National Collaborating Centre for Cancer

Melanoma

assessment and management

Clinical Guideline

Appendices

December 2014

Draft for Submission

Commissioned by the National Institute for Health and Care Excellence

Disclaimer
Healthcare professionals are expected to take NICE clinical guidelines fully into account when exercising their clinical judgement. However, the guidance does not override the responsibility of healthcare professionals to make decisions appropriate to the circumstances of each patient, in consultation with the patient and/or their guardian or carer.

Funding
Funded to produce guidelines for the NHS by NICE

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Appendix A: The cost-effectiveness of sentinel node biopsy alongside wide excision versus wide excision only in patients with clinicopathological stage IA to stage IIC melanoma

A.1 Background

Primary melanoma is treated by surgical excision. The removed melanoma is examined by a pathologist who measures the depth of skin penetration by the tumour,the Breslow thickness, which is an important prognostic marker. Invasion of blood vessels or lymphatics and microscopic ulceration of the melanoma surface, are also prognostic indicators. The clinical presentation of metastatic melanoma to regional lymph nodes or other parts of the body is most common in the first three years after diagnosis of primary melanoma but can occur many years later.

Staging is a process by which reported histopathological features of the primary, and evidence of metastasis are used to estimate prognosis. Sentinel lymph node biopsy (SLNB) has become part of that staging process. SLNB was developed in the hope that the procedure would also have a therapeutic effect but the procedure is associated with some morbidity. The safety and cost effectiveness of the use of SLNB has therefore been the subject of some debate.

A.2 Aims of analysis

The aim of the economic evaluation was to assess the cost effectiveness of SLNB for the staging of melanoma alongside wide excision (WEX) versus WEX and nodal observation in patients with clinicopathological stage IA to stage IIC melanoma. All analyses were conducted from a National Health Service (NHS) and Personal Social Services (PSS) perspective.

A.3 Economic evidence statement

A systematic literature review was performed to assess the current economic literature in this area. The review identified 303 possibly relevant economic papers relating to melanoma. Of these, six full papers were obtained for appraisal. A further four papers were excluded as they only reported costs. Two papers (Morton et al, 2009; Wilson et al, 2001) were included in the current review of published economic evidence for this topic. The included studies are summarised in Table 1.

Wilson et al produced a cost-utility analysis comparing four alternative treatment strategies for patients with stage II melanoma. Two different SLNB strategies followed by tailored interferon treatment (IFN) strategies and two non SLNB strategies (treat all patients with low dose IFN or with surgery only). The base case analysis concluded that SLNB followed by treating patients who have a positive result with high dose IFN and those with a negative result with low dose IFN was the most effective treatment in terms of quality adjusted relapse free life-years (QArfLY). This equated to an ICER of $18,700/QArfLY compared to the surgery only approach and $31,100 compared to only treating patients with a positive SLNB. The ‘treat all’ approach was deemed not cost effective as a result of extended dominance.

The study was considered to be only partially applicable to the decision problem as it considered a US third party payer perspective and considered interventions post SLNB which were not widely used within the NHS. The study was also deemed to have serious limitations including a potential conflict of interest (the study was funded by a manufacturer of IFN), the duration component of the QALYs using relapse free survival as opposed to overall survival and an inappropriate time horizon.

Morton et al reported a cost-utility analysis comparing wide-excision (WEX) alone to SLNB (with complete lymph node dissection (CLND) for patients with positive SLNBs) alongside WEX in patients with primary melanoma of >1mm in thickness using a decision tree and Markov model. The base-case concluded that adding SLNB to WEX resulted in an incremental cost per QALY of AU$1,923 compared to WEX alone. The estimated cost ranged from SLNB being both cheaper and more effective to AU$90,959 per QALY during sensitivity analyses. These results were sensitive to the probability of distant metastasis post-intervention, the probability of nodal metastasis post WEX and the cost of WEX, SLNB and delayed CLND.

The study was deemed only partially applicable as it considered an Australian healthcare perspective. Potentially serious limitations were also identified most notably that probabilistic sensitivity analysis was not presented in the report.

Given the large differences in treatments onsidered following SLNB the results of the two studies are difficult to compare.

1 **Table 1: Modified GRADE profile for included economic studies**

Study	Population	Comparators	Costs	Effects	Incr costs*	Incr effects	ICER	Uncertainty	Applicability	Limitations
Wilson et al. 2002 USA)	Hypothetical cohort of patients with Stage II malignant melanoma after surgical excision. Age, performance status and other demographic details were not reported for this cohort.	Treat no one with IFN, surgery and clinical observation only.	$18,400	3.06	Reference			One-way sensitivity analysis For test and treat some versus surgery and test and treat appropriately versus test and treat some reducing the cost of relapse to $10,000 increased the ICER to $21,900/QArfLY and $35,900/QArfLY respectively. Increasing the cost of relapse to $50,000 reduced the ICERs by $14,500/QArfLY and $26,100/QArfLY respectively Sensitivity and specificity of SLNB and the probability of dose changing toxicities were reported to have an insignificant effect on the ICER for both comparisons. Probabilistic Sensitivity Analysis (PSA) Varying across all variables for test and treat some versus surgery the median, 25th and 75th percentiles of the PSA are $19,605,$10,291 and $36,659 per QArfLY respectively. For test and treat appropriately versus test and treat some the median, 25th	Partially Applicable Not conducted from a UK health service perspective.	Very serious limitations. Study funded by manufacturer. Inappropriate time horizon.
		Test with SLNB. Treat patients with a positive result with high dose IFN and those with a negative low dose IFN (test and treat appropriately).	$24,200	3.37	$5,800	0.31	$18,700/ QArfLY			
		Treat all with low dose IFN following surgery.	$30,500	3.48			Extended dominated			
		Test with SLNB. Treat patients with a positive result with high dose IFN and those with a negative with surgery alone (Test and	$33,800	3.68	$9,600	0.31	$31,100/ QArfLY			

Study	Population	Comparators	Costs	Effects	Incr costs*	Incr effects	ICER	Uncertainty	Applicability	Limitations
		treat some)						and 75th percentiles $30,229, $16,766 and $58,823 per QArfLY respectively.		
	Comments: The survival component of the QALY uses relapse free survival and not overall survival.									
Morton et al 2009 (Australia)	Hypothetical cohort of patients with biopsy proven Melanoma ≥1mm	WEX	AU$23,182	9.90 QALYs	Reference			Increasing the probability for distant metastasis post WEX to 0.02 or reducing the post WEX+SLNB probability to 0.01 resulted in SLNB+WEX becoming less costly and more effective (dominant). Decreasing post WEX probability to 0.01 decreases the ICER to $90,959/QALY whilst increasing the WEX+SLNB to 0.022 increases the ICER to $52,436/QALY. Increasing and decreasing the probability of nodal metastasis post WEX to 0.04 and 0.0275 results in WEX+SLNB becoming dominant and $6,273/QALY respectively. Increasing the cost of delayed CLND to $27,000 again results in WEX+SLNB becoming dominant whilst reducing the cost to $8,717results in an ICER of $3,815. Increasing and decreasing the costs of WEX+SLNB between $4,339	Partially applicable Not conducted from a UK health service perspective.	Potentially serious limitations Probabilistic sensitivity analysis was not performed.
		WEX+SLNB	AU$24,045	10.34 QALYs	$863	0.44	$1,983/ QALY			

Study	Population	Comparators	Costs	Effects	Incr costs*	Incr effects	ICER	Uncertainty	Applicability	Limitations
								and $9811 results in ICERS of $397/QALY and $12,976/QALY.		
	Comments:									

**Incremental values in comparison to strategy above except when ruled out through extended dominance.*

A.4 *De novo* economic model

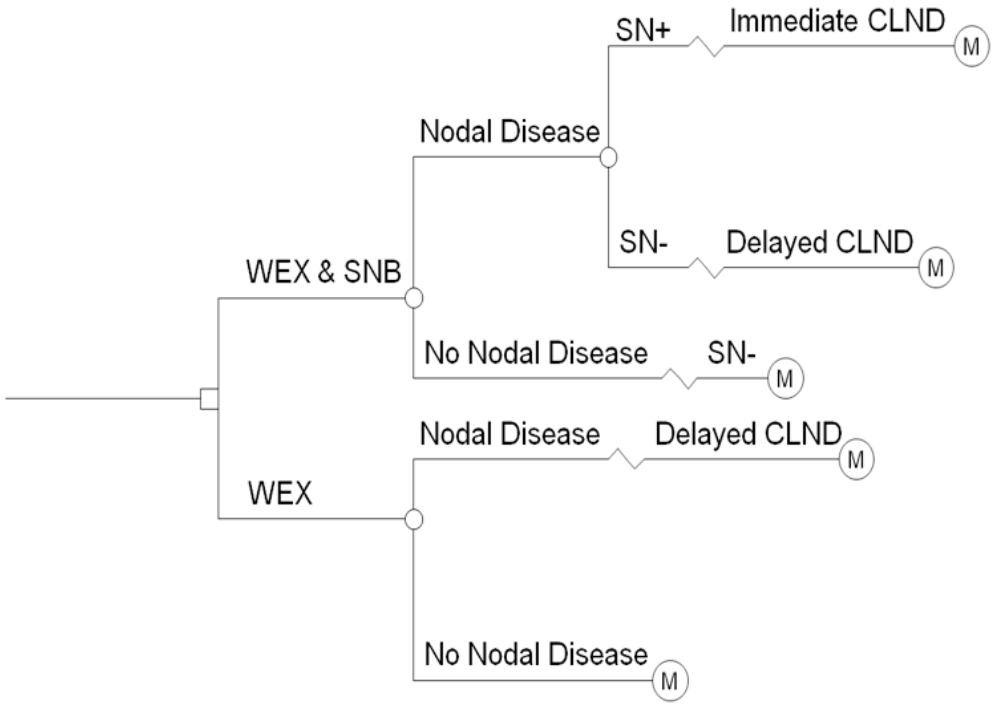
The current economic literature did not adequately address the decision problem, and so a de novo economic evaluation was created to assess cost effectiveness.

A.4.1 Model structure

A decision tree (Figure 1) and Markov model (Figure 2) were developed, in Microsoft Excel 2007, with a cycle length of one year and a time horizon of 20 years. In the initial decision tree stage the following assumptions were made:

- all patients receive a wide excision to remove their primary melanoma.
- depending on the arm of the model, patients receive either no SLNB or a SLNB at the time of excision to identify any nodal disease
- patients identified with nodal disease receive an immediate complete lymph node dissection (ICLND).
- all patients are followed-up by regular clinical examination
- patients who did not have SLNB or who had a negative SLNB and who subsequently develop palpable nodal disease receive a delayed complete lymph node dissection (DCLND).
- all patients with nodal disease, not identified or investigated by SLNB, will eventually develop observable nodal disease and go on to receive a DCLND.
- that there will be no false positives from staging with SLNB (based on the evidence from the accompanying evidence review).

Figure 1: Decision tree structure



Following the decision tree phase of the model patients progress through one of three Markov models (see Figure 2) depending on whether they have received an CLND or not. The Markov model consisted of six mutually exclusive health states:

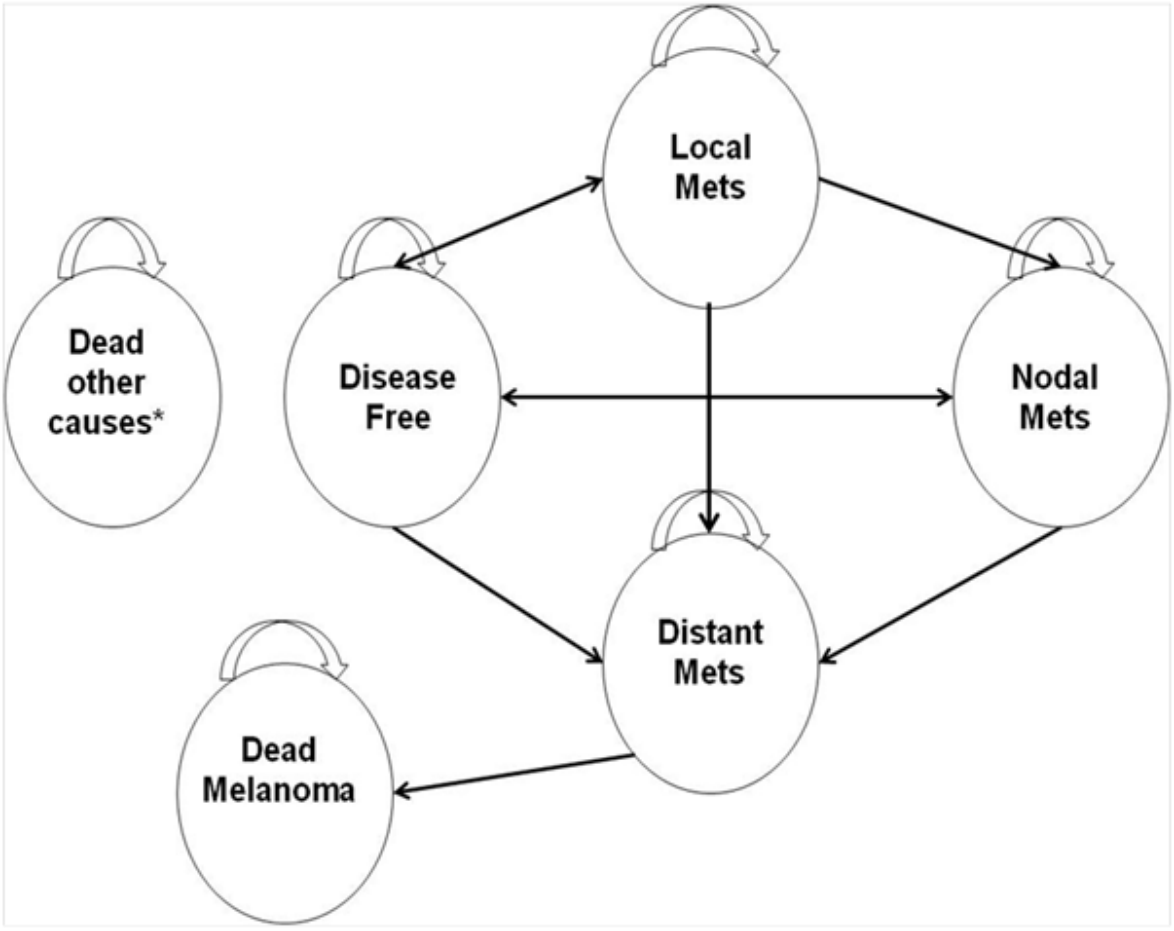
- disease-free

- local metastases
- nodal metastases
- distant metastases
- dead from melanoma
- dead other causes

Only one transition could occur during each annual cycle. The Markov transition probabilities for both the CLND and the no CLND group only differed in the probability of nodal recurrence from 'disease-free'. For ease of modelling once patients had moved to the 'distant metastases' state they remained there until death. The probability of moving from this state to death allows for a proportion of the cohort to have similar survival to that of the 'disease-free' state.

A hypothetical cohort of patients were modelled. The age (52 years) and sex were taken from the MSLT-I trial explained in detail below. The prevalence of micrometastases (20%) when entering the model was taken from the accompanying clinical evidence review. Lifetime total costs and QALYs were captured. The total costs included all costs associated with inital treatment, surveillance, further treatment and management. AQLYs were calculated by multiplying the life years that patients spend in each health state by th associated quality of life weighting. QALY and quality of life weights are discussed in more detail in later sections

Figure 2: Markov model structure



**The model cohort can enter the 'dead other causes' state from any other non-dead health state*

A.4.21 Clinical input data

All clinical inputs for the model were taken from the MSLT-I trial (Morton et. al, 2009; Faries et al, 2010; Morton et al, 2014; Morton et al, 2006) reports and cost effectiveness analysis and the accompanying review of the clinical evidence for this guideline. The MSLT-I trial was a randomised controlled trial comparing WEX+SLNB to WEX alone. Patients identified with nodal micrometastases during sentinel node biopsy received an ICLND. The primary study group of the trial were patients with intermediate thickness (1.2mm to 3.5mm) cutaneous melanoma (n=1347). Patients had an average age of 52 years and were 57% male. The proportion of patients with nodal disease, identifiable by SLNB was estimated to be 15.8%. The final trial report (Morton el at, 2014) found that disease-free survival in patients with intermediate thickness melanoma was significantly higher in the biopsy group (71.3% versus 64.7%) but there was no significant difference in 10-year melanoma specific survival (81.4% versus 78.3%). Disease-free survival was converted to an annual probability and used to inform the difference in nodal recurrence between the ICLND and no DCLND group for the transition probabilities (Tables 2 and 3). Office of National Statistics interim life tables were used to inform the probability of death other causes based on the age of the cohort during the relevant cycle.

Table 2: Annual transition probabilities following ICLND for year 1 of the model

	Disease Free	Local Mets	Nodal Mets	Distant Mets	Dead melanoma	Dead Other Causes
Disease Free	93.1%	1.6%	3.3%	1.6%	0.0%	0.3%
Local Mets	93.2%	1.5%	3.4%	1.6%	0.0%	0.3%
Nodal Mets	72.0%	0.0%	2.8%	24.9%	0.0%	0.3%
Distant Mets	0.0%	0.0%	0.0%	58.2%	41.8%	0.0%
Dead melanoma	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Dead Other Causes	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

Table 3: Annual transition probabilities following DCLND for year 1 of the model

	Disease Free	Local Mets	Nodal Mets	Distant Mets	Dead melanoma	Dead Other Causes
Disease Free	92.2%	1.6%	4.3%	1.6%	0.0%	0.3%
Local Mets	93.2%	1.5%	3.4%	1.6%	0.0%	0.3%
Nodal Mets	72.0%	0.0%	2.8%	24.9%	0.0%	0.3%
Distant Mets	0.0%	0.0%	0.0%	58.2%	41.8%	0.0%
Dead melanoma	0.0%	0.0%	0.0%	0.0%	100.0%	0.0%
Dead Other Causes	0.0%	0.0%	0.0%	0.0%	0.0%	100.0%

A.4.21.1 Prevalence

The MSLT-1 trial reported a prevalence of micrometastases of 15.9% amongst the patient group (Morton et al, 2005). This differed from studies identified by the accompanying clinical evidence review, with studies having a prevalence of between 16% and 25%. The GDG therefore felt an estimate of 20% would more closely reflect the true prevalence in this population.

A.4.21.2 Transition probabilities

Transition probabilities between each disease state, for ICLND and DCLND were those reported by Morton et al (2009) (see Tables 2 and 3). The model assumed that the only

difference in recurrence rate between the two groups was in terms of transitions from the 'disease free' health state to 'nodal metastases' and that all other transition probabilities were identical between the groups. Transitions for patients not receiving any CLND were not modelled other than for adverse events, although the model assumes that this proportion would be identical between the two arms and therefore health outcomes and non-adverse event related costs in both groups would cancel out during incremental analysis.

A.4.2.3 Diagnostic accuracy

Sensitivity and specificity were taken from the accompanying systematic review of the clinical evidence for this guideline. The sensitivity of SLNB in identifying micrometastatic nodal disease, for patients with clinicopathological stage I-II melanoma was estimated to be 88.7% (95%CI: 76.1% to 95.1%) based on five studies with 1766 data points. Specificity was 100% as reported in all five studies included in the review.

A.4.2.4 Adverse events

Adverse events for patients receiving SLNB were taken from Wasserberg et al (2004) a retrospective case series of SLNB performed on 309 lymphatic basins on 250 patients. Wasserberg et al (2004) reported complications in 42 cases. For our base-case we therefore used a complication rate of 13.6% for SLNB. The GDG felt that this may be an overestimate of complication rates during contemporary surgery and therefore a complication rate of 3%, based on GDG estimate, was tested during deterministic sensitivity analysis.

Morbidity and additional bed days of ICLND and DCLND were taken from the MSLT-1 trial (Faries et al, 2010). The trial also found that both mild/moderate (17.4% vs. 11.4%) and severe lymphoedema (3.0% vs. 1.0%) were significantly higher in the DCLND group than for patients receiving ICLND. These values were used in the model as the rate of lymphoedema for both treatments. The trial found a non-significant higher rate of both weakness and dysesthesia for ICLND, however given that the differences were not statistically significant and that only a small proportion had severe symptoms these adverse events were not included in the model.(Table 4)

Table 4: Adverse events assoicated with surgical procedures

Adverse Event	Percentage of patients
SLNB	13.6%
Mild/moderate lymphoedema (ICLND)	11.4%
Severe lymphoedema (ICLND)	1.0%
Mild/moderate lymphoedema (DCLND)	17.4%
Severe lymphoedema (DCLND)	3.0%

A.4.2.5 Quality of life

No high quality evidence on quality of life were identified for melanoma. Quality of life data were therefore taken from a range of sources and were similar to those sourced in previous economic evaluations (Morton et al, 2009). 'No evidence of disease' was set as equal to the 'disease-free' state in Kilbridge et al. (2001) Preferences were elicited from 107 patients receiving adjuvant interferon alfa-2b therapy using the standard gamble technique in the USA. Utilities of 'disease-free' were assumed to be identical to that of 'no disease' in this patient group.

Utilities for local metastases were taken from general cancer population values given a lack of evidence specific to melanoma (Torrance et al, 1989). The utility for the 'nodal metastases' health state was assumed to be identical to that of treatment for local or in-

transit metastases. Values for regional disease were based on an average of old and new stage III patients from a US population (Bendeck et al, 2004).

Utilities for 'distant metastases' were assumed to be identical to those reported by Morton et al for diagnosis of distant disease. This figure was based on a cost effectiveness analysis for interferon alpha-2a (Lafuma et al, 2001).

There was a paucity of evidence around age-specific utilities. Whilst age-specific utility values were identified for a general UK population although these were unlikely to accurately reflect any health state included in the model.

Given the large uncertainty around these utility values, they were given a wide confidence interval during probabilistic sensitivity analysis.

The quality of life weightings applied in the model are shown in Table 5.

Table 5: Quality of life weightings applied in the model

Health state	Utility Value
Disease Free	0.96
Local Metastases	0.67
Regional Metastases	0.52
Distant Metastases	0.50
Death	0.00

A.4.3 Costs

Costs were taken from NHS Reference Costs 2012-2013 unless otherwise stated. Costs were inflated to 2013 prices, using the hospital & community health services (HCHS) index, where appropriate. (Table 6)

A.4.3.1 Surgical costs

The additional costs for performing SLNB alongside WEX were estimated to be £2,088 per patient. Surgical costs for wide excision, SLNB and CLND were taken from NHS reference costs. Faries et al (2010) reported an increase in bed days following inpatient admission following DCLND of 1.6 days compared to ICLND. These additional bed days, calculated from NHS reference costs, have been added to the cost of DCLND.

A.4.3.2 Adverse event costs

No sources of costs were identified for adverse events. The costs of lymphoedema were estimated based on estimates from one NHS Lymphoedema Service. Costs for complications associated with SLNB were based on Morton et al (2009) which estimated that complications from SLNB would result in an average of seven general surgery outpatient visits, 4 wound clinics and 4 physiotherapy sessions. This resulted in an additional cost of £1421, based on NHS reference costs.

A.4.3.3 Health state costs

Health states costs were based on a typical follow-up regime for patients entering each transition state. All patients were assumed to have a consultant-led follow-up every 3 months in the first and second year and twice yearly until 5 years following their initial surgery (Bishop et al, 2002).

Patients transitioning to 'local metastases' were assumed to receive WEX and an additional consultant-led appointment. Patients transitioning to 'nodal recurrence' received CLND as

well as staging by whole body CT scan and MRI head. The follow-up schedule described above would also restart following either of these transitions. Patients transitioning into the 'distant metastases' state were assumed to be treated with either ipilimumab (50%), dacarbazine (15%) or vemurafenib (35%). Total lifetime costs for this group were taken from a single technology assessment. Average total lifetime costs for ipilimumab were £90,688 and £11,468 for dacarbazine. In the absence of evidence it was assumed that the lifetime costs of vemurafenib were identical to that of ipilimumab. All costs, discounted for future years, were added when patients first transitioned into a health state for ease of modelling.

Table 6: Unit costs as applied in the model

	Cost	Reference
Definitive surgery	£1141	NHS reference costs 2012-201311
SLNB	£2088	NHS reference costs 2012-2013
MRI scan	£169	NHS Reference Cost 2012-2013
Follow-up appointment	£139	NHS Reference Cost 2012-2013
Surgery follow up	£119	NHS reference costs 2012-2013
Wound follow-up	£102	NHS Reference Cost 2012-2013
Physiotherapy	£44	NHS Reference Cost 2012-2013
Cost ICLND	£3,534	NHS reference costs 2012-2013
Additional bed days DCLND	1.6	Faries et al (2010)
Mild/moderate lymphoedema	£67	Lymphoedema service estimate
Severe lymphoedema	£3,360	Lymphoedema service estimate
Disease free	£2105	NHS reference costs 2012-2013
Local metastases	£3246	NHS reference costs 2012-2013
Nodal metastases	£7187	NHS reference costs 2012-2013
Distant metastases	£78,805	Ipilimumab STA
Death (one off cost)	£5,527	Ipilimumab STA

A.4.4 Discounting

All costs and health outcomes were discounted at a rate of 3.5% per annum in line with NICE guidance.

A.4.5 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that are used in the base case are replaced with values drawn from distributions around the mean values.

A.4.6 Results

The base-case results estimate that WEX+SLNB had an increased in lifetime cost of £1,638 and a small increase in QALYs of 0.048. This equates to an incremental cost effectiveness ratio (ICER) of £34,402 per QALY above the NICE threshold of £20,000 per QALY (Table 7). The stochastic results were very similar in terms of costs and QALY with an ICER of £30,103 per QALY

Table 7: Base case results

Outcome	WEX+SNB	WEX	Incremental
Cost	£33,320	£31,682	£1,638
Quality adjusted life years (QALYs)	11.34	11.29	0.048
Cost per QALY gained			£34,402

A series of deterministic sensitivity analyses were also conducted, whereby a parameter or parameters were changed to assess its influence on the outcomes. The results of the deterministic sensitivity analysis are shown in Table 8.

Table 8: Deterministic sensitivity analysis results

Change made	Incremental Cost	Incremental QALY	ICER
100% sensitivity SLNB	£1,590	0.054	£29,631
Prevalence=16%	£1,766	0.038	£46,380
Prevalence=25%	£1,477	0.060	£24,820
Half difference disease free survival.	£1,829	0.031	£59,130
No difference in disease free survival	£2,016	0.015	£138,364
Complications SLNB=3%	£1,487	0.048	£31,237
Difference in costs between WEX=SLNB and WEX halved	£594	0.048	£12,468
Cost ICLND=DCLND	£1,740	0.048	£36,559
Identical lymphoedema rates for CLND	£1,813	0.033	£54,898
QoL=0.8 for all non-dead health states	£526	0.019	£27,667

The deterministic sensitivity analysis showed that the ICER was sensitive to the difference in costs between WEX+SLNB and WEX alone. When the difference in cost between the two was halved the ICER reduced to £12,468 per QALY. The ICER was also sensitive to the prevalence of nodal micrometastases with the ICER ranging from £24,820 to £46,380 per QALY when prevalence was varied between the range of that identified by the accompanying evidence review. The ICER was also sensitive to the rate of disease free survival; when the difference in disease free survival was halved between the SLNB and SLNB+WEX group the ICER increased to £138,364 above the conventionally held willingness to pay threshold.

A.4.14 Probabilistic sensitivity analysis

The probabilistic sensitivity analysis (Figure 3) was run for 1000 iterations and resulted in WEX+SLNB being more or as expensive in 87% and more effective in over 99% of iterations compared to WEX alone. The cost effectiveness acceptability curve (Figure 4) for WEX+SLNB compared with WEX alone showed that WEX+SLNB was preferred 43.8% of the time at a willingness to pay threshold of £20,000 per QALY. WEX+SLNB was the preferred choice in over 50% of iterations when the WTP threshold was above £24,000 per QALY.

Figure 3: Cost effectiveness plane

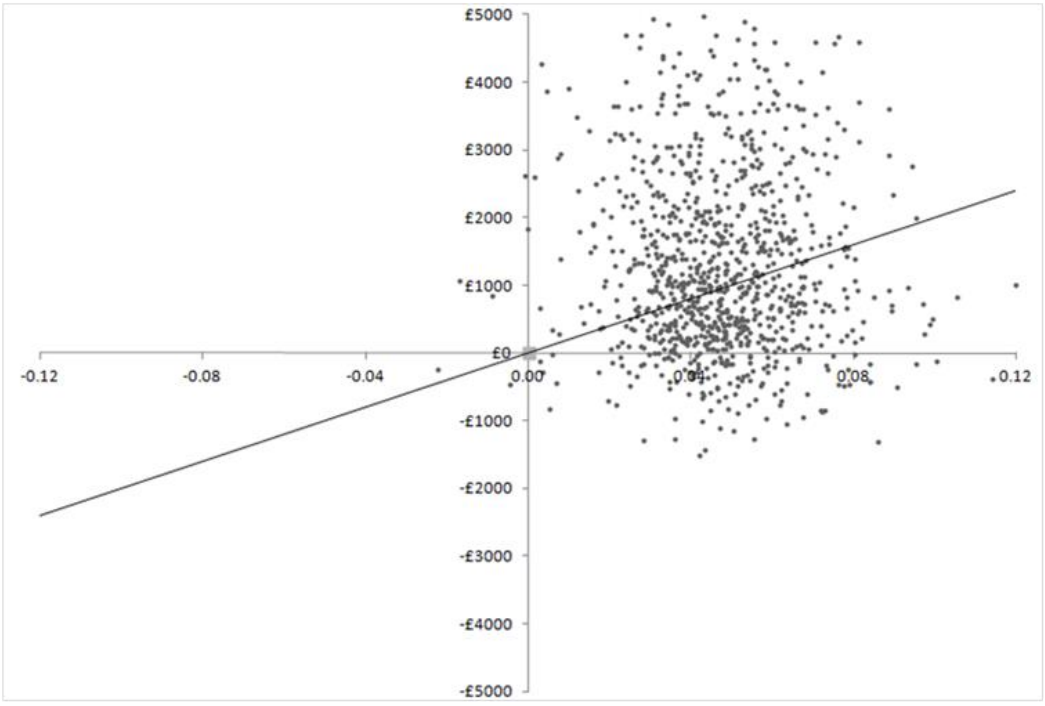
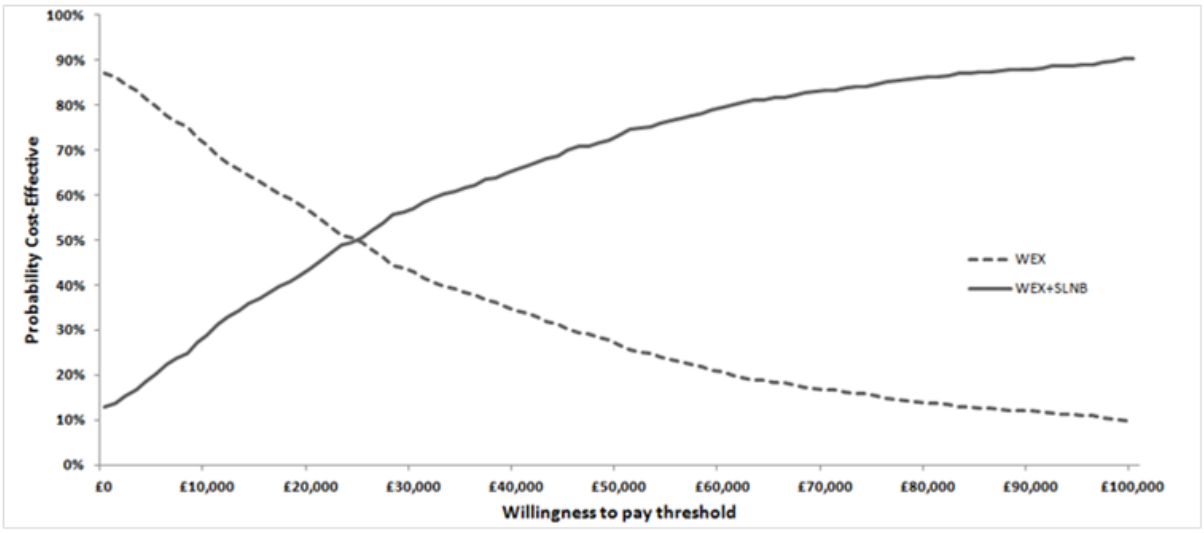


Figure 4: Cost effectiveness acceptability curve



A.4.8 Conclusion

Under the base case assumptions WEX+SLNB was not cost effective at the NICE threshold of £20,000 per QALY although there is uncertainty around our estimate. This result is sensitive to both difference in disease free survival between the two groups and the size of the impact in terms of quality of life from any increase in disease-free survival.

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1 Full list of parameters and distributions used in the model

	Value	Reference	PSA Distribution
Age	52	Morton et al (2006)	Normal(Mean=52,SD=0.01)
Male	57%	Morton et al (2006)	
Sensitivity	88.7%	Evidence Review	Beta(α=53.2,β=8.4)
Specificity	100%	Evidence Review	Fixed
Prevalence	20.0%	Evidence Review	Uniform(16%,25%)
Annual transition probabilities (1st year)			
No disease to nodal disease (ICLND)	3.3%	Morton et al (2014)	Beta(α=704,β=20736)
No disease to nodal disease (DCLND)	4.2%	Morton et al (2014)	Beta(α=913,β=20527)
Complications			
SLNB	13.6%	Wasserberg et al (2004)	Uniform (0%,15%)
Mild/moderate lymphoedema (ICLND)	11.4%	Faries et al (2010)	Beta(α=26,β=199)
Severe lymphoedema (ICLND)	1.0%	Faries et al (2010)	Beta(α=2,β=223)
Mild/moderate lymphoedema (DCLND)	17.4%	Faries et al (2010)	Beta(α=23,β=109)
Severe lymphoedema (DCLND)	3.0%	Faries et al (2010)	Beta(α=3,β=129)
Costs			
Definitive surgery	£1141	NHS reference costs 2012-201311	Gamma(α=83.9, β=13.6)
SLNB	£2088	NHS reference costs 2012-2013	Gamma(α=1.8, β=1196.2)
MRI scan	£169	NHS Reference Cost 2012-2013	Gamma (α =53.8,β = 2.3)
Follow-up appointment	£139	NHS Reference Cost 2012-2013	Gamma (α =9.1,β = 15.2)
Complications			
Surgery follow up	£119	NHS reference costs 2012-2013	Gamma(α=12.1, β=9.8)
Wound follow-up	£102	NHS Reference Cost 2012-2013	Gamma (α =10.2,β=10.0)
Physiotherapy	£44	NHS Reference Cost 2012-2013	Gamma (α =12.2,β=3.6)
Cost ICLND	£3,534	NHS reference costs 2012-2013	Gamma (α =7.0,β=507.2)
Additional bed days DCLND	1.6	Faries et al (2010)	Uniform(0,3.2)
Mild/moderate lymphoedema	£67	Lymphoedema service estimate	
Severe lymphoedema	£3,360	Lymphoedema service estimate	
Health state costs			
Disease free	£2105	NHS reference costs	Summation of other

	Value	Reference	PSA Distribution
		2012-2013	variables
Local metastases	£3246	NHS reference costs 2012-2013	Summation of other variables
Nodal metastases	£7187	NHS reference costs 2012-2013	Summation of other variables
Distant metastases	£78,805	Ipilimumab STA	Summation of other variables
Death (one off cost)	£5,527	Ipilimumab STA	Gamma (α=0.6,β=8906.7)
Health state utilities			
Disease free	0.96	Kilbridge et al (2001)	Beta(α=0.98,β=0.02
Local metastases	0.67	Torrance et al (1989)	Beta(α=0.67,β=0.33)
Nodal metastases	0.52	Bendeck et al (2004)	Beta(α=0.52,β=0.48)
Distant metastases	0.5	Lafuma et al (2001)	Beta(α=0.5,β=0.5)

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Appendix B: Cost-effectiveness of different follow-up strategies in high risk cutaneous melanoma

B.1 Background

After a melanoma is treated, patients have regular checkups to look for signs of:

- local recurrence
- nodal or distant metastases
- new primary melanomas

Current follow-up strategies were developed at a time when effective systemic treatments for advanced disease was not available. Recently ipilimumab and vemurafenib have been licensed for use in the UK and show significant survival benefits in phase 3 trials. Therefore the GDG postulated that it might be beneficial to have a more intensive follow-up regimen (including imaging which has not previously been the norm) to try and identify recurrent disease earlier, that may benefit from earlier systemic treatment. However, this would lead to an increase in resource use because of increased imaging (CT, PET-CT, MRI etc) and staff time, and an increased radiation dose for a significant proportion of patients who would never go on to develop stage IV disease.

B.2 Aim of analysis

The aim of the analysis was to estimate the cost effectiveness of adding routine imaging of asymptomatic patients to current standard follow-up in patients with stage III melanoma. Currently patients attend clinical review as set out in Table 9 and are encouraged to self-examine to look for signs of recurrence between appointments. In addition to clinical review, regular routine imaging could be used, consisting of MRI head and CT chest, abdomen and pelvis to identify missed recurrences and indentify asymptomatic recurrences earlier. The frequency of routine imaging investigated, as suggested by the GDG was to be 6 monthly during the first 3 years after treatment with curative intent.

Table 9: Frequency of clinical reviews for patients with stage III melanoma

Year	Frequency
Years 1-3	3 Monthly
Years 4-5	6 Monthly
Years 6-10	Annual

B.3 Existing economic evidence

A systematic literature review was performed to assess the current economic literature in this area. The review identified 303 possibly relevant economic papers relating to melanoma. Of these, eight full papers were obtained for appraisal. A further 4 papers were excluded as they only reported costs and 2 were excluded as they were not relevant to the PICO. Two papers (Mooney et al (1997) and Krug et al (2010)) were included in the current review of published economic evidence for this topic. The included studies are summarised in Table 10.

Mooney et al was a cost-utility analysis, conducted from a US healthcare payer perspective comparing usual follow-up to usual follow-up with life-long annual chest x-rays for local, regional or metastatic recurrence in a hypothetical cohort of patients diagnosed with intermediate-thickness [Clark's level III], local, cutaneous melanoma. The study used a Markov model and a 20-year time horizon. The model estimated an additional cost per patient of $755 and an increase in Quality Adjusted Life Years (QALYs) of 0.035 resulting in an incremental cost effectiveness ratio (ICER) of $215 000. During deterministic sensitivity analyses screening was always more costly and effective with the ICER ranged from $109,000 to $765,000 per QALY for the lifetime (20year) screening option. When also altering the frequency and total duration of the screening programme the ICER ranged from $143,000 to $240,000. Mooney et al was deemed to be only partially applicable with very serious limitations. The study was also relatively old and treatment for identified metastatic recurrences has changed significantly since then.

Krug et al was a cost-utility analysis, conducted from a Belgian healthcare perspective. The authors developed a Markov model with a 10-year time horizon to compare whole body CT to FDG-PET CT for patients with suspected pulmonary metastases in a hypothetical cohort of patients with resected stage IIc and stage III malignant melanoma. In the base-case the model estimated that investigation with FDG-PET CT was both more effective and cost saving. During probabilistic sensitivity analysis FDG-PET had a 71.0% chance of being both more effective and cost saving although whole body CT was more effective and less costly in 22.6% of iterations. The uncertainty was largely as a result of uncertainty around the effectiveness of preventing unnecessary surgery. The study was deemed to be only partially applicable and have potentially serious limitations as a result of a lack of transparency around the model inputs. As with Mooney et al the treatment after identification of recurrence has also changed significantly since publication of this analysis.

1 **Table 10: Modified GRADE profile for included economic studies**

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
Mooney et al. 2000 (USA)	Hypothetical cohort of patients diagnosed with intermediate-thickness [Clark's level III], local, cutaneous melanoma. The cohort had an average age of 52 years and was 53% male	Usual follow-up.	Not reported	Not reported	Reference			One-way Sensitivity Analysis One-way sensitivity analyses were conducted with ICER ranging from $109,000/QALY to $765,000/QALY for the lifetime (20year) screening option. When altering the frequency and total duration of the screening program the ICER ranged from $143,000 to $240, 000. Screening was always more costly and effective.	Partially Applicable Not conducted from a UK perspective.	Very Serious Limitations. Lack of PSA relevant costs not included in the analysis
		Usual follow-up plus life-long annual CXR for local, regional or metastatic recurrence.	Not reported	Not Reported	$755a	0.035 QALYsb	$215 000			
	Comments:									
Krug et al 2010 (Belgium)	Patients with resected stage IIc and stage III malignant	Follow-up with suspected pulmonary metastases being examined with whole	$4 384	90.41 Life months	Reference			Probabilistic Sensitivity Analysis: PET-CT was dominant in 71.0%	Partially Applicable Not conducted from a UK	Potentially serious limitations. Lack of transparency

b Calculated by NCC-C health economist from reported data

Study	Population	Comparators	Costs	Effects	Incr costs	Incr effects	ICER	Uncertainty	Applicability	Limitations
	melanoma.	body CT.						of iterations and dominated in 22.6% of iterations versus WB-CT.	health service perspective .	around clinical inputs
	Age performance status and other demographic data was not reported for this cohort	Follow-up with suspected pulmonary metastases being examined with fluorine-18 fluoro-2-deoxyglucose (FDG) positron emission tomography (PET) with X-Ray computed tomography(CT)	$3 438	90.61 Life Months	-€946	0.20	PET-CT dominant (Both cost saving and health improving).			
	Comments:									

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B.4 *De novo* economic model

Since the current economic literature did not adequately address the decision problem, a de novo economic evaluation was undertaken to assess cost effectiveness.

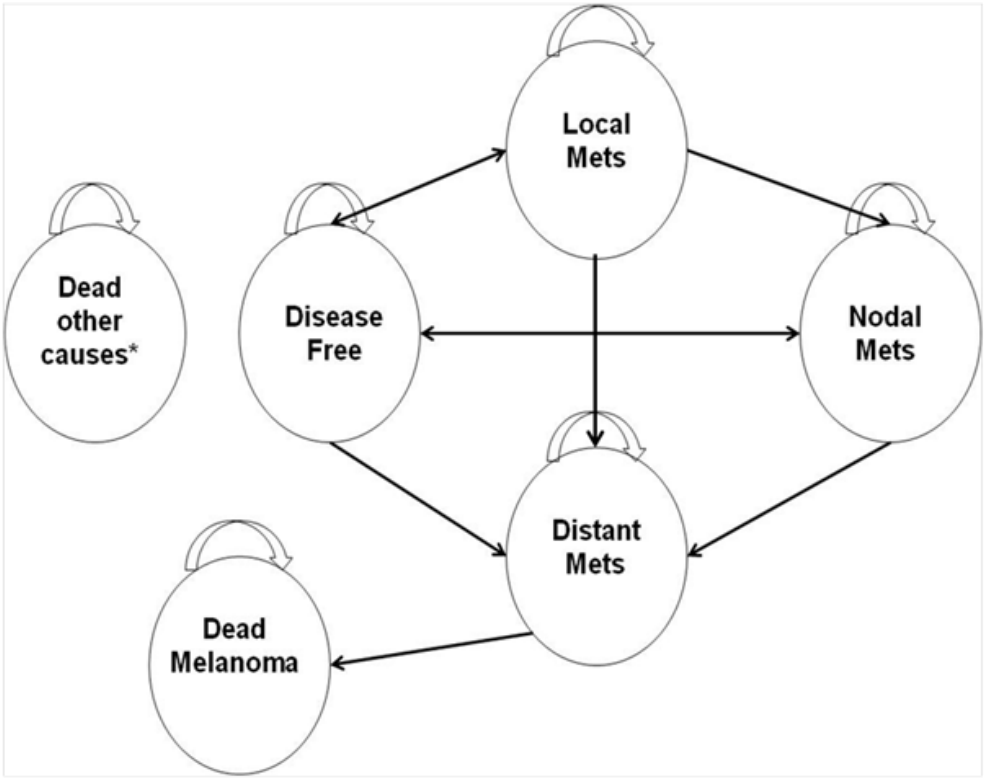
B.4.1 Model structure

A Markov model comparing follow-up with and without routine imaging was developed, in Microsoft Excel 2007, with a cycle length of 3 months and a time horizon of 20 years. . Six mutually exclusive health states were included in the model:

- no evidence of disease
- loco-regional recurrence
- distant recurrence
- treatment for distant recurrence
- death from melanoma
- death from other causes

Only one transition could take place during each 3 month cycle. The model structure is represented in Figure 5.

Figure 5: Model structure



**Patients can transition to Death Other Cause from any other non-dead health state*

In the model the following assumptions were made:

- patients with stage IIIA, IIIB and IIIC disease, who have previously received treatment with curative intent and have no evidence of disease are followed-up clinically to assess for recurrence of disease.
- patients receive a clinical review every 3 months during the first 3 years, every 6 months for 4-5 years and then annually 5-10 years following treatment.

- patients receive imaging if either the patient or doctor identifies possible recurrence or there has been a change or progression in symptoms indicative of recurrence.
- depending upon the arm of the model patients may also be given routine imaging, independent of this clinical assessment, by MRI head plus CT.
- patients identified as having a loco-regional recurrence receive surgery to remove the disease
- if the surgery is successful then the patient returns to the 'no evidence of disease' state.
- if surgery is unsuccessful or the patient is not suitable for surgery or refuses surgery, they remain in the 'loco-regional recurrence' state.
- patients in the 'loco-regional recurrence' state have an increased probability of moving to 'distant recurrence' or death from melanoma
- if recurrences are missed by the patients, doctor or routine imaging patients have an increased probability of moving to 'distant recurrence' or 'death from melanoma
- patients identified as having distant recurrence are offered systemic treatment and remain in the treatment for distant recurrence until death.
- A hypothetical cohort of patients were modelled. The cohort had an age of 57 years and were 645% male tkane from one retrospective study described below. Lifetime total costs and QALY were captured. The total costs included all costs associated with initial treatment, surveillance, further treatment and management. QALY were calculated by multiplying the life years that patients spend in each health state by the associated quality of life weighting. QALY and quality of life weights are discussed in more details in later sections.

B.4.2 Clinical input data

B.4.2.1 Demographic

Demographic data were taken from Romano et al (2010). This was a retrospective study at one cancer centre in the USA of 429 patients with Stage III melanoma who were rendered free of disease. The cohort had a mean age of 57 years and was 64% male.

The proportion in each stage of melanoma as staged before initial treatment was taken from the East of England Cancer Registry (Table 11).

Table 11: Proportion of cohort in each disease stage in the model

Disease stage	Proportion of cohort
Stage IIIA	36.0%
Stage IIIB	42.2%
Stage IIIC	21.8%

B.4.2.2 Risk of recurrence

The 3-monthly risk of recurrence for stage IIIC melanoma was taken as the same as that calculated by Rueth et al (2014) based on 1600 patient records between 1992 and 2004 at a US cancer centre (Table 12). Rueth et al reported monthly transition probabilities which were converted to 3 monthly probabilities using standard conversion equations. Recurrence rates for stages IIIA and IIIB melanoma were calculated using recurrence data from Romano et al to adjust stage IIIC probabilities.

Table 12: Three monthly probability of recurrence applied in the model

Disease stage	Year 0- 1	Year 1-2	Year 2-3	Year 3-5	Year 5-10

Disease stage	Year 0- 1	Year 1-2	Year 2-3	Year 3-5	Year 5-10
Stage IIIA	12.2%	2.8%	2.2%	1.5%	1.5%
Stage IIIB	13.5%	3.1%	2.5%	1.7%	1.7%
Stage IIIC	23.4%	5.6%	4.4%	2.9%	2.9%

B.4.2.31 Site of recurrence

Estimates for site of recurrence were taken from Romano et al who calculated that 49% of recurrences would be loco-regional and 51% would be distant.

Table 13: Site of recurrence

Site	Percentage
Loco-regional	49%
Distant	51%

B.4.2.46 Progression of loco-regional disease to distant disease

It was assumed that loco-regional recurrence that is untreated or untreatable will have a probability of progressing to distant recurrence. From clinical experience, Rueth et al (2014) estimated that this would happen to all untreated loco-regional recurrences after 6 months. Progression for the de novo model was estimated by calculating a 3-monthly probability that would predict that 95% of the untreated recurrences would progress after 6 months for stage IIIC melanoma. This was reduced by 5% for stage IIIB melanoma and 10% for stage IIIA (Table 14). Given that there was no evidence for these estimates and that it was difficult to get GDG consensus on its value, it was assigned a wide uniform distribution during probabilistic sensitivity analysis and various assumptions tested during sensitivity analysis. It was also examined during deterministic sensitivity analysis.

Table 14: Three monthly probability of progression applied in the model

Disease stage	Probability of Progression
Stage IIIA	75%
Stage IIIB	80%
Stage IIIC	85%

B.4.2.518 Probability of death

A 3-monthly probability of death for patients with no evidence of disease was taken from Office of National Statistics Life Tables 2010 – 2012. The probabilities of death following unidentified, untreatable, unsuccessfully treated or missed loco-regional recurrence and distant recurrence were calculated from the median survival reported in Meyers et al (2009) for patients who refused or were unsuitable for surgical treatment. This was a retrospective case-series study of 180 patients with Stage II and Stage III melanoma. Meyers et al calculated a median survival of 22 and 7 months following loco-regional and distant recurrence respectively. This equated to a 3 monthly probability of death of 6.7% and 19.9%. As the 19.9% was lower than our estimate for treatment with dacarbazine we inflated this figure to 26.1% the highest 3 monthly transition calculated from the DeQuen et al (2012) study discussed later.

B.4.2.6 Diagnostic accuracy

Romano et al (2010) estimated that there was a probability of 68% that a recurrence would be identified without routine imaging i.e. by patient self-examination, through physician examination during follow-up or through new or changing symptoms. As imaging was performed 3 monthly during the first 2 years in the Romano study the GDG agreed that this figure was likely to be lower than with the 6 monthly imaging used in the model. Higher proportions of recurrences identified outside of routine imaging were tested during deterministic sensitivity analysis.

If routine imaging was included as part of usual follow-up it was considered that CT was more likely to be used than PET-CT given it is both less costly and more widely available. The sensitivity and specificity of CT plus MRI head imaging were taken as 86% and 96% from Koskivuo et al (2007) estimate for PET-CT. No evidence was identified for the diagnostic accuracy of CT scan plus MRI head or for any modality of imaging of the head for recurrence. Therefore no adjustments were made to diagnostic accuracy for either CT scan or for brain imaging. A sensitivity analysis assuming perfect accuracy in detecting recurrences was performed given that the GDG considered this a likely underestimate of the true diagnostic accuracy. (Table 15)

Table 15: Diagnostic accuracy as applied to the model

	Percentage
Loco-regional recurrence	
Sensitivity	86%
Specificity	96%
Distance recurrence	
Sensitivity	86%
Specificity	96%
Probability recurrence picked up outside routine imaging	85%

B.4.2.7 Treatment efficacy

No evidence was identified on the proportion of recurrences going onto surgery or the effectiveness of surgery in rendering patients free of disease and therefore an estimate by the GDG was used for this variable. It was estimated that 90% of patients with a loco-regional recurrence would be suitable for surgery and that of these 70% would become disease-free. (Table 16)

Table 16: GDG estimates of efficacy of surgery

	Percentage
Proportion suitable surgery	90%
Proportion successful surgery	70%

Recent chances in treatment with ipilimumab means there was uncertainty around the proportion of patients likely to start each type of treatment and that previous sources were likely to underestimate the proportion of patients starting ipilmumab. Therefore, estimates by the GDG were used for the proportion of patients starting each type of systemic treatment

(table 17). The GDG decided there were three treatments; dacarbazine, ipilimumab and vemurafenib which would be considered in the model.

Table 17: GDG estimates of percentage of patients starting each treatment following identified distant recurrence

Treatment	Number first cycle
Ipilimumab	50%
Dacarbazine	15%
Vemurafenib	35%

Survival following treatment for distant recurrence was taken from the DeQuen et al (2012) systematic review and meta-analysis of randomised controlled trials, comparing alternative treatments in the management of unresectable stage III or IV melanoma. Overall mean survival was calculated for ipilimumab (18.8 months) single-agent chemotherapy (12.3 months), chemotherapy combinations (12.2 months), biochemotherapies (11.9 months), single-agent immunotherapy (11.1 months), and immunotherapy combinations (14.1 months). The study did not identify any studies which allowed vemurafenib to be included in the meta-analysis. Therefore it was assumed to result in identical survival to ipilimumab.

Although it is possible for patients to recover from distant disease and return to the no evidence of disease' state this transition was not included in the model structure to avoid double counting of survival from DeQuen et al (2012).

B.4.2.8 Additional benefits of earlier detection

During our base-case analysis there was no additional assumed benefit to picking the disease up by routine imaging compared to identification by the patient or doctor. However it has been hypothesised that if recurrences are picked up earlier before becoming symptomatic, the disease is more likely to be of small volume and so there might be greater effectiveness of systemic treatments. Patients are also more likely to have ECOG performance status 0 or 1 shortly after recurrence and before they become symptomatic, a pre-requisite to treatment with ipilimumab. Newer drugs including immunotherapy are leading to longer survival with a long-term survival benefit estimated up to 40% for some therapies in early development.

However, it is unclear what the difference in lead time is between identification of recurrence by imaging and by patient or doctor or how this relates to the volume of disease and performance status. No evidence on this was identified during the clinical evidence review.

Survival for this group was identical to that reported in DeQuen et al (2012) prior to a 15% survival plateau being reached. Following this patients follow survival as estimated from ONS life tables (The Office for National Statistics, 2013).

B.4.2.9 Quality of life

Quality of life data were taken from Kilbridge et al (2001). Preferences were elicited from 107 patients receiving adjuvant interferon alfa-2b therapy using the standard gamble technique in the USA. Utilities of no evidence of disease were assumed to be identical to that of no disease in this patient group and distant recurrence was assumed to be equal to treatment for recurrence. No utility value was identified for loco-regional recurrence so the mean of no evidence of disease and distant recurrence was assumed.

Using the estimated survival and quality of life weights from the model it was calculated that under the secondary analysis assumption of a 15% long-term survival for patients identified through routine imaging and treated with ipilimumab would gain an additional 1.507 QALYs. The additional QALYS were added at the time of identification of distant recurrence for ease of modelling.

There was paucity of evidence around age-specific utilities. Whilst age-specific utility values were identified for a general UK population although these were unlikely to accurately reflect any health state included in the model

The quality of life weightings applied in the model are shown in the Table 18.

Table 18: Quality of life weightings applied in the model

Health state	Utility Value
No Evidence of Disease	0.96
Loco-regional Recurrence	0.79
Distant Recurrence	0.61
Death	0.00

B.4.3 Costs

Costs were taken from NHS Reference Costs 2012-2013 unless otherwise stated. Costs were inflated to 2013 prices, using the hospital and community health services (HCHS) index, where appropriate. All costs are reported in table 19.

B.4.3.1 Follow-up and imaging costs

Each follow-up appointment was estimated to cost £139 (consultant led face to face non-admitted follow-up) excluding any imaging or additional tests. The cost of MRI (£169) and CT scan (£125) were taken from NHS reference costs. It was assumed that the cost associated with false positive results from imaging was identical to that of one follow-up appointment.

B.4.3.2 Cost of recurrence

It was assumed that, following a confirmed recurrence, each patient would have a consultant appointment, BRAF test (£95) and be restaged using CT and MRI head resulting in a restaging cost of £530.

