\ melanoma\ per\ annum) = e^{(\alpha+\beta W)}$
$\alpha \sim N(-10.270{,}0.186)$
$\beta \sim N(0.117, 0.008)$
W = Williams risk score.

Calculating Relative Risks

Expected relative risk between two scores is estimated by calculating the ratio between the equation evaluated at two points. For example, the expected incidence for a person with zero risk score = $e^{(-10.270+0)} = 0.000035$. The expected incidence for a person with risk score 16 is $e^{(-10.270+0.117*16)} = 0.000225$. The relative risk of a person with score 16 vs 0 is $\frac{0.000225}{0.000035} = 6.4$.

Appendix 4: Calculation of transition probabilities in undetected and hence untreated melanoma

Data from the expert elicitation exercise[20] are in the form of parameters for a series of scaled-beta distributed 'Z' parameters. The relevant probabilities of these are estimated as products of the Z's. This ensures correlations between the probabilities are preserved and that they sum to 1. Note that for the purpose of the model risk of death was factored out of these distributions as mortality is calculated separately.

For example, the Z parameters for the probability of moving from in situ LM to any other stage thought possible by the experts (in this case 6 other states) are reported as per Table A4.1. Note the reported medians in Table A4.1 do not sum to 1 as they represent an aggregate of individual expert beliefs. However, each sampled set of probabilities does, by definition, sum to 1. The ordering of the Z parameters must be preserved correctly calculate the probabilities.

Table A4.1: Z parameters for modified CM distribution to sample transition probabilities from IS LM to IS LM, 1B, 1A, 2A, 2B and death

From > To	a	B	L	U	LL	MED	UL
IS LM > IS LM	0.167	0.102	0.023	0.999	0.02	0.92	1.00
IS LM > 1A	9.624	2.133	0.073	0.956	0.00	0.06	0.88
IS LM > 1B	9.885	9.988	0.039	0.604	0.00	0.00	0.11
IS LM > 2A	2.412	9.960	0.101	0.994	0.00	0.00	0.07
IS LM > 2B	9.964	3.223	0.019	0.665	0.00	0.00	0.09
IS LM > 2C	9.810	9.970	0.649	0.964	0.00	0.00	0.07
IS LM > 3A	n/a	n/a	n/a	n/a	0.00	0.00	0.02

LL = lower 95% Credibility limit; MED = median; UL = upper 95% credibility limit

We sampled from a modified CM distribution[20] with 6 Z-parameters (where the number of Z-parameters is number of dimensions – 1).

Thus:

Z_1 ~ ScaledBeta (0.167, 0.102, 0.023,0.999)
Z_2 ~ ScaledBeta (9.624, 2.133, 0.073, 0.956)
Z_3 ~ ScaledBeta (9.885, 9.988, 0.039, 0.604)
Z_4 ~ ScaledBeta (2.412, 9.960, 0.101, 0.994)
Z_5 ~ ScaledBeta (9.964, 3.223, 0.019, 0.665)
Z_6 ~ ScaledBeta (9.810, 9.970, 0.649, 0.964)

And:

$P_1 = P(\text{IS LM > IS LM}) = Z_1$
$P_2 = P(\text{IS LM > 1A}) = Z_2(1-Z_1)$
$P_3 = P(\text{IS LM > 1B}) = Z_3(1-Z_2)(1-Z_1)$
$P_4 = P(\text{IS LM > 2A}) = Z_4(1-Z_3)(1-Z_2)(1-Z_1)$
$P_5 = P(\text{IS LM > 2B}) = Z_5(1-Z_4)(1-Z_3)(1-Z_2)(1-Z_1)$
$P_6 = P(\text{IS LM > 2C}) = Z_6(1-Z_5)(1-Z_4)(1-Z_3)(1-Z_2)(1-Z_1)$
$P_7 = P(\text{IS LM > 3A}) = (1-Z_6)(1-Z_5)(1-Z_4)(1-Z_3)(1-Z_2)(1-Z_1)$

Where P_1 is the probability of remaining in ISLM, P_2 is the probability of progressing to 1A etc.

The simplest approach to calculating the marginal probability distributions is to sample a large number of sets of probabilities and calculate the empirical median, lower and upper 95% credibility limits as shown in Table A4.2. The estimated medians and 95% credibility intervals match the elicited values in Table A4.1, suggesting the sampling has worked.

Table A4.2: Z parameters for modified CM distribution to sample transition probabilities from IS LM to IS LM, 1B, 1A, 2A, and 2B, and estimated mean, median and 95%CrI(6m probabilities)

	Z hyper-parameters				Associated probabilities	
From > To	a	b	L	U	median	95% CrI
IS LM > IS LM	0.167	0.102	0.023	0.999	0.92	(0.02, 1.00)
IS LM > 1A	9.624	2.133	0.073	0.956	0.06	(0.00, 0.88)
IS LM > 1B	9.885	9.988	0.039	0.604	0.00	(0.00, 0.11)
IS LM > 2A	2.412	9.960	0.101	0.994	0.00	(0.00, 0.07)
IS LM > 2B	9.964	3.223	0.019	0.665	0.00	(0.00, 0.09)
IS LM > 2C	9.810	9.970	0.649	0.964	0.00	(0.00, 0.07)
IS LM > 3A	n/a	n/a	n/a	n/a	0.00	(0.00, 0.02)

These represent the elicited transition probabilities over six months. The transition period in the model is 12 months therefore to adjust to 12 month transitions, the following edit was made:

12m probability of remaining in the same state, e.g. $P(ISLN>ISLM)_{12} = P(ISLM > ISLM)_6$^2

12m probability of moving to another state

eg $P(ISLM>1B)_{12} = P(ISLM>1B)_6 + (P(ISLM > ISLM)_6 * P(ISLM>1B)_6)$

where subscript 6 = 6 month probability; 12 = 12 month probability. Resulting probabilities are in table A4.3.

Table A4.3: Z parameters for modified CM distribution to sample transition probabilities from IS LM to IS LM, 1B, 1A, 2A, and 2B, and estimated mean, median and 95%CrI over 12m

	Z-hyper-parameters				Associated probabilities (12m)		
From > To	a	b	L	U	mean	median	95% CrI
IS LM > IS LM	0.167	0.102	0.023	0.999	0.637	0.674	(0.123, 0.985)
IS LM > 1A	9.624	2.133	0.073	0.956	0.103	0.092	(0.004, 0.249)
IS LM > 1B	9.885	9.988	0.039	0.604	0.150	0.104	(0.002, 0.515)
IS LM > 2A	2.412	9.960	0.101	0.994	0.072	0.040	(0.000, 0.298)
IS LM > 2B	9.964	3.223	0.019	0.665	0.038	0.021	(0.000, 0.157)
IS LM > 2B	9.810	9.970	0.649	0.964	0.038	0.021	(0.000, 0.157)
IS LM > 2B	n/a	n/a	n/a	n/a	0.038	0.021	(0.000, 0.157)

Appendix 5: UK specific Lifetables

Source: ONS, Life tables for UK, 2012-14[25]

Age	Male	Female	Age	Male	Female	Age	Male	Female
0	0.004352	0.00357	34	0.000924	0.000538	68	0.016131	0.010748
1	0.00033	0.000257	35	0.001016	0.000564	69	0.01797	0.011719
2	0.000177	0.00013	36	0.001047	0.0006	70	0.019796	0.013122
3	0.000116	0.000114	37	0.001176	0.000635	71	0.022073	0.014429
4	0.000098	0.000087	38	0.001355	0.000732	72	0.025273	0.016475
5	0.000098	0.000087	39	0.00142	0.000822	73	0.027243	0.018281
6	0.000093	0.000081	40	0.001576	0.000883	74	0.029995	0.020211
7	0.00009	0.000079	41	0.001626	0.000957	75	0.033205	0.022532
8	0.000083	0.000069	42	0.00169	0.001058	76	0.036573	0.025116
9	0.00009	0.000066	43	0.001882	0.001156	77	0.040211	0.028226
10	0.000095	0.000075	44	0.002062	0.00127	78	0.045461	0.031273
11	0.000094	0.000065	45	0.002248	0.001382	79	0.049611	0.035843
12	0.000109	0.000066	46	0.00236	0.001446	80	0.056322	0.040816
13	0.000115	0.000093	47	0.002502	0.001622	81	0.06328	0.045772
14	0.000131	0.000106	48	0.002677	0.00171	82	0.071519	0.051697
15	0.000147	0.000128	49	0.00294	0.001924	83	0.079828	0.058965
16	0.000215	0.000143	50	0.003101	0.002156	84	0.089056	0.067661
17	0.000308	0.00016	51	0.003423	0.002344	85	0.100248	0.076098
18	0.000443	0.000183	52	0.003702	0.002558	86	0.111772	0.085623
19	0.000477	0.000198	53	0.004067	0.00278	87	0.123954	0.096404
20	0.000467	0.000202	54	0.004528	0.002977	88	0.137712	0.106974
21	0.000473	0.000207	55	0.004865	0.003402	89	0.152512	0.122022
22	0.000468	0.000214	56	0.005353	0.003674	90	0.166455	0.136144
23	0.000555	0.000232	57	0.005962	0.004033	91	0.182981	0.151001
24	0.000521	0.000227	58	0.006607	0.004385	92	0.208161	0.171558
25	0.000559	0.000255	59	0.007416	0.004772	93	0.222733	0.185224
26	0.000641	0.000259	60	0.008002	0.005226	94	0.231918	0.2023
27	0.00062	0.000274	61	0.008809	0.005808	95	0.259055	0.219153
28	0.000627	0.000343	62	0.009679	0.006283	96	0.286001	0.251076
29	0.000709	0.000321	63	0.01034	0.006755	97	0.308416	0.2675
30	0.000755	0.00037	64	0.011306	0.007356	98	0.33083	0.289642
31	0.000793	0.000422	65	0.012111	0.007936	99	0.347717	0.315701
32	0.000796	0.000424	66	0.013191	0.008579	100	0.35592	0.329873
33	0.000875	0.000469	67	0.014606	0.009639			

Appendix 6: Odds Ratio of survival as a function of disease stage at diagnosis

Five year survival data were extracted from Figure 1, panels B&D, and Figure 2, panel A of Balch et al.[22] The odds ratio of all stages vs 1A was then calculated, as well as the log-OR and standard error of log-OR. We assumed that stage 1A disease has no impact on overall survival,[51] then the annual probability of death is calculated as the age/gender baseline rate for the general population, adjusted for the odds ratio. This is calculated by converting the probability into odds, summing the log-odds and the log-odds-ratio, exponentiating and converting back into a probability.

