Melanoma

Consultation on draft guideline
Stakeholder comments table

30/01/15 to 13/03/15

Comments forms with attachments such as research articles, letters or leaflets cannot be accepted.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
211	Alder Hey Children's NHS Foundation Trust	General	General	General	Specific issues relating to both Children and the Teenage and Young Adult population are not well covered. In particular – what support is required for these groups. What is the role of the TYA and Paediatric Treatment and Diagnosis MDTs and how do they interact with the Melanoma MDT – this is very important.	Thank you for your comment. These services issues are covered by the NICE guidance on 'Improving outcomes for people with skin tumours including melanoma' and cancer standards
42	Association for Palliative Medicine of Great Britain & Ireland	General	General	General	There is little or no mention of palliative care in this draft guideline, yet many patients with melanoma are referred to specialist palliative care services with significant symptom burden. It is alluded to in some of the sections wen research is looked at comparing a treatment with best supportive care. We feel it should be made explicit that specialist palliative care can be beneficial to patients and is likely to be cost effective	Thank you for your comment. Palliative care was already covered by the NICE guidance on 'Improving outcomes for people with skin tumours including melanoma' so was not considered a priority for investigation in this guideline.
105	Bristol-Myers Squibb Pharmaceuticals Ltd	Full	27	3	In line with comments number 1-3 above, please amend textboxes to **BRAF positive** • Ipilimumab - only if the manufacturer provides this drug with the discount agreed in the patients access scheme • Vemurafenib or dabrafenib - only if the manufacturer provides this drug with the discount agreed in the patients access scheme • Consider dacarbazine* if immunotherapy or targeted therapy are not suitable **BRAF negative**	Thank you for your comments. All of these agents (with the exception of dacarbazine) are the subject of NICE technology appraisals. The GDG were therefore limited in what aspects of the care pathway they could investigate. Specifically we were unable to rank treatments or suggest a care pathway. The recommendations have been re-ordered in a way that we believe is more logical. We have also changed the algorithm to be consistent with the recommendations made in the guideline.

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					• Ipilimumab - only if the manufacturer provides this drug with the discount agreed in the patients access scheme • Consider dacarbazine* if immunotherapy or targeted therapy are not suitable	
106	Bristol-Myers Squibb Pharmaceuticals Ltd	Full	27	4	Typo. Please correct to "*Do not offer further chemotherapy to people previously treated with dacarbazine except in the context of a clinical **trial**."	Thank you. The typo has been corrected.
107	Bristol-Myers Squibb Pharmaceuticals Ltd	Full	193	General	In line with comments number 1-3 above, please amend recommendations to: **BRAF positive:** **Ipilimumab** For adults, ipilimumab[1] is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who are previously untreated or have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme'. [This recommendation is from NICE's technology appraisal guidances on 'ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma' and 'ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'.] **Vemurafenib** For adults, 'Vemurafenib is recommended as an option for treating BRAF V600 mutation-positive unresectable or metastatic melanoma only if the manufacturer provides vemurafenib with the discount agreed in the patient access scheme'. [This recommendation is from the NICE's technology appraisal guidance on vemurafenib for treating locally advanced or metastatic BRAF V600 mutation-positive	Thank you for your comment. The NICE process for linking to other NICE guidance is documented in section 8.1 of 'Developing NICE guidelines: the manual' (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). This accounts for the differences in presentation that you describe. Because all of these agents (except dacarbazine) are the subject of published or on-going NICE technology appraisals, the GDG were limited in what aspects of the care pathway they could investigate. The recommendations have been re-ordered in a way that we believe is more logical.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					malignant melanoma.] **Dabrafenib** Dabrafenib is recommended as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company provides dabrafenib with the discount agreed in the patient access scheme. [This recommendation is from NICE's technology appraisal guidance on dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.] **Dacarbazine** Consider dacarbazine for people with stage 4 metastatic melanoma if immunotherapy or targeted therapy are not suitable. Do not offer further cytotoxic chemotherapy for stage 4 metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial. **BRAF negative:** **Ipilimumab** For adults, ipilimumab[1] is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who are previously untreated or have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme'. [This recommendation is from NICE's technology appraisal guidances on 'ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma' and 'ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'.] **Dacarbazine** Consider dacarbazine for people with stage 4 metastatic	

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					melanoma if immunotherapy or targeted therapy are not suitable. Do not offer further cytotoxic chemotherapy for stage 4 metastatic melanoma to people previously treated with dacarbazine except in the context of a clinical trial.	
102	Bristol-Myers Squibb Pharmaceuticals Ltd	Full NICE	193 21	General	(p21-22) For clarity we suggest to divide the systemic treatments section into a section for 'BRAF positive' and one for BRAF negative' options to be in line with the flowchart of 'Management of stage 4 melanoma' (see full draft guideline, page 27). We further propose to rank the 'systemic anticancer therapy for unresectable or metastatic melanoma' in the following logical order (our additional annotations are in grey below): **BRAF positive** 1. Ipilimumab ○ [as recommended as an option for previously untreated and treated patients, irrespective of BRAF mutation status] 2. Vemurafenib or dabrafenib ○ [restricted to patients testing positive for the BRAF mutation (no preference as to which one should be listed first)] 3. Dacarbazine ○ [recommended only if immunotherapy or targeted therapy are not suitable] **BRAF negative** 1. Ipilimumab ○ [as recommended as an option for previously untreated and treated patients, irrespective of BRAF mutation status] 2. Dacarbazine ○ [recommended only if immunotherapy or targeted therapy are not suitable]	Thank you for your comments. Because all of these agents except dacarbazine are the subject of on-going or published NICE technology appraisals, the GDG were limited in what aspects of the care pathway they could investigate. Specifically they were unable to rank treatments. The recommendations have been re-ordered in a way that we believe is more logical. We have also changed the algorithm to be consistent with the recommendations made in the guideline.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
103	Bristol-Myers Squibb Pharmaceuticals Ltd	FULL NICE	193 21	General	On pages 21-22 the draft NICE guideline states: ***Ipilimumab*** *1.8.8 For adults, 'Ipilimumab is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme'. [This recommendation is from NICE's technology appraisal guidance on ipilimumab for previously treated advanced (unresectable or metastatic) melanoma.]* *1.8.9 Refer to NICE's technology appraisal guidance on ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma for adults.* We suggest replacing this section by the following to improve logic, clarity and consistency: **Ipilimumab** 1.8.? For adults, ipilimumab[1] is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who are previously untreated or have received prior therapy, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme'. [This recommendation is from NICE's technology appraisal guidances on 'ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma' and 'ipilimumab for previously treated advanced (unresectable or metastatic) melanoma'.] Alternatively, in case a separation as per NICE TA guidance is required, replace as follows:	Thank you for your comment. The NICE process for linking to other NICE guidance is documented in section 8.1 of 'Developing NICE guidelines: the manual' (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). This accounts for the differences in presentation that you describe.

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					Ipilimumab 1.8.? 'Ipilimumab[1] is recommended as an option for treating adults with **previously untreated** advanced (unresectable or metastatic) melanoma, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme'. [This recommendation is from NICE's technology appraisal guidance on ipilimumab for previously untreated advanced (unresectable or metastatic) melanoma.] 1.8.? For adults, 'ipilimumab[1] is recommended as an option for treating advanced (unresectable or metastatic) melanoma in people who have **received prior therapy**, only if the manufacturer provides ipilimumab with the discount agreed in the patient access scheme'. [This recommendation is from NICE's technology appraisal guidance on ipilimumab for previously treated advanced (unresectable or metastatic) melanoma.] [1] Ipilimumab has a UK marketing authorisation 'for the treatment of advanced (unresectable or metastatic) melanoma in adults'.	
104	Bristol-Myers Squibb Pharmaceuticals Ltd	FULL NICE	193 21	General	On page 21 the draft NICE guideline states: ***Dabrafenib*** *1.8.5 Refer to NICE's technology appraisal guidance on dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma for adults.* We suggest replacing this section by the following to improve clarity and consistency: **Dabrafenib** 1.8.? Dabrafenib[2] is recommended as an option for treating unresectable or metastatic BRAF V600 mutation-positive melanoma only if the company	Thank you for your comment. The NICE process for linking to other NICE guidance is documented in section 8.1 of 'Developing NICE guidelines: the manual' (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). This accounts for the differences in presentation that you describe.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					provides dabrafenib with the discount agreed in the patient access scheme. [This recommendation is from NICE's technology appraisal guidance on dabrafenib for treating unresectable or metastatic BRAF V600 mutation-positive melanoma.] [2] Dabrafenib has a marketing authorisation in the UK in monotherapy for the treatment of adult patients with unresectable or metastatic melanoma with a BRAF V600 mutation.	
108	Bristol-Myers Squibb Pharmaceuticals Ltd	Full	209	22-26	On page 209 the draft guideline states: *"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. 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."* It is not reasonable to assume that vemurafenib results in same survival advantage as ipilimumab. Published clinical evidence and reported experience show that ipilimumab is the only current option to offer potential long-term survival for melanoma patients (Schadendorf et al. 2015) while BRAF inhibitors, such as vemurafenib, are associated with rapid but short-term benefit (Jang et al. 2013). The latest data cut from the BRIM-3 trial shows that the Kaplan-Meier curves cross between 25 and 30 months, indicating that there is no OS benefit of vemurafenib over DTIC in the long-term (Hausschild et al. 2013). Based on the above, we strongly advise to critically review and revise survival assumptions for vemurafenib. Full citation of mentioned references:	Thank you for your comments. Survival data for vemurafenib has been updated accordingly and included in the revised economic model. However this has not affected the conclusions from the model.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					• Hauschild A, McArthur G, Robert C, et al. Vemurafenib Improves Overall Survival Compared With Dacarbazine in Advanced BRAF V600-Mutated Melanoma: Updated Results From a Phase 3 Randomized, Multicenter Trial. 10th International Meeting of the Society for Melanoma Research;Philadelphia, US. November 17-20, 2013. Poster. • Jang S and Atkins MB. Which drug, and when, for patients with BRAF-mutant melanoma? The Lancet Oncology. 2013; 14(2):e60-e9. • Schadendorf et al. Pooled Analysis of Long-Term Survival Data From Phase II and Phase III Trials of Ipilimumab in Unresectable or Metastatic Melanoma JCO 2015 - Published Ahead of Print on February 9, 2015 as 10.1200/JCO.2014.56.273	
109	Bristol-Myers Squibb Pharmaceuticals Ltd	Full	209	34-38	On page 209 the draft guideline states: *"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."* Given treatment costs of ipilimumab are finite based on 4 doses whereas vemurafenib treatment continues until progression, the assumption that ipilimumab and vemurafenib result in identical costs is inappropriate. As published guidance is available for vemurafenib (NICE TA269, 2012) and for ipilimumab* in the first line setting (NICE TA319, 2014), we strongly advise to extract cost estimates from these more recent appraisals and to revise the model calculations accordingly. *This includes the comparison versus vemurafenib in a first-line setting.	Thank you for your comment. Costs for vemurafenib have been updated accordingly using more recent evidence. The results of the economic model have also been updated but this has not affected the conclusions.
182	British Association of Dermatologists	Full	General		Management of melanoma in special situations such as pregnancy, and recommendations for genetic screening in patients with family history of melanoma seems to have been missed.	Thank for your comment. We agree that these topics are of interest and cause concern but they were not raised during consultation on the guideline scope and therefore were not prioritised for inclusion

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						in the guideline.
167	British Association of Dermatologists	Full	6		Dermoscopy – diagnosis and follow-up: Please see the "Comments on implementation" below.	Thank you for your comments. This is a copy of the response to your comments on dermoscopy. The GDG recognised the importance of training in its recommendation on dermoscopy. The quality of evidence reported to support its use was considered to be good. Frequency of imaging has now been included in this recommendation, based on the clinical experience of the GDG. The GDG acknowledge that practice variation may result from the recommendation but because of uncertainty in the evidence they were unable to make a strong recommendation in favour of a specific imaging policy. The recommendation leaves the final decision to the SSMDT, if funding is identified or it is available as part of a clinical trial. The GDG felt that the evidence supporting the use of photography was sufficient to make this recommendation. Dermoscopy imaging can be performed by any medical illustration department with an adapted dermoscope. As the NHS moves to digital records then these images can be provided in the clinic digitally and the GDG felt it important that this recommendation is implemented.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						The use of dermoscopy increases diagnostic accuracy and this is supported by the data. Using dermoscopic images increases the quality of photography and therefore clinical utility. The GDG therefore made the recommendation in order to both reduce the likelihood of delayed diagnosis of melanoma and reduce unnecessary surgery. The role of self assessment in monitoring naevi is outside the scope of the guideline which is about the management of suspected and diagnosed melanoma.
168	British Association of Dermatologists	Full	7		Sentinel lymph node biopsy: Please see the "Comments on implementation" below.	Thank for your comment. Although there is no clear economic benefit for ICLD compared to DCLND, the GDG did report evidence of benefit in terms of reduced morbidity for ICLD compared with DCLND and better staging. The additional predictive value resulting from SLNB is fairly modest but there are as yet no prognostic biomarkers which perform as well as SLNB. Therefore for the time being this procedure may have benefits for patients. The GDG agreed that better prognostic biomarkers would be identified and the value of SLNB could be revisited when the guideline is reviewed.
169	British Association of Dermatologists	Full	7		Lentigo maligna: What evidence is there that Mohs surgery is going to offer a better alternative than simple excision ensuring complete excision irrespective of clinical margin? Why should Mohs be	Thank for your comment. This is a recommendation for future research not a recommendation for clinical practice. The GDG were aware that Mohs micrographic surgery is used in some centres but

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					carried out for lentigo maligna rather than any other type of *in-situ* melanoma?	could find no substantial evidence to support this technique. Two of the key outcomes of such a trial would be investigation of local recurrence and cosmetic result. This evidence would be more reliable than any observational study of current practice. The research recommendation was made specifically for this sub-type of stage 0 melanoma, because the GDG's experience was that it is in this sub-type that Mohs is being used. Mohs has been used for this particular subtype of stage 0 melanoma as there is a well described lack of correlation between the clinical and histological margins making tissue sparing on the face difficult to accomplish safely.
170	British Association of Dermatologists	Full	21		Algorithm on diagnosing melanoma: 1. Guidance is unclear regarding subsequent follow up/discharge in patients assessed with photographs after 3 months who do not need excision. There should be a mechanism for discharging patients with these lesions back to the GP. If they are kept under follow-up until the lesion is excised, it would lead to increased burden on clinics and would lead to increase in benign lesions being excised. Also, the algorithm gives no guidance regarding follow-up for multiple atypical naevi.	Thank for your comments. The algorithms are a pictorial representation of the recommendations made in the guideline. They do not represent a complete pathway of care. We have added text to the start of the Algorithms section to clarify this. The question of what to do with atypical melanocytic lesions that remain stable on photography at 3 months was not investigated by the guideline and no recommendations have been made on this. Therefore we are not able to include this in the updated algorithm which we have corrected.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					2. The statement "Do not routinely use confocal microscopy or computer assisted diagnostic tools to assess pigmented lesions" is very negative and suggests these may be harmful. This could be rephrased to "Confocal microscopy or computer assisted diagnostic tools are not routinely required". 3. Suspected atypical spitzoid lesion – it is unclear from the algorithm whether this is based on a clinical suspicion/dermoscopic diagnosis or histological diagnosis before referral to the SSMDT. 4. Discharge: should include advice regarding changes to look for in future and sensible sun protection.	The term "Do not" does not necessarily mean that something is harmful. In this instance it reflects that there is insufficient evidence to support the use of this intervention. The algorithm refers to histological diagnosis. This has been amended for clarity. Recommendation 1.9.8 in the short version specifically addresses this issue. We have amended the algorithm to include this information.
171	British Association of Dermatologists	Full	24		Stage 2: Breslow thickness 2 mm or more' but this does not include stage 2A with Breslow 1.01-2 mm with ulceration. Where does it fall in the algorithm?	Thank you for your comment. The recommendation relating to stage II has been amended to remove Breslow thickness. The GDG has tried to use stage consistently through the Guideline to define management groups.
172	British Association of Dermatologists	Full	26		Follow-up of Stage 1B: Not all pathology laboratories report on mitotic rate for melanomas with Breslow of 1 mm or below, in order to classify as pT1a or pT1b – it should be stressed that this is required as it is part of the Royal College of Pathologists' NICE-accredited minimum dataset for reporting melanoma.	Thank you for your comment. The RCPath data sets are now considered mandatory for histopathologists and we therefore did not feel that it was necessary to restate this here.
173	British Association of Dermatologists	Full	26		Imaging; The role of CT-PET should be discussed	Thank you for your comment. The role of CT-PET was discussed by the GDG. They concluded that this imaging modality did provide better sensitivity, but until it is established that earlier

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						treatment is beneficial it was not of general benefit given issues with its availability and the fact that it results in a higher radiation dose than other imaging modalities. Consequently its use was not recommended.
174	British Association of Dermatologists	Full	26		"Personalised follow-up": We are not sure what "personalised follow-up" means. There should be a clear definition for this and it would be good to define it in the algorithm as well.	Thank you for your comment. The word "personalised" is one in common parlance, used to indicate something that is appropriate to a particular individual and we have used the word in that context. In advanced melanoma follow up is determined by the particular needs or treatment of the patient so that no more specific description of the follow up is possible.
175	British Association of Dermatologists	Full	34		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)."* This statement seems redundant due to the sentence *"..in 2012 was higher for men (25.0 melanomas per 100,000 men) than for women (22.1 melanomas per 100,000 women)"*.	Thank you for your comment. We have removed this statement...
176	British Association of Dermatologists	Full	56		Patient Information: It is much more important for patients to have information that is stage-appropriate than the histopathological subtype.	Thank you for your comment. The GDG have stated that certain recommendations from the NICE guideline on 'improving outcomes for people with skin tumours including melanoma' are followed. This is why 'histopathological type' is specified. The GDG would expect information specific to 'type of treatment' to be stage appropriate. As these recommendations have been quoted from another NICE

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						guidance we are not able to amend the wording of their recommendations.
177	British Association of Dermatologists	Full	84		The role of ulceration and mitosis in staging should be addressed.	Thank you for your comment. Mitotic index showing more than 1-2 mitoses is not a part of the AJCC staging system which it was agreed should be used at the time of scoping. Although mitotic index was not excluded from the evidence searches it was not considered as a separate topic. Ulceration is crucial to the AJCC staging system.
178	British Association of Dermatologists	Full	107		Staging recommendations: In the follow-up, the recommendations are to *consider* surveillance imaging for stage 2C patients who did not have SLNB. But the staging recommendations say to *offer* staging imaging only to stage 3 or suspected stage 4 melanoma patients. Hence there is a disparity between the recommendation not to offer staging imaging for stage 2C patients (without SLNB) but to consider surveillance imaging for stage 2c patients.	Thank you for your comment. We have amended the recommendation on p 108 to include stage IIC who have not had SLNB. We have also amended the Linking Evidence to Recommendations (LETR) statements to explain this amendment. The LETR statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).
179	British Association of Dermatologists	Full	119		Stage 0 melanoma: It is well known that clinical margins and histological margins in lentigo maligna are very discordant. Hence suggesting 0.5 cm margin may not be valid. Practically it might be better to advise to aim to achieve clear margins ideally of at least 0.5	Thank you for your comment. The recommendation is for a clinical margin which the GDG feels is appropriate. The recommendation then suggests MDT review of the histology to take a view on whether the margin achieved was