B.4.3.3 Treatment costs

The cost of surgery to remove localised metastases was £835. The lifetime costs of ipilimumab (£90,688) and dacarbazine (£11,469) for treatment of distant recurrence was taken from revised estimates for the lifetime costs reported by Dickson et al (2011) which includes all associated costs including additional imaging and follow-up during treatment. No estimates of the cost of vemurafenib were identified and so it was assumed to be identical to that of ipilimumab but this was varied during probabilistic sensitivity analysis. Discounted lifetime costs were added to the total costs at the first cycle after the identification of a distant recurrence for ease of modelling. It was assumed that these costs would not change as a result of the long-term survival modelled in the secondary analysis.

B.4.3.4 Terminal care costs

Studies of resource use in cancer show a peak in costs towards the final months of life. A terminal care cost (£5,527), taken from NICE TA319, was therefore added for patients in their final years of life.

Table 19: Unit costs as applied in the model

	Cost	
CT scan	£125	NHS Reference Cost 2012-2013
MRI scan	£169	NHS Reference Cost 2012-2013
BRAF test	£97	NICE (2012)
Surgical removal localised metastases	£835	NHS Reference Cost 2012-2013
Follow-up appointment	£139	NHS Reference Cost 2012-2013
Consultant outpatient oncology visit	£139	NHS Reference Cost 2012-2013
Ipilimumab (lifetime)	£90,688	Dickson et al 2011
Dacarbazine (lifetime)	£11,469	Dickson et al 2011
Vemurafenib (lifetime)	£90,688	Dickson et al 2011

B.4.4 Discounting

All costs and health outcomes were discounted at a rate of 3.5% as recommended by the NICE Guidelines Manual (2012)

B.4.5 Probabilistic sensitivity analysis

Probabilistic sensitivity analysis (PSA) was also conducted to assess the combined parameter uncertainty in the model. In this analysis, the mean values that were used in the base case were replaced with values drawn from distributions around the mean values. Two scenarios were used during the PSAs using survival estimates from DeQuen et al (2012) and one using a fixed 15% plateau for patients identified asymptomatically by routine imaging.

B.4.6 Results

The deterministic base case results of the model are shown in the table 20. The addition of routine imaging during follow-up lead to an increase in lifetime costs of £2,281 and an increase in QALYs of 0.12. This equates to an incremental cost effectiveness ratio (ICER) of £18,806 per QALY below the NICE threshold of £20,000 per QALY. Under the assumption of a long term survival benefit of 15% the addition of routine imaging lead to an increase in lifetime QALYs of 0.2159 (Table 21).

Table 20: Deterministic base case results

Outcome	Addition of Imaging	Standard Follow-up	Incremental
Cost	£52,150	£49,869	£2,281
Quality adjusted life years (QALYs)	5.8777	5.7564	0.1213
Cost per QALY gained			**£18,806**

Table 21: Additional benefit indentified earlier

Outcome	Addition of Imaging	Standard Follow-up	Incremental
Cost	£52,150	£49,869	£2,281
Quality adjusted life years (QALYs)	5.9723	5.7564	0.2159
Cost per QALY gained			**£10,565**

The stochastic base case results of the model, calculated from the means of the PSA, are shown in Table 22. The addition of routine imaging during follow-up lead ot an increase in lifetime costs of “2,782 and an increase in QALYs of 0.09. This equates to an incremental cost effectiveness ration (ICER) of £30,301 per QALY above the NICE threshold of £20,000 per QALY. Under the assumption of a long-term survival benefit of 15% the cost per QALY was £15,322 again below the NICE threshold. (Table 23) The base-case results differ considerably to the deterministic base-case results. This is as a result of none symmetrical distributions around a number of key parameters.

Table 22: Stochastic base case results

Outcome	Addition of Imaging	Standard Follow-up	Incremental
Cost	£49,652	£46,870	£2,782
Quality adjusted life years (QALYs)	6.0492	5.9574	0.0918
Cost per QALY gained			£30,301

Table 23: Additional benefit identified earlier

Outcome	Addition of Imaging	Standard Follow-up	Incremental
Cost	£49,714	£46,873	£2,841
Quality adjusted life years (QALYs)	6.0985	5.9131	0.1854
Cost per QALY gained			£15,322

A series of deterministic sensitivity analyses were also conducted around out base-case, whereby an input parameter was changed to assess its influence on the overall result. The results of the deterministic sensitivity analysis are shown in Table 24.

Table 24: Deterministic sensitivity analysis results

Change made	Incremental cost	Incremental QALYs	ICER
Identified outside routine imaging (=80%)	£1,630	0.0747	£21,818
Perfect diagnostic accuracy	£2,473	0.1415	£17,469
Sensitivity CT=70%	£2,024	0.0983	£20,587
3 monthly probability of transition from loco-regional to distant halved	£2,504	0.0899	£27,848
3 monthly probability of transition from loco-regional disease identical to those with no evidence of disease	£2,567	0.0530	£48,419
Cost of CT scan doubled	£3,251	0.1213	£26,809
Distant recurrence drug costs increased by 50%	£2,592	0.1213	£21,375
Life years instead of QALYs	£2,281	0.1255	£18,169

It can be seen from the results of the deterministic sensitivity analysis that the ICER was sensitive to the probability of moving from ‘loco-regional recurrence’ to ‘distant recurrence’ if the recurrence is not identified. Under the conservative assumption that moving to ‘distant disease’ has the same probability in this group to that of the ‘no disease’ group the resultant ICER is £48,419 and when the probability was halved (i.e. fewer patients with unidentified recurrence would progress to distant recurrence) the ICER value increased to £27,848. This

was a parameter for which no evidence was identified and for which there was difficulty in obtaining a consensus amongst the GDG. The higher this probability and thus the greater the benefit of identifying local recurrent, the more cost-effective the addition of 'routine imaging' would be with the ICER lower than the NICE threshold for probabilities at the hight end of the range. The resulting ICER was less sensitive to other GDG assumptions (e.g. the proportion of patients starting each systemic treatment, diagnostic accuracy of CT etc).

The evidence around quality of life was weak but it made no difference to cost effectiveness when life-years were used instead of QALYs resulting in a cost per life-year gained of under £20 000 although again there was large uncertainty around this estimate. The ICER was also sensitive to both the additional benefit from being identified through imaging and the cost of the imaging modality. The ICER was above £20,000 per QALY in the majority of the sensitivity analyses.

B.4.7 Probabilistic sensitivity analysis

Despite being below the threshold the cost effectiveness plane shows there is considerable uncertainty around the base-case estimate. All 1000 iterations of the probabilistic sensitivity analysis resulted in routine imaging being more effective and more costly; 99.8% of iterations were in the north-west quadrant of the cost effectiveness plane (Figure 6). Usual follow-up was preferred in 74.5% of iterations compared to usual follow-up with the addition of routine imaging at NICE's threshold of £20,000 per QALY. Usual care with the addition of routine imaging was cost effective over 50% of the time, compared to usual care, only when the threshold was above £34,000 per QALY (Figure 7).

Figure 6: Cost effectiveness plane

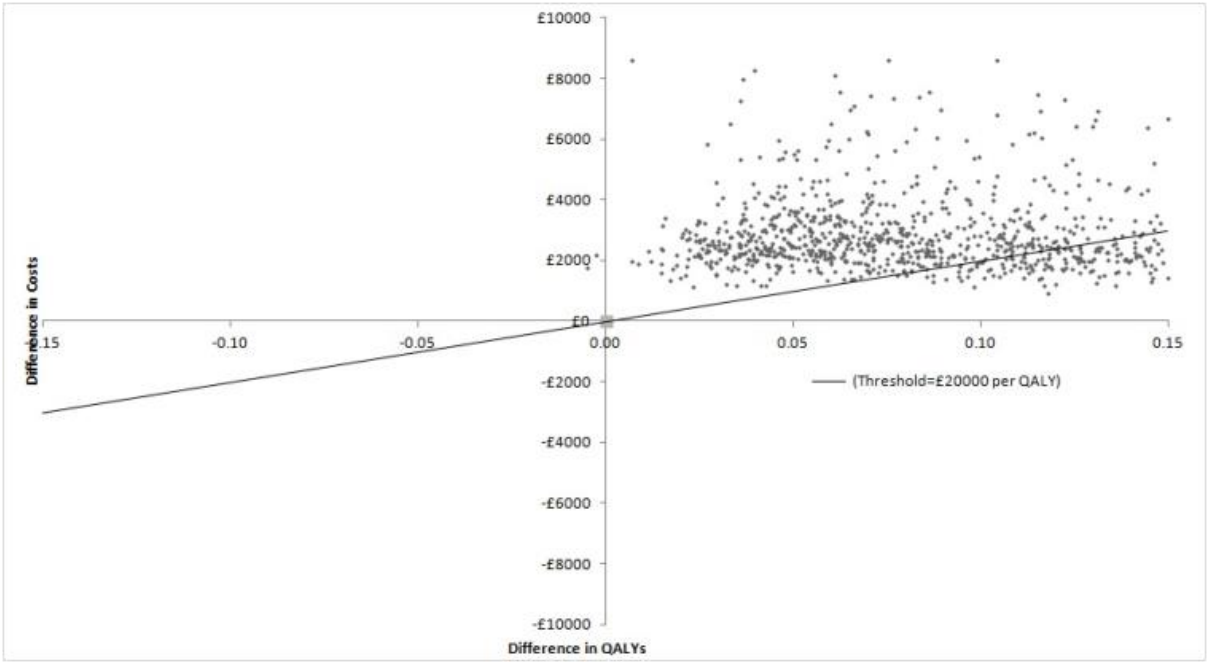
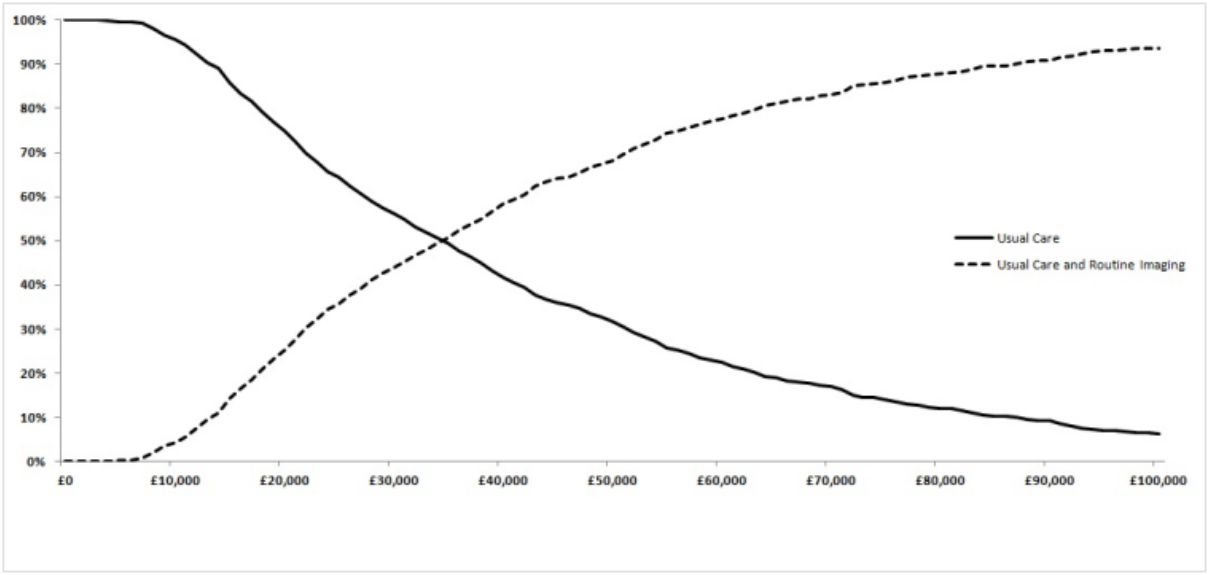


Figure 7: Cost effectiveness acceptability curve



When a fixed additional 15% survival benefit is added for those patients identified through imaging and treated with ipilimumab, all 1000 iterations are both more effective and costly (Figure 8). During probabilistic sensitivity analysis there was estimated to be a 77.1% probability that the addition of routine imaging was cost effective at a threshold of £20,000 per QALY (Figure 9).

Figure 8: Cost effectiveness plane under 15% survival benefit assumption

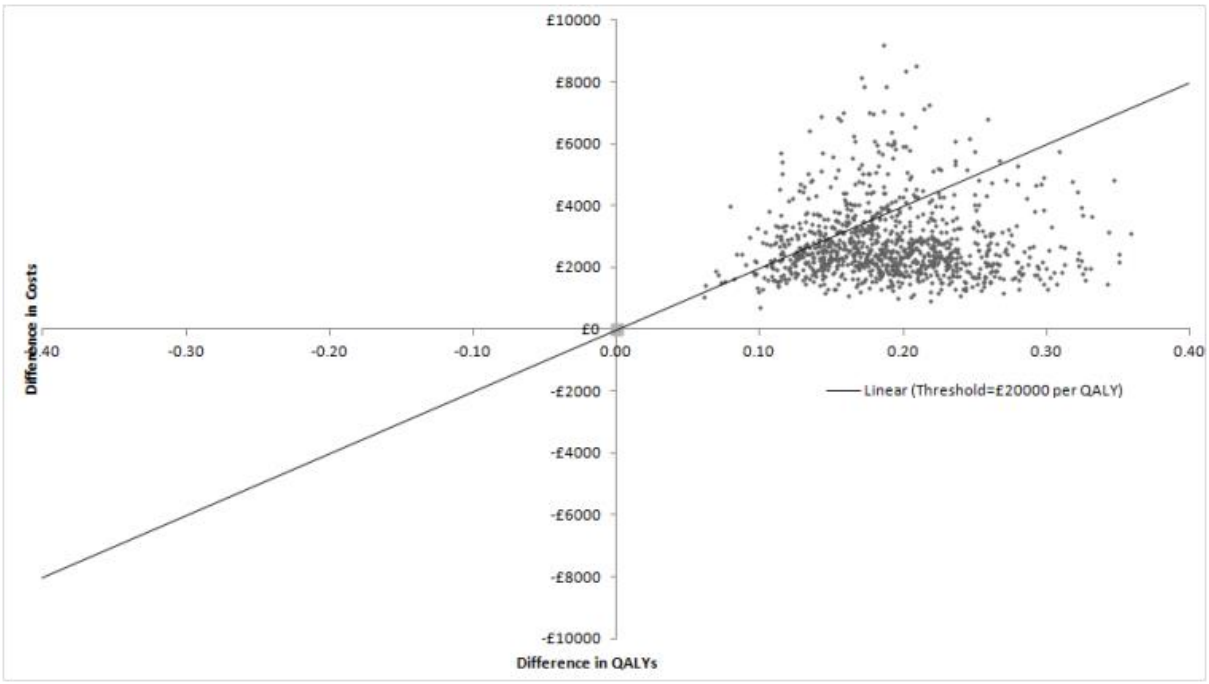
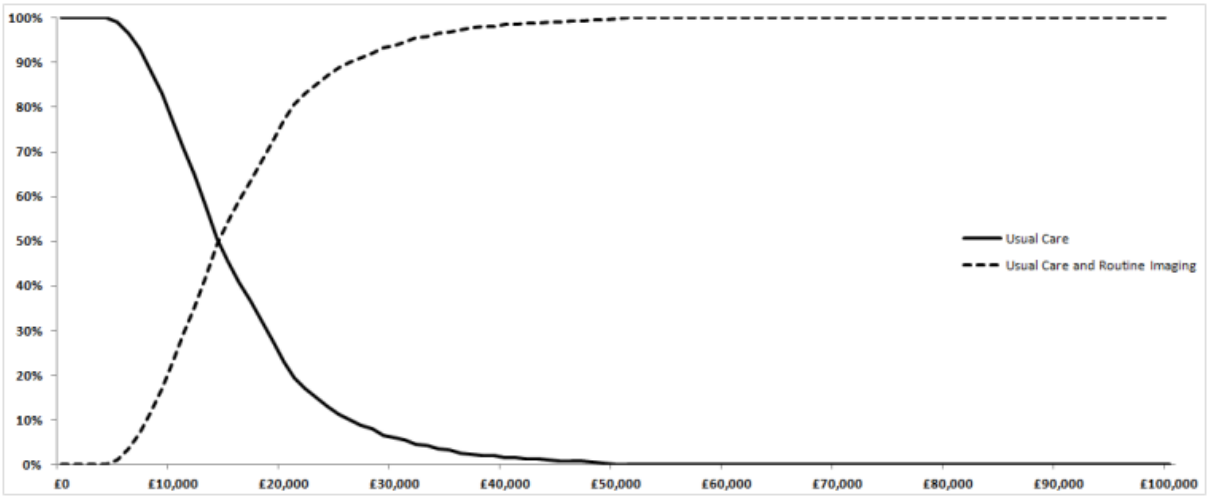


Figure 9: Cost effectiveness acceptability curve under 15% survival benefit assumption



Patients whose disease does not recur and completed the three years of routine imaging would receive six additional scans compared to the no additional imaging arm. Increased exposure to radiation from CT scans has been associated with an increased risk of lifetime cancer attributable to imaging. It was estimated that one whole body CT would increase the risk of lifetime cancer by 0.04% per scan over a 5 year period (Smith-Bindman et al, 2012). Given the difficulties in modelling cancer attributable to imaging and that 40% percent of the modelled cohort had died by 5 years and the majority by the end of the 20 year time horizon, we did not model any effect on life expectancy, quality of life or costs as a result of increased exposure to radiation in the routine imaging arm. An increased incidence of cancer attributable to imaging would weigh against the cost effectiveness of the addition of routine imaging to follow-up.

B.4.8 Conclusion

Under the base case assumptions standard follow-up was cost effective at a £20,000 willingness-to-pay threshold but there is uncertainty around the estimate with nearly three quarters of iterations in the probabilistic sensitivity analysis being above the NICE threshold of £20,000 per QALY. There is a stronger case that the addition of routine imaging to standard follow-up is cost effective if patients identified by routine imaging when asymptomatic are assumed to have a lower volume of disease and improved outcomes from treatment as a result. However, further research is needed to investigate this hypothesis.

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1 Full list of parameters and distributions used in the model

Parameter	Value	Reference	PSA Distribution
Demographics			
Age	57	Romano et al (2010)	Fixed
Male	64.1%	Romano et al (2010)	Beta(α=218,β=122)
Disease stage			
IIIA	36.0%	East of England Cancer registry (2009)	Dirichlet
IIIB	42.2%	East of England Cancer registry (2009)	Dirichlet
IIIC	21.8%	East England Cancer registry (2009)	Dirichlet
3 monthly probability recurrence			
Stage IIIA			
Month 0-12	12.2%	Rueth et al (2014)	Beta(α=16,β=120)
Month 13-24	2.8%	Rueth et al (2014)	Beta(α=3,β=133)
Month 25-36	2.2%	Rueth et al (2014)	Beta(α=3,β=133)
Month 37-60	1.5%	Rueth et al (2014)	Beta(α=2,β=134)
Month 61-120	1.5%	Rueth et al (2014)	Beta(α=2,β=134)
Stage IIIB			
Month 0-12	13.5%	Rueth et al (2014)	Beta(α=50,β=318)
Month 13-24	3.1%	Rueth et al (2014)	Beta(α=11,β=357)
Month 25-36	2.5%	Rueth et al (2014)	Beta(α=9,β=359)
Month 37-60	1.7%	Rueth et al (2014)	Beta(α=6,β=362)
Month 61-120	1.7%	Rueth et al (2014)	Beta(α=6,β=362)
Stage IIIC			
Month 0-12	23.4%	Rueth et al (2014)	Beta(α=70,β=230)
Month 13-24	5.6%	Rueth et al (2014)	Beta(α=17,β=283)
Month 25-36	4.4%	Rueth et al (2014)	Beta(α=13,β=287)
Month 37-60	3.0%	Rueth et al (2014)	Beta(α=9,β=291)
Month 61-120	3.0%	Rueth et al (2014)	Beta(α=9,β=291)
Site of first recurrence			
Loco-regional	49%	Romano et al (2010)	Beta(α=157,β=163)
Distant	51%	Romano et al (2010)	1-p(loco-regional)
Probability of progression loco-regional to distant			
IIIA	75%	GDG	Uniform(0.12,1)
IIIB	80%	GDG	Uniform(0.14,1)
IIIC	85%	GDG	Uniform(0.23,1)
Efficacy surgery			
Proportion suitable surgery	90%	GDG	Uniform(0.80,1)
Proportion successful surgery	70%	GDG	Uniform(0.22,1)
3-monthly probability death			
Death unidentified LR	6.7%	Meyers et al (2009)	Beta(α=7,β=93)
Death unidentified DR	26.1%	Meyers et al (2009)	Highest 3 monthly

Parameter	Value	Reference	PSA Distribution
			probability dacarbazine
Diagnostic accuracy PET-CT/CT			
Loco-regional recurrence			
Sensitivity	86%	Koskivuo et al (2007)	Beta(α=6,β=1)
Specificity	96%	Koskivuo et al (2007)	Beta(α=22,β=1)
Distance recurrence			
Sensitivity	86%	Koskivuo et al (2007)	Beta(α=6,β=1)
Specificity	96%	Koskivuo et al (2007)	Beta(α=22,β=1)
Probability recurrence picked up outside routine imaging	85%	Romano et al (2010)	Beta(α=231,β=109)
Proportion starting treatment			
Dacarbazine	15%	GDG	Dirichlet
Ipilimumab	50%	GDG	Dirichlet
Vemurafenib	35%	GDG	Dirichlet
Costs			
CT scan	£125	NHS Reference Cost 2012-2013	Gamma(α = 7.2, β = 23.5)
MRI scan	£169	NHS Reference Cost 2012-2013	Gamma(α =53.8 , β = 2.3)
BRAF test	£97	NICE (2012)	Fixed
Surgical removal localised metastases	£835	NHS Reference Cost 2012-2013	Gamma(α = 9.2, β = 91.1)
Follow-up appointment	£139	NHS Reference Cost 2012-2013	Gamma(α=9.1, β=15.2)
Consultant outpatient oncology visit	£139	NHS Reference Cost 2012-2013	=Follow-up appointment
Ipilimumab (lifetime)	£90,688	Dickson et al 2011	Uniform(45344,136033)
Dacarbazine (lifetime)	£11,469	Dickson et al 2011	Uniform(5735,17203)
Vemurafenib (lifetime)	£90,688	Dickson et al 2011	Uniform(45344,136033)
Utilities (3 months)			
NED	0.24	Kilbridge et al (2001)	Beta(α=0.98,β=0.02)†
Loco-regional recurrence	0.20	Kilbridge et al (2001)	Beta(α=0.80,β=0.2)†
Distant recurrence	0.15	Kilbridge et al (2001)	Beta(α=0.6,β=0.4)†
Dead	0		Fixed
†-Distribution divided by four			

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Appendix C: Abbreviations

AJCC	American Joint Committee on Cancer
BNF	British national Formulary
CGD	Combined superficial and deep groin dissection
CLND	Complete lymph node dissection
CNS	Clinical Nurse Specialist
CT	Computed tomography
DCLND	Delayed complete lymph node dissection
DNA	Deoxyribonucleic acid
DTIC	Dacarbazine
ECT	Electrochemotherapy
EORTC	Eurpoean organisation for research and treatment of cancer
FISH	Fluorescence in situ hybridisation
FNAC	Fine-needle aspiration cytology
GDG	Guideline development group
GRADE	Grading of recommendations, assessment, development and evaluation
HILP	Hyperthermic isolated limb perfusion
HNA	Holistic needs assessment
HR	Hazard ratio
HRQoL	Health related quality of life
ICER	Incremental cost effectiveness ratio
ICLND	Immediate complete lymph node dissection
IFN	Interferon
ILI	Isolated limb infusion
ILP	Isolated limb perfusion
LETR	Linking evidence to recommendations
LND	Lymph node dissection
LSMDT	Local hospital skin cancer multidisciplinary team
MDT	Multidisciplinary team
MILND	Minimally invasive inguinal lymph node dissection
MRI	Magnetic resonance imaging
NCPES	National cancer patient experience survey
NHS EED	National Health Service economic evaluation database
NPV	Negative predictive value
OECD	Organisation for economic co-operation and development
OILND	Open inguinal lymph node dissection
PET	Positron emission tomography
PFS	Progression free survival
PPV	Positive predictive value
PSA	Probabilistic sensitivity analysis
PSS	Personal social services
RCTs	Random controlled trials
QALY	Quality adjusted life years

QArfLY	Quality adjusted relapse free life-years
QoL	Quality of Life
QUADAS	Quality assessment of diagnostic accuracy studies
SGD	Superficial groin dissection
SLNB	Sentinel lymph node biopsy
SMDT	Specialist multidisciplinary team
SSE	Skin self examination
SSMDT	Specialist skin cancer multidisciplinary team
STR	Stereotactic radiotherapy
TEM	Temozolomide
WEX	Wide excision
WBRT	Whole-brain radiation therapy

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Appendix D: Glossary

Ablation/ablative

The destruction of deposits of cancer using a variety of technologies such as radiation or cryotherapy (freezing the tissue).

Adjuvant treatment

A treatment given after the main treatment for cancer to reduce the risk of recurrence.

Adverse event

Detrimental change in health occurring in a person receiving the treatment whether or not it has been caused by the treatment.

Asymptomatic

Without obvious signs or symptoms of disease. Cancer may cause symptoms and warning signs, but, especially in its early stages, cancer may develop and grow without producing any symptoms.

Atypical naevus

A “mole” or melanocytic naevus that is bigger than average (5mm or more in diameter) and has more variation in colour and in its edge which is either irregular or ill defined.

Atypical spitzoid melanocytic lesion

A skin lesion with an appearance that is neither typical of a harmless mole nor of a melanoma.

Axillary

In the armpit.

Benign

Non-cancerous; not malignant.

Biopsy

Removal of a sample of tissue from the body to assist in diagnosis or inform the choice of treatment of a disease.

Breslow thickness

A scale for measuring the thickness of melanomas by the pathologist using a microscope, measured in mm from the top layer of skin to the bottom of the tumour.

***BRAF* 600 mutation**

BRAF is a human gene that makes a protein called B-Raf which is involved in the control of cell growth. *BRAF* mutations (damaged DNA) occur in around 40% of melanomas, which can then be treated with particular drugs.

Cellularity

The state of a tissue or other mass as regards the number of constituent cells. In this respect the number of tumour cells in the sample will determine how likely the test for a mutation is to give a valid result.

Chemotherapy

The use of medication (drugs) that is toxic to cancer cells, given with the aim of killing the cells or preventing or slowing their growth.

Clinico-pathological

Relating to the signs and symptoms that are observed in a patient, in conjunction with the results of laboratory examination

Cohort studies

Research studies in which groups of patients with a particular condition or specific characteristic are compared with matched groups who do not have it, or patients within the cohort are compared with each other.

Computed tomography (CT)

Imaging technique in which the person lies on a table within a x-ray gantry. The images are acquired using a spiral (helical) path and banks of detectors, allowing presentation of the internal organs and blood vessels in different projections including 3-D views.

Confocal microscopy

Confocal microscopy is a specific technique that increases the optical resolution of microscopy by cutting out unfocused light.

Cosmesis

The degree to which the surgery has allowed the restoration or preservation of the normal appearance of that person.

Cryotherapy

Cryotherapy is a surgical technique that uses a low temperature probe to remove tissue

Cutaneous

Related to the skin

Dehiscence

Separation of the layers of a surgical wound: or “opening up” of the wound.

Dermoscopy/dermatoscopy

A technique for inspecting the skin surface directly using a special hand held magnifying device (dermatoscope) which allows health care professionals to view naevi or moles in more detail.

Dysaesthesia

Dysaesthesia is impaired sense of touch resulting in an unpleasant sensation.

Erythema

Reddening of the skin.

Excision

Removal by surgery

False negative

An individual who is truly positive for a disease, but whom a diagnostic test classifies them as disease-free.

False positive

An individual who is truly disease-free, but whom a diagnostic test classifies them as having the disease

Fluorescence in situ hybridisation (FISH)

A molecular test carried out on biopsy or cytology samples to show whether extra copies of specific genes are present or absent.

GRADE

The GRADE approach is a method of grading the quality of evidence and strength of recommendations in healthcare guidelines. It is developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

Holistic needs assessment

This term is used in the NHS to describe a formal process of assessment of the needs of people with cancer and, if they wish, their partners, families or carers. Carrying out a holistic needs assessment should lead to the provision of an individualised package of information and support.

Iliac/obturator dissection

The removal of lymph nodes in regions within the pelvis which are called obturator or iliac nodes.

Immunohistochemistry

Immunohistochemistry (IHC) is a technique that uses specific antibodies to show whether particular proteins are present when tissues are inspected through a microscope.

Immunotherapy

The use of vaccines or drugs that stimulate the immune system to treat diseases.

Immunosuppression

Suppression of the body’s immune system.

In situ tumours

Tumours which remain within the superficial layers of the skin (epidermis) and have not progressed to grown down to deeper layers.

Incidence

The number of new cases of a disease in a given time period

Inguinal

Lymph nodes in or just above or just below the groin

Infrared (IR) laser

A laser that uses light in the infrared spectrum for treatment

Isolated limb perfusion (ILP)

ILP is a technique for giving high doses of anti-cancer drugs directly into a limb using a tourniquet to isolate the limb from the rest of the body and a pump to push fluid containing the drug through the limb's circulation.

Isolated limb infusion (ILI)

ILI is technique for giving high doses of anti-cancer drugs directly into a limb using a tourniquet to isolate the limb's blood circulation from the rest of the body and infuse a solution of the drug by gravity.

Lentigo maligna (stage 0)

Lentigo maligna is a particular type of in situ melanoma (most commonly on the face) associated with signs under the microscope of chronic sun damage to the skin.

Local recurrence

Regrowth of a tumour in the area from which it was originally removed

Lymphadenectomy

Lymphadenectomy or lymph node dissection is a surgical operation to remove one or more groups of lymph nodes.

Lymphoscintagraphy

Lymphoscintigraphy (sentinel lymph node mapping) is an imaging technique used to identify the lymph drainage basin, determine the number of sentinel nodes, differentiate sentinel nodes from subsequent nodes, locate the sentinel node in an unexpected location, and mark the sentinel node over the skin for biopsy. It requires the injection of a radio-isotope into the skin around the biopsy scar and a scan some hours later to determine to which lymph nodes the tracer has travelled.

Malignant

A tumour that can invade and destroy nearby tissue and spread to other parts of the body.

Magnetic resonance imaging (MRI)

A type of scan which uses a magnetic field and radio waves to produce images of sections of the body.

Melanocytic lesion

A growth or proliferation in the body which has developed from melanocytes (cells which produce pigment or melanin).

Meta-analysis

A form of statistical analysis used to synthesise results from a collection of individual studies.

Metastases/metastatic disease

Spread of cancer away from the primary site to somewhere else through the bloodstream or the lymphatic system.

Micrometastases

Micrometastases are metastases so small that they can only be seen under a microscope .

Morbidity

Detrimental effects on health.

Mortality

Either (1) the condition of being subject to death; or (2) the death rate, which reflects the number of deaths per unit of population in relation to any specific region, age group, disease, treatment or other classification, usually expressed as deaths per 100, 1,000, 10,000 or 100,000 people.

Multi disciplinary team (MDT)

A team with members from different health care professions and specialties (e.g. urology, oncology, pathology, radiology, nursing). Cancer care in the NHS uses this system to ensure that all relevant health professionals are engaged to discuss the best possible care for that patient.

Multi disciplinary team meeting (MDTM)

A meeting where members of the Multi Disciplinary Team discuss and make recommendations about the care of people.

Nevomelanocytic

Of a benign or harmless growth or proliferation in the skin (a mole) which has developed from melanocytes (cells which produce pigment or melanin).

Oncology

The study of cancers. This term also refers to the medical specialty of cancer care, with particular reference to the use of radiotherapy or drugs to treat cancer. The medical specialty is often split into Clinical Oncology (doctors who use radiotherapy and drug treatment) and Medical Oncology (doctors who use drug treatment).

Oligometastatic disease

A poorly defined condition in which a patient has a few metastases which could all be removed surgically or with high dose radiotherapy in the hope of cure.

Palliative

Anything which serves to alleviate symptoms due to the underlying cancer but is not expected to cure it.

Prevalence

The proportion of a population found to have a condition

Primary care

Services provided in a community setting, outside hospitals (secondary care), with which people usually have first contact.

Primary tumour

Original site of the first cancer.

Prognosis

A prediction of the likely outcome or course of a disease; the chance of recovery, recurrence or death.

Prognostic factors

Specific characteristics of a cancer or the person who has it which might affect the patient's prognosis.

Progressive disease

Here this means cancer that is growing and spreading beyond the organ where it started. This is judged either by physical examination, scans, or blood tests.

Prospective study

A study in which people are entered into research and then followed up over a period of time with future events recorded as they happen.

Psychosocial support needs

Psychosocial means something which relates to one's psychological development in, and interaction with, a social environment. The individual needs not be fully aware of this relationship with his or her environment Cancer has many effects on life related to concern about the future, the demands of treatment and the effects of ill health and the resultant effects of all these impact on quality of life.

Psychosocial support is an approach to victims of disaster, catastrophe or violence to foster resilience of communities and individuals. It aims at easing resumption of normal life, facilitating affected participation of affected people in their convalescence and preventing pathological consequences of potentially traumatic situations.

Punch biopsy

Punch biopsy is a technique for taking a full thickness skin biopsy using a specific instrument. which takes a small core of skin, usually 4mm in diameter, leaving a small wound which may need to be stitched afterwards.

Qualitative research

Research in which the outcomes are usually recorded in words, rather than with numbers. Often used to explore and understand peoples' beliefs, experiences, attitudes, behaviour and interactions.

Quality adjusted life years (QALYs)

A measure of health outcome, which looks at both length of life and quality of life. QALYs are calculated by estimating the years of life remaining for a patient following a particular care pathway and weighting each year with a quality of life score (on a 0-1 scale). One QALY is equal to 1 year of life in perfect health, or 2 years at 50% health, and so on.

Quantitative research

Research which uses numerical measurement techniques (e.g. measuring survival times after treatment).

Radiotherapy

The use of radiation, usually high energy x-rays to control the growth of cancer cells.

Randomised controlled trial (RCT)

An experimental clinical trial (study) investigating the effectiveness of different treatments in which participants are assigned at random to different groups which receive the intervention being assessed or a 'control' treatment. RCTs give the most reliable (i.e. least biased) form of evidence on clinical effectiveness.

Radioembolisation

Radioembolisation is a cancer treatment in which radioactive particles are delivered to a tumour through the bloodstream.

Recurrence

Recurrence is when new cancer cells are detected following treatment. This can occur either at the site of the original tumour or at other sites in the body.

Reflectance confocal microscopy

Reflectance confocal microscopy is a specific technique to examine the skin that increases the optical resolution of microscopy by cutting out unfocused light.

Relapse

Where cancer starts to grow again after treatment.

Sensitivity

In this context the term is used to mean the proportion of individuals with a disease who have that disease correctly identified by the study test

Sensitivity analysis

A means of representing uncertainty in the results of economic evaluations. Uncertainty may arise from missing data, imprecise estimates or methodological controversy. Sensitivity analysis also allows for exploring the generalisability of results to other setting. The analysis is repeated using different assumptions to examine the effect on the results.

Spitz naevus

Spitz naevus is a rare type of benign melanocytic naevus or mole seen mainly in mainly in children and young adults which may cause concern because of the difficulty in distinguishing it from melanomas, when they occur after puberty.

Staging

Clinical description of the size and spread of a patient's tumour, fitting into internationally agreed categories.

Stereotactic radiotherapy

A technique for delivering high dose radiotherapy very accurately to small areas inside the body which reduces the damage done by the radiotherapy to adjacent healthy tissues.

Survival

Survival is the time alive after diagnosis of a disease

Systematic review

A review of the literature carried out in order to address a defined question and using quantitative methods to summarise the results.

Systemic treatment

Treatment, usually given by mouth or by injection, that reaches and affects cancer cells throughout the body rather than targeting one specific area.

Teledermatology

Teledermatology is a technique for using telecommunications to transmit images of the patient's skin to a specialist at a distant location.

Ultrasound

A type of scan in which high-frequency sound waves are used to outline a part of the body.

Appendix E: Guideline scope

E.1 Guideline title

Melanoma: assessment and management of melanoma

E.1.1 Short title

Melanoma

E.2 The remit

The Department of Health has asked NICE to develop a clinical guideline on assessment and management of malignant melanoma.

E.3 Clinical need for the guideline

E.3.1 Epidemiology

Melanoma is the third commonest skin cancer in the UK. However, it is the cause of more cancer deaths than all other skin cancers combined. In 2010, there were 2,746 deaths from skin cancer in the UK. This includes 2,203 deaths from melanoma and 546 from other forms of skin cancer.

In 2010, 12,818 people in the UK were diagnosed with melanoma. Although the disease is more common in older age groups, it is often diagnosed in younger people. In the late seventies, there were around 290 cases of melanoma among 15-34 year-olds each year. Now more than 900 young Britons are being diagnosed with the disease each year - more than two a day (CR UK statistics).

The incidence of melanoma is rising rapidly and is predicted to increase by 50% in the next 15 years. This is the fastest projected increase in incidence for any cancer. Most melanomas occur in white skinned people. The risk factors are skin which tends to burn in the sun, having many melanocytic naevi, intermittent sun exposure and sunburn.

Mortality rates for melanoma are also rising rapidly, especially in older men. In 2010, 62% of deaths from melanoma were in people aged 65 years or older, whereas 5% of deaths were in people aged 15 to 39 years.

There appear to be variations in survival across different cancer networks, and poorer survival may be attributable to late presentation or delays in diagnosis and initiation of treatment.

E.3.2 Current practice

The majority of melanomas are initially clinically diagnosed by dermatologists with 41% of cases being referred via the 2-week wait process.

Primary melanoma is treated by complete excision, pathological analysis and subsequent wide local excision. There remains some uncertainty about optimal final excision margins and this topic is the subject of current research.

Imaging (for example CT, MRI or positron emission tomography [PET]-CT) for staging purposes is not currently indicated for people with stage 1 or 2 disease. Sentinel node biopsy (SNB) is used to stage melanomas according to the American Joint Committee on Cancer

(AJCC) staging system and is also used to identify people who might be eligible for adjuvant therapy clinic trials and to stratify during analysis of those trials. However, SNB has not been shown to confer any survival advantage and the cost effectiveness of SNB is uncertain. There is thought to be variation in practice in the use of CT and PET-CT imaging for people with more advanced disease.

Adjuvant chemotherapy and immunotherapy are not currently indicated for management of melanoma and continue to be the subject of research trials. Adjuvant radiotherapy for stage IIIB and IIIC melanoma is used in some centres but with little supporting evidence.

Cutaneous metastases are excised if it is technically feasible. In-transit metastases are multiple skin and subcutaneous metastases (usually in a limb) which are generally treated with loco-regional therapies. Multiple in-transit metastases confined to one limb may be treated by a number of modalities including isolated limb infusion and isolated limb perfusion

Some people with small numbers of apparently localised metastases to other organs may also be offered surgical resection, although this is not supported by randomised trial evidence.

People whose metastatic melanoma carries BRAF mutations may be treated with specific BRAF inhibitors. These drugs have a very rapid effect on tumours but unfortunately the majority of people who take them develop resistance and the tumour relapses. Use of vemurafenib was associated with a median survival of 13.2 months in a phase 3 trial.

People with systemic metastases whose tumours are not found to carry BRAF mutations are usually treated with dacarbazine but response rates are low. Ipilimumab may be used as second-line therapy.

Radiotherapy may be used to treat isolated cerebral metastases and for palliation.

E.4 The guideline

The guideline development process is described in detail on the NICE website (see section 6, ‘Further information’).

This scope defines what the guideline will (and will not) examine, and what the guideline developers will consider. The scope is based on the referral from the Department of Health.

The areas that will be addressed by the guideline are described in the following sections..

E.5 Population

E.5.1 Groups that will be covered

- Children, young people and adults with suspected melanoma.
- Children, young people and adults with newly diagnosed cutaneous melanoma, including vulval and penile melanoma.
- Subgroups identified as needing specific consideration will be considered during development of the guideline.

E.5.2 Groups that will not be covered

- People with primary ocular melanoma.
- People with melanoma arising in mucosal sites. (see 4.1.1 b)

E.6 Healthcare setting

All settings in which NHS-funded care is provided.

E.7 Clinical management

E.7.1 Key clinical issues that will be covered

- The specific information and support needs of people with melanoma and their carers at diagnosis, at treatment planning, and during and after treatment.
- The best approach to increasing clinical diagnostic accuracy and appropriate prompt excision.
- The best approach to resolving clinico-pathological diagnostic uncertainty for borderline or Spitzoid melanocytic lesions.
- The best approach for mutation testing of tumours for prognostic and predictive purposes.
- The most effective method of staging melanoma:
  - the role of sentinel lymph node biopsy in newly diagnosed melanoma
  - imaging for newly diagnosed and recurrent melanoma.
- The most effective surgical treatment for stage 0-II melanoma
- The most effective surgical treatment for stage III melanoma (including the effectiveness of sentinel lymph node biopsy).
- The indications for adjuvant radiotherapy for stage III melanoma after resection.
- The most effective treatment for in-transit melanoma metastases.
- The role of surgery, stereotactic radiotherapy and image guided ablative techniques including radioembolisation in stage IV melanoma.
- The role of systemic anti-cancer therapy in the treatment of metastatic melanoma (for example, dacarbazine and temozolomide).
- The optimum methods, setting and frequency of follow-up for people with melanoma.
- The role of measuring vitamin D levels and of supplementation in people who have been diagnosed with melanoma.
- The role of imiquimod in the treatment of melanoma.
- Management of other intercurrent conditions with drug therapies which may increase the risk of death from melanoma (for example, immunosuppressants, levodopa, metformin)

E.7.2 Clinical issues that will not be covered

- Referral from primary care with suspected melanoma. (This will be covered by 'Suspected cancer', the update of Referral guidelines for suspected cancer [NICE clinical guideline 27]).
- Awareness and prevention of melanoma.
- Ipilimumab for the treatment of stage III or IV melanoma. (This is the subject of an ongoing NICE technology appraisal. Publication expected August 2013).
- Vemurafenib for the treatment of BRAF V600 mutation-positive, unresectable metastatic melanoma. (This is covered by NICE technology appraisal guidance 269 [2012]).
- Dabrafenib for the treatment of BRAF V600 mutation-positive, unresectable, advanced or metastatic melanoma. (This is the subject of an ongoing NICE technology appraisal. Publication expected April 2014).
- Ipilimumab for the treatment of previously untreated unresectable stage III or IV melanoma. (This is covered by NICE technology appraisal guidance 268 [2012]).
- Adjuvant immunotherapy.

- End-of-life care.
- Complementary therapies.

E.8 Main outcomes

- Overall survival.
- Disease-free survival.
- Progression-free survival.
- Melanoma-related morbidity.
- Melanoma-related mortality.
- Treatment-related morbidity.
- Treatment-related mortality.
- Psychological wellbeing.
- Number and length of admissions to hospital after diagnosis.
- Number and severity of adverse events.
- Health-related quality of life.
- Cost effectiveness.
- Patient-reported outcomes.

E.9 Review questions

Review questions guide a systematic review of the literature. They address only the key clinical issues covered in the scope, and usually relate to interventions, diagnosis, prognosis, service delivery or patient experience.

Please note that these review questions are draft versions and will be finalised with the Guideline Development Group.

- What are the specific information and support needs of people with melanoma and their carers:
  - at the point of first diagnosis
  - at treatment planning
  - during treatment
  - after treatment (including follow-up and at discharge)? [4.3.1a]
- What is the diagnostic accuracy of dermoscopy, history-taking and visual examination for the clinical identification of melanoma? [4.3.1b]
- What is the best approach to resolving clinico-pathological diagnostic uncertainty for borderline or Spitzoid melanocytic lesions? [4.3.1c]
- Is the accuracy of current tests for melanoma affected by reader experience (for example, comparing consultants with trainees)? [4.3.1c]
- Is photography an effective method of monitoring progression of pigmented lesions? [4.3.1c]
- What is the most appropriate tumour block (primary or secondary) on which to carry out genetic testing to identify people who might benefit from targeted therapies? [4.3.1d]
- What is the best time and method to adopt in order to carry out genetic testing of the stored tumour for a person who may benefit from targeted therapies (early stage [I-IIIA] versus late stage [IIIB-IV])? [4.3.1d]
- Should sentinel lymph node biopsy be available to all patients with newly diagnosed melanoma? [4.3.1e]

- What is the best approach to staging disease in people diagnosed with a) new disease and b) recurrent disease (including but not limited to CT, PET, PET-CT)? [4.3.1e]
- What is the most effective surgical treatment for stage 0-II melanoma to achieve clear margins and improved patient outcomes? [4.3.1f]
- What are the appropriate margins when surgically treating stage 0-II melanoma? [4.3.1f]
- What is the most effective surgical treatment for stage III melanoma? [4.3.1g]
- Who should carry out surgery for stage III melanoma? [4.3.1g]
- What is the effectiveness of adjuvant radiotherapy for stage III melanoma in people who have undergone curative resection? [4.3.1h]
- What is the role for different treatments for in-transit melanoma metastases (for example, surgery, isolated limb infusion, isolated limb perfusion, palliative radiotherapy, cryotherapy, electro-chemotherapy or the laser)? [4.3.1i]
- What is the effectiveness of surgery or image guided ablative techniques (including stereotactic RT) compared with systemic drug therapy or supportive care in the management of stage IV melanoma. [4.3.1j]
- How effective is surgery in the treatment of oligometastatic disease? [4.3.1j]
- What are the factors which indicate the use of dacarbazine in people with stage IV melanoma? [4.3.1k]
- What is the effectiveness of temozolomide compared with dacarbazine in the treatment of patients with stage 4 metastatic melanoma? (Temozolomide is subject to agreement with the NICE Technology Appraisal programme). [4.3.1k]
- In asymptomatic patients who have undergone treatment with curative intent for melanoma, what is the optimal method, frequency and duration of follow-up? [4.3.1l]
- What is the optimal setting for follow-up of asymptomatic patients who have undergone treatment with curative intent for melanoma? [4.3.1l]
- What are the indications for imaging for brain metastasis as part of follow-up in asymptomatic patients? [4.3.1l]
- Is CT or MRI the most appropriate method of imaging for brain metastasis as part of follow-up for asymptomatic patients? [4.3.1l]
- Do vitamin D levels at diagnosis and during follow-up predict cancer-related or bone-related outcomes for people with melanoma? [4.3.1m]
- How should sub-optimal vitamin D levels be managed in people with melanoma (including supplements and monitoring)? [4.3.1m]
- How effective is imiquimod in the treatment of melanoma? [4.3.1n]
- What is the most effective approach to the management of the risks associated with concurrent drug therapies used to treat other conditions, which may increase the risk of death from melanoma (for example, immunosuppressants, levadopa, metformin)? [4.3.1o]

E.10 Economic aspects

Developers will take into account both clinical and cost effectiveness when making recommendations involving a choice between alternative interventions. A review of the economic evidence will be conducted and analyses will be carried out as appropriate. The preferred unit of effectiveness is the quality-adjusted life year (QALY), and the costs considered will usually be only from an NHS and personal social services (PSS) perspective. Further detail on the methods can be found in 'The guidelines manual' (see ‘Further information’).

E.11 Status

E.11.1 Scope

This is the final scope.

E.11.2 Timing

The development of the guideline recommendations will begin in May 2013.

E.12 Related NICE guidance

E.12.1 Published guidance

NICE guidance to be updated

This guideline will not update or replace any NICE guidance.

NICE guidance to be incorporated

Vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive malignant melanoma. NICE technology appraisal guidance 269 (2012).

Ipilimumab for previously treated advanced (unresectable or metastatic) melanoma. NICE technology appraisal guidance 268 (2012).

Other related NICE guidance

- Neutropenic sepsis. NICE clinical guideline 151 (2012).
- Opioids in palliative care. NICE clinical guideline 140 (2012).
- Patient experience in adult NHS services. NICE clinical guideline 138 (2012).
- Endoscopic radical inguinal lymphadenectomy. NICE interventional procedure guidance 398 (2011).
- Skin cancer prevention: information, resources and environmental changes. NICE public health guidance 32 (2011).
- MIST therapy system for the promotion of wound healing in chronic and acute wounds. NICE medical technologies guidance 5 (2011).
- Skin tumours including melanoma. NICE cancer service guidance (2010)
- Medicines adherence. NICE clinical guideline 76 (2009).
- Surgical site infection. NICE clinical guideline 74 (2008).
- Improving supportive and palliative care for adults with cancer. NICE cancer service guidance (2004).

E.12.2 Guidance under development

NICE is currently developing the following related guidance (details available from the NICE website):

- Melanoma (BRAF V600, unresectable, metastatic) – dabrafenib. NICE technology appraisal guidance ID605. Publication expected April 2014
- Implementing Vitamin D guidance. NICE public health guidance. Publication expected June 2014.

- Melanoma (previously untreated unresectable stage III or IV) – ipilimumab. NICE technology appraisal guidance ID74. Publication expected June 2014.
- Suspected cancer: recognition and management of suspected cancer in children, young people and adults (update). NICE clinical guideline. Publication date to be confirmed.
- Sunlight exposure: benefits and safety. NICE public health guidance. Publication date to be confirmed.
- Melanoma (advanced and metastatic) – temozolomide. NICE technology appraisal guidance ID316 (suspended).

E.13 Further information

Information on the guideline development process is provided in the following documents, available from the NICE website:

- How NICE clinical guidelines are developed: an overview for stakeholders the public and the NHS
- The guidelines manual.

Information on the progress of the guideline will also be available from the NICE website.

Appendix F:People and organisations involved in production of the guideline

F.1 Members of the Guideline Development Group

GDG Chair	
Dr Fergus Macbeth	Chair, Clinical advisor, Wales Cancer Trials Unit, Cardiff University
GDG Lead Clinician	
Prof. Julia Newtown-Bishop	Lead Clinician, Professor of Dermatology, University of Leeds
Group Members	
Prof. Barry Powell	Consultant Plastic Surgeon, St George's Hospital
Dr Laszlo Igali	Consultant Histopathologist, Norfolk and Norwich University Hospital NHS Foundation Trust
Mr Martin Telfer	Consultant Maxillofacial Surgeon, York Teaching Hospital NHS Foundation Trust
Dr Racheal Robinson	GP & GPSI Dermatology, Stockwell Road Surgery, Knarlesborough
Mrs Gillian Godsell	Skin Cancer Clinical Nurse Specialist, Nottingham University Hospitals NHS Trust
Dr Julia Schofield	Consultant Dermatologist, United Lincoln Hospitals NHS Trust
Dr Sara Stoneham	Paediatric & Adolescent Oncology Consultant, University College Hospital, London
Mrs Saskia Reeken	CNS, Skin Cancer & Dermatology, Kingston Hospital NHS Trust
Dr Stephen Keohane	Consultant Dermatologist, Portsmouth Hospitals NHS Trust, Portsmouth Dermatology Centre
Dr Charles Kelly	Consultant Clinical Oncologist, Northern Centre for Cancer Care
Dr Jonathan Smith	Consultant Radiologist, Leeds Teaching Hospital Trust
Dr Christine Parkinson	Consultant in Medical Oncology, Addenbrookes Hospital, Cambridge
Mr Richard Jackson	Patient/carer member
Mr John Rouse	Patient/carer member

F.1.1 Declarations of interest

Name	Interest declared	Type of Interest	Decision Taken
Barry Powell	Received a fee from Roche for chairing an advisory board on BRAF inhibitors in malignant melanoma. Donate fee to charity.	Personal Pecuniary Interest, Specific	Declare and withdraw from discussions on all topics regarding the BRAF inhibitors until July 2013. However, discussion on BRAF inhibitors will not take place until July 2013.
Barry Powell	Novartis have offered a fee to take part in a future advisory board on MEK inhibitors in melanoma. Not yet accepted.	Personal Pecuniary Interest, Specific	If accepted, declare and withdraw from discussions on all topics regarding the MEK inhibitors until 12 months after date of advisory board. However, MEK inhibitors will not be investigated by the guideline.
Barry Powell	Enrols patients into the EORTC 18091 trial (A Phase I/II Open	Personal Non-	Declare and participate in discussion on all topics as no

Name	Interest declared	Type of Interest	Decision Taken
	Label Multicenter Study of ONTAK® as Treatment for advanced melanoma (stage IIIc and stage IVM1a)). No fee received for doing this and no involvement past enrolling of patients.	Pecuniary Interest, Specific	involvement in trial protocol.
Barry Powell	Principle investigator for the UK for the EORTC MINITUB study (looking at low volume disease in sentinel nodes). Study not yet started. Funded by individual trusts.	Personal Non-Pecuniary Interest, Specific	Declare and participate in discussion on all topics as no supervisory responsibility on trials.
Barry Powell	Chair of the Pathway Group for Skin Cancer for the London Cancer Alliance (working group on provision of skin cancer care in London).	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics.
Barry Powell	Wrote an editorial for Surgery journal giving opinions on the management of malignant melanoma.	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics.
Barry Powell	Received reimbursement of travelling expenses and subsistence from IGEA for attending a meeting regarding data collection for Electrochemotherapy.	Personal Pecuniary, Specific	Declare and participate in discussion on all topics as data collection for Electrochemotherapy is not being investigated by the guideline.
Christine Parkinson	Received a fee from Boehringer Ingelheim for attending an advisory board and giving advice on a trial for their ovarian cancer drug BIBF1120. Fee was donated to charity.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as ovarian cancer is not being covered by the guideline.
Christine Parkinson	Received reimbursement of registration fee and accommodation from Boehringer Ingelheim for attending the International Gynaecological Cancer Society conference.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as Gynaecological cancer is not being covered by the guideline
Christine Parkinson	Co-investigator on the COMBI-V (phase III, randomised, double-blinded study evaluating the combination of MEK and BRAF Inhibitors vs dabrafenib in patients with unresectable (Stage IIIC) or metastatic (Stage IV) BRAF V600E/K mutation-positive cutaneous melanoma). Funded by GSK.	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as no supervisory responsibility on trials.
Christine Parkinson	Co-investigator on the PACMEL (Paclitaxel with or without MEK inhibitor GSK1120212 for treatment of melanoma). Sponsored by University of Oxford. Funded by GSK	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as no supervisory responsibility on trials.