For example, the baseline probability of death for a 40-year-old male is 0.1576%, whereas the probability of death for a 40-year-old male with stage 3A melanoma is 2.23% (Table A6.2).

Table A6.1: Relative Odds of death as a function of disease stage

	5yr survival p	dead	alive	sum	Odds of death	OR vs 1A	Ln(OR)	SE(Ln(OR))
1A	0.98	189	9263	9452	0.020	1		
1B	0.92	713	8205	8918	0.087	4.261	1.449	0.007
2A	0.8	929	3715	4644	0.250	12.250	2.506	0.007
2B	0.7	968	2260	3228	0.429	21.000	3.045	0.007
2C	0.54	643	754	1397	0.852	41.741	3.731	0.008
3A	0.78	263	933	1196	0.282	13.821	2.626	0.010
3B	0.6	556	835	1391	0.667	32.667	3.486	0.008
3C	0.42	418	302	720	1.381	67.667	4.215	0.011
4	0.136	6890	1082	7972	6.369	312.104	5.743	0.006

Table A6.2: Calculating probability of death for a 40-year-old male with stage 3A melanoma

Operation	Equation	Calculation
Convert to odds	$O = \frac{P}{(1-P)}$	$\frac{0.001576}{(1-0.001576)} = 0.00158$
Take the natural log	$\ln(O)$	$\ln(0.00158) = -6.451$
Sum the log OR	$\ln(O) + \ln(OR)$	-6.451 + 2.626 = -3.825
Exponentiate	$e^{\ln(O)+\ln(OR)}$	$e^{-3.808} = 0.022$
Convert to probability	$P = \frac{O}{(1+O)}$	$\frac{0.022}{(1-0.022)} = 0.0223$

Appendix 7: Opportunistic presentation rate

The opportunistic presentation rate was determined as follows. In 2013 there were 14509 cases of melanoma diagnosed.[1] An estimated 12% of cases referred to secondary care are melanoma.[27] This implies that there were approximately 120908 referrals in the UK (=14509*0.12). An estimated 26% of patients presenting in primary care are referred to secondary care,[26] suggesting 465031 patients presented in primary care. The UK population in 2013 was estimated at 64,105,654.[23] Therefore 0.725% of the population presented in primary care with a mole they were concerned about.

Nr melanoma cases 2013		14509	Cancer Research UK[1]
% of referred cases that are melanoma	12%		Cox et al. 2004[27]
Inferred number of referrals		120908	
% patients presenting in primary care referred to secondary	26%		Molemate data – per patient (not lesion) basis.[26]
Inferred number of patients presenting in primary care		465031	
UK population in 2013		64105654	Office for National Statistics[23]
% of population presenting in primary care		0.725%	

Appendix 8: Costs of treatment by disease stage and costs in final year of life.

Treatment costs are based on 2010 UK guidelines,[31] and are calculated using the same approach the authors used in a previous study.[14] The text and table A8.1 below are based on Wilson et al.[14] with updated unit costs.

Patients who undergo any intervention in secondary care firstly undergo biopsy excision (at which point the disease is staged according to AJCC guidelines[22]), followed by definitive surgery. Patients with stage 0, Ia and Ib disease undergo no further treatment. Patients with stage IIa and higher disease undergo sentinel lymph node biopsy, and patients with stage IIb and higher disease also undergo chest x-ray, CT scan, liver function test and full blood count. Patients with a positive sentinel node biopsy undergo follow-up surgery for lymph node involvement, comprising pre-operative CT scan and radical lymph node basin dissection. Patients with stage IV disease undergo surgery for removal of localised metastases, a course of 10 fractions of radiotherapy and 6 cycles of dacarbazine-based chemotherapy.

Follow-up

It is recommended that patients with in-situ (Stage 0) disease have only 1 follow-up appointment. Patients with stage I disease should be followed up every three months for three years before discharge (total 12 visits), and patients with stage II followed up as per stage I, followed by twice-yearly checks for a further two years (total 16 visits).[31] For ease of modelling, the discounted cost of all these visits was added to the first year cost.

Terminal care costs

In the model, patients with stage 0 or Ia disease have a normal lifespan. Therefore, it is assumed they do not die as a result of their disease. Patients with stage Ib disease and above have a reduced life expectancy and are therefore assumed to die as a result of their disease. Previous studies of lifetime melanoma-related costs of melanoma patients show peaks in resource consumption at initial treatment and terminal phase for all patients, irrespective of stage at diagnosis.[52] Therefore the costs in the final year of life for patients with Ib disease and above are assumed to be the same as for the treatment of metastatic disease (surgical removal of localised metastases, radiotherapy and chemotherapy).

Table A8.1 - Treatment and terminal care costs (means)

	unit cost	0	1a	1b	2a	2b	2c	3a	3b	3c	4
Initial treatment											
Biopsy excision	£143.00	1	1	1	1	1	1	1	1	1	1
Definitive surgery	£156.00	1	1	1	1	1	1	1	1	1	1
Investigations											
CXR	£30.00					1	1	1	1	1	1
CT scan	£132.00					1	1	1	1	1	1
Liver function test	£3.00					1	1	1	1	1	1
FBC	£3.00					1	1	1	1	1	1
Sentinel node biopsy (carried out at same time as definitive surgery)	£29.00				1	1	1	1	1	1	1
Follow-up surgery for positive lymph nodes											
pre-operative CT scan	£132.00							1	1	1	
radical lymph node dissection	£991.00							1	1	1	
Metastatic disease											
Surgical removal of localised metastases	£725.00										1
Radiotherapy	£2,055.00										1
Chemotherapy (dacarbazine)	£1,485.00										1
Follow-up											
single follow-up	£97.00	1									
3 monthly for 3 years then discharge = 12 visits	£1,164.00		1	1							
3 monthly for 3 yrs then 2 yrly for 2 yrs = 16 visits	£1,552.00				1	1	1	1	1	1	1
Terminal care											
Assume same as metastatic disease	£4,265.00			1	1	1	1	1	1	1	1
Year 1 cost		£396.00	£1,463.00	£1,463.00	£1,880.00	£2,048.00	£2,048.00	£3,171.00	£3,171.00	£3,171.00	£4,761.00
Terminal year cost		£0.00	£0.00	£4,265.00	£4,265.00	£4,265.00	£4,265.00	£4,265.00	£4,265.00	£4,265.00	£4,265.00

Appendix 9: Model Stability

Stability of the model was determined by calculating the coefficient of variation (CoV) of estimates of the expected cost and QALYs and standard error of mean cost and QALYs from 50 repeated iterations, using different numbers of simulations and cohort sizes for one of the modelled scenarios. For example, the model was set to simulate the 'do nothing' scenario in a cohort of 1000 patients, 10 times and the expected and SE cost and QALYs recorded. This was repeated 50 times and the CoV for mean cost was 3.44%, for the standard error of cost 24.12%, for mean QALYs 0.11% and SE of QALYs, 25.97%.

A 'rule of thumb' of a CoV of around 2% or below was considered sufficiently stable. The CoV was much more sensitive to the number of simulations rather than the cohort size (Table A9.1). 1000 simulations of a 1000-patient cohort provided sufficient stability whilst not consuming excessive computational time.

Table A9.1: Coefficient of variation of mean cost, SE of mean cost, mean QALYs and SE of mean QALYs from various numbers of simulations and cohort sizes.

	simulations	cohortsize	mean£	SE£	mQALY	SEQALY
1	10	1000	3.44	24.12	0.11	25.97
2	10	1000	3.5	27.66	0.12	22.3
3	10	5000	3.32	21.96	0.05	27.46
4	10	10000	4.21	26.29	0.03	25.03
5	10	25000	3.78	25.52	0.02	26.86
6	20	1000	2.84	16.82	0.09	14.84
7	30	1000	1.97	12.35	0.07	11.98
8	50	1000	1.97	11.56	0.06	12
9	70	1000	1.73	9.66	0.05	8.54
10	90	1000	1.33	8.17	0.04	6.88
11	100	1000	0.99	6.68	0.03	7.9
12	100	2000	1.12	6.96	0.03	5.81
13	250	1000	0.9	5.41	0.02	4.09
14	500	1000	0.63	3.57	0.02	3.06
15	1000	1000	0.39	2.21	0.01	1.93
16	2000	1000	0.27	1.55	0.01	1.35

Appendix 10: Expected Cost, QALYs and Net Benefit of each policy by risk score

The model was calculated at risk scores of 10, 17, 20, 25, 30, 50 and 60, and weighted according the distribution of risk scores in the UK.[24] Interim risk scores were calculated by linear interpolation. Net benefit was calculated at £20,000 and £30,000 per QALY gained. The policy yielding the highest net benefit for each risk score is mathematically identical to the policy with the highest incremental cost-effectiveness ratio below the threshold after taking into account dominated and extended-dominated strategies. The most cost-effective strategy for each risk score is highlighted in bold. Where there is a difference in recommendation at the £20,000 and £30,000 thresholds, both policies are highlighted. This occurs where the incremental cost-effectiveness ratio of the optimal strategy compared with the next best (non-dominated) option is between £20,000 and £30,000, thus would be rejected at the £20,000 threshold but accepted at £30,000.

