Melanoma: assessment and management

Consultation on draft guideline - Stakeholder comments table
28/01/22 to 11/03/22

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AMLo Biosciences Ltd	Evidence review G	111	2	Melfo study- The authors support the use of a stage-adjusted reduced follow up regimen for IB-IIC based on patient-reported outcome measures, but do not incorporate a biomarker-based classification of personalised risk. There is a variation in rates of metastasis within each substage, and biomarkers are required in order to identify cases who have a genuinely low risk before modifying or reducing current follow-up. Thus, this should not be the only factor considered when stepping down patients.	Thank you for your comment. The committee concluded that the Melfo study demonstrated that a reduction in the frequency of follow-up for people with stage IB-IIC did not lead to a significant reduction in quality of life and there was no indication that this reduction would lead to an increase in recurrences and/or mortality. The committee agreed that based on this (and the added safety net of considering cross-sectional imaging surveillance for stages IIB-C) it was safe to offer a recued frequency follow-up for people with these stages of melanoma.
AMLo Biosciences Ltd	Evidence review G	188	1	This is an important paper since it provides evidence that patients develop a recurrence within 2 years of initial surgical resection, especially in patients over the age of 75. Thus, is this not a time when you would wish to reduce the number of follow-ups without biomarkers in order to provide clinicians with assurance?	Thank you for your comment. The committee noted the high rates of melanoma recurrence within the first 2 years following surgical resection however they were unable to make specific recommendations regarding biomarkers as this was out of scope for this update. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2).
AMLo Biosciences Ltd	Evidence review G	203	2	When deciding how to change the follow up levels for patients, Jurtz's paper should be given greater weight. Moreover, this acknowledges the need for more	Thank you for your comment. The follow-up schedule recommended by the committee was based on a combination of evidence and their expertise. The Melfo study provided evidence that a risk-stratified follow-up

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				precise surveillance in early stage melanoma in order to enable stratification. According to its findings, a chest X-ray as part of the follow-up was not more accurate than a physical examination. As a result, this does indicate that a biomarker is more accurate in comparison to current practices.	in low-stage melanoma is safe and does not impact negatively on quality of life. Additionally, rates of 5- and 10-year recurrence are low in stages IA-IIA melanoma. The committee felt that evidence regarding risk factors (for recurrence and/or mortality) was not strong enough to make more specific recommendations. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2).
AMLo Biosciences Ltd	Evidence review G	235	1	This paper shows that male sex and Breslow thickness are the most important factors for the recurrence of localised cutaneous melanoma in a Korean population. This is not directly comparable to the UK population, a typically melanomas in the Korean population are acral in nature which is a much smaller proportion of the total number of melanomas diagnosed in the UK.	Thank you for your comment. The committee noted the differences in population between some of the studies included in this update, and the difficulties extrapolating these populations to the UK.
AMLo Biosciences Ltd	Evidence review G	35	30	For the purpose of supporting patients' pathways and clinician decision-making, this section indicates that there is still insufficient evidence to support the step down. A reliable and consistent biomarker is necessary to determine an individual's risk level, and therefore, to determine the type of follow-up necessary. This is further supported by the report which highlights / acknowledges in the 'quality of	Thank you for your comment. The committee noted the lack of good quality (and conclusive) evidence regarding risk factors for recurrence following surgical resection among people with melanoma. Due to this, they agreed that they could not make more specific recommendations than the ones given. The committee agreed

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				evidence summary' in this section that current prognostic studies for resected stage I-II cancers still lack consistency and were not based on the correct hazard ratio assessment, causing contradictions. Additionally, the prognostic studies included largely did not include multivariate analyses. There is, therefore, a lack of prognostic evidence that would allow a change in follow-up or specifically a reduction in follow-up for stage I/II patients that lack a reliable marker that can be assessed in accordance with specific guidelines.	that the use of biomarkers is increasing important within melanoma, for risk-stratification and monitoring. However, this area was not included in the scope of this update and therefore the committee were not able to make recommendations on their use. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2).
AMLo Biosciences Ltd	Evidence review G	39	15	It would seem that changes to the clinical pathway of follow-ups have been driven more by outcomes than by factors such as patient anxiety and stratification. In addition, statements regarding metastatic disease occurring within 5-10 years seem out of sync with current findings, which indicate that most patients between a stage IA and IIB would experience metastases in 18-24 months, and not over 5-10 years. Further, the reduction in follow-up for stage IA should be accompanied by an intervention/marker to support the identification of truly low-risk subsets of patients.	Thank you for your comment. The committee agree that people are at highest risk of recurrence during the initial years following diagnosis. However, they also made reference to rates of recurrence and mortality up to 10 years to emphasise the long-term risk of developing a recurrence and as these timepoint are references in the AJCC 8th edition (Gershenwald, 2017). The committee made recommendations to account for the greater risk in the initial few years following diagnosis, recommending a greater number of clinical visits in the

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					first 2 years following resection. The committee attempted to account for patient anxiety and quality of life in their recommendations. Firstly, they noted that the reduced-intensity follow-up schedule in the MELFo study did not lead to a significant difference in state-trait anxiety. Secondly, lay members and experience of the committee informed that decreasing clinic visits for stage IA to just a single visit in the first year may lead to an increase in anxiety for that specific cohort and they therefore agreed to increase this to 2 visits.
AMLo Biosciences Ltd	Evidence review G	43	32	It is concerning that limited information was available to inform the decision-making process regarding pathway changes. The introduction of better monitoring during outpatient appointments and the provision of more diagnostic services in a system that is already under strain should be considered before any changes to the current follow up regime is introduced Consequently, a further justification for modifying the follow up should be supported by robust cost-effectiveness and budget impact analyses.	Thank you for your comment. The provision of diagnostic services and impact on pathway changes was beyond the scope of this guideline update. Within a guideline there is a limited number of economic models that can be built due to time and resources. All the questions are assessed for available economic evidence and then a discussion takes place with the committee about which questions are most appropriate for an economic model to be built and in which areas there is the most uncertainty in which an economic model would be able to help. After discussion with the committee, it was felt that stage III was the most important stage to model as that was