Name	Interest declared	Type of Interest	Decision Taken
Christine Parkinson	Co-investigator on the Phase 1, Open Label, Dose Finding Study to Assess the Safety and Tolerability of IMCgp100, a Monoclonal T Cell Receptor Anti-CD3 scFv Fusion Protein in Patients With Advanced Malignant Melanoma). Sponsored and funded by Immunocore Ltd	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as no supervisory responsibility on trials.
Christine Parkinson	Co-investigator on the NICAM (Nilotinib for patients with advanced acral or mucosal melanoma). Sponsors by Royal Marsden Foundation Trust and Institute of Cancer Research. Funded by CTAAC	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as no supervisory responsibility on trials.
Christine Parkinson	Co-investigator on the IMAGE (observational study looking at quality of life in patients on ipilimumab). Funded by Bristol Myers Squibb	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as no supervisory responsibility on trials.
Christine Parkinson	Co-investigator on the SUAVE (randomised phase II study of Sunitinib versus Dacarbazine in the treatment of patients with metastatic uveal melanoma). Sponsor is Clatterbridge Centre for Oncology NHS Trust. Funded by Pfizer Limited and CTAAC.	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as no supervisory responsibility on trials.
Christine Parkinson	Co-investigator on the MelResist (translational study in melanoma – collection of blood and tissue samples). Funded by Cambridge University Hospitals NHS Foundation Trust	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as no supervisory responsibility on trials.
Christine Parkinson	Principle investigator on the PARAGON trial (Phase II study of aromatase inhibitors in women with potentially hormone responsive recurrent/metastatic gynaecological neoplasms). Sponsored by NHS Greater Glasgow & Clyde. Funded by CRUK.	Non-Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as aromatase inhibitors in women with potentially hormone responsive recurrent/metastatic gynaecological neoplasms is not being covered by the guideline.
Christine Parkinson	Received reimbursement of travel and subsistence expenses from CLOVIS for attending an investigator meeting for the ARIEL2 and ARIEL3 trials for ovarian cancer.	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics in discussions as ovarian cancer is not being covered by the guideline.
Fergus Macbeth	Chief investigator of a CRUK funded trial supported by Pfizer with free drug and unrestricted educational grant.	Non-Personal Pecuniary, Non Specific	Declare and participate in discussions on all topics as lung cancer is not being covered by the guideline.

Name	Interest declared	Type of Interest	Decision Taken
Fergus Macbeth	Received reimbursement of travel and subsistence expenses for attending the World lung cancer conference.	Personal Pecuniary, Non Specific	Declare and participate in discussions on all topics as lung cancer is not being covered by the guideline.
Gill Godsell	Received reimbursement of travel and subsistence expenses from Almirall (manufacturers of topical treatments for pre-cancerous lesions) for attending an European Academy of Dermatology and Venerology meeting.	Personal Pecuniary, Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Gill Godsell	Vice Chair of the Karen Clifford Skin Cancer Charity. Give advice on clinical aspects of skin cancer – not specific treatments.	Personal Non-Pecuniary	Chair persons action to declare and participate in discussions on all topics
Jonathan Smith	Reviewed a systematic review on PET-CT in stage III melanoma for publication in the journal of surgical oncology.	Personal Non-Pecuniary, Specific	Chair person's action to declare and participate in discussions on all topics as only reviewed article, no opinion was expressed.
Jonathan Smith	Received reimbursement of, subsistence and course fee from Nucletron for attending the annual UK prostate brachytherapy course.	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as prostate brachytherapy is not being covered by the guideline.
Jonathan Smith	Received travel and accommodation from the Royal College of Radiologists to give a lecture on 'how to run a radiology discrepancy' at the royal college of radiology autumn scientific meeting	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as how to run a radiology discrepancy is not being covered by the guideline.
Jonathan Smith	Reports CT studies in the STAR trial, which is an RCT multi-centre trial in drug therapy for metastatic renal cell cancer.	Non Specific	Declare and participate in discussion on all topics as reporting CT studies for renal cell cancer is not being covered by the guideline.
Julia Newton-Bishop	Received an honorarium from Roche for giving advice on cutaneous toxicity from Vemurafenib.	Personal Pecuniary, Specific	Declare and participate in discussion on all topics as Vemurafenib is covered by a published TA and therefore will not being investigated by the guideline.
Julia Newton-Bishop	Research funds received an honorarium from Roche for giving advice on cutaneous toxicity from Vemurafenib.	Non-Personal Pecuniary	Declare and participate in discussion on all topics as Vemurafenib is covered by a published TA and therefore will not being investigated by the guideline.
Julia Newton-Bishop	Received reimbursement of travelling expenses from Irish Association of Dermatologists for giving a talk on vitamin D and melanoma.	Personal Pecuniary, Specific	Declare and participate in discussion on all topics as expenses are not beyond a reasonable amount.

Name	Interest declared	Type of Interest	Decision Taken
Julia Newton-Bishop	Received an honorarium from Irish Association of Dermatologists for giving a talk on vitamin D and melanoma.	Personal Pecuniary, Specific	Declare and participate in discussion on all topics as payment was received by a professional body.
Julia Newton-Bishop	Received reimbursement of travelling expenses from the Melanoma Study Group (MSG) for giving a talk at the Focus on Melanoma conference on the levels of vitamin D in melanoma patients.	Personal Pecuniary, Specific	Declare and participate in discussion on all topics as expenses are not beyond a reasonable amount.
Julia Newton-Bishop	Received reimbursement of travelling expenses from Beatson Institute, for attending a seminar and giving a talk on the genetics of susceptibility and survival of melanoma.	Personal Pecuniary	Declare and participate in discussion on all topics as expenses are not beyond a reasonable amount.
Julia Newton-Bishop	Received reimbursement of travelling expenses from London Strategic Health Authority for attending a ECRIC Cancer Registry meeting to discuss NCIN work designed to understand cancer registration	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as cancer registration is not being covered by the guideline.
Julia Newton-Bishop	Received reimbursement of travelling expenses from Public Health England for chairing a NCIN Chair's meeting regarding national data collection on skin cancer.	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as data collection is not being covered by the guideline.
Julia Newton-Bishop	Received reimbursement of travelling expenses from Public Health England for chairing the skin SSCRG group covering national data collection on skin cancer.	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as data collection is not being covered by the guideline.
Julia Newton-Bishop	Received reimbursement of travelling expenses from conference organisers giving a talk on the genetics of melanoma survival at the 8th World Congress of Melanoma.	Personal Pecuniary, Specific	Declare and participate in discussion on all topics as expenses are not beyond a reasonable amount.
Julia Newton-Bishop	Received reimbursement of travelling expenses from Public Health England for chairing a NCIN workshop on national data collection on skin cancer.	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as data collection is not being covered by the guideline.
Julia Newton-Bishop	Received reimbursement of travelling expenses from Roche for attending a meeting and giving a talk on the biology of melanoma.	Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as the biology of melanoma is not being covered by the guideline..
Julia Newton-Bishop	Department received payment from Roche for giving an introductory talk on the biology of melanoma.	Non-Personal Pecuniary, Specific	Declare and participate in discussion on all topics as the biology of melanoma is not being covered by the guideline.

Name	Interest declared	Type of Interest	Decision Taken
Julia Newton-Bishop	Received an honorarium from Roche for attending an advisory board meeting on the management of skin toxicity.	Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as the management of skin toxicity is not being covered by the guideline.
Julia Newton-Bishop	Received an honorarium from Roche for attending an advisory board meeting on the management of skin toxicity.	Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as the management of skin toxicity is not being covered by the guideline.
Julia Newton-Bishop	Department received payment from Roche for attending an advisory board meeting on the management of skin toxicity.	Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as the management of skin toxicity is not being covered by the guideline.
Julia Newton-Bishop	Department received payment from Roche for making a training video on the management of skin toxicity.	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as the management of skin toxicity is not being covered by the guideline.
Julia Newton-Bishop	Department received payment from Roche for giving a talk on 'why do people get melanoma and what determines whether or not they survive' at the annual British Association of Dermatologists conference.	Non-Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as why do people get melanoma and what determines whether or not they survive' is not being covered by the guideline.
Julia Newton-Bishop	Co-Author on paper published in 2013 regarding the toxicity of vemurafenib.	Personal Non-Pecuniary Interest	Declare and participate in discussion on all topics as vemurafenib is covered by a published TA and therefore will not being investigated by the guideline.
Julia Newton-Bishop	Co-Author on paper published in 2013 regarding the toxicity of vemurafenib.	Personal Non-Pecuniary Interest	Declare and participate in discussion on all topics as vemurafenib is covered by a published TA and therefore will not being investigated by the guideline.
Julia Schofield	Received a fee from Basilea in for giving advise on their product toctino (treatment for hand eczema) into the market place.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as hand eczema is not being covered by the guideline.
Julia Schofield	Received a fee and reimbursement of travel expenses from Leo Pharmaceuticals for giving a lecture on GPs with a special interest	Personal Pecuniary Interest	Declare and participate in discussion on all topics as GPs with a special interest is not being covered by the guideline.
Julia Schofield	Received a fee and reimbursement of travel expenses from the British Dermatology Nursing Group for giving a lecture on dermosocopy and teledermatology in relation to skin cancer (including melanoma).	Personal Pecuniary Interest, Specific	Declare and participate as not funded by healthcare industry.
Julia Schofield	Received a fee and reimbursement of travel expenses	Personal Pecuniary	Declare and participate in discussion on all topics as

Name	Interest declared	Type of Interest	Decision Taken
	from the Dowling Club (national dermatology educational society) to present at a meeting for dermatology trainees on delivering dermatology services.	Interest, Non Specific	delivering dermatology services is not being covered by the guideline.
Julia Schofield	Received a fee and reimbursement of travel expenses from the Primary Care Dermatology Society for presenting at a meeting on the management of pre-cancerous lesions in primary care.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as management of pre-cancerous lesions in primary care is not being covered by the guideline
Julia Schofield	Received a fee and reimbursement of travel expenses from the Irish Primary Care Dermatology Society for presenting at a meeting on recognising skin lesions and paediatric dermatology problems.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as recognising skin lesions and paediatric dermatology problems is not being covered by the guideline
Julia Schofield	During 2012, acted as an advisory to Buckinghamshire NHS Trust on re-designing their dermatology services.	Personal pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as re-designing their dermatology services is not being covered by the guideline
Julia Schofield	External advisor to All Party Parliamentary Group on Skin	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics
Julia Schofield	Trustee of the Psoriasis Association	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics
Laszlo Igali	Received a fee from St James' University Hospital, Leeds in for speaking at a symposium on alopecia and immunohistochemistry in dermatopathology.	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as alopecia and immunohistochemistry is not being covered by the guideline.
Laszlo Igali	Received reimbursement of travelling expenses from the Royal College of Pathologists for attending a council meeting.	Personal Pecuniary	Chair person's action to declare and participate in discussions on all topics.
Laszlo Igali	Involved in the EUR-GAST II study (investigating environmental factors, H. pylori infection and genetic susceptibility in gastric cancer risk in the European population). Was the pathologist responsible for co-ordinating specimen collection and evaluation from the UK. No commercial funding	Non-Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as environmental factors, H. pylori infection and genetic susceptibility in gastric cancer risk in the European population is not being covered by the guideline.
Laszlo Igali	Involved in the EPIC study (european prospective investigation into cancer). Did selective pathology data	Non-Personal Pecuniary Interest	Declare and participate in discussion on all topics as pathology data collection and evaluation is not being covered

Name	Interest declared	Type of Interest	Decision Taken
	collection and evaluation. No commercial funding.		by the guideline.
Laszlo Igali	Supervised an MSc student investigating optimal fixation of metastatic melanoma for tissue banking	Non-Personal Pecuniary Interest, Specific	Declare and participate as not funded by healthcare industry.
Laszlo Igali	Involved in a new prospective study looking at BRAF immunostaining in metastatic melanoma to stratify patients for future treatment. Role is to do the immunohistochemistry and report on the BRAF status. Research funded by employer.	Non-Personal Pecuniary Interest, Specific	Declare and participate as not funded by healthcare industry.
Laszlo Igali	Ran a workshop on teledermatopathology as part of the American Society of Dermatopathology annual congress in. No fee received for this activity.	Personal Non-Pecuniary Interest	Declare and participate in discussion on all topics as teledermatopathology is not being covered by the guideline
Laszlo Igali	Holds the post of Editor of the Bulletin of the Royal College of Pathology.	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics.
Laszlo Igali	Provides ad hoc advice to EZDerm on developing an integrated dermatology/ electronic record system. No fee received for this activity.	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics.
Laszlo Igali	Member of the Interim Body to the Professional Records Standard Body. Provides IT advice on how their electronic records should be set up.	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics.
Laszlo Igali	Received travelling expenses and accommodation from the British Association of Plastic, Reconstructive and Aesthetic Surgeons (BAPRAS) for giving a lecture at the Skin Cancer course on Basal cell carcinoma and squamous cell carcinoma, conventional and MOHS histology.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as Basal cell carcinoma and squamous cell carcinoma is not being covered by the guideline.
Laszlo Igali	Treasurer for the professional record standard body (PRSB) for patient data standards.	Personal Non-Pecuniary Interest	Declare and participate in discussion on all topics as patient data standards is not being covered by the guideline.
Martin Telfer	Gave a presentation on "anatomical restrictions in the surgical excision of Scalp Sq CCa: does this effect local recurrence and regional nodal metastasis" to the British Association of Oral and	Personal Non-Pecuniary	Chair person's action to declare and participate in discussions on all topics

Name	Interest declared	Type of Interest	Decision Taken
	Maxillofacial Surgeons. No fee received.		
Martin Telfer	Presented at the Yorkshire & Humber Regional Clinical Effectiveness Meeting on “Facial Skin Cancer Surgery: Patient Satisfaction”. No fee received.	Personal Non-Pecuniary	Chair person’s action to declare and participate in discussions on all topics.
Rachael Robinson	Received a fee from the RCGP for taking part in a panel reviewing a musculoskeletal e-learning package	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as musculoskeletal e-learning package is not being covered by the guideline.
Rachael Robinson	Received a fee from Galderma in for chairing an educational meeting of the Leeds Skin Club on the treatment of acne and the red face.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as the treatment of acne and the red face is not being covered by the guideline.
Rachael Robinson	Received reimbursement of travel expenses from the Yorkshire Deanery for attending a meeting to talk about the new curriculum for GP registrars.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as new curriculum for GP registrars is not being covered by the guideline.
Rachael Robinson	Practice recruits patients into the 3C – cough complications co-hort study, organised by Oxford University. Practice receives an income for this activity which is shared amongst the GPs	Non-Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as cough complications is not being covered by the guideline.
Rachael Robinson	Practice recruits patients into the early arthritis study, organised by Leeds University. Practice receives an income for this activity which is shared amongst the GPs.	Non-Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as early arthritis is not being covered by the guideline.
Rachael Robinson	Practice recruits patients into a study on transdermal patches for the treatment of chronic pain, organised by IMS Health. Practice receives an income for this activity which is shared amongst the GPs.	Non-Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as transdermal patches for the treatment of chronic pain is not being covered by the guideline.
Rachael Robinson	Currently involved in reviewing an acne decision aid tool for the BMJ patient decision aid group. No fee is being received	Personal Non-Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as acne decision aid tools is not being covered by the guideline.
Sara Stoneham	Received a fee from the Royal Marsden for giving a lecture on renal tumours in paediatric oncology as part of their MSc in Oncology	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as renal tumours is not being covered by the guideline.
Sara Stoneham	Principle investigator for the CNS 9204 trial (Neuropsychological, academic and functional	Non-Personal Pecuniary	Declare and participate in discussion on all topics as Neuropsychological, academic

Name	Interest declared	Type of Interest	Decision Taken
	outcomes in survivors of infant ependymoma (UKCCSG CNS 9204)). Funded by CRUK. Not involved in designing the trial protocol.	Interest, Non Specific	and functional outcomes in survivors of infant ependymoma is not being covered by the guideline.
Sara Stoneham	Was principle investigator for the GC 2005 04 (GC-3) trial (Protocol for the treatment of Extracranial Germ Cell Tumours in children and adolescents). Trial closed in 2009, 1 patient still in follow up. Sponsored by University Hospitals of Leicester NHS Trust. Funded by Children's Cancer and Leukaemia Group (CCLG).	Non-Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as Protocol for the treatment of Extracranial Germ Cell Tumours in children and adolescents is not being covered by the guideline.
Sara Stoneham	Co-investigator in the HERBY trial (study of high grade paediatric glioma. Funded by Roche	Non-Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as as paediatric glioma is not being covered by the guideline.
Saskia Reeken	Received an honorarium from Leo Pharmaceuticals for attending an advisory board on dermatology (their psoriasis treatments and new products – none relating to melanoma)	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as psoriasis treatments are not being covered by the guideline and other products are not relating to melanoma.
Saskia Reeken	Received an honorarium from the British Dermatology Nursing Group for giving a lecture on topical treatments for dermatology (specifically steroid creams)	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as steroid creams are not being covered by the guideline.
Saskia Reeken	Received reimbursement of travel expenses (from the organizer) for attending the British Association of Dermatology Nursing annual conference.	Personal Pecuniary, Non Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Saskia Reeken	Received a fee from Janssen for giving a lecture to dermatology nurses on the recognition of skin cancer lesions (including melanoma) in patients with psoriasis and the practical skills for lymph node examination.	Personal Pecuniary, Specific	Declare and withdraw from discussions on all topics regarding the recognition of melanoma until May 2013. However, guideline development commenced in May 2013 so can participate in discussion on all topics.
Saskia Reeken	Received reimbursement of travel and subsistence expenses from the Danish Embassy in Copenhagen for attending a meeting in on sun radiation and the effect on the environment.	Personal Pecuniary, Non Specific	Declare and participate in discussions as sun radiation and the effect on the environment is not being covered by the guideline.
Saskia Reeken	Member of the CRUK Sun Smart Advisory Board – looks at strategies for sun awareness and health promotion	Personal Non-Pecuniary Interest	Chair persons action to declare and participate in discussions on all topics

Name	Interest declared	Type of Interest	Decision Taken
Saskia Reeken	Member of the Melanoma Task Force – interested in improving the care of patients with melanoma	Personal Non-Pecuniary Interest	Chair persons action to declare and participate in discussions on all topics
Saskia Reeken	Nurse representative on the British Association of Dermatology skin cancer committee	Personal Non-Pecuniary Interest	Chair persons action to declare and participate in discussions on all topics
Saskia Reeken	Nurse representative on Skin Cancer UK – provides advice on skin cancer issues.	Personal Non-Pecuniary Interest	Chair persons action to declare and participate in discussions on all topics.
Saskia Reeken	Received sponsorship from LEO p[harmaceuticals and Dermal Laborities Limited for attending a study day on Maximising Capacity and Productivity in your Dermatology Service.	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as capacity and productivity in ddermatology services. is not being covered by the guideline.
Saskia Reeken	Received a practice development award of £900 from the British Dermatology Nursing Group. The award is to be used for professional development and will be put towards a MSc module of child health.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as practice development is not being covered by the guideline.
Stephen Keohane	Received a fee from Meda for attending an advisory board on their new treatment for actinic keratosis (Zyclara)	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as for actinic keratosis is not being covered by the guideline.
Stephen Keohane	Received a fee from Almirall for giving a lecture on new advances in non melanoma skin cancer	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as for actinic keratosis is not being covered by the guideline.
Stephen Keohane	Received a fee from Leo Pharmaceuticals for attending an advisory board on their new treatment for actinic keratosis (Picato).	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as for actinic keratosis is not being covered by the guideline.
Stephen Keohane	Received a fee from Roche for attending an advisory board on their treatment for advanced basal cell carcinoma (Everidge).	Personal Pecuniary, Non Specific	Declare and participate in discussion on all topics as basal cell carcinoma is not being covered by the guideline.
Stephen Keohane	Received reimbursement of expenses (travel, accommodation, subsistence and conference fee) from Leo Pharmaceuticals for attending the American Academy of Dermatology conference	Personal Pecuniary, Non Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
Stephen Keohane	Local principle investigator for a trial on Ingenol (treatment of facial and scalp actinic keratoses). Trial is funded by Leo Pharmaceuticals. Responsible for	Non-Personal Pecuniary Interest, Non	Declare and participate in discussion on all topics as for actinic keratosis is not being covered by the guideline.

Name	Interest declared	Type of Interest	Decision Taken
	administrating the trial locally. Not involved in designing the trial protocol	Specific	
Stephen Keohane	Chaired a meeting in on advanced melanoma management (content of the meeting was investigation and management and covered new therapeutic treatments including ipilumimab, vemfuranib, MEK inhibitors and DNA vaccines. The event was sponsored by Bristol Myers Squibb. Did not receive a fee or organise the meeting.	Personal Non-Pecuniary Interest	Declare and participate in discussion on all topics as Vemurafenib & Ipilumimab are both covered by a published TA and therefore will not being investigated by the guideline. MEK inhibitors (dabrafenib and trametinib) are the subject of on-going TA's and will not be investigated by the guideline. The scope of the guideline does not cover DNA vaccines.
Stephen Keohane	Member of the National Cancer Intelligence Network Skin Reference Group – look at changing trends in skin cancer and how these impact on service provision.	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics
Stephen Keohane	Chair of the British Association of Dermatologists Skin Cancer Committee – look at service provision and ensuring the quality of skin cancer care provided by dermatologists is equitable across the UK.	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics
Stephen Keohane	Chair of the Skin Cancer Site Specific Group of the Central South Coast Cancer Network – look at local service provision and co-ordinate regional audits etc.	Personal Non-Pecuniary Interest	Chair person's action to declare and participate in discussions on all topics
John Rouse	Member of the NCRI/Astra Zeneca patient reference panel.	Personal Non-Pecuniary Interest	Declare and participate in discussion on all topics as agreed to suspend membership of this panel until publication of the final guideline.
John Rouse	Received travelling expenses, subsistence allowance and overnight accommodation for a NCRI/Astra Zeneca patient reference meeting at Alderley Park on the 26th September 2013.	Personal Pecuniary Interest, Non Specific	Declare and participate in discussion on all topics as meeting was an induction training for the patient reference panel and no content of the guideline was covered.
John Rouse	Received travelling expenses, subsistence allowance and overnight accommodation from ESO and M-icab for attending a conference on Patient Participation in Melanoma Clinical Research.	Personal Pecuniary Interest, Specific	Declare and participate in discussion on all topics as patient participation in melanoma clinical research is not being covered by the guideline.

Name	Interest declared	Type of Interest	Decision Taken
Richard Jackson	Interviewed for the Daily Mail on the effectiveness of Ipilimumab for metastatic melanoma.	Personal Non-Pecuniary Interest	Declare and participate in discussion on all topics as Ipilimumab i is covered by a published TA and therefore will not being investigated by the guideline.
Julia Schofield	Received travel and accommodation costs from Conference Plus for a giving a lecture in an educational program for GPs. The lectures will include a session on skin lesion diagnosis.	Non-Personal Pecuniary Interest, Non Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
John Rouse	Received a bursary from the NCRN to attend the NCRI conference in Liverpool	Personal Pecuniary Interest, Non Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
John Rouse	Received travelling expenses, overnight accommodation and subsistence allowance paid for by CRUK for attending the NCRN/ECMC Combinations Alliance AZ Workshop	Personal Pecuniary Interest, Non Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.
John Rouse	Received travelling expenses costs from Macmillan Cancer support and accommodation costs from the meeting organisers for attending the Britain Against Cancer conference and Quality in Care awards	Personal Pecuniary Interest, Non Specific	Declare and participate in discussions on all topics as expenses not beyond a reasonable amount.

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F.2 Organisations invited to comment on the guideline development

Aintree University Hospital NHS Foundation Trust	Alder Hey Children's NHS Foundation Trust
Allocate Software PLC	Amgen UK
Association for Family Therapy and Systemic Practice in the UK	Association for Palliative Medicine of Great Britain
Association of Anaesthetists of Great Britain and Ireland	Association of British Insurers
Association of Chartered Physiotherapists in Oncology and Palliative Care	Barnsley Hospital NHS Foundation Trust
Belfast Health and Social Care Trust	Boots
Bristol-Myers Squibb Pharmaceuticals Ltd	British Association of Dermatologists
British Association of Plastic Reconstructive and Aesthetic Surgeons	British Association of Skin Camouflage
British Association of Skin Cancer Specialist Nurses	British Association of Spinal Surgeons
British Dermatological Nursing Group	British HIV Association
British Lymphology Society	British Medical Association
British Medical Journal	British National Formulary
British Nuclear Cardiology Society	British Nuclear Medicine Society
British Psychological Society	British Red Cross
British Society for Dermatopathology	British Society for Paediatric Dermatology
Calderstones Partnerships NHS Foundation Trust	Cambridge University Hospitals NHS Foundation Trust
Cancer Commissioning Team	Cancer Research UK
Cancer52	Capsulation PPS
Care Quality Commission	Celgene UK Ltd
Chartered Society of Physiotherapy	Clarity Informatics Ltd
CLEAR Cannabis Law Reform	Covidien Ltd.
Croydon Clinical Commissioning Group	Croydon Council
Croydon Health Services NHS Trust	Croydon University Hospital
Cumbria Partnership NHS Foundation Trust	CWHHE Collaborative CCGs
Department of Health	Department of Health, Social Services and Public Safety - Northern Ireland
East and North Hertfordshire NHS Trust	East Kent Hospitals University NHS Foundation Trust
Economic and Social Research Council	Ethical Medicines Industry Group
False Allegations Support Organisation	Five Boroughs Partnership NHS Trust
GlaxoSmithKline	Glebe Road Surgery GP
Globe Microsystems Ltd	Gloucestershire Hospitals NHS Foundation Trust
GP update / Red Whale	Greater Manchester, Lancashire and South Cumbria Strategic Clinical Network
Health and Care Professions Council	Health and Social Care Information Centre
Healthcare Improvement Scotland	Healthcare Infection Society
Healthcare Quality Improvement Partnership	Healthwatch East Sussex

Herts Valleys Clinical Commissioning Group	Hockley Medical Practice
Humber NHS Foundation Trust	IGEA Medical
Institute of Biomedical Science	Isabel Hospice
King's College Hospital NHS Foundation Trust	Launch Diagnostics
Leeds Teaching Hospitals NHS Trust	Local Government Association
London cancer alliance	Luton and Dunstable Hospital NHS Trust
Lymphoedema support network	Macmillan Cancer Support
Medical Directorate Services	Medicines and Healthcare products Regulatory Agency
Melanoma Focus	Melanoma UK
Merck Sharp & Dohme UK Ltd	Ministry of Defence
Muslim Doctors and Dentists Association	National Association of Primary Care
National Clinical Guideline Centre	National Collaborating Centre for Cancer
National Collaborating Centre for Mental Health	National Collaborating Centre for Women's and Children's Health
National Deaf Children's Society	National Institute for Health Research Health Technology Assessment Programme
National Institute for Health Research	National Patient Safety Agency
NHS Barnsley Clinical Commissioning Group	NHS Choices
NHS Connecting for Health	NHS County Durham and Darlington
NHS Cumbria Clinical Commissioning Group	NHS England
NHS Hardwick CCG	NHS Health at Work
NHS Improvement	NHS Medway Clinical Commissioning Group
NHS Plus	NHS Sheffield
NHS South Cheshire CCG	NHS Wakefield CCG
NHS Warwickshire North CCG	NHS West Cheshire CCG
Nordion	Norfolk and Suffolk Palliative Care Academy
North and East London Commissioning Support Unit	North of England Commissioning Support
North of England Dermatopathology Service	North West London Hospitals NHS Trust
Northern Health and Social Care Trust	Nottingham City Council
Novartis Pharmaceuticals	Nursing and Midwifery Council
Nutricia Advanced Medical Nutrition	Oxford Health NHS Foundation Trust
Oxfordshire Clinical Commissioning Group	Parenteral and Enteral Nutrition Group
Primary Care Dermatology Society	Primary Care Pharmacists Association
Primrose Bank Medical Centre	Public Health Agency for Northern Ireland
Public Health England	Public Health Wales NHS Trust
Public Health Wales NHS Trust	Queen Elizabeth Hospital King's Lynn NHS Trust
Rarer Cancers Foundation	Roche Diagnostics
Roche Products	Royal College of Anaesthetists
Royal College of General Practitioners	Royal College of General Practitioners in Wales
Royal College of Midwives	Royal College of Nursing
Royal College of Obstetricians and Gynaecologists	Royal College of Paediatrics and Child Health
Royal College of Pathologists	Royal College of Physicians
Royal College of Physicians and Surgeons of Glasgow	Royal College of Psychiatrists

Royal College of Radiologists	Royal College of Speech and Language Therapists
Royal College of Surgeons of Edinburgh	Royal College of Surgeons of England
Royal Cornwall Hospitals NHS Trust	Royal Liverpool and Broadgreen University Hospitals NHS Trust
Royal Pharmaceutical Society	Royal Surrey County Hospital NHS Trust
Sanofi	SciBase
Scottish Intercollegiate Guidelines Network	Sheffield Teaching Hospitals NHS Foundation Trust
Skcin - Karen Clifford Skin Cancer Charity	Skin research specialist interest group
Social Care Institute for Excellence	Society and College of Radiographers
Society of Chiropodists & Podiatrists	Somerset, Wiltshire, Avon and Gloucestershire Cancer Services Operational Group
South East Coast Cancer Strategic Clinical Network	South Eastern Health and Social Care Trust
South London & Maudsley NHS Trust	South Wales Cancer Network
South West Public Health Observatory	South West Yorkshire Partnership NHS Foundation Trust
Southern Health & Social Care Trust	Southport and Ormskirk Hospital NHS Trust
St Georges Healthcare NHS Trust	St Mary's Hospital
Staffordshire and Stoke on Trent Partnership NHS Trust	Stockport Clinical Commissioning Group
Takeda UK Ltd	Teenagers and Young Adults with Cancer
The College & Fellowship of Podiatric Medicine	The Institute of Cancer Research
The Patients Association	The University of Birmingham
University Hospital Birmingham NHS Foundation Trust	university hospital Southampton
University Hospital Southampton NHS Foundation Trust	University Hospitals Birmingham
Velindre NHS Trust	Walsall Local Involvement Network
Welsh Government	Welsh Kidney Patients Association
Welsh Scientific Advisory Committee	West Suffolk Hospital NHS Trust
Western Health and Social Care Trust	Western Sussex Hospitals NHS Trust
Wicked Minds	Wigan Borough Clinical Commissioning Group
York Hospitals NHS Foundation Trust	

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F.3 Individuals carrying our literature reviews and complementary work

Overall Co-ordinators	
Dr John Graham	Director, National Collaborating Centre for Cancer, Cardiff
Dr Andrew Champion	Centre Manager, National Collaborating Centre for Cancer, Cardiff
Angela Bennett	Assistant Centre Manager, National Collaborating Centre for Cancer, Cardiff
Project Managers	
Lianne Gwillim	National Collaborating Centre for Cancer, Cardiff
Coral McCarthy	National Collaborating Centre for Cancer, Cardiff
Senior Researcher	
Dr Nathan Bromham	National Collaborating Centre for Cancer, Cardiff
Researchers	
Susan O'Connell	National Collaborating Centre for Cancer, Cardiff
Laura Bunting	National Collaborating Centre for Cancer, Cardiff
Angharad Morgan	National Collaborating Centre for Cancer, Cardiff
Information Specialists	
Stephanie Arnold	National Collaborating Centre for Cancer, Cardiff
Sabine Berendse	National Collaborating Centre for Cancer, Cardiff
Delyth Morris	National Collaborating Centre for Cancer, Cardiff
Senior Health Economist	
Matthew Prettyjohns	National Collaborating Centre for Cancer, Cardiff
Health Economist	
James Hawkins	National Collaborating Centre for Cancer, Cardiff
Needs Assessment	
Veronique Poirier	Knowledge and Intelligence Team (South West), Public Health England
Tim Jones	Knowledge and Intelligence Team (South West), Public Health England

F.41 Expert advisors to the Guideline Development Group

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Mr Howard Peach	Consultant Plastic and Reconstructive Surgeon, University of Leeds
Prof. Meirion Thomas	Consultant Surgeon, the Royal Marsden

F.4.13 Declarations of interest

Expert advisor	Interest declared	Type of interest	Decision taken
Mr Howard Peach	Received a payment from Lifecell for teaching on their national and international courses about abdominal wall reconstruction	Personal pecuniary non-specific	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Mr Howard Peach	Received an educational grant to attend an Abdominal Wall Reconstruction conference in Washington DC.	Personal pecuniary non-specific	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Mr Howard Peach	Has given talks on the benefits of sentinel node biopsy	Personal non-pecuniary	Declare and can participate in discussions as is a source of expert advise and will not be involved in drafting of recommendations
Prof. Meirion Thomas	None declared		

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Appendix G: Needs assessment

G.1 Introduction

Melanoma is the fifth most common cancer in the UK, with 13,348 cases diagnosed in the UK in 2011 (CRUK, 2013a). In males and females separately, melanoma is the 6th most common cancer (4% each of the male and female total).

In 2012 there were 2,148 deaths from melanoma in the UK making it the eighteenth most common cause of cancer death (CRUK, 2013b).

The incidence of melanoma has increased at all anatomical locations in the last decade. In males, the most common sites are the trunk, particularly the back and on the head and neck. In women melanoma is more common on the limbs, especially the legs.

There are a number of well-known risk factors for melanoma, including ultraviolet radiation from sun exposure and sun beds. This risk is more strongly linked to intermittent exposure to high-intensity sunlight rather than to chronic or continuous sunlight exposure. Intermittent exposure of high-intensity sunlight is associated with sunburn, and a history of sunburn increases the risk of melanoma. There are other risk factors in developing melanoma including the number of moles (naevi) present, and the presence of atypical naevi which are larger or more unusually shaped than normal.

Having a family history malignant melanoma doubles the risk of developing the condition and having had an organ transplant also doubles the risk. A previous history of having had a melanoma increases the risk of a second melanoma by approximately a factor of 10 and this risk is higher in women. Also having a past history of one of a wide range of other cancers, for example, thyroid cancer or some lymphomas also increases the risk of developing melanoma.

G.2 Methods

This chapter consists of two main parts. The first provides an up to date report on the epidemiology of melanoma in England looking a trends in incidence, mortality, survival and prevalence. The effects of sex, age, primary tumour site, tumour thickness at diagnosis and income deprivation have been investigated and reported (sections G.3 to G.6). The second part presents the results of a survey of skin cancer multidisciplinary teams (MDTs) in England and Wales, planned in collaboration with the Guideline Development Group (GDG), investigating aspects of current service provision of relevance to the guideline. The topics included systemic therapy use, advice on vitamin D, genetic testing of tumour samples, advice on sentinel lymph node biopsy, and the provision of patient information and support (section G.7).

This report was prepared on behalf of the GDG and the National Collaborating Centre for Cancer by the South West Knowledge and Intelligence Team at Public Health England.

G.2.1 Epidemiology

Epidemiological data for this report were obtained from the National Cancer Information Service and the Office for National Statistics (ONS).

Incident cases were extracted from the National Cancer Registration Service (NCRS) in England. The following codes were used to identify cases:

- C43 'Malignant melanoma of skin'

All deaths in England and Wales are certified by a medical professional and then processed by the Office for National Statistics (ONS). The ONS derive a single underlying cause of death which is used to identify bladder cancer deaths.

Deprivation in England has been measured using the income deprivation component of the English Indices of Deprivation (DCLG, 2012).

Melanoma incidence and mortality are reported as age-standardised rates (per 100,000 population) using the 2013 European Standard Population (http://www.ons.gov.uk/ons/guide-method/user-guidance/health-and-life-events/revised-european-standard-population-2013--2013-esp-/index.html). Analysis of trends in age-standardised incidence and mortality rates was carried out using variance-weighted log-linear regression.

Survival figures are reported as age-standardised net survival using the Pohar Perme estimator (Pohar Perme et al, 2012). In order to provide robust estimates of survival, three-year rolling time periods were used. A mixed 'cohort' and 'period' approach for survival calculations was used. When every member of a three-year cohort could be followed up for five years (e.g., 2001-2003 followed up to the end of 2008), the 'cohort' survival approach was used, essentially calculating the true survival for this cohort. For the most recent three-year period (i.e., 2010-2012), the 'period' survival approach was used. For three-year periods in-between when not everybody could be followed up for a full five years (e.g., 2007-2009), a combination of the two techniques was used, where patients' true 'cohort' follow-up to the end of 2012 was combined with a 'period' approach to provide the extra information about conditional survival later on (e.g., 4-5 years). All survival calculations were carried out using the strs module (Paul Dickman) for STATA statistical software (Stata Corporation, College Station, Texas). This 'mixed' approach allows us to use true follow-up for patients wherever possible; it should give survival statistics that most closely reflect the true survival for each time period, given the data available at the current time.

Analysis of trends in age-standardised net survival was carried out using variance-weighted linear regression, with time split into four periods: 2001-2003; 2004-2006; 2007-2009; and 2010-2012.

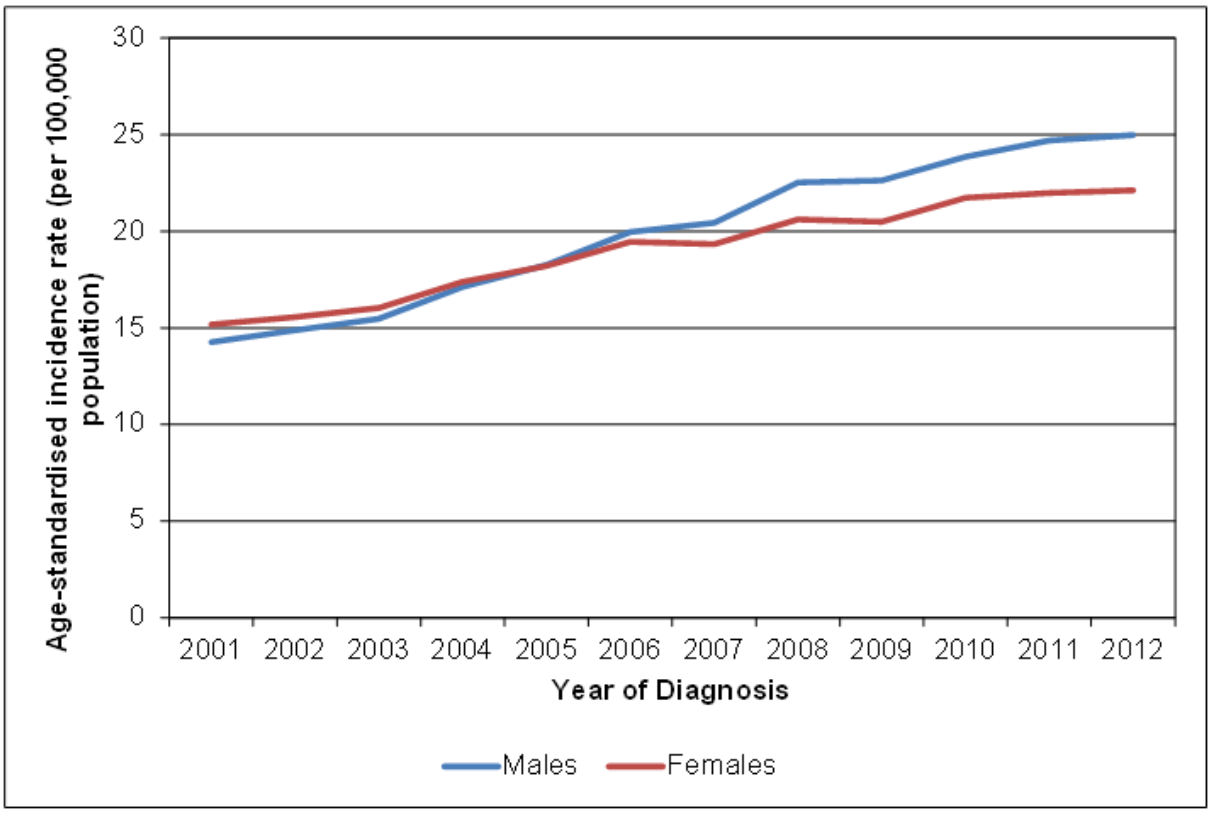
Prevalence (or survivorship) represents the number of people living with a cancer diagnosis within the last 'n' years. Here, the number of melanomas diagnosed between 2008 and 2012 in people alive at the end of 2012 are reported. The number of melanomas is used rather than the number of patients, in order that the information can be separated by tumour-level variables such as Breslow thickness and stage, even for patients who have more than one tumour.

G.3 Incidence

G.3.1 Sex

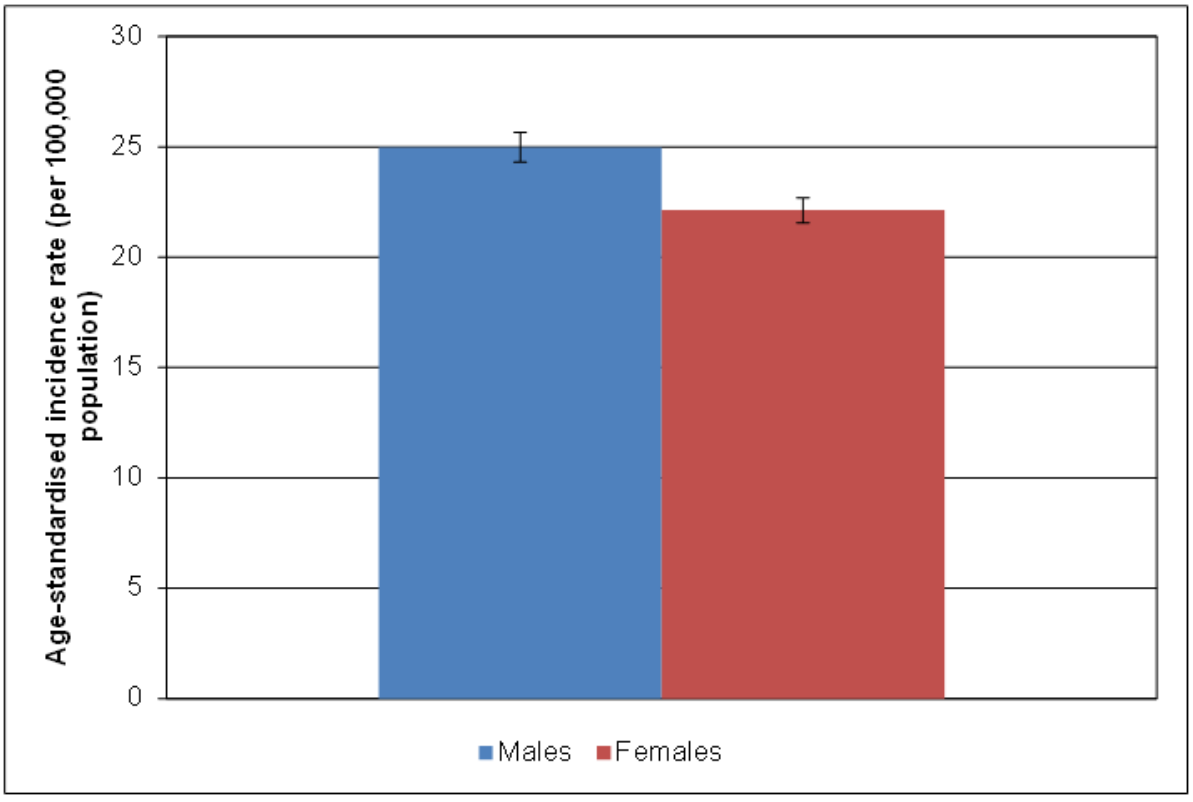
The age-standardised incidence rate for melanoma in England has increased for both sexes over the last decade (Figure 10). The average annual increase was significantly higher for men (5.5%) than for women (3.7%). Figure 11 shows that the age-standardised incidence rate in 2012 was higher for men (25.0 melanomas per 100,000 men) than for women (22.1 melanomas per 100,000 women). However, it is worth noting that in 2012 there were actually slightly fewer new melanoma diagnoses for men (5,572) than for women (5,782). The higher age-standardised incidence rate in men is due to a smaller population of men, and a different age distribution of new diagnoses for men and women (see section 3.2); men have higher incidence rates among the older age groups than women. The melanoma incidence in men and women (age standardised rate per 100,000 population) by Clinical Commissioning Group (CCG) in England is presented in Figures 12 and 13 respectively.

Figure 10: Age-standardised incidence rates (per 100,000 population) of melanoma by sex, England, 2001-2012



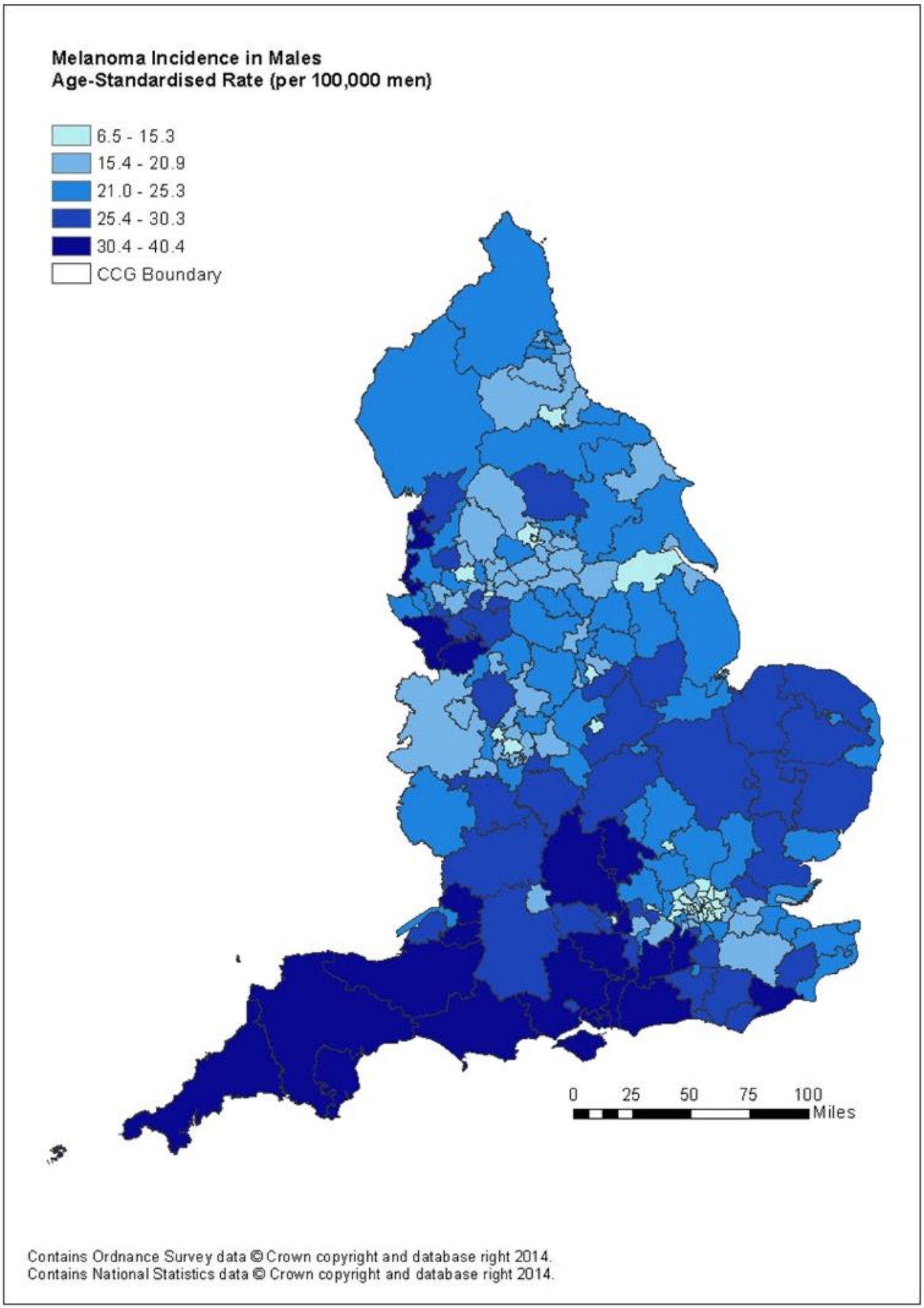
Source: National Cancer Registration Service; Office for National Statistics

Figure 11: Age-standardised incidence rates (per 100,000 population) of melanoma by sex, England, 2012



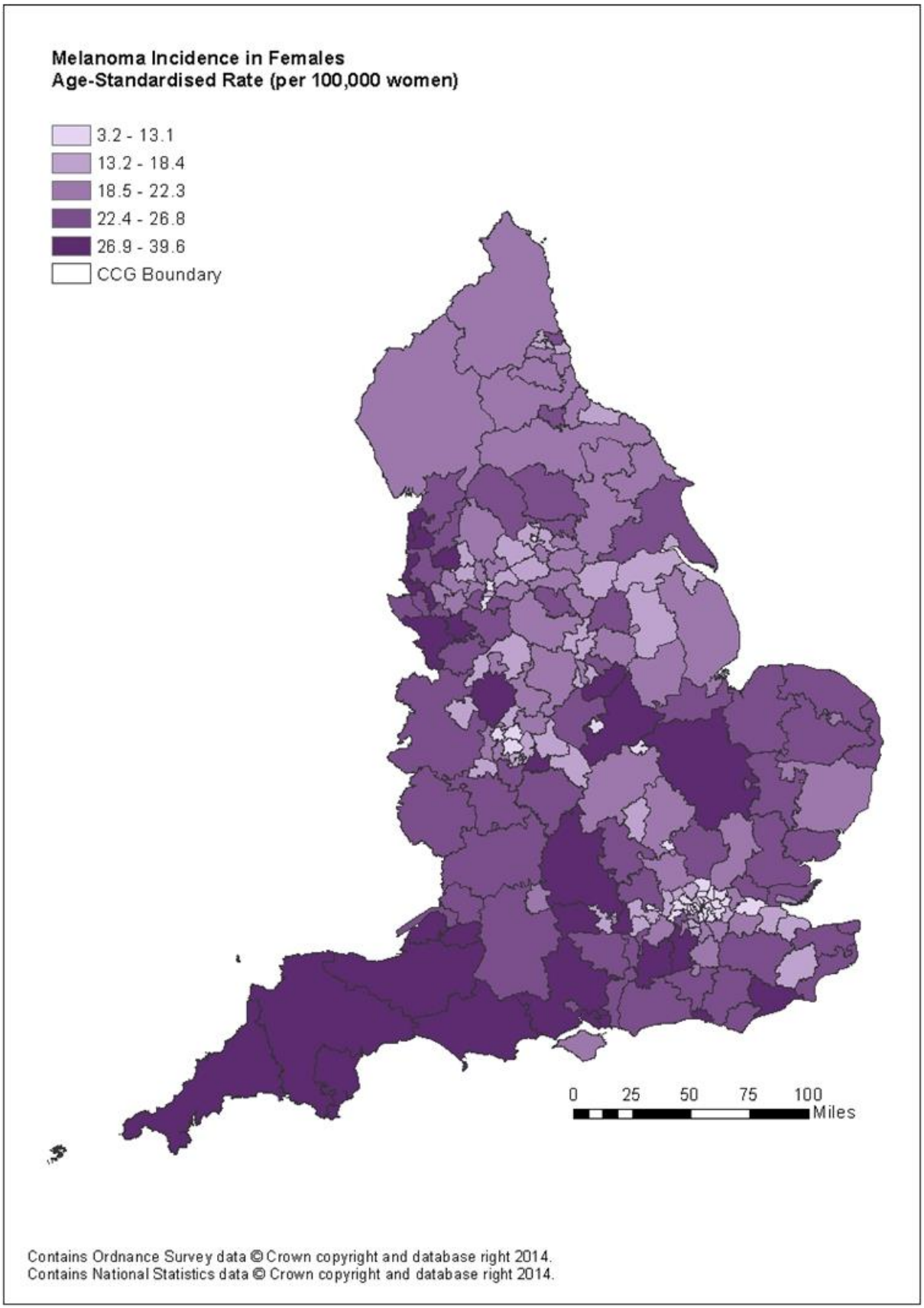
Source: National Cancer Registration Service; Office for National Statistics

Figure 12: Male age-standardised melanoma incidence rates (per 100,000 men) by Clinical Commissioning Group (CCG) in England, 2008-2012



Source: National Cancer Registration Service; Office for National Statistics

Figure 13: Female age-standardised melanoma incidence rates (per 100,000 women) by Clinical Commissioning Group (CCG) in England, 2008-2012



Source: National Cancer Registration Service; Office for National Statistics

G.3.21 Age

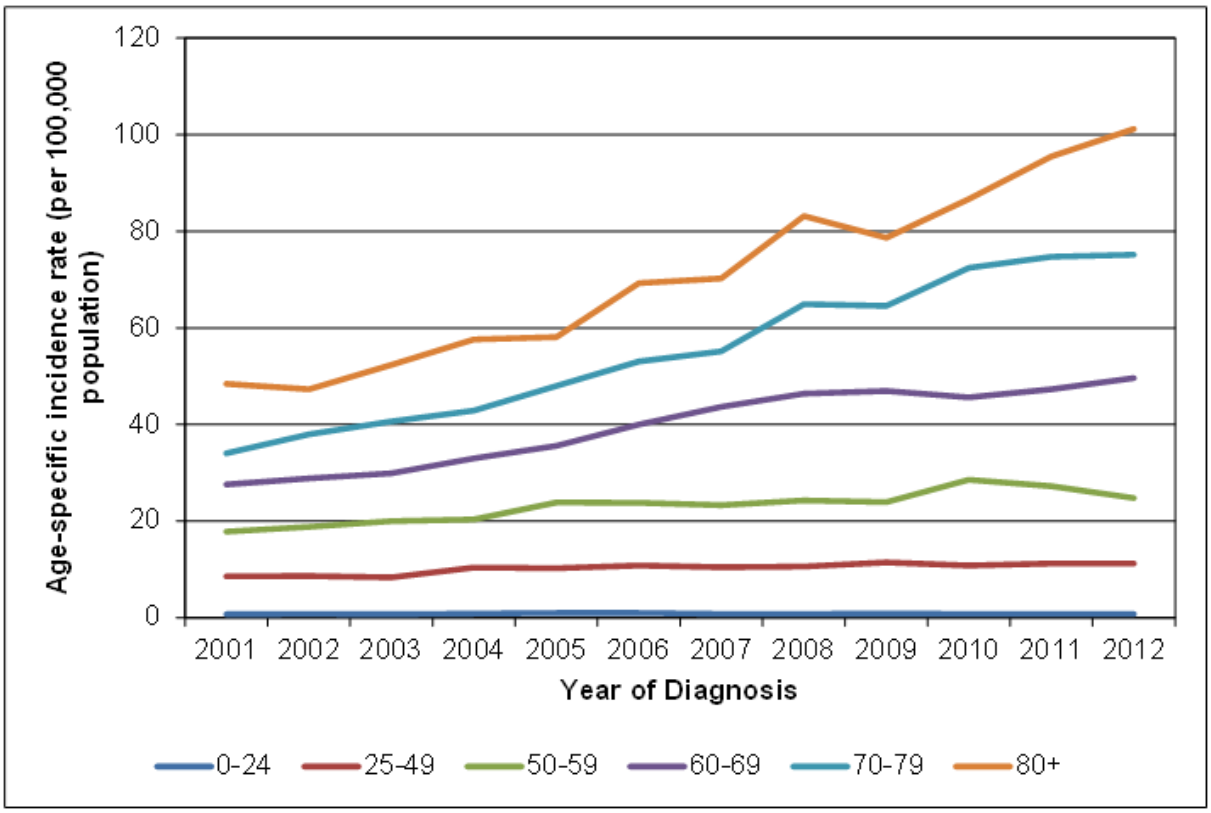
The increasing incidence of melanoma between 2001 and 2012 was especially marked in those over the age of 60 and that increase was greater in men than in women (Table 25 and Figures 14 and 15). Melanoma has generally been more common in women but recent data suggest that this may be changing. In 2012, the age-specific incidence rates for men (over 60 were higher than for older women (Figure 16).