Table A10.1: Cost, QALYs and net benefit by risk score

							@£20,000 per QALY		@£30,000 per QALY	
Risk	Strategy	Cost	SE(Cost)	QALYs	SE(QALYs)	Cov(£, QALYs)	NB	SE(NB)	NB	SE(NB)
10	**Do nothing**	**£21.22**	**£5.14**	**17.532**	**0.287**	**-0.295**	**£350,613.37**	**£1,810.58**	**£525,930.66**	**£2,715.68**
	One off exam	£147.57	£18.30	17.533	0.286	-0.282	£350,512.07	£1,768.01	£525,841.90	£2,651.87
	monitor every 5 years	£407.19	£50.43	17.536	0.284	0.900	£350,315.39	£1,819.50	£525,676.68	£2,729.20
	monitor every 4 years	£494.19	£61.40	17.537	0.283	1.344	£350,241.18	£1,788.23	£525,608.86	£2,682.01
	monitor every 3 years	£658.61	£81.84	17.539	0.284	1.986	£350,120.79	£1,803.34	£525,510.49	£2,704.73
	monitor every 2 years	£930.45	£115.67	17.538	0.283	2.781	£349,832.12	£1,798.58	£525,213.40	£2,696.66
	Annual monitor	£2,206.62	£276.04	17.537	0.286	9.029	£348,537.01	£1,801.90	£523,908.83	£2,688.90
11	**Do nothing**	**£21.88**	**£5.45**	**17.530**	**0.259**	**-0.265**	**£350,580.93**	**£1,810.73**	**£525,882.34**	**£2,715.87**
	One off exam	£147.94	£18.30	17.532	0.258	-0.247	£350,492.65	£1,774.47	£525,812.94	£2,661.54
	monitor every 5 years	£406.93	£50.15	17.535	0.256	0.775	£350,299.28	£1,816.34	£525,652.39	£2,724.40
	monitor every 4 years	£493.70	£61.04	17.536	0.255	1.159	£350,226.46	£1,790.82	£525,586.54	£2,685.86
	monitor every 3 years	£657.71	£81.33	17.538	0.257	1.727	£350,105.50	£1,801.84	£525,487.10	£2,702.45
	monitor every 2 years	£928.86	£114.98	17.537	0.256	2.414	£349,818.25	£1,801.05	£525,191.81	£2,700.32
	Annual monitor	£2,201.75	£274.27	17.537	0.259	7.866	£348,538.31	£1,807.89	£523,908.33	£2,698.33
12	**Do nothing**	**£22.54**	**£5.76**	**17.529**	**0.231**	**-0.234**	**£350,548.50**	**£1,810.88**	**£525,834.02**	**£2,716.06**
	One off exam	£148.30	£18.30	17.531	0.230	-0.212	£350,473.23	£1,780.93	£525,783.99	£2,671.21
	monitor every 5 years	£406.68	£49.87	17.534	0.229	0.651	£350,283.17	£1,813.17	£525,628.09	£2,719.61
	monitor every 4 years	£493.20	£60.68	17.535	0.228	0.973	£350,211.75	£1,793.41	£525,564.22	£2,689.72
	monitor every 3 years	£656.81	£80.82	17.537	0.229	1.468	£350,090.21	£1,800.34	£525,463.71	£2,700.17
	monitor every 2 years	£927.26	£114.30	17.537	0.228	2.048	£349,804.39	£1,803.53	£525,170.21	£2,703.97
	Annual monitor	£2,196.87	£272.49	17.537	0.231	6.703	£348,539.60	£1,813.89	£523,907.84	£2,707.76
13	**Do nothing**	**£23.20**	**£6.08**	**17.527**	**0.203**	**-0.204**	**£350,516.06**	**£1,811.04**	**£525,785.69**	**£2,716.25**
	One off exam	£148.66	£18.30	17.530	0.202	-0.177	£350,453.81	£1,787.38	£525,755.04	£2,680.88
	monitor every 5 years	£406.43	£49.59	17.534	0.201	0.527	£350,267.05	£1,810.01	£525,603.79	£2,714.82
	monitor every 4 years	£492.70	£60.32	17.534	0.200	0.787	£350,197.03	£1,796.00	£525,541.90	£2,693.58
	monitor every 3 years	£655.90	£80.31	17.537	0.201	1.209	£350,074.92	£1,798.84	£525,440.33	£2,697.90
	monitor every 2 years	£925.66	£113.62	17.536	0.201	1.681	£349,790.52	£1,806.01	£525,148.61	£2,707.62
	Annual monitor	£2,191.99	£270.72	17.537	0.203	5.540	£348,540.90	£1,819.89	£523,907.35	£2,717.19
14	**Do nothing**	**£23.86**	**£6.39**	**17.525**	**0.175**	**-0.173**	**£350,483.63**	**£1,811.19**	**£525,737.37**	**£2,716.44**
	One off exam	£149.02	£18.30	17.529	0.174	-0.141	£350,434.38	£1,793.84	£525,726.09	£2,690.55
	monitor every 5 years	£406.17	£49.32	17.533	0.173	0.402	£350,250.94	£1,806.85	£525,579.49	£2,710.03

	monitor every 4 years	£492.20	£59.95	17.534	0.173	0.601	£350,182.32	£1,798.59	£525,519.58	£2,697.43
	monitor every 3 years	£655.00	£79.80	17.536	0.173	0.950	£350,059.62	£1,797.33	£525,416.94	£2,695.62
	monitor every 2 years	£924.06	£112.93	17.535	0.173	1.315	£349,776.66	£1,808.48	£525,127.02	£2,711.27
	Annual monitor	£2,187.12	£268.95	17.536	0.175	4.377	£348,542.20	£1,825.88	£523,906.85	£2,726.61
15	**Do nothing**	**£24.52**	**£6.70**	**17.524**	**0.147**	**-0.142**	**£350,451.19**	**£1,811.35**	£525,689.05	£2,716.64
	One off exam	**£149.39**	**£18.29**	**17.528**	**0.146**	**-0.106**	£350,414.96	£1,800.30	**£525,697.13**	**£2,700.21**
	monitor every 5 years	£405.92	£49.04	17.532	0.145	0.278	£350,234.82	£1,803.69	£525,555.20	£2,705.24
	monitor every 4 years	£491.70	£59.59	17.533	0.145	0.416	£350,167.61	£1,801.19	£525,497.26	£2,701.29
	monitor every 3 years	£654.10	£79.29	17.535	0.145	0.691	£350,044.33	£1,795.83	£525,393.55	£2,693.34
	monitor every 2 years	£922.46	£112.25	17.534	0.146	0.948	£349,762.79	£1,810.96	£525,105.42	£2,714.92
	Annual monitor	£2,182.24	£267.18	17.536	0.147	3.214	£348,543.49	£1,831.88	£523,906.36	£2,736.04
16	**Do nothing**	**£25.18**	**£7.02**	**17.522**	**0.119**	**-0.112**	**£350,418.76**	**£1,811.50**	£525,640.72	£2,716.83
	One off exam	**£149.75**	**£18.29**	**17.527**	**0.118**	**-0.071**	£350,395.54	£1,806.76	**£525,668.18**	**£2,709.88**
	monitor every 5 years	£405.67	£48.76	17.531	0.118	0.153	£350,218.71	£1,800.52	£525,530.90	£2,700.45
	monitor every 4 years	£491.20	£59.23	17.532	0.118	0.230	£350,152.89	£1,803.78	£525,474.94	£2,705.14
	monitor every 3 years	£653.20	£78.78	17.534	0.117	0.432	£350,029.04	£1,794.33	£525,370.16	£2,691.06
	monitor every 2 years	£920.86	£111.56	17.533	0.118	0.581	£349,748.93	£1,813.44	£525,083.83	£2,718.58
	Annual monitor	£2,177.36	£265.40	17.536	0.120	2.051	£348,544.79	£1,837.87	£523,905.87	£2,745.47
17	**Do nothing**	**£25.84**	**£7.33**	**17.521**	**0.091**	**-0.081**	**£350,386.32**	**£1,811.65**	£525,592.40	£2,717.02
	One off exam	**£150.11**	**£18.29**	**17.526**	**0.091**	**-0.036**	£350,376.11	£1,813.22	**£525,639.23**	**£2,719.55**
	monitor every 5 years	£405.42	£48.48	17.530	0.090	0.029	£350,202.60	£1,797.36	£525,506.60	£2,695.65
	monitor every 4 years	£490.70	£58.86	17.531	0.090	0.044	£350,138.18	£1,806.37	£525,452.61	£2,709.00
	monitor every 3 years	£652.30	£78.27	17.533	0.090	0.173	£350,013.75	£1,792.83	£525,346.77	£2,688.79
	monitor every 2 years	£919.26	£110.88	17.533	0.091	0.215	£349,735.07	£1,815.91	£525,062.23	£2,722.23
	Annual monitor	£2,172.48	£263.63	17.536	0.092	0.888	£348,546.09	£1,843.87	£523,905.37	£2,754.90
18	**Do nothing**	**£26.95**	**£7.76**	**17.518**	**0.091**	**-0.096**	**£350,337.06**	**£1,818.49**	£525,519.06	£2,727.19
	One off exam	**£151.40**	**£18.57**	**17.524**	**0.091**	**-0.051**	£350,321.72	£1,818.04	**£525,558.29**	**£2,726.70**
	monitor every 5 years	£406.79	£48.86	17.529	0.090	0.034	£350,167.75	£1,798.17	£525,455.02	£2,696.88
	monitor every 4 years	£492.22	£59.29	17.530	0.090	0.042	£350,105.05	£1,804.87	£525,403.69	£2,706.73
	monitor every 3 years	£653.72	£78.83	17.531	0.090	0.181	£349,971.03	£1,796.58	£525,283.40	£2,694.44
	monitor every 2 years	£920.69	£111.50	17.532	0.091	0.142	£349,712.45	£1,817.51	£525,029.01	£2,724.20
	Annual monitor	£2,174.10	£265.02	17.534	0.091	0.870	£348,514.97	£1,832.78	£523,859.50	£2,737.93
19	**Do nothing**	**£28.05**	**£8.19**	**17.516**	**0.091**	**-0.112**	**£350,287.80**	**£1,825.33**	£525,445.73	£2,737.37
	One off exam	**£152.70**	**£18.86**	**17.521**	**0.091**	**-0.066**	£350,267.34	£1,822.86	**£525,477.35**	**£2,733.84**
	monitor every 5 years	£408.17	£49.23	17.527	0.090	0.038	£350,132.90	£1,798.97	£525,403.44	£2,698.11
	monitor every 4 years	£493.74	£59.71	17.528	0.090	0.039	£350,071.93	£1,803.37	£525,354.77	£2,704.45
	monitor every 3 years	£655.13	£79.38	17.529	0.090	0.189	£349,928.31	£1,800.33	£525,220.03	£2,700.09
	monitor every 2 years	£922.11	£112.12	17.531	0.091	0.068	£349,689.83	£1,819.12	£524,995.80	£2,726.17
	Annual monitor	£2,175.71	£266.41	17.533	0.091	0.852	£348,483.84	£1,821.69	£523,813.62	£2,720.96
20	**Do nothing**	**£29.16**	**£8.62**	**17.513**	**0.092**	**-0.127**	**£350,238.55**	**£1,832.17**	£525,372.40	£2,747.55
	One off exam	**£153.99**	**£19.15**	**17.518**	**0.091**	**-0.080**	£350,212.95	£1,827.68	**£525,396.41**	**£2,740.99**
	monitor every 5 years	£409.55	£49.61	17.525	0.090	0.043	£350,098.06	£1,799.78	£525,351.86	£2,699.34
	monitor every 4 years	£495.26	£60.13	17.527	0.090	0.037	£350,038.81	£1,801.87	£525,305.85	£2,702.18
	monitor every 3 years	£656.55	£79.94	17.527	0.090	0.196	£349,885.58	£1,804.08	£525,156.65	£2,705.74
	monitor every 2 years	£923.53	£112.74	17.530	0.091	-0.005	£349,667.21	£1,820.72	£524,962.58	£2,728.14
	Annual monitor	£2,177.32	£267.80	17.532	0.090	0.834	£348,452.72	£1,810.60	£523,767.74	£2,703.98
21	**Do nothing**	**£31.10**	**£9.64**	**17.509**	**0.092**	**-0.173**	**£350,155.98**	**£1,846.72**	£525,249.52	£2,769.12
	One off exam	**£155.81**	**£19.70**	**17.515**	**0.092**	**-0.120**	£350,149.15	£1,834.00	**£525,301.63**	**£2,750.26**