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					where the most uncertainty was. The committee noted that there was a large variation in practice around the country with some patients receiving CT, some receiving PET-CT and some receiving no imaging at all. Given the differing cost of these types of imaging there was potential for a large budget impact. Therefore, the committee made their decision on the other stages using their clinical judgement and the available evidence.
AMLo Biosciences Ltd	Evidence review G	44		For adults with stage IIB and IIC melanoma, the committee made recommendations to reduce the number of clinical follow-up appointments, from 16 over 5 years to 10 over 5 years, based on the results of the MelFo RCT. However, the low rates of melanoma-specific survival observed in these populations were noted to be lower than patients with stage IIIA melanoma, and similar to patients with stage IIIB melanoma. This data used to define the AJCC 8th edition stages (Amin 2017), Given the lower melanoma specific survival in IIB and IIC populations compared to IIIA/B populations, step down of follow up appears risky without stratification of the population on an individual level by use of a biomarker for example.	Thank you for your comment. The committee agreed that people with stages IIB/C melanoma are at high risk of recurrence. As you mention, reductions to the number of clinical visits for people with these stages was based on the results of the MELFo trial However, the committee attempted to compensate for this step-down by making recommendations to consider cross-sectional imaging in these groups of people, as to identify recurrences / disease spread.
AMLo Biosciences Ltd	Evidence review G	44	9	It was evident that ultrasound did not have sufficient evidence to demonstrate that it was beneficial. Additionally, the variation across the UK was wide, as well as no information was available on the impact on	Thank you for your comment. The committee considered this issue and noted that ultrasound scanning was shown by the evidence to be more sensitive than clinical examination and alternative imaging modalities (particularly CE-CT) for detecting

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				mortality. In contrast, reducing follow-ups was seen as a positive step, as there is a safety net of ultrasound, which is not evidence-based. As a result, in order to better understand the risk for these patients, we need a reliable biomarker to assure both the patient and clinician of the change in practice.	local lymph node metastases. They therefore recommended ultrasound surveillance for 3 years for people with a positive sentinel lymph node. The committee have added to the guideline rationale acknowledging the practical implications of ultrasound imaging during follow-up such as providing increased numbers of scans and variable experience of healthcare professionals involved in follow-up. The use of biomarkers was beyond the scope of this guideline update. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2).
AMLo Biosciences Ltd	Evidence review G	44	25	This change in pathway appears to have taken place without providing any assurance that biomarkers are available to identify low risk patients and allow them to be stepped down. Again, reviewing mortality over a period of 5 to 10 years, when AJCC staging report evidence of metastasis within the first 2 years in stage I patients.	Thank you for your comment. The use of biomarkers in the pathway was beyond the scope of this guideline update. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2). The committee agree that people are at highest risk of recurrence during the initial years following diagnosis. However, they also made reference to rates of recurrence and mortality up to 10 years to emphasise

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					the long-term risk of developing a recurrence and as these timepoint are references in the AJCC 8th edition (Gershenwald, 2017). The committee made recommendations to account for the greater risk in the initial few years following diagnosis, recommending a greater number of clinical visits in the first 2 years following resection.
AMLo Biosciences Ltd	Evidence review G	473	1	This study supports the use of intensive follow-up for early detection of recurrence in stage II melanoma and as such does not support the proposed step down of follow up suggested in the NG14 consultation document.	Thank you for your comment. The study by Podlipnik (2016) helped, in conjunction with other studies, to support recommendations made in the guideline to consider cross-sectional imaging during follow-up for people with stage IIB/C disease due to the high risk of recurrence (please see the response to comment 21 for more detail). Additionally, several studies (such as Ibrahim 2020 in evidence review G) identified that almost 50% of people stage IIB-IIIC disease recur asymptomatically and would therefore only be detected if imaged. The committee therefore agreed to recommend imaging be considered in this population but to step-down the number of clinical visits, in accordance with the MELFo trial and to coincide with the recommended imaging schedule.
AMLo Biosciences Ltd	Guideline	17	26	1.9.6 – Personalized follow-up is recommended for patients at increased risk. However, under the NHS England PSFU (Personalised Stratification Follow-up program), what about those at low risk, where there is clear evidence and biomarkers demonstrate stepping those patients down. There is a need for evidence, but	Thank you for your comment. The committee agreed that due to limited evidence in this area and the highly diverse nature of the condition of people with unresectable stage III or IV melanoma, they could not give more specific recommendations in this area. As you mention, the committee envisions that follow-up of

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				we believe this could be presented in a more balanced manner	these groups of people be considered on a case-by-case basis.
AMLo Biosciences Ltd	Guideline	18	8	1.9.9 – Additionally, the increased number of patients who will undergo a full examination at the follow up would have a direct impact on the clinician's time. Therefore, any standard costing for dermatology appointments may be understated and would need to be modified to reflect actual costs	Thank you for your comment. The updated recommendation is similar to the existing recommendation, and additionally states that the clinician performing the exam must have expertise and skills in skin and lymph node examination. The committee felt that this would already be being performed in practice and therefore there would be no increase in appointment time. There are also a few stages that have a reduced number of follow up appointments which would therefore increase the time available for more severe melanomas.
AMLo Biosciences Ltd	Guideline	19	20	Following-up after stages I to IV melanoma (Table) - The current table provided describing alterations to follow ups has been constructed with only limited evidence, and in some cases, no evidence at all, aside from reducing the burden on the system. In other words, to reduce follow up for IAs from the current 2-4, down to 2 is significant, without additional information on individual risk using for example biomarkers will also be likely to increase anxiety for the patient. In a recent white paper published in 2021 entitled "Getting under the skin of Melanoma follow up; can resources be optimized?" (https://www.healthanalyticalsolutions.co.uk/resources/melanoma-skin-cancer), it was reported that 62% of all	Thank you for your comment. The committee agreed that people with melanoma experience high levels of anxiety following diagnosis. Primarily, the number of clinical visits recommended in the follow-up table draws from evidence provided in the MELFo trials (which you reference in subsequent comments, in particular please see our reply to comment 160 for further detail on this). This study demonstrated that a reduced frequency follow-up was both safe and did not have a significant impact on patient-reported anxiety, and quality of life. In the MELFo trial, people with stage IB underwent a reduced frequency follow-up of 1 visit for each of the 5-years of follow-up. The committee agreed that in people with stage IB melanoma, a single visit during the first year following surgical resection was too few due to the high levels of uncertainty and