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					cm.	adequate or not. The GDG agree that this is the best approach to a difficult issue. Review of the patient by the medical team in clinic, and the histology sample, allows a discussion around the pathology and the clinical prospects of further treatment.
180	British Association of Dermatologists	Full	126		Imiquimod and lentigo maligna: Evidence for all non-surgical forms of treatment of lentigo maligna is weak and it is surprising that imiquimod should be given clear preference over, for instance, cryotherapy when there is very little evidence available (Stage 0-2 melanoma).	Thank you for your comment. Following consultation on the draft scope, this topic was considered to be a priority for inclusion in the guideline, due to its increasing use in clinical practice. Cryotherapy was included as a comparator but no comparative evidence was identified.
181	British Association of Dermatologists	Full	226		Advice on vitamin D: The management of patients with normal vitamin D levels at diagnosis of melanoma requires more specific guidance. Normal vitamin D levels at diagnosis do not rule out development of vitamin D deficiency in the future due to sun protection advice that would have been given at the time of diagnosis. If the GDG recommendation wishes to avoid development of vitamin D deficiency and possibly the treatment leading to benefits in overall survival, it would be advisable to repeat the tests intermittently in order to identify patients who develop vitamin D deficiency after diagnosis.	Thank you for your comment. In view of the uncertainty around vitamin D the GDG felt unable to make any strong recommendations except that it should be measured. By making this recommendation, patients would be identified who have very low levels (known to be associated with poor bone health) and probably just as importantly would identify people with high levels or levels that are adequate. The GDG is concerned about the possible deleterious effects of high levels and wished to promote avoidance of that. In the text of the guideline the GDG explained why they felt that advice on monitoring could not be made: that the data are even more uncertain about the validity of this.
166	British	IMP	6		Vitamin D:	Thank you for your comment. In view of

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Association of Dermatologists	Full			Please see the "Comments on implementation" below.	the uncertainty in the evidence for this topic that the GDG felt unable to make any strong recommendations about vitamin D except that it should be measured. By making this recommendation, patients who have very low levels (known to be associated with poor bone health) would be identified and probably just as importantly people with high levels or levels that are adequate would also be identified. In the text of the guideline the GDG explained why they felt that advice on monitoring could not be made: that the data are even more uncertain about the validity of this.
183	British Association of Dermatologists	Implementation	General	General	The recommendation about use of dermoscopy in diagnosis and follow-up should be qualified by a caveat about the risks of this technique giving false reassurance when practitioners are not thoroughly trained in its application. The studies supporting its use are subject to the limitation that they are generally performed on groups of typical rather than difficult pigmented lesions. The recommendation of imaging for follow-up was left for local policies to decide without any precise guidelines on how frequent it should be. We think that it would be very useful to suggest a range period to arrange for such a test. Plus, such surveillance imaging as "agreed by local policy/funding" appears to be a recipe for postcode variation in care – is this appropriate for a national guideline?	Thank you for your comments. The GDG recognised the importance of training in its recommendation on dermoscopy. The quality of evidence reported to support its use was considered to be good. Frequency of imaging has now been included in this recommendation, based on the clinical experience of the GDG. The GDG acknowledge that practice variation may result from the recommendation but because of uncertainty in the evidence they were unable to make a strong recommendation in favour of a specific imaging policy. The recommendation

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						leaves the final decision to the SSMDT, if funding is identified or it is available as part of a clinical trial.
					Not sure if baseline photographs especially for dermoscopic features of "atypical melanocytic lesion not requiring excision" is practical in terms of service implications or even required as a national guideline recommendation. Not clear that the benefits of this are proven on the scale proposed, whether cost-effective, and to what extent such a recommendation would drive us towards even more surgery. Appreciate the aspiration, but is this suitable for a national guideline? We would prefer to have this as an option rather than a recommendation.	The GDG felt that the evidence supporting the use of photography was sufficient to make this recommendation. Dermoscopy imaging can be performed by any medical illustration department with an adapted dermoscope. As the NHS moves to digital records then these images can be provided in the clinic digitally and the GDG felt it important that this recommendation is implemented.
					For all the clinical images of moles that are taken, there are very limited cases where melanoma was picked up purely from a change relative to photographic image; dermoscopy imaging would be similar. Standardising the colour in photos is very difficult as lighting can vary in clinics. Dermoscopic follow-up would require recorded and reproducible photo-documentation.	The use of dermoscopy increases diagnostic accuracy and this is supported by the data. Using dermoscopic images increases the quality of photography and therefore clinical utility. The GDG therefore made the recommendation in order to both reduce the likelihood of delayed diagnosis of melanoma and reduce unnecessary surgery.
					There should be a further emphasis on a self-monitoring element which is to define the naevus for the patient in terms that they can recognise, e.g. shape, size, colour and symptoms and then document this in a letter and ask them to monitor and ask again if there are changes. It may be good practice to monitor with repeated dermoscopy images, but it is not something that is going to improve the chance of patients monitoring themselves effectively and is not practical for many clinicians with limited resources.	The role of self assessment in monitoring naevi is outside the scope of the guideline which is about the management of suspected and diagnosed melanoma.
184	British Association	Implement ation	General	Gener al	Evidence of a critical role for vitamin D deficiency in melanoma is limited and it is surprising that measurement of	Thank you for your comment. In view of the uncertainty in the evidence for this

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	of Dermatologists				vitamin D levels in all melanoma patients is given as a key implementation priority on the basis of the existing evidence. The measurement of vitamin D levels would appear to need more evidence before wider recommendation.	topic that the GDG felt unable to make any strong recommendations about vitamin D except that it should be measured. By making this recommendation, patients who have very low levels (known to be associated with poor bone health) would be identified and probably just as importantly people with high levels or levels that are adequate would also be identified. Measuring vitamin D levels at diagnosis allows healthcare professionals to both identify patients with low vitamins D levels who might benefit from supplementation in line with national policies, and those with high levels who do not require supplementation (and indeed in whom supplementation might be harmful). These were the main reasons why the GDG chose this topic as a matter for implementation.
185	British Association of Dermatologists	Implementation	General	General	The recommendation to consider sentinel node biopsy routinely in stage 1B melanoma patients is not well supported by the study of cost-effectiveness, making it difficult to support its use out with the context of clinical trials.	Thank you for your comment. The GDG has reported that there is no clear economic benefit but reports evidence of benefit in terms of reduced morbidity for ICLD compared with DCLND, and better staging. The additional predictive value resulting from SLNB is fairly modest but there are as yet no biomarkers which perform as well as SLNB, therefore for the time being this procedure may have benefits for patients.
50	British Association	Full	7	2	Breslow of ≥1mm, yet stage 1B is defined as > 1mm as ≤1mm is stage 1a	Thank for your comment. Whilst the margin trials have been based upon

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	of Plastic Reconstructive and Aesthetic Surgeons					thickness, prognosis is currently best predicted by AJCC stage. Clinical trial recruitment and stratification is therefore predominantly based upon stage and therefore the GDG adopted the approach of using stage where possible for consistency. We have removed the reference to Breslow thickness in the recommendation to avoid confusion.
51	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	7	9	4/5 represents only those patients in whom involved LNs have not been found. Microscopic deposits may be present and would present as macro deposits had they been left. It should be mentioned that the results of MSLT-2 are awaited	Thank for your comment. The GDG accepts that this estimate is based upon the fact that 20% of completion lymphadenectomy specimens have detectably involved nodes when reviewed by the histopathologists less meticulously than at SLNB. That estimate was based on the only evidence available currently. It is true that MSLT2 should establish the figure more accurately. The guideline will be reviewed, in line with NICE process, and this recommendation will be updated if appropriate.
52	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	7	11	There is no evidence for the routine use of surveillance imaging. This term allows any imaging on any timeframe to be justified. Equally there is no evidence that early treatment of systemic disease results in better outcomes.	Thank for your comment. If metastases are identified earlier, the GDG agreed the outcomes for the person might be better, especially with the newer agents that are currently available and in development. Although the GDG acknowledges that there is no strong clinical or cost effectiveness evidence that earlier detection of metastases results in improved outcomes they agreed that there was an increasing belief that it might be important to identify them. In

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						particular, the GDG was receptive to the view that immunotherapies (T cell checkpoint inhibitors) are likely to produce long term benefit yet they are relatively slow to act. Therefore there might be some sense in identifying metastases early enough for the patient to be well enough to tolerate the immunotherapies for sufficient time to benefit from them. The modelling showed that regular imaging may be a cost effective if the increased long term survival following systemic therapy was 15%. The GDG recognised further that there are potential disadvantages of regular imaging. The recommendation leaves the final decision about this to the SSMDT, if funding is identified, patients are fully aware of the potential advantages and disadvantages, or as part of a clinical trial. A table has now been included with the recommendation so that the disadvantages and advantages of regular imaging are made clear and this can be used to inform SSMDTs and in discussion with patients. In addition a frequency for imaging has now been included in the recommendation, based on the clinical experience of the GDG.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
53	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	21	3	If single atypical lesion, excise and discharge if benign pathology. If part of an AMS then long term follow-up may be appropriate.	Thank for your comment. The algorithms are a pictorial representation of the recommendations made in the guideline. They do not represent a complete pathway of care. We have added text to the start of the Algorithms section to clarify this. The question of what to do with a single atypical lesion was not investigated by the guideline and no recommendations have been made on this. Therefore we are not able to include this in the algorithm. The follow up of people with AMS is included in the follow-up algorithm on page 28 of the full guideline and recommendation 1.9.2 in the short version.
54	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	23	1	Stage 1b on basis of mitosis have a risk of having +ve SLNB. if Breslow is >0.75mm risk is 10%; if Stage 1b with Breslow ≤1mm, risk deemed to be equivalent % to Breslow i.e. 0.3mm 1b = 3% risk of +ve SN. Whether to offer SLNB to this group should be made on a risk threshold basis not stage	Thank for your comment. The probability of a positive SLNB is related to thickness. The GDG based their recommendation on the observation that the probability is so low in patients with a thickness less than 1mm that potentially SLNB has less value in this group: these patients are for example less likely to have positive nodes and less likely to have reduced morbidity for nodal surgery as a result of a SLNB rather than DLND. The GDG took the view that stage IB melanomas of this thickness have a low probability of being SLNB positive and that the costs and harms of SLNB in this group were likely to outweigh the advantages. If in the future, a survival benefit for the procedure was demonstrated or effective adjuvant therapies were reported for melanoma, then the GDG would expect

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						the recommendations to change. The recommendation is made as the evidence to date shows no evidence of a survival benefit from SLNB.
56	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	24	1(stage3)	Completion Lymph node dissection, following a +ve SNB, should be current recommendations until it is proven that SN alone is adequate. Await MSLT-2 data. There may be a few patients with very minimal disease where one might consider observation alone, in which case Ultrasound scanning is frequently used.	Thank you for your comment. The GDG considered the evidence on SLNB very carefully. NICE terminology is such that the word 'consider' when used in a recommendation expresses a lack of strong evidence that a procedure is beneficial. The committee therefore feels that using this term is appropriate.
55	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	24	1(stage 2)	Stage 2 also includes ulcerated melanoma >1mm-≤2mm. This group does not need a margin of at least 2cm	Thank you for your comment. We agree that the inclusion of Breslow thickness in the recommendation was confusing and this has now been removed. However, although there are no randomised clinical trial data that refer to patients with a T2B tumour, these tumours are associated with the same outcome as other stage IIA tumours. Therefore the GDG decided to make the same recommendation for all stage II tumours. The GDG took the view that grouping thinner tumours with microscopic ulceration with thicker tumours reflected a poorer prognosis and that encouraging a wider margin was an appropriately more cautious recommendation.
57	British Association of Plastic Reconstructive and Aesthetic	Full	26	Brain Img	The proposed screening programme from the Melanoma Focus charity changed its policy of routine regular CT of the head and neck due to the risk of cataracts and thyroid toxicity. Where is the evidence for this policy.	Thank you for your comment. The GDG accept that there are risks of thyroid cancer with CT of the head and neck and this has now been made clear in the recommendations. However imaging departments have a variety of techniques

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Surgeons					that they can use to mitigate this risk and so the GDG considered the recommendation to be appropriate. We do not know what evidence was used as the basis of the Melanoma Focus policy.
58	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	26	Stg 1b-2c	Typo - Melanoma	Thank you, this has been corrected.
59	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	26	Stg 2c-3	There is no evidence for routine surveillance imaging. There has been no economic cost evaluation for this, nor a safety assessment for the radiation exposure associated with this policy – see comments later	Thank you for your comment. This strategy was included in the cost-effectiveness model developed to investigate this question. If metastases are identified earlier, the GDG agreed the outcomes for the person might be better, especially with the newer agents that are currently available and in development. Although the GDG acknowledge that there is no strong clinical or cost effectiveness evidence that earlier detection of metastases results in improved outcomes they agreed that there was an increasing belief that it might be important to identify them. The modelling showed that it was likely to be a cost effective if the long term survival following systemic therapy was 15%. The recommendation leaves the final decision about this to the SSMDT if funding is identified or it is available as part of a

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						clinical trial. A table has now been included with the recommendation so that the disadvantages and advantages of regular imaging are known (including radiation exposure) and this can be used to inform SSMDTs and in discussion with patients. In addition a frequency for imaging has now been included in the recommendation, based on the clinical experience of the GDG
60	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	83	18	Typo 'of' … wide local excision OF the primary tumour	Thank you for your comment. We have made this correction.
61	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	87	7	Why was this not considered - MORTON et al 2014? "Biopsy-based management improved the 10-year rate of distant disease–free survival (hazard ratio for distant metastasis, 0.62; P=0.02) and the 10-year rate of melanoma-specific survival (hazard ratio for death from melanoma, 0.56; P=0.006) for patients with intermediate-thickness melanomas and nodal metastases. Accelerated-failure-time latent-subgroup analysis was performed to account for the fact that nodal status was initially known only in the biopsy group, and a significant treatment benefit persisted." This benefit was not seen in those patients with thick melanomas See comments later relating to assumptions within the analysis of screening imaging and presumed benefit of early detection and improved distant disease free survival.	Thank you for your comment. Morton et al (2014) was included in the evidence review, however the GDG concluded that there were several methodological issues with the study, which meant that they were not comfortable basing recommendations on the evidence from the trials. The reasons for this are outlined in the Linking Evidence to Recommendations (LETR) statements and GRADE tables. The LETR statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).
62	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	87	40	A reduction in lymphoedema represents a therapeutic benefit for those SLNB+ve patients who have a ICLND compared to those that have a DCLND	Thank you for your comment. The GDG were aware of this advantage and this was taken into account in the health economic analysis. We have made this explicit in the table of advantages and disadvantages below the recommendation on completion lymphadenectomy on p140. As part of the implementation tools we are developing a specific options grid (see www.optiongrid.org) to help healthcare professionals and patients with this difficult decision.
63	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	100	18-21	The argument of no survival advantage has hinged over whether there is a proportion of +ve SNB patients who are 'false +ve' and therefore would never have gone on to develop nodal disease hence skewing the survival figures in favour of SNBx. This analysis has assumed that nodal metastases are equal in both groups. This means that you must therefore consider the survival advantage of (SNB+ve & CLND) over DCLND in this analysis.	Thank you for your comment. Both ICLND following +ve SLNB and DCLND have different transition matrices. In the base case ICLND has a survival advantage over DCLND (p 103). The text has been updated to clarify this.
64	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	102	20	Morton et al. 2014 have shown that there is an increased risk of distant disease in the DCLND group compared to ICLND group. Therefore the groups will not equally be 1.6%.	Thank you for your comment. In the base case analysis distant disease free survival would be higher in the ICLND group compared to the DCLND group. This is because the model assumes that patients are more likely to have distant recurrence following nodal recurrence and nodal recurrence is lower (4.3% vs 3.3%) in the ICLND group. When a

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						prevalence of micrometastases equal to Morton et al. 2014 is assumed the model had similar distant disease free and melanoma specific survival to that reported in Morton et al. 2014. The text has been updated to clarify this.
65	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	103	33	The analysis fails to include:- 1.The extra CT scans required in the DCLND group as all patients will have a CT staging, those in the ICLND group will not. 2. The increased costs of a DCLND especially in the groin area where a pelvic node dissection should also be performed. 3.Distant disease free survival advantage of SNB + ICLND vs DCLND also needs to be added into the calculation 4. The cost of radiotherapy is missing. Radiotherapy is never given following an ICLND, because disease volume is microscopic. However after a DCLND it certainly needs to be considered at least as an outpatient cost and also costed if given.	Thank you for your comments. The model assumed that patients would receive restaging prior to both a ICLND and DCLND as there may be patients eligible for systemic treatment. The GDG therefore felt the difference in resource use between the two groups, in this regard, would be minimal. DCLND does incur an increased cost in the model. This difference was included as part of the base case model DCLND does incur an increased cost in the model. The GDG acknowledged that there was considerable uncertainty in the model around both the costs and clinical outcomes and that clinical practice would vary between different centres. A wide range of sensitivity analyses was performed and the large uncertainty was reflected in these results. This uncertainty was carefully considered when writing these recommendations.
66	British	Full	107	Disadv	This is statement cannot be as dogmatic. You have to	Thank you for your comment. The GDG

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Association of Plastic Reconstructive and Aesthetic Surgeons			antage of SNB	acknowledge that there is significant disagreement in the medical population. There is clear evidence of disease progression (number of involved nodes, tumour volume) from ICLND cf. DCLND. There is evidence either from the MSLT-1 trial or the accelerated latent sub-group analysis that there is a survival advantage for those who are SNB+ve and have an ICLND vs those who do not, but later require a DCLND.	were aware of the possible survival benefit shown by the post-hoc subgroup analysis. However the risk of bias associated with this type of analysis meant that the GDG considered that "there is no good evidence that people who have the operation live longer". This has been documented in the Linking Evidence to Recommendations (LETR) statements. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).
67	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	107	Disadvantage of SNB	Is the GDG absolutely certain that the survival difference calculated in MSLT-1 (comparing SNB+ve & ICLND vs DCLND) is wholly and ONLY due to the statistical sub-group analysis. If there is any doubt then there has to be an acknowledgement of potential survival advantage.	Thank you for your comment. The GDG is confident that there is no good evidence of a survival benefit and that is what is stated in the guideline.
68	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	107	Disadvantage of SNB	It is not the general anaesthetic that causes a 4-10% rate of complications. It should be pointed out that sometimes people require a general anaesthetic for just their wide local excision.	Thank you for your comment. Thank you for highlighting this issue. We have corrected this text which was a textual error rather than intended.
71	British Association	Full	108	Expert Views	Clear data comparing SNB + ICLND vs DCLND was presented to the GDG:-	Thank you for your comment. As there is a lack of data about the value of CLND