	monitor every 5 years	£411.13	£49.68	17.523	0.090	0.022	£350,049.68	£1,807.69	£525,280.08	£2,711.09
	monitor every 4 years	£496.51	£60.20	17.524	0.090	0.014	£349,991.24	£1,804.58	£525,235.12	£2,706.12
	monitor every 3 years	£657.29	£79.81	17.525	0.090	0.161	£349,840.71	£1,807.88	£525,089.71	£2,711.24
	monitor every 2 years	£923.55	£112.56	17.528	0.091	0.048	£349,637.68	£1,817.49	£524,918.29	£2,723.59
	Annual monitor	£2,173.98	£267.44	17.530	0.090	0.949	£348,427.76	£1,815.89	£523,728.62	£2,712.62
22	Do nothing	£33.05	£10.67	17.505	0.093	-0.219	£350,073.42	£1,861.26	£525,126.65	£2,790.70
	One off exam	**£157.63**	**£20.25**	**17.512**	**0.092**	**-0.160**	**£350,085.36**	**£1,840.32**	£525,206.85	£2,759.52
	monitor every 5 years	**£412.70**	**£49.76**	**17.521**	**0.091**	**0.001**	£350,001.29	£1,815.60	**£525,208.29**	**£2,722.85**
	monitor every 4 years	£497.77	£60.27	17.522	0.090	-0.009	£349,943.67	£1,807.29	£525,164.38	£2,710.06
	monitor every 3 years	£658.02	£79.68	17.523	0.091	0.126	£349,795.84	£1,811.67	£525,022.76	£2,716.74
	monitor every 2 years	£923.56	£112.38	17.527	0.091	0.101	£349,608.14	£1,814.25	£524,873.99	£2,719.04
	Annual monitor	£2,170.64	£267.07	17.529	0.091	1.063	£348,402.79	£1,821.18	£523,689.50	£2,721.25
23	Do nothing	£35.00	£11.70	17.501	0.094	-0.265	£349,990.85	£1,875.81	£525,003.78	£2,812.27
	One off exam	**£159.45**	**£20.79**	**17.509**	**0.092**	**-0.199**	**£350,021.57**	**£1,846.64**	£525,112.07	£2,768.79
	monitor every 5 years	**£414.28**	**£49.83**	**17.518**	**0.091**	**-0.019**	£349,952.91	£1,823.52	**£525,136.50**	**£2,734.60**
	monitor every 4 years	£499.02	£60.34	17.520	0.090	-0.031	£349,896.10	£1,810.01	£525,093.65	£2,714.00
	monitor every 3 years	£658.76	£79.55	17.520	0.091	0.090	£349,750.96	£1,815.46	£524,955.82	£2,722.24
	monitor every 2 years	£923.58	£112.20	17.525	0.090	0.154	£349,578.60	£1,811.02	£524,829.69	£2,714.48
	Annual monitor	£2,167.29	£266.71	17.527	0.091	1.177	£348,377.83	£1,826.46	£523,650.39	£2,729.88
24	Do nothing	£36.94	£12.72	17.497	0.094	-0.312	£349,908.29	£1,890.35	£524,880.90	£2,833.85
	One off exam	**£161.27**	**£21.34**	**17.506**	**0.093**	**-0.239**	**£349,957.77**	**£1,852.96**	£525,017.29	£2,778.06
	monitor every 5 years	**£415.85**	**£49.90**	**17.516**	**0.092**	**-0.040**	£349,904.53	£1,831.43	**£525,064.72**	**£2,746.36**
	monitor every 4 years	£500.27	£60.40	17.517	0.091	-0.054	£349,848.52	£1,812.72	£525,022.92	£2,717.94
	monitor every 3 years	£659.49	£79.42	17.518	0.091	0.055	£349,706.09	£1,819.25	£524,888.88	£2,727.73
	monitor every 2 years	£923.60	£112.02	17.524	0.090	0.207	£349,549.06	£1,807.79	£524,785.39	£2,709.93
	Annual monitor	£2,163.95	£266.35	17.526	0.091	1.291	£348,352.86	£1,831.75	£523,611.27	£2,738.51
25	Do nothing	£38.89	£13.75	17.493	0.095	-0.358	£349,825.72	£1,904.90	£524,758.03	£2,855.42
	One off exam	**£163.09**	**£21.89**	**17.503**	**0.093**	**-0.278**	**£349,893.98**	**£1,859.29**	£524,922.51	£2,787.32
	monitor every 5 years	**£417.42**	**£49.98**	**17.514**	**0.092**	**-0.060**	£349,856.15	£1,839.34	**£524,992.93**	**£2,758.11**
	monitor every 4 years	£501.52	£60.47	17.515	0.091	-0.076	£349,800.95	£1,815.43	£524,952.19	£2,721.88
	monitor every 3 years	£660.23	£79.29	17.516	0.091	0.019	£349,661.21	£1,823.04	£524,821.93	£2,733.23
	monitor every 2 years	£923.62	£111.84	17.522	0.090	0.260	£349,519.52	£1,804.55	£524,741.09	£2,705.38
	Annual monitor	£2,160.61	£265.99	17.524	0.092	1.405	£348,327.90	£1,837.03	£523,572.15	£2,747.14
26	Do nothing	£42.92	£15.65	17.485	0.096	-0.489	£349,666.89	£1,929.93	£524,521.80	£2,892.34
	One off exam	**£166.99**	**£23.04**	**17.497**	**0.094**	**-0.391**	**£349,769.06**	**£1,881.85**	£524,737.09	£2,820.60
	monitor every 5 years	**£420.92**	**£50.39**	**17.509**	**0.092**	**-0.105**	£349,754.72	£1,842.93	**£524,842.54**	**£2,763.26**
	monitor every 4 years	£504.88	£60.65	17.511	0.091	-0.106	£349,707.25	£1,821.20	£524,813.31	£2,730.37
	monitor every 3 years	£663.45	£79.46	17.513	0.091	0.003	£349,590.36	£1,824.76	£524,717.26	£2,735.72
	monitor every 2 years	£926.68	£111.85	17.518	0.090	0.254	£349,436.79	£1,807.29	£524,618.53	£2,709.46
	Annual monitor	£2,163.80	£265.60	17.521	0.091	1.310	£348,250.71	£1,834.19	£523,457.96	£2,742.38
27	Do nothing	£46.95	£17.54	17.478	0.097	-0.621	£349,508.07	£1,954.97	£524,285.57	£2,929.26
	One off exam	£170.89	£24.20	17.491	0.095	-0.504	£349,644.15	£1,904.41	£524,551.67	£2,853.88
	monitor every 5 years	**£424.41**	**£50.81**	**17.504**	**0.092**	**-0.150**	**£349,653.30**	**£1,846.53**	**£524,692.16**	**£2,768.40**
	monitor every 4 years	£508.24	£60.84	17.506	0.091	-0.136	£349,613.54	£1,826.97	£524,674.43	£2,738.87
	monitor every 3 years	£666.67	£79.62	17.509	0.091	-0.013	£349,519.51	£1,826.48	£524,612.59	£2,738.21
	monitor every 2 years	£929.75	£111.86	17.514	0.090	0.247	£349,354.06	£1,810.04	£524,495.96	£2,713.54
	Annual monitor	£2,166.98	£265.22	17.517	0.091	1.214	£348,173.52	£1,831.34	£523,343.77	£2,737.61
28	Do nothing	£50.97	£19.44	17.470	0.099	-0.752	£349,349.24	£1,980.01	£524,049.35	£2,966.18