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				NHS Trusts which responded completed 4 follow ups for individual cases. Therefore, without the evidence to support the step down, and also without a diagnostic test for these patients, it does not appear to be supported by the current evidence.	anxiety during this period. They agreed to modify the schedule used in the MELFo trial to 2 visits to account for this. Consequentially, the committee agreed to modify the number of visits recommended for stage IA to be congruent with this, recommending 2 visits in the first year (stepped-down from a recommendation of 2-4 visits in the previous update)
AMLo Biosciences Ltd	Guideline	19	20	Follow up after stages I through IV of melanoma (Table) - It seems that again the reduction in follow-ups for IB to IIB has not been influenced by evidence of risk, but rather by the outcome of recurrence. As a result, not knowing the implications of stepping down poses a risk to the system and also increases patient anxiety. Furthermore, a recent white paper published in 2021 entitled, "Getting under the skin of Melanoma follow-up; can resources be optimized" (https://www.healthanalyticalsolutions.co.uk/resources/melanoma-skin-cancer) reported that 100% of NHS Trusts included in this study completed 16 follow-ups during a five-year period in accordance with the NICE guidelines for IB to IIB. In this case, reducing this would appear to go against established current practice without data as to the implications.	Thank you for your comment. The committee agreed that people with melanoma experience high levels of anxiety following diagnosis. Primarily, the number of clinical visits recommended in the follow-up table draws from evidence provided in the MELFo trials (which you reference in subsequent comments, in particular please see our reply to comment 160 for further detail on this). This study demonstrated that a reduced frequency follow-up was both safe and did not have a significant impact on patient-reported anxiety, and quality of life. In the MELFo trial, people with stage IB underwent a reduced frequency follow-up of 1 visit for each of the 5-years of follow-up. The committee agreed that in people with stage IB melanoma, a single visit during the first year following surgical resection was too few due to the high levels of uncertainty and anxiety during this period. They agreed to modify the schedule used in the MELFo trial to 2 visits to account for this. Consequentially, the committee agreed to modify the number of visits recommended for stage IA to be congruent with this, recommending 2 visits in the

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					first year (stepped-down from a recommendation of 2-4 visits in the previous update)
AMLo Biosciences Ltd	Guideline	19	20	Follow-up after stages I to IV melanoma (Table) - The introduction of diagnostic ultrasound and CE-CT scans, appears to be adding to the resource demands of the NHS, and detracting from dermatological services. There is a significant increase in non-obstetric ultrasounds, which now have the highest diagnostic waiting time. In January 2022, there were 475,825 people waiting, representing 32.8% of the overall waiting list. Consequently, by introducing a new cost and resource into the pathway for these patients, but by reducing follow-ups, not only will it add burden, but it could be more costly than the actual follow-ups. According to the analysis and the economic model, this does not appear to be costed. Additionally, CT scans are at an all time high in terms of waiting times which is 185,023 in January 2022, which again will place a significant strain on the system if this does not change.	Thank you for your comment. The current melanoma guideline advises patients with stage IIC with no SLNB or stage III to consider surveillance imaging. The updated guideline gives more advice on the type of imaging that should be used and when. The cost-effectiveness model shows that CT scans at the recommended follow up schedule is the most cost-effective option. While the waiting list for CT might be significant, this may be due to Covid 19. The committee felt that the overall changes to the follow up schedule would be cost saving, this is due to reducing the number of follow up appointments for the lower stages.
AMLo Biosciences Ltd	Guideline	8	4	1.4.1 – Our understanding is that Sentinel Lymph Node Biopsy (SLNB) is performed on IA patients, based on the clinician's discretion. Nevertheless, this remains unchanged from the previous NG14 recommendations of 2015, but without any understanding of risk factors. As a result, we believe	Thank you for your comment. Health economic modelling from the previous update identified that SLNB was not a cost-effective procedure. The recommendations made in this update reflect the committee's desire to limit the number of people receiving SLNB. They agreed that SLNB should not be offered to people with stage IA melanoma due to the

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				that this decision should remain in the hands of the clinician. In a white paper published in 2021 entitled "Getting under the skin of Melanoma follow-up; can resources be optimised?" (https://www.healthanalyticalsolutions.co.uk/resources/melanoma-skin-cancer), it is stated that 9% of patients in IA received a SLNB	low risk of sentinel node positivity and the high cost implications associated with so many people being eligible for the procedure. For similar reasons, they agreed to only recommend it in people with 0.8-1.0mm melanomas if additional risk factors are present.
AMLo Biosciences Ltd	Guideline	9	17	1.5.3 It seems that the clinical margin excision is not being considered at the subgroup level, but only at the primary stage. Therefore, this should be amended to include sub-stage allocation to ensure the correct levels are considered. In addition, this will lead to an increase in costs, as skin grafts will be required depending on the extent of the excision. This will lead to an increase in costs and a reduction in patient mobility due to the high levels of lower limb melanoma found in the NHS.	Thank you for your comment. The committee discussed this issue and acknowledged that smaller margins may be needed for cosmetic reasons on sites such as the face, head and digits. However, the use of smaller margins should be discussed within the specialist skin cancer multidisciplinary team, the reasoning justified and with clinical surveillance. Furthermore, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team.
AMLo Biosciences Ltd	Question - What would help users overcome any	General	General	At present, clinicians are unable to provide assurance over the current AJCC staging guidance that earlier stage patients will not develop metastases, therefore, they are hesitant to alter their treatment plans. The adoption and implementation of a biomarker prognostic test, which could be used to support their decision making and also to reduce patient anxiety,	Thank you for your comment however the adoption and implementation of a biomarker prognostic test was beyond the scope of this guideline update. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2).