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	of Plastic Reconstructive and Aesthetic Surgeons				Significant increased numbers of involved nodes and therefore significant increased tumour volume; reduced lymphoedema; reduced rates of extra-capsular spread; reduced hospital stay;	after a positive SLNB, the GDG chose to divide the recommendations into SLNB and subsequent CLND. These data were taken into account (1.7.1 of the short version and on p140 of the full version) when describing that "The operation is less complicated and safer than waiting until the cancer develops in the remaining lymph nodes". These important data were also considered as part of the health economic evaluation.
70	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	108	*Post-hoc*	The accelerated latent sub-group analysis was clear that SNB may offer a survival advantage. The GDG should have acknowledged this	Thank you for your comment. The GDG were aware of the possible survival benefit shown by the post-hoc subgroup analysis. However the risk of bias associated with this type of analysis meant that the GDG considered that "there is no good evidence that people who have the operation live longer". This has been documented in the Linking Evidence to Recommendations (LETR) statements. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).
69	British Association of Plastic Reconstructi	Full	108	Rel Value	This is why you should consider Distant Disease Free Survival - as was addressed in MSLT-1 and not disease free survival. You did consider that early detection of loco-regional disease affected overall survival in you screening analysis, so	Thank you for your comment. Although distant disease-free survival is important to patients the GDG agreed that in the SLNB analysis, overall survival was the

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	ve and Aesthetic Surgeons				why not in the SNBx analysis?	more meaningful measure. When balancing the possible benefits and harms of surgery, the GDG believed the lack of evidence that surgery reduced the risk of dying from the melanoma was more important than surgery appearing to reduce the risk of distant spread.
72	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	109	Final paragraph in Trade off section	This contradicts the previous statement that stated "no evidence was found to suggest that earlier treatment of metastatic disease improves survival …"	Thank you for your comment. The benefits from better staging information resulting from SLNB include possible access to clinical trials and better information for patients about the future. We have not implied that this has any survival benefit.
73	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	110		Why has the QALY value changed? When SNBx was initially discussed at the GDG, SLNB was below the NICE threshold of £20,000? It now appears to be significantly above the threshold level?	The cost per QALY for SLNB was agreed by the GDG at their final meeting. The GDG discussed the impact of the costs and incidence of complications associated with CLND in their discussion. This QALY figure for SLNB was included in the version of the guideline that was issued for consultation. This figure did not change as a result of the stakeholder consultation process.
74	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	110		If there is no distant disease survival benefit, no evidence for improved survival from earlier treatment and a cost per QALY above the NICE threshold, why are the NICE GDG recommending SLNB at all?	Thank you for your comment. The GDG were aware of the uncertainty around the cost effectiveness of the addition of SLNB, particularly in the absence of any survival benefit. However they believed that the benefits of better staging information (resulting in access to clinical trials and better information about prognosis), which were not evaluated in the economic model, were important recommendations.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
75	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	113	21	It needs to be noted that the 1vs3cm trial specifically excluded SLNB to stage patients prior to randomisation. It is possible that the increased rate of nodal recurrence in the 1cm, was due to a bias at the point of randomisation and not as a result of a narrower wide local excision margin.	Thank you for your comment. We disagree that this is a potential bias of this trial. The poor quality of the evidence for this question was considered by the GDG and documented in the Linking Evidence to Recommendations (LETR) statements on p121. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).
77	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	119	Quality of evidence	These are multi-professional guidelines to which members of the BAD contributed, they are not the BAD guidelines. They were also published by JPRAS Sept 2010 63(9) 1401-1419	Thank you for your comment. We have clarified that the British Association of Plastic and Reconstructive and Aesthetic Surgeons also contributed to these guidelines.
76	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	119	6	Stage 2 patients are those with melanoma >2mm, NOT ≥2mm	Thank you for your comment. Whilst the margin trials have been based upon thickness, prognosis is currently best predicted by AJCC stage. Clinical trial recruitment and stratification is therefore predominantly based upon stage and so the GDG adopted the approach of using stage where possible for consistency. We have removed the reference to Breslow thickness in the recommendation to avoid confusion.
78	British	Full	121	Mohs	Mohs micrographic surgery could also result in excessive	Thank you for your comment. This is a

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Association of Plastic Reconstructive and Aesthetic Surgeons			– why is this important	resection of tissue in an area of field change. It would be more prudent to look at recurrence rates to assess whether there is a problem with current practice, before advocating a new solution. Excision with a 5mm margin would appear reasonable, one study from Sydney suggests that there were no recurrences with an 8mm margin. How does the GDG suggest that Lentigo Maligna, if excised with Mohs undergoes double reporting by dermatopathology as is currently recommended in the NICE IOG for skin cancer, for all pigmented lesions?	recommendation for future research not a recommendation for clinical practice. The GDG were aware that Mohs micrographic surgery is used in some centres but could find no substantial evidence to support this technique. Two of the key outcomes of such a trial would be investigation of local recurrence and cosmetic result. This evidence would be more reliable than any observational study of current practice.
79	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	126	Recommendation	An option not considered is the use of Imiquimod, post resection of a lentigo maligna, when either there is concern about the margin of excision or evidence of extensive field change in the are of excision.	Thank you for your comment. We agree that this is potentially a very useful approach to treatment, but at the time of scoping this issue was not prioritised for inclusion within the guideline.
80	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	129	35	There are only 44 Specialist Skin MDTs, which deal with melanoma (42 Specialist and 2 Melanoma Specialist) MDTs. Therefore if 62 local teams respond one would expect that 18 of these teams were responding in the capacity as a local team so would not be expected to offer SNBx as this is a Specialist Skin MDT function. The 17 units that did not offer SNB, could be local units affiliated to Specialist units, which do not have a SNBx facility. There is therefore an inherent bias in quoting it the 17 as 60%, because it could reflect 3 or 4 specialist units without SNBx, looking after 17 local units	Thank you for your comment. Thank you for pointing out this error. We have amended the text for clarity, documenting that of the 29 specialist MDTs who replied, 13 (45%) either offered SLNB themselves (11) or via another service (2).
81	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	208	37	It is interesting that the assumption, 'all untreated loco-regional recurrences after 6 months would progress to distant disease', is deemed valid - when the early removal of microscopic disease by ICLND following a +ve SNBx, is deem irrelevant to the development of distant disease when compared with DCLND for macroscopic disease	Thank you for your comment. In modelling the possible value of regular imaging in follow-up, some assumptions about the rate of progression of melanoma had to be made because of a lack of good quality data (see Appendix B for more information). This particular assumption does not necessarily

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						invalidate the proposition that removal of involved regional nodes does not affect overall survival. It is possible that the development of regional nodal disease is a marker of an increased risk of developing metastases and removal of the regional disease may not affect this risk, as implied by MSLT-1.
82	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	209	26	There is no evidence to suggest that survival following Vemurafenib is identical to that of Ipilimumab. This assumption is invalid. Median disease free progression is about 7 months.	Thank you for your comment. Survival data for vemurafenib has been updated accordingly and included in the revised economic model. The results of the economic model has been updated but this has not affected the conclusions.
83	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	209	41	What allowance has been made for the costs of investigating the false +ve scans, estimated to be at least 10%	Thank you for your comment. Appendix B contains discussion on how false positive scans (pg32) are integrated into the economic model.
84	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	210	10	This analysis is seriously distorted. No allowance has been made for:- the increased costs of screening patients prior to starting treatment eg. ophthalmology assessment, echocardiography.	Thank you for your comment. In the *de novo* economic model all patients starting treatment following distant recurrence received a consultant outpatient oncology appointment prior to commencement of treatment. The study did not explicitly consider individual tests during pre-treatment screening although the appointment cost was varied during sensitivity analysis to account for any

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					the treatment of serious adverse side-effects eg. colitis, hypophysitis, uveitis etc. the treatment of minor side-effects eg. excisaon of SCC induced by treatment The analysis for surgical interventions included the costs of treating lymphoedema, a consequence of surgery, therefore you must also count the cost of treating the adverse effects of chemotherapy.	possible underestimate of costs. Wade et al included the costs of adverse events associated with treatment. A full list of both serious and minor adverse events included and their average costs can be found in Wade et al (table 19 – Appendix B). Total health care related costs for ipilimumab, vemurafenib and dacarbazine were taken from Wade et al 'Ipilimumab for previously untreated unresectable malignant melanoma: A Single Technology Appraisal.' CRD and CHE Technology Assessment Group, 2013
85	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	210	14	No adjustment to the QALY has been made for the 2% death rate associated with Ipi. (published data by the company themselves)	Thank you for your comment. This would have been captured by the DeQuen et al (2012) meta-analysis used to inform survival.
86	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	210	14	Does this analysis allow for the high ≤40% withdrawal from treatment of patients given Ipi?	Thank you for your comment. Both costs and health outcomes used to inform the *de novo* economic model accounted for withdrawal from treatment. Total health care related costs for ipilimumab, vemurafenib and dacarbazine were taken from Wade et al. For ipilimumab a withdrawal rate of 46.2% was reported and this was reflected in the total cost used in the *de*

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						novo model. The network meta-analysis (DeQuen et al 2002), used to inform survival in the economic model, included clinical trials with similar adherence.
87	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	211	15	See previous comment about SNBx. You cannot say early detection of loco-regional disease reduces progression to distant disease only when detected by Scan and not SNBx - particularly when SNB sensitivity is significantly greater in detecting disease compared to current imaging.	Thank you for your comment. In modelling the possible value of regular imaging in follow-up, some assumptions about the rate of progression of melanoma had to be made because of a lack of good quality data (see Appendix B for more information). This particular assumption does not necessarily invalidate the proposition that removal of involved regional nodes does not affect overall survival. It is possible that the development of regional nodal disease is a marker of an increased risk of developing metastases and removal of the regional disease may not affect this risk, as implied by MSLT-1. The economic model did not take account of the risk of radiation induced cancer but the reasons for this are clearly described in section 4.7 of Appendix B.
88	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	212	1-16	The analysis has made no account for the increasing radiation dose associated with repeat scanning. A national charity had to change it's planned routine 9 screening whole body CT scan protocol when it was recognised that there was a significant risk of developing cataracts or thyroid disease. The radiation dose from a single PET CT is 50% more than the total annual recommended radiation dose for someone working in the nuclear energy industry. Similar doses of radiation are experienced with whole body CT, such that there is an estimated 2% risk of a 40yr old female developing a radiation induced malignancy	Thank you for your comment. The economic model did not take account of the risk of radiation induced cancer but the reasons for this are clearly described in section 4.7 of Appendix B.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					with a '9 Scan' protocol, this risk increases to 4% for a 20 yr old female. Similar order but lower risks are seen with increasing age and male sex. It is irresponsible to countenance a routine radiation based screening programme without considering these risks, especially within the QALY framework.	
89	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	214	10-11	There is no evidence to suggest that early detection and treatment results in improved outcomes. There is real concern that tumour biology (slower growing disease) is responsible for the reported outcomes rather than the early treatment. There is evidence from other disease sites that early treatment is in fact detrimental to patients. With Ipi only 15% benefit, so 85% endure serious side-effects without benefit, but if treated early during a period when they are relatively symptom free.	Thank you for your comment. The GDG agreed that if metastases are identified earlier then the outcomes for the person might be better, especially with the newer agents that are currently available and in development. The particular concern is that patients who present with large volume stage IV melanoma may not survive long enough to benefit from the emerging immunotherapies that are effective in melanoma. Although the GDG acknowledge there is no strong clinical or cost effectiveness evidence that earlier detection of metastases results in improved outcomes, they acknowledged an increasing belief that it might be important to still identify them (as explained above). The modelling showed that it was likely to be a cost effective if increased long term survival following systemic therapy was 15%. The recommendation leaves the final decision about this to the SSMDT if the patient was fully informed about the potential advantages or disadvantages and if funding was available locally, or it was offered as part of a clinical trial.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						A table has now been included with the recommendation so that the disadvantages and advantages of regular imaging are known and can be used to inform SSMDTs and can be used in discussion with patients.
91	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	218	Other considerations	Were the elements of radiation induced cancers and false positive scans factored into the QALY and health economic arguments?	Thank you for your comment. Appendix B contains discussion of how radiation exposure (pg.3) and false positive scans (pg.32) are integrated into the economic model.
90	British Association of Plastic Reconstructive and Aesthetic Surgeons	Full	218	3rd Para	Did the GDG consider that the majority of the high risk patients, would not benefit from early detection, but would have to deal with the side-effects of treatment?	Thank you for your comment. The GDG agreed that if metastases are identified earlier then the outcomes for the person might be better, especially with the newer agents that are currently available and in development. In particular, the argument that patients presenting with large volume stage IV melanoma may not live long enough to benefit from immunotherapies (which take longer to have an effect) was considered. Although the GDG acknowledge there is no strong clinical or cost effectiveness evidence that earlier detection of metastases results in improved outcomes, they acknowledged an increasing belief that it might be important to still identify them. The modelling showed that it was likely to be a cost effective if increased long term survival following systemic therapy was

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						15%. The recommendation leaves the final decision about imaging in this group to the SSMDT, if funding is identified or as part of a clinical trial. A table has now been included with the recommendation so that the disadvantages and advantages of regular imaging are made clear to SSMDTs and which can be used in discussion with patients.
119	British Association of Skin Cancer Specialist Nurses	Full	General	General	Guidance regarding free prescription for melanoma and Squamous Cell Carcinoma patients. - What stage of disease free prescriptions are valid. - Guidance with regards to when verbal and written information should be offered to the patient regarding free prescription.	Thank for your comments. NHS guidance for doctors states that cancer patients may apply for exemption certificates if they are undergoing treatment for cancer or its effects, or for the results of treatment for that cancer e.g. lymphoedema. The certificates last for 5 years. As such this was not an issue that was investigated by the guideline, because it affects all patients with cancer and is not specific to melanoma.
129	British Association of Skin Cancer Specialist Nurses	Full	General	General	The need for education for skin examination, lifestyle, sun protection etc. - should also be highlighted in the recommendation section.	Thank for your comment. There is specific reference to the avoidance of further sun damage and self examination in recommendations 1.1.3 and 1.9.8 in the short version. In addition, there is NICE guidance in development on 'Sunlight exposure- benefits and risk'.
130	British Association of Skin	Full	General	General	There is not information about pregnancy related issues probably because there has been no research but a comment recognising that this may be an issue for discussion	Thank for your comment. We agree that these topics are of interest and cause concern but they were not raised during

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Cancer Specialist Nurses				if patients who have had a melanoma treated wish to become pregnant. For instance those who have had a more aggressive one would be better advised on the prudence of waiting a few years or what about those who want to donate sperm or ovum for future.	consultation on the guideline scope and therefore were not prioritised for inclusion in the guideline.
120	British Association of Skin Cancer Specialist Nurses	Full	4		**Algorithms:** Diagram headed "**All pigmented lesions referred for further assessment**" – Down the pathway it says 'use baseline photography (preferable dermatoscopic)'. Not everyone has access to using photography in this way and how cost effective would it be? Diagram headed "**Review the clinical appearance of the lesion using baseline photography 3 months after presentation to identify early signs of melanoma**". We would have to know the cost of photographs, storage and consenting.	Thank for your comments. The GDG considered the additional cost of photography when agreeing their recommendations. This has been documented on p67 of the full guideline. In addition, the questionnaire survey of LSMDTs and SSMDTs performed as part of the needs assessment showed that 87% of responding LSMDTs and 95% of responding SSMDTs already use photography. This information is available on p49 of the full guideline. Specific equipment for dermoscopic photography is likely to be less widely available but its provision is unlikely to be very costly. Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
122	British Association of Skin Cancer Specialist Nurses	Full	23		**I** would like to clarify where it says that for people with stage 1a and 1b melanoma with a Breslow thickness less than 1mm - *do not* offer imaging or Sentinel lymph node biopsy. At the present time, in the Leeds area, all stage 1b patients are considered for referral for Sentinel node biopsy with a Breslow thickness <1mm.	Thank for your comment. The Guideline recommends that people with stage IA and IB melanoma with a Breslow thickness less than 1mm should not be offered imaging or SLNB.
121	British Association of Skin Cancer	Full	24		**Management of Stage 0-3 Melanoma:** Is it saying that we have to measure Vitamin D levels for all diagnosed melanoma patients? How would that Vitamin D be followed up with regard to	Thank you for your comments. The guideline does not recommend routine supplementation of vitamin D and

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Specialist Nurses				prescriptions, further blood tests? **Follow up for people with Stage 0 melanoma:** It says discharge following completion of treatment. Surely this should be reviewed following wide local excision, offered an appointment to discuss self-examination of skin, preventative measures they can take for themselves and early presentation, which is important and then the patient can be discharged. **Follow up for Stage 1a melanoma:** Again, this has no mention of survivorship follow up appointments regarding self-examination of skin, lymph	indeed by measuring levels unnecessary supplementation would be avoided. In view of this uncertainty in the evidence for this topic the GDG were unable to make any strong recommendations about vitamin D except that it should be measured. The GDG agreed that there are many uncertainties about the significance of biochemical indicators of vitamin D status and the association between those levels and various health outcomes. These and other important issues such as potential adverse effects of high vitamin D levels are being considered by the Scientific Advisory Committee on Nutrition (SACN). This is detailed in the Linking Evidence to Recommendations (LETR) statements on p230. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). The GDG believes that more specific advice for health professionals will be available as a result of this guideline. The GDG was also of the view that

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					nodes, preventative measures they can take for themselves and early presentation. All follow up policies should include reinforcing robust advice about self-examination, which cannot be done in the middle of a busy clinic, and advice on Vitamin D and how to continue taking and being monitored for Vitamin D. The follow up regime in all the pathways there is no mention of access to the CNS service.	measuring vitamin D levels to identify patients with sub-optimal levels who should NOT take supplements was an important result of testing. Please see NICE public health guidance on Vitamin D, recommendation 7 (Vitamin D: increasing supplement use among at-risk groups | 1-recommendations | Guidance and guidelines | NICE) We have put the full recommendation, which includes advice about self examination and health promotion into this box on the algorithm. The importance of continuing information and support is acknowledged in all algorithms by the presence of an adjacent arrow titled 'patient information and support'. We have added text to the algorithm section to highlight this. It is implicit throughout the guideline, that a CNS would be part of the melanoma team, as described in the NICE improving outcomes guidance for people with skin cancer, including melanoma. Published guidelines undergo surveillance reviews every 2 years after publication to decide if an update is needed at that time. This surveillance review decision is informed by a number of stages of intelligence gathering to identify any potential new sources of