	One off exam	£174.79	£25.35	17.485	0.096	-0.617	£349,519.23	£1,926.97	£524,366.24	£2,887.15
	monitor every 5 years	**£427.90**	**£51.23**	**17.499**	**0.092**	**-0.195**	**£349,551.88**	**£1,850.12**	**£524,541.77**	**£2,773.54**
	monitor every 4 years	£511.60	£61.02	17.502	0.091	-0.165	£349,519.84	£1,832.74	£524,535.55	£2,747.36
	monitor every 3 years	£669.89	£79.78	17.506	0.091	-0.029	£349,448.65	£1,828.21	£524,507.92	£2,740.70
	monitor every 2 years	£932.82	£111.87	17.510	0.091	0.240	£349,271.32	£1,812.78	£524,373.40	£2,717.62
	Annual monitor	£2,170.17	£264.84	17.513	0.091	1.119	£348,096.33	£1,828.49	£523,229.58	£2,732.85
29	Do nothing	£55.00	£21.34	17.462	0.100	-0.884	£349,190.41	£2,005.05	£523,813.12	£3,003.10
	One off exam	£178.68	£26.50	17.479	0.097	-0.729	£349,394.32	£1,949.53	£524,180.82	£2,920.43
	monitor every 5 years	**£431.40**	**£51.65**	**17.494**	**0.093**	**-0.240**	**£349,450.46**	**£1,853.72**	£524,391.38	£2,778.69
	monitor every 4 years	£514.95	£61.20	17.497	0.092	-0.195	£349,426.13	£1,838.51	£524,396.68	£2,755.86
	monitor every 3 years	**£673.11**	**£79.94**	**17.503**	**0.091**	**-0.045**	£349,377.80	£1,829.93	**£524,403.26**	**£2,743.19**
	monitor every 2 years	£935.89	£111.88	17.506	0.091	0.234	£349,188.59	£1,815.52	£524,250.83	£2,721.70
	Annual monitor	£2,173.35	£264.45	17.510	0.091	1.024	£348,019.14	£1,825.64	£523,115.39	£2,728.08
30	Do nothing	£59.03	£23.23	17.455	0.101	-1.015	£349,031.58	£2,030.09	£523,576.89	£3,040.02
	One off exam	£182.58	£27.65	17.473	0.098	-0.842	£349,269.40	£1,972.09	£523,995.39	£2,953.70
	monitor every 5 years	**£434.89**	**£52.07**	**17.489**	**0.093**	**-0.285**	**£349,349.03**	**£1,857.32**	£524,241.00	£2,783.83
	monitor every 4 years	£518.31	£61.39	17.493	0.092	-0.225	£349,332.43	£1,844.28	£524,257.80	£2,764.35
	monitor every 3 years	**£676.34**	**£80.10**	**17.499**	**0.091**	**-0.062**	£349,306.95	£1,831.65	**£524,298.59**	**£2,745.68**
	monitor every 2 years	£938.96	£111.89	17.502	0.091	0.227	£349,105.86	£1,818.26	£524,128.27	£2,725.77
	Annual monitor	£2,176.54	£264.07	17.506	0.091	0.928	£347,941.95	£1,822.79	£523,001.20	£2,723.32
31	Do nothing	£76.34	£32.74	17.420	0.118	-5.418	£348,324.26	£2,379.76	£522,524.55	£3,559.71
	One off exam	£199.50	£36.57	17.443	0.113	-4.708	£348,666.25	£2,285.10	£523,099.12	£3,418.56
	monitor every 5 years	£450.01	£58.69	17.469	0.101	-2.297	£348,930.19	£2,022.57	£523,620.29	£3,027.74
	monitor every 4 years	£532.08	£66.80	17.474	0.098	-1.755	£348,951.41	£1,977.97	£523,693.16	£2,961.42
	monitor every 3 years	**£687.79**	**£83.63**	**17.483**	**0.096**	**-1.048**	**£348,970.25**	**£1,927.63**	**£523,799.28**	**£2,886.96**
	monitor every 2 years	£946.98	£113.19	17.489	0.094	-0.283	£348,824.31	£1,880.39	£523,709.95	£2,817.28
	Annual monitor	£2,171.55	£262.73	17.495	0.092	1.015	£347,723.41	£1,856.08	£522,670.90	£2,773.86
32	Do nothing	£93.64	£42.25	17.386	0.135	-9.821	£347,616.93	£2,729.42	£521,472.22	£4,079.41
	One off exam	£216.42	£45.48	17.414	0.129	-8.574	£348,063.10	£2,598.10	£522,202.86	£3,883.41
	monitor every 5 years	£465.14	£65.31	17.449	0.108	-4.308	£348,511.34	£2,187.83	£522,999.58	£3,271.64
	monitor every 4 years	£545.85	£72.22	17.456	0.105	-3.286	£348,570.40	£2,111.66	£523,128.52	£3,158.49
	monitor every 3 years	**£699.25**	**£87.15**	**17.467**	**0.101**	**-2.035**	**£348,633.56**	**£2,023.62**	**£523,299.96**	**£3,028.25**
	monitor every 2 years	£955.00	£114.50	17.475	0.097	-0.793	£348,542.76	£1,942.52	£523,291.64	£2,908.79
	Annual monitor	£2,166.56	£261.38	17.484	0.094	1.101	£347,504.87	£1,889.37	£522,340.59	£2,824.40
33	Do nothing	£110.95	£51.77	17.351	0.152	-14.224	£346,909.60	£3,079.09	£520,419.88	£4,599.11
	One off exam	£233.35	£54.40	17.385	0.144	-12.440	£347,459.94	£2,911.10	£521,306.59	£4,348.27
	monitor every 5 years	£480.26	£71.92	17.429	0.116	-6.320	£348,092.50	£2,353.08	£522,378.87	£3,515.55
	monitor every 4 years	£559.62	£77.64	17.437	0.111	-4.817	£348,189.38	£2,245.34	£522,563.88	£3,355.56
	monitor every 3 years	**£710.70**	**£90.68**	**17.450**	**0.105**	**-3.022**	**£348,296.87**	**£2,119.60**	£522,800.65	£3,169.54
	monitor every 2 years	**£963.01**	**£115.80**	**17.461**	**0.100**	**-1.304**	£348,261.21	£2,004.65	**£522,873.32**	**£3,000.30**
	Annual monitor	£2,161.57	£260.04	17.472	0.096	1.187	£347,286.33	£1,922.66	£522,010.28	£2,874.94
34	Do nothing	£128.26	£61.28	17.317	0.169	-18.627	£346,202.28	£3,428.76	£519,367.55	£5,118.81
	One off exam	£250.27	£63.31	17.355	0.159	-16.306	£346,856.79	£3,224.11	£520,410.32	£4,813.12
	monitor every 5 years	£495.38	£78.54	17.408	0.124	-8.331	£347,673.65	£2,518.34	£521,758.17	£3,759.46
	monitor every 4 years	£573.38	£83.06	17.419	0.117	-6.348	£347,808.37	£2,379.03	£521,999.25	£3,552.63
	monitor every 3 years	£722.16	£94.21	17.434	0.110	-4.008	£347,960.17	£2,215.59	£522,301.34	£3,310.83
	monitor every 2 years	**£971.03**	**£117.11**	**17.448**	**0.103**	**-1.814**	**£347,979.66**	**£2,066.78**	**£522,455.01**	**£3,091.81**
	Annual monitor	£2,156.58	£258.70	17.461	0.098	1.274	£347,067.79	£1,955.95	£521,679.98	£2,925.48