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	challenges? (For example, existing practical resources or national initiatives, or examples of good practice.)			would enhance the adoption and implementation of a reduction in surveillance policy. In our opinion, AMBLor (AMBRA1 and loricrin antibody test) could be a good additional intervention for patients with Stage IA to IIB non-ulcerated melanoma to determine suitable people with low risk melanoma to as evidence-based candidates for a reduction in follow-ups. This would help to relieve patient anxiety, give clinicians assurance that they are stepping down the right people, and the NHS would gain the benefit of reduced appointments at a time of need to help towards the NHS England recovery plan and the need to reduce the 6.1 million elective admissions and nearly 1 million diagnostic procedures that are waiting to be seen each month.	
AMLo Biosciences Ltd	Question - Which areas will have the biggest impact on practice and be challenging to	General	General	The draft guidance places high emphasis on changing the frequency of follow-ups for patients following a melanoma diagnosis but with low quality evidence to support the changes. Consequently, we do not believe that the unsubstantiated recommendations will be sufficient to support widespread adoption of change. As a result of our discussions with clinicians, including dermatologists, pathologists, and other stakeholders in this pathway, we have found that assurance must be provided to patients and clinicians that stepping down can be conducted accurately and reliably. It is	Thank you for your comment and for providing practice feedback. The committee agree that people are at highest risk of recurrence during the initial years following diagnosis. However, they also made reference to rates of recurrence and mortality up to 10 years to emphasise the long-term risk of developing a recurrence and as these timepoint are references in the AJCC 8th edition (Gershenwald, 2017). The committee agreed that the use of biomarkers is increasing important within melanoma, for risk-stratification and monitoring. However, this area was

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	implement? Please say for whom and why.			apparent from the white paper in 2021 " Getting under the skin of Melanoma follow up; can resources be optimized?" (https://www.healthanalyticalsolutions.co.uk/resources/melanoma-skin-cancer) that NICE's recommendations in the current NG14 2015 guidelines of Stage IAs being seen between 2 and 4 in year one and IBs to IIBs being seen up to 16 times over five years is being closely followed. Of the Trusts surveyed, 62% said they saw Stage IA people 4 times and 100% said they saw Stage IB to IIB people the full 16 times i.e., current NG14 is widely implemented. Therefore, it will take substantial evidence to effect changes in practice. Implementing a less intensive follow-up regime makes sense, however there is an urgent need for evidence or intervention, and without a reliable biomarker that can predict the risk of recurrence, this will prove challenging to implement.	not included in the scope of this update and therefore the committee were not able to make recommendations on their use. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2).
AMLo Biosciences Ltd	Question - Would implementation of any of the draft recommendations	General	General	No full cost analysis has been completed to support the changes for the follow-up reduction. In addition as we believe that costs in the economic sections have been applied incorrectly, we suggest there will be unforeseen financial implications. For example, the use of diagnostic imaging resources for ultrasound, CT and PET-CT scans has increased dramatically over the last 15 years. It could have a significant impact on	Thank you for your comment. Within a guideline there is a limited number of economic models that can be built due to time and resources. All the questions are assessed for available economic evidence and then a discussion takes place with the committee about which questions are most appropriate for an economic model to be built and in which areas there is the most uncertainty in which an economic model would be able to help. After

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	have significant cost implications?			patient outcomes if patients cannot undergo scanning due to pre-existing waiting times. If the number of follow-ups for those people, who might be at unsubstantiated risk of metastasis is reduced, then an increase in costs would accrue, along with attendant downstream treatments. Currently for stage I or II diagnoses this has little impact, but due to delays, they may become necessary. We note that the additional step of additional CT-Scanning to replace follow-ups has an unquantified cost implication.	discussion with the committee, it was felt that stage III was the most important stage to model as that was where the most uncertainty was. The committee noted that there was a large variation in practice around the country with some patients receiving CT, some receiving PET-CT and some receiving no imaging at all. Given the differing cost of these types of imaging there was potential for a large budget impact. Therefore, the committee made their decision on the other stages using their clinical judgement and the available evidence. We have included multiple scenario analyses to consider the impact of alternative assumptions regarding costs, and found that the results of our model remain robust to each of these assumptions. The committee acknowledged that often a patient will receive a scan of multiple areas and therefore a further scenario analysis was done to remove the costs of one area for CT, PET-CT and MRI. No evidence could be found to show that all patients who are being followed up would be only categorised as outpatients. Therefore, it was felt that it would be more accurate to use all the available costs. When calculating the scan costs (CT, PET-CT and MRI) the costs for Direct Access, Outpatient and Other were used and a weighted average was used. When testing this in the model and only using Outpatients costs the result of CT being the most cost-effective option does not change. This has been

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					included in the report under the scenario analysis. The committee felt that the overall changes to the follow up schedule would be cost saving, this is due to reducing the number of follow up appointments for the lower stages.
Association for Palliative Medicine of Great Britain and Ireland	Guideline	General	General	No reference to consideration of referral to specialist palliative care services for patients with non-curable malignant melanoma. This patient group have a high symptom burden and palliative care need and should be considered for referral at an early stage.	Thank you for your comment. The committee considered this issue and agreed to add a recommendation (1.8.16) to consider referring people with incurable melanoma to specialist palliative care services for symptom management.
British Association of Dermatologists	General	General	General	Thank you for the opportunity to comment on this draft guideline.	Thank you for your comment.
British Association of Dermatologists	Guideline	12	23	Other topical agents such as diphencyprone have also been used and the rationale for imiquimod seems justifiable but perhaps needs to make it broader – so could say, "for example, imiquimod or diphencyprone".	Thank you for your comment. Diphencyprone is an unlicensed product. It would be preferable to use a licensed product, off-label (i.e., imiquimod) over a product that is unlicensed (i.e., diphencyprone). The MHRA have previously provided guidance on the hierarchy for the use of unlicensed medicines (in circumstances where a licensed medicinal product does not meet the patient's special needs). This guidance recommends that if a licensed product used 'off-label' can meet the patient's special needs then this should be used instead of an unlicensed product.
British Association	Guideline	17	24	What does "personalised follow-up" mean? A minor point but a little ambiguous and may be interpreted	Thank you for your comment. The committee agreed that due to limited evidence in this area and the highly