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						evidence.
128	British Association of Skin Cancer Specialist Nurses	Full	50		I am pleased to note that page 50 and pages 52 onwards all the information highlighted as written information should be given to the patient as both written and verbal information during the care pathway and in the Follow up clinic but also tailored to individual requirements.	Thank you.
123	British Association of Skin Cancer Specialist Nurses	Full	53		**3:** All information given at breaking bad news regarding disease and treatment should be specific to their stage of disease and their treatment options. Global information can be given later if requested or deemed helpful. • They need timely information access to people who can discuss their needs in a timely manner and who have the experience and training to be able to do this, taking into account the patient's physical, psychosocial and psychological holistic wellbeing, leaving realistic hope. • Ideally information should be given by the CNS/Key Worker at their breaking bad news consultation instead of being left for them (information given on a 1:1 can be discussed briefly, it does not need to be gone into in detail, as long as follow up contact numbers are left for them to clarify as and when). • Sun protection should be given on a 1:1 in a timely manner in a way that does not impact on their psychological wellbeing and leaves them free to enjoy the sun safely. **33:** • At diagnosis, if at all possible, staging should be given. However, at the time when staging is robust, then the staging should be discussed and given in written format.	Thank you for your comments. The text you cite refers to the clinical question that was investigated by the GDG and the evidence that was found. The recommendations made, based on this evidence can be found on p58 of the full version and section 1.1 of the short version. These comments are all pertinent to good practice communication with patients. We believe that our recommendations are broadly in line with what you suggest but in view of the limited specific evidence, the GDG were not able to make more detailed recommendations.
124	British Association	Full	54		**9:** The CNS can also be included in giving psychological	Thank you for your comments. The text you cite refers to the evidence that was

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	of Skin Cancer Specialist Nurses				support. This can be given at different levels in accordance with training. **27:** Support needs: I agree they should be told they can bring someone with them **42:** During follow up: It is the general experience of cancer patients that they feel anxious before a follow up visit and reassured afterwards. Some patients eventually feel they can look after themselves as long as they have access back into the service. Other patients need the reassurance of periodical profession examination.	found. The recommendations made, based on this evidence can be found on p58 of the full version and section 1.1 of the short version. These comments are all pertinent to good practice communication with patients. We believe that our recommendations are broadly in line with what you suggest but in view of the limited specific evidence, the GDG were not able to make more detailed recommendations.
125	British Association of Skin Cancer Specialist Nurses	Full	55		**6**. • The most effective way of meeting the patient's information needs is to give timely written and verbal information in accordance with their stage of disease and treatment. • The most effective way of meeting the patient's support needs is giving timely access and contact numbers; so that the patient feels that they have a safety net there. This often results in people not accessing it but knowing it is there is very reassuring. **7. Using photographs** Patients can actually take their own photographs of different lesions or specific lesions which they may find difficult to	Thank you for your comments. The text you cite refers to the clinical question that was investigated by the GDG and the evidence that was found. The recommendations made, based on this evidence can be found on p58 of the full version and section 1.1 of the short version. These comments are all pertinent to good practice communication with patients. We believe that our recommendations are broadly in line with what you suggest but in view of the limited specific evidence, the GDG were not able to make more detailed recommendations. The use of photography by the patient or their relatives as a part of self-surveillance was not a clinical question

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					examine monthly.	investigated by the guideline. Therefore the clinical evidence on this has not been examined and we are therefore not able to make any recommendations.
126	British Association of Skin Cancer Specialist Nurses	Full	56		Have we got a ratio of patients to CNSs?	Thank you for your comment. When reviewing the literature for this topic the GDG did not find any evidence about CNS staffing levels, including an absence of data on the number of CNS that are currently employed as a ratio to the number of patients diagnosed with melanoma.
117	British Association of Skin Cancer Specialist Nurses	Full	61 General	 General	The use of Dermoscopy routinely in skin surveillance within clinics - this will probably mean the additional training of clinicians and GPs with specialist interest. I think it is important to include skin cancer CNS in this group so that we don't miss out if this is implemented and additional training is provided	Thank you for your comment. We agree that all clinical staff reviewing pigmented lesions should be trained to use dermoscopy. The recommendation therefore refers to "healthcare professionals" and does not specify particular professional groups.
118	British Association of Skin Cancer Specialist Nurses	Full	215 General	 General	There is limited advice on systemic therapy except giving the options. The follow up of high risk patients is in line with our practice and the UK consensus statement, including FU, imaging, BRAF testing, except: They don't recommend follow up imaging for 2c patients if SNB negative, only if unknown. These patients still have only a 50% five year survival and are therefore at high risk of developing metastatic disease.	Thank you for your comments. Because all of these agents except dacarbazine are the subject of on-going or published NICE technology appraisals, the GDG were limited in what aspects of the care pathway they could investigate. Specifically we were unable to rank treatments. The recommendations have been re-ordered in a way that we believe is more logical. We do not agree that Stage 2C patients who are SNB negative are at such a high risk of death and so do not believe that regular imaging would be justified. We are not clear whether the suggestion

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					Imaging should be for those who would be considered for systemic therapy, which seems reasonable. Also clinical follow up is for 5 years only, again maybe we should consider this with escalating clinic numbers Imaging: They have recommended imaging follow up recognising there isn't RCT evidence of improved outcomes but haven't recommended frequency or modality. The cost analysis was based on the sensitivity and specificity of PET though not CT.	made is for follow up to be longer or shorter than 5 years. The GDG agreed to keep the recommendation on 5 year follow up. The frequency for imaging has now been included in the recommendation, based on the clinical experience of the GDG The cost analysis did use data on the sensitivity and specificity of CT as documented on p30 of the appendices.
127	British Association of Skin Cancer Specialist Nurses	Full	226 General	Gener al	Whilst there are difficulties with definitive doseaging re Vit D supplements I find these comments more confusing than helpful. There is no mention that I can see about dangers of overdosing and advice on how much daylight we should be exposing our skin to and even how much of ours skin. There has been quite a bit of research on this in Australia that could use as good practice even advice that sunscreen is **not** a sun block so that vit D intake can occur even when wearing sunscreen.	Thank you for your comment. In the Linking Evidence to Recommendations statements (LETR) on page 229 of the full guideline the GDG has alluded to concerns about overdose in particular for patients with melanoma. The Linking Evidence to Recommendations statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). Please see NICE public health guidance

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						on Vitamin D, recommendation 7 (Vitamin D: increasing supplement use among at-risk groups | 1-recommendations | Guidance and guidelines | NICE In view of this uncertainty the GDG felt unable to make any strong recommendations about vitamin D except that it should be measured. By making this recommendations, patients would be identified who have very low levels (known to be associated with poor bone health) and probably just as importantly would identify people with high levels or levels that are adequate. The GDG was aware of the possible adverse effects from high levels and wished to minimise the risk. The GDG agrees that there are many uncertainties about the significance of biochemical indicators of vitamin D status and the association between those levels and various health outcomes. In particular, the vitamin D committee of SACN is currently considering what levels of measured 25-hydroxyvitamin D_3 in the blood should indicate a need for supplementation, how that supplementation should be given and whether there is evidence for an adverse effect of high levels. Therefore the GDG agreed to recommend advice on vitamin D supplementation and monitoring in line with local policies and NICE guidance should be given to give people whose vitamin D levels are thought to be

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						suboptimal. These and other important issues are detailed in the Linking Evidence to Recommendations (LETR) statements on p229
160	British Society for Dermatopthology	Full	General	General	Throughout the document the staging should be identical to the AJCC7 staging: Pathological staging should be T1 ≤1.0mm, T2 1.01-2.0 etc. (rather than "Breslow thickness less than 1mm.." etc). Clinical Stage of melanoma should be in Roman numerals as in the AJCC7 staging eg Stage IIA rather than 2A.	Thank for your comment. We agree and have re-inserted Roman numerals throughout the guideline.
161	British Society for Dermatopthology	Full	General	General	The use of Stage 0 melanoma throughout the document when referring to in situ melanoma (i.e. non-invasive with no potential for metastatic disease) has the potential to cause confusion for both patients and health care professionals, as this terminology is not in standard use. Instead, referring to it as "in situ melanoma (i.e. Stage 0 melanoma)" would reduce potential for confusion. Likewise use of the term "in situ melanoma (lentigo maligna subtype)" rather than simply "lentigo maligna" has less potential for confusion and error, as the term "lentigo maligna" is not always well understood and sometimes confused with lentigo maligna melanoma, for example by junior doctors and nurses new to melanoma care. This is evident from errors on pathology request forms of biopsy proven lentigo maligna.	Thank for your comments. The GDG agreed to use AJCC staging system throughout the guideline for consistency and because it is now universally used. The simplified table has been removed and replaced with a cross reference to the full AJCC staging system in both the full and short guideline. Thank you for the comment. The GDG have tried to use stage where possible and the text does specify stage 0, so we would prefer to retain this.
162	British Society for Dermatopthology	Full	General	General	Throughout the document measurements should be in one unit of measurement ie.mm to reduce potential for error, as has been the RCPath standard for many years now. Both mm and cm are used in the same sentence (as often clinical trials for surgical margins use cm).	Thank for your comment. The RCPath recommends that mm are used in approved pathological reports. It is usual surgical practice to use cm. The GDG agreed that both units of measure needed to be included in the recommendations for them to be appropriate to both audiences.
163	British	Full	70		The terminology regarding borderline and Spitzoid tumours	Thank you for your comment. We agree

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Society for Dermatopthology		General	General	and Spitzoid tumours of uncertain malignant potential potential needs to be unform throughout the document eg. Melanocytic tumours of uncertain malignant potential (borderline lesions) including Spitzoid tumours of uncertain malignant potential could be used, since the papers used in evidence incorporate a myriad of terms for such lesions.	that the use of different terminologies can be confusing. Unfortunately the text on p69-71 reflects the terminology that is used in the current evidence base and therefore cannot be changed. However in the recommendations and Linking Evidence to Recommendations (LETR) statements. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). We have ensured that we use consistent terminology. We have also added extra definitions to the glossary.
165	British Society for Dermatopthology	Full	107 General	General	Although, as stated in the draft guidelines, there is some evidence for sentinel node biopsy use for melanoma 0.75mm – 1.00mm, it would be advisable to contact [redacted] since they perform SLNB on these patients as they believe there is evidence is good for this, and they have provided almost half the data in trials eg MSLT-1.	Thank you for your comment. The GDG concluded that there is no evidence of a clinically significant survival benefit resulting from SLNB. As a staging tool any possible benefit must be balanced against harm and cost. The GDG took the view that stage IB melanomas of this thickness have a low probability of being SLNB positive and that the costs and harms of SLNB in this group were likely to outweigh the advantages.
164	British Society for Dermatopthology	FULL NICE	107 26	1.5.2	Trial entry requiring sentinel node staging is an important reason for implementing sentinel node biopsy and should be included in the guidelines.	Thank you for your comment. This is already included in the table describing possible advantages and disadvantages of SLNB (see page 108).
133	Department	General	General	Gener	Thank you for the opportunity to comment on the draft for the	Thank you.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	of Health			al	above clinical guideline. I wish to confirm that the Department of Health has no substantive comments to make, regarding this consultation.	
101	East Midlands Strategic Clinical Network (Cancer)	FULL NICE	226 16	10	1.3 Managing suboptimal vitamin D levels. There is concern that the evidence is not supportive of this. It was felt that this was not the role of skin cancer MDT members. It was felt that this advice should be incorporated into the NICE Vitamin D guidance for GPs.	Thank you for your comment. The recommendation the GDG made was not to specify who or how supplementation should take place but that the approach in melanoma patients should be led by the guidelines generated by NICE and in particular the SACN. Please see p230 of the full guideline where we have included information on what the SACN will report on. The GDG also agreed that the melanoma guideline should be read in conjunction with the SACN report.
100	East Midlands Strategic Clinical Network (Cancer)	NICE	15	4	1.2.3 Photography. Regarding (preferably dermoscopic). Although agreed gold standard, have the health economics of these been considered fully? This has huge implications financially.	Thank you for your comment. The GDG considered the additional cost of photography when agreeing their recommendations. This has been documented on p66 of the full guideline. In addition, the questionnaire survey of LSMDTs and SSMDTs performed as part of the needs assessment showed that 87% of responding LSMDTs and 95% of responding SSMDTs already use photography. This information is available on p48 of the full guideline. Specific equipment dermoscopic photography is likely to be less widely available but its provision is unlikely to be very costly. Dermoscopy imaging can be performed by any medical illustration department with an adapted dermoscope. As the NHS moves to digital records then these images can be

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						provided in the clinic digitally and so the GDG felt it important to implement this recommendation.
111	Gloucestershire Hospitals NHS Foundation Trust	Full	General	General	How much significance should be given to the mitotic index after 1 – 2 mitoses? If very high mitosis should we be considering wider excision margins.	Thank for your comment. Mitotic index showing more than 1-2 mitoses is not a part of the AJCC staging system which it was agreed should be used at the time of scoping. Although mitotic index was not excluded from the evidence searches it was not considered as a separate topic and therefore no specific recommendations could be made.
114	Gloucestershire Hospitals NHS Foundation Trust	Full	General	General	The staging should stay identical to the AJCC7 staging (i.e. stages in Roman numerals etc; Breslow thickness identical to what AJCC7 uses)	Thank for your comment. We agree and have re-inserted Roman numerals throughout the guideline.
115	Gloucestershire Hospitals NHS Foundation Trust	Full	107 General	General	Sentinel node biopsy will not detect chest or other metastasis, should we then not stay with CT for stage 2 (particularly if patients decline SNB)	Thank you for your comment. The evidence shows that SLNB is the most sensitive means of detecting any metastasis and is therefore the most appropriate staging procedure. It was suggested that CT would detect more distant metastases and the GDG looked for evidence of the likelihood of this. No good quality evidence was however identified to allow the GDG to confirm this.
116	Gloucestershire Hospitals NHS Foundation Trust	Full	107 General	General	Offering sentinel node biopsy for 1B will have significant impact on surgery time and capacity. Wide excisions which only require 1cm wide excision, according to new guidelines, will now have to go through GA for SNBSLNB, whilst otherwise could have been done in outpatients in the minor ops.	Thank you for your comment. The recommendation specifically says that the advantages and disadvantages of SLNB need to be discussed with patients. It is not possible to predict whether this will overall lead to an increase or decrease in uptake of the

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						procedure.
112	Gloucestershire Hospitals NHS Foundation Trust	Full	137 General	General	In head & neck there is minimal risk of lymphedema following lymphadenectomy – this is one of the reasons stated for favouring immediate lymphadenectomy over delayed lymphadenectomy. Since this is a very low risk of this complication in head and neck tumours, can this be clarified in the guideline	Thank you for your comment. We have amended the text to clarify that lymphoedema may develop, and is more likely if the operation is in the groin and least likely in the head and neck.
113	Gloucestershire Hospitals NHS Foundation Trust	Full	137 General	General	Completion lymphadenectomy should be discussed after SNB, but we do not have MSLT11 data to base an informed decision on.	Thank you for your comment. We agree. MLST I was included in the evidence review for this topic but MLST II is currently ongoing and at the time of consultation no results were available (published or unpublished). According to ClinicTrials.gov the final data collection date for primary outcome measures is September 2022 and the website gives no indication of any planned interim analysis. The guideline will be reviewed, in line with NICE process, and this recommendation will be updated if appropriate.
214	Guy's and St Thomas' NHS Foundation Trust	General	General	General	We would like to ask that the term "wide excision" is used in preference to "wide local excision". Measuring the Vit D level should be considered and perhaps advice given to take supplements on an individual case by case. Sentinel node should be offered in centres which are audited.	Thank you for your comments. 'Wide local excision' was adopted because it is the term most commonly used. The guideline recommends measuring vitamin D, see recommendation 1.3.1 in the short version. The guideline includes a recommendation on SLNB biopsy but it did not investigate where this should be done or the appropriate arrangements for clinical governance.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
134	Melanoma Focus	Full	General	General	There is no advice given on adjuvant systemic therapy, radiotherapy after cranial metastatectomy, or palliative whole brain radiotherapy. These are all major clinical questions addressed regularly by the SSMDT and deserving of guidance.	Thank for your comment. It was not possible for the guideline to cover all aspects of clinical care for patients with melanoma. These particular questions were not raised by the GDG. In addition, when the scope of a NICE Clinical Guideline is issued for consultation the intent is for stakeholders to identify important issues. Further opportunity to comment arises at the Scoping Workshop. At neither point in the process were these clinical issues suggested for inclusion in the scope.
135	Melanoma Focus	Full	24	General	Management algorithm should include patients for who SLN biopsy should be considered	Thank you for your comment. The management algorithm includes patients who have been considered for SLNB see p24.
136	Melanoma Focus	Full	75		Recommendation on fing. There is no recommendation made on which mutation should tested for. Specifically there should be consideration given to ckit testing in patients with acral melanoma given that these patients may be considered for targeted therapy with imatinib off trial.	Thank you for your comments. The GDG could only consider targeted therapies with licensed drugs. The guideline will be reviewed and if other targeted therapies are licensed, then this may form the rationale for an update.
137	Melanoma Focus	Full	77	9	There is a challenge in identifying high risk patients for genetic testing and imaging. The AJCC staging system is not consistent in terms of higher stage being associated with worse prognosis. Patients Stage 3A disease have a better prognosis than patients with Stage 2C. The UK Consensus Paper 2014 www.melanomafocus.com , representing the views of 41 senior clinicians, adopted a patient specific risk approach. This identified high risk patients as expected 5 year survival of ≤ 50%. The majority of Stage 3A patients would not fulfil these criteria,	Thank you for your comment. The AJCC staging system included a number of stage IIC patients who had not had SLNB and who therefore might have been under-staged. We do not believe that there is any convincing evidence to support changing the current recommendations.
139	Melanoma	Full	107		It is inappropriate to mandate the advice given to patients	Thank you for your comment. The GDG