35	Do nothing	£145.57	£70.79	17.282	0.186	-23.030	£345,494.95	£3,778.43	£518,315.21	£5,638.50
	One off exam	£267.19	£72.23	17.326	0.174	-20.172	£346,253.64	£3,537.11	£519,514.06	£5,277.97
	monitor every 5 years	£510.51	£85.16	17.388	0.132	-10.343	£347,254.80	£2,683.59	£521,137.46	£4,003.37
	monitor every 4 years	£587.15	£88.47	17.401	0.124	-7.878	£347,427.36	£2,512.72	£521,434.61	£3,749.70
	monitor every 3 years	£733.61	£97.74	17.418	0.114	-4.995	£347,623.48	£2,311.57	£521,802.03	£3,452.12
	monitor every 2 years	**£979.05**	**£118.41**	**17.434**	**0.106**	**-2.324**	**£347,698.11**	**£2,128.91**	**£522,036.69**	**£3,183.32**
	Annual monitor	£2,151.59	£257.35	17.450	0.099	1.360	£346,849.25	£1,989.24	£521,349.67	£2,976.02
36	Do nothing	£162.88	£80.30	17.248	0.203	-27.433	£344,787.62	£4,128.09	£517,262.88	£6,158.20
	One off exam	£284.11	£81.14	17.297	0.189	-24.038	£345,650.49	£3,850.12	£518,617.79	£5,742.83
	monitor every 5 years	£525.63	£91.78	17.368	0.140	-12.354	£346,835.96	£2,848.85	£520,516.75	£4,247.27
	monitor every 4 years	£600.92	£93.89	17.382	0.130	-9.409	£347,046.34	£2,646.41	£520,869.97	£3,946.77
	monitor every 3 years	£745.07	£101.26	17.402	0.119	-5.981	£347,286.79	£2,407.55	£521,302.72	£3,593.40
	monitor every 2 years	**£987.07**	**£119.71**	**17.420**	**0.108**	**-2.835**	**£347,416.56**	**£2,191.04**	**£521,618.38**	**£3,274.83**
	Annual monitor	£2,146.60	£256.01	17.439	0.101	1.446	£346,630.71	£2,022.53	£521,019.37	£3,026.56
37	Do nothing	£180.19	£89.81	17.213	0.220	-31.836	£344,080.30	£4,477.76	£516,210.54	£6,677.90
	One off exam	£301.03	£90.06	17.267	0.204	-27.904	£345,047.34	£4,163.12	£517,721.52	£6,207.68
	monitor every 5 years	£540.75	£98.40	17.348	0.148	-14.366	£346,417.11	£3,014.10	£519,896.04	£4,491.18
	monitor every 4 years	£614.69	£99.31	17.364	0.136	-10.940	£346,665.33	£2,780.09	£520,305.33	£4,143.84
	monitor every 3 years	£756.52	£104.79	17.385	0.123	-6.968	£346,950.10	£2,503.54	£520,803.41	£3,734.69
	monitor every 2 years	**£995.09**	**£121.02**	**17.407**	**0.111**	**-3.345**	**£347,135.01**	**£2,253.17**	**£521,200.06**	**£3,366.34**
	Annual monitor	£2,141.60	£254.67	17.428	0.103	1.533	£346,412.17	£2,055.82	£520,689.06	£3,077.10
38	Do nothing	£197.50	£99.32	17.179	0.237	-36.239	£343,372.97	£4,827.43	£515,158.21	£7,197.59
	One off exam	£317.95	£98.97	17.238	0.220	-31.770	£344,444.19	£4,476.12	£516,825.26	£6,672.53
	monitor every 5 years	£555.88	£105.02	17.328	0.156	-16.377	£345,998.27	£3,179.36	£519,275.34	£4,735.09
	monitor every 4 years	£628.46	£104.73	17.346	0.143	-12.471	£346,284.31	£2,913.78	£519,740.70	£4,340.91
	monitor every 3 years	£767.98	£108.32	17.369	0.128	-7.955	£346,613.40	£2,599.52	£520,304.10	£3,875.98
	monitor every 2 years	**£1,003.11**	**£122.32**	**17.393**	**0.114**	**-3.855**	**£346,853.46**	**£2,315.30**	**£520,781.75**	**£3,457.85**
	Annual monitor	£2,136.61	£253.32	17.417	0.104	1.619	£346,193.63	£2,089.10	£520,358.75	£3,127.64
39	Do nothing	£214.81	£108.83	17.144	0.254	-40.642	£342,665.64	£5,177.10	£514,105.87	£7,717.29
	One off exam	£334.87	£107.88	17.209	0.235	-35.636	£343,841.04	£4,789.13	£515,928.99	£7,137.39
	monitor every 5 years	£571.00	£111.64	17.308	0.163	-18.389	£345,579.42	£3,344.62	£518,654.63	£4,979.00
	monitor every 4 years	£642.22	£110.14	17.327	0.149	-14.001	£345,903.30	£3,047.47	£519,176.06	£4,537.98
	monitor every 3 years	£779.43	£111.84	17.353	0.132	-8.941	£346,276.71	£2,695.51	£519,804.78	£4,017.27
	monitor every 2 years	**£1,011.13**	**£123.63**	**17.379**	**0.117**	**-4.365**	**£346,571.91**	**£2,377.43**	**£520,363.43**	**£3,549.36**
	Annual monitor	£2,131.62	£251.98	17.405	0.106	1.706	£345,975.09	£2,122.39	£520,028.45	£3,178.17
40	Do nothing	£232.12	£118.34	17.110	0.271	-45.045	£341,958.32	£5,526.76	£513,053.54	£8,236.99
	One off exam	£351.80	£116.80	17.179	0.250	-39.502	£343,237.88	£5,102.13	£515,032.72	£7,602.24
	monitor every 5 years	£586.12	£118.26	17.287	0.171	-20.401	£345,160.57	£3,509.87	£518,033.92	£5,222.90
	monitor every 4 years	£655.99	£115.56	17.309	0.155	-15.532	£345,522.28	£3,181.15	£518,611.42	£4,735.05
	monitor every 3 years	£790.89	£115.37	17.337	0.137	-9.928	£345,940.02	£2,791.49	£519,305.47	£4,158.56
	monitor every 2 years	**£1,019.15**	**£124.93**	**17.365**	**0.120**	**-4.876**	**£346,290.36**	**£2,439.56**	**£519,945.12**	**£3,640.87**
	Annual monitor	£2,126.63	£250.64	17.394	0.108	1.792	£345,756.55	£2,155.68	£519,698.14	£3,228.71
41	Do nothing	£249.43	£127.85	17.075	0.288	-49.448	£341,250.99	£5,876.43	£512,001.20	£8,756.69
	One off exam	£368.72	£125.71	17.150	0.265	-43.368	£342,634.73	£5,415.14	£514,136.46	£8,067.10
	monitor every 5 years	£601.25	£124.87	17.267	0.179	-22.412	£344,741.73	£3,675.13	£517,413.22	£5,466.81
	monitor every 4 years	£669.76	£120.98	17.291	0.162	-17.063	£345,141.27	£3,314.84	£518,046.78	£4,932.12
	monitor every 3 years	£802.34	£118.90	17.320	0.141	-10.914	£345,603.33	£2,887.47	£518,806.16	£4,299.84
	monitor every 2 years	**£1,027.17**	**£126.23**	**17.352**	**0.123**	**-5.386**	**£346,008.81**	**£2,501.69**	**£519,526.80**	**£3,732.38**

	Annual monitor	£2,121.64	£249.29	17.383	0.110	1.878	£345,538.01	£2,188.97	£519,367.83	£3,279.25
42	Do nothing	£266.74	£137.36	17.041	0.305	-53.851	£340,543.66	£6,226.10	£510,948.87	£9,276.38
	One off exam	£385.64	£134.63	17.121	0.280	-47.233	£342,031.58	£5,728.14	£513,240.19	£8,531.95
	monitor every 5 years	£616.37	£131.49	17.247	0.187	-24.424	£344,322.88	£3,840.38	£516,792.51	£5,710.72
	monitor every 4 years	£683.53	£126.40	17.272	0.168	-18.594	£344,760.26	£3,448.53	£517,482.15	£5,129.19
	monitor every 3 years	£813.80	£122.42	17.304	0.146	-11.901	£345,266.63	£2,983.46	£518,306.85	£4,441.13
	monitor every 2 years	**£1,035.18**	**£127.54**	**17.338**	**0.126**	**-5.896**	**£345,727.26**	**£2,563.82**	**£519,108.49**	**£3,823.89**
	Annual monitor	£2,116.65	£247.95	17.372	0.111	1.965	£345,319.47	£2,222.26	£519,037.53	£3,329.79
43	Do nothing	£284.05	£146.88	17.006	0.322	-58.253	£339,836.34	£6,575.77	£509,896.53	£9,796.08
	One off exam	£402.56	£143.54	17.092	0.296	-51.099	£341,428.43	£6,041.14	£512,343.93	£8,996.80
	monitor every 5 years	£631.50	£138.11	17.227	0.195	-26.435	£343,904.04	£4,005.64	£516,171.80	£5,954.63
	monitor every 4 years	£697.30	£131.81	17.254	0.174	-20.124	£344,379.24	£3,582.21	£516,917.51	£5,326.26
	monitor every 3 years	£825.25	£125.95	17.288	0.150	-12.888	£344,929.94	£3,079.44	£517,807.54	£4,582.42
	monitor every 2 years	**£1,043.20**	**£128.84**	**17.324**	**0.129**	**-6.407**	**£345,445.71**	**£2,625.95**	£518,690.17	£3,915.40
	Annual monitor	**£2,111.66**	**£246.60**	**17.361**	**0.113**	**2.051**	£345,100.93	£2,255.55	**£518,707.22**	**£3,380.33**
44	Do nothing	£301.35	£156.39	16.972	0.339	-62.656	£339,129.01	£6,925.43	£508,844.19	£10,315.78
	One off exam	£419.48	£152.46	17.062	0.311	-54.965	£340,825.28	£6,354.15	£511,447.66	£9,461.66
	monitor every 5 years	£646.62	£144.73	17.207	0.203	-28.447	£343,485.19	£4,170.89	£515,551.09	£6,198.54
	monitor every 4 years	£711.06	£137.23	17.235	0.181	-21.655	£343,998.23	£3,715.90	£516,352.87	£5,523.33
	monitor every 3 years	£836.71	£129.48	17.271	0.155	-13.874	£344,593.25	£3,175.43	£517,308.23	£4,723.71
	monitor every 2 years	**£1,051.22**	**£130.15**	**17.311**	**0.132**	**-6.917**	**£345,164.16**	**£2,688.08**	£518,271.86	£4,006.91
	Annual monitor	**£2,106.67**	**£245.26**	**17.349**	**0.115**	**2.137**	£344,882.39	£2,288.84	**£518,376.92**	**£3,430.87**
45	Do nothing	£318.66	£165.90	16.937	0.356	-67.059	£338,421.68	£7,275.10	£507,791.86	£10,835.48
	One off exam	£436.40	£161.37	17.033	0.326	-58.831	£340,222.13	£6,667.15	£510,551.39	£9,926.51
	monitor every 5 years	£661.74	£151.35	17.186	0.211	-30.458	£343,066.34	£4,336.15	£514,930.39	£6,442.44
	monitor every 4 years	£724.83	£142.65	17.217	0.187	-23.186	£343,617.21	£3,849.59	£515,788.24	£5,720.40
	monitor every 3 years	£848.17	£133.01	17.255	0.159	-14.861	£344,256.55	£3,271.41	£516,808.91	£4,865.00
	monitor every 2 years	**£1,059.24**	**£131.45**	**17.297**	**0.135**	**-7.427**	**£344,882.61**	**£2,750.21**	£517,853.54	£4,098.41
	Annual monitor	**£2,101.68**	**£243.92**	**17.338**	**0.116**	**2.224**	£344,663.85	£2,322.13	**£518,046.61**	**£3,481.41**
46	Do nothing	£335.97	£175.41	16.903	0.373	-71.462	£337,714.36	£7,624.77	£506,739.52	£11,355.17
	One off exam	£453.32	£170.29	17.004	0.341	-62.697	£339,618.98	£6,980.15	£509,655.13	£10,391.36
	monitor every 5 years	£676.87	£157.97	17.166	0.219	-32.470	£342,647.50	£4,501.40	£514,309.68	£6,686.35
	monitor every 4 years	£738.60	£148.07	17.199	0.193	-24.717	£343,236.20	£3,983.27	£515,223.60	£5,917.46
	monitor every 3 years	£859.62	£136.53	17.239	0.164	-15.848	£343,919.86	£3,367.39	£516,309.60	£5,006.28
	monitor every 2 years	**£1,067.26**	**£132.76**	**17.283**	**0.138**	**-7.938**	**£344,601.06**	**£2,812.34**	£517,435.23	£4,189.92
	Annual monitor	**£2,096.69**	**£242.57**	**17.327**	**0.118**	**2.310**	£344,445.31	£2,355.42	**£517,716.30**	**£3,531.95**
47	Do nothing	£353.28	£184.92	16.868	0.390	-75.865	£337,007.03	£7,974.44	£505,687.19	£11,874.87
	One off exam	£470.25	£179.20	16.974	0.356	-66.563	£339,015.82	£7,293.16	£508,758.86	£10,856.22
	monitor every 5 years	£691.99	£164.59	17.146	0.226	-34.481	£342,228.65	£4,666.66	£513,688.97	£6,930.26
	monitor every 4 years	£752.37	£153.48	17.180	0.200	-26.247	£342,855.18	£4,116.96	£514,658.96	£6,114.53
	monitor every 3 years	£871.08	£140.06	17.223	0.168	-16.834	£343,583.17	£3,463.38	£515,810.29	£5,147.57
	monitor every 2 years	**£1,075.28**	**£134.06**	**17.270**	**0.141**	**-8.448**	**£344,319.51**	**£2,874.47**	£517,016.91	£4,281.43
	Annual monitor	**£2,091.70**	**£241.23**	**17.316**	**0.120**	**2.396**	£344,226.77	£2,388.71	**£517,386.00**	**£3,582.49**
48	Do nothing	£370.59	£194.43	16.834	0.407	-80.268	£336,299.71	£8,324.10	£504,634.85	£12,394.57
	One off exam	£487.17	£188.12	16.945	0.371	-70.429	£338,412.67	£7,606.16	£507,862.59	£11,321.07
	monitor every 5 years	£707.11	£171.21	17.126	0.234	-36.493	£341,809.81	£4,831.92	£513,068.27	£7,174.17
	monitor every 4 years	£766.14	£158.90	17.162	0.206	-27.778	£342,474.17	£4,250.65	£514,094.32	£6,311.60
	monitor every 3 years	£882.53	£143.59	17.206	0.173	-17.821	£343,246.48	£3,559.36	£515,310.98	£5,288.86