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of Dermatologists				differently – although it does leave it open for clinicians/patients to step out of the recommended timelines. Perhaps this is the intention?	diverse nature of the condition of people with unresectable stage III or IV melanoma, they could not give more specific recommendations in this area. As you mention, the committee envisions that follow-up of these groups of people be considered on a case-by-case basis.
British Association of Dermatologists	Guideline	18	1	Other relevant familial cancer syndromes are mentioned – it might be useful to add a table or comment to highlight the ones we know about at the moment as a reference, e.g., CDKN2A, CDK4, POT1, BAP1 and BRCA – this would be helpful for users of the guidelines to refer to and the associated other cancers with these syndromes.	Thank you for your comment. Familial cancer syndromes are beyond the scope of this guideline update.
British Association of Dermatologists	Guideline	18	8	Suggest adding dermoscopic examination here as part of the routine follow-up as this is important. Whether you also add medical photography should be encouraged where relevant?	Thank you for your comment. The committee considered your feedback and agreed to amend recommendation 1.9.11 outlining that a full examination of the skin should be done by a healthcare professional who has skills and expertise in skin cancer and lymph node examination. They should have access to dermoscopy and medical photography as part of examinations.
British Association of Dermatologists	Guideline	19	Table	Stage IB. Do not consider follow up if SLNB was done – please refer to https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.16892: *"Stage IA, with a negative sentinel lymph node biopsy (pN0), now includes pT1b. This is clinically relevant as the National Institute for Health and Care Excellence*	Thank you for your comment. The committee agreed that people with pT1b melanomas and a negative SLNB have a good long-term prognosis and therefore it is suitable to treat them like other people with stage IA melanomas and offer a follow-up of just 1 year.

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				(NICE) recommends a 1-year follow-up, and not a 5-year follow-up as was previously the case when categorized under stage IB in TNM7. The UICC TNM8 stage for pT1b, with no clinical nodal enlargement and when no sentinel lymph node biopsy has been undertaken, is not stated clearly in the TNM publications, although this is expected to be clarified in a forthcoming publication of the UICC TNM8 supplement (personal communication, D.N.S.). In the interim, the British Association of Dermatologists and the Royal College of Pathologists consider it appropriate to interpret this situation as clinical stage IB and for the patient to have a 5-year and not 1-year follow-up."	The committee agreed that for people with a pT1b melanoma who have unknown sentinel lymph node status, for consistency with the rest of the guideline, it is suitable to treat this group as Stage IB despite not being covered in the UICC and AJCC.
British Association of Dermatologists	Guideline	4	3	AJCC is written by the USA primarily for the USA. Use in clinical practice outside the USA requires a paid-for licence; without it, users can be fined. The NHS does not purchase a global licence so it would have to be bought by individual Trusts. Therefore, other than the USA, the rest of the world including the WHO uses UICC in clinical practice. The PHE supported UICC for skin cancer and NCRAS (National Cancer Registration and Analysis Service) covering cancer registries and NHS cancer data (COSD). Hence, the Royal College of Pathologists (RCPath) followed PHE *et al.* in using UICC and will continue to do so for skin cancer. As did	Thank you for your comment. This text on the stages of melanoma has been removed and now refers to the UICC and AJCC staging methods.

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				the BAD for its clinical guidelines on managing people with cSCC https://onlinelibrary.wiley.com/doi/10.1111/bjd.19621 and BCC https://onlinelibrary.wiley.com/doi/10.1111/bjd.20524. Also, for reference: https://onlinelibrary.wiley.com/doi/full/10.1111/bjd.16892. Could NICE clarify why AJCC was used in this guideline development rather than UICC?	
British Association of Dermatologists	Guideline	4	8	The line 'this first step is followed by the option of a second,' is confusing at it implies that all those in the first step may have the option of the second step which is not the case. Calling it the first step and then the second step is an odd choice of phrase.	Thank you for your comment. The text has been amended to clarify this point.
British Association of Dermatologists	Guideline	7	1	"Use baseline photography (preferably with additional dermoscopic views)'' – would be better than having dermoscopic images only as plate pressure can blanch all vessels, especially of pink lesions can be inconclusive.	Thank you for your comment. The issue you have raised is beyond the scope of this guideline update.

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British Association of Dermatologists	Guideline	7	2	Ideally, images should be done with the same camera or device as different devices perform differently and images can therefore appear significantly different even when they are not. There should be standardisation of photographic technique/protocols that are reproducible for accurate comparison of images.	Thank you for your comment. The issue you have raised is beyond the scope of this guideline update.
British Association of Dermatologists	Guideline	7	10	"Manage a spitzoid lesion of uncertain malignant potential as melanoma." Greater clarity is needed as to what stage of melanoma a spitzoid lesion would be equivalent. Is this based on the Breslow thickness?	Thank you for your comment. The issue you have raised is beyond the scope of this guideline update.
British Association of Dermatologists	Guideline	8	8	This could be contentious as all melanomas, regardless of ulceration, mitotic rate, lymphovascular invasion that are 0.8-1 mm are now classified as stage 1B and many centres now consider these patients for SLNB following discussion at an MDT. Mitotic rate and lymphovascular invasion have been shown not to be reliably reproducible between histopathologists, hence in particular mitotic rate was taken out of the AJCC and UICC staging. Also, there is no comment on the melanomas that are less than 0.8 mm with ulceration that are now classified as stage 1B and whether discussion through	Thank you for your comment. Health economic modelling from the previous update identified that SLNB was not a cost-effective procedure. The recommendations made in this update reflect the committee's desire to limit the number of people receiving SLNB. The committee agreed that decisions surrounding people with melanomas <0.8mm with ulceration should be made on a case-by-case basis. Consequentially, the focus of the present evidence review was on people with melanomas between 0.8 and 1.0mm and as such, the committee only looked at evidence in this area and were unable to make