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Focus				considering sentinel node biopsy or completion lymphadenectomy, but not for any other advice or intervention given in the guidance.	would expect that patients would be fully informed before any of the recommendations were implemented. They felt that there were particular difficulties in the decision about whether or not to have SLNB and then whether to have a completion lymph node dissection if the SLNB result was positive. Therefore it was of particular importance that the advantages and disadvantages should be clearly laid out to aid discussion with the patient. As part of the implementation tools we are developing a specific options grid (see www.optiongrid.org) to help healthcare professionals and patients with this difficult decision.
138	Melanoma Focus	Full	107	General	The recommendation on sentinel node staging is welcome. However there is no justification for not including patients with Stage 1B disease, as this is an international standard of care	Thank you for your comment. The GDG concluded that there is no evidence of a clinically significant survival benefit resulting from SLNB. As a staging tool any possible benefit must be balanced against harm and cost. The GDG took the view that stage IB melanomas of this thickness have a low probability of being SLNB positive and that the costs and harms of SLNB in this group were likely to outweigh the advantages. Additional detail has been added to the Linking Evidence to Recommendations (LETR) statements to explain this. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).
140	Melanoma Focus	Full	109		The arguments on the choice of imaging are misguided and need to be reconsidered. There is no evaluation of the risk of radiation exposure. If the reason to carry out imaging is to detect metastatic disease, then the most sensitive and specific test should be used, PET CT. The use of PET CT in the UK for all cancers is at least 20% less than rest do Western Europe and 50% less that US. NHS England recently announced a big investment in PET CT scanning to redress this, though much of this will be through private providers. Similarly the advice on MR brain is incorrect due to the increased sensitivity and lower radiation dose. In addition, it is often easier to access MR than CT scanning due to capacity issues at sites. The Consensus Statement published on the Melanoma Focus website includes advise from melanoma imaging experts on imaging modality, and advice on radiation exposure, age and gender specific risk of second cancers.	Thank you for your comments. The text you cite on p109 (now p110) relates to the use of imaging for staging. The decision not to recommend PET-CT was based on the understanding that there was no evidence that early detection of metastatic disease by a more sensitive but more costly diagnostic modality would lead to survival benefit. The recommendation on the use of CT brain imaging in adults with suspected metastatic disease was made because it could be done most efficiently at the time of the whole body CT. Although there is a theoretical risk of radiation dose causing cancer and cataracts, the GDG did not consider this to be relevant in people with metastatic disease. This consideration has been added to the Linking Evidence to Recommendations (LETR) statements. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). We have also amended the

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						recommendation on imaging of the brain to clarify that it refers to people with suspected stage 4 melanoma. For patients contemplating regular imaging after diagnosis we have specified the potential risks associated with imaging of the brain in a table below the recommendations.
141	Melanoma Focus	Full	126	6	The LIMIT-1 study measured the pathological complete response rate of lentigo maligna to 12 weeks treatment with topical imiquimod. 27 patients were evaluable, and only 10 had a complete pathological response. Moreover, it was not possible to accurately predict pathological complete response by the post-treatment combination of absence of pigmentation and negative biopsy. The guideline development group may wish to consider this data before making any recommendation about the use of imiquimod to treat lentigo maligna. This data has not yet been published; the writing group for the study are aware of this submission to NICE. if further clarification is required please contact the Chief Investigator.	Thank you for your comment. The GDG made a 'consider' recommendation for imiquimod which indicates uncertainty about its effectiveness compared to surgery. The group felt that it may be appropriate to use imiquimod in selected cases where surgery with a 0.5cm margin would lead to unacceptable disfigurement or mobility. The GDG would have considered the results from the LIMIT-1 trial if they had been published and available in the public domain. The LIMIT-1 trial would not have been graded as high quality evidence as it was a small non comparative trial, however the LIMIT-1 results quoted by the stakeholder are consistent with the evidence the GDG looked at. The published evidence suggested biopsy overestimates the imiquimod complete response rate when compared to wide local excision of the tumour location. The complete response rate of 10/27 (37%) quoted from the

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						LIMIT-1 trial is somewhat lower than the 53% to 64% in the published evidence. The GDG recommended that repeat skin biopsy for histopathological assessment after treatment with topical imiquimod for stage 0 melanoma might be needed due to the uncertainty about its effectiveness. The guideline will be reviewed in the future, in line with NICE process, and this recommendation will be updated if appropriate.
142	Melanoma Focus	Full	137		As before, it is inappropriate to specify the information given to patient wrt completion lymphadenectomy and not do so form any other intervention or procedure.	Thank you for your comment. The GDG would expect that patients would be fully informed before any of the recommendations were implemented. They felt that there were particular difficulties in the decision about whether or not to have SLNB and then whether to have a completion lymph node dissection if the SLNB result was positive. Therefore it was of particular importance that the advantages and disadvantages should be clearly laid out to aid discussion with the patient. As part of the implementation tools we are developing a specific options grid (see www.optiongrid.org) to help healthcare professionals and patients with this difficult decision. We have also produced a table of potential advantages and disadvantages of regular imaging which we will also develop into an options grid.
143	Melanoma Focus	Full	186		The comment that targeted therapy is not associated with long term survival is not justifiable, as we do not have long	Thank you for your comment. We have changed this to 'uncertain'.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					enough follow-up on patents in trials. There is emerging evidence that some patients may go on to be long term survivors.	
144	Melanoma Focus	Full	193		The statement on chemotherapy is overly prescriptive. There are a small group of patients that who benefit chemotherapy and may benefit from second line therapy. The PRISM Study (Hauschild et al) showed that the outcomes for patients treated with second line chemotherapy was as good as firstline, reflecting patient selection. Whilst the majority of patients will not be suitable for second line therapy, and absolute statement against this is not justified and may compromise care. Combination BRAF and MEK inhibition has been shown to be associated with a survival benefit in 3 randomised phase 3 studies. This treatment will be licensed later in 2015 and subject initially to CDF then NICE evaluation (both already initiated). These data need to be included if the document is not to be out of date as soon as it is published. Similarly there needs to be consideration of the role do anti-PD1 antibodies. Nivolumab and pembrolizumab will be licensed in 2015. CDF applications are in hand and NICE has identified both for evaluation.	Thank you for your comment. We have modified the recommendation to clarify that second line chemotherapy should not be *routinely* used outside clinical trials, which would be more permissive. The GDG did want to support access to clinical trials in this context. Thank you for the information on the Hauschild paper, but this study would not have been included in our evidence review as their comparison was not the focus of our question. Thank you for this information. These agents may be assessed by NICE in the future as technology appraisals. However as they are not currently licensed they cannot be considered by this guideline. As these have already been identified by NICE for evaluation it is not possible to investigate them in this clinical guideline.
145	Melanoma Focus	Full	215		A standard of care in the UK is to follow up high risk patients for 10 years. There needs to be justification for reducing this to 5 years.	Thank you for your comments. The most recent British Association of Dermatology guidelines state 10 years but they previously stated 5 and there was no change in evidence to justify this change. Given the pressures on the NHS the GDG therefore felt that there was no justification for increasing this to 10 years.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					It is inappropriate to mandate that specific funding has to be identified for imaging follow up where there is no requirement for identification of funds for any other recommendation - sentinel node, molecular testing high risk patients, clinical follow-up. Specifically, the recommendation to measure Vitamin D levels is new and not currently standard of care, yet there is no requirement to identify funding for this. The Consensus Statement written by 41 UK clinicians indicates that surveillance imaging is already considered standard of care.	The impact on radiology departments of regular follow-up imaging is considerable and the economic model suggests that it is only cost effective if the assumptions about the effect of new systemic agents on long term survival are confirmed. The GDG felt that a general recommendation for regular imaging could not be made but in view of the rapidly changing evidence base on long term survival, did not want to prevent those teams that had identified funding and were carrying out the imaging in line with the Consensus Statement for carrying on with their existing policy
146	Melanoma Focus	Full	220		Please see comments on brain imaging before.	Thank you. The previous comment was about brain imaging for *staging*. As this section is about brain imaging for follow up therefore the comment does not apply to this section..
147	Melanoma Focus	Full	226		It is very clear from the detailed discussion that the recommendation on Vitamin D measurement and supplementation is premature.	Thank you for your comment. The guideline does not recommend routine supplementation of vitamin D and indeed by measuring levels unnecessary supplementation would be avoided. The dietary reference values for vitamin D, the significance of measured levels and other important issues such as potential adverse effects of high vitamin D levels are being considered by the Scientific Advisory Committee on Nutrition (SACN). This is detailed in the Linking Evidence to Recommendations

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						statements on p229. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). In view of this uncertainty the GDG were unable to make any strong recommendations about vitamin D except that it should be measured. The NICE Guideline on vitamin D is intended to be read in conjunction with the SACN report and the GDG agreed that this was also necessary for the melanoma guideline.
187	Melanoma Taskforce	FULL NICE	119 18	All	The Taskforce *Best Practice Pathway* recommends that *Patients newly diagnosed with stage 2B or higher melanoma (or stage ≥1B if SLNB is offered) should be referred to a SSMDT in line with current national guidance.*	Thank you for this information.
188	Melanoma Taskforce	FULL NICE	172 20	1.8	(p20-21) The Taskforce *Best Practice Pathway* recommends that *Patients with advanced cutaneous melanoma should have equitable access to the full range of available clinically-appropriate therapeutic options.*	Thank you for this information.
192	Melanoma Taskforce	FULL NICE	215 22	1.9	The Taskforce *Best Practice Pathway* recommends *At each follow-up appointment, whether it is with a dermatologist, plastic surgeon or CNS the patient's surgical scar, skin and lymph nodes should be examined. The patient will be asked to undress down to their underwear, removing their shoes and stockings to enable all of the patient's skin to be*	Thank you. The Guideline does specify full examination of the skin and regional lymph nodes.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					examined at each visit.	
189	Melanoma Taskforce	FULL NICE	219 22	1.9	The Taskforce *Best Practice Pathway* recommends that *Patients (AJCC stage 1B to IV) will have regular specialist follow up, 3 monthly for 3 years, thereafter 6 monthly for 2 years, which can include protocol-led clinical nurse specialist follow-up. After the 5 year period of specialist follow-up, Deferred Discharge is discussed with the patient.*	Thank you – this is not inconsistent with what we have recommended.
190	Melanoma Taskforce	FULL NICE	219 22	1.9	The Taskforce *Best Practice Pathway* recommends that *People having treatment for melanoma are offered timely and personalised information and support including an appropriately-tailored written follow up care plan.*	Thank you – this is not inconsistent with what we have recommended.
191	Melanoma Taskforce	FULL NICE	219 22	1.9	The Taskforce *Best Practice Pathway* recommends *Clinical Commissioning Groups should manage the workforce capacity in accordance with the increasing demand for specialist skin cancer services to ensure that patients within their commissioning area have equitable access to high quality melanoma care.*	Thank you for your comment. Workforce capacity was not prioritised as a topic for inclusion in this guideline during the scoping process.
186	Melanoma Taskforce	NICE	General	General	The Taskforce would like to submit its report *Quality In Melanoma Care: A Best Practice Pathway* for consideration by the guideline development group. It can be found here: http://melanomataskforce.com/wp-content/uploads/2013/04/LOW-RES_FINAL_QUALITY-IN-MELANOMA-CARE_A-BEST-PRACTICE-PATHWAY.pdf	Thank you for your comment. NICE guidelines are not able to cross-reference documents from other organisations. As this is a consensus document it would also not meet the inclusion criteria for appraisal as part of the evidence review.
193	Melanoma Taskforce	NICE	General	General	The Taskforce Pathway report also highlights that *All MDTs should have a defined referral pathway to a nominated clinical team for patients requiring palliative care input.* The Taskforce would like to see this considered in the guideline recommendations.	Thank you for your comment. This was not a clinical question that was prioritised for investigation by the guideline. Hence we are not able to make any recommendations on this issue.
194	Melanoma Taskforce	NICE	General	General	The Taskforce is also keen to see a better incentivised and highly skilled workforce for melanoma in primary care. The Pathway report highlights that: G*Ps should be sufficiently incentivised to train as GPwSIs in order to build a workforce with the necessary expertise in skin cancer. This could include financial incentives and a place on the local MDT.* The report also recommends that: *All GPs should have access to training in the diagnosis, triage and referral of*	Thank you for this information. It was not within the remit of this clinical guideline to address issues around providing a better incentivised and highly skilled workforce for managing melanoma in primary care. Workforce capacity was not prioritised as a topic for inclusion in this guideline during the scoping process.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					patients with suspected melanoma. This training should be made available to undergraduate and postgraduate medical students and be part of GP training and continuous professional development. The group would suggest that the Royal College of General Practitioners (RGCP) is best placed to take this recommendation forward.	
195	Melanoma Taskforce	NICE	General	General	The Taskforce also believes it is important that systems for delivering melanoma care should be integrated, regardless of the status of provider. The pathway report recommends that: *The provision of melanoma care must be delivered via an integrated system, irrespective of the provider. Private and public sector providers must be able to communicate effectively and ensure that decisions on the patient's care pathway are made with all of the necessary members of the clinical team involved.*	Thank you for your comment. It was not within the remit of this clinical guideline to address issues of service provision and integration which were previously covered by the NICE guidance on 'Improving outcomes for people with skin tumours including melanoma'.
196	Melanoma Taskforce	NICE	General	General	It is important that workforce factors are taken into account in order to ensure the best quality care can be provided to patients. The Pathway report recommends that: *Clinical Commissioning Groups should manage the workforce capacity in accordance with the increasing demand for specialist skin cancer services to ensure that patients within their commissioning area have equitable access to high quality melanoma care.*	Thank you for your comment. It was not within the remit of this clinical guideline to address issues around workforce.
131	Merck Sharp & Dohme Limited	Full	27	2	In the boxes which state "options are…" we suggest this should be re-worded to "Currently recommended options are…" to emphasise the point that although the technologies listed are reflective of current NICE guidance, this list is subject to grow as new technologies are developed and reviewed by NICE	Thank you for your comment. Although this list of technologies may grow we think the current wording of the algorithm is appropriate since these reflect the situation at this time.
132	Merck Sharp & Dohme Limited	NICE	31		(p31-32) Section "Related NICE guidance – under development": Please ensure that the following technology and topic is included in this list, as this single technology appraisal (STA) has now been formally referred to NICE by the Department of Health and the appraisal is scheduled into the NICE work programme:	Thank you for your comment. We have made this change.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					Melanoma (unresectable, metastatic) - pembrolizumab (after ipilimumab) [ID760]: NICE technology appraisal guidance. Anticipated publication date: December 2015 (http://www.nice.org.uk/guidance/indevelopment/gid-tag501)	
36	NHS Choices	General	General	General	We welcome the guidance and have no comment on the contents as part of the consultation.	Thank you.
44	NHS England	General	General	General	Thank you for the opportunity to comment on the above clinical guideline. I wish to confirm that NHS England have no substantive comments to make regarding this consultation.	Thank you.
96	North of England Dermatopathology Service	Full	20		AJCC staging table. This contains errors (these are same as part of Comment 1 above) 1A Should state AT OR below (not just below) 1.0 (not 1) mm 1B Should state AT OR below (not just below) 1.0 (not 1)mm	Thank for your comment. We acknowledge that in order to make the recommendations more accessible to the general public, the table on p22 was over-simplified, giving rise to some inaccuracies. The table has now been removed and replaced with a cross reference to the full AJCC staging system in both the full and short guideline.
99	North of England Dermatopathology Service	Full	70		Recommendations Same comments as Comment 4 above on NICE document	Thank you for your comment. We have amended the title to 'Atypical spitzoid lesions'. Although the term borderline lesion was in the clinical question, there was no relevant evidence identified. The GDG agreed that the evidence suggested there were no tests available to distinguish benign spitzoid lesions from malignant ones and therefore referral to the SSMDT would concentrate the management of rare and difficult lesions in centres. The GDG do not anticipate a significant increase in workload resulting from this recommendation as such lesions remain uncommon.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						The GDG assessed the evidence for FISH (page 72). They reported the evidence to be of low quality and it was judged to be insufficient to justify the use of FISH. The guideline will be reviewed, in line with NICE process, and this recommendation will be updated if appropriate. The GDG reviewed the evidence and concluded that spitzoid lesions which do not look obviously malignant histopathologically do sometimes behave as melanoma, and there is no robust test to distinguish them. The resulting recommendation is acknowledged to result in "excessive" treatment for a proportion of the patients, but the GDG felt that this was justifiable to avoid undertreating melanomas. This has been explained in the Linking Evidence to Recommendations (LETR) statements. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). The advice to treat spitzoid tumours of unknown malignant potential as

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						melanoma means that margins would be selected as they would be for all melanomas, so that is the thickness was 2.5mm then a margin of at least 2cm is recommended. The role of SLNB was discussed, and on the concern about the quality of reported sentinel node biopsy studies is documented on page 72. The GDG felt therefore that no recommendation could be made on this issue and have stated this in the Linking Evidence to Recommendations (LETR) statements.
95	North of England Dermatopathology Service	FULL NICE	70 15		BORDERLINE AND SPITZOID LESIONS TITLE The title is incorrect as borderline melanocytic lesions in general are not discussed in the NICE draft. The draft only discusses Spitzoid lesions. The title has inappropriately been transcribed from the full guidance where more than purely spitzoid lesions is discussed. The title should be only Spitzoid lesions 1.2.4 With no accepted definition of either spitzoid or atypical , sending all suspected cases to a SSMDT is unreasonable significant extra work – especially given the current poor funding and national staffing problems. It would be far more sensible to recommend that any suspected spitzoid lesion should be doubly reported histopathologically , always including at least one pathologist participating in the National Specialist Dermatopathology EQA (as the NICE and Cancer Peer Review definition of a specialist Dermatopathologist) and receive MDT review. Cases should be referred to the SSMDT where involvement of a NSDEQA pathologist is not possible and all cases of spitzoid tumours of uncertain malignant potential (STUMP)	Thank you for your comments. We have amended the title to 'Atypical spitzoid lesions'. Although the term borderline lesion was in the clinical question, there was no relevant evidence identified. The GDG agreed that the evidence suggested there were no tests available to distinguish benign spitzoid lesions from malignant ones and therefore referral to the SSMDT would concentrate the management of rare and difficult lesions in centres. The GDG do not anticipate a significant increase in workload resulting from this recommendation as these lesions are uncommon.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					1.2.5 All cases of unknown malignant potential (STUMP) warrant FISH melanoma-probes analysis. Although most will be negative, at least those that are positive are then proven to be melanoma and can be treated as such. 1.2.6 Managing STUMP as melanoma is simply clinically wrong – especially when FISH negative. Most will not be melanoma, many will be on cosmetically sensitive areas in young people and as many are over 2mm, they will receive 20mm un-necessary excision margins. This is defensive and clinically damaging treatment for the very few that are melanoma.If FISH negative the margin need not be greater than 10mm. PLUS No advice is provided on clinical margins for benign and atypical spitzoid lesions (?5mm) No mention that SLNB has no role in this group of disorders (as many biologically atypical cases will be found in lymph nodes) . A positive SLNB in this group of disorders does not necessarily indicate melanoma and indeed most will not be.	The GDG assessed the evidence for FISH (page 72). They reported the evidence to be of low quality and was judged to be insufficient to justify use of FISH currently. The guideline will be reviewed, in line with NICE process, and this recommendation will be updated if appropriate. The GDG reviewed the evidence and concluded that spitzoid lesions which do not appear obviously malignant histopathologically do sometimes behave as melanoma, and there is no robust test to distinguish them. The resulting recommendation is acknowledged to result in "excessive" treatment for a proportion of the patients, but the GDG felt that this was justifiable to avoid undertreating melanomas. This has been explanined in the Linking Evidence to Recommendations (LETR) statement. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						The advice to treat spitzoid tumours of unknown malignant potential as melanoma means that margins would be selected as they would be for all melanomas , so that is the thickness was 2.5mm then a margin of at least 2cm is recommended. The role of SLNB was discussed and the concern about the quality of reported sentinel node biopsy studies is documented on page 72. The GDG felt therefore that no recommendation could be made on this issue and have stated this in the Linking Evidence to Recommendations (LETR) statements.
98	North of England Dermatopathology Service	Full	107		Recommendations Same comments as Comment 3 above on NICE document	Thank you for your comment. The probability of a positive SLNB is related to thickness. The GDG based their recommendation on the observation that the probability is so low in patients with a thickness less than 1mm that as a staging tool SLNB has less value in this group. The GDG took the view that stage IB melanomas of this thickness have a low probability of being SLNB positive and that the costs and harms of SLNB in this group were likely to outweigh the advantages. If in the future, a survival benefit for the procedure was demonstrated or effective adjuvant therapies were reported for melanoma, then the GDG would expect the recommendations to change. The GDG was aware that in some