Table 25: Annual percentage change in incidence rates by age group, 2001-2012

Age Groups (years)	Male AAPC	Female AAPC
0-24	0	-0.4
25-49	2.6*	2.9*
50-59	3.6*	2.3*
60-69	5.6*	5.0*
70-79	7.8*	4.9*
80+	7.4*	4.7*

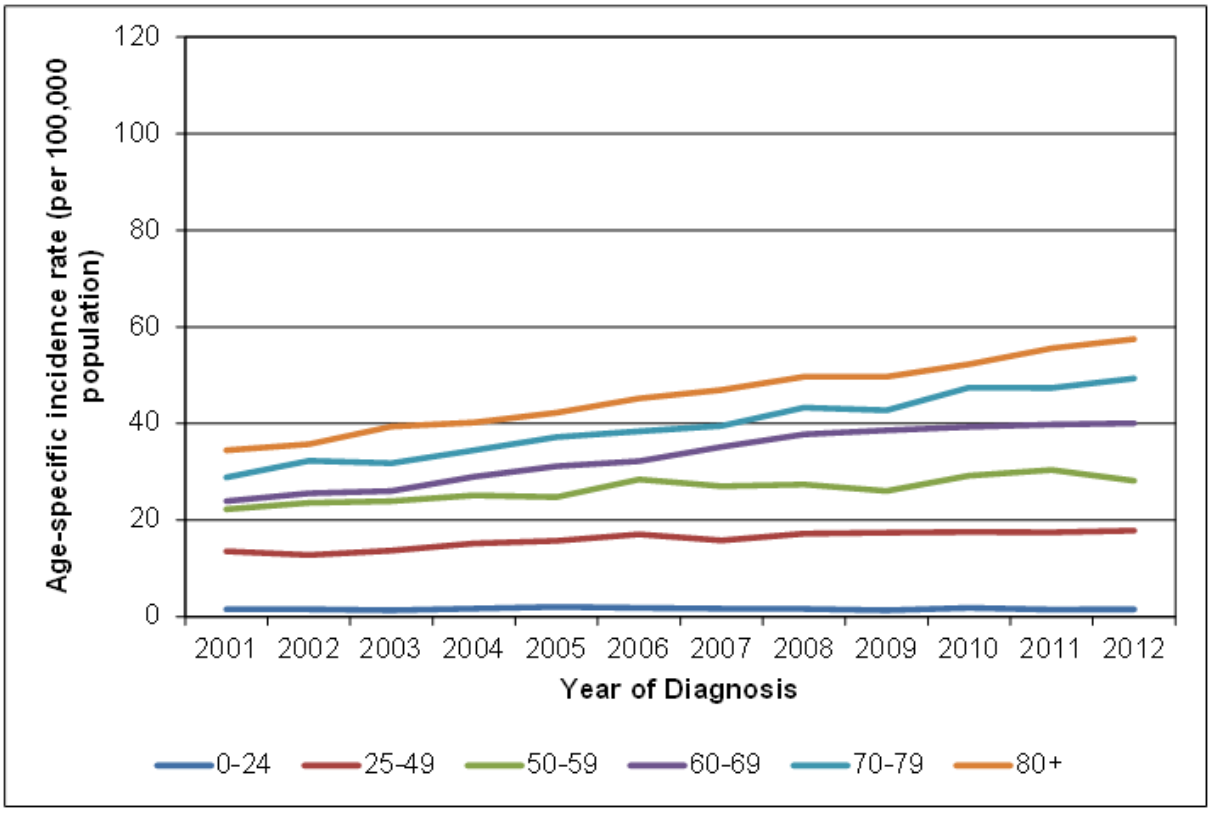
*AAPC = Average Annual Percentage Change; * = p < 0.05*

Figure 14: Age-specific melanoma incidence rates for males (per 100,000 men) by age group, England, 2001-2012



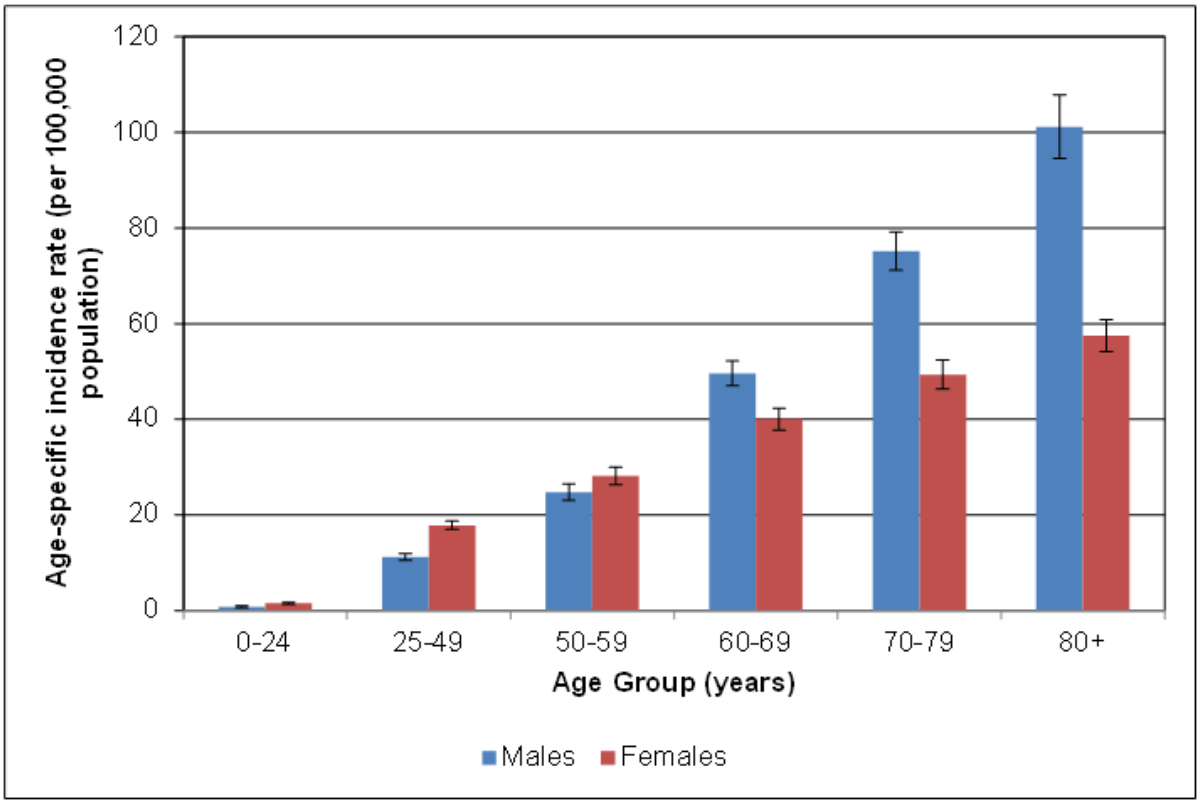
Source: National Cancer Registration Service; Office for National Statistics

Figure 15: Age-specific melanoma incidence rates for females (per 100,000 women) by age group, England, 2001-2012



Source: National Cancer Registration Service; Office for National Statistics

Figure 16: Age-specific melanoma incidence rates (per 100,000 people) by sex and age group, England, 2012



Source: National Cancer Registration Service; Office for National Statistics

G.3.3 Anatomical site

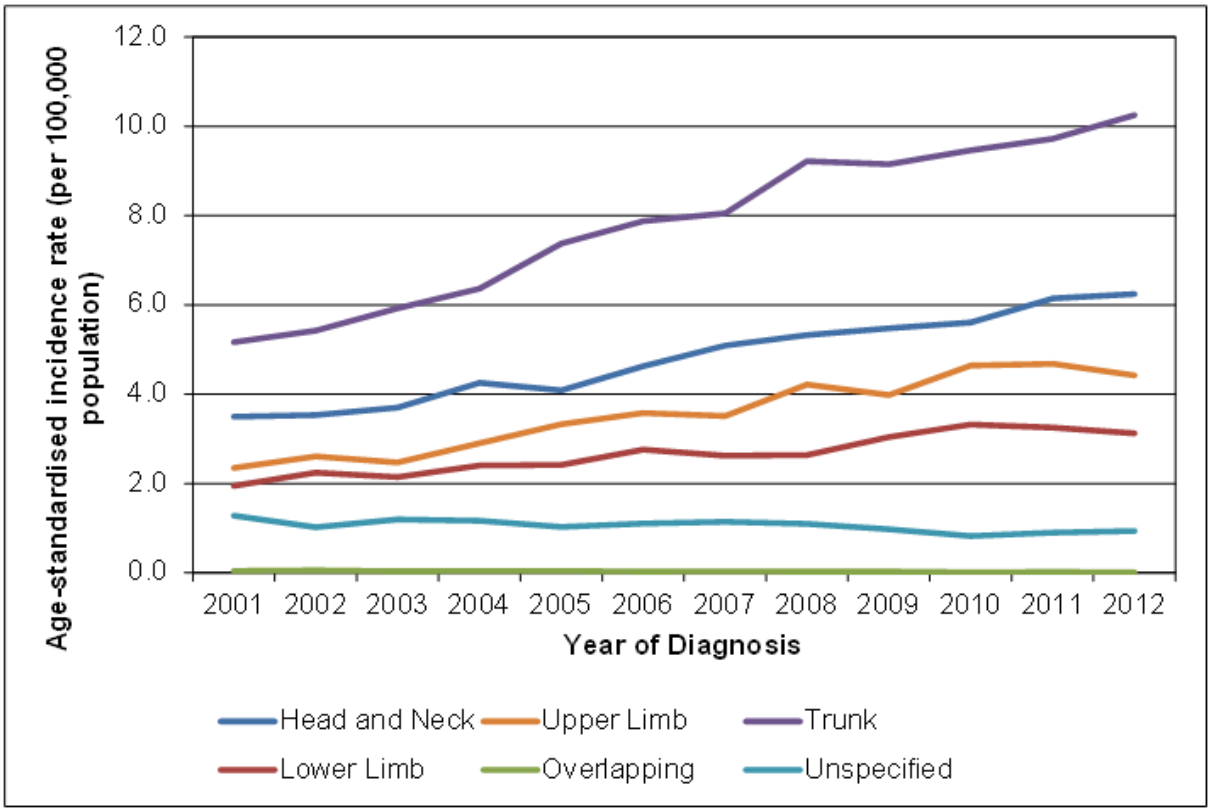
The incidence of melanoma has increased between 2001 and 2012 at all anatomical sites (Table 26 and Figures 17 and 18). In men, the most common sites are the trunk, particularly the back, and on the head and neck but in women these are the limbs, especially the legs. The number of melanomas with an unspecified location has decreased, suggesting better recording; this will contribute to the increase at other anatomical sites. In 2012, there was a higher rate of melanoma diagnoses on the head, neck, and trunk for men compared to women; and a higher rate on the limbs for women compared to men (Figure 19).

Table 26: Annual percentage change in incidence rates by anatomical site, 2001-2012

Anatomical site	Male AAPC	Female AAPC
Head and Neck	5.7*	3.1*
Lower Limb	4.6*	2.9*
Overlapping	n/a	n/a
Trunk	6.4*	5.6*
Unspecified	-2.9*	-3.7*
Upper Limb	6.6*	5.4*

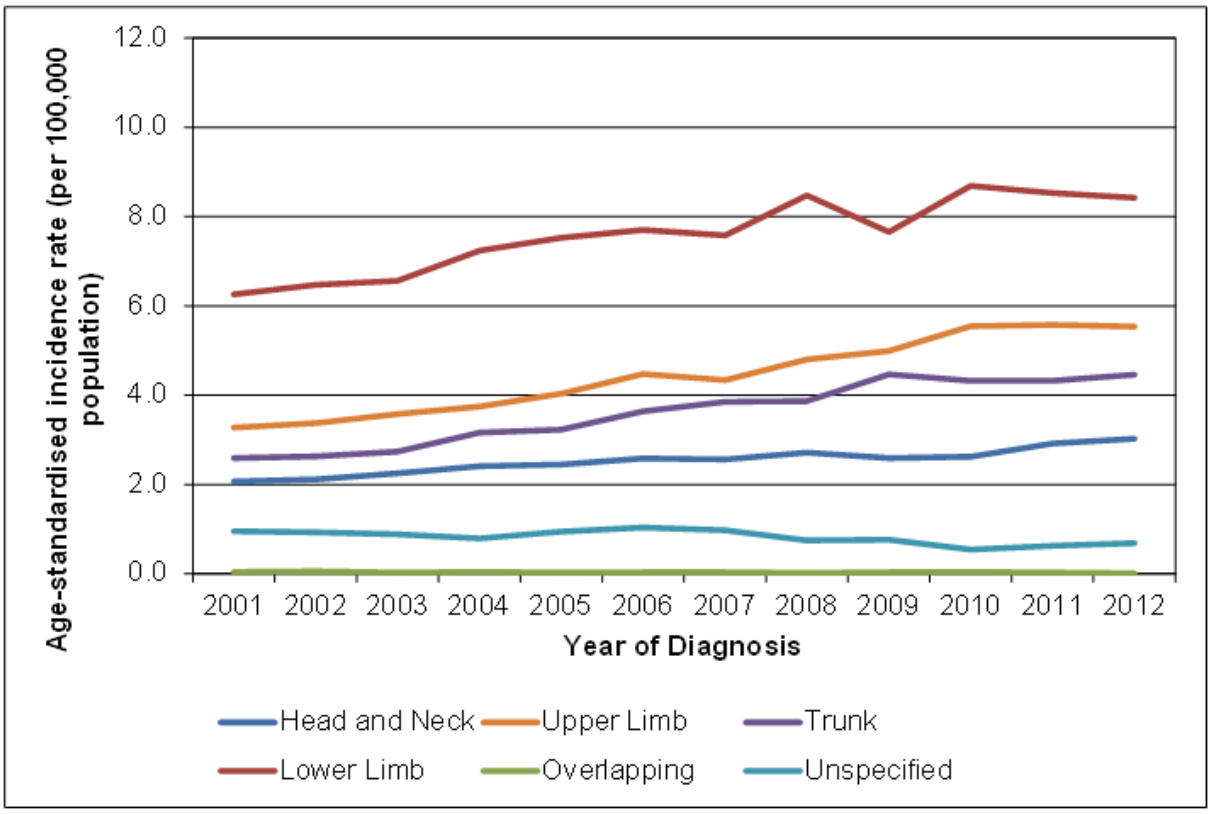
*AAPC = Average Annual Percentage Change; * = p < 0.05; There were too few cases of melanomas at overlapping regions to ascertain a trend.*

Figure 17: Male age-standardised melanoma incidence rates (per 100,000 men) by anatomical location, England, 2001-2012



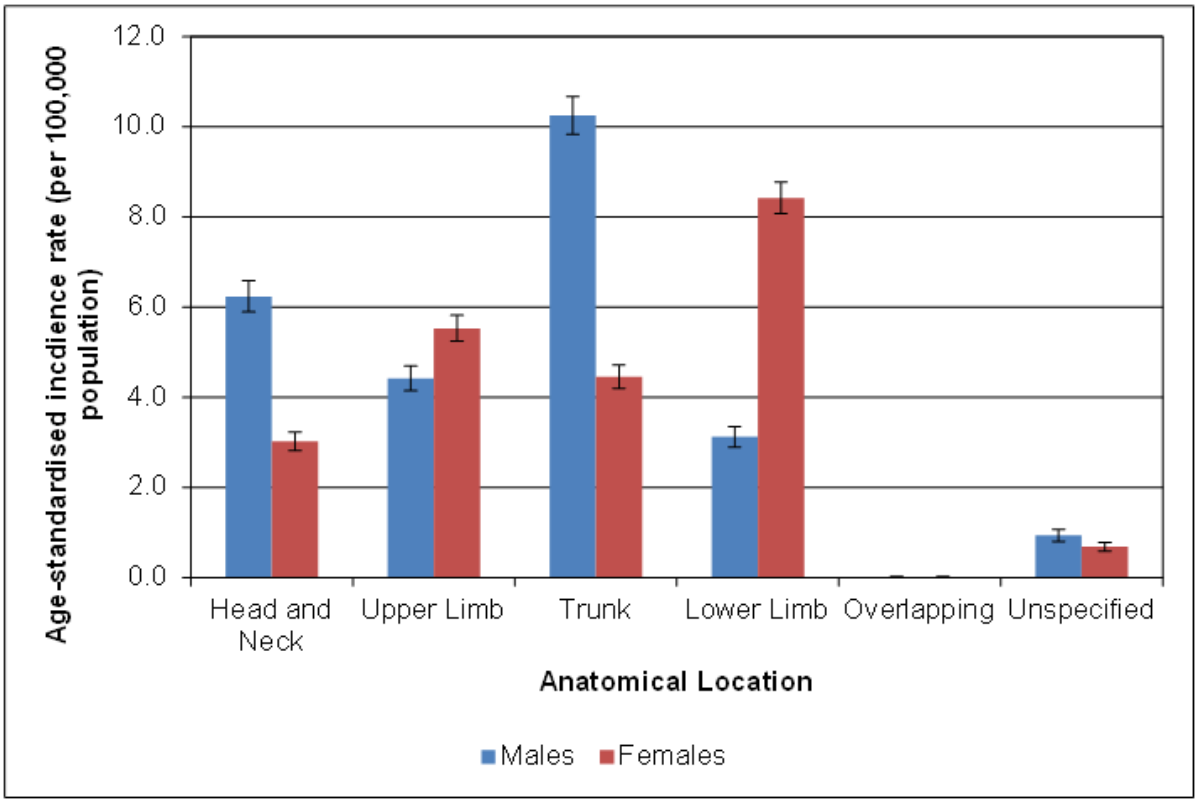
Source: National Cancer Registration Service; Office for National Statistics

Figure 18: Female age-standardised melanoma incidence rates (per 100,000 women) by anatomical location, England, 2001-2012



Source: National Cancer Registration Service; Office for National Statistics

Figure 19: Age-standardised melanoma incidence (per 100,000 people) by sex and anatomical location, England, 2012



Source: National Cancer Registration Service; Office for National Statistics

G.3.41 Tumour thickness (Breslow)

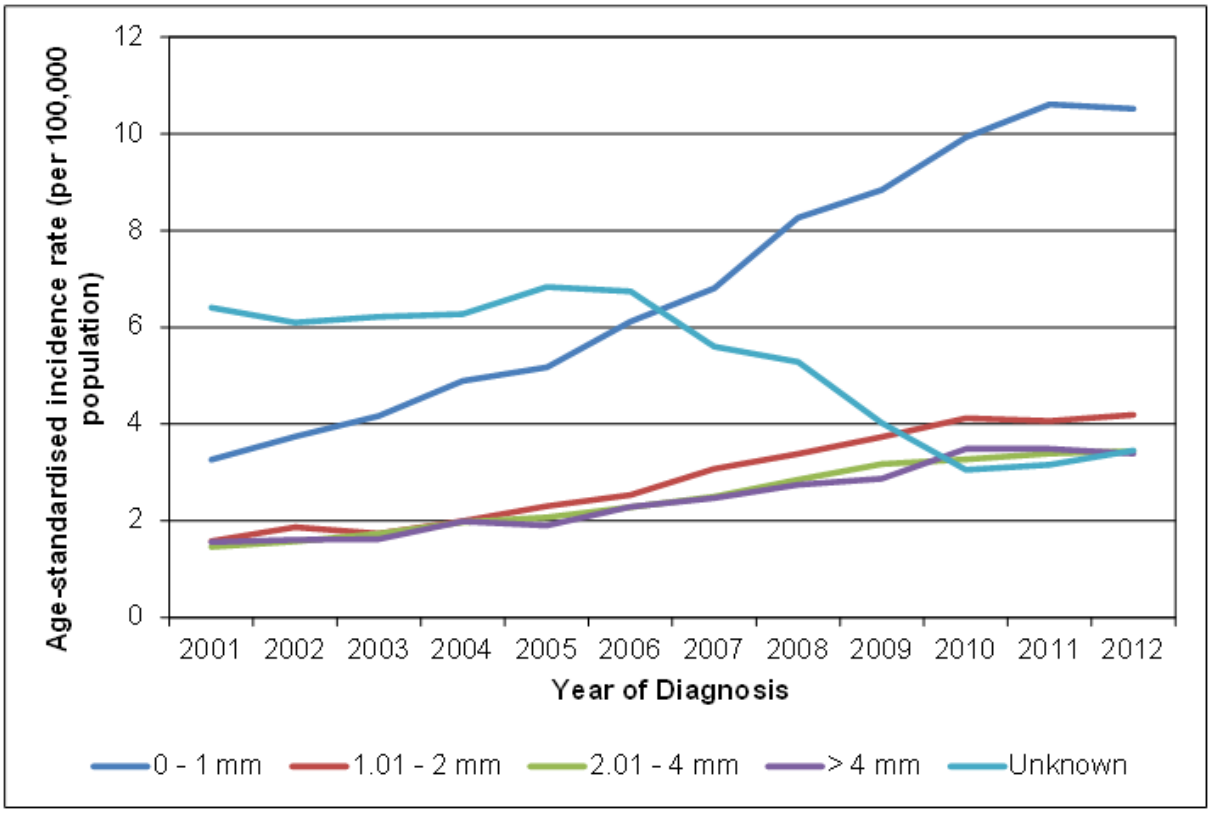
2 Melanoma incidence rates for all Breslow thickness groups increased between 2001 and
3 2012, although this increase was highest for the thinner tumours (Table 27 and Figures 20
4 and 21). The number of tumours with an unknown or unspecified Breslow thickness
5 significantly decreased, indicating an improvement in recording which appears to have been
6 initiated around 2005. In 2012, the majority of melanomas were 2 mm thick or less (Figure
7 22). Men were more likely than women to be diagnosed with melanomas thicker than 2 mm.

8 **Table 27: Annual percentage change in melanoma incidence rates by Breslow**
9 **thickness, 2001-2012**

Breslow Thickness	Male AAPC	Female AAPC
0 - 1 mm	11.7*	8.7*
1.01 - 2 mm	10.1*	8.5*
2.01 - 4 mm	8.6*	7.1*
> 4 mm	8.6*	6.1*
Unknown	-6.5*	-8.2*

10 *AAPC = Average Annual Percentage Change; * = p < 0.05*

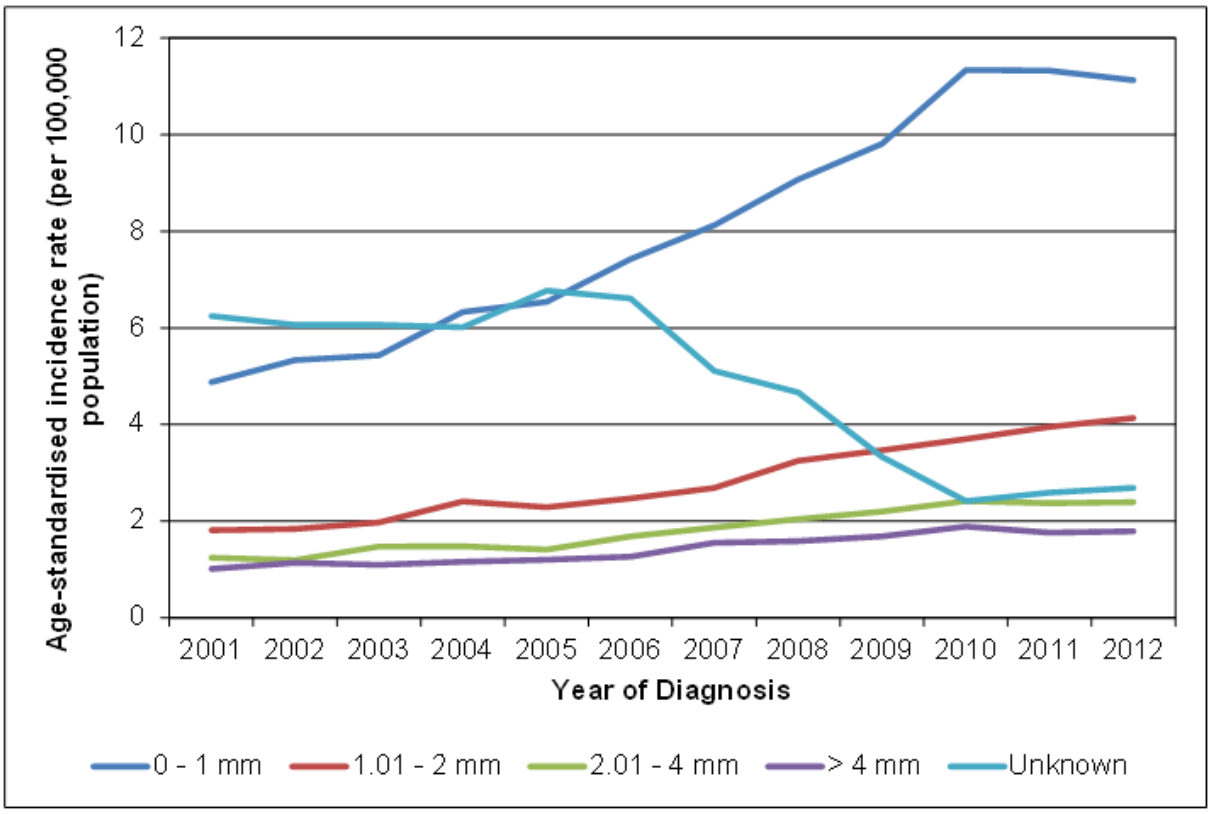
11 **Figure 20: Male age-standardised melanoma incidence rates (per 100,000 men) by**
12 **Breslow thickness, England, 2001-2012**



13

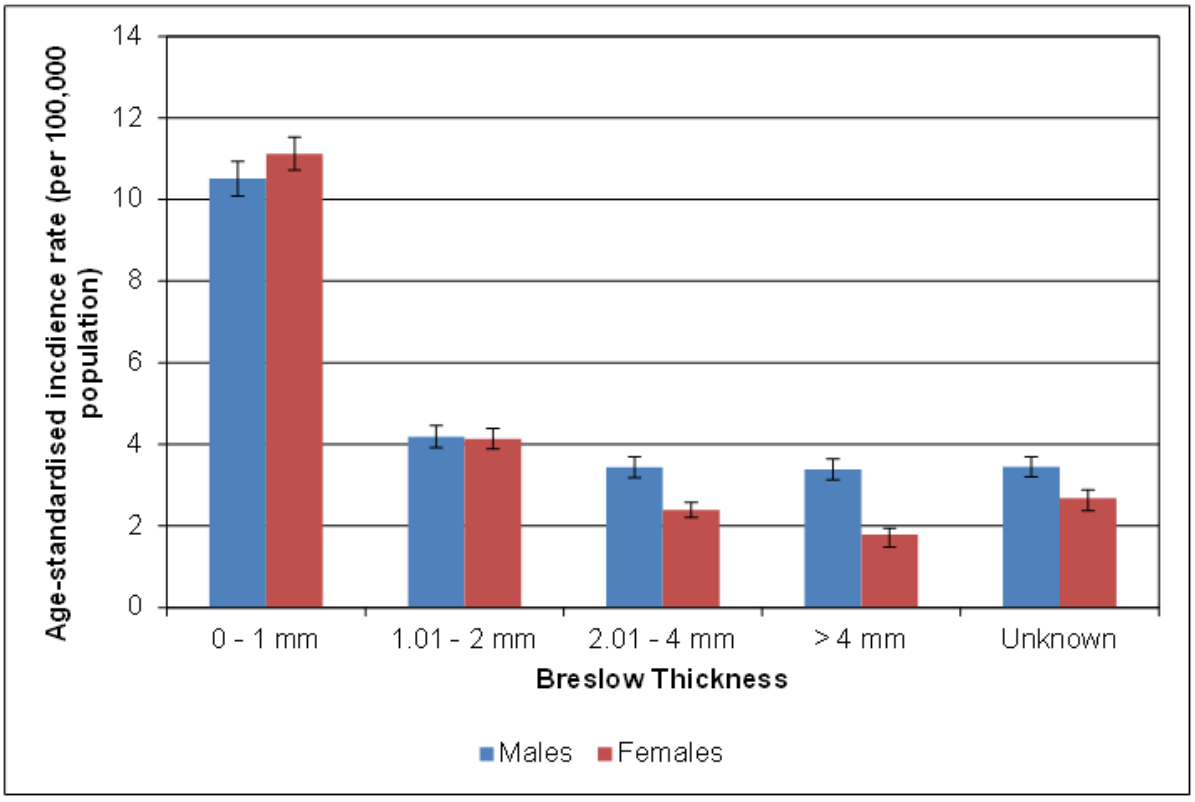
14 *Source: National Cancer Registration Service; Office for National Statistics*

Figure 21: Female age-standardised melanoma incidence rates (per 100,000 women) by Breslow thickness, England, 2001-2012



Source: National Cancer Registration Service; Office for National Statistics

Figure 22: Age-standardised melanoma incidence (per 100,000 people) by sex and Breslow thickness, England, 2012



Source: National Cancer Registration Service; Office for National Statistics

G.3.51 Income deprivation

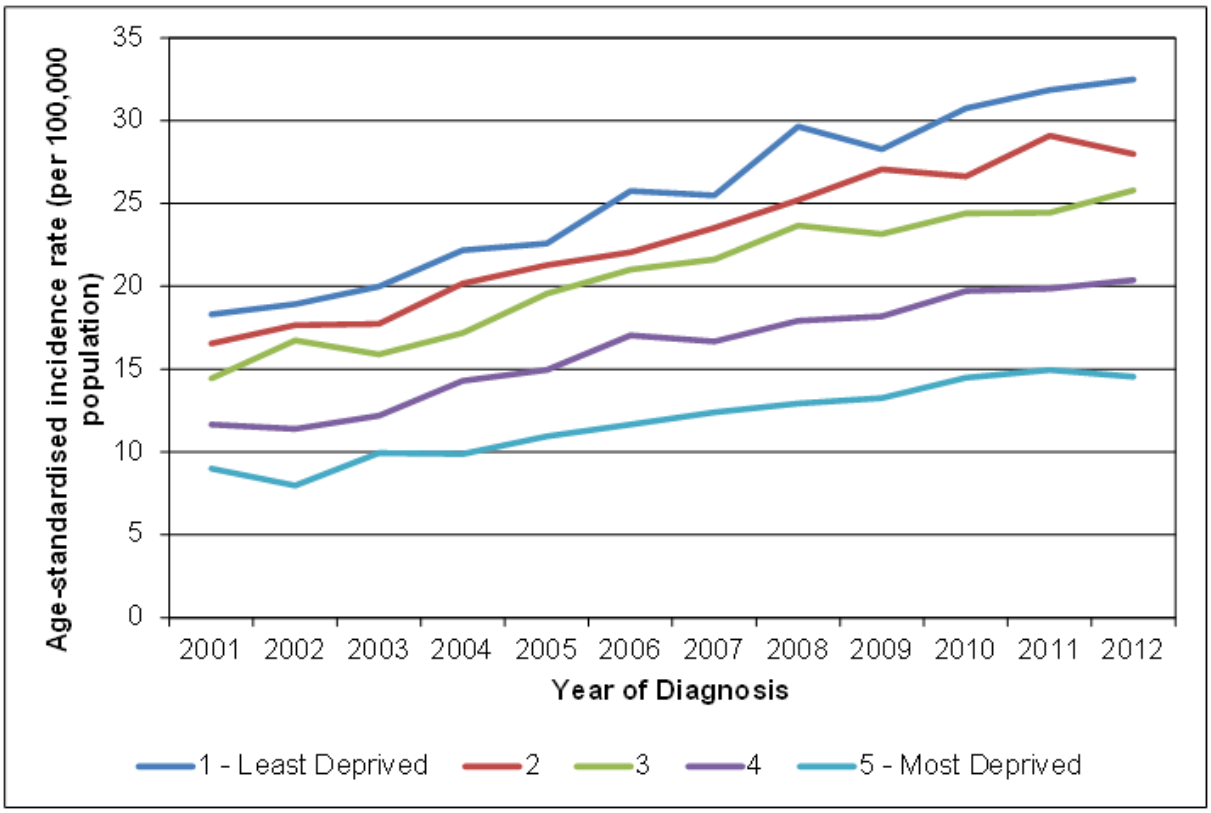
Melanoma incidence in 2012 was highest in the least deprived quintile of the population. Melanoma is unusual in showing an inverse relationship between incidence and deprivation, for both men and women. During 2001-2012 the incidence increased at a similar rate in all income deprivation quintiles (i.e. there was no significant interaction between deprivation and year of diagnosis when modelling the age-standardised rates), and so the effect of deprivation was similar throughout this period (Table 228 and Figures 23 and 24). In 2012, the impact of being in the next more deprived quintile was to reduce the melanoma incidence rate by 16% for men and 15.7% for women; this reduction was not significantly different between the sexes (Figure 25).

Table 28: Annual percentage change in melanoma incidence rates by income deprivation quintile, 2001-2012

Deprivation Quintile	Male AAPC	Female AAPC
1 - Least Deprived	5.6*	3.7*
2	5.3*	3.5*
3	5.1*	3.7*
4	5.6*	3.7*
5 - Most Deprived	5.5*	3.1*

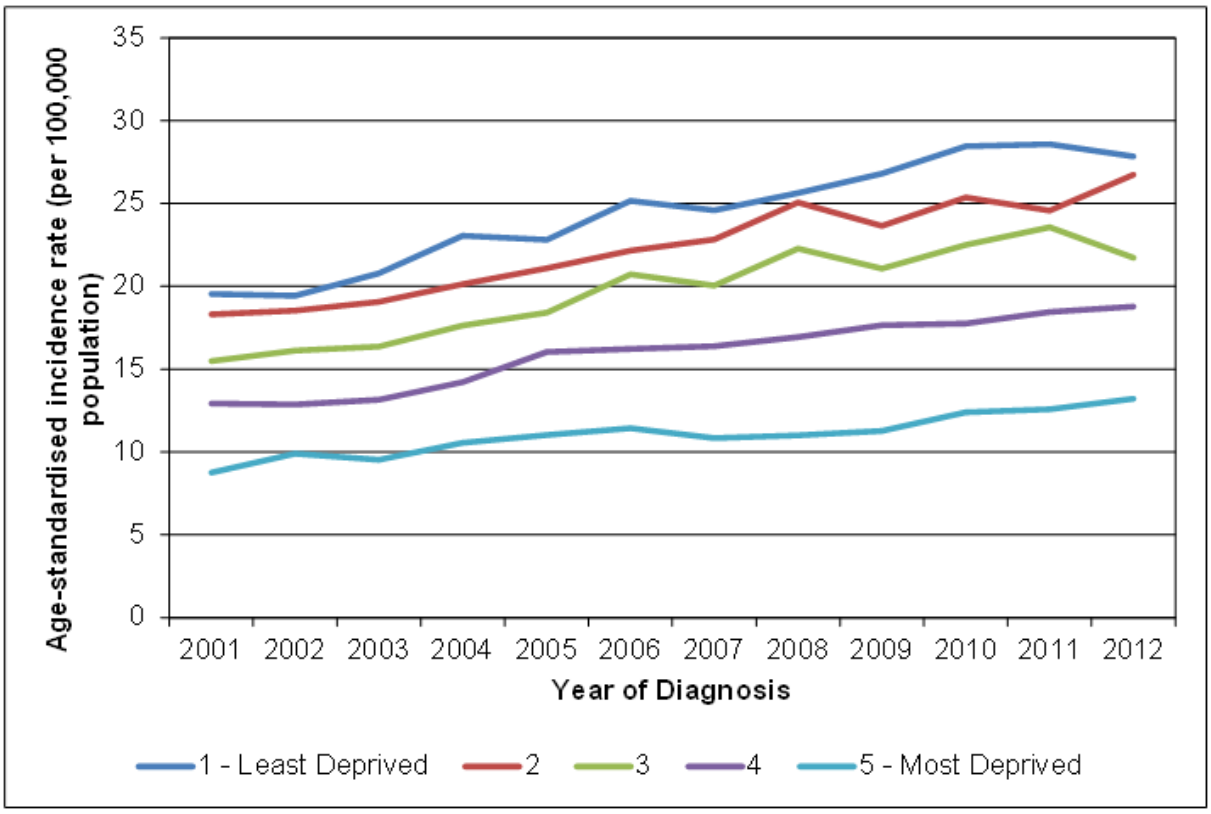
*AAPC = Average Annual Percentage Change; * = p < 0.05*

Figure 23: Male age-standardised melanoma incidence rates (per 100,000 men) by income deprivation, England, 2001-2012



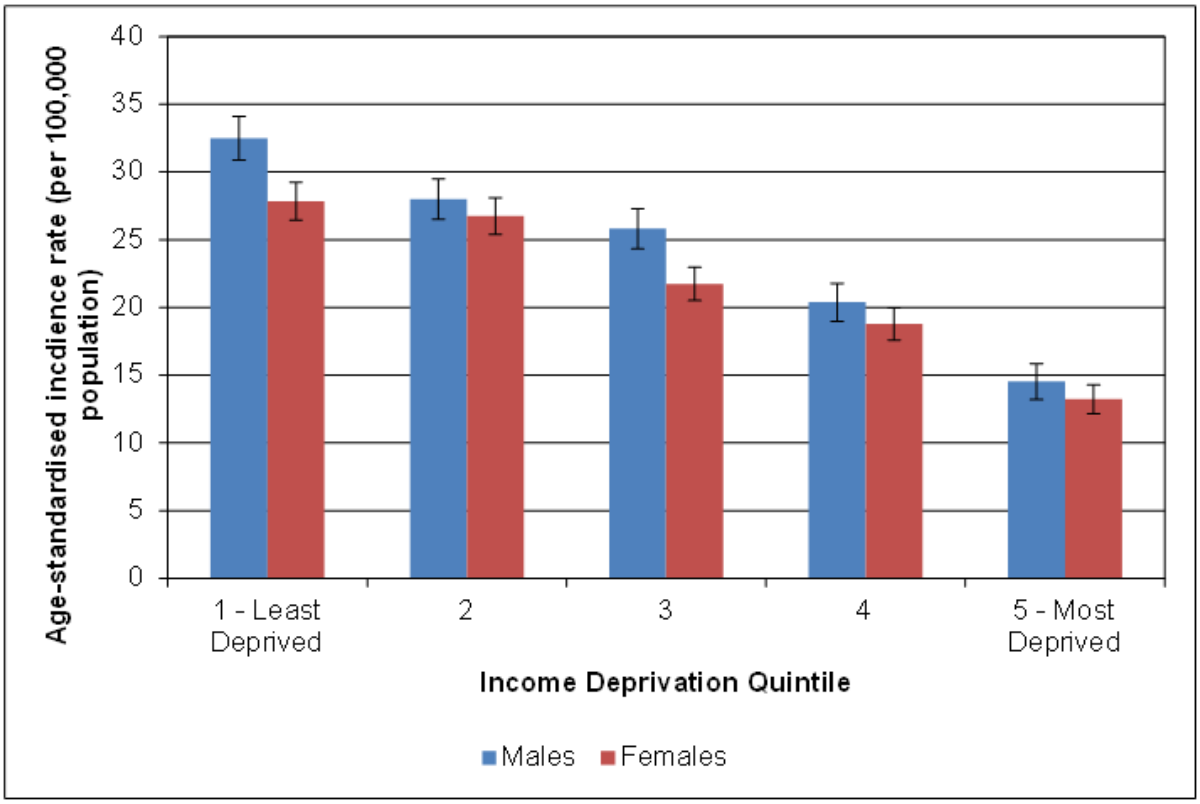
Source: National Cancer Registration Service; Office for National Statistics

Figure 24: Female age-standardised melanoma incidence rates (per 100,000 women) by Breslow thickness, England, 2001-2012



Source: National Cancer Registration Service; Office for National Statistics

Figure 25: Age-standardised melanoma incidence (per 100,000 people) by sex and income deprivation, England, 2012



Source: National Cancer Registration Service; Office for National Statistics

G.3.61 Tumour morphology

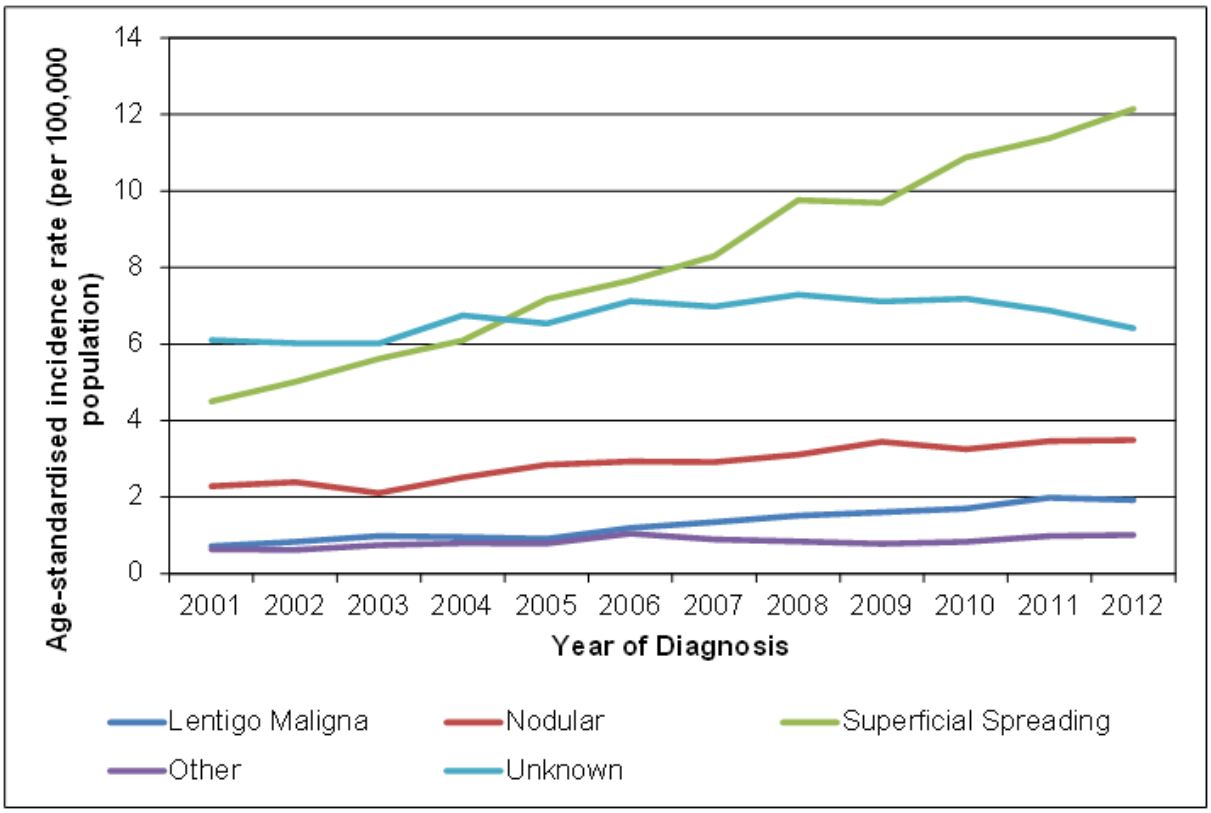
Melanoma incidence rates increased more quickly for lentigo maligna and superficial spreading tumours among both men and women than for other tumour types between 2001 and 2012 (Table 29 and Figures 26 and 27). In 2012, the most common tumour morphology was superficial spreading (Figure 28); men had a greater incidence of lentigo maligna and nodular tumours than women.

Table 29: Annual percentage change in melanoma incidence rates by tumour morphology, 2001-2012

Tumour Morphology	Male AAPC	Female AAPC
Lentigo Maligna	9.7*	5.4*
Nodular	4.4*	2.5*
Superficial Spreading	9.3*	7.2*
Other	3.3*	1.6
Unknown	1.2*	-0.7

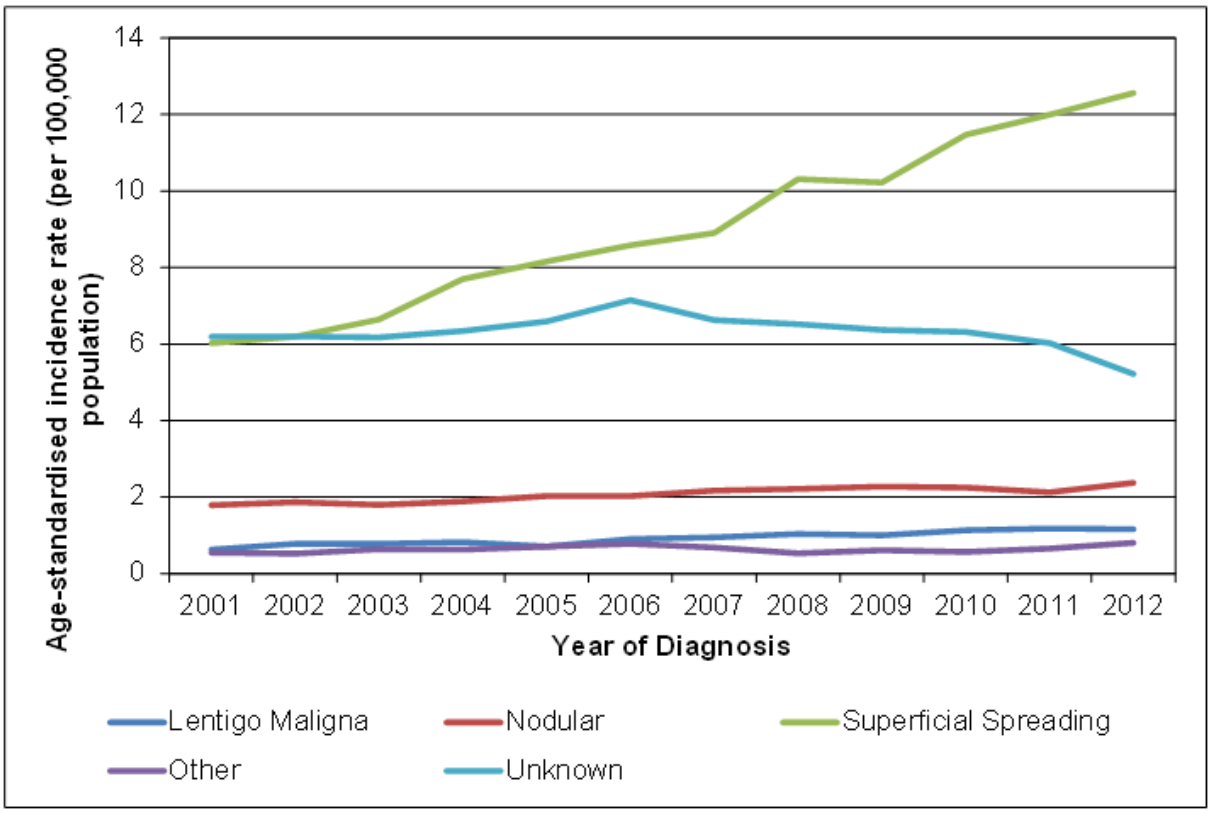
*AAPC = Average Annual Percentage Change; * = p < 0.05*

Figure 26: Male age-standardised melanoma incidence rates (per 100,000 men) by tumour morphology, England, 2001-2012



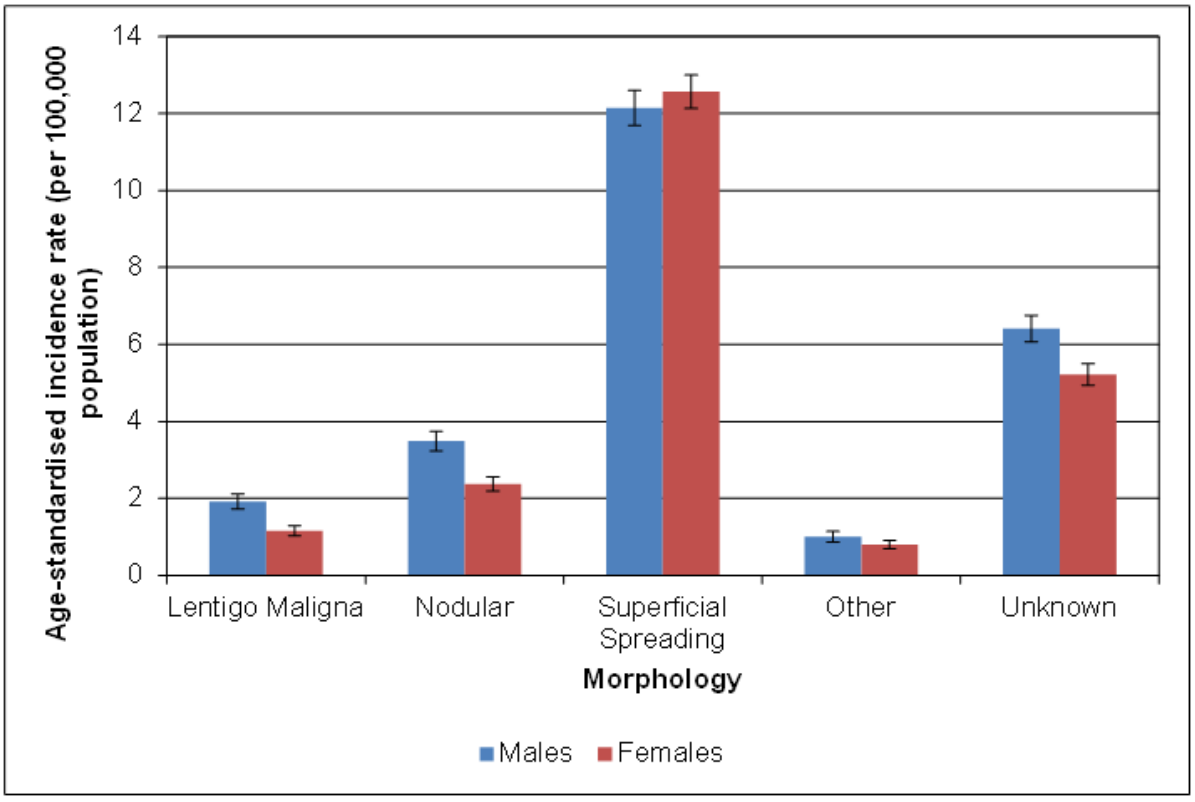
Source: National Cancer Registration Service; Office for National Statistics

Figure 27: Female age-standardised melanoma incidence rates (per 100,000 women) by tumour morphology, England, 2001-2012



Source: National Cancer Registration Service; Office for National Statistics

Figure 28: Age-standardised melanoma incidence rates (per 100,000 people) by sex and tumour morphology, England, 2012



Source: National Cancer Registration Service; Office for National Statistics

G.3.7 Projected incidence of melanoma

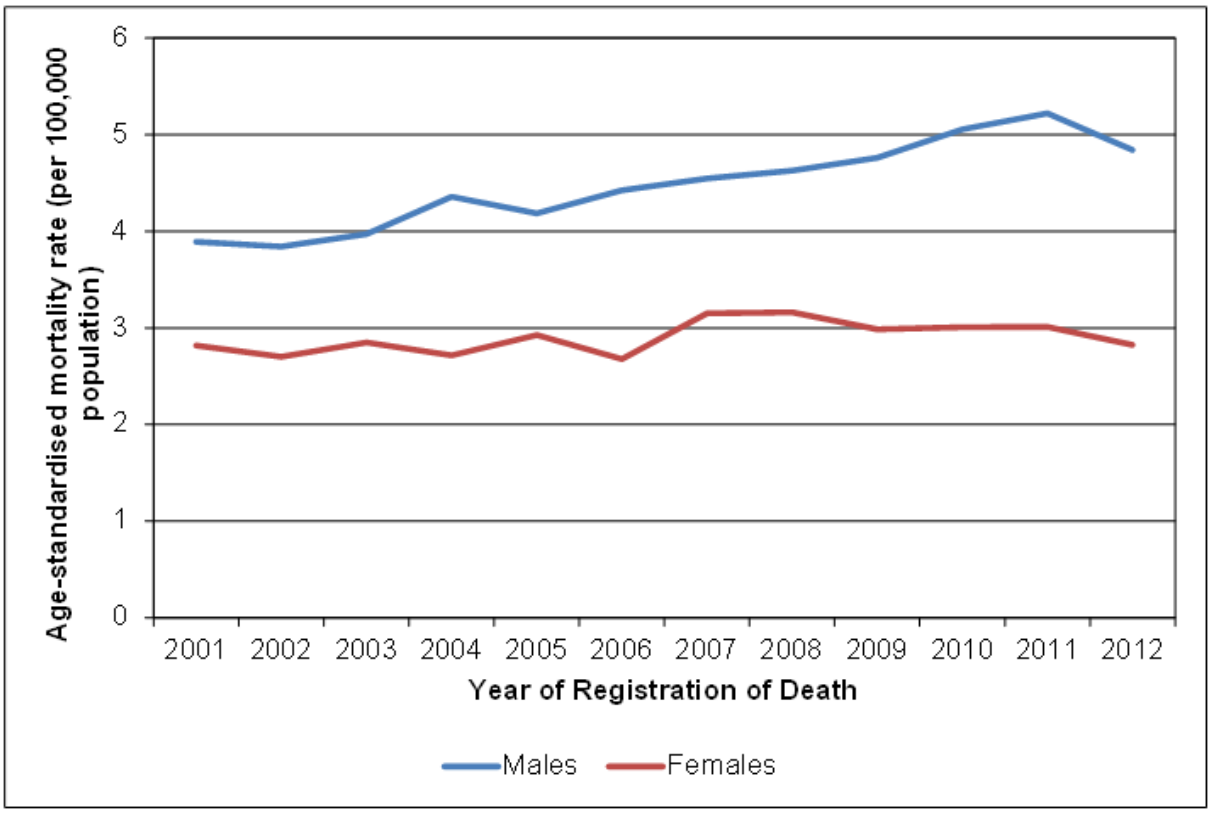
The age-standardised rates of melanoma are projected to increase by > 1% per year from 14.6 per 100,000 for men and 15.4 per 100,000 for women in 2007 to 22.3 and 23.4 respectively in 2030 (Mistry et al, 2011). Melanoma was the 14th most common cancer in men in 1984 (1% of all male cancers) and is predicted to become the fourth most common accounting for almost 5% of cases by 2030 (Mistry et al, 2011).