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				an MDT of these cases and whether they should have SLNB – generally, SLNB is not offered to these cases, but it needs to be mentioned or commented on.	recommendations for people with melanomas of other Breslow thicknesses. They agreed to only recommend SLNB in people with 0.8-1.0mm melanomas if additional risk factors are present due to the large number of people who would otherwise receive the procedure and the high-cost implications associated with this.
British Association of Dermatologists	Guideline	9	3	MRI of the head and CT of chest abdomen pelvis are often conducted in patients requiring imaging. Perhaps MRI of the head should be added as an alternative option to CT of the head throughout this section rather than limiting to the criteria stated. We are not aware of any evidence that suggests not to do this, and MRI is better at detecting brain metastases earlier. Limiting it generally to high mitotic index or scalp melanomas is questionable without good evidence, agree with it being the preferred choice in children and young adults and pregnant women.	Thank you for your comment. The committee considered this issue and have added a recommendation (1.4.11) to consider staging with brain MRI, instead of CE-CT, if locally available and after discussion and agreement with the specialist skin cancer multidisciplinary team.
British Association of Dermatologists	Guideline	9	10	This needs to be clearer. Is this referring to excision margins once the primary excision has been performed and the patient is undergoing a wider excision? It could be assumed so, but it could also be interpreted as the primary excision – so perhaps labelling it as re-excision or wider excision may be helpful.	Thank you for your comment. The committee considered your feedback and agreed to add a further clarification to the excisional margin recommendations (1.5.1 – 1.5.3) that the clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin. Furthermore, the committee agreed that the guideline recommendations should not be considered standard

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					practice in all cases and there is a need for individual interpretation within specialist skin cancer MDTs.
British Association of Dermatologists	Guideline	9	13	Excision margins of stage 0 (1.5.2) are always muddled at MDT. The recommendation states that a 0.5 cm clinical margin should be taken when excising a stage 0 melanoma. For any suspected melanoma, an initial 2 mm margin is recommended to excise the lesion in its entirety, for histological confirmation and then further surgical wider excision is based on the stage and Breslow thickness once the primary histopathology report comes through. Therefore, when 0.5 cm margin is referred to, do they mean the secondary wider excision. It also says that if the histological margin is not adequate this should be discussed with MDT. This is confusing as it muddles clinical and histological margins. The following areas could be clarified to help with this uncertainty: 1. Is a further 0.5 cm clinical margin adequate for MIS and LM if the lesion is excised? 2. Should we treat MIS and LM differently? 3. What is an inadequate histological margin? Stage 0 says adequate histological margin but there is no definition of "adequate"?	Thank you for your comment. The committee considered your feedback and agreed to add a further clarification to the excisional margin recommendations (1.5.1 – 1.5.3) that the clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin. The committee acknowledged that smaller margins may be needed for cosmetic reasons on sites such as the face, head and digits. However, the use of smaller margins should be discussed within the specialist skin cancer multidisciplinary team, the reasoning justified and with clinical surveillance. Furthermore, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team.
British Association	Guideline	9	16	Stage I and II states the strong recommendation (no-flexibility) term "Use" (N.B. 1.5.1 uses the weaker	Thank you for your comment. The committee discussed this issue and agreed to keep 'use' in

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of Dermatologists				recommendation term "Consider"). It mentions clinical margins but no mention of histological margins and their potential influence on clinical margins.	recommendation 1.5.3 but acknowledged that smaller margins may be needed for cosmetic reasons on sites such as the face, head and digits. However, the use of smaller margins should be discussed within the specialist skin cancer multidisciplinary team, the reasoning justified and with clinical surveillance. The committee also agreed to add a further clarification to the excisional margin recommendations (1.5.1 – 1.5.3) that the clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin. Furthermore, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team. The committee acknowledged continuing uncertainty about optimal excision margins, particularly in stage 0 disease, and made a recommendation for research on histological margins.
British Association of Dermatologists	Guideline	General	General	Additional comments – there is no mention of education, which is essential in diagnosing melanoma at an early stage. The journey of every melanoma begins more or less in Primary Care. Suggestions:	Thank you for your comment. The issues you have highlighted are beyond the scope of this guideline update.

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				• Melanoma should be part of the curriculum across all GP training schemes. • As part of provider contracts, monies should be set aside for education of GPs and other relevant Primary Care healthcare professionals in melanoma and NMSCs. • The diagnosis in Primary Care should mainly be focused on the clinical recognition of melanoma; given that up to 50% of nodular melanomas are hypomelanotic then the EFG rule should be added on to the ABCD rule. EFG stands for ALL of Elevated, plus Firm, plus Growing (persistent, more than 1 month) Other than those who have had dermoscopy training and see skin lesions on a regular basis, the main role of dermoscopy in Primary Care should be to screen out common benign non-melanocytic lesions such as seborrhoeic keratoses.	
British Association of Dermatologists	Guideline	General	Geneal	For invasive melanoma, the randomised data is limited to (measured) clinical margins. Melanoma trials largely ignored histological input for margins. There is also the common situation of a lesion being excised that transpires to be melanoma and will have numerical histological margins.	Thank you for your comment. The committee considered your feedback and agreed to add a further clarification to the excisional margin recommendations (1.5.1 – 1.5.3) that the clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin. Furthermore, the committee agreed that the guideline recommendations should not be considered standard

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				The same applies to an excision biopsy of melanoma. In both these cases, a diagnostic excision would normally be done with 2 mm lateral margins. There is no guideline advice that subsequent wider excision can be reduced by 2 mm. Just another source of variance in actual margin size, which is rather larger than we might assume, e.g. do you cut on the inside, middle or outside of the blue surgical marker outline?	practice in all cases and there is a need for individual interpretation within specialist skin cancer MDTs.
British Association of Dermatologists	Guideline	General	General	Margins have been debated for the past few decades – the "1-2-3 cm" proposals from circa 10 years ago were not based on high-quality evidence but consensus. Margins of 5 mm is similarly consensus-based, and some surgeons worked on the basis of total margin. It does not matter whether one cuts in/out/through the skin marking (the line is often 1 mm anyway and leaks wider), it is where the measurement fits with the marking. More importantly, is it relaxed or stretched skin that is marked? This can be a very different size in those circumstances. Some have taken the approach of offering (and recording) 5 mm margins with dysplastic lesions with the explanation that it may be unnecessary but can save a second-stage procedure – and reduce surgical service pressures.	Thank you for your comment. The committee agreed that further research is needed in this area. However, the evidence confirmed that larger margins of 4 cm to 5 cm are associated with more adverse events and no improvement in outcomes. Furthermore, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer MDTs.