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						centres SLNB is not performed for patients with tumours thicker than 4mm. However we found no evidence that SLNB offered less prognostic value in these thicker tumours.
94	North of England Dermatopathology Service	FULL NICE	107 8		SENTINEL LYMPH NODE BIOPSY 1.5.1 Many/most UK and international centres would recommend SLNB for pT1b melanoma. Unlike the recommendation this would include melanomas below 1 mm with ulceration or mitotic activity 1.5.2 SLNB is advised here for Stage 2C This includes pT4b ie greater than 4mm with ulceration. Many/most UK and international centres would consider , however , that there is insufficient evidence base to use SLNB over 4mm – especially just as a staging modality.	Thank you for your comments. The probability of a positive SLNB is related to thickness. The GDG based their recommendation on the observation that the probability is so low in patients with a thickness less than 1mm that as a staging tool SLNB potentially has less value in this group. The GDG took the view that stage IB melanomas of this thickness have a low probability of being SLNB positive and that the costs and harms of SLNB in this group were likely to outweigh the advantages. If in the future, a survival benefit for the procedure was demonstrated or effective adjuvant therapies were reported for melanoma, then the GDG would expect the recommendations to change. The GDG was aware that in some centres SLNB is not performed for patients with tumours thicker than 4mm. However we found no evidence that SLNB offered less prognostic value in these thicker tumours.
97	North of England Dermatopathology Service	Full	119		6.Recommendations Same comments as Comment 2 above on NICE document	Thank you for your comment. Whilst the margin trials have been based upon thickness, prognosis is currently best predicted by AJCC stage. Clinical trial recruitment and stratification is therefore predominantly based upon stage and so

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						the GDG adopted the approach of using stage where possible for consistency. We have removed the reference to Breslow thickness in the recommendation to avoid confusion. We acknowledge that in order to make the recommendations more accessible to the general public, the table on p22 was over-simplified, giving rise to some inaccuracies. The table has now been removed and replaced with a cross reference to the full AJCC staging system in both the full and short guideline. The clinical trial data are based upon measured clinical excision margin and Breslow thickness. There is established considerable inter-observer variation and intra-observer variation in both measures and the GDG was not concerned that a difference in 0.01mm in Breslow thickness for example would make the recommendations inappropriate.
93	North of England Dermatopathology Service	Full NICE	119 18	1.6.3 and 1.6.4	MANAGING STAGES 0-2 OF MELANOMA British, European and most international Guidelines use Breslow thickness in relation to recommendations on clinical excision margins. This is not by accident as the evidence base invariably relates to BT rather than staging and conversion into staging is not straightforward. The current NICE draft , however, uses staging rather than the more usual Breslow thickness. Without doubt this approach was chosen to seemingly convey apparent simplicity in what to do and when.	Thank you for your comments. Whilst the margin trials have been based upon thickness, prognosis is currently best predicted by AJCC stage. Clinical trial recruitment and stratification is therefore predominantly based upon stage and so the GDG adopted the approach of using stage where possible for consistency. We have removed the reference to Breslow thickness in the recommendation to avoid confusion.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					Sadly however the GDG have generated inaccuracies in their recommendations , by using definitions of staging based on inaccurate Breslow thicknesses (see Comment 1) . The GCGs recommendations then become partly inaccurate with case overlap. With specific reference to the NICE draft, the following errors require correction and decimal points must be introduced to obtain the necessary accuracy. 1.6.3 Stage 1 includes pT2a ie 1.01-2.0 mm This therefore needs to state Breslow thickness AT OR below 2.0mm (NOT JUST BELOW 2) 1.64 Stage 2 includes pT2b ie 1.01-2.0mm with ulceration This therefore needs to state Breslow thickness ABOVE 2.0mm (NOT 2 OR MORE) Far better to use Breslow thickness rather than stage and speak the same language that every other UK /European body has done.	We acknowledge that in order to make the recommendations more accessible to the general public, the table on p11 was over-simplified, giving rise to some inaccuracies. The table has now been removed and replaced with a cross reference to the full AJCC staging system in both the full and short guideline. The clinical trial data are based upon clinical measured excision margin and Breslow thickness. There is considerable, established inter observer variation and intra observer variation in both measures and the GDG was not concerned that a difference in 0.01mm in Breslow thickness for example would make the recommendations inappropriate. Whilst the margin trials have been based upon thickness, prognosis is currently best predicted by AJCC stage. Clinical trial recruitment and stratification is therefore predominantly based upon stage and so the GDG adopted the approach of using stage where possible for consistency. We have removed the reference to Breslow thickness in the recommendation to avoid confusion.
92	North of England Dermatopathology Service	NICE	11	Table	TABLE: STAGES OF MELANOMA It is disappointing that the national experts on the NICE Guidance Development Group did not seem to be aware of the accurate AJCC/UICC 7 staging for melanoma. Their errors in Breslow thickness then	Thank you for your comments. We acknowledge that in order to make the recommendations more accessible to the general public, the table on p 11was over-simplified, giving rise to some

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					automatically introduce later errors when using staging for areas such as margins of excision 1A should be AT OR less (NOT JUST LESS) than 1.0 (NOT 1) (PLUS W/O ULCER/MITOSIS)…….. 1B should be AT OR less (NOT JUST LESS) than 1.0 (NOT 1) with ulceration….. 1B should be 1.01 (NOT 1) -2.0 (NOT 2) with no ulceration….. 2A should be 1.01 (NOT 1) – 2.0 (NOT 2) with ulceration…… 2A should be 2.01 (NOT 2) – 4.0 (NOT 4) with no ulceration…….. 2B should be 2.01 (NOT 2) – 4.0 (NOT 4) with ulceration 2B should be more than 4.0 (NOT 4) with no ulceration 2C should be more than 4.0 (NOT 4) with ulceration The GDG failure to acknowledge the AJCC7 use of decimal points in melanoma staging , completely compromises their advice in some areas such as excision margins. It may seem tedious but accepted international accuracy cannot be simply ignored to create erroneous clinical simplicity. These important errors immediately compromise the overall credibility of the draft. It is surprising that the GDG overlooked these errors of basic international proven fact.	inaccuracies. The table has now been removed and replaced with a cross reference to the full AJCC staging system in both the full and short guideline.
217	Primary Care Dermatology Society	FULL NICE General	56 1.1.2 General	!.2 Challenges	We would much prefer to see our aim represented i.e. that all GP practices should have access to a dermatoscope and for there to be more than one clinician trained to be able to "confidently diagnose the obviously benign" As such we feel that the numbers of presenting patients and the huge number of inappropriate 2 week wait cancer referrals requires most GPs to be trained in the use of just another "scope!" (c.f ophthalmoscope) Thus we recommend GPs and GPSIs to be trained and revalidated along with other GP topics.	Thank you for your comment. Thank you for your response. We have passed it to the NICE implementation support team to inform their support activities for this guideline.
216	Primary Care Dermatology	FULL NICE	56 1.1.2	Recommendations	This again assumes you are starting from a referred patient with a suspicious lesion when the first step is in primary care.	Thank you for your comment. The scope of this guideline only covers children, young people and adults with suspected

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Society	General	General	1.2		melanoma and children, young people and adults with newly diagnosed cutaneous melanoma. Recommendations on referral of people with suspected melanoma presenting in primary care can be found in the NICE guideline on Suspected Cancer (see Cancer: general and other | Guidance and guideline topic | NICE
215	Primary Care Dermatology Society	FULL NICE General	56 1.1.1 General	1.1 Key Priorities for implementation	We are disappointed to see very little about prevention and the opportunistic case finding of melanomas as ideally carried out in primary care and via the media. Since we know that up to 20% of melanomas are not the index case presented to secondary care, general skin examination is vital. The absence of such comments may lead the public and primary care health practitioners to ignore the whole guideline as irrelevant to their practice.	Thank you for your comment. The scope of this guideline did not include the prevention or opportunistic case finding of melanoma. However NICE have already published guidance on Skin Cancer Prevention.
219	Primary Care Dermatology Society	FULL General	56 General	1.2, 3	Again we feel the requirement for vitamin D measurement and supplementation is also an issue for primary care in identifying those at risk as well as catch up once melanoma has occurred.	Thank you for your comment. Recommendations on measurement and management of suboptimal vitamin D levels have been made on p229 of the full guideline and section 1.3 of the short version. Recommendation 1.1.3 is to ensure that patients are given advice that appropriately balances the competing risks of sun exposure and vitamin D depletion. Please see NICE public health guidance on Vitamin D, recommendation 7 (Vitamin D: increasing supplement use among at-risk groups | 1-recommendations | Guidance and guidelines | NICE
218	Primary Care Dermatology	FULL General	66 General	1.2, 3	Photography…We feel that to make this guideline useful for all then a comment such as always refer any "New.Raised and Growing" lesion and which is not obviously benign, since	Thank you for your comment. We have amended the recommendation to make clear that it refers to the use of

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Society				these are not suitable for photography. Any suspicious melanocytic lesion should normally be excised for histology.	photography in secondary and tertiary care. Referral from primary care is outside the scope of this guideline.
220	Primary Care Dermatology Society	Implementation	General	General	It is important to include the Primary HealthCare team at all stages despite the fact that most of the care after diagnosis is in secondary or tertiary care. The family and community can all benefit from the awareness and knowledge gained. This guideline is obviously not aimed at primary care but the most important aspects of melanoma are prevention and early diagnosis, neither of which does this guideline significantly enhance.	Thank you for your comment. We agree that primary care has a supportive role in the management of patients with diagnosed melanoma. The NICE guideline on suspected cancer covers referral from primary to secondary care.
45	Roche Products Ltd	FULL NICE	77 15	1.2.7, 1.2.9 & 1.2.10	(p15-16) We support the guideline recommendations on genetic testing of tissue samples in patients for whom a targeted systemic therapy is a treatment option. We also support consideration for genetic testing being given to patients with stage 2C and stage 3 melanoma.	Thank you.
46	Roche Products Ltd	FULL NICE	193 21	1.8.5 & 1.8.10	(p21-22) As NICE guidance for dabrafenib and vemurafenib are identical with respect to the populations covered by the guidance, nature of the recommendations, and availability of patient access schemes, it is not clear the wording of these two paragraphs is different. To avoid the potential for confusion to the reader, we suggest the text in these sections of the final guideline should be identical to one another.	Thank you for your comment. Thank you for your comment. The NICE process for linking to other NICE guidance is documented in section 8.1 of 'Developing NICE guidelines: the manual' (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). This accounts for the differences in presentation that you describe.
47	Roche Products Ltd	FULL NICE	193 21	1.8.8 & 1.8.9	(p21-22 & 31) Recommendations for ipilimumab described in the draft guideline are restricted to those made in TA268 (Ipilimumab for previously treated advanced melanoma). In 2014, NICE published TA319 (Ipilimumab for previously untreated advanced melanoma), although these are not captured within the draft guideline, despite page 31 referring to TA319 as 'Related NICE Guidance', along with TA268. Again, to avoid potential confusion for the reader, we suggest that all relevant NICE recommendations are described in the	Thank you for your comment. The NICE process for linking to other NICE guidance is documented in section 8.1 of 'Developing NICE guidelines: the manual' (https://www.nice.org.uk/Media/Default/About/what-we-do/our-programmes/developing-NICE-guidelines-the-manual.pdf). This accounts for the differences in

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					final guideline.	presentation that you describe.
48	Roche Products Ltd	NICE	31	'Under development'	Depending on the timing of final guideline publication and formal referral from Ministers, the planned NICE STA for 'Vemurafenib with Cobimetinib for Malignant melanoma previously untreated BRAFV600-mutation positive, unresectable, locally advanced or metastatic (TS ID 7416)' should be listed in this section.	Thank you for your comment. This will be added if it has formally been referred to NICE at the time of publication.
49	Roche Products Ltd	NICE	48	Stephen Keohane interest	We believe the detail of Stephen Keohane's 4th declared interest contains a spelling error: "(Everidge)" should be replaced with "(Erivedge)".	Thank you for your comment. This change has been made.
212	Royal College of General Practitioners	General	General	General	I have read through the Melanoma Clinical Practice Guideline. The content is excellent and very informative. The use of different colours is helpful. I have no specific comments.	Thank you
213	Royal College of Nursing	General	General	General	This consultation was sent to nurses working in this area of health. Feedback suggests that there are no comments to submit to inform on the consultation at this time. Thank you for the opportunity.	Thank you
43	Royal College of Paediatrics and Child Health	General	General	General	Thank you for inviting the Royal College of Paediatrics and Child Health to comment on the Melanoma draft guideline consultation. We have not received any responses for this consultation.	Thank you.
205	Royal College of Pathologists	Full	General	General	This is an impressive and considerable body of work on melanoma, however,it is very long and may benefit from editing with the intention of shortening the document.	Thank for your comment. NICE produces a shorter version of the guideline which contains only the recommendations. A copy of the short version can be found on the NICE website (please see Skin cancer | Guidance and guideline topic | NICE).

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
197	Royal College of Pathologists	Full	8	General	What consultation with the melanoma community was performed to identify these as ''key research requirements''?	Thank for your comment. The recommendations were based on the conclusions of the GDG once they had reviewed the evidence. This information was then issued as part of the guideline for a six week consultation with stakeholders in line with NICE methodology (please see https://www.nice.org.uk/article/PMG20/chapter/1%20Introduction%20and%20overview).
200	Royal College of Pathologists	Full	59	Diagnosis	This seems to launch into dermoscopy and even more esoteric methodology rather than dealing with simple ABCD criteria. The value of newer techniques is no doubt great but some may not have access to these.	Thank you for your comment. The guideline does not cover all aspects of the diagnostic pathway – it focuses on areas of uncertainty or variation in practice. The GDG found high quality evidence that dermoscopy was more sensitive and specific than clinical examination alone. This evidence informed the recommendation. Getting access to dermoscopes and training in their use will be a matter for implementation of the guideline.
204	Royal College of Pathologists	FULL NICE	70 15	Spitz	1.2.5. The statement ''Make the diagnosis of a spitzoid tumour of unknown malignant potential on the basis of the histology, clinical features and behaviour'' is rather simplistic. Firstly, most work uses the term ''uncertain'' rather than ''unknown''. Secondly, just because it doesn't metastasise does not mean it isn't melanoma. Most melanomas of usual type don't metastasise either yet we do not re-badge those as being of uncertain potential. Conversely, some Spitz lesions do metastasise to a regional node but these then fail to progress and some argue that even this does not	Thank you for your comments. We have changed 'unknown' to 'uncertain'. This recommendation reflects the necessity to consider the full clinical picture rather than just rely upon histopathology. It refers to the person's age at appearance, whether it had grown quickly or not and what it looked like. Therefore if the pathologist in the SSMDT

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					necessarily indicate true malignancy. It might be best to leave the diagnosis of a STUMP primarily to the histological features. 1.2.6. There was some concern that the statement ''manage spitzoid tumours of unknown malignant potential as melanoma'' might lead to overtreatment. There have been papers on the objective grading of the severity of atypia in Spitz lesions. Since many Spitz lesions occur on the face the concern might be that lesions with only limited atypia might then be subjected to fairly major and likely unnecessary wide excision.	is reassured by the histology, the GDG took the view that if the lesion was reported to have grown rapidly in an older person, then this should be brought into consideration. This justifies the recommendation that such lesions should be considered at the SSMDT. The GDG has clearly acknowledged on p72 that overtreatment is a justifiable risk. It is also the GDG's experience that atypical spitzoid lesions are less common on the face than on the limbs and trunk.
201	Royal College of Pathologists	FULL NICE	107 8	Diagnosis	Again no mention of clinical features and the inclusion of genetic testing for targeted therapy of advanced disease in this section on diagnosis is odd!	Thank you for your comment. The guideline does not cover all aspects of the diagnostic pathway – it focuses on areas of uncertainty or variation in practice. The section on genetic testing was included in "diagnosis" as genetic testing of the paraffin embedded tumour would be considered at the time of diagnosis.
202	Royal College of Pathologists	Full	113	Excision	(p113 onwards) It is difficult to think of any other melanoma guideline where width of excision relates to clinical stage rather than being determined by Breslow thickness. This is extremely confusing and is one reason why the AJCC7 pT table is important. It also follows that the advice in the short document is incorrect given the inaccuracies in the staging table (point 3).	Thank you for your comment. Whilst the margin trials have been based upon thickness, prognosis is currently best predicted by AJCC stage. Clinical trial recruitment and stratification is therefore predominantly based upon stage and therefore the GDG adopted the approach of using stage where possible for consistency. We have removed the reference to Breslow thickness in the recommendation to avoid confusion. We acknowledge that in order to make the recommendations more accessible to

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						the general public, the table on p 21 was over-simplified, giving rise to some inaccuracies. The table has now been removed and replaced with a cross reference to the full AJCC staging system in both the full and short guideline.
203	Royal College of Pathologists	Full	193	Therapy	There is mention of the potential value of imatinib (Glivec) in managing Kit mutated melanomas (usually of acral or mucosal types).	Thank you for your comment. This intervention was not prioritised for investigation in the guideline so the evidence on it has not been appraised and therefore no recommendations can be made.
198	Royal College of Pathologists	NICE	4	Children	Is this part of mistreatment of children a standard requirement for NICE guidelines? It seems rather superfluous.	Thank you for your comment. This is standard text that forms part of the short version.
199	Royal College of Pathologists	NICE	11	Staging	This table is factually incorrect and differs from the version in the full guideline. For example Stage 1A and Stage 1B ought to state that the Breslow is ''at or below'' 1mm and for Stage 2A it should read 1.01-2.0mm. The same errors in thickness are compounded throughout the table. In addition to this Staging the AJCC7 table for pathological staging of the primary tumour should also be provided showing the pTNM stages pTis-pT4b. As it stands the current table is confusing for pathologists.	Thank you for your comment. We acknowledge that in order to make the recommendations more accessible to the general public, the table on p11 was over-simplified, giving rise to some inaccuracies. The table has now been removed and replaced with a cross reference to the full AJCC staging system in both the full and short guideline.
148	Royal College of Physicians, National Cancer Research Institute, Association of Cancer Physicians	Full	77	9	Also NICE version, page 16, line 2. The point of genetic testing of resected melanoma is to provide information which can be used when these patients relapse in order to make treatment decisions in a timely fashion. Therefore the group to be tested should be those considered to be at high risk of relapse. Stage 2B melanoma patients are generally considered to be at high risk of recurrence (see entry criteria for UK and EORTC adjuvant trials conducted in patients with resected melanoma at high risk of recurrence) and therefore should also have genetic testing performed.	Thank you for your comment. The GDG accepts that selecting patients for testing is contentious. As for the rationale related to cost, and the probability that the nature of the tests will improve in the near future, tests will evolve in which resistance may also be predicted and that it may be preferable to retain the small amount of primary tumour tissue stored for those tests. The guideline discusses tumour heterogeneity and the clones of tumour cells of relevance for