	monitor every 2 years	**£1,083.30**	**£135.36**	**17.256**	**0.144**	**-8.958**	**£344,037.97**	**£2,936.60**	£516,598.60	£4,372.94
	Annual monitor	**£2,086.70**	**£239.89**	**17.305**	**0.122**	**2.483**	£344,008.23	£2,421.99	**£517,055.69**	**£3,633.03**
49	Do nothing	£387.90	£203.94	16.799	0.424	-84.671	£335,592.38	£8,673.77	£503,582.52	£12,914.27
	One off exam	£504.09	£197.03	16.916	0.387	-74.295	£337,809.52	£7,919.17	£506,966.33	£11,785.92
	monitor every 5 years	£722.24	£177.82	17.106	0.242	-38.505	£341,390.96	£4,997.17	£512,447.56	£7,418.07
	monitor every 4 years	£779.90	£164.32	17.144	0.212	-29.309	£342,093.16	£4,384.34	£513,529.69	£6,508.67
	monitor every 3 years	£893.99	£147.11	17.190	0.178	-18.807	£342,909.78	£3,655.35	£514,811.67	£5,430.15
	monitor every 2 years	£1,091.32	£136.67	17.242	0.147	-9.468	£343,756.42	£2,998.73	£516,180.28	£4,464.45
	Annual monitor	**£2,081.71**	**£238.54**	**17.294**	**0.123**	**2.569**	**£343,789.69**	**£2,455.28**	**£516,725.38**	**£3,683.57**
50	Do nothing	£405.21	£213.45	16.765	0.441	-89.074	£334,885.05	£9,023.44	£502,530.18	£13,433.96
	One off exam	£521.01	£205.95	16.886	0.402	-78.161	£337,206.37	£8,232.17	£506,070.06	£12,250.78
	monitor every 5 years	£737.36	£184.44	17.085	0.250	-40.516	£340,972.11	£5,162.43	£511,826.85	£7,661.98
	monitor every 4 years	£793.67	£169.74	17.125	0.219	-30.840	£341,712.14	£4,518.02	£512,965.05	£6,705.74
	monitor every 3 years	£905.44	£150.64	17.174	0.182	-19.794	£342,573.09	£3,751.33	£514,312.36	£5,571.44
	monitor every 2 years	£1,099.34	£137.97	17.229	0.150	-9.979	£343,474.87	£3,060.86	£515,761.97	£4,555.96
	Annual monitor	**£2,076.72**	**£237.20**	**17.282**	**0.125**	**2.655**	**£343,571.14**	**£2,488.57**	**£516,395.08**	**£3,734.11**
51	Do nothing	£453.36	£234.11	16.638	0.502	-121.754	£332,302.97	£10,252.37	£498,681.14	£15,267.56
	One off exam	£567.16	£224.62	16.787	0.453	-104.366	£335,167.86	£9,265.32	£503,035.37	£13,791.51
	monitor every 5 years	£776.85	£199.26	17.021	0.276	-52.575	£339,643.01	£5,695.73	£509,852.94	£8,454.23
	monitor every 4 years	£828.33	£182.11	17.067	0.240	-39.667	£340,504.80	£4,963.06	£511,171.37	£7,366.68
	monitor every 3 years	£932.44	£159.41	17.122	0.199	-25.191	£341,515.20	£4,100.45	£512,739.02	£6,090.11
	monitor every 2 years	£1,115.75	£142.07	17.184	0.162	-12.514	£342,558.88	£3,323.06	£514,396.19	£4,946.31
	Annual monitor	**£2,053.25**	**£237.34**	**17.244**	**0.135**	**3.392**	**£342,822.39**	**£2,687.12**	**£515,260.21**	**£4,033.51**
52	Do nothing	£501.50	£254.77	16.511	0.562	-154.434	£329,720.89	£11,481.30	£494,832.09	£17,101.16
	One off exam	£613.31	£243.30	16.687	0.503	-130.571	£333,129.35	£10,298.47	£500,000.68	£15,332.25
	monitor every 5 years	£816.33	£214.08	16.957	0.302	-64.634	£338,313.90	£6,229.04	£507,879.02	£9,246.49
	monitor every 4 years	£862.99	£194.48	17.008	0.262	-48.494	£339,297.46	£5,408.10	£509,377.68	£8,027.61
	monitor every 3 years	£959.44	£168.17	17.071	0.216	-30.589	£340,457.31	£4,449.57	£511,165.68	£6,608.79
	monitor every 2 years	£1,132.16	£146.17	17.139	0.175	-15.049	£341,642.89	£3,585.26	£513,030.41	£5,336.67
	Annual monitor	**£2,029.78**	**£237.48**	**17.205**	**0.145**	**4.128**	**£342,073.63**	**£2,885.67**	**£514,125.34**	**£4,332.92**
53	Do nothing	£549.65	£275.42	16.384	0.622	-187.115	£327,138.82	£12,710.23	£490,983.05	£18,934.76
	One off exam	£659.47	£261.97	16.588	0.554	-156.775	£331,090.84	£11,331.61	£496,966.00	£16,872.98
	monitor every 5 years	£855.82	£228.90	16.892	0.328	-76.692	£336,984.80	£6,762.34	£505,905.11	£10,038.74
	monitor every 4 years	£897.66	£206.84	16.949	0.284	-57.321	£338,090.12	£5,853.14	£507,584.00	£8,688.55
	monitor every 3 years	£986.44	£176.94	17.019	0.233	-35.986	£339,399.41	£4,798.70	£509,592.34	£7,127.46
	monitor every 2 years	£1,148.58	£150.27	17.094	0.188	-17.585	£340,726.90	£3,847.45	£511,664.64	£5,727.02
	Annual monitor	**£2,006.31**	**£237.61**	**17.167**	**0.155**	**4.864**	**£341,324.88**	**£3,084.22**	**£512,990.47**	**£4,632.32**
54	Do nothing	£597.80	£296.08	16.258	0.683	-219.795	£324,556.74	£13,939.17	£487,134.00	£20,768.35
	One off exam	£705.62	£280.65	16.488	0.605	-182.980	£329,052.33	£12,364.76	£493,931.31	£18,413.71
	monitor every 5 years	£895.31	£243.72	16.828	0.354	-88.751	£335,655.70	£7,295.65	£503,931.20	£10,831.00
	monitor every 4 years	£932.32	£219.21	16.891	0.305	-66.148	£336,882.78	£6,298.18	£505,790.32	£9,349.48
	monitor every 3 years	£1,013.43	£185.70	16.968	0.250	-41.383	£338,341.52	£5,147.82	£508,019.00	£7,646.14
	monitor every 2 years	£1,164.99	£154.37	17.049	0.201	-20.120	£339,810.91	£4,109.65	£510,298.86	£6,117.37
	Annual monitor	**£1,982.84**	**£237.75**	**17.128**	**0.165**	**5.601**	**£340,576.12**	**£3,282.77**	**£511,855.60**	**£4,931.73**
55	Do nothing	£645.95	£316.74	16.131	0.743	-252.475	£321,974.66	£15,168.10	£483,284.96	£22,601.95
	One off exam	£751.77	£299.32	16.388	0.656	-209.185	£327,013.83	£13,397.91	£490,896.62	£19,954.45
	monitor every 5 years	£934.79	£258.54	16.763	0.379	-100.810	£334,326.59	£7,828.95	£501,957.28	£11,623.25
	monitor every 4 years	£966.98	£231.58	16.832	0.327	-74.975	£335,675.43	£6,743.21	£503,996.64	£10,010.42