G.4 Mortality

G.4.1 Sex

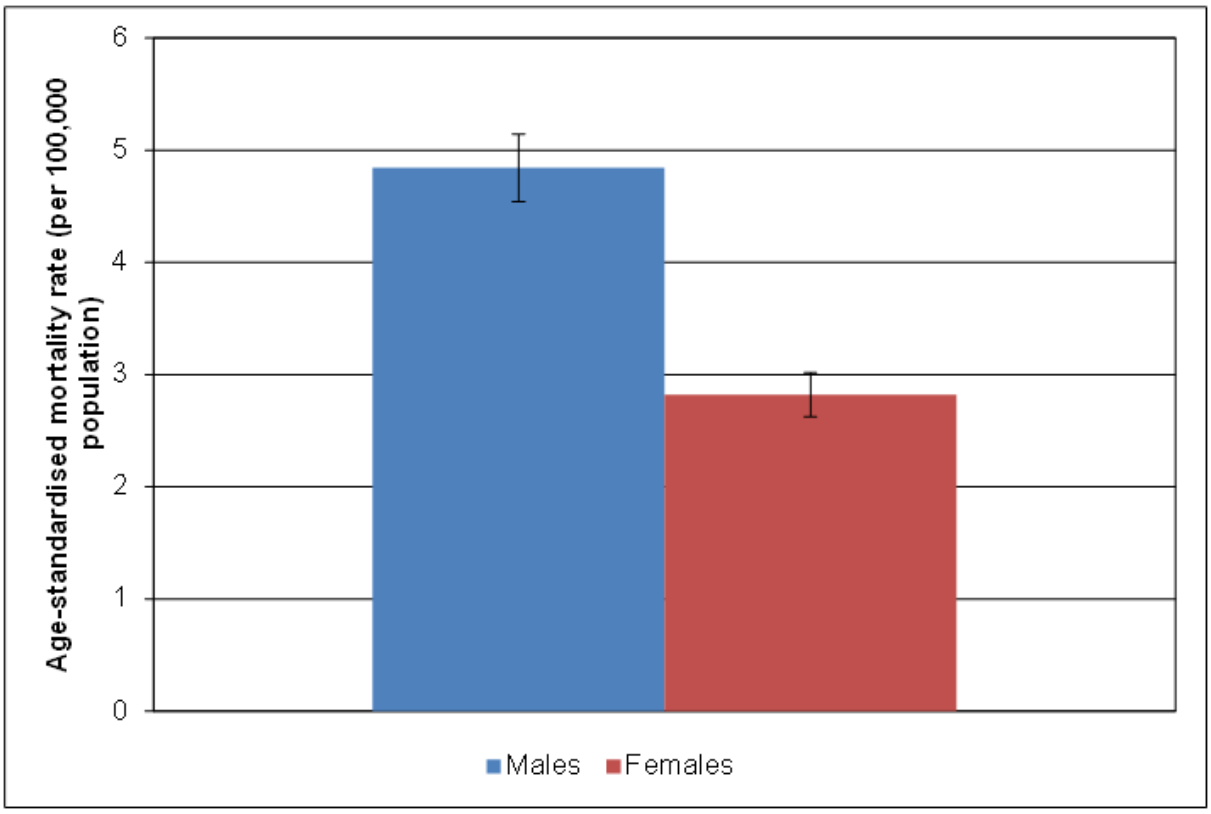
The age-standardised mortality rate for melanoma in England has significantly increased for men but not women between 2001 and 2012 (Figure 29). The average annual increase was 2.7% for men and 0.8% for women. . In 2012 the age-standardised mortality rate for melanoma was higher for men (4.8 deaths per 100,000) than for women (2.8 deaths per 100,000) (Figure 30). The male and female age-standardised melanoma mortality rates (per 100,000 population) by Clinical Commissioning Group (CCG) in England are presented in Figures 31 and 32 respectively.

Figure 29: Age-standardised mortality rates (per 100,000 population) for melanoma by sex, England, 2001-2012



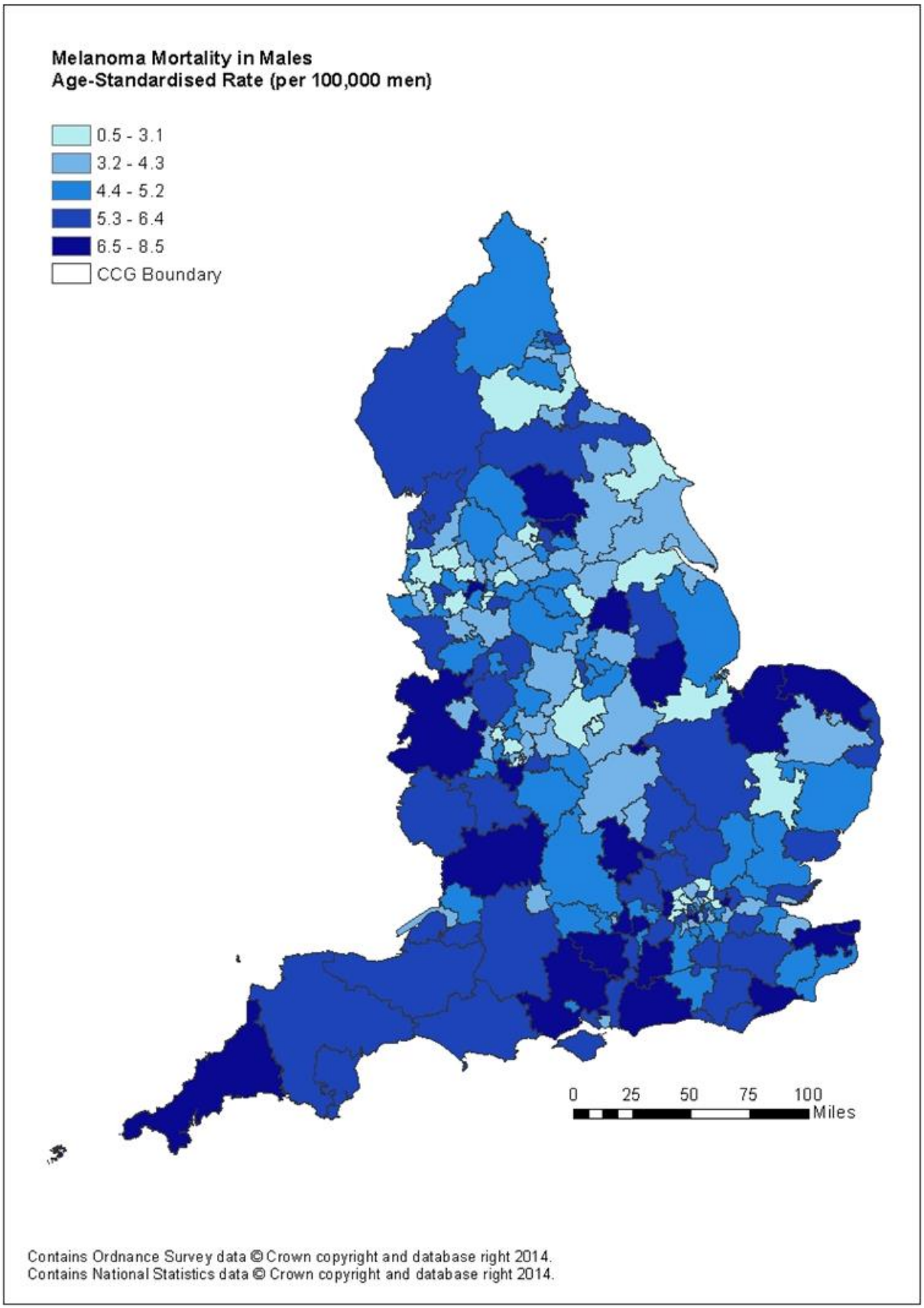
Source: Office for National Statistics

Figure 30: Age-standardised mortality rates (per 100,000 population) for melanoma by sex, England, 2012



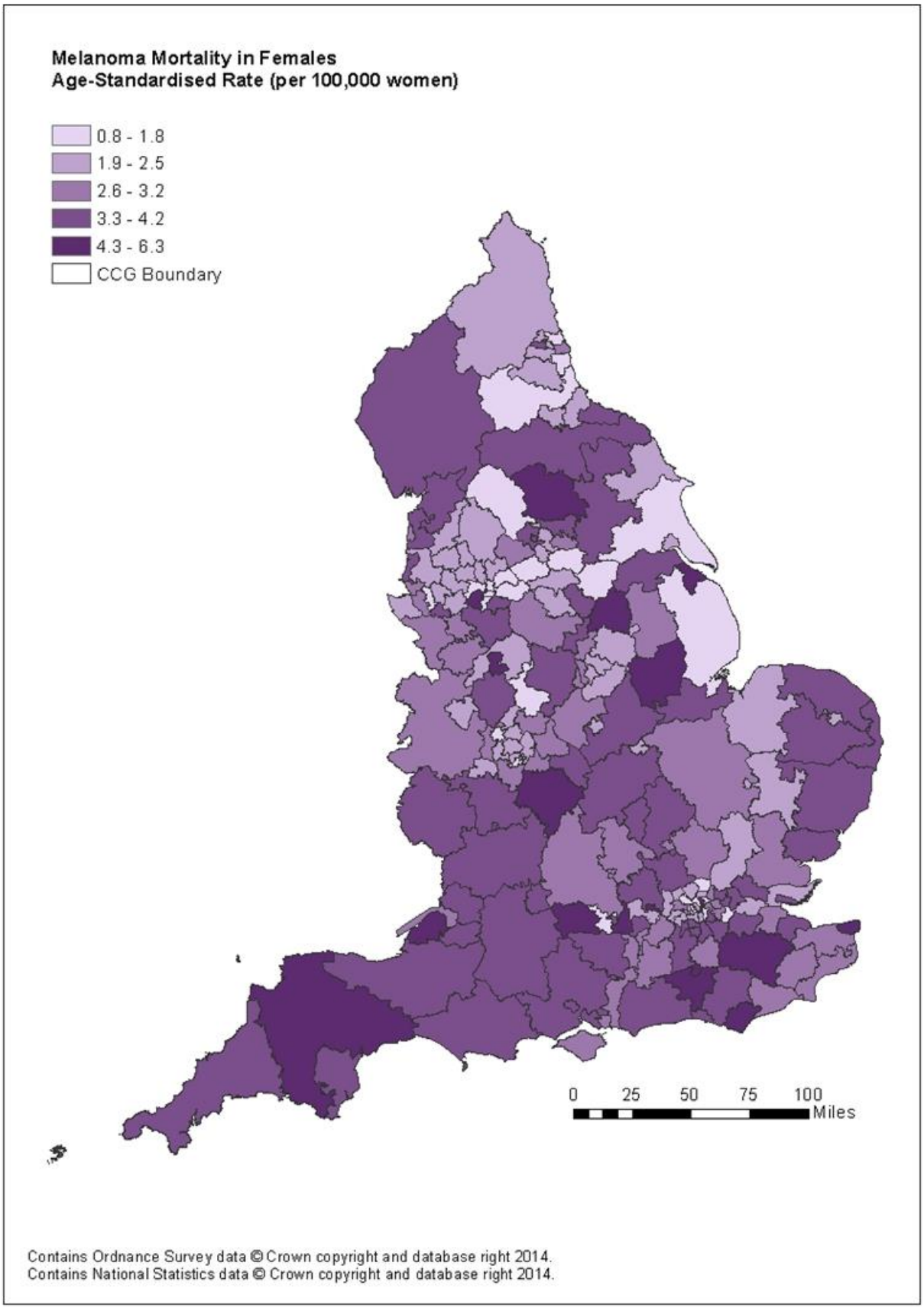
Source: Office for National Statistics

Figure 31: Male age-standardised melanoma mortality rates (per 100,000 men) by Clinical Commissioning Group (CCG) in England, 2008-2012



Source: Office for National Statistics

Figure 32: Female age-standardised melanoma mortality rates (per 100,000 women) by Clinical Commissioning Group (CCG) in England, 2008-2012



Source: Office for National Statistics

G.4.21 Age

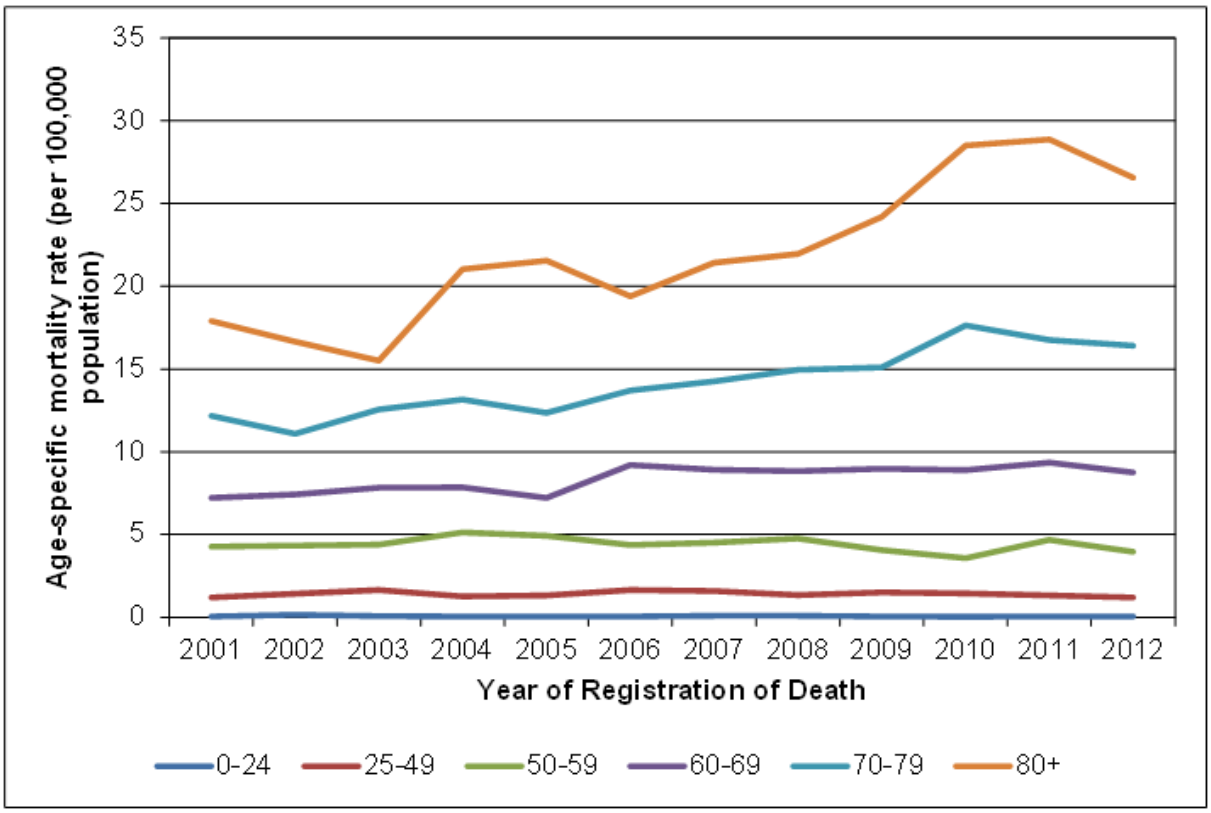
The mortality rates for melanoma have mostly increased in the older age groups and particularly for men between 2001 and 2012 (Table 30 and Figures 33 and 34). In 2012, the age-specific mortality rates for older men (60+ years old) were higher than for older women (Figure 35).

Table 30: Annual percentage change in melanoma mortality rates by age group, 2001-2012

Age Groups (years)	Male AAPC	Female AAPC
0-24	-6.4	-4.6
25-49	-0.7	-1.3
50-59	-0.8	-0.8
60-69	2.2*	1.8
70-79	3.8*	0.4
80+	5.3*	2.4*

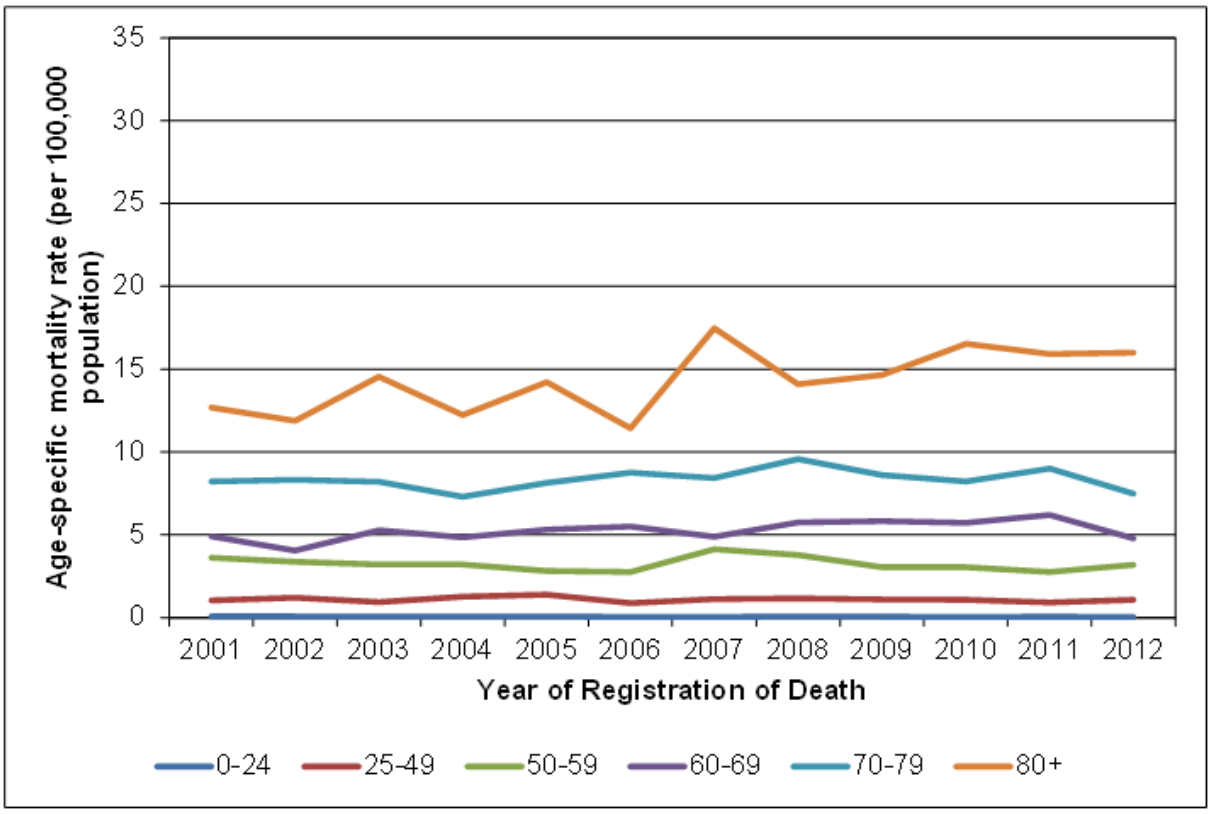
*AAPC = Average Annual Percentage Change; * = p < 0.05*

Figure 33: Age-specific melanoma mortality rates for males (per 100,000 men) by age group, England, 2001-2012



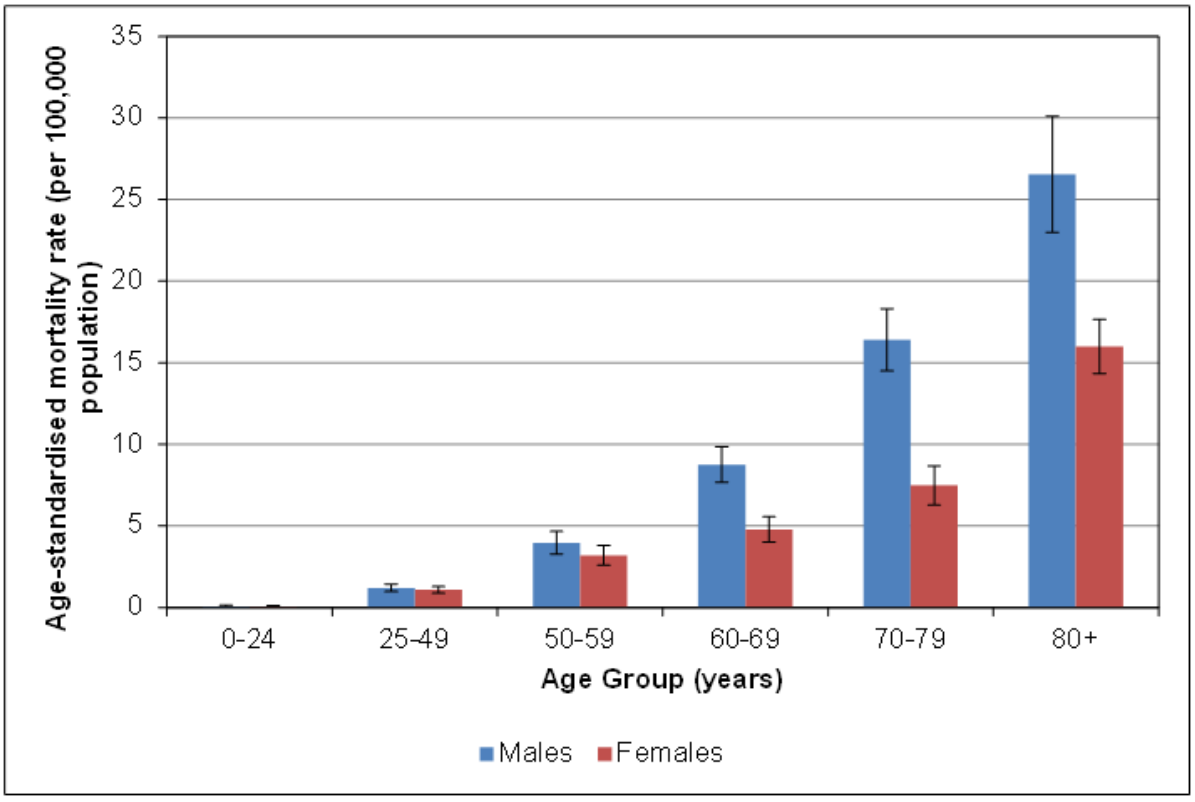
Source: Office for National Statistics

Figure 34: Age-specific melanoma mortality rates for females (per 100,000 women) by age group, England, 2001-2012



Source: Office for National Statistics

Figure 35: Age-specific melanoma mortality (per 100,000 people) by sex and age group, England, 2012



Source: Office for National Statistics

G.4.31 Income deprivation

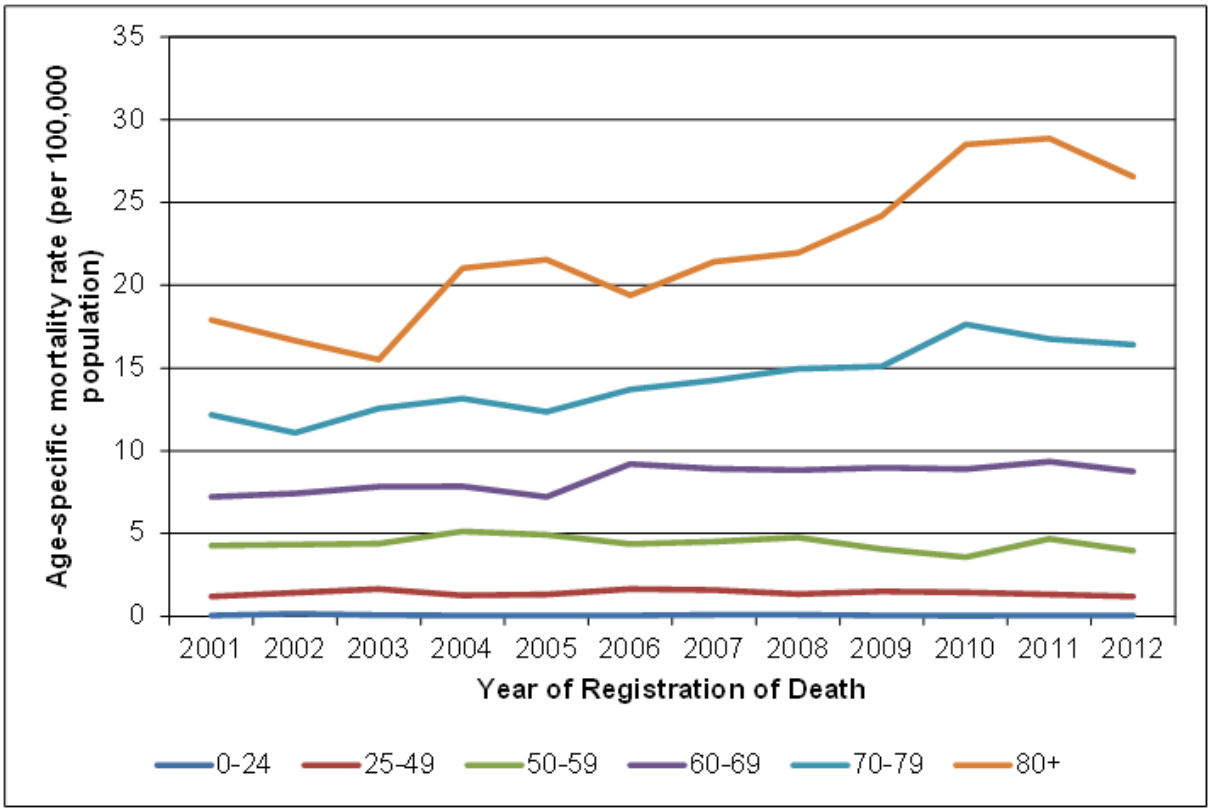
Melanoma mortality rates are highest in the least deprived sections of the population (Figures 36, 37 and 38), where the incidence is also highest. During the period 2001-2012, mortality increased at a faster rate for men than women (Table 31 and see Figures 36 and 37), although this difference was not statistically significant (p = 0.06). In 2012, the impact of being in the next more deprived quintile was to reduce the melanoma mortality rate by 11% for men and 10% for women; this effect of deprivation was not significantly different between the sexes (see Figure 38).

Table 31: Annual percentage change in melanoma mortality rates by income deprivation quintile, 2001-2012

Deprivation Quintile	Male AAPC	Female AAPC
1 - Least Deprived	2.3*	1.2
2	1.7*	1
3	3.5*	0.3
4	2.8*	0.9
5 - Most Deprived	2.8*	-0.3

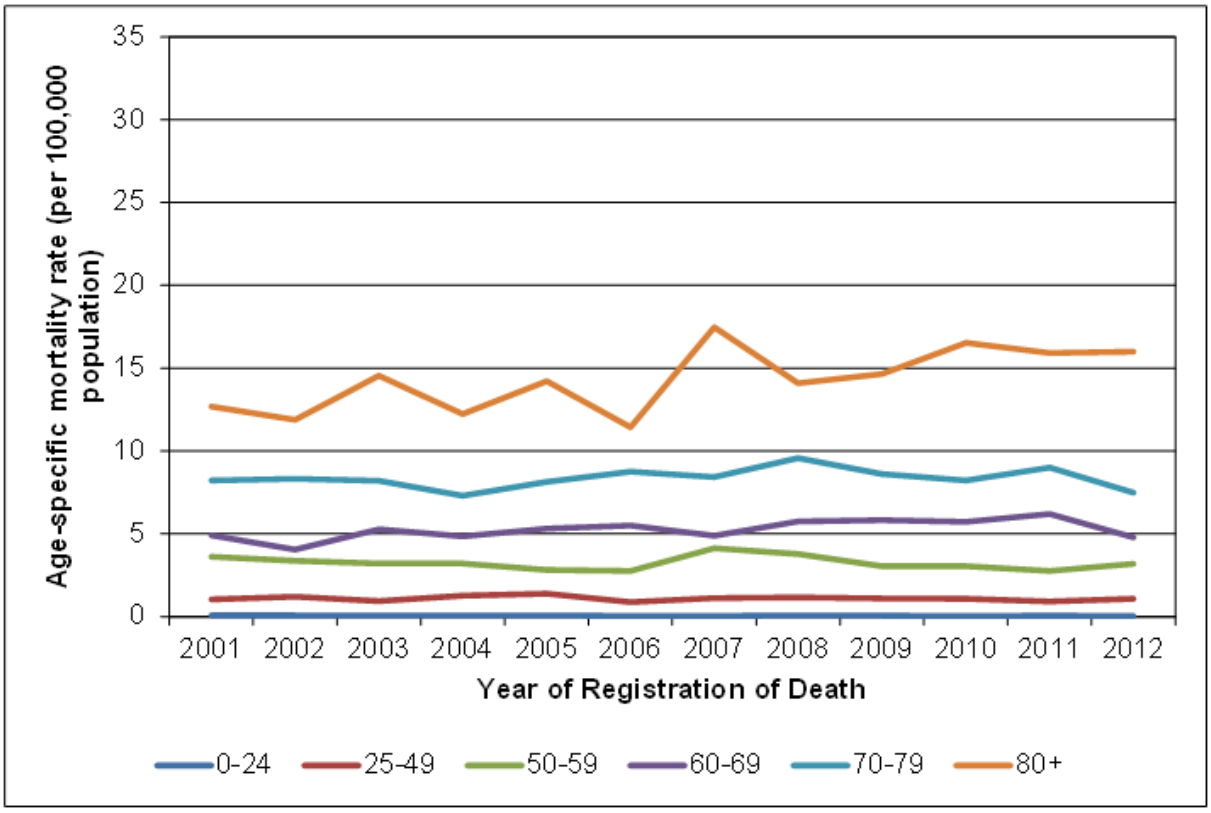
*Notes: AAPC = Average Annual Percentage Change; * = p < 0.05*

Figure 36: Age-specific melanoma mortality rates for males (per 100,000 men) by age group, England, 2001-2012



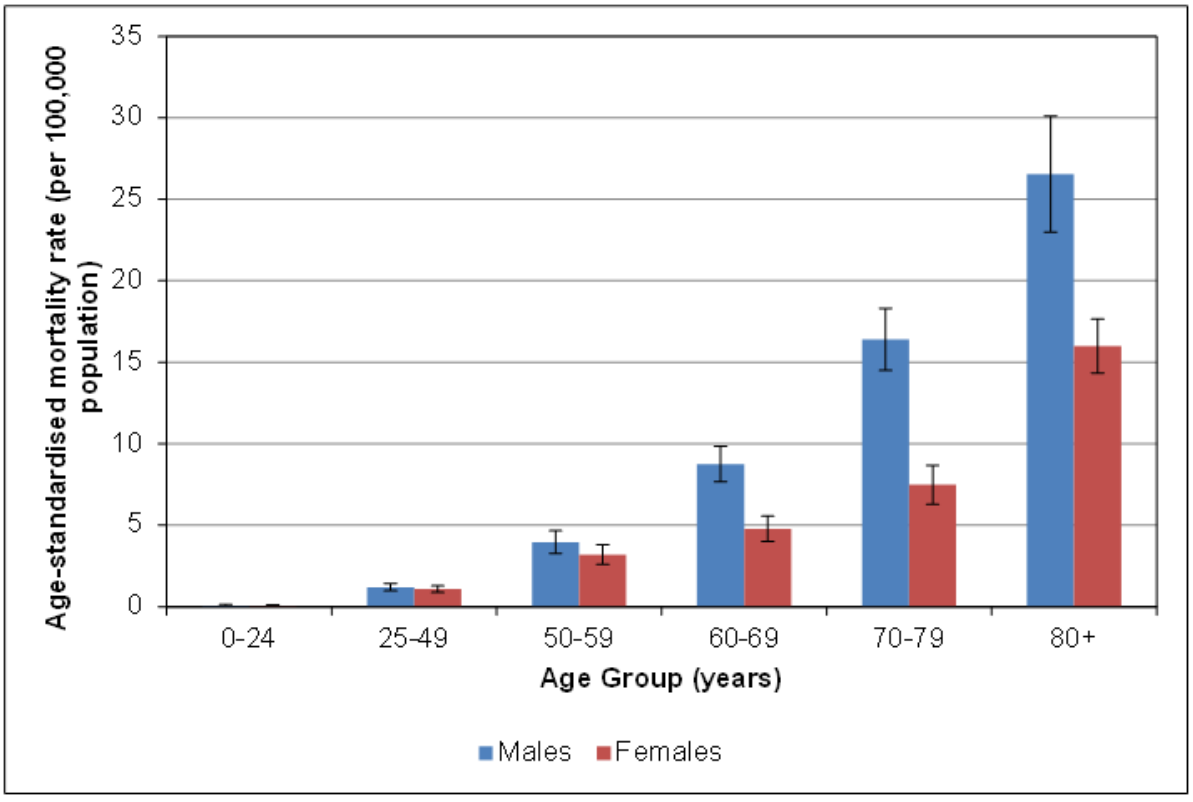
Source: Office for National Statistics

Figure 37: Age-specific melanoma mortality rates for females (per 100,000 women) by age group, England, 2001-2012



Source: Office for National Statistics

Figure 38: Age-specific melanoma mortality (per 100,000 people) by sex and age group, England, 2012



Source: Office for National Statistics

G.4.41 Income deprivation

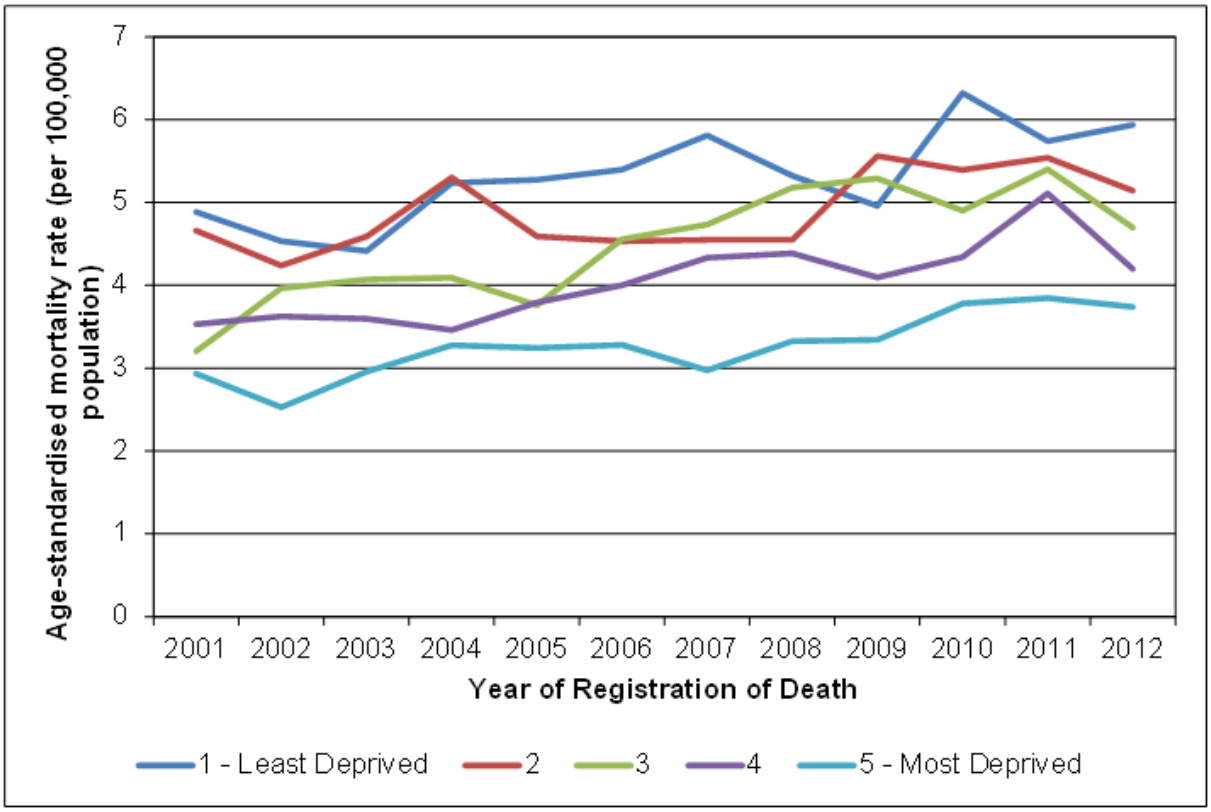
Melanoma mortality rates are highest in the least deprived sections of the population (Figures 39, 40 and 41), where the incidence is also highest. During the period 2001-2012, mortality increased at a faster rate for men than women (Table 32 and see Figures 39 and 40), although this difference was not statistically significant (p = 0.06). In 2012, the impact of being in the next more deprived quintile was to reduce the melanoma mortality rate by 11% for men and 10% for women; this effect of deprivation was not significantly different between the sexes (see Figure 41).

Table 32: Annual percentage change in melanoma mortality rates by income deprivation quintile, 2001-2012

Deprivation Quintile	Male AAPC	Female AAPC
1 - Least Deprived	2.3*	1.2
2	1.7*	1
3	3.5*	0.3
4	2.8*	0.9
5 - Most Deprived	2.8*	-0.3

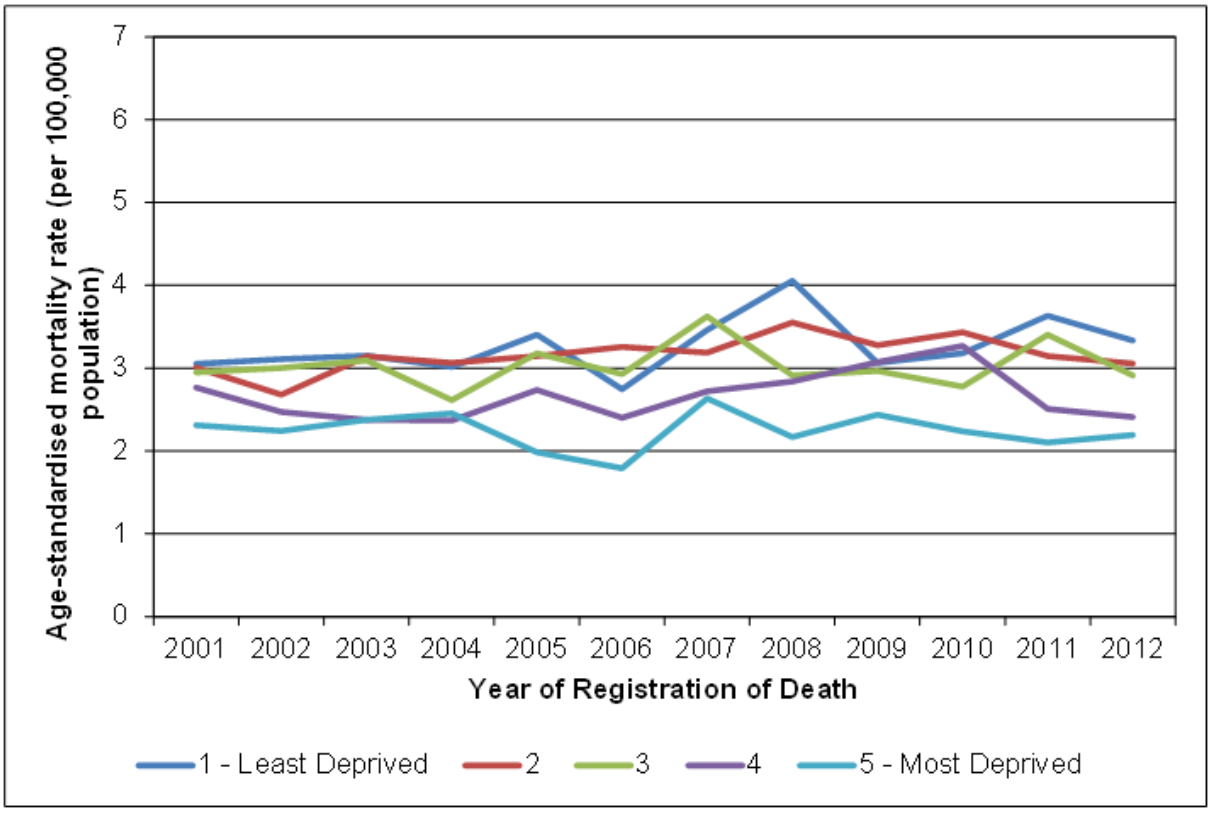
*AAPC = Average Annual Percentage Change; * = p < 0.05*

Figure 39: Male age-standardised melanoma mortality rates (per 100,000 men) by income deprivation, England, 2001-2012



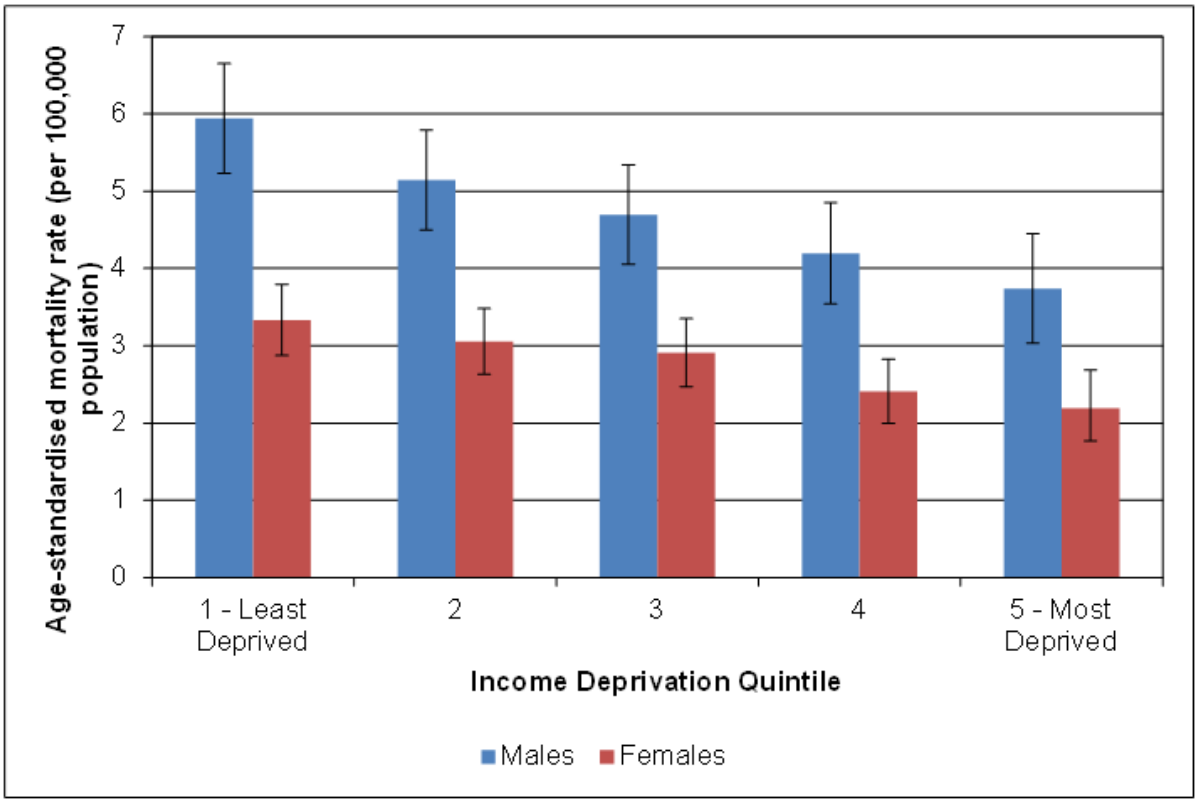
Source: National Cancer Registration Service; Office for National Statistics

Figure 40: Female age-standardised melanoma mortality rates (per 100,000 women) by Breslow thickness, England, 2001-2012



Source: National Cancer Registration Service; Office for National Statistics

Figure 41: Age-standardised melanoma mortality rates (per 100,000 people) by sex and income deprivation, England, 2012



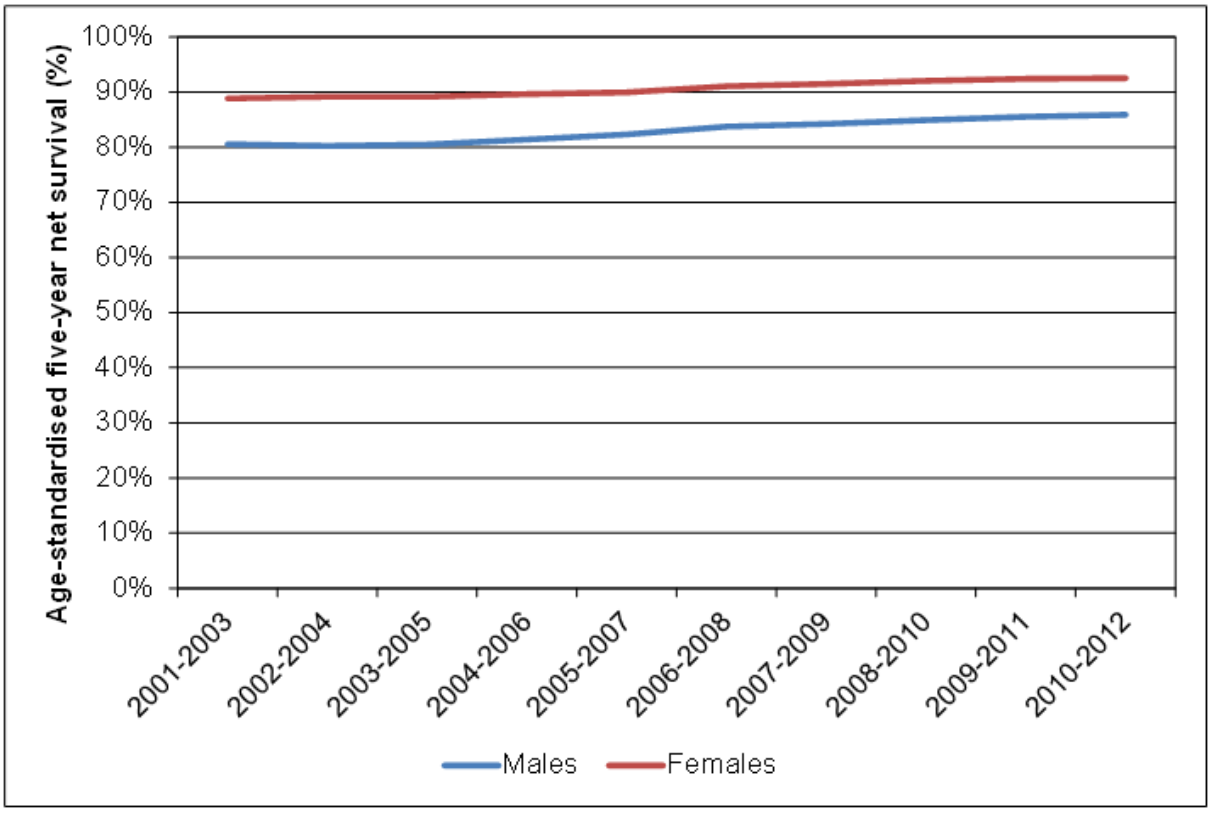
Source: National Cancer Registration Service; Office for National Statistics

G.5 Survival

G.5.1 Sex

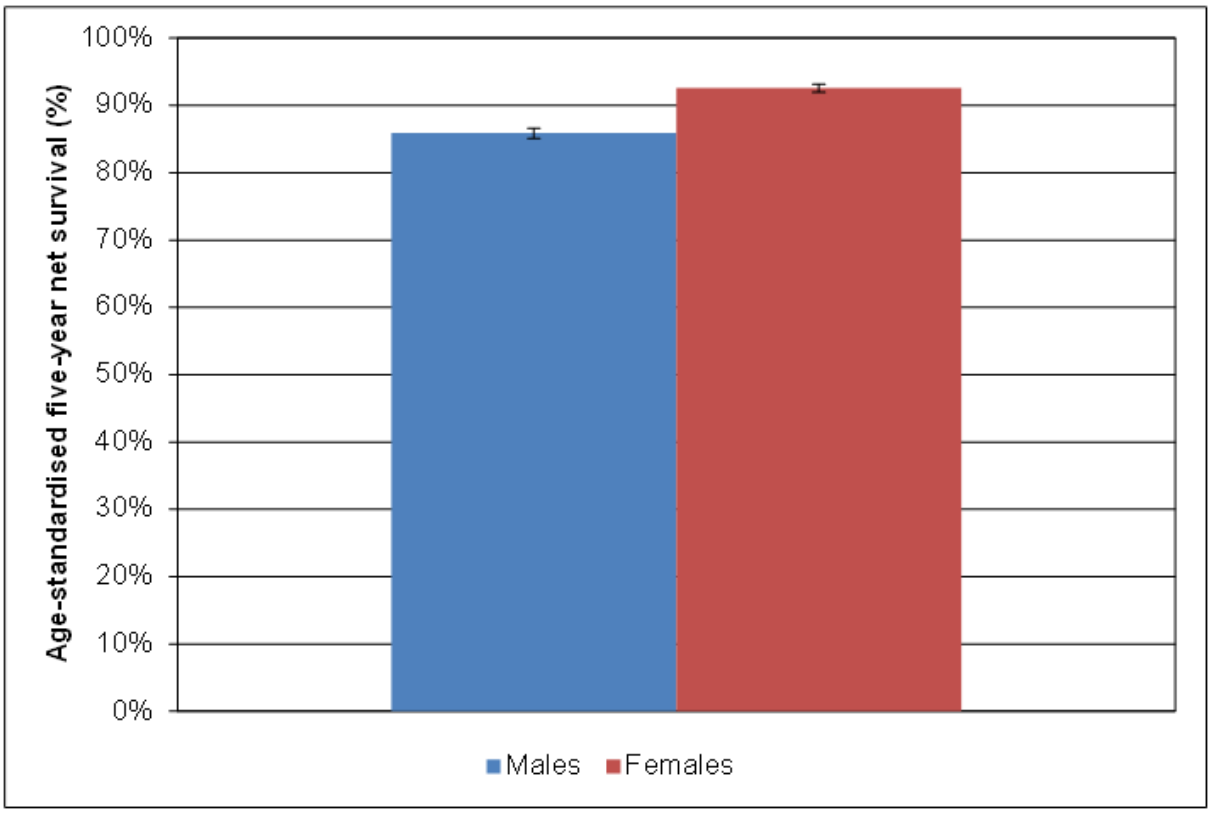
The age-standardised five-year net survival for melanoma in England has significantly increased for both men (an absolute increase of 0.6 percentage points per year) and women (0.4 percentage points per year) between 2001 and 2012 (Figure 42). Figure 43 shows that the age-standardised five-year net survival for melanoma in 2010-2012 was higher for women (93%) than for men (86%). The male and female five year net survival for melanoma by Clinical Commissioning Group (CCG) in England is presented in Figures 44 and 45 respectively.

Figure 42: Age-standardised five-year net survival (%) for melanoma by sex, England, 2001-2012<Insert graphic title here>



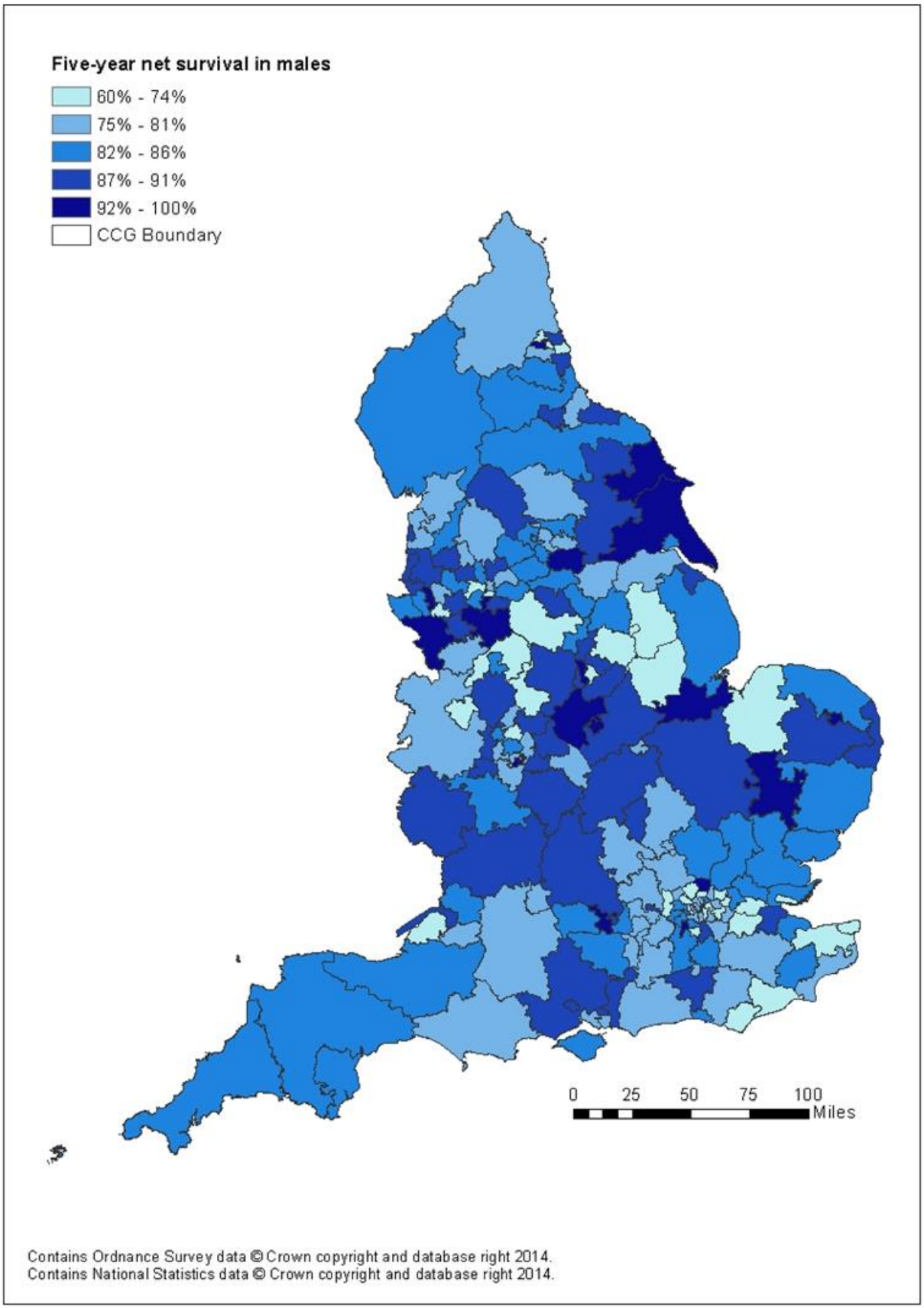
Source: National Cancer Registration Service

Figure 43: Age-standardised five-year net survival (%) for melanoma by sex, England, 2010-2012



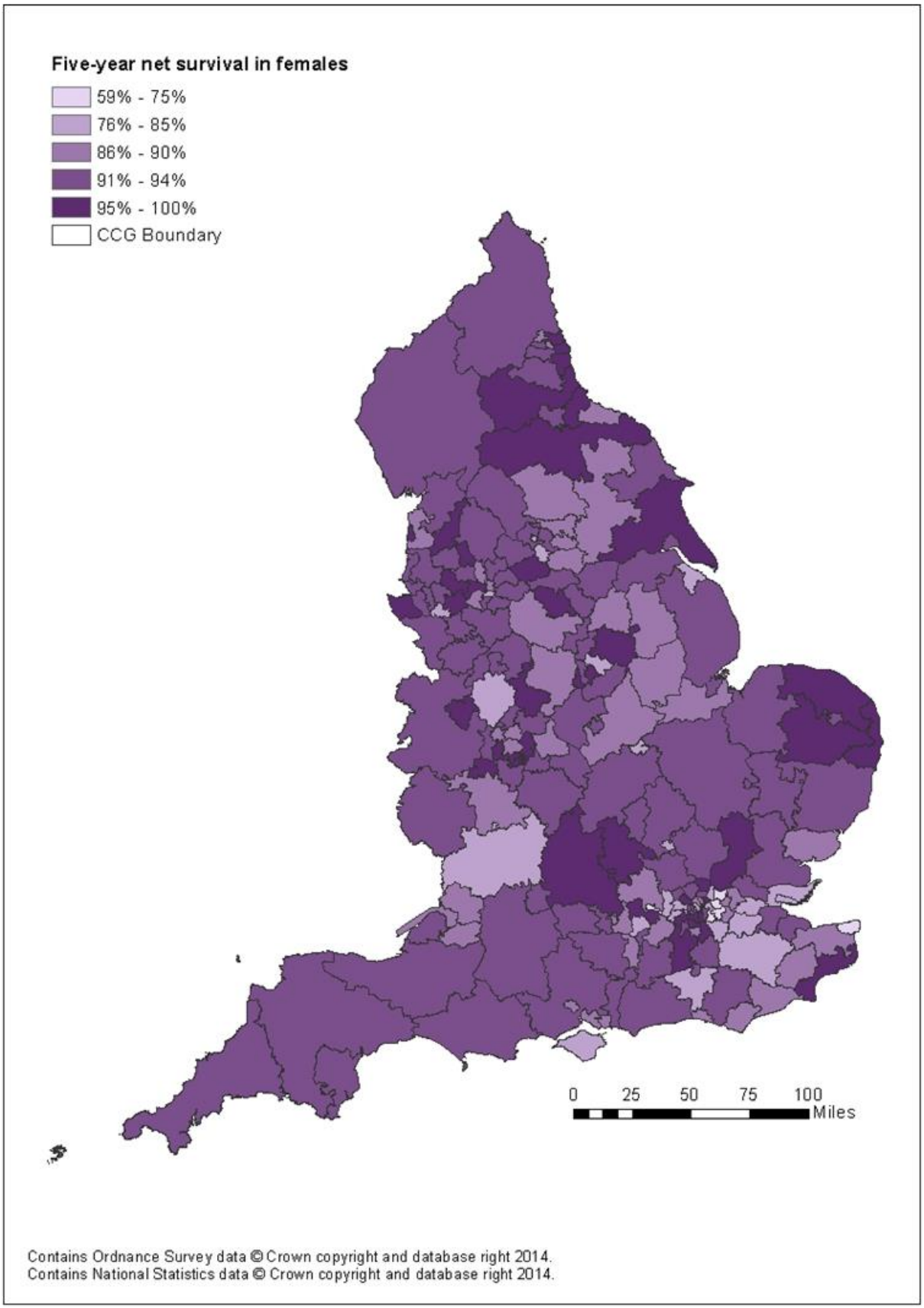
Source: National Cancer Registration Service

Figure 44: Male five-year net survival (%) for melanoma by Clinical Commissioning Group (CCG) in England, 2008-2012



Source: National Cancer Registration Service

Figure 45: Female five-year net survival (%) for melanoma by Clinical Commissioning Group (CCG) in England, 2008-2012



Source: National Cancer Registration Service

G.5.21 Age

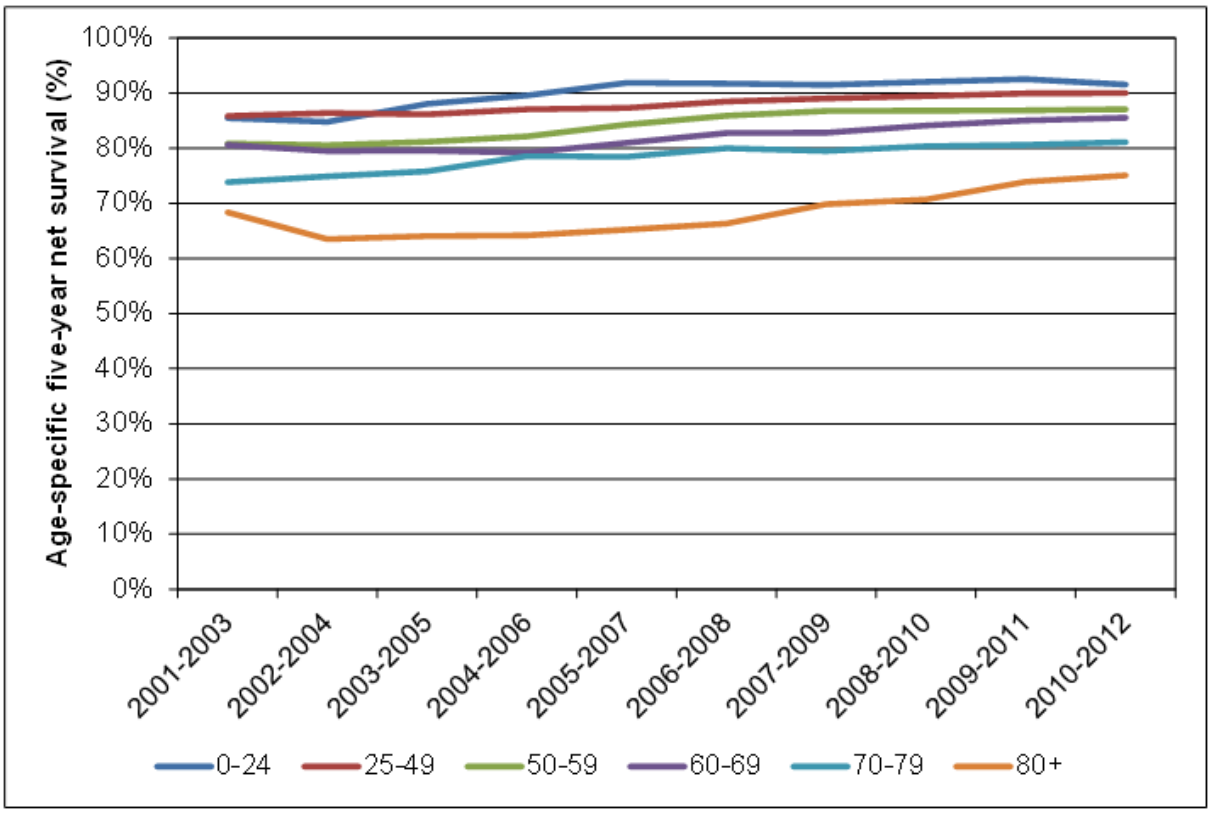
Survival from melanoma is increasing in all age groups, although this is not always statistically significant (Table 33 and Figures 46 and 47). The increase is greater for older age groups, with a significant interaction between age group and time period for females. It is worth noting that this increase is not necessarily regular, particularly for the 80+ age group; for females it seems there was an improvement between 2003-2005 and 2006-2008 which has levelled off. In 2012 (Figure 48), five-year net survival was significantly lower for older age groups for men (an absolute decrease in net survival of 3% with increasing age group) and for women (an absolute decrease of 2.4% with increasing age group). Again, it is noticeable that this decrease with age is not linear, but there is a more rapid lowering of net survival for the older age groups.