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						the treatment of stage IV disease will likely be those present in metastatic tissues. It may be that in the relatively near future testing primaries will be considered to have lower predictive value. The guideline makes it clear that the GDG had to review evidence which was in a state of rapid evolution, and these recommendations may be changed when the guideline is updated in line with NICE policy.
151	Royal College of Physicians, National Cancer Research Institute, Association of Cancer Physicians	Full	106	11	Also NICE version, page 16, line 25. We are concerned that SLNB is being recommended for only a subset of patients with stage 1B melanoma with Breslow thickness > 1mm. We believe that SLNB should be offered to all patients with stage 1B disease, irrespective of Breslow thickness	Thank you for your comment. The GDG concluded that there is no evidence of a clinically significant survival benefit resulting from SLNB. As a staging tool any possible benefit must be balanced against harm and cost. The GDG took the view that stage IB melanomas of this thickness have a low probability of being SLNB positive and that the costs and harms of SLNB in this group were likely to outweigh the advantages.
152	Royal College of Physicians, National Cancer Research Institute, Association of Cancer Physicians	Full	145	17	The question as worded does not specify identification of the most effective LOCAL treatment for in transit metastases, but the modalities evaluated are confined to local interventions. It needs to be made clear that in some cases, systemic therapy will be an appropriate treatment for in transit metastases	Thank you for your comment, which is correct. Although we cannot change the wording of the clinical question, the evidence appraised was entirely about local treatment. In the background section we listed systemic treatments and we have amended the text to include systemic treatments.
153	Royal College of Physicians, National	Full	193		Also NICE version, page 21, line 12. Please note that Ipilimumab was approved by NICE for use as first line therapy in July 2014 (NICE TA319) and this additional guidance needs to be referred to here	Thank you for your comment. In line with NICE process, we have cross-referenced to both TA319 and TA268 rather than reproducing the full recommendations

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Cancer Research Institute, Association of Cancer Physicians					because both of these TAs are now scheduled for update.
154	Royal College of Physicians, National Cancer Research Institute, Association of Cancer Physicians	FULL NICE	193 21	5	The option for patients with unresectable or metastatic melanoma to be offered participation in a clinical trial as treatment of choice should be stated at the start of this section	Thank you for your comment. Although the GDG agrees with the principle that patients should be encouraged to participate in clinical trials, we are not able to make such a recommendation on the basis of the clinical questions that were investigated.
156	Royal College of Physicians, National Cancer Research Institute, Association of Cancer Physicians	FULL NICE	215 24	10	It is surprising that the guidelines have not specified frequency of follow-up in resected stage IIC/III melanoma. Please refer to the Melanoma Focus consensus guidelines - could these be included here?	Thank you for your comment. The recommendation on p217 states that follow up should be every 3 months for the first 3 years and then every 6 months for the next 2 years. The GDG are aware of the guideline produced by Melanoma Focus. However we are unable to reproduce recommendations from other organisations within NICE guidelines.
155	Royal College of Physicians, National Cancer Research Institute, Association of Cancer	Full	220	3	Also NICE version, page 22, line 22. It is not clear why CT is being recommended in preference to MRI for imaging of the head in adult patients. In all age groups, MRI avoids radiation exposure associated with CT imaging, while CNS MDTs always require MRI of head prior to making any decisions regarding intervention. Therefore, MRI is in fact the imaging modality of choice for the brain, whatever age of the patient. However, some institutions have limited access to MRI and in these institutions, we agree that	Thank you for your comment. The GDG acknowledge that MRI is more sensitive than CT in detecting small volume metastases. However, they recognised that MRI is more expensive and would involve the patient in a second visit to hospital, whereas CT brain could be carried out at the same time as imaging the rest of the body. Therefore the GDG

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Physicians				use of CT scanning as an alternative brain imaging modality should be considered acceptable.	agreed that the additional cost would not justify the relatively small benefits of finding brain metastases earlier. This information is included in the Linking Evidence to Recommendations (LETR) statements in the full version of the guideline. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).
150	Royal College of Physicians, National Cancer Research Institute, Association of Cancer Physicians	FULL NICE	226 General	1.3.1 1.3.2 General	The need for further research to evaluate the role of Vitamin D supplementation in changing outcomes is identified as a research priority. It should be noted that there is an ongoing trial in Australasia (https://anzmtg.org/trialdetails.aspx?trialno=12) which might be used to inform decision making regarding future Vitamin D supplementation and related melanoma research studies that should be undertaken.	Thank you for this information - the GDG is aware of this trial. **Published guidelines undergo surveillance reviews every 2 years after publication to decide if an update is needed at that time. This surveillance review decision is informed by a number of stages of intelligence gathering to identify any potential new sources of evidence.**
149	Royal College of Physicians, National Cancer Research Institute,	Full	226	6	Also NICE version, page 16, line 11. We are concerned that the recommendation to measure Vitamin D levels at diagnosis in all people with melanoma is premature. The evidence to justify this recommendation is limited and controversial. For example, unpublished data from the UK adjuvant AVAST-M randomised controlled trial has not shown any relationship between recurrence or	Thank you for your comment. In view of the uncertainty in the evidence for this topic that the GDG felt unable to make any strong recommendations about vitamin D except that it should be measured. The GDG agreed that there are many uncertainties about the

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Association of Cancer Physicians				survival and vitamin D levels. Implementation of this recommendation has significant resource implications, which is difficult to justify. We fully support the need to supplement people with suboptimal vitamin D levels, but believe that the current NICE vitamin D recommendations (Nov 014) should prevail in identifying these people and that melanoma is not as yet a proven indication for mandating measurement of Vitamin D. We disagree that the resources involved to implement this change in practice are small. We are also concerned that there is uncertainty regarding what constitutes optimal supplementation. We strongly recommend that this matter be the subject of further research before implementing change in standard practice.	significance of biochemical indicators of vitamin D status and the association between those levels and various health outcomes. These and other important issues such as potential adverse effects of high vitamin D levels are being considered by the Scientific Advisory Committee on Nutrition (SACN). This is detailed in the Linking Evidence to Recommendations (LETR) statements on p230. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). The GDG were aware of the AVAST-M trial however it was not designed to assess Vitamin D. The aim of the trial is to assess the use of bevacizumab after surgery and was therefore not identified in the systematic evidence search for this topic.
158	Royal College of Physicians, National Cancer Research Institute,	Implement ation	General	Gener al	We do not agree that it is appropriate to introduce measurement of Vitamin D in all patients diagnosed with melanoma. We believe the current NICE guidance on Vitamin D (Nov 2014) should be adhered to.	Thank you for your comment. In view of the uncertainty in the evidence for this topic that the GDG felt unable to make any strong recommendations about vitamin D except that it should be measured. By making this recommendation, patients who have very

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Association of Cancer Physicians					low levels (known to be associated with poor bone health) would be identified and probably just as importantly people with high levels or levels that are adequate would also be identified. In the text of the guideline the GDG explained why they felt that advice on monitoring could not be made: that the data are even more uncertain about the validity of this.
159	Royal College of Physicians, National Cancer Research Institute, Association of Cancer Physicians	Implementation	General	General	Currently, there is no national commissioned process for melanoma genotyping. This needs to be formally addressed, urgently. This is both an issue for service implementation and for research - for example, immunohistochemical testing is probably as reliable as BRAF genotying for identifying the V600D mutation and is far less expensive compared with gene sequencing. On the other hand, new treatments are likely to become available for patients with other genetic mutations, including NRAS and CKIT. Multigene testing is now feasible, but needs to be provided in a systematic way across the country, in order to provide equity of access for patients who might be candidates for clinical trials as well as new treatments entering the clinic in the near future.	Thank you for your comment. The GDG acknowledges that testing will evolve rapidly. However, commissioning services for melanoma genotyping is a service issue and was not investigated by the guideline. Therefore we are unable to make any recommendations.
157	Royal College of Physicians, National Cancer Research Institute, Association of Cancer Physicians	NICE	29	Section 3	We are disappointed that the guidelines do not recommend the need for research to identify optimal excision margins for primary melanoma surgery. We consider this to be a far higher priority compared with lentigo maligna Mohs versus conventional surgery question, which is highly likely to be imminently modified by emerging technologies, particularly confocal microscopy. We believe excision margins is a key research question since - 1. The issue is unresolved for up to 45% of all melanoma patients, not just the high-risk minority, according to the latest Cochrane review (Sladden MJ, Balch C, Barzilai DA, Berg D, Freiman A, Handiside T, Hollis S, Lens MB, Thompson JF.	Thank you for your comment. The GDG were aware of the weakness of the evidence but did not feel that this was a high priority for further research because the scale and multinational nature of a trial sufficiently powered to answer this question made it unrealistic.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					Surgical excision margins for primary cutaneous melanoma. Cochrane Database Syst Rev. 2009 Oct 7;(4):CD004835. doi: 10.1002/14651858.CD004835.pub2. Review. PubMed PMID: 19821334.) 2. The same Cochrane review on the topic concluded that it was needed, given that the majority of the trials were inappropriately designed (not non-inferiority), were underpowered and inappropriately staged. No new trials, including the Scandinavian study have modified this opinion. 3. The issue has major socio-economic implications for the UK and other major economic nations	
206	Royal College of Radiologists	Full	General	General	The RCR is in broad agreement with the draft guideline. The guideline seems to be appropriate and largely in line with existing UK practice. The RCR's detailed comments are given below.	Thank you.
207	Royal College of Radiologists	Full	6	39	The RCR is concerned that this recommendation may be difficult to implement in all centres and may carry additional cost.	Thank for your comment. The GDG agrees that there is a cost implication to this recommendation. However the need to establish Vitamin D levels at diagnosis was considered to be important enough to justify its inclusion. Further detail and supporting information can be found in the Linking Evidence to Recommendations (LETR) statements on pages 229-231. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
208	Royal College of Radiologists	Full	7	1	The RCR supports this recommendation. However, this may be difficult to implement due to geographical variation regarding the availability of sentinel lymph node biopsy and this needs to be addressed.	Thank for your comment. The GDG accepts that implementation will be challenging but the evidence review provided support for the technique as a staging tool. The GDG agreed that all melanoma patients should have access to this staging tool, wherever they live. NICE will provide some additional tools to support implementation.
209	Royal College of Radiologists	Full	7	15	The RCR is concerned that this recommendation could lead to widespread variation across the country, with differing imaging policies depending on location of SSMDT.	Thank for your comment. The GDG agrees that practice variation may result but were unable to make a strong recommendation in favour of a specific imaging policy. Although the GDG acknowledges that there is no strong clinical or cost effectiveness evidence that earlier detection of metastases results in improved outcomes they agreed that there was an increasing belief that it might be important to identify them. The modelling showed that it was likely to be cost effective if the increased long term survival following systemic therapy was 15%, for which there is some early evidence. The recommendation leaves the final decision about this to the SSMDT, if funding is identified or as part of a clinical trial and the patient is fully aware of the potential advantages and disadvantages of regular imaging. A table has now been included with the recommendation so that the disadvantages and advantages of regular

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						imaging are clear to SSMDTs and to be used in discussion with patients.
210	Royal College of Radiologists	Full	26	General	The RCR would like to suggest a different emphasis with regard to brain imaging and asks NICE to consider the following: • Inclusion of the brain at baseline and in clinically suspected metastatic disease • CT will often be more appropriate as conducted as part of the wholebody study • MRI brain should be considered in the following situations: o a normal CT brain, but clinical suspicion for cerebral metastases o detection of low volume disease will influence management o children and young people.	Thank you for your comments. The GDG considered this issue but agreed to retain their current recommendation, based on their consensus view. We agree and this is what has been recommended. The GDG acknowledge that MRI is more sensitive than CT in detecting small volume metastases. However they recognise that MRI is more expensive and would involve the patient in a second visit to hospital, whereas CT brain could be carried out at the same time as imaging the rest of the body. Therefore the GDG agreed that the additional cost would not justify the relatively small benefits of finding brain metastases earlier. We agree and this is what has been recommended.
41	Royal College of Surgeons of England	FULL NICE	172 20	1.8.2	Patients with Bone Metastases need referral to bone tumour/metastatic bone disease MDT – this should be included	Thank you for your comment. We have clarified the requirement for involvement of other site specific MDTs in the recommendation.
232	Royal Surrey County Hospital NHS Foundation	FULL NICE	21	1.8.7	This is a non-sensical blanket order. If a patient is post dacarbazine, unsuitable for immunotherapy, but fit for treatment then all options need to be considered. Rephrase as advice not direct prohibition.	Thank for your comment. There is no evidence to support the use of any specific chemotherapy in this situation, and the GDG was keen to promote access to clinical trials. We have

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Trust					modified the recommendation to clarify that second line chemotherapy should not *routinely* be used outside clinical trials.
235	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE General	56 1.1.2 General	General	Primary care. We note this http://www.pulsetoday.co.uk/clinical/more- clinical-/dermatology/nice-melanoma-guidelines-need-greater-primary-care-focus/ 20009082.article#.VQKxf46sVg0 . We do not believe that GPs should be considering that adoption of dermoscopy gives automatic ability for discretion between lesions that need biopsy and those that don't. We strongly believe that experienced, expert dermatology assessment is needed. Spending money on the technology (often driven commercially) is falsely offset with saving money on referrals; all suspicious moles should be referred.	Thank you for your comment. This guideline is not recommending that all GPs should be using dermoscopy for the diagnosis of melanoma. We have amended the recommendation to clarify that it refers specifically to lesions being referred for assessment and those having follow-up in secondary and tertiary care.
225	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	56 14	1.2.1	Use of dermoscopy - We do not feel that the benefit of dermoscopy over experienced clinical judgment is proven with respect to deciding about whether to biopsy lesions or not. Together with the absence of economic appraisal, we do not feel that dermoscopy can be considered obligatory at present.	Thank you for your comment. The GDG found high quality evidence that dermoscopy was more sensitive and specific than clinical examination alone. This evidence informed the recommendation that was made. We acknowledge that no health economic analysis was performed for this question as documented in the Linking Evidence to Recommendations (LETR) statements on P63 of the full guideline. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						guideline (page 19). - 'the group considered that improvements in diagnostic accuracy and the associated reduction in the costs of unnecessary surgery and histopathology would outweigh the costs of equipment, training and clinical time.
221	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	56 13	14	We do not agree that written information should be nationally standardised. It should be nationally benchmarked; providers should be encouraged to put their information online (with author and date) so it is freely available and best practice can be shared.	Thank you for your comment. This recommendation has been incorporated from the NICE guidance on' improving outcomes for people with skin tumours including melanoma' and so we cannot change the wording. The GDG feel that nationally standardised information is beneficial as it ensures a minimum standard. Local departments can add to that information in response to identified particular needs.
223	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	75 15	1.2.7	Tissue testing – see above. "Genetic testing" is a misleading term which is usually used to refer to germline rather than somatic testing. Suggest 'mutation testing'.	Thank you for your comment. The recommendation refers to treatment for stage IV melanoma and tissue samples. The GDG did not feel that this was likely to be confused with germline testing for inherited susceptibility genes.
228	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	77 16	1.2.10	There is no strong rationale for this 'workflow', preferential testing of secondary tissue. Test primary and secondary tissue.	Thank you for your comment. The guideline considered a number of published papers in which there was an inconsistency between primary and secondary tumours (page 74, full guideline) in the results of testing for driver mutations. It is not fully understood as yet what that inconsistency relates to but is often likely to relate to technical failure of tests when the very small amount of tumour in melanoma primaries is tested. This was felt to justify

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						preferential choice of the secondary tissue. This is discussed in the Linking Evidence to Recommendations (LETR) statements on page 76 of the full. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). guideline.
227	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	77 16	1.2.8	What is the rationale for not testing stage 2A -2B?	Thank you for your comment. The GDG accepts that selecting patients for testing is contentious, but considered that testing all melanoma patients at the time of diagnosis would be an inappropriate use of NHS resources given that approximately 80% of patients would currently never require a test result. The GDG thought it was likely that better genetic tests would be available shortly (to test for multiple genetic changes of predictive value) and therefore currently it might be preferable to reserve the small amount of tumour in primary melanomas of stage IIA to IIB for use if and when metastases develop. The guideline discusses tumour heterogeneity and the likelihood that the clones of tumour cells of relevance for

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						the treatment of stage IV disease may in the future be those present in metastatic tissues. It may be that testing primaries will be considered to have lower predictive value. The guideline makes it clear that the GDG had to review evidence which was evolving rapidly, and that these recommendations may be changed when the guideline is updated in line with NICE policy.
224	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	107 16	1.5.2	(p16-17) We agree with the recommendation for sentinel node biopsy. It would be simpler to state the indication as ">1mm Breslow thick with mitoses" rather than state staging categories such as 1B-2C	Thank you for your comment. We have tried to relate guidance to AJCC stage where possible as this is the norm for prognostic estimation and clinical trial stratification/eligibility considerations and is required now by Cancer Outcomes and Services Dataset. We have clarified this by adding 'or those IB melanomas with a Breslow thickness of less than or equal to 1mm' to the recommendation. Additional detail has been added to the Linking Evidence to Recommendations (LETR) statements to explain why SLNB was not offered to these patients. The LETR statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19).
222	Royal Surrey	FULL	193	Gener	There is no clinical evidence to support the experimental	Thank you for your comment. The GDG