	monitor every 3 years	£1,040.43	£194.47	16.916	0.267	-46.780	£337,283.63	£5,496.94	£506,445.66	£8,164.81
	monitor every 2 years	£1,181.41	£158.47	17.004	0.214	-22.655	£338,894.92	£4,371.85	£508,933.08	£6,507.73
	Annual monitor	**£1,959.37**	**£237.89**	**17.089**	**0.175**	**6.337**	**£339,827.37**	**£3,481.32**	**£510,720.74**	**£5,231.13**
56	Do nothing	£694.09	£337.40	16.004	0.804	-285.155	£319,392.58	£16,397.03	£479,435.91	£24,435.55
	One off exam	£797.92	£318.00	16.289	0.706	-235.389	£324,975.32	£14,431.06	£487,861.94	£21,495.18
	monitor every 5 years	£974.28	£273.36	16.699	0.405	-112.869	£332,997.49	£8,362.26	£499,983.37	£12,415.51
	monitor every 4 years	£1,001.64	£243.95	16.773	0.348	-83.802	£334,468.09	£7,188.25	£502,202.96	£10,671.35
	monitor every 3 years	£1,067.43	£203.23	16.865	0.284	-52.178	£336,225.74	£5,846.06	£504,872.32	£8,683.49
	monitor every 2 years	£1,197.82	£162.57	16.959	0.226	-25.191	£337,978.93	£4,634.05	£507,567.31	£6,898.08
	Annual monitor	**£1,935.89**	**£238.03**	**17.051**	**0.185**	**7.074**	**£339,078.61**	**£3,679.86**	**£509,585.87**	**£5,530.54**
57	Do nothing	£742.24	£358.05	15.878	0.864	-317.836	£316,810.50	£17,625.96	£475,586.87	£26,269.14
	One off exam	£844.07	£336.67	16.189	0.757	-261.594	£322,936.81	£15,464.21	£484,827.25	£23,035.92
	monitor every 5 years	£1,013.77	£288.17	16.634	0.431	-124.928	£331,668.38	£8,895.56	£498,009.45	£13,207.76
	monitor every 4 years	£1,036.30	£256.32	16.715	0.370	-92.629	£333,260.75	£7,633.29	£500,409.28	£11,332.29
	monitor every 3 years	£1,094.43	£212.00	16.813	0.301	-57.575	£335,167.85	£6,195.18	£503,298.98	£9,202.16
	monitor every 2 years	£1,214.24	£166.67	16.914	0.239	-27.726	£337,062.94	£4,896.24	£506,201.53	£7,288.43
	Annual monitor	**£1,912.42**	**£238.17**	**17.012**	**0.195**	**7.810**	**£338,329.86**	**£3,878.41**	**£508,451.00**	**£5,829.94**
58	Do nothing	£790.39	£378.71	15.751	0.925	-350.516	£314,228.42	£18,854.89	£471,737.82	£28,102.74
	One off exam	£890.23	£355.35	16.089	0.808	-287.799	£320,898.30	£16,497.35	£481,792.56	£24,576.65
	monitor every 5 years	£1,053.25	£302.99	16.570	0.457	-136.986	£330,339.28	£9,428.87	£496,035.54	£14,000.01
	monitor every 4 years	£1,070.96	£268.69	16.656	0.392	-101.456	£332,053.41	£8,078.33	£498,615.60	£11,993.22
	monitor every 3 years	£1,121.43	£220.76	16.762	0.318	-62.972	£334,109.95	£6,544.30	£501,725.65	£9,720.84
	monitor every 2 years	£1,230.65	£170.77	16.869	0.252	-30.261	£336,146.95	£5,158.44	£504,835.75	£7,678.78
	Annual monitor	**£1,888.95**	**£238.31**	**16.974**	**0.205**	**8.546**	**£337,581.10**	**£4,076.96**	**£507,316.13**	**£6,129.35**
59	Do nothing	£838.54	£399.37	15.624	0.985	-383.196	£311,646.34	£20,083.83	£467,888.78	£29,936.34
	One off exam	£936.38	£374.03	15.990	0.859	-314.004	£318,859.79	£17,530.50	£478,757.87	£26,117.38
	monitor every 5 years	£1,092.74	£317.81	16.505	0.483	-149.045	£329,010.17	£9,962.17	£494,061.63	£14,792.27
	monitor every 4 years	£1,105.62	£281.06	16.598	0.413	-110.283	£330,846.07	£8,523.37	£496,821.91	£12,654.16
	monitor every 3 years	£1,148.43	£229.52	16.710	0.335	-68.370	£333,052.06	£6,893.43	£500,152.31	£10,239.51
	monitor every 2 years	£1,247.06	£174.87	16.824	0.265	-32.797	£335,230.96	£5,420.64	£503,469.98	£8,069.14
	Annual monitor	**£1,865.48**	**£238.44**	**16.935**	**0.216**	**9.283**	**£336,832.35**	**£4,275.51**	**£506,181.26**	**£6,428.75**
60	Do nothing	£886.68	£420.03	15.498	1.046	-415.876	£309,064.26	£21,312.76	£464,039.74	£31,769.94
	One off exam	£982.53	£392.70	15.890	0.909	-340.208	£316,821.28	£18,563.65	£475,723.19	£27,658.12
	monitor every 5 years	£1,132.23	£332.63	16.441	0.509	-161.104	£327,681.07	£10,495.48	£492,087.71	£15,584.52
	monitor every 4 years	£1,140.28	£293.43	16.539	0.435	-119.110	£329,638.73	£8,968.41	£495,028.23	£13,315.09
	monitor every 3 years	£1,175.43	£238.29	16.658	0.352	-73.767	£331,994.17	£7,242.55	£498,578.97	£10,758.19
	monitor every 2 years	£1,263.48	£178.97	16.779	0.278	-35.332	£334,314.97	£5,682.84	£502,104.20	£8,459.49
	Annual monitor	**£1,842.01**	**£238.58**	**16.896**	**0.226**	**10.019**	**£336,083.59**	**£4,474.06**	**£505,046.39**	**£6,728.16**

Appendix 11: Additional Figures

Below are additional figures illustrating the results. Figures A11.1a and A11.1b show the expected net benefit of each of the seven policies as a function of risk score. At low risk scores there is very little difference between the policies. However, at scores above 30, the net benefit of the less intensive policies drops dramatically: this is due to failure to detect melanomas, thus patients suffer reduced life expectancy, and the NHS suffers increased costs from treatment of late stage disease.

Figure A11.2 shows the incremental net benefit +/- 95% credibility interval of the optimal risk-stratified policy (as described in the results and Table 1), compared with the status quo, as a function of willingness to pay for a QALY.

Figures A11.1a & A11.1b: Expected net benefit for each strategy as a function of risk score at (a) £20,000 and (b) £30,000 per QALY gained

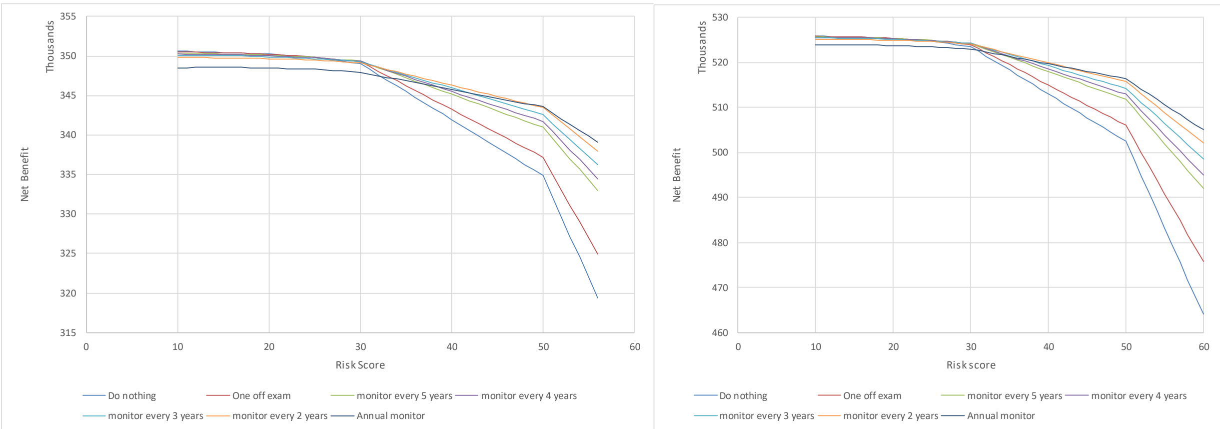
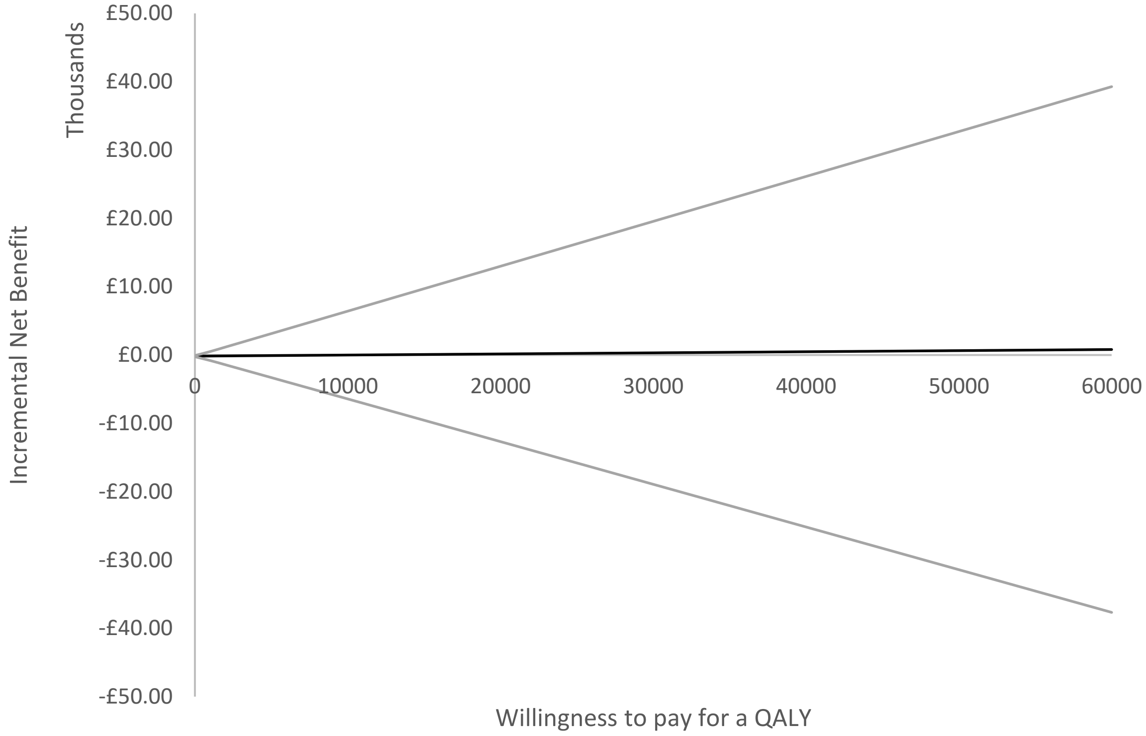


Figure A11.2: Incremental Net Benefit +/- 95% Credibility Interval for compound risk-stratified policy vs status quo.



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