Table 33: Average absolute annual increase in five-year net survival (%) by age group, 2001-2012

Age Groups (years)	Males	Females
0-44	0.6	0.3
25-49	0.5*	0.2*
50-59	0.8	0.2
60-69	0.7	0.3
70-79	0.7	0.9*
80+	0.9	1.4

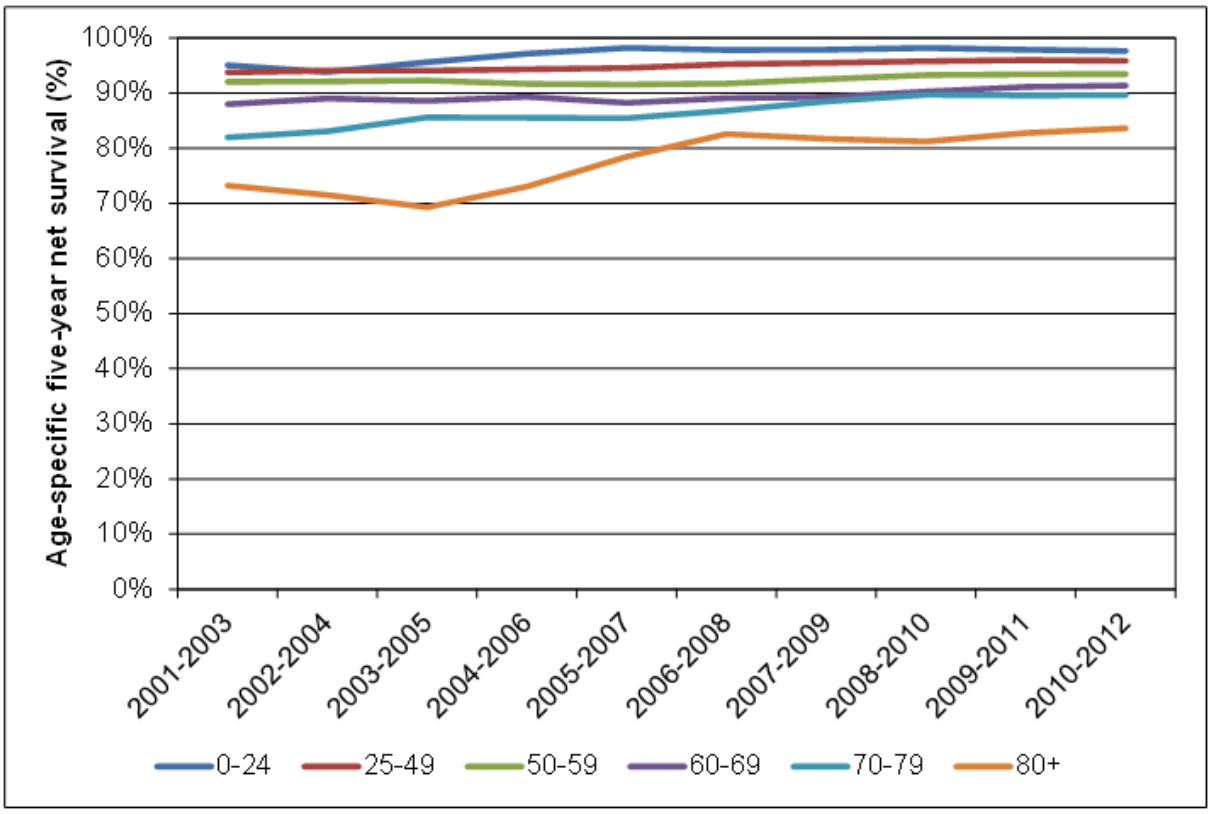
** = $p < 0.05$*

Figure 46: Age-specific five-year net survival for melanoma in males, by age group, England, 2001-2012



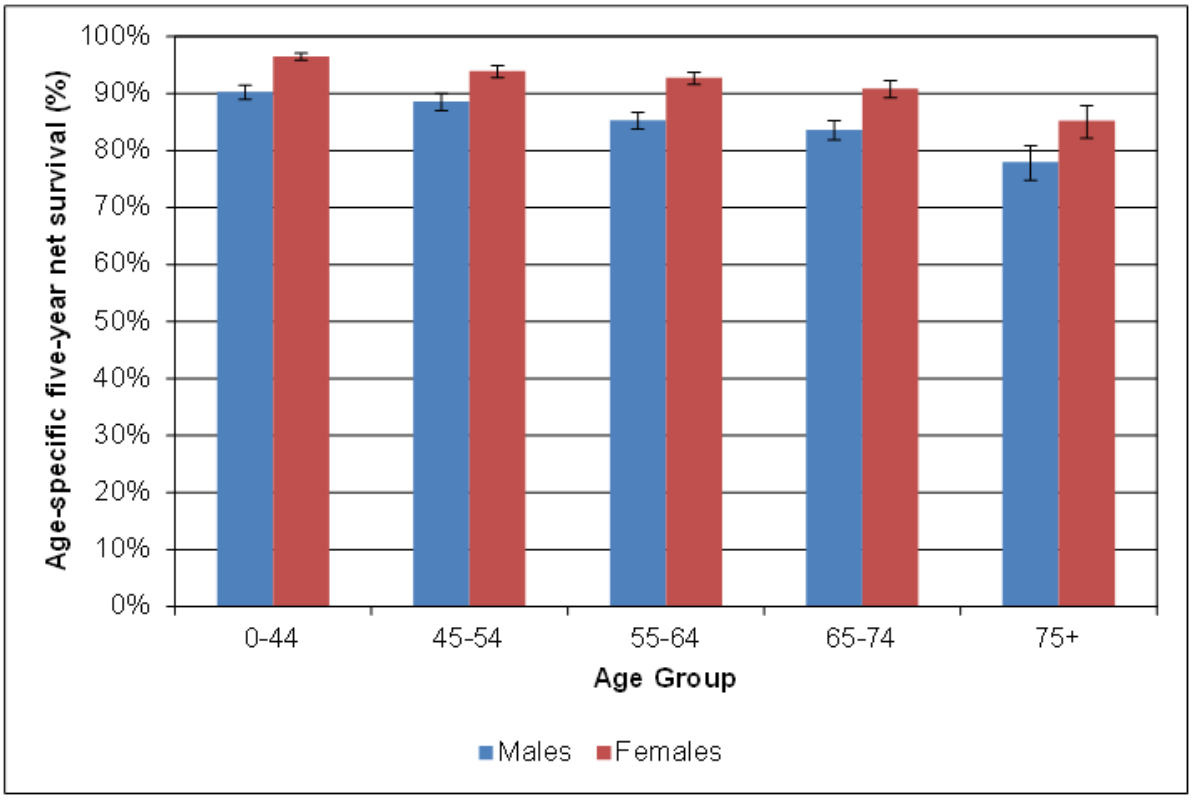
Source: National Cancer Registration Service

Figure 47: Age-specific five-year net survival for melanoma in females, by age group, England, 2001-2012



Source: National Cancer Registration Service

Figure 48: Age-specific five-year net survival for melanoma by sex and age group, England, 2010-2012



Source: National Cancer Registration Service

G.5.31 Anatomical site

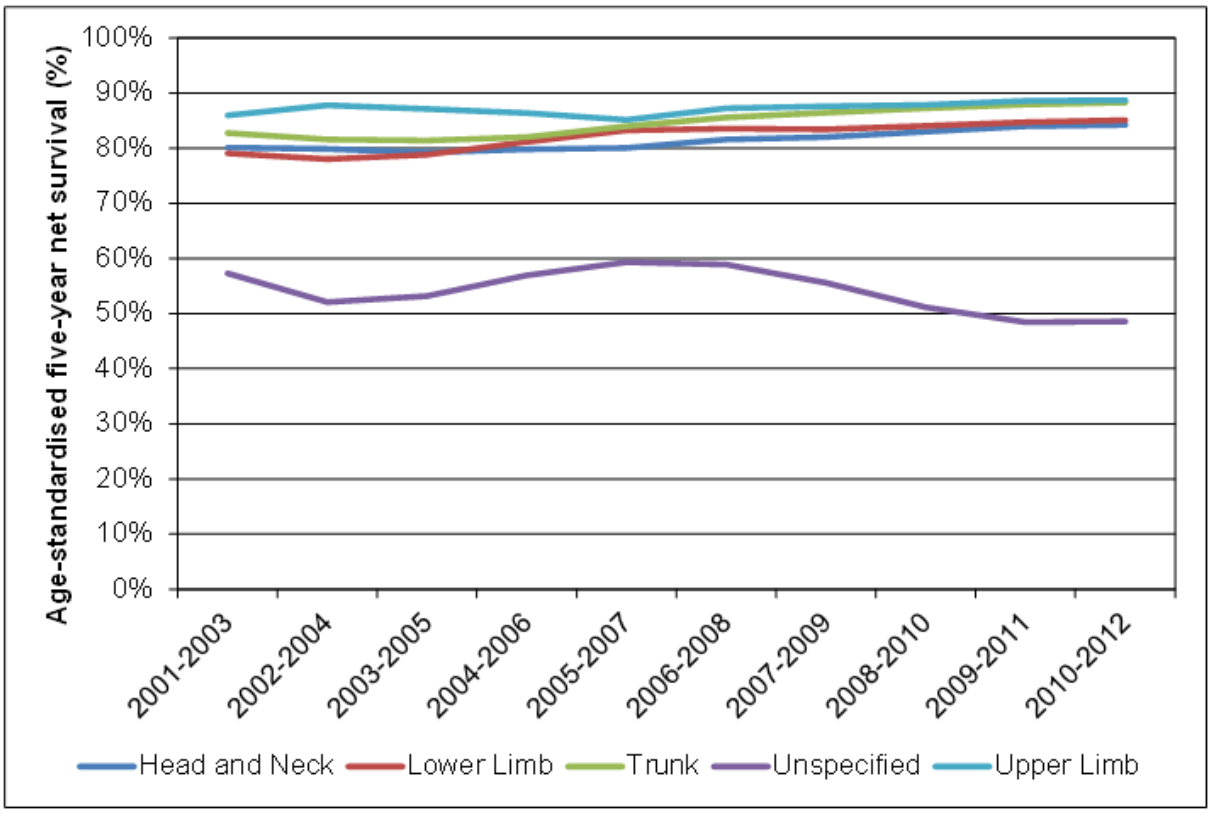
There has generally been an upward trend in survival at each anatomical site (except perhaps the overlapping and unspecified regions), although the trend is not always statistically significant (Table 34 and Figures 49 and 50). In 2012, survival was generally worse for men than women, although this was not the case for melanomas on the trunk where there was no gender difference (Figure 51). The prognosis for melanomas with an unspecified anatomical location is much worse than for the other locations, possibly because these are tumours that are diagnosed at a late stage. Upper limb melanomas have the best survival for both sexes.

Table 34: Average absolute annual increase in five-year net survival (%) by anatomical site, 2001-2012

Anatomical site	Males	Females
Head and Neck	0.5	0.6*
Lower Limb	0.7*	0.4
Overlapping	n/a	-0.6
Trunk	0.7	0.2
Unspecified	-0.9	0.06
Upper Limb	0.3*	0.3*

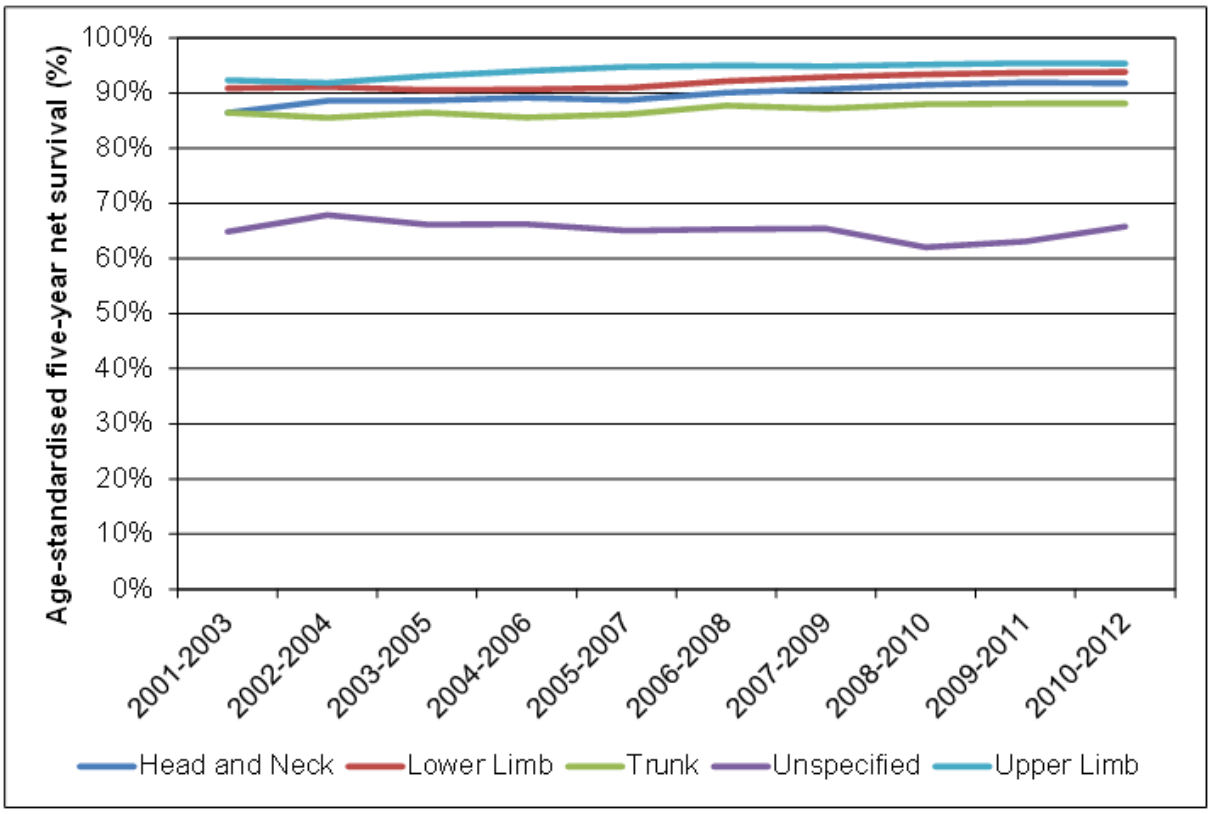
** = p < 0.05; There were too few cases of melanomas at overlapping regions in males to ascertain a trend.*

Figure 49: Age-standardised five-year net survival for melanoma in males, by anatomical site, England, 2001-2012



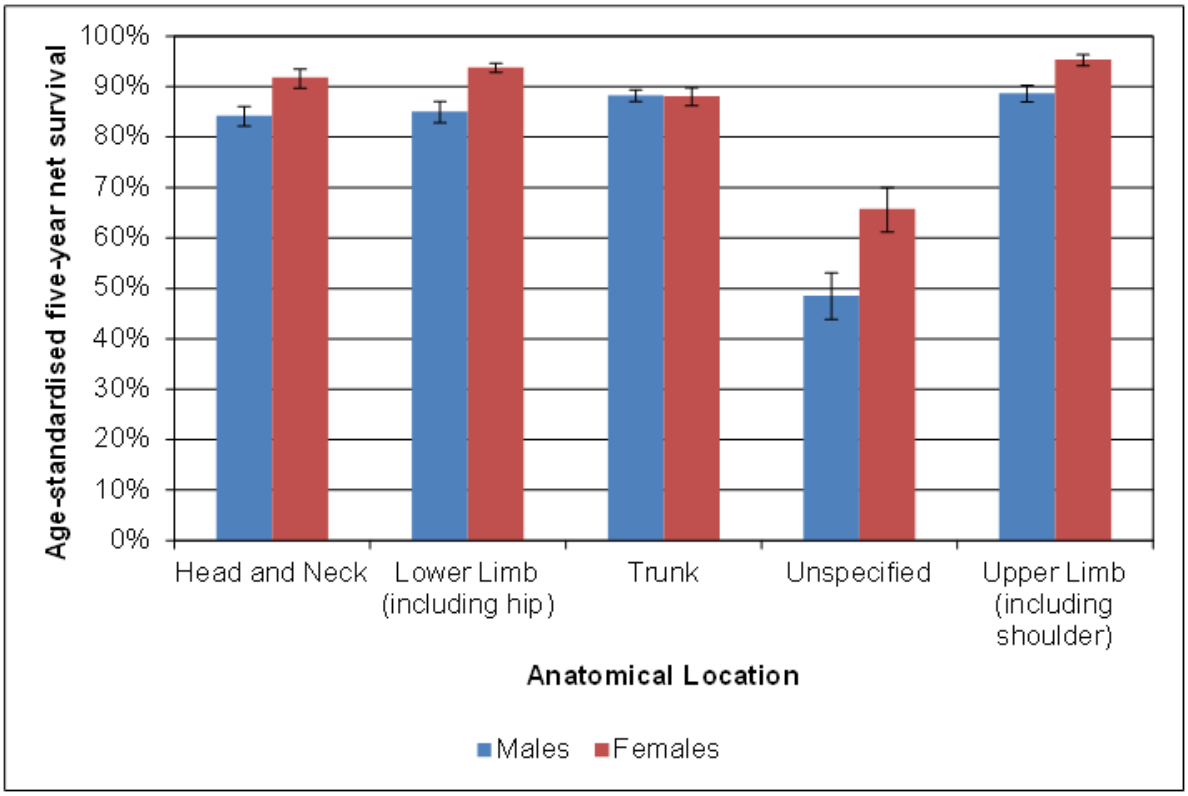
Source: National Cancer Registration Service

Figure 50: Female age-standardised melanoma incidence rates (per 100,000 women) by anatomical site, England, 2001-2012



Source: National Cancer Registration Service

Figure 51: Age-standardised five-year net survival (%) for melanoma by sex and anatomical site, England, 2010-2012



Source: National Cancer Registration Service

G.5.41 Tumour thickness (Breslow)

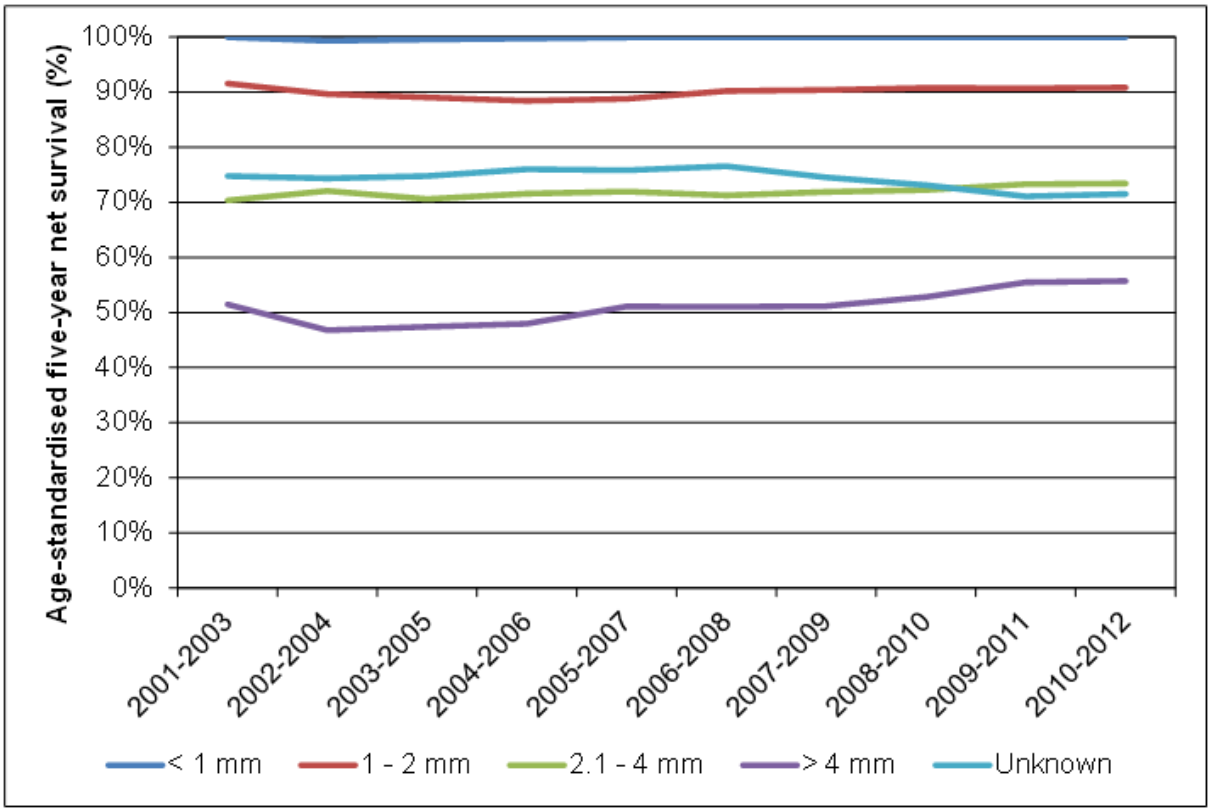
Survival has broadly either stayed the same or slightly increased for each Breslow thickness; although most of the trends were not statistically significant (Table 35 and Figures 52 and 53). It is worth noting that for melanomas with a Breslow thickness less than 1 mm, survival is essentially the same as for the background population (i.e. net survival is around 100%). Survival generally decreases with the thickness of the melanoma (Figure 54); melanomas on the register without a known Breslow thickness have survival roughly equivalent to the 2.01-4 mm group.

Table 35: Average absolute annual increase in five-year net survival (%) by Breslow thickness, 2001-2012

Breslow thickness	Males	Females
0 - 1 mm	n/a	n/a
1.01 - 2 mm	0.02	0.2
2.01 - 4 mm	0.3*	0.2
> 4 mm	0.6	0.2
Unknown	-0.4	-0.2

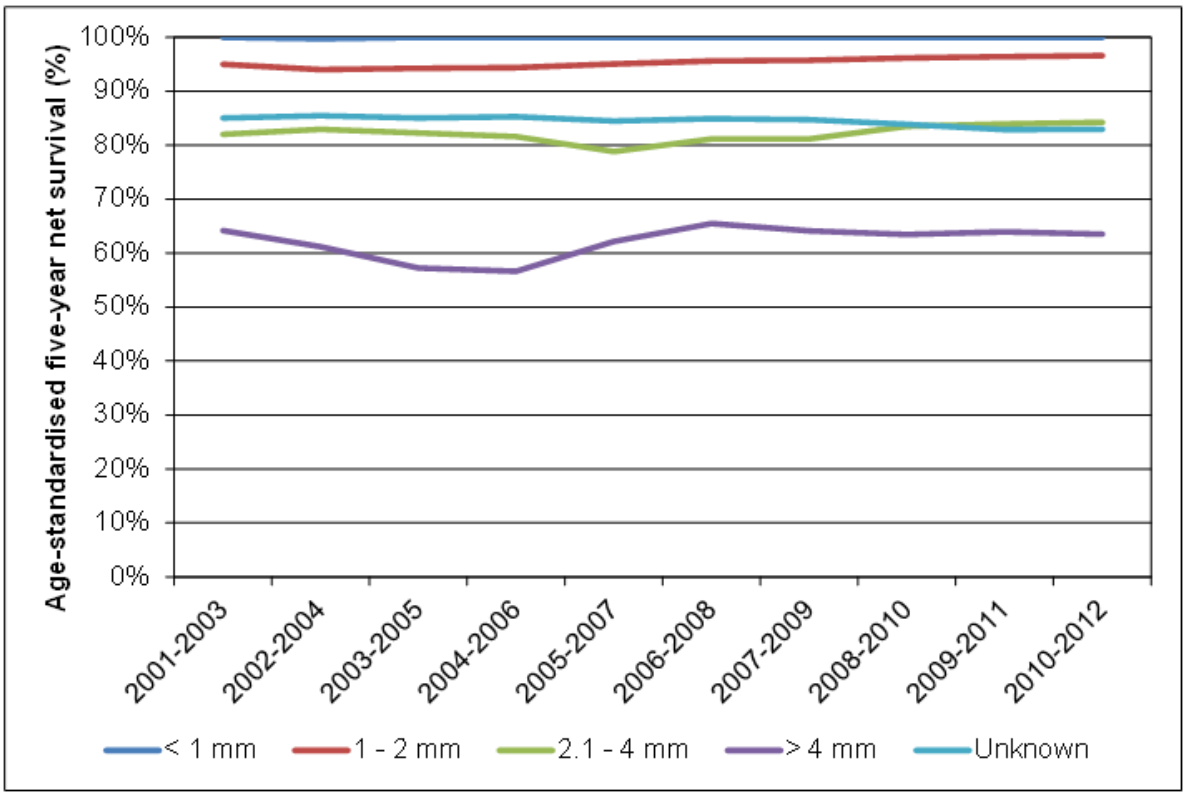
** = $p < 0.05$*

Figure 52: Age-standardised five-year net survival for melanoma in males, by Breslow thickness, England, 2001-2012



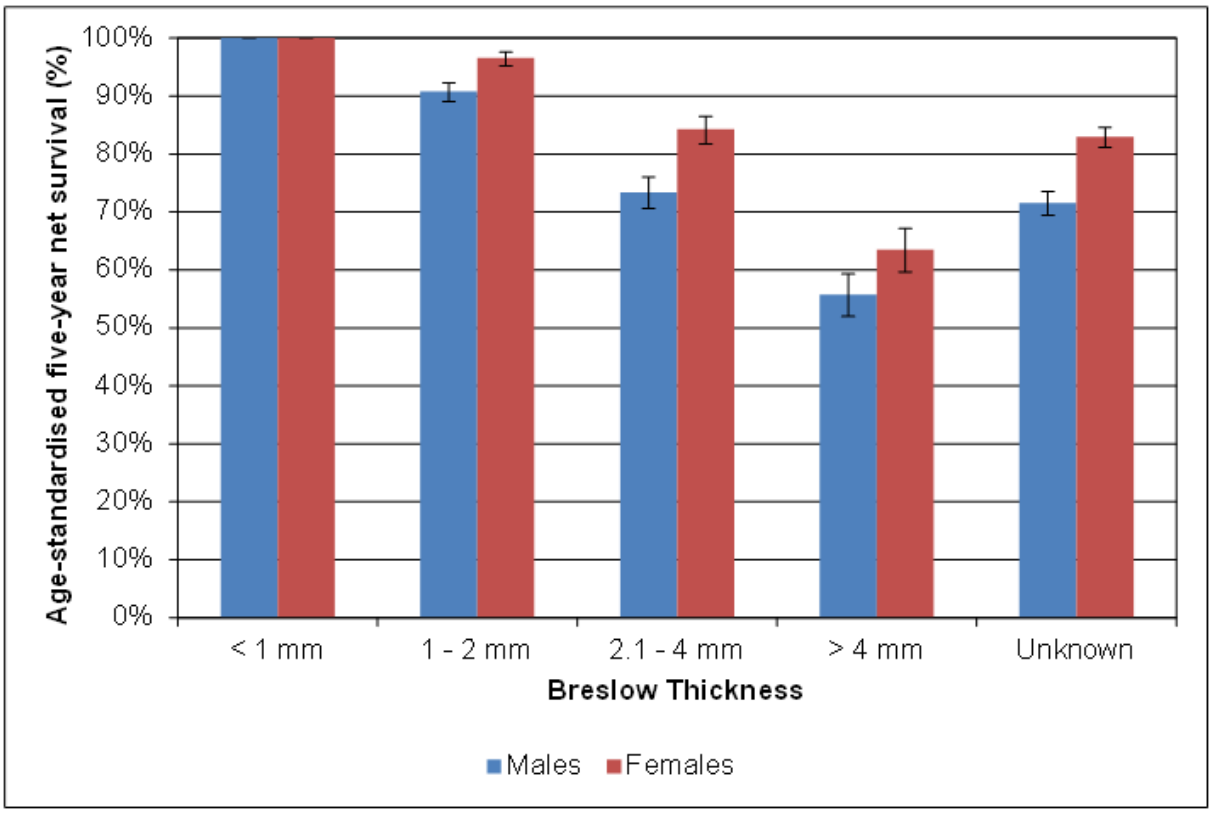
Source: National Cancer Registration Service

Figure 53: Age-standardised five-year net survival for melanoma in females, by Breslow thickness, England, 2001-2012



Source: National Cancer Registration Service

Figure 54: Age-standardised five-year net survival (%) for melanoma by sex and Breslow thickness, England, 2010-2012



Source: National Cancer Registration Service

G.5.51 Income deprivation

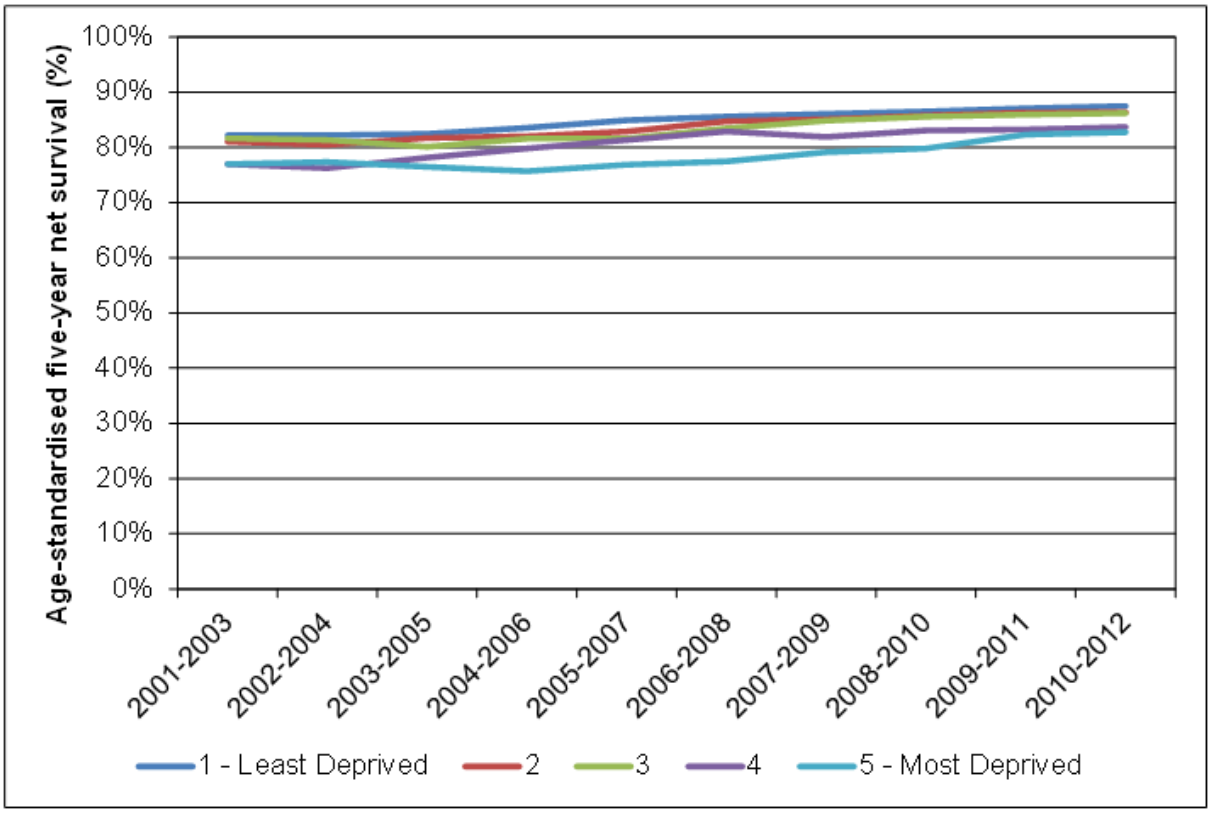
Survival between 2001 and 2012 increased for all income deprivation quintiles (Table 36 and Figures 55 and 56), and at a fairly similar rate (i.e., there was no interaction between deprivation quintile and period of diagnosis for men or women). In 2012, there was still a deprivation effect on five-year net survival from melanoma. The impact of being in the next more deprived quintile was to reduce the five-year net survival by 1.2% for men and 0.9% for women; this reduction was not significantly different between the sexes (Figure 57).

Table 36: Average absolute annual increase in five-year net survival (%) by income deprivation quintile, 2001-2012

Deprivation Quintile	Male AAPC	Female AAPC
1 - Least Deprived	0.6*	0.4*
2	0.6*	0.4
3	0.6	0.3*
4	0.7*	0.6*
5 - Most Deprived	0.7	0.4

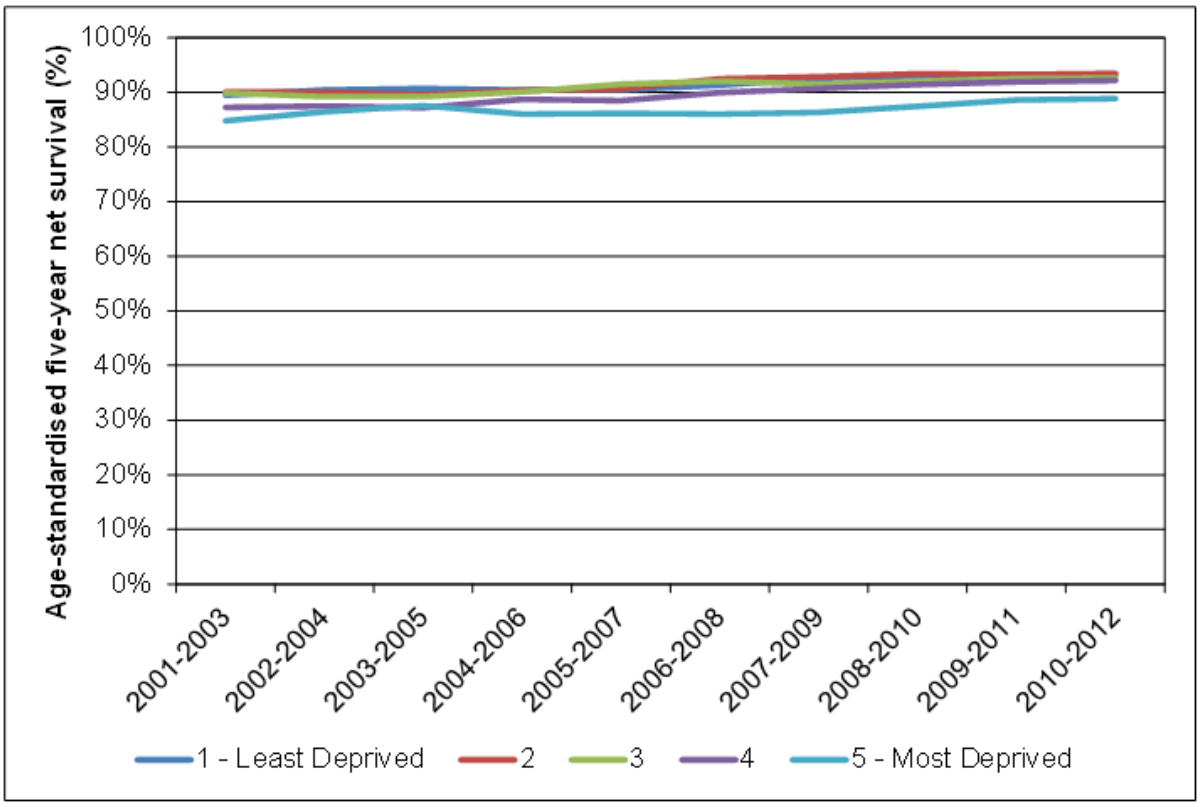
** = $p < 0.05$*

Figure 55: Age-standardised five-year net survival for melanoma in males, by income deprivation quintile, England, 2001-2012



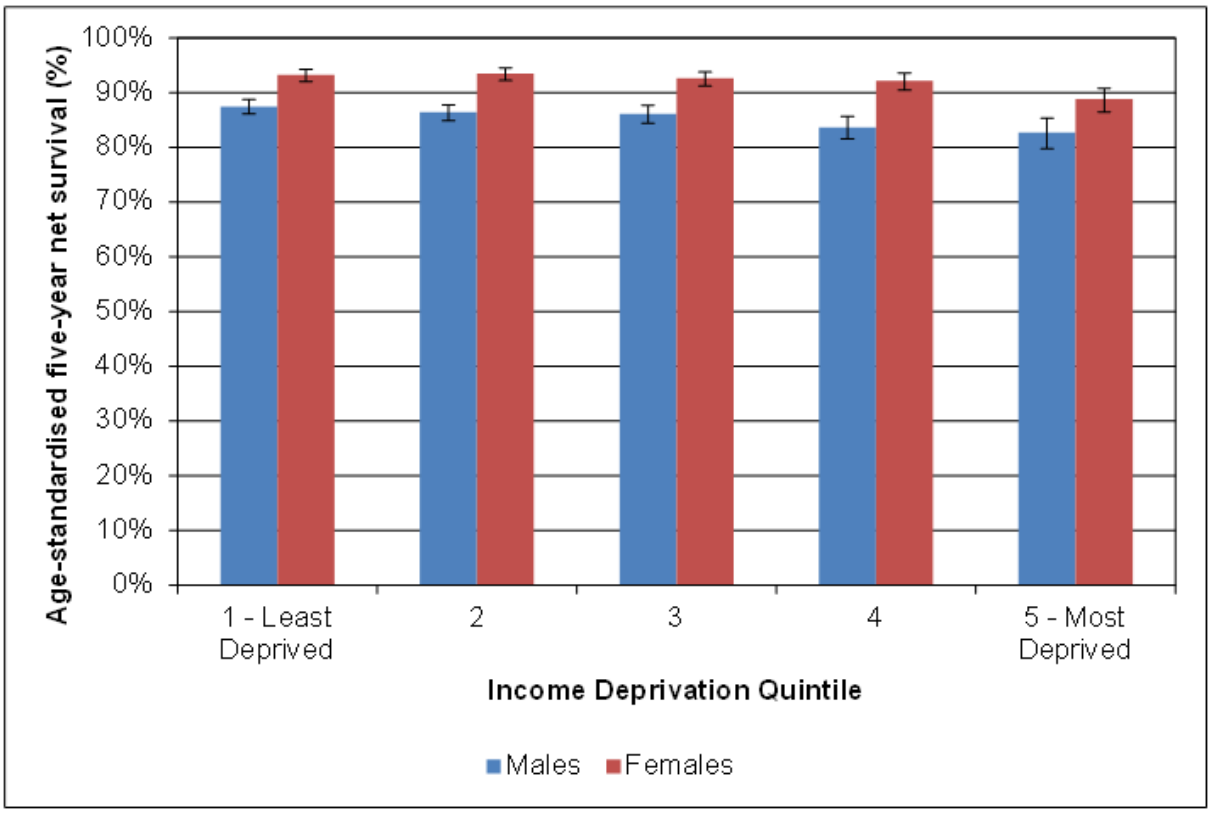
Source: National Cancer Registration Service

Figure 56: Age-standardised five-year net survival for melanoma in females, by income deprivation quintile, England, 2001-2012



Source: National Cancer Registration Service

Figure 57: Age-standardised five-year net survival (%) for melanoma by sex and income deprivation quintile, England, 2010-2012



Source: National Cancer Registration Service

G.5.61 Tumour morphology

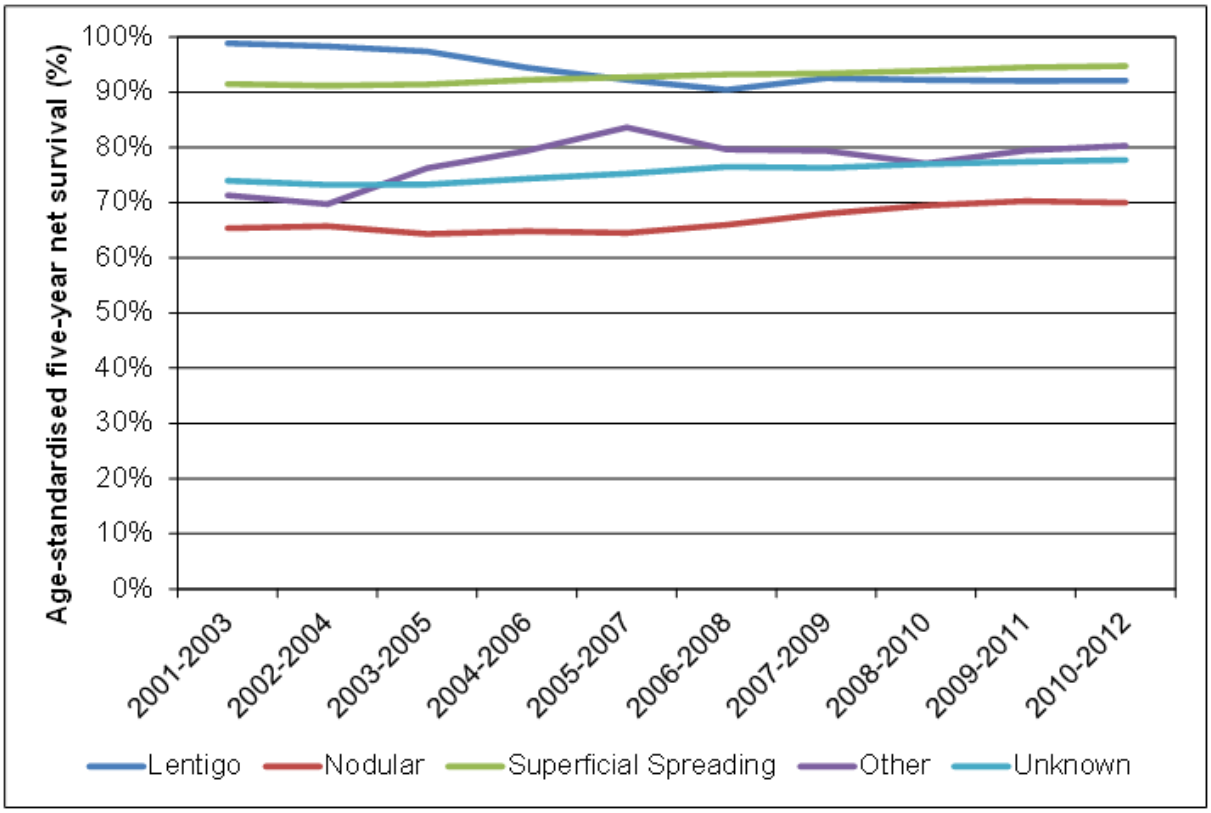
The age-standardised five-year net survival from melanoma has generally increased for all tumour morphologies between 2001 and 2012, although this trend was not always statistically significant (Table 37 and Figures 58 and 59). The exception to this was for lentigo melanomas, where there was a slightly decreasing (but non-significant) trend for men and no change for women because survival was already equivalent to the background population. In 2012, nodular melanomas had the worst net survival (Figure 60).

Table 37: Average absolute annual increase in five-year net survival (%) by tumour morphology, 2001-2012

Tumour Morphology	Male AAPC	Female AAPC
Lentigo Maligna	-0.8	0
Nodular	0.6	0.4
Superficial Spreading	0.4*	0.2*
Other	0.8	0.4
Unknown	0.4*	0.4*

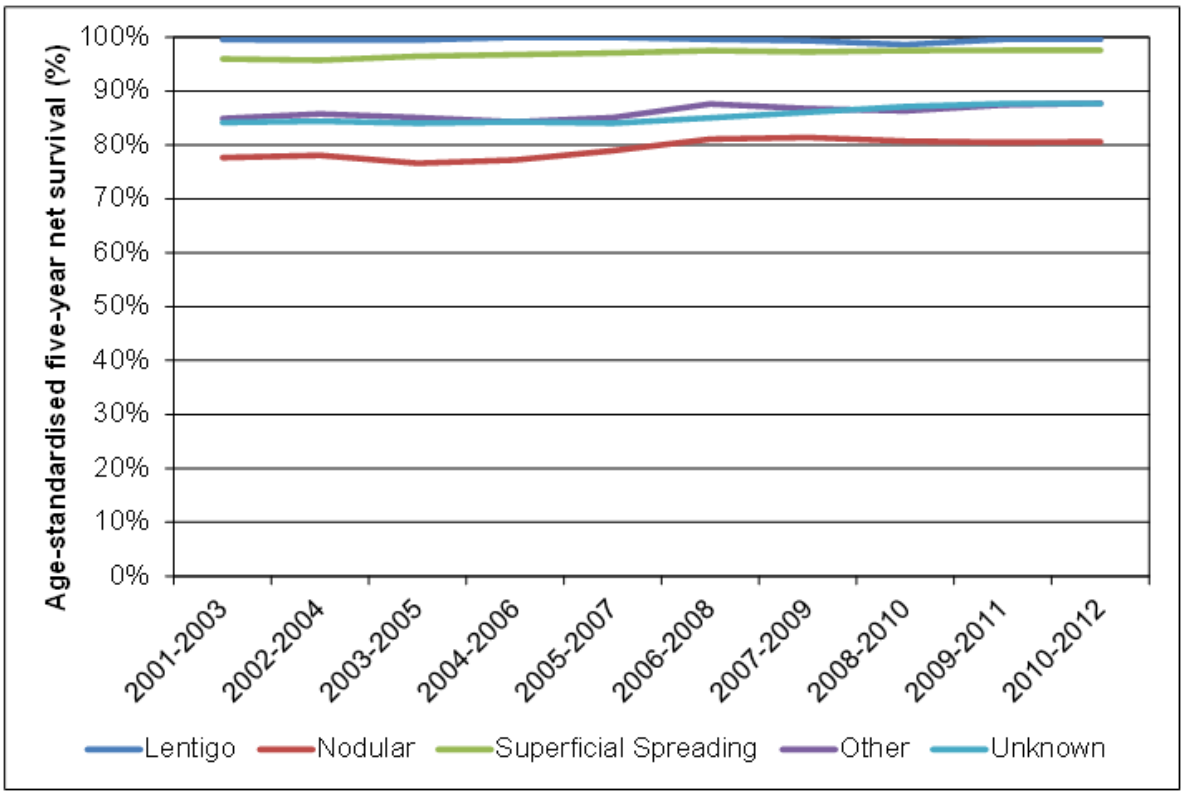
** = $p < 0.05$*

Figure 58: Age-standardised five-year net survival for melanoma in males, by tumour morphology, England, 2001-2012



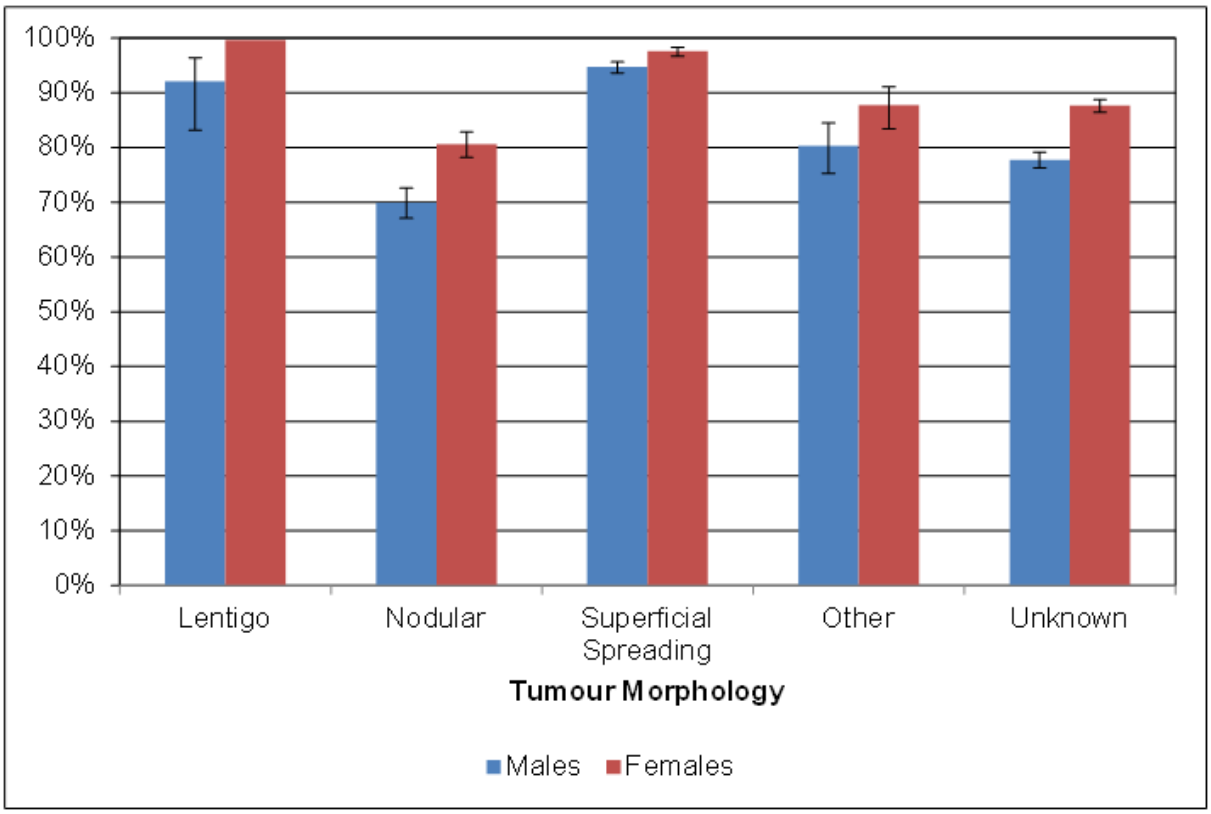
Source: National Cancer Registration Service

Figure 59: Age-standardised five-year net survival for melanoma in females, by tumour morphology, England, 2001-2012



Source: National Cancer Registration Service

Figure 60: Age-standardised five-year net survival (%) for melanoma by sex and tumour morphology, England, 2010-2012

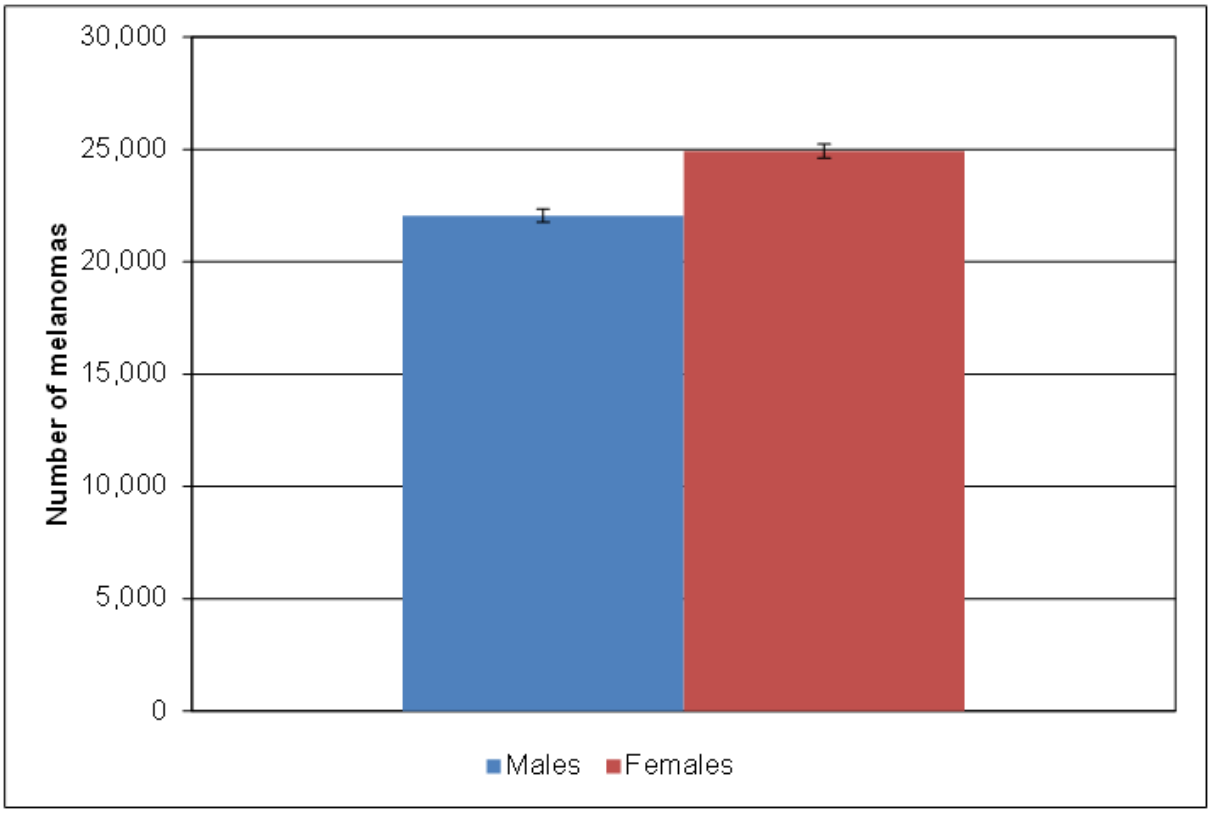


Source: National Cancer Registration Service

G.6 Prevalence (survivorship)

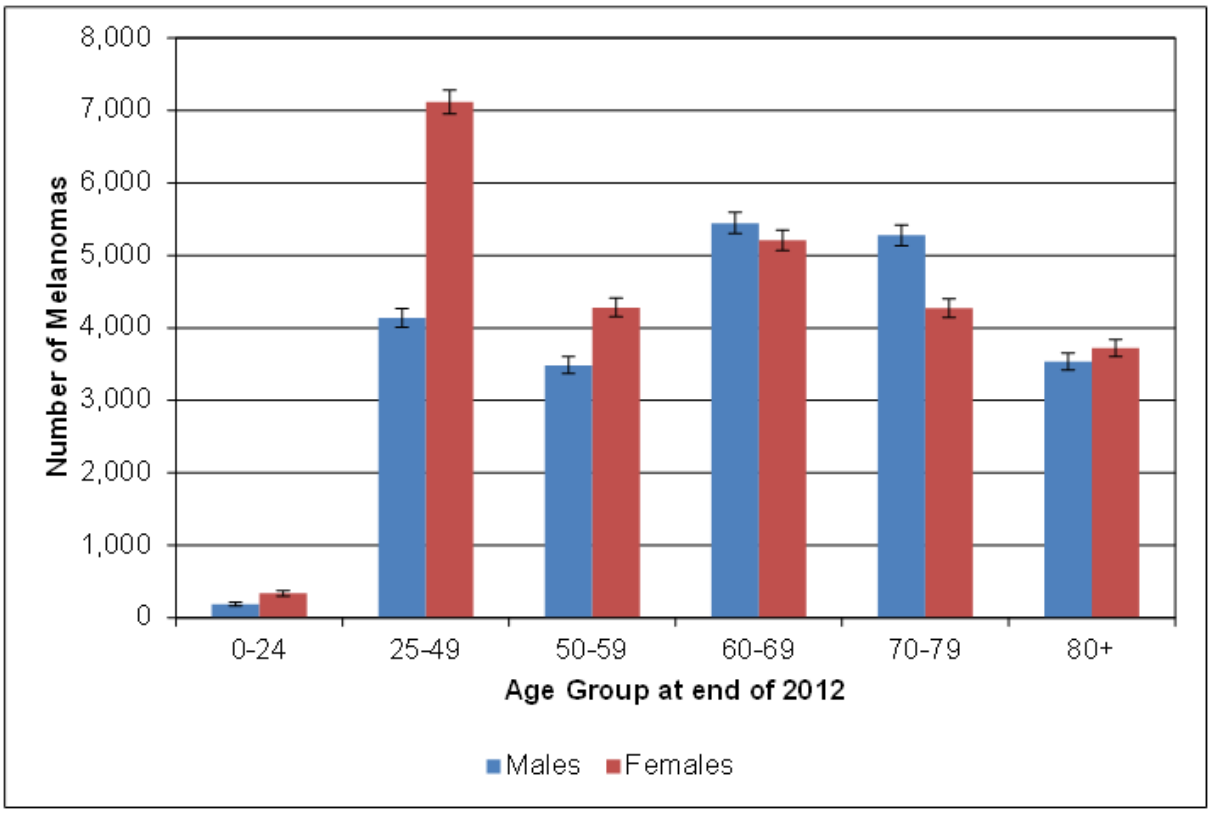
In total, there were 46,782 melanomas diagnosed between 2008 and 2012 in people who were still living at the end of 2012. Figures 61 to 66 show this prevalence information split by sex, age group, anatomical site, Breslow thickness, income deprivation quintile, tumour morphology, and CCG of residence. Note that these figures are counts of individual melanomas rather than rates. The male and female five year prevalence for melanoma by Clinical Commissioning Group (CCG) in England is presented in Figures 67 and 68 respectively.