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British Association of Dermatologists	Guideline	General	General	The BAD supports a personalised approach to care, based on available evidence and patient preference.	Thank you for your comment. The committee considered this issue and were in agreement.
British Association of Plastic Reconstructive and Aesthetic Surgeons	Evidence Review B	26	18-23	The stratification of those T1b tumours who require SLNB is very useful and will likely reduce the burden on surgical capacity.	Thank you for your comment.
British Association of Plastic Reconstructive and Aesthetic Surgeons	Evidence Review E	5	11	For Stage III disease with microsatellites could NICE consider re phrasing this to allow for head and neck melanoma to have SLNB to stage the nodal disease. As we are still offering neck dissection in micro metastatic disease, for these patients it would still be worth doing it prior to a referral to oncology.	Thank you for your comment. We have added text to this paragraph to clarify this.
British Association of Plastic Reconstructive and Aesthetic Surgeons	Guideline	4	8	Agree that lymph node dissection is unnecessary in microscopic disease, except for head and neck where the risk of developing bulky disease in this area far outweighs the risk of dissection.	Thank you for your comment. The committee were in agreement with your comment and recommended to consider completion lymph node dissection for people if there are factors that might make recurrent nodal disease difficult to manage, for example: • the person has melanoma of the head and neck (recommendation 1.6.2)

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British Association of Plastic Reconstructive and Aesthetic Surgeons	Guideline	General	General	The BAPRAS Skin SIAG commends NICE for this comprehensive and very clear update of guidance for the treatment of melanoma skin cancer.	Thank you for your comment.
British Association of Plastic Reconstructive and Aesthetic Surgeons	Guideline	General	General	The overall feeling is that most units are already on a par with the updates.	Thank you for your comment.
Cambridge University Hospitals NHS Foundation Trust	Evidence review	27	9	It's not clear why the committee would want to encourage an increase in use of CE-CT, which leads to increase in ionising radiation exposure which could be avoided with MRI.	Thank you for your comment. The committee considered this issue and agreed that the radiation risk from ionising radiation exposure is not serious. Furthermore, increased use of MRI instead of CE-CT will have practical implications and will place an increased burden on MRI capacity.
Cambridge University Hospitals NHS Foundation Trust	Guideline			The guideline does not mention use of ipilimumab as an approved immunotherapy treatment for patients progressing after anti-PD1 monotherapy. This has a NICE TA (268) recommendation and should be cited here.	Thank you for your comment. A recommendation to offer ipilimumab for previously treated advanced (unresectable or metastatic) melanoma in line with TA268 has now been included. We have also included recommendations for other second-line treatment options for these patients.

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Cambridge University Hospitals NHS Foundation Trust	Guideline	10	2	Rec 1.5.4 Use of imiquimod for stage 0 – is off licence use – what's the recommendation frequency, duration of imiquimod?	Thank you for your comment. The use of imiquimod is beyond the scope of this update so the committee did not consider the evidence. A note has been added to the guideline indicating it's off-label use. Information on dosage is outlined in the SPC (summaries of product characteristics).
Cambridge University Hospitals NHS Foundation Trust	Guideline	10	5	Rec 1.5.5 How soon after treatment to consider repeat skin biopsy? Skin biopsy may not represent the whole area responding to imiquimod	Thank you for your comment how this issue is beyond the scope of this guideline update.
Cambridge University Hospitals NHS Foundation Trust	Guideline	11	3	Please note that the AJCC v8 staging refers to stage IIIA-D. Please include IIID in recommendations 1.6.3 and 1.6.5	Thank you for your comment. This has been amended.
Cambridge University Hospitals NHS Foundation Trust	Guideline	11	17	Rec 1.6.5 - this is very vague. Although most patients in this situation will be receiving adjuvant systemic therapy to try and improve overall survival, there will be a proportion of patients not suitable for adjuvant sytemic therapy. The randomised TROG trial (Burmeister et al Lancet Oncol 2012; 13: 589-97) does however give some useful guidance on which patients likely to benefit in terms of local	Thank you for your comment how this issue is beyond the scope of this guideline update. The committee has not considered the evidence for adjuvant systemic therapy and has referred to the NICE's technology appraisal guidance on dabrafenib with trametinib, pembrolizumab and nivolumab.

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				control and gives information on likelihood of lymphoedema (We note this was reviewed in 2015, in the evidence section, as a low quality trial, and no mention was made of it in the guidelines document). There was however a 50% reduction in regional recurrence. Please can the committee consider adjusting 1.6.5 to be more specific and therefore more useful.	
Cambridge University Hospitals NHS Foundation Trust	Guideline	14	10	Rec 1.8.7 – When NICE uses the term, 'offer', our understanding is that this is a strong statement of expectation that this is the treatment of choice of these patients. This guideline is therefore defining nivolumab+ipilimumab (ipinivo) as the default treatment for all patients with advanced melanoma. This is an inappropriate and unsafe recommendation. The Checkmate 067 trial is the only large scale randomised phase III trial comparing ipinivo with anti-PD1 monotherapy – in this case, nivolumab. The trial has consistently reported over time (ref. Wolchok J et al, 2017 and 2021) a small gain in progression-free (6.5 year PFS 34% vs 29%) and overall survival (6.5 year OS 49% vs 42%) for ipinivo compared with nivolumab, but ipinivo is associated with a very much greater risk of serious, life threatening and life changing toxicities compared with nivolumab (grade 3-4 AEs 59% vs 21%). Furthermore, when comparing	Thank you for your comment. While CheckMate-067 is indeed the only large-scale randomised phase III trial comparing that compares nivolumab plus ipilimumab with nivolumab monotherapy, we based our analyses on a network meta-analysis (NMA) that we conducted as part of this guideline update. This was necessary as most trials only directly compared 2 or at most 3 treatments. In doing an NMA, we obtain estimates of relative effects for all treatments of interest if they comprise a connected network. Additionally, this method is mathematically validated and frequently used in the HTA reports submitted to NICE by manufacturers seeking approval for their technologies for routine use on the NHS. In our NMA, we also included CheckMate-069. Although this trial is a phase II trial and is smaller than CheckMate-067 (N = 142 vs. N = 945), it nonetheless is a useful inclusion as it adds more data and means we have not one, but two trials comparing nivolumab plus ipilimumab with anti-PD1 monotherapy. Furthermore, NMAs also have the