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	County Hospital NHS Foundation Trust	NICE	General	al	concern that BRAF inhibitor therapy accelerates the growth of BRAF wild-type tumours. Therefore our overall aim should be to 'fish' for BRAF mutations by testing as much tissue as possible, as quickly as possible. In practice this can mean testing the stored primary whilst awaiting confirmation and testing of a relapse site. In other words we believe the recommendation should be to test as much tissue as possible, the primary and at least one secondary site. The cost of this is no longer an obstacle and the benefit to the patient of finding a BRAF mutation is huge. It will also advance knowledge in the field. Willing to discuss this further, [redacted]	accepts that selecting samples for testing is contentious, not least because the data are not yet available to fully inform the discussion. The guideline discusses tumour heterogeneity, and the clones of tumour cells of relevance for the treatment of stage IV disease will likely be those present in metastatic tissues. It may be that in the relatively near future testing primaries will be considered to have lower predictive value. The guideline acknowledges that the GDG was reviewing evidence which is in state of rapid evolution. The guideline will be reviewed in the future, in line with NICE process, and this recommendation will be updated if appropriate.
233	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	193 22	1.8.10	Comment on treatment section in general (1) do not take into account widely-used expanded access programmes (early 2015) (2) are likely to be out of date very soon (3) should encourage clinical trial participation	Thank you for your comment. The GDG were limited to what could be covered in this topic as certain drug therapies were concurrently being considered by the NICE TA process.
231	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	193 21	1.8.6	You may receive opposition to a continued recommendation for dacarbazine. We believe it still has a place and agree with this recommendation.	Thank you for your comment. Thank you.
234	Royal Surrey County Hospital NHS Foundation	FULL NICE	220 23	1.9.4	What is the point of surveillance CT brain? Strongly disagree with this. If cost argument, be explicit and state costs in support document.	Thank you for your comment. Brain metastases are common in melanoma patients and imaging has hitherto not surveyed this site in many institutions. The advent of stereotactic radiotherapy

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Trust					and its established palliative efficacy for small brain metastases argues that avoiding late detection would be beneficial for a significant proportion of patients. This argument is detailed on page 218 -221 of the full guideline.
229	Royal Surrey County Hospital NHS Foundation Trust	FULL NICE	226 16	1.3.2	VIT D - Quality of evidence on the role of Vit D in melanoma is weak. We agree this should be a research question. If everyone gets vit D then a change in default practice has occurred with loss of equipoise and therefore no opportunity for a clinical trial.	Thank you for your comment. The guideline does not recommend routine supplementation of vitamin D, indeed by measuring levels unnecessary supplementation would be avoided. A UK study has shown that low levels of vitamin D are common in melanoma patients at diagnosis and three studies have shown that within the pale skinned peoples those with the most sun-sensitive skin (a risk factor for melanoma) have lower vitamin D levels. Please see NICE public health guidance on Vitamin D, recommendation 7 (Vitamin D: increasing supplement use among at-risk groups | 1-recommendations | Guidance and guidelines | NICE The GDG considered that measuring the level and responding as judged appropriate by experts such as the SACN would serve the following purposes:- • Avoiding exacerbation of vitamin D depletion at diagnosis otherwise resulting from advice to limit sun exposure • The identification of patients with normal or high vitamin D who do not require supplementation,

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
						indeed might be harmed by that supplementation • The identification of patients who would benefit from supplementation for bone health at least, even if there is no established role for vitamin D in melanoma outcome. See Linking Evidence to Recommendations (LETR) statements in the full guideline. These statements explain how the Guideline Development Group used the evidence to develop the recommendations, and describes the relative value placed on outcomes, benefits and harms, resource use, and the overall quality of the evidence, as well as other considerations of the Group.' Further detail can be found in the methodology section of the full guideline (page 19). We are aware of clinical trials to address the role of adjuvant vitamin D supplementation in Italy and in Australia, and the results will be considered if available when the Guideline is reviewed. It may be that work currently taking place internationally to further understand the role of vitamin D in melanoma may justify an additional UK adjuvant trial.
236	Royal Surrey County Hospital NHS	General	General	General	Not sure why so much presentation of epidemiology in evidence document. It does not feel like a full and balanced appraisal of all current evidence.	Thank you for your comment. The epidemiology in chapter 1 was there to set the context for the guideline and was not part of the evidence used to make

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
	Foundation Trust					recommendations.
237	Royal Surrey County Hospital NHS Foundation Trust	Implement ation	General	Gener al	Implementation of sentinel node biopsy - In our specialist MDT we have been providing SLNB for melanomas for over 10 years. This has grown into specialist services that anatomically covers sentinel nodes above and below the clavicle (eg: had and neck surgeons vs melanoma / general surgeons). This is a very important consideration for surgical pathways such as those needing a bloc dissection in different parts of the body. A bloc dissection of the neck is a different operation altogether than ones below the clavicle and probably best done by those that carryout late numbers of head and neck resections. Such division of work as lead to provision of an highly subspecialised service which has gone hand in hand with improved outcomes.	Thank you for this information. Provision of SLNB will be a matter for implementation.
230	Royal Surrey County Hospital NHS Foundation Trust	NICE	General	Gener al	Would help if you added explicit sentence: "In particular, patients with primary melanoma in the head and neck region should be referred for discussion in the melanoma MDT meeting and not receive routine adjuvant neck irradiation"	Thank you for your comment. We assume this refers to the recommendation about adjuvant radiotherapy for people with stage IIIB or IIIC melanoma. The GDG agreed that the existing recommendation was sufficiently clear.
226	Royal Surrey County Hospital NHS Foundation Trust	NICE	17	1.5.3	Role of PET/CT in detecting systemic disease in stage III is undervalued in the document. Meta-analysis by Meguerditichian et al (2014) showed a sensitivity of 89% for detecting systemic disease with PET in stage III disease. More importantly a negative predictive value of 4%. The guidance should be worded to leave imaging protocols to local MDT's. This links with brain imaging with CT would be a substandard imaging modality compared to brain MRI. The Specialist MDT should have the ability to judge which staging modality is indicated on a case by case and according to locally derived protocols	Thank you for your comment. The decision not to recommend PET-CT was based on the understanding that there was no evidence that early detection of metastatic disease by a more sensitive but more costly diagnostic modality would lead to survival benefit. It will be up to local MDTs to make individual clinical decisions if there is uncertainty from CT imaging.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
38	SciBase AB	Full	59	9-11	The draft guideline states that "…New technologies have been developed using dermoscopic images and artificial intelligence systems to replace clinical inspection but their diagnostic accuracy is uncertain." This statement should be reconsidered. See for example: Malvehy J, Hauschild A, Curiel-Lewandrowski C et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol 2014;171:1099-107, which shows that Nevisense provides the potential to increase overall accuracy by complementing the clinical inspection (with or without dermoscopy) with additional non-visual information allowing the physician to make a more informed decision when considering excision. The Malvehy et al paper, together with other studies of EIS, report results in approximately 4,000 patients and 5,000 lesions, a very substantial research effort in the detection of melanoma.	Thank you for your comment. This text is the background to why the GDG decided to investigate this clinical issue. The paper you cite was published after our cut off for literature searches. **Published guidelines undergo surveillance reviews every 2 years after publication to decide if an update is needed at that time. This surveillance review decision is informed by a number of stages of intelligence gathering to identify any potential new sources of evidence**.
37	SciBase AB	Full	59	3.1	(p59-66) The review of the literature on dermoscopy and other visualisation techniques is not comprehensive and should be revisited. Further, the guideline should include references to the added value of non-visual technologies. These complement visual evaluation with additional information which increase overall accuracy when considering whether to excise a lesion which might be a melanoma. Many studies which are not referenced in the draft guidelines have shown that both visual and non-visual techniques for evaluating pigmented lesions have the potential to improve diagnostic accuracy at different points in the clinical pathway (to be considered in relation to the Clinical Pathway for Dermoscopic Evaluation of Pigmented Lesions on page 21 of the draft guideline). These include techniques such as total body photography, confocal microscopy, Raman spectroscopy, multispectral imaging, automated dermoscopy image analysis, genomic detection of melanoma by stratum corneum stripping, and electrical impedance spectroscopy (EIS). See for example:	Thank you for your comment. When agreeing the evidence review question the GDG prioritised the comparison of naked eye examination with dermoscopy and related visualisation techniques. For this reason studies of non-visual techniques (like electrical impedance spectroscopy) were not included. This is why the Aberg (2011), Boden (2013), Lui (2012), Mohr (2013) and Wachman (2011) studies were not included. While some of the studies listed in your comment were included as evidence (Monheit, 2011; Guitera, 2012 – earlier publications from this cohort) the exclusion reasons for the remainder were:

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					• Malvehy J, Hauschild A, Curiel-Lewandrowski C et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol 2014;171:1099-107. • Aberg P, Birgersson U, Elsner P et al. Electrical impedance spectroscopy and the diagnostic accuracy for malignant melanoma. Exp Dermatol 2011;20:648–52. • Mohr P, Birgersson U, Berking C et al. Electrical impedance spectroscopy as a potential adjunct diagnostic tool for cutaneous melanoma. Skin Research Technol 2013;19:75–83. • Terushkin V, Oliviera S, Marghoob A et al. Use of and beliefs about total body photography and dermatoscopy among US dermatology training programs: an update. J Am Acad Dermatol 2010;62:794–803. • Salerni G, Carrera C, Lovatto L et al. Benefits of total body photography and digital dermatoscopy ("two-step method of digital follow-up") in the early diagnosis of melanoma in patients at high risk for melanoma. J Am Acad Dermatol 2012;67:17–27. • Curiel-Lewandrowski C, Williams CM, Swindells KJ et al. Use of in vivo confocal microscopy in malignant melanoma: an aid in diagnosis, and assessment of surgical and non-surgical therapeutic approaches. Arch Dermatol 2004;140:1127–32. • Guitera P, Menzies SW, Longo C et al. In vivo confocal microscopy for diagnosis of melanoma and basal cell carcinoma using a twostep method: analysis of 710 consecutive clinically equivocal cases. J Invest Dermatol 2012;132:2386–94. • Lui H, Zhao J, McLean D et al. Real-time Raman spectroscopy for in vivo skin cancer diagnosis. Cancer Res 2012;72:2491–500.	• Terushkin (2010) not a diagnostic accuracy study • Curiel-Lewandrowski (2004) was a case report of 3 patients • Menzies (2005) used clinical images for the naked eye clinical examination arm and was not prospective. • Salemi (2012) the population was not relevant but this study was included for another topic (follow-up of suspicious lesions) • Malvehy (2014) published after the search cut-off date, and used a non-visual technique. Published guidelines undergo surveillance reviews every 2 years after publication to decide if an update is needed at that time. This surveillance review decision is informed by a number of stages of intelligence gathering to identify any potential new sources of evidence

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					• Boden I, Nystro€m J, Lundskog B et al. Non-invasive identification of melanoma with near-infrared and skin impedance spectroscopy. Skin Res Technol 2013;19:473–8. • Moheit G, Cognetta A, Ferris L et al. The performance of MelaFind. Arch Dermatol 2011;147:188–94. • Menzies SW, Bischof L, Talbot H et al. The performance of SolarScan: an automated dermoscopy image analysis instrument for the diagnosis of primary melanoma. Arch Dermatol 2005;141:1388–96. • Wachsman W, Morhenn V, Palmer T et al. Noninvasive genomic detection of melanoma. Br J Dermatol 2011;164:797–806. As drafted, the guideline does not assess the value which these new techniques can offer both patients and the NHS.	
40	SciBase AB	Full	59	28-29 (also Table 10 p 60)	The draft guideline states that some new technologies were "…optimised for high sensitivity at the expense of specificity". The GDG should take account of spectrum bias when comparing diagnostic accuracy of various technologies. For example, in a study of EIS (Malvehy J, Hauschild A, Curiel-Lewandrowski C et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol 2014;171:1099-107), all lesions studied had already been selected for excision because of clinical concern about the possibility of melanoma after initial clinical visual examination: in these circumstances (by definition, the specificity of the dermatologists was 0%), the specificity of EIS at 34.4% offers substantial benefits to both patients and the NHS from avoided unnecessary excisions. This specificity was achieved while maintaining sensitivity of 96·6% in a cohort consisting mostly of in situ and early invasive melanoma. The observed sensitivity of the EIS device used increased with Breslow thickness, and no invasive melanoma at stages T1b–T4 was missed.	Thank you for your comment. Patient selection bias was considered when assessing the quality of the evidence, using the QUADAS-2 checklist. The setting of each study (primary care, initial tests in secondary care and tests for equivocal lesions in secondary care) was also considered. The GDG also discussed the influence of melanoma prevalence on the positive and negative predictive value of the tests.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
39	SciBase AB	Full	61	Table below line 8	We agree with the GDG that the "…Use of a more sensitive and specific combination of tests should lead to earlier diagnosis of melanomas (with better prognosis) as well as a reduced biopsy rate for benign lesions". A study of 2416 lesions in 1951 patients (Malvehy J, Hauschild A, Curiel-Lewandrowski C et al. Clinical performance of the Nevisense system in cutaneous melanoma detection: an international multicentre, prospective and blinded clinical trial on efficacy and safety. Br J Dermatol 2014;171:1099-107.) found that EIS had an observed sensitivity of 96.6% (exact one-sided 95% lower confidence bound estimated at 94.2% for melanoma and an observed specificity of 34.4% (exact two-sided 95% confidence bound estimated at 32.0–36.9%). The lesions included in the study had already been selected for excision because of clinical concern about the possibility of melanoma after initial visual examination which therefore had, by definition, a specificity of 0%. At 34.4%, the specificity of Nevisense without a loss of sensitivity provides information which will avoid the need for many unnecessary biopsies, with obvious benefits to both patients and the NHS.	Thank you for your comment. The paper you cite was published after our cut off for literature searches. Published guidelines undergo surveillance reviews every 2 years **after publication to decide if an update is needed at that time. This surveillance review decision is informed by a number of stages of intelligence gathering to identify any potential new sources of evidence**.
110	University of Birmingham and University of Nottingham	Full	General	General	I am commenting on the guideline on behalf of the joint University of Birmingham and University of Nottingham team currently holding an NIHR Cochrane Programme Grant to carry out test accuracy systematic reviews for diagnosis and staging of melanoma and keratinocyte skin cancers. Our comments relate only to the diagnosis and staging sections of the guidelines. As we are only in the first year of a 3-year project we are not able to fully comment on the recommendations, however we would like to commend the review team on the extent to which they have been able to review available tests for the guideline. Presumably due to time and resource constraints existing quality systematic reviews with some supplementary searching for additional primary studies have been used to support the guideline recommendations. Although a	Thank for your comments. We acknowledge the limitations of the review but look forward to the outcome of your work on this important topic. We are in contact with the Cochrane group and are aware of the ongoing work on this topic and we will be contributing in any capacity we can.

ID	Stakeholder	Document	Page No	Line No	Comments Please insert each new comment in a new row	Developer's response Please respond to each comment
					justifiable approach given these constraints, this does limit any attempts to compare the accuracy of different tests and to evaluate test accuracy in different settings or according to examiner experience for example. Our project will ultimately produce a suite of high quality systematic reviews in the field, to allow some of these issues to be covered in more detail in time for the next update of this guideline.	

These organisations were approached but did not respond:

Abbott Molecular UK
Aintree University Hospital NHS Foundation Trust
Allocate Software PLC
Almirall Ltd
Amgen UK
Association of Anaesthetists of Great Britain and Ireland
Association of Chartered Physiotherapists in Oncology and Palliative Care
Barnsley Hospital NHS Foundation Trust
Barts and the London NHS Trust
Belfast Health and Social Care Trust
Betsi Cadwaladr University Health Board
Boots
British Association of Skin Camouflage
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 Paediatric Dermatology
Calderstones Partnerships NHS Foundation Trust
Cambridge University Hospitals NHS Foundation Trust
Cancer Commissioning Team
Cancer Research UK
Cancer52
Caplond Services
Capsulation PPS
Care Quality Commission
Celgene UK Ltd
Chartered Society of Physiotherapy
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, Social Services and Public Safety - Northern Ireland

East and North Hertfordshire NHS Trust

East Kent Hospitals University NHS Foundation Trust

East of England Strategic Clinical Network

Economic and Social Research Council

Ethical Medicines Industry Group

Faculty of Pharmaceutical Medicine

False Allegations Support Organisation

Five Boroughs Partnership NHS Trust

GlaxoSmithKline

Glebe Road Surgery GP

Globe Microsystems Ltd

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

Hywel Dda University Health Board

IGEA Medical

Institute of Biomedical Science

Isabel Hospice

King's College Hospital NHS Foundation Trust

Launch Diagnostics

Leeds Teaching Hospitals NHS Trust

Leo Pharma

Local Government Association

London cancer alliance

London North West Healthcare NHS Trust

Luton and Dunstable Hospital NHS Trust

Lymphoedema support network

Medical Directorate Services

Medicines and Healthcare Products Regulatory Agency

Melanoma UK

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

Newcastle upon Tyne Hospitals NHS Foundation Trust

NHS Barnsley Clinical Commissioning Group

NHS Chorley and South Ribble CCG

NHS Connecting for Health

NHS County Durham and Darlington

NHS Cumbria Clinical Commissioning Group

NHS Gloucestershire CCG

NHS Hardwick CCG

NHS Health at Work

NHS Liverpool CCG

NHS Medway Clinical Commissioning Group

NHS North East Lincolnshire CCG

NHS Plus

NHS Sheffield

NHS South Cheshire CCG

NHS Wakefield CCG

NHS Warwickshire North CCG

NHS West Cheshire CCG

Nordion

Norfolk and Norwich University Hospitals NHS Foundation Trust

Norfolk and Suffolk Palliative Care Academy

North and East London Commissioning Support Unit

North of England Commissioning Support

Northern Health and Social Care Trust

Novartis Pharmaceuticals

Nursing and Midwifery Council

Nutricia Advanced Medical Nutrition

Oxford Health NHS Foundation Trust

Parenteral and Enteral Nutrition Group

Primary Care Pharmacists Association

Primrose Bank Medical Centre

Public Health England

Public Health Wales

Public Health Wales NHS Trust

Public Health Wales NHS Trust

Queen Elizabeth Hospital King's Lynn NHS Trust

Rarer Cancers Foundation

Roche Diagnostics

Royal College of Anaesthetists

Royal College of General Practitioners in Wales

Royal College of Midwives

Royal College of Obstetricians and Gynaecologists

Royal College of Physicians and Surgeons of Glasgow

Royal College of Psychiatrists

Royal College of Speech and Language Therapists

Royal College of Surgeons of Edinburgh

Royal Cornwall Hospitals NHS Trust

Royal Liverpool and Broadgreen University Hospitals NHS Trust

Royal Pharmaceutical Society

Sandoz Ltd

Sanofi

Scottish Intercollegiate Guidelines Network

Sensemakers

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 Wales Cardiac 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 Melanoma Taskforce

The Patients Association

University Hospital Birmingham NHS Foundation Trust

University Hospital Southampton NHS Foundation Trust

University Hospitals Birmingham

Velindre NHS Trust

Welsh Government

Welsh Kidney Patients Association

Welsh Scientific Advisory Committee

West Suffolk Hospital NHS Trust

Western Health and Social Care Trust

Wicked Minds

Wigan Borough Clinical Commissioning Group

York Hospitals NHS Foundation Trust