Figure 61: Five-year prevalence of melanoma in England by sex, end of 2012



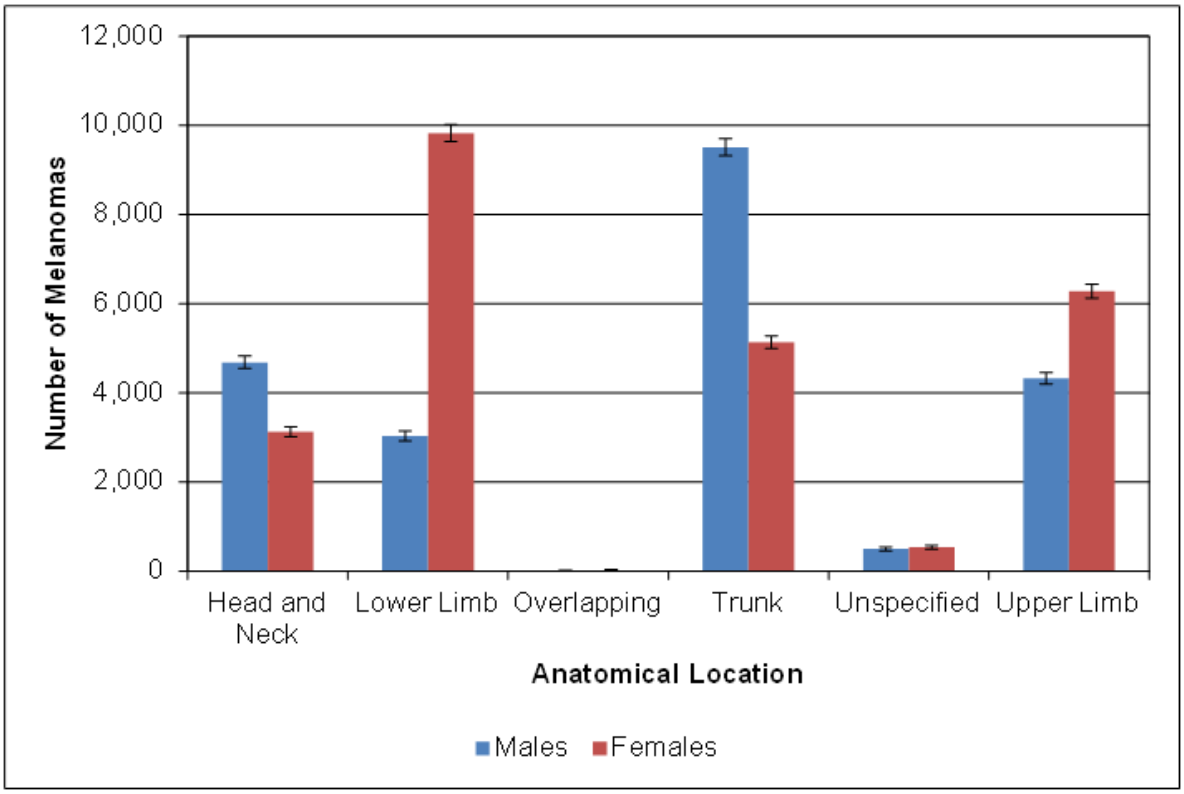
Source/Note: *National Cancer Registration Service*

Figure 62: Five-year prevalence of melanoma in England by sex and age group, end of 2012



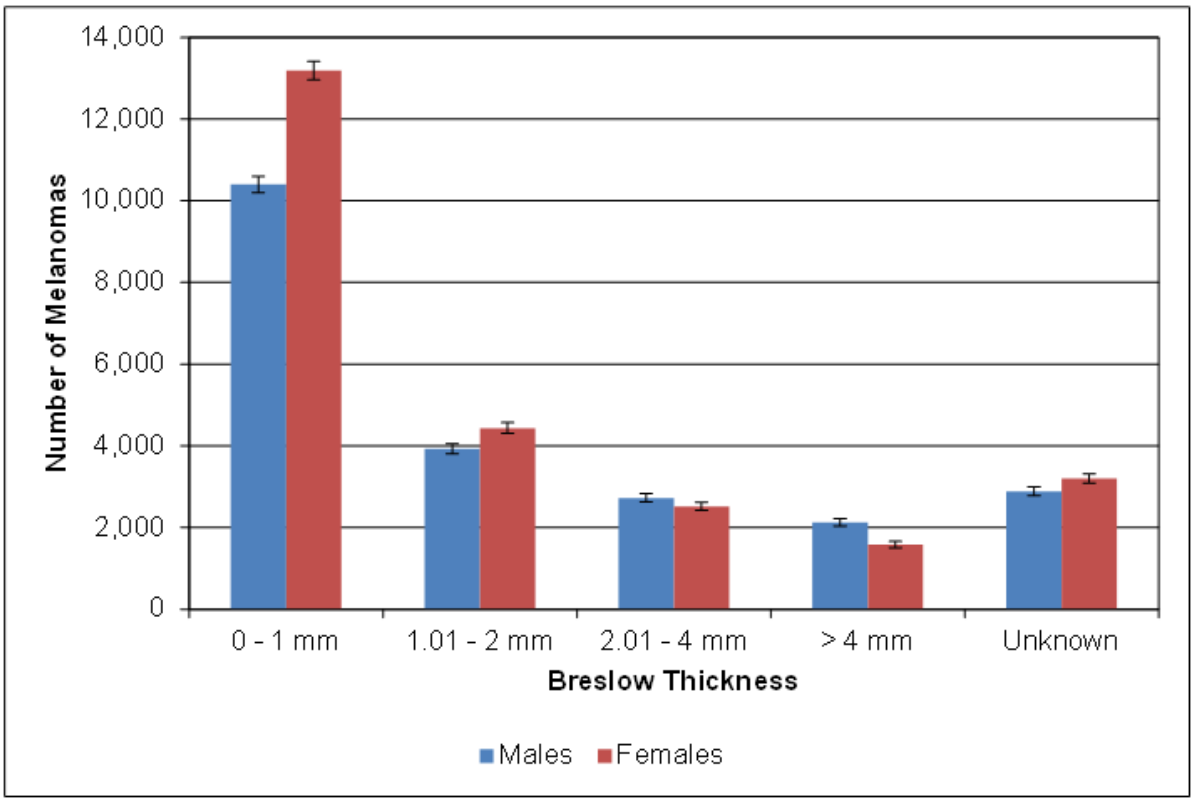
Source/Note: National Cancer Registration Service

Figure 63: Five-year prevalence of melanoma in England by sex and anatomical site, end of 2012



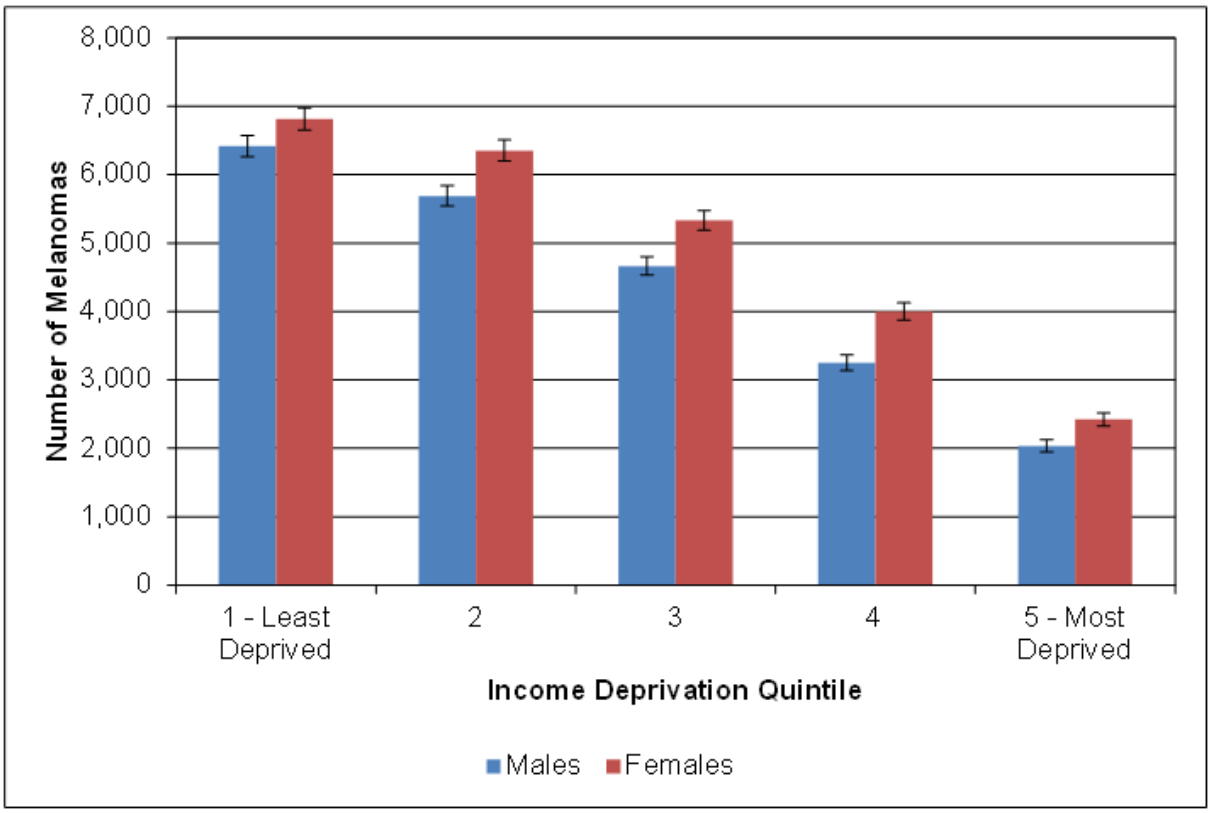
Source: National Cancer Registration Service

Figure 64: Five-year prevalence of melanoma in England by sex and Breslow thickness, end of 2012



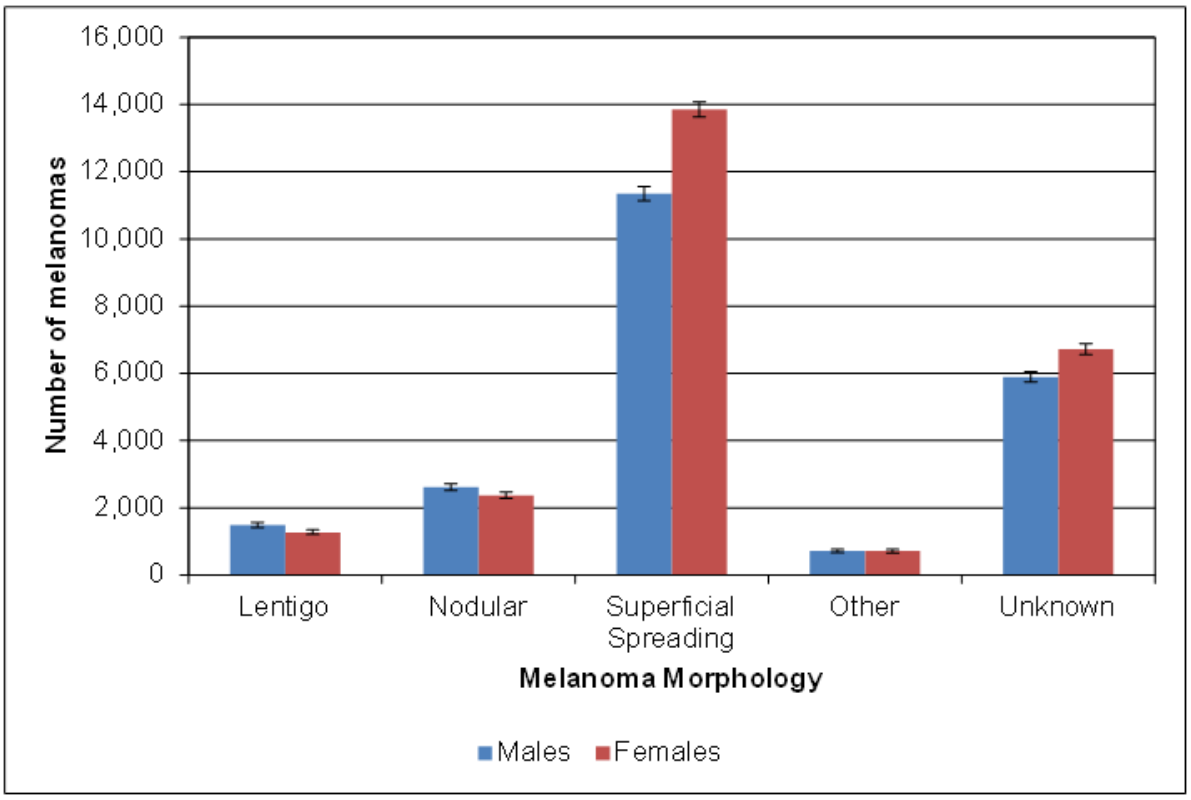
Source: National Cancer Registration Service

Figure 65: Five-year prevalence of melanoma in England by sex and income deprivation quintile, end of 2012



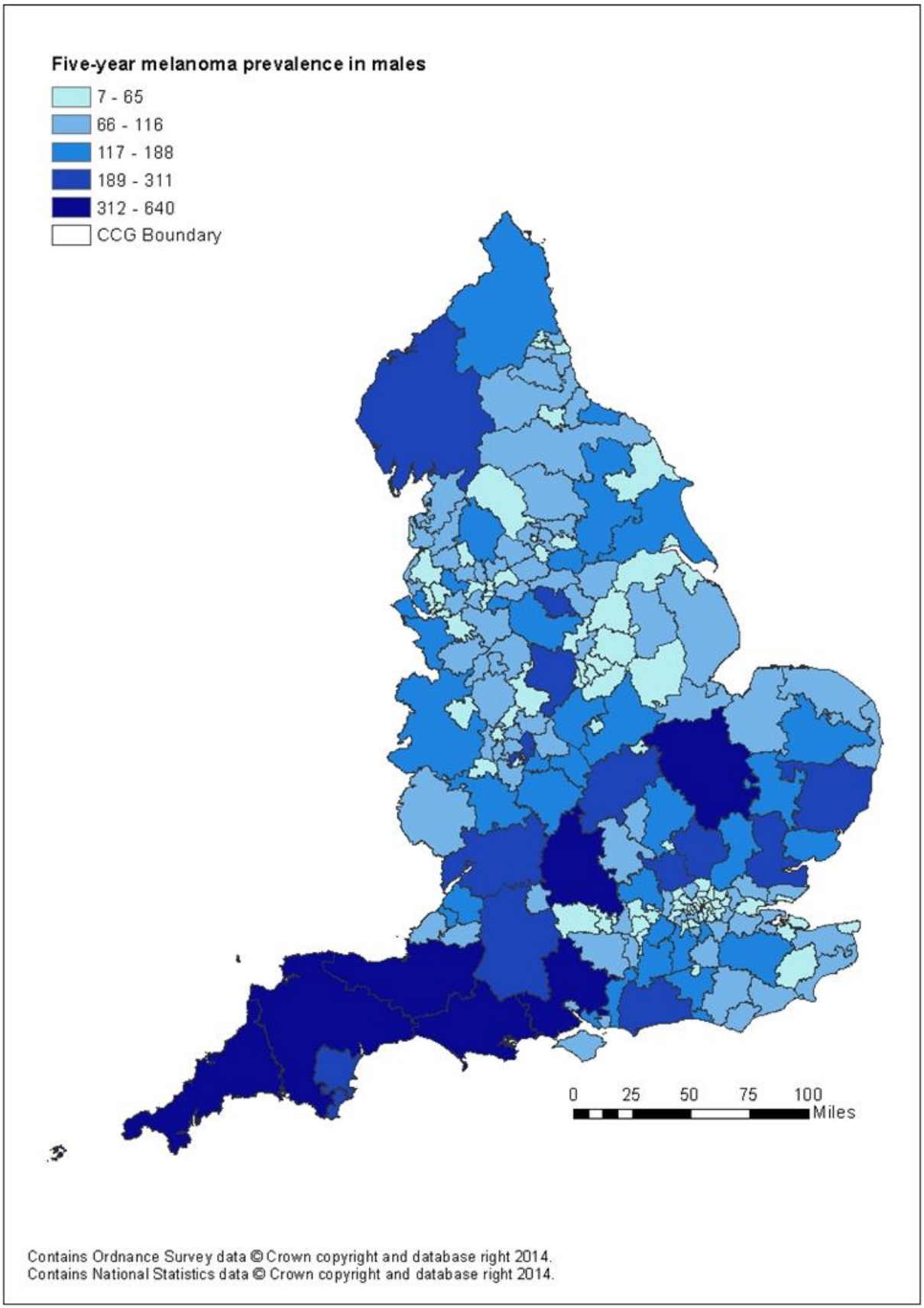
Source: National Cancer Registration Service

Figure 66: Five-year prevalence of melanoma in England by sex and tumour morphology, end of 2012



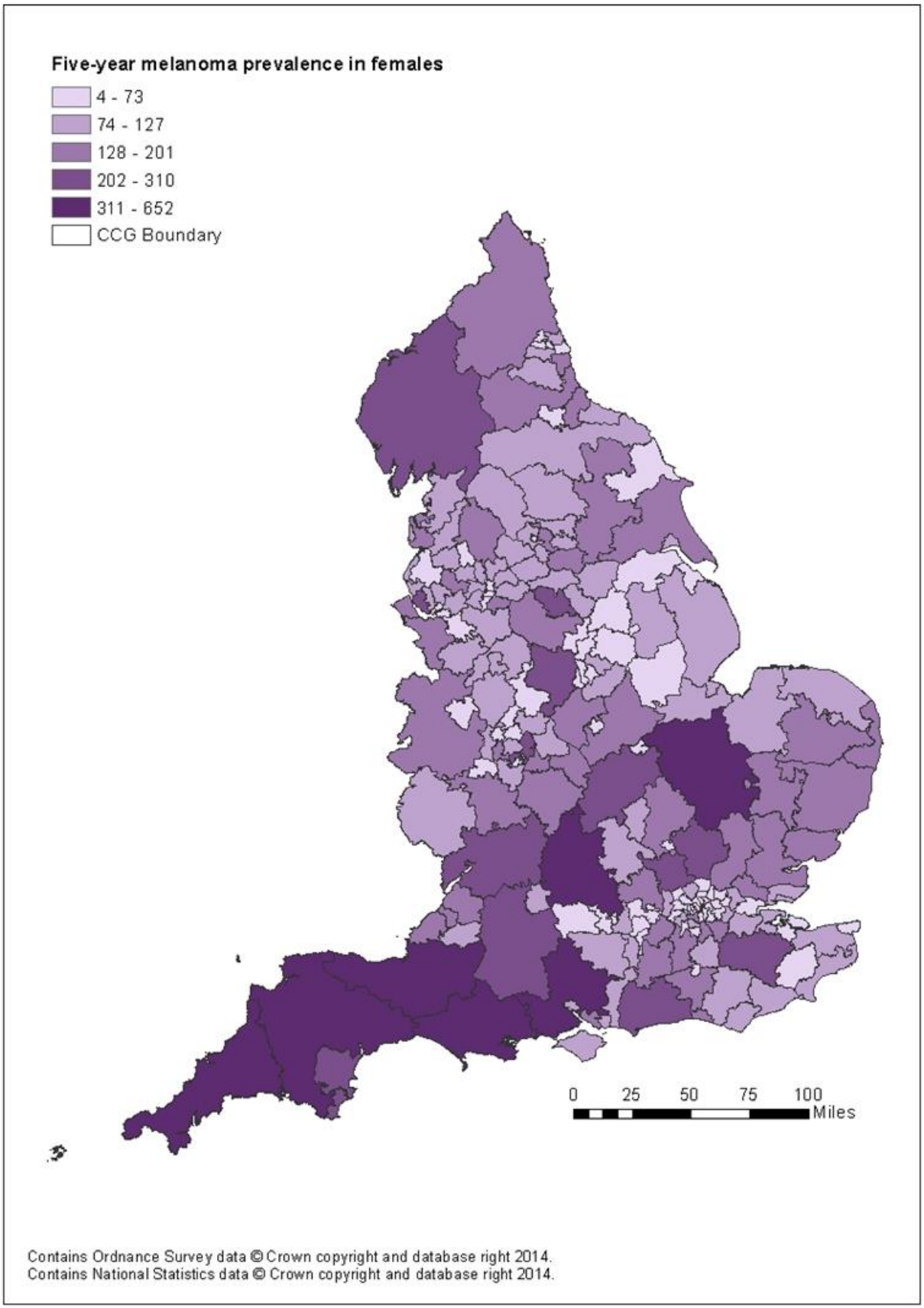
Source: National Cancer Registration Service

Figure 67: Male five-year prevalence for melanoma by Clinical Commissioning Group (CCG) in England, 2012



Source: National Cancer Registration Service

Figure 68: Female five-year prevalence for melanoma by Clinical Commissioning Group (CCG) in England, 2012



Source: National Cancer Registration Service

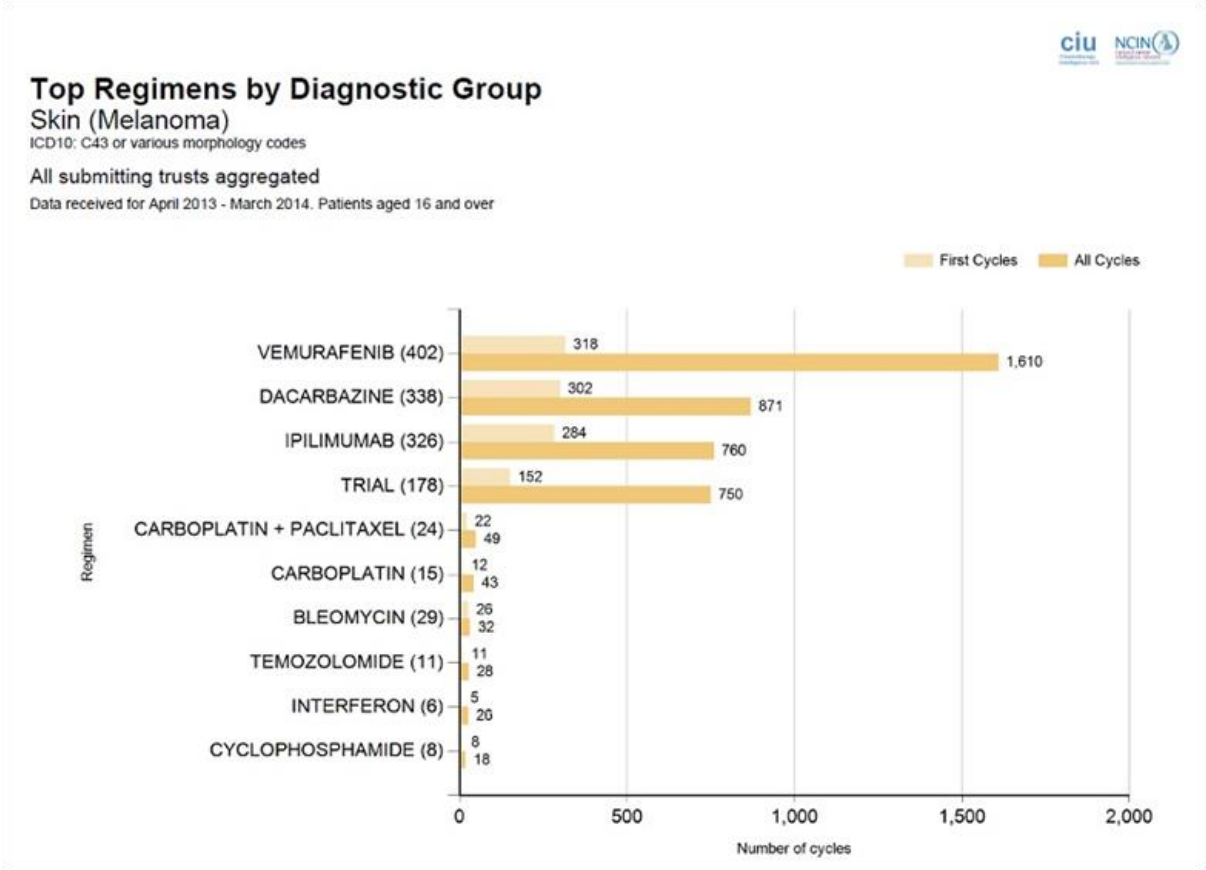
G.7 Skin cancer MDT survey (England and Wales)

In order to better understand current clinical practice for some specific issues the GDG developed a questionnaire survey. This was sent electronically (with a covering letter) to all skin cancer multidisciplinary teams (MDTs) in England and Wales during July 2014 who were asked to complete the questionnaire on line. All information was treated confidentially and no hospital or healthcare professional has been identified in the final guideline or any associated report. All the data was analysed and presented by the team at the South West Knowledge and Intelligence Team at Public Health England.

A total of 77 skin cancer MDTs replied to the survey, comprising 48 local skin cancer MDTs (LSMDT) and 29 specialist skin cancer MDTs (SSMDTs). The findings of this survey are presented below and data were used to support the evidence based of several topics in the full guideline.

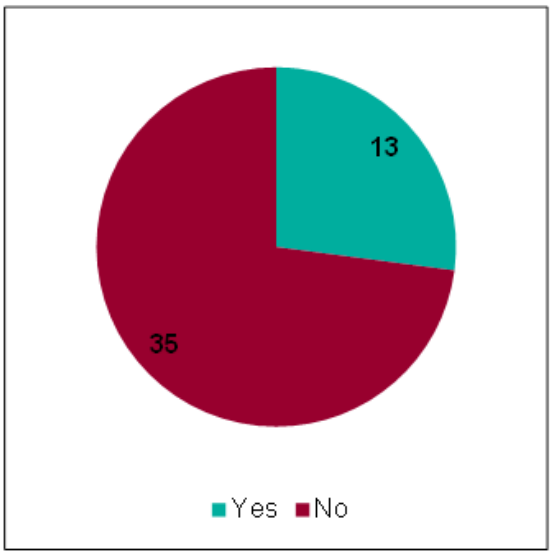
G.7.1 Systemic treatment

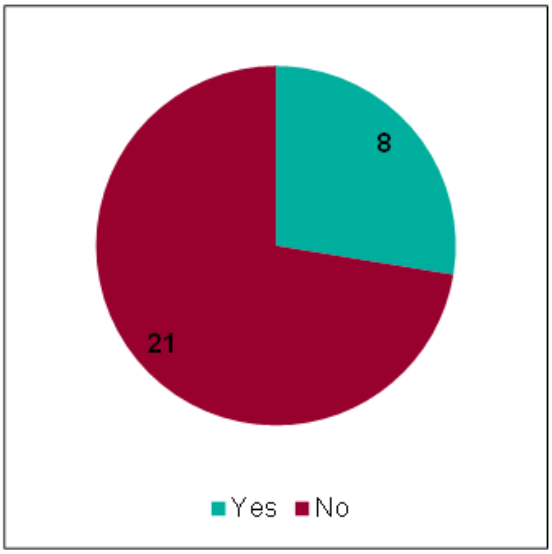
Figure 69: Top regimens by diagnostic group, Skin (melanoma)



G.7.21 Vitamin D

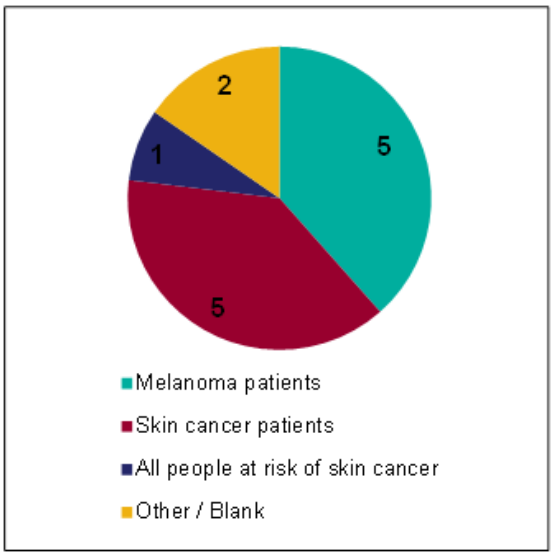
Figure 70: Does your skin cancer team give advice about avoiding depletion of vitamin D levels as a result of sun protection?

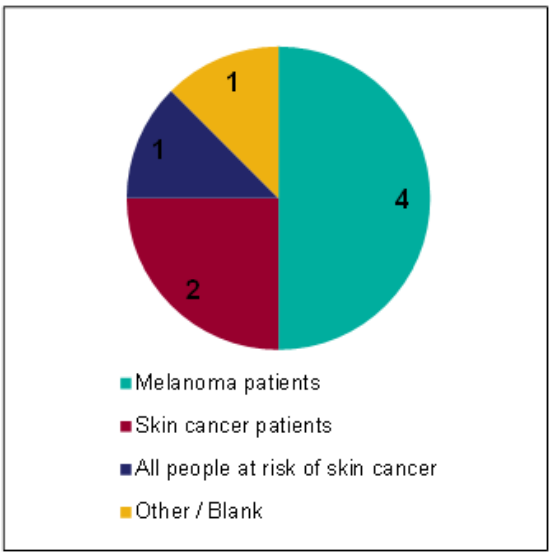




LSMDT (n = 48) *SSMDT (n = 29)*

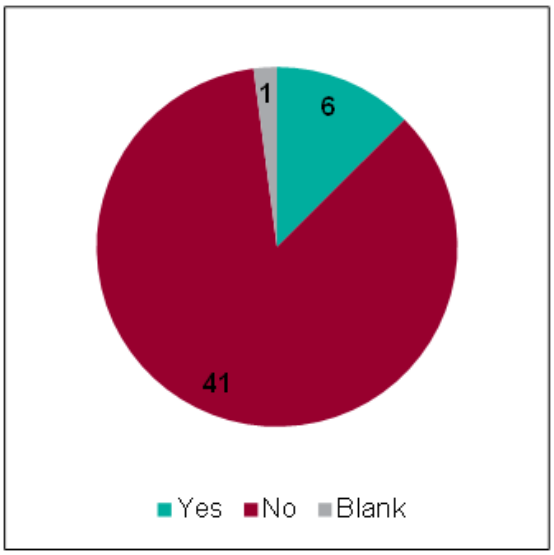
Figure 71: If yes, to whom is this advice given?

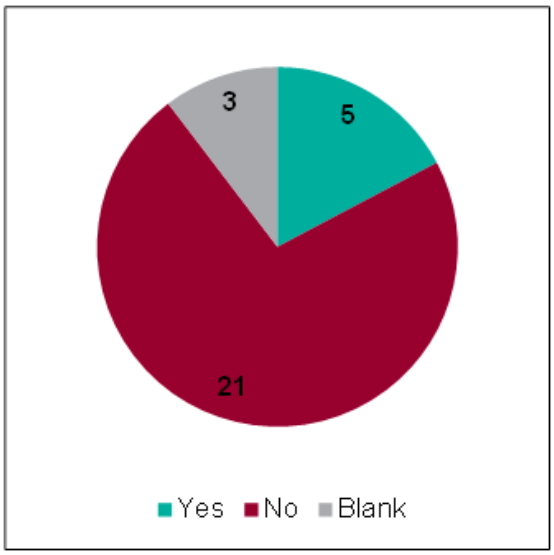




LSMDT (n = 13) *SSMDT (n = 8)*

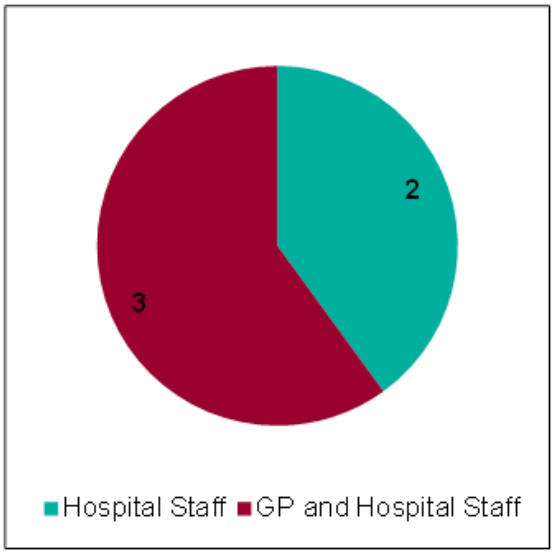
Figure 72: Are blood levels of vitamin D routinely measured in melanoma patients after diagnosis?





LSMDT (n = 48) *SSMDT (n = 29)*

Figure 73: If so, who measures blood levels?

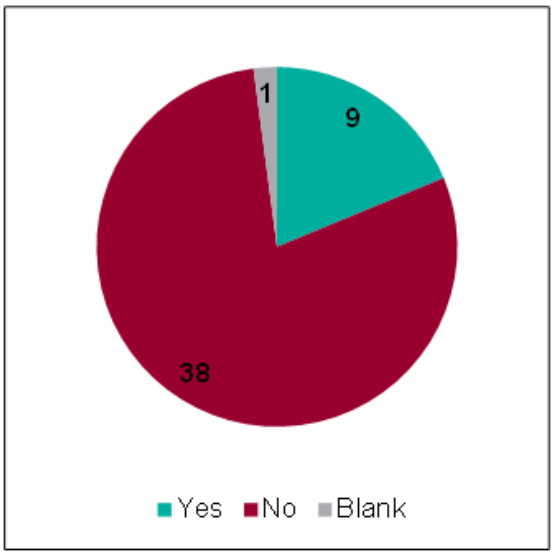


LSMDT (n = 6) *SSMDT (n = 5)*

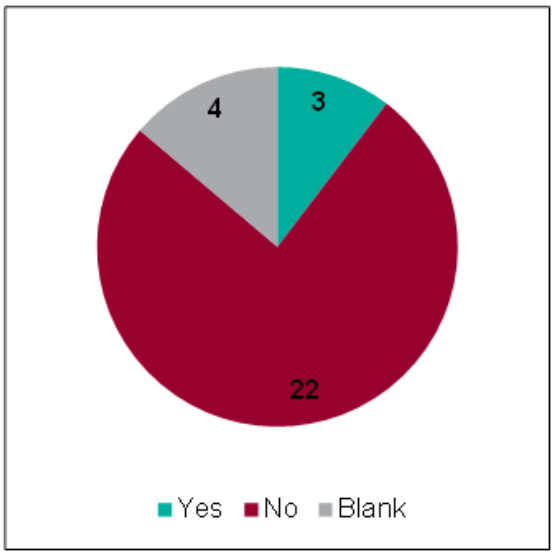
<u>What are the optimum blood levels suggested for melanoma patients?</u>

Both LSMDT and SSMDT responses were between 50 nmol/L and 100nmol/L; some of the SSMDT responses suggested allowance for season (e.g., Summer / Winter) and age in children.

Figure 74: Does the skin cancer MDT routinely recommend vitamin D supplements to melanoma patients?

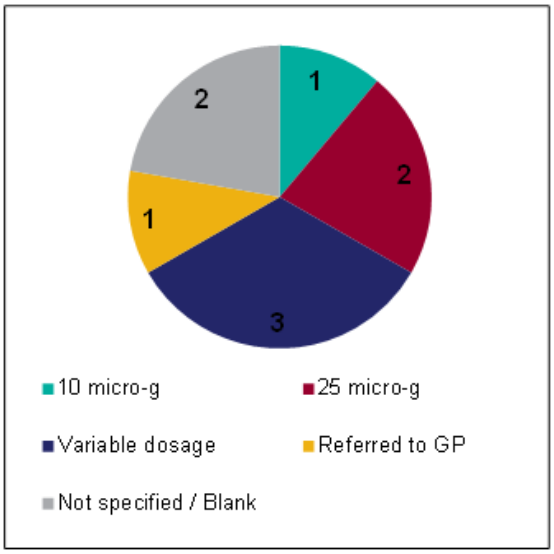


LSMDT (n = 48)

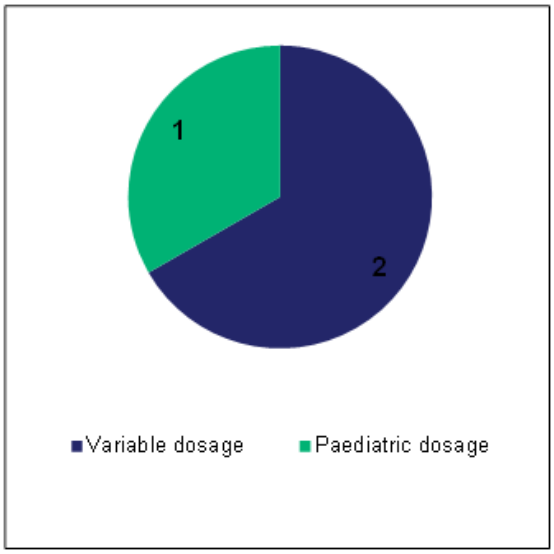


SSMDT (n = 29)

Figure 75: If supplements are recommended, what dosage of vitamin D is recommended per day?



LSMDT (n = 9)

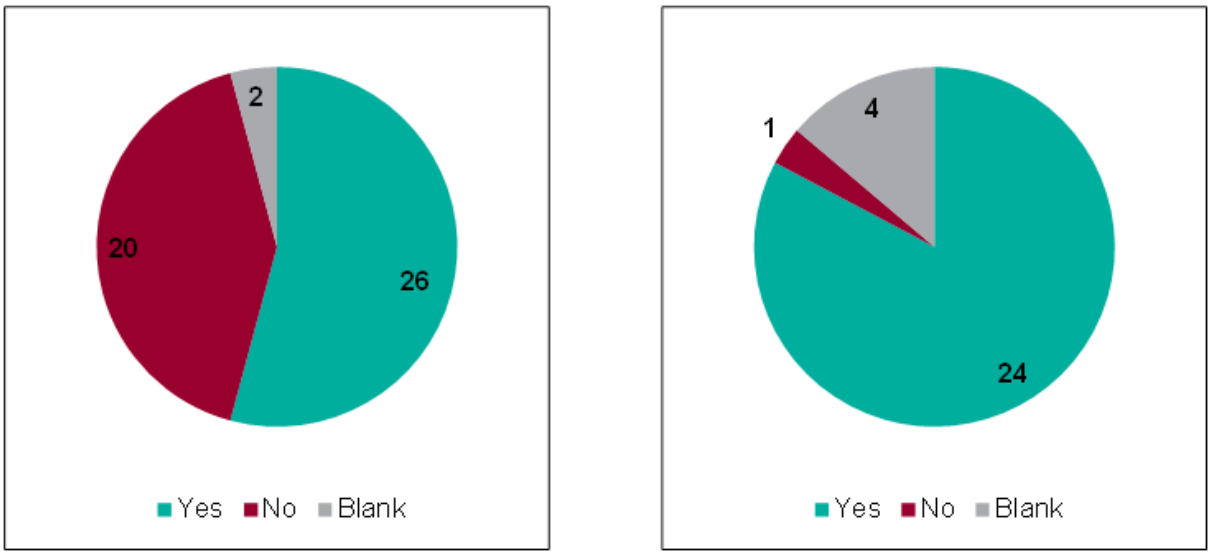


SSMDT (n = 3)

G.7.3 Genetic testing of melanoma samples

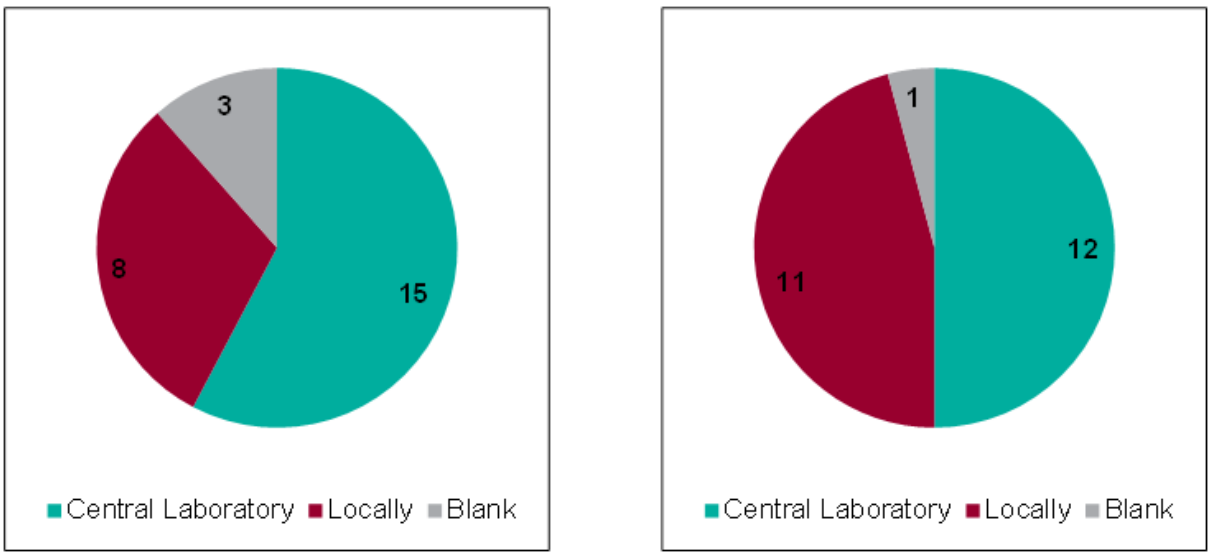
G.7.3.1 Over the past 2 years

Figure 76: Have you arranged testing of tumour blocks for BRAF mutations?



LSMDT (n = 48) *SSMDT (n = 29)*

Figure 77: If yes, where was the testing carried out?



LSMDT (n = 26) *SSMDT (n = 24)*

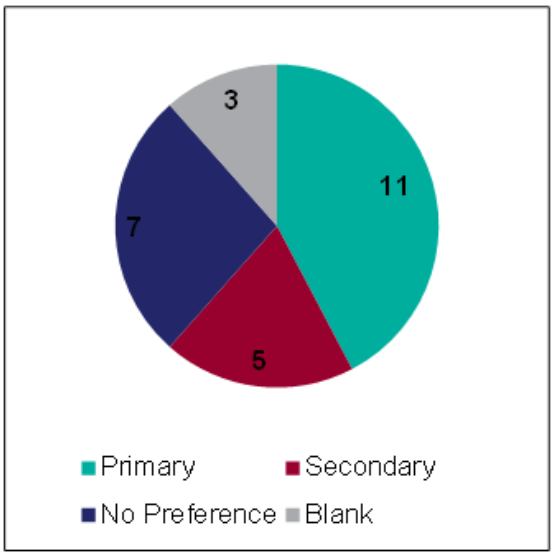
Central laboratories included: Birmingham, Manchester, Liverpool, Cardiff, Royal Surrey, Norfolk Centre for Pathology, Mount Vernon.

Table 38: Which stages of melanoma did you test?

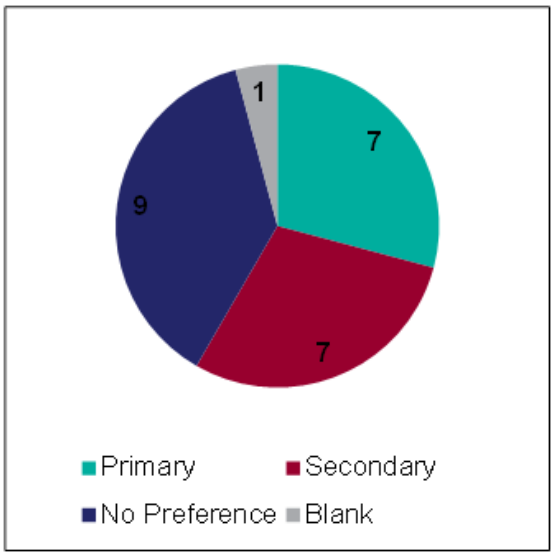
Stages	LSMDT (n = 26)	SSMDT (n = 24)
2a+	1	2
2b+	1	3
2c+	3	2
3a+	4	3

Stages	LSMDT (n = 26)	SSMDT (n = 24)
3b+		2
3c+		1
4	2	
All	2	1
Only melanomas in patients being considered for BRAF inhibitors	10	9
Blank	3	1

Figure 78: Was there a preference as to which melanoma tissue to test?

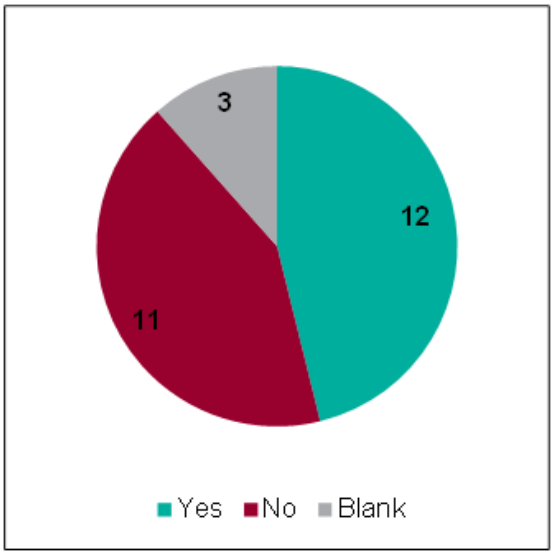


LSMDT (n = 26)

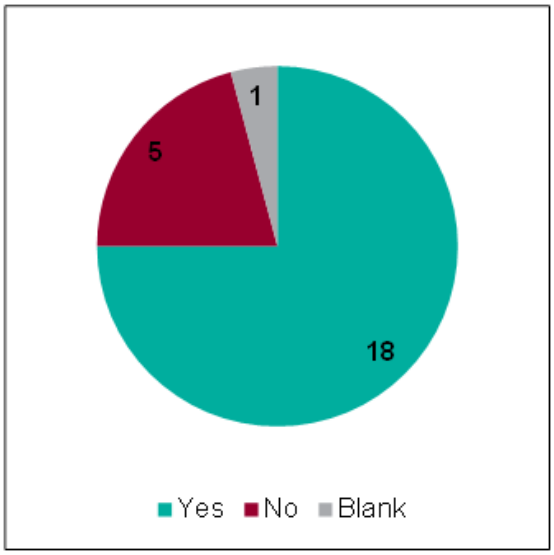


SSMDT (n = 24)

Figure 79: Did you use the Roche testing service?



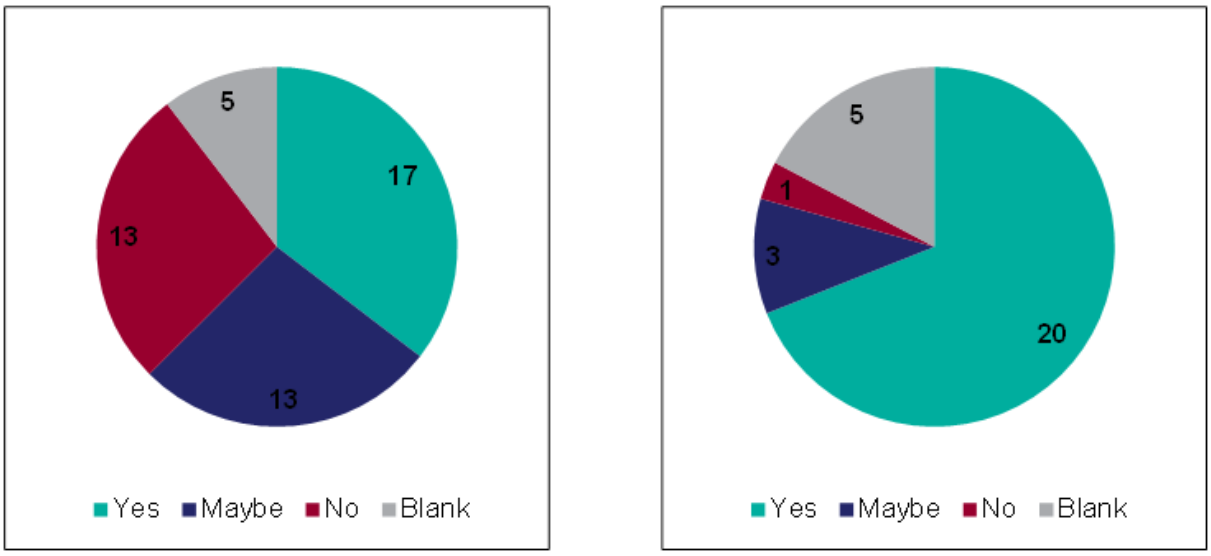
LSMDT (n = 26)



SSMDT (n = 24)

G.7.3.2 The MDT's genetic testing plans for the future

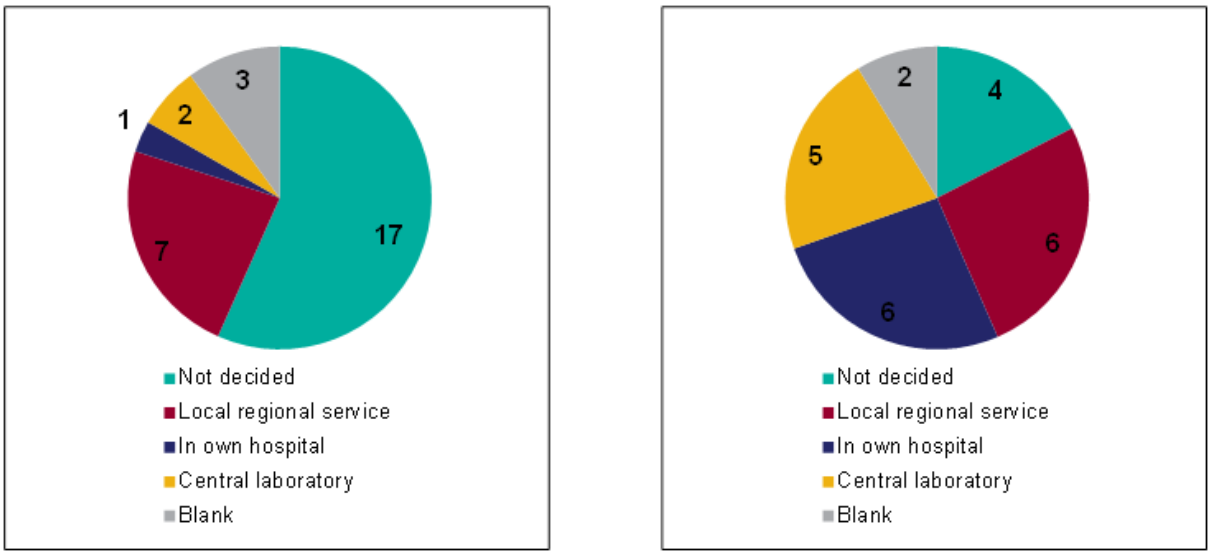
Figure 80: Will you test tumour blocks for BRAF mutations in the future?