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				outcomes of those patients with either BRAF mutant or BRAF WT melanoma, the benefits of ipinivo compared with nivolumab appear to be virtually all in the BRAF mutant patient population (6.5 yr OS rates 57% vs 43%) with very little gain in BRAF WT patients (6.5 year OS rates 46% vs 42%). Therefore, there is a fine balance between small gain in efficacy versus high chance of greater toxicity when using ipinivo. Management of immunotherapy-related toxicities is complex, requiring multidisciplinary support and access to ITU services. A high proportion of patients are treated in smaller hospitals were access to these resources is limited. Pushing these teams into using ipinivo by default increases risks to patients unnecessarily with potential for generating harm rather than benefit. Patients recruited to the Checkmate 067 trial were a fit group: mean age was 60 years (60% < 65 years, only 12% > 75 years), all were ECOG PS 0-1 and only 3% had known brain metastases. The real world UK population being treated for metastatic melanoma are not so fit, particularly with our ageing population and likely co-morbidities. This further adds to the risks of harm mandating use of ipinivo in preference to single agent anti-PD1 agents.	advantage of giving an increase in power and precision in the estimation of relative effects. This is because the NMA includes all participants across all included studies. In our NMA, we had data from 10 studies consisting of 4,597 people in total. This is >4 times the number of people in Checkmate 067 alone. Nevertheless, the outcomes of the NMA support the results of the CheckMate-067 trial, with 48% and 41% survival at 6.5 years predicted for nivolumab plus ipilimumab and nivolumab, respectively. The committee considered this benefit to overall and progression-free survival to be meaningful, and, when combined with treatment costs, toxicity and other factors within the cost-effectiveness analysis, nivolumab plus ipilimumab was considered to be the most cost-effective treatment. We noted that a post-hoc subgroup analysis of CheckMate-067 indicated that there may be a greater survival benefit in people with BRAF-mutant melanoma compared with those with BRAF-wild type melanoma. We wished to be cautious and conservative about the interpretation of data in subgroups, particularly in relatively small Phase 3 trials. Furthermore, the committee believed that the choice between anti-PD1 monotherapy and nivolumab plus ipilimumab is mainly driven by factors such as tumour burden, LDH, brain metastases and disease tempo; patient age and BRAF

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				We understand that the committee may be swayed towards use of ipinivo for health economic reasons. It is important to remind the committee that the published data that supports a short treatment duration associated with ipinivo, with longer time off treatment compared with anti-PD1 monotherapy completely ignores the fact that the main reason for stopping ipinivo is for unacceptable toxicity, from which patients are symptomatic, likely to be hospitalised and may require a variety of other interventions including chronic steroid use and access to multiple other support services/investigtations/treatments. None of this is costed in terms of finance, nor in terms of impact on patient quality of life – there is currently no quality data assessing survivorship and long term effects of using intensive immunosuppressants to manage complex immunotherapy toxicities. Therefore, the health-economic argument in our view is flawed.	mutational status are much less relevant factors. We noted that there was little difference in PFS for nivolumab plus ipilimumab between the two BRAF subgroups, suggesting that the benefit may be due to treatments received after discontinuation; however, the opposite phenomenon occurred in the nivolumab arm, whereby there was little difference between OS outcomes between the subgroups but a small difference in PFS. Therefore, we felt that these outcomes should be interpreted with a high degree of caution. However, to explore the impact of BRAF status on relative treatment effect, we conducted several scenario analyses with our NMA. In one analysis (Network 3), we only included people with BRAF-wild type melanoma with immunotherapy strategies only. In this analysis, nivolumab plus ipilimumab continued to show the greatest benefit in both overall survival (OS) and progression-free survival (PFS), and nivolumab monotherapy had the second-best benefit in OS and PFS. Notably however, the difference between nivolumab plus ipilimumab and nivolumab between Network 3 and Network 1 (which included people with both BRAF-wild type and BRAF-mutant melanoma and both targeted therapies and immunotherapies) was reduced. When the NMA outcomes from Network 3 were included in the economic analysis, the cost-

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					effectiveness results still favoured nivolumab plus ipilimumab. The committee were aware that nivolumab plus ipilimumab was associated with a shorter treatment duration than the other immunotherapy single agent treatment options. This was incorporated into the economic model using time on treatment data generated by SACT and from the clinical trials. The economic analysis also took into account the impact of Grade 3-4 toxicities captured in the trials, both in terms of their management cost and their quality-of-life decrement. We acknowledge that some of the more long-term toxicities are less likely to be captured within the trials, however, the committee agreed that at least some of these were addressed in the adverse event NMA conducted. The committee also advised that some of these long-term side effects and conditions are asymptomatic and therefore would not fall into the category of Grade 3-4 adverse event. Therefore, this limitation is not expected to change the conclusions of the analysis. Since these immunotherapies in melanoma have already been evaluated and approved through the NICE TA process and have been in use for some time, the committee believed that these toxicities are already

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					managed and supported across NHS cancer services. The resource impact for anti-cancer treatments have been assessed when the respective technology appraisals were conducted and RIA tools were published alongside the technology appraisal guidance. Despite nivolumab plus ipilimumab being the most effective treatment in the NMA and cost-effective treatment in the economic analysis, there may be some patients in which the risk of combination therapy may be outweighed by their potential benefit, and who are not representative of patients enrolled in the RCTs. Therefore, we have added in an additional recommendation within this section of the guideline to give greater weight to clinical judgement in determining the most appropriate treatment for people with melanoma. We have now noted a number of different patient-, tumour- and treatment-related factors, including tolerance of therapy, comorbidities and toxicity, when making treatment decisions. We are aware that there is little long-term evidence on patients and have included a research recommendation