LSMDT (n = 48) *SSMDT (n = 29)*

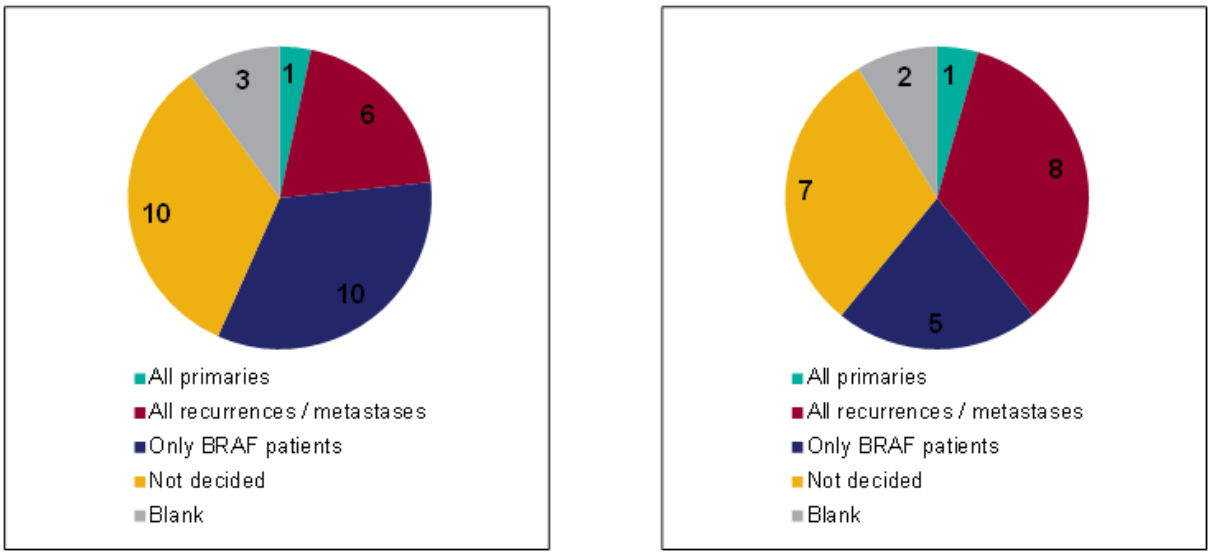
[Most of the LSMDTs that responded 'maybe' would refer their patients to the SSMDT or they said it would be dependent on NICE guidance and funding. All of the SSMDTs who responded 'maybe' were considering setting up their own service].

Figure 81: If yes or maybe, where would you send samples to be tested?



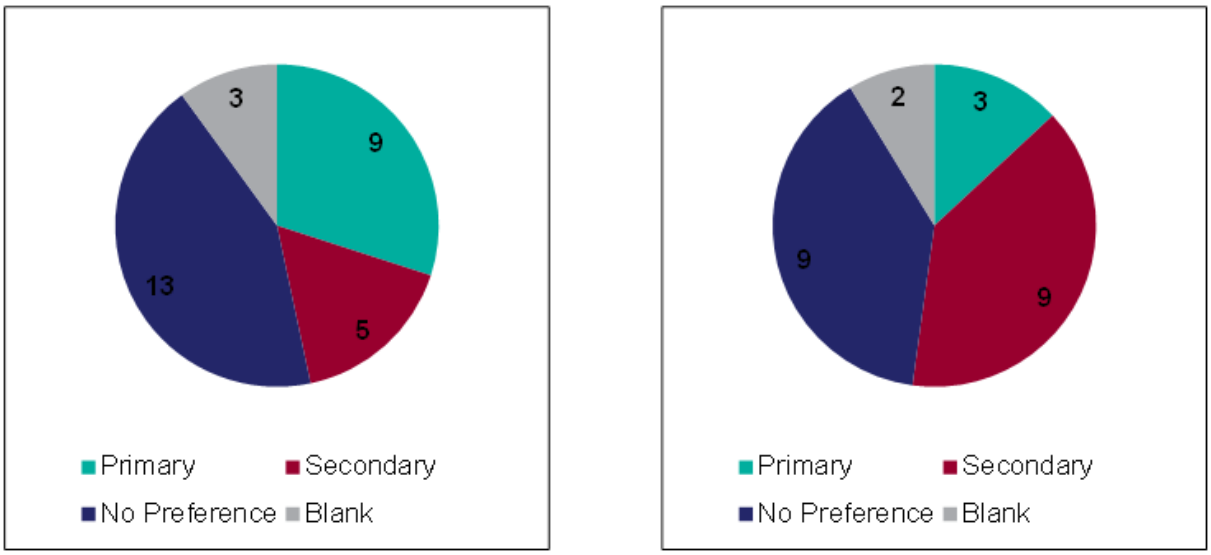
LSMDT (n = 30) *SSMDT (n = 23)*

Figure 82: Which melanomas do you plan to test?



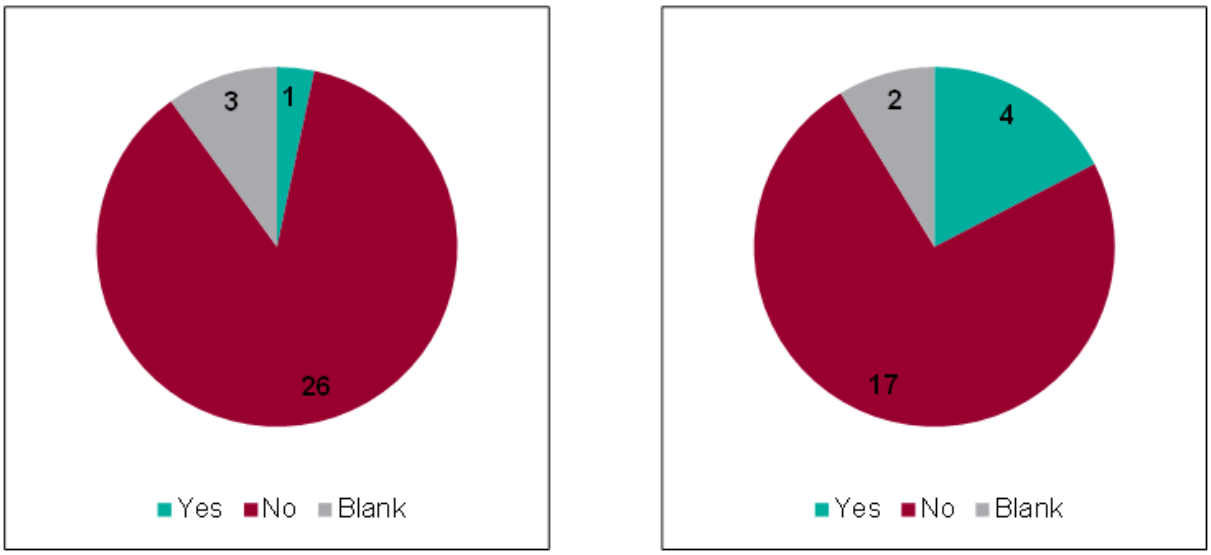
LSMDT (n = 30) *SSMDT (n = 23)*

Figure 83: Will there be a preference as to which melanoma tissue to test?



LSMDT (n = 30) *SSMDT (n = 23)*

Figure 84: Once the Roche testing service has finished, have you identified further funding for mutation testing?

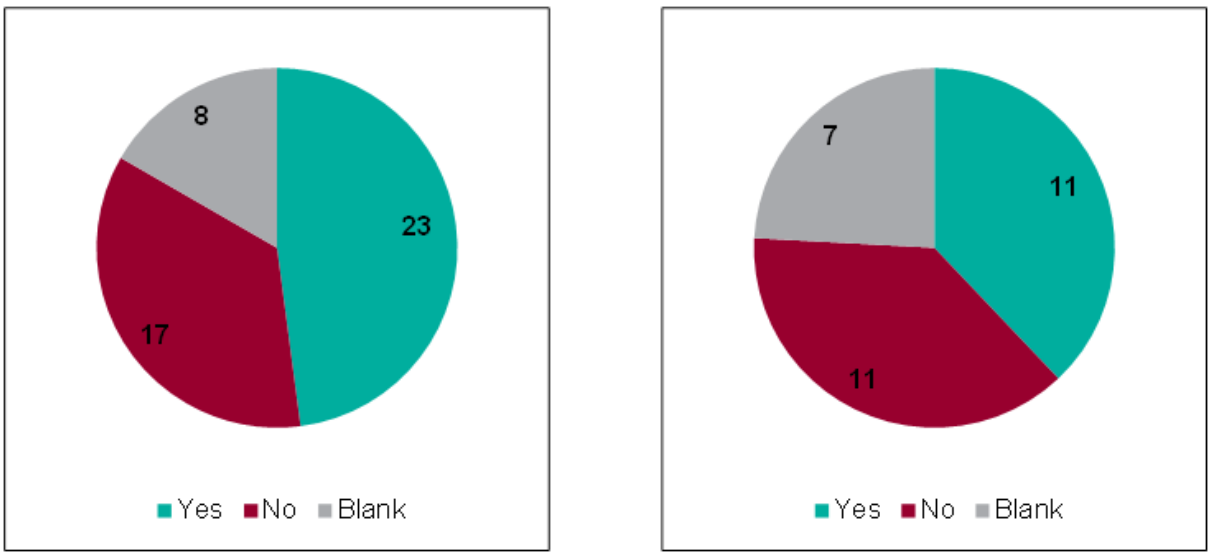


LSMDT (n = 30) *SSMDT (n = 23)*

[The one LSMDT that responded yes would continue to send samples to a tertiary centre; the three SSMDTs who responded yes would either set up testing in-house or had a budget plan in place with commissioners].

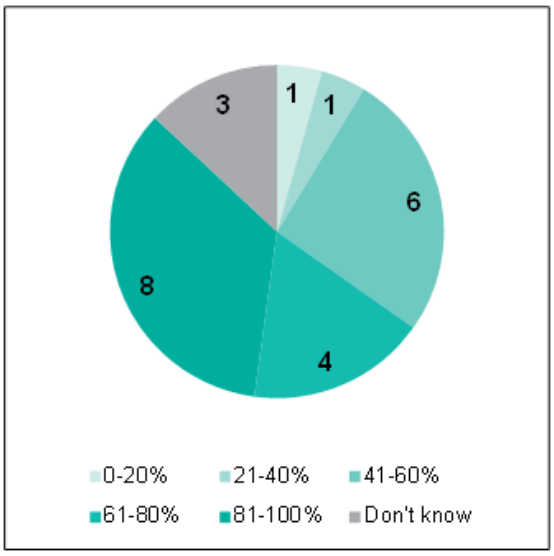
G.7.4 Sentinel lymph node biopsy

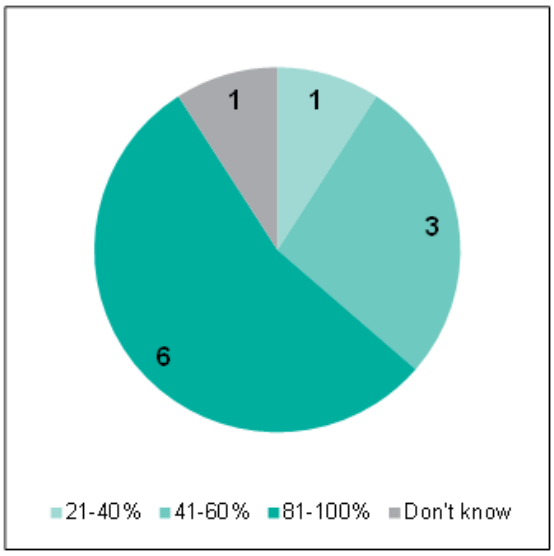
Figure 85: Do you offer sentinel lymph node biopsy (SLNB) within your MDT?



LSMDT (n = 48) *SSMDT (n = 29)*

Figure 86: If so, roughly what percentage of patients offered SLNB accept?

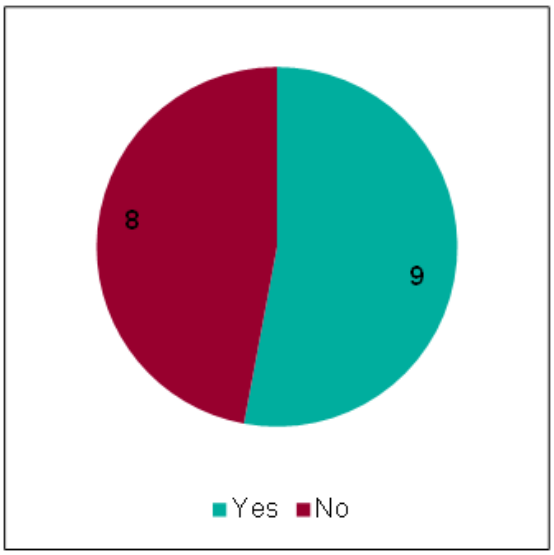


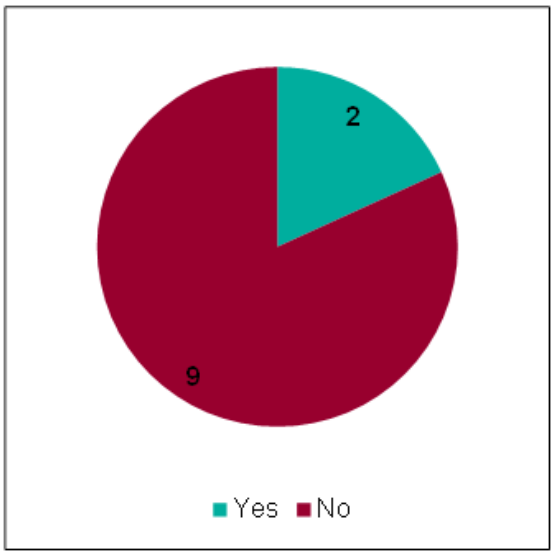


LSMDT (n = 23)

SSMDT (n = 11)

Figure 87: If you do not offer SLNB within your MDT, do you offer it via other MDTs?

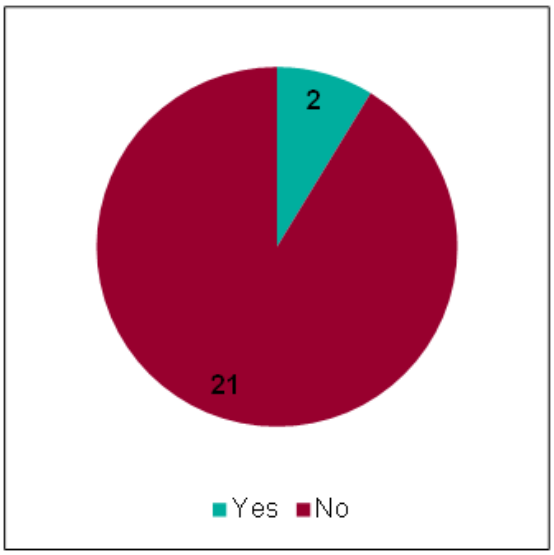




LSMDT (n = 17)

SSMDT (n = 11)

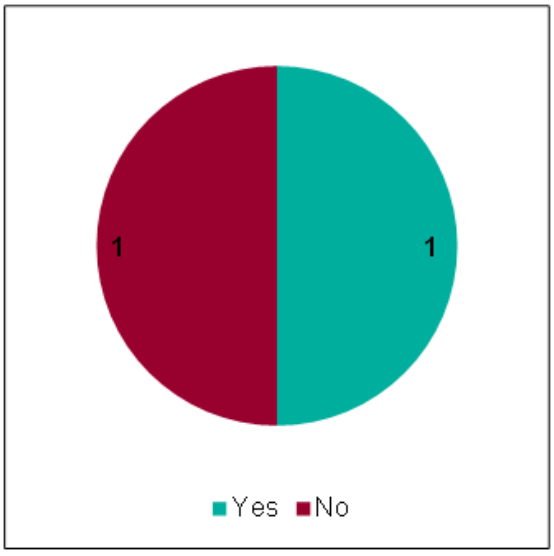
Figure 88: If you offer SLNB, have you surveyed your patients about their experiences of sentinel lymph node biopsy?



LSMDT (n = 23)

SSMDT (n = 11)

Figure 89: If yes, are you happy to give us sight of the data?

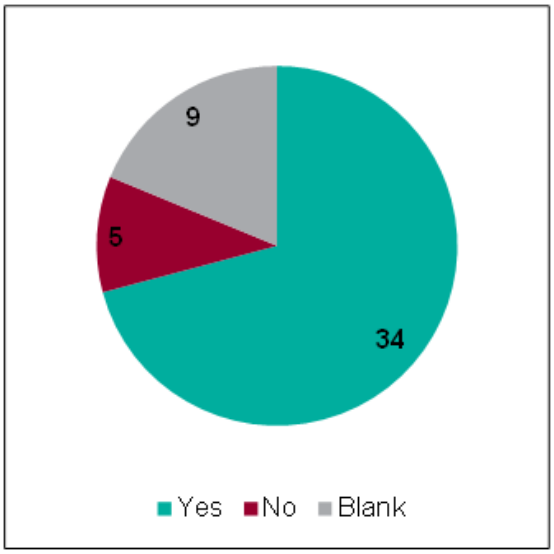


LSMDT (n = 2)

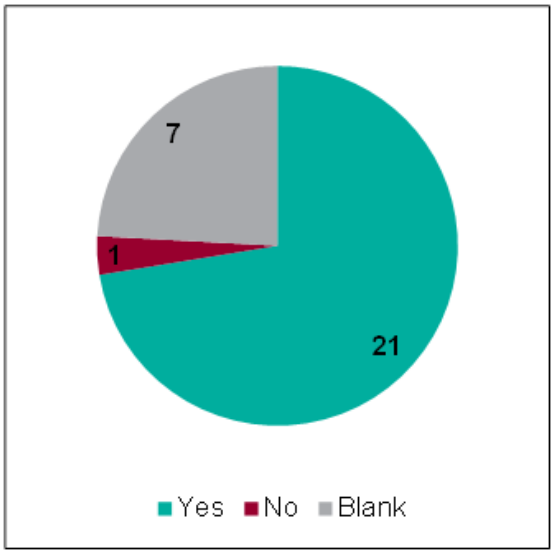
SSMDT (n = 1)

G.7.51 Photography

Figure 90: Do you use photography in the pigmented lesion clinic or skin cancer clinic to aid in early detection of change?

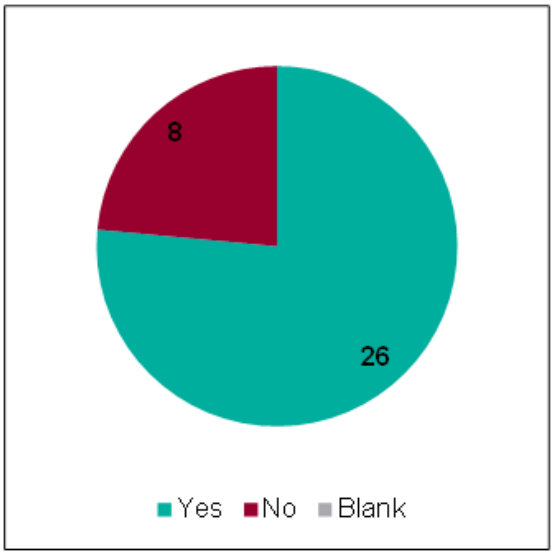


LSMDT (n = 48)

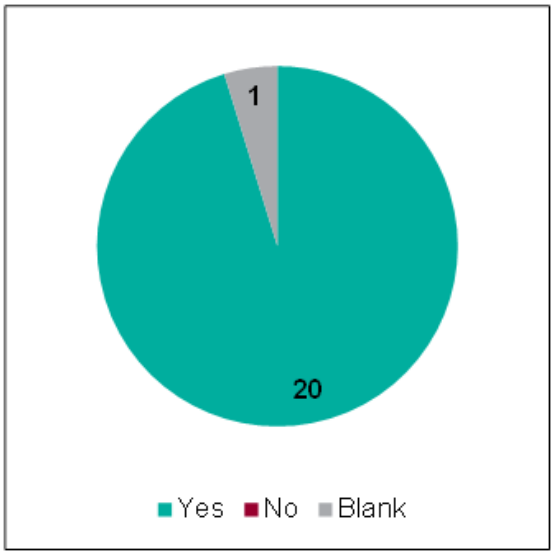


SSMDT (n = 29)

Figure 91: If yes, do you have a medical illustration department for photography in your hospital?

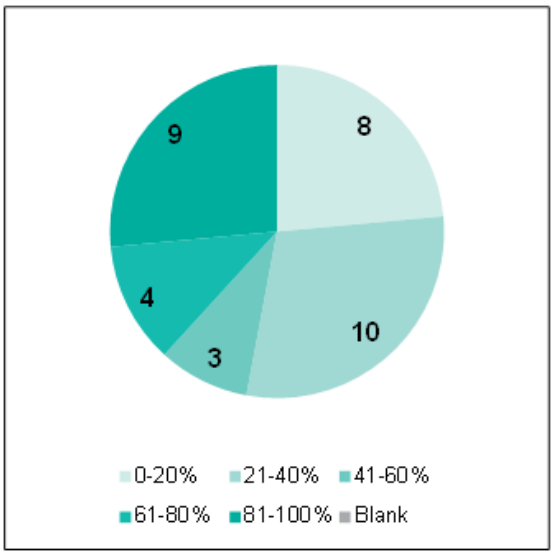


LSMDT (n = 34)

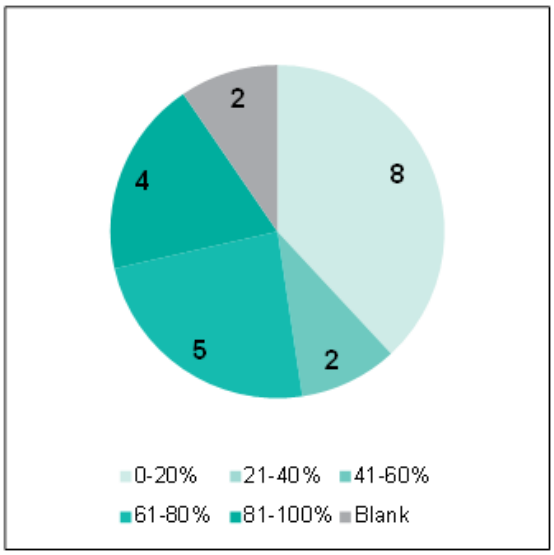


SSMDT (n = 21)

Figure 92: Could you estimate what percentage of patients with pigmented lesions who attend the clinic have photographs?

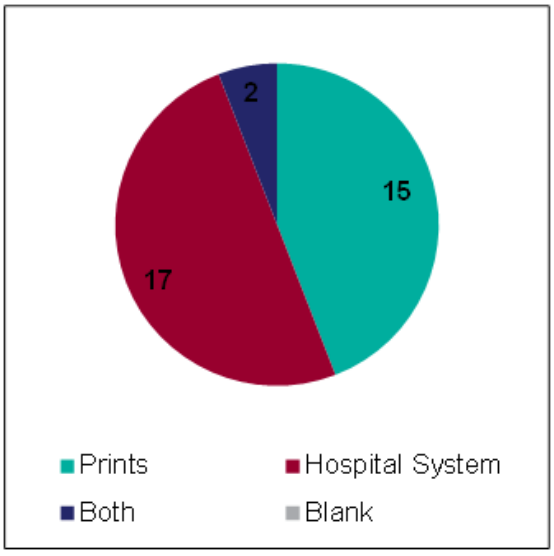


LSMDT (n = 34)

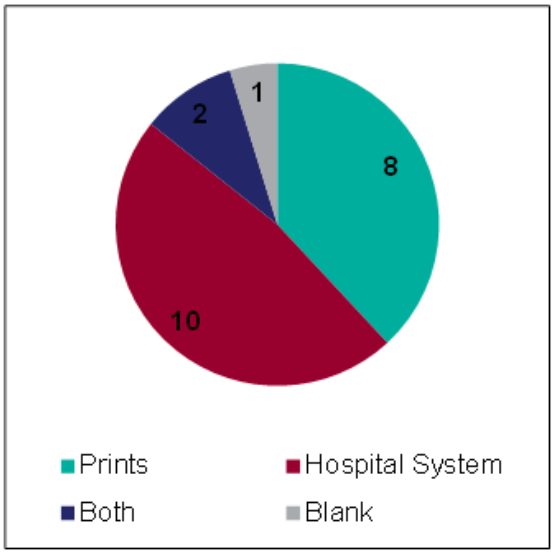


SSMDT (n = 21)

Figure 93: How do you access these photographs?

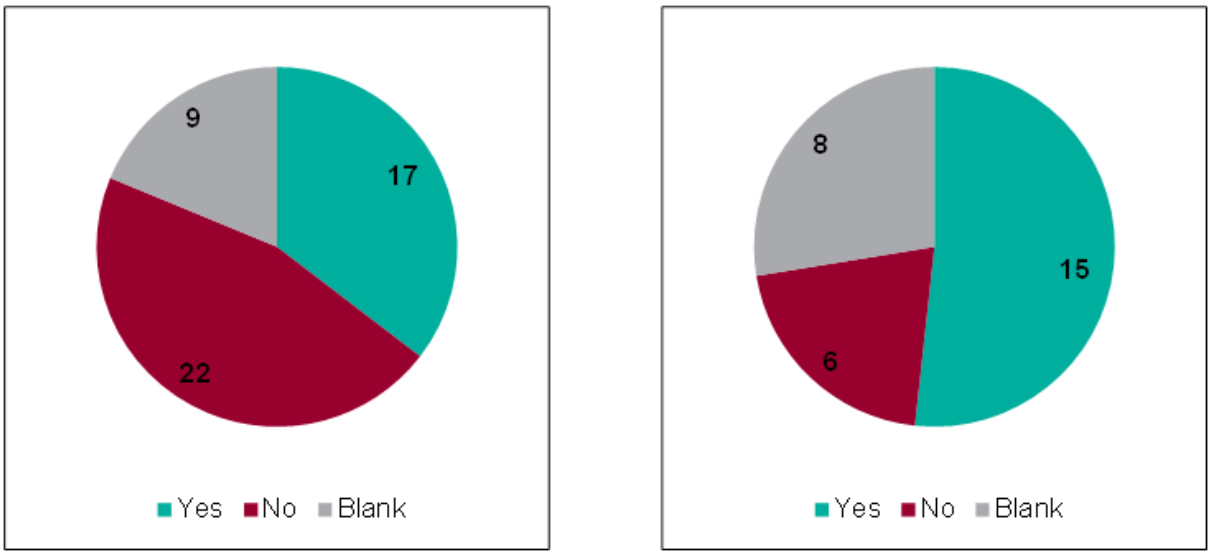


LSMDT (n = 34)



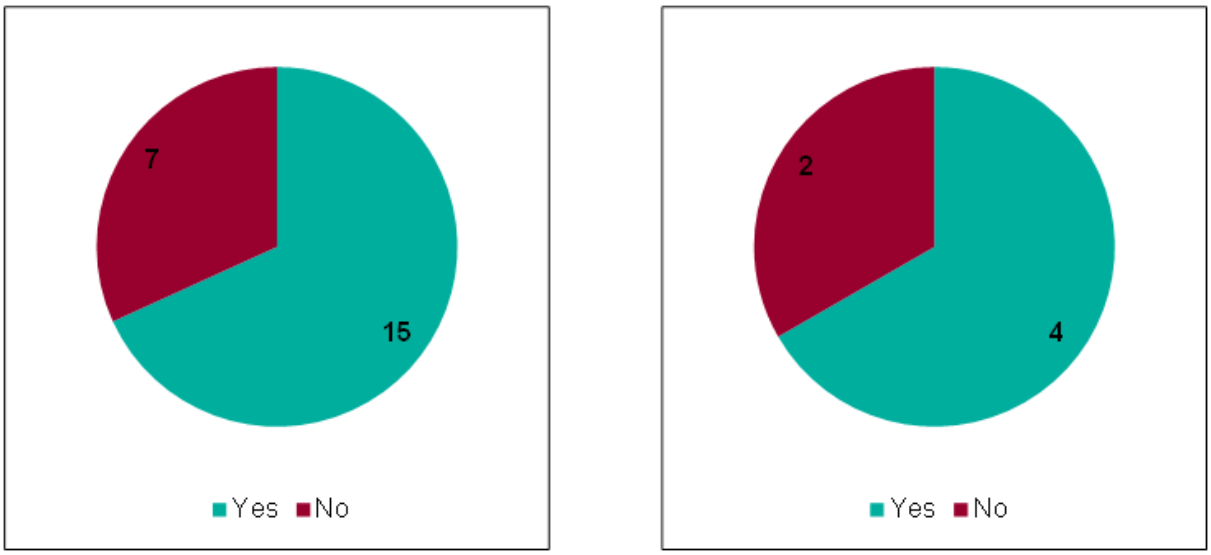
SSMDT (n = 21)

Figure 94: Do you have access to photography using a dermoscope?



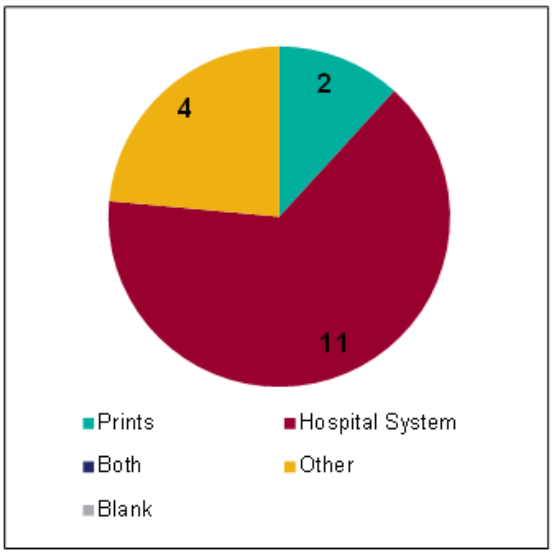
LSMDT (n = 48) *SSMDT (n = 29)*

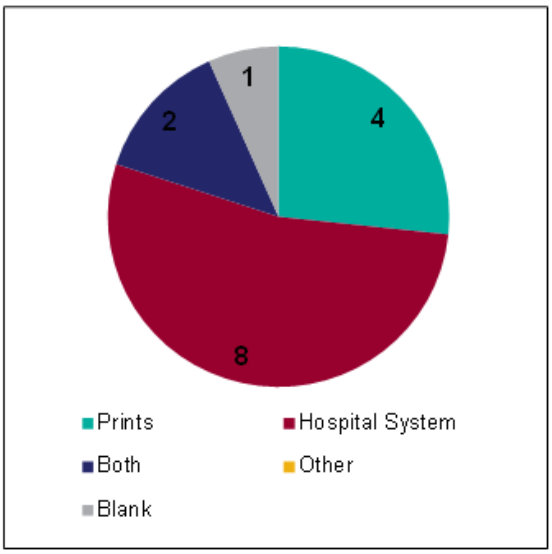
Figure 95: If not, would you like to take dermoscopic images?



LSMDT (n = 22) *SSMDT (n = 6)*

Figure 96: If yes, how are the dermoscopic images stored?

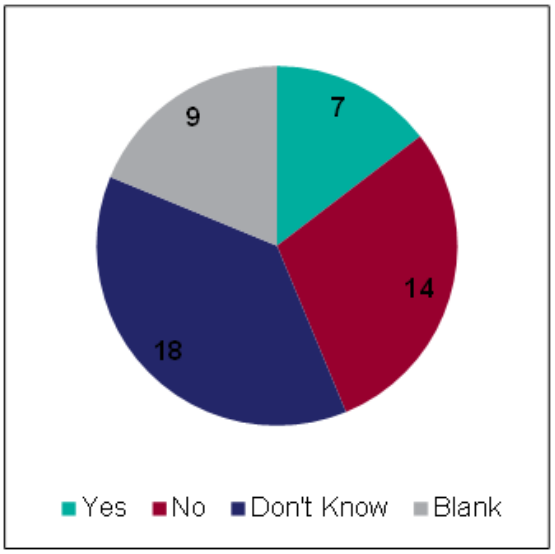


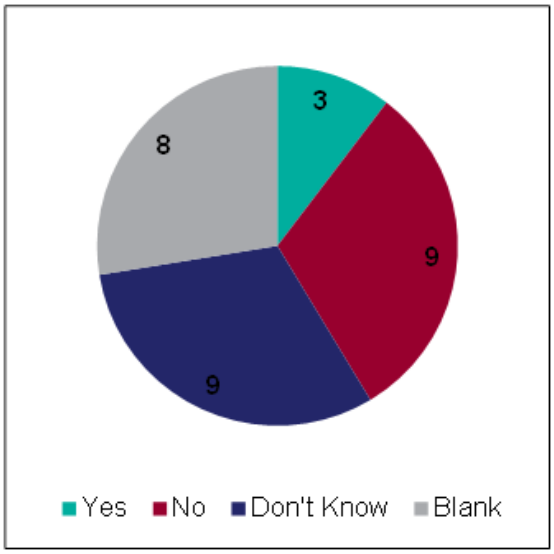


LSMDT (n = 17) *SSMDT (n = 15)*

G.7.6 Patient satisfaction

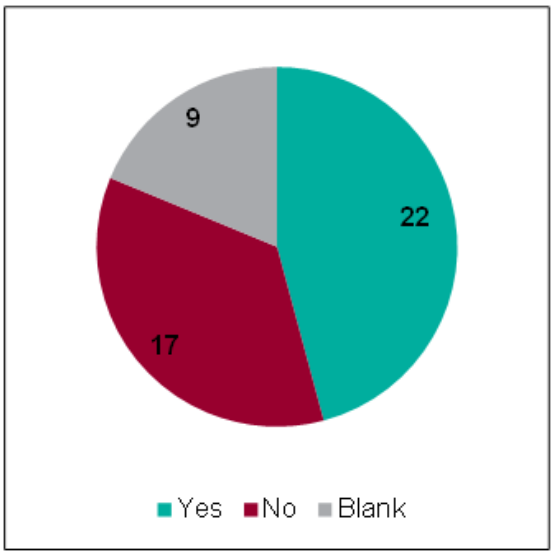
Figure 97: Do you consider the National Cancer Patient Experience Survey to be representative of your patients' experiences?

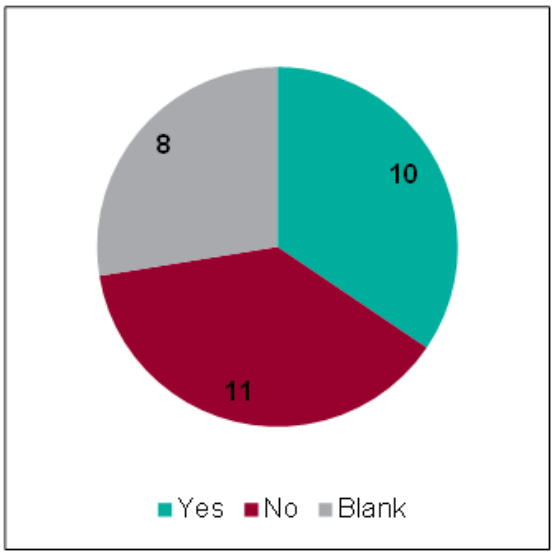




LSMDT (n = 48) *SSMDT (n = 29)*

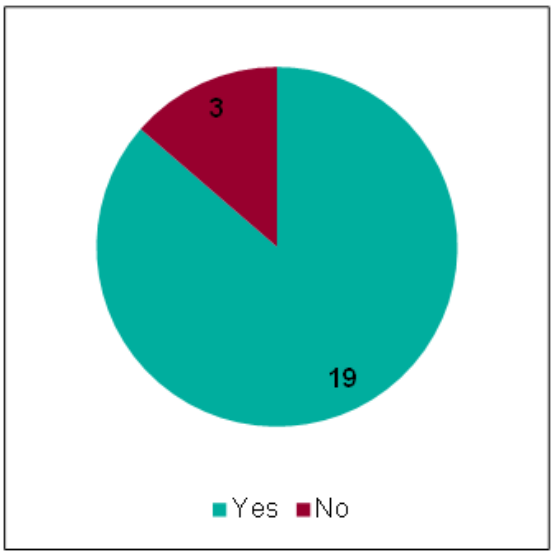
Figure 98: Have you designed and used your own survey for melanoma patients?

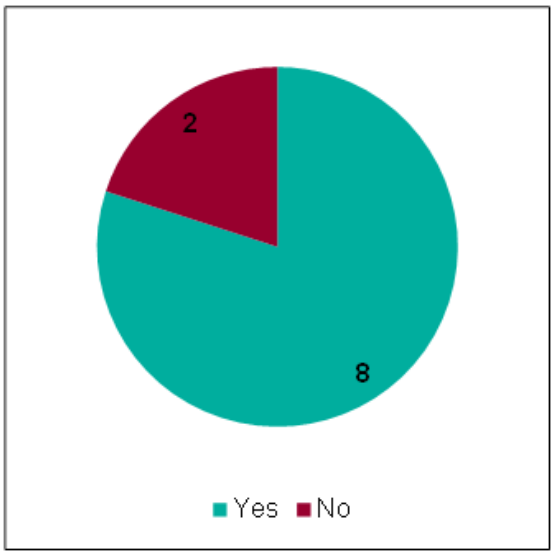




LSMDT (n = 48) *SSMDT (n = 29)*

Figure 99: If yes, would you be happy to provide us with the survey that you used?

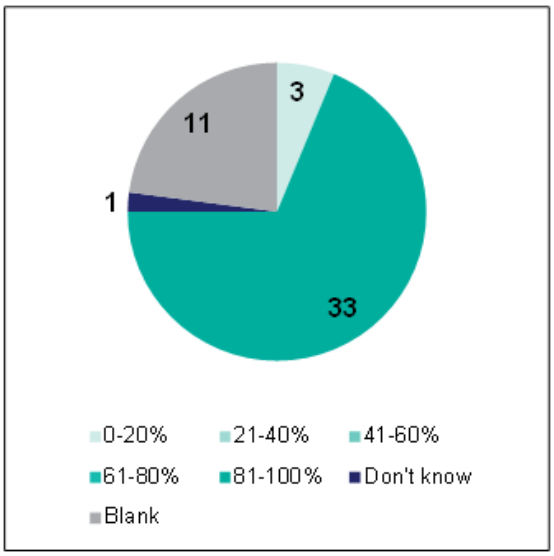




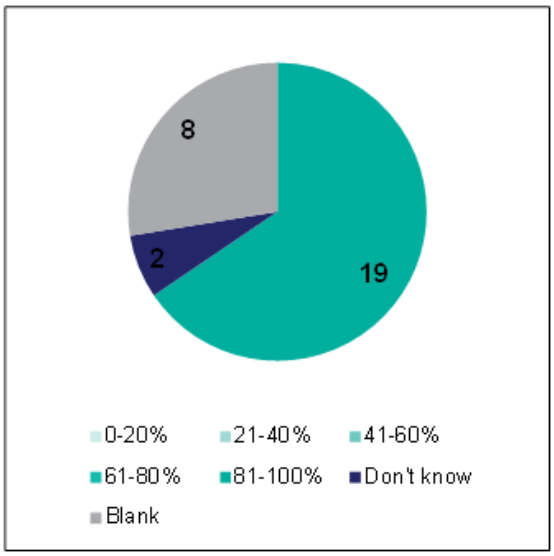
LSMDT (n = 22) *SSMDT (n = 10)*

G.7.71 Patient support

Figure 100: Roughly what percentage of the MDT's melanoma patients are given the name and contact details of a skin cancer clinical nurse specialist (CNS) at diagnosis?

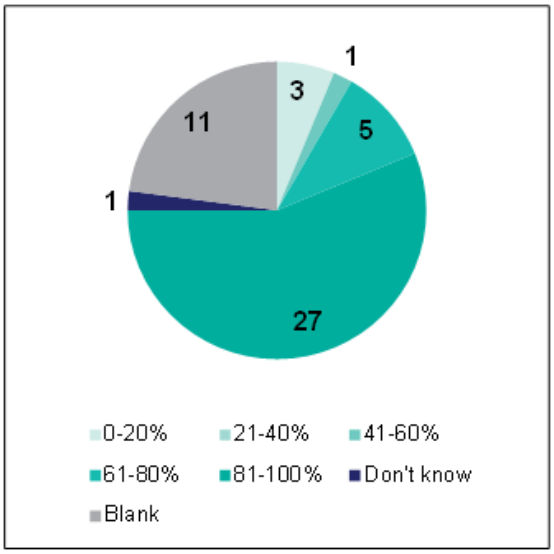


LSMDT (n = 48)

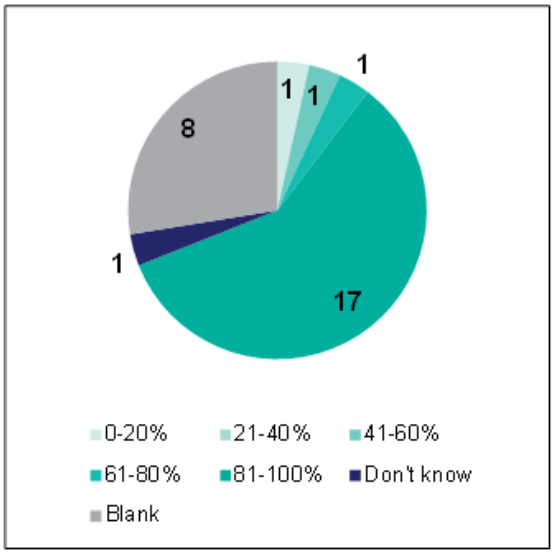


SSMDT (n = 29)

Figure 101: For roughly what percentage of MDT meetings is the skin cancer CNS present for the entire meeting?



LSMDT (n = 48)



SSMDT (n = 29)

Figure 102: What written information do you provide to patients?

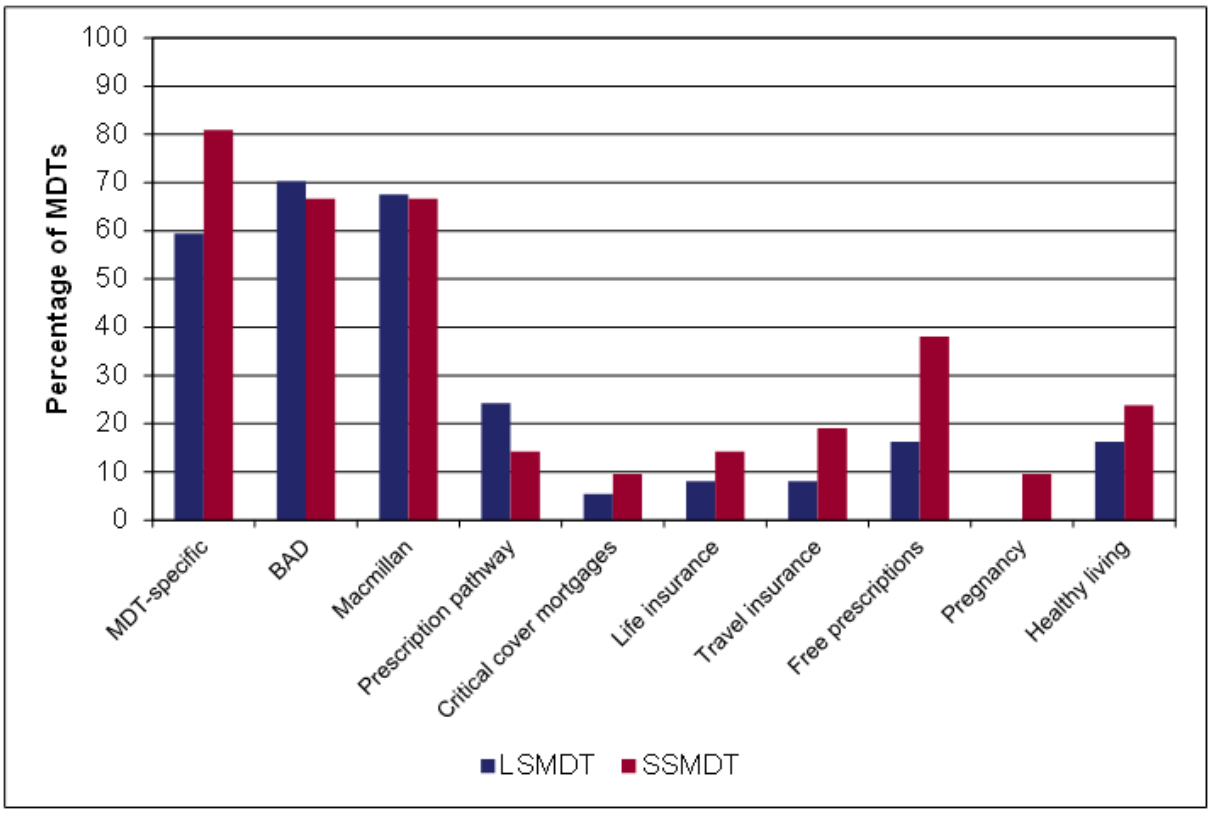
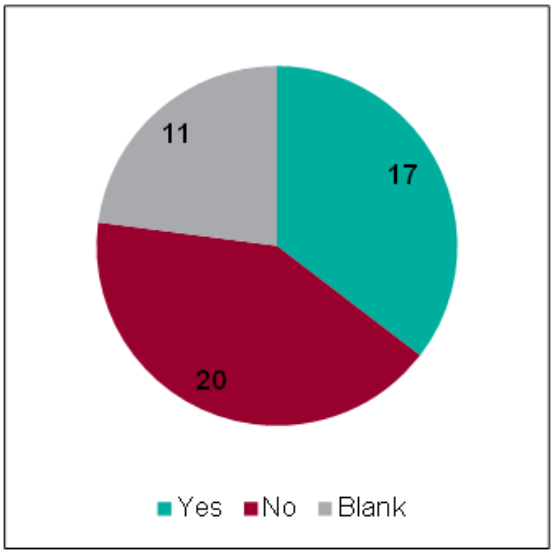
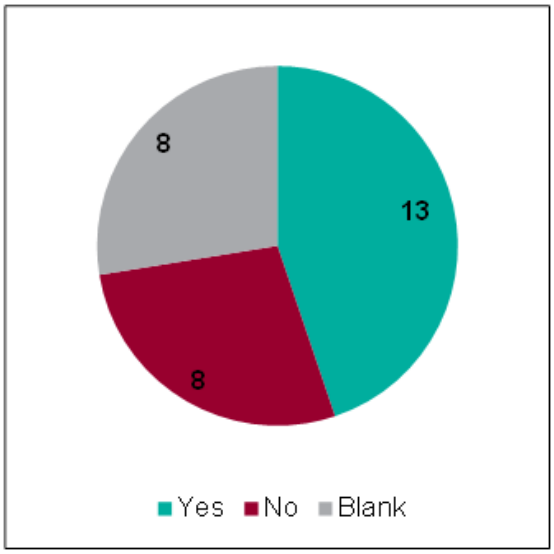


Figure 103: Do you give specific advice to melanoma patients about support groups?

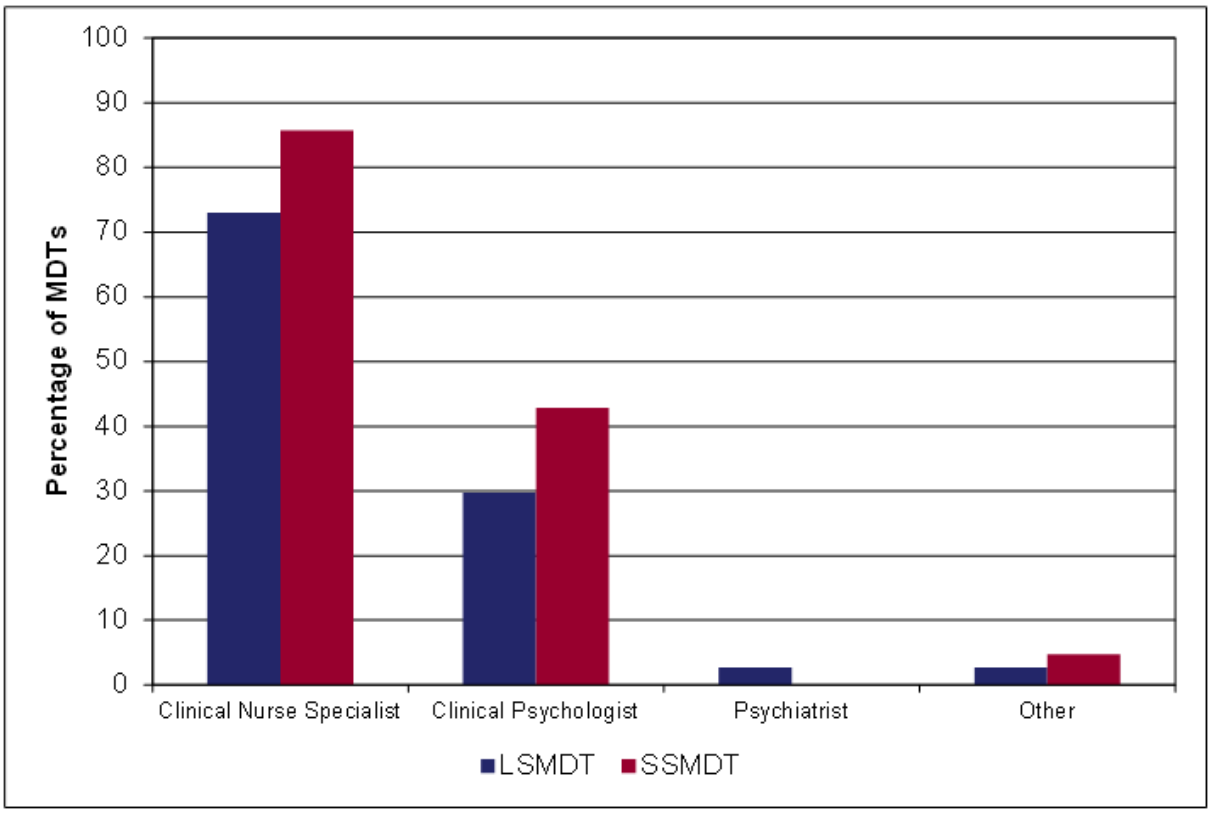


LSMDT (n = 48)



SSMDT (n = 29)

Figure 104: Do your patients have access to any of the following psychological support?



Note: Percentage of MDTs who provided any responses; 'No' was an option.

[Other information: Macmillan, Bacup, MASCOT, CRUK. Local support group, Rowan Tree, Ray of Light Wales, Julie Street, Tenovus, Caring Matters Now, International Melanoma Forum.]

G.7.88 Individual LSMDT responses

Is there any more information you wish to add with regard to how your skin cancer MDT supports / works with patients with melanoma?

- "Our local skin MDT has not had a dedicated skin CNS until July 2014. Therefore, all clinicians involved in the care of malignant melanoma patients have acted as their patients key worker and our details have been given to the patient. We have an ENT CNS who has supported the head and neck malignant melanoma patients who will continue in this role. Our patient satisfaction survey was not specific to patients with MM."
- "We do not have enough CNS hours to cope with the increase in cancer diagnosis year on year"
- "We try to track our patients who have been referred out of the trust for Plastics, Radiotherapy or Oncology treatment, as these are not provided by our Trust"
- "We use the BAD leaflets for melanoma - but we have had to alter them because they don't always fit with what we offer for sentinel node biopsy - which is decided by our MDT and also in line with our network guidelines."
- "We have not had a CNS in post but have just appointed so patients should get more support in future"
- "The support for our local skin cancer MDT is woefully inadequate from many perspectives including histopathology, clerical, clinical photography and much else. There just aren't the resources in the system to come anywhere near meeting the national guidelines."

- "We are an in house LSMDT, (mainly lower risk skin tumours but also share a SSMDT with XXXX which deals specifically with our melanomas and higher risk tumours (and provides SLNB service, ISLP topical chemo for satellite mets etc) both MDT's are via video link, as we have centralised/shared pathology services. We also have a separate lymphoma MDT. Paediatric/ and some TAYA's melanoma mostly go YYYY hospital."
- "We are a local MDT well supported by our Regional MDT at the XXXX. Our patients are seen across both sites with SLNB being performed and specialist oncology at the regional centre."
- "We have an excellent well attended MDT with committed members who ensure that the decisions made at MDT are followed in the clinic setting. We have a very multidisiplinary approach to their care."

G.7.9 Individual SSMDT responses

- "We do not have a CNS for melanoma but two other CNS who cover some of the work related to melanoma but not all aspects so my answers in relation to CNS support and presence at the MDT are based on not having a specific CNS for melanoma."
- "Telephone helpline. Flexible nurse led clinic for assessment/ advice. CNS attendance at dermatology, plastic surgery and oncology clinics. Consistent, targeted support available from diagnosis to end of life care"
- "Individual patients mostly get copies of clinic letters and are often copied into decisions made after MDT. Patients get copies of their own mole maps. Vitamin D and its importance is often discussed at diagnosis, but probably not routinely. Advice re how best to protect their skin from photodamage is always given and the importance of photoprotection to other members of the family often discussed"
- "We are asking our patients whether they would like us to set up a support group. We have just agreed to check Vitamin D levels and supplement where necessary. We are attempting to shorten the time to get BRAF testing. The CNS talks about prescriptions and life insurance queries"
- "The MDT is arranged as a parallel clinic, with dermatologists (x3), plastic surgeon (x2), medical oncologists (x2), clinical oncologist (x1), CNS (x1) and research nurses (pathology is also immediately available for FNA and reporting within 30 mins). This ensures patients are seen, can be walked around to appropriate clinics if needed and so have a comprehensive treatment plan for just one clinic visit. Information relevant for their situation is then provided: surgery, radiotherapy, travel insurance etc, rather than a blanket bundle of information some of which is irrelevant."

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2 68, 113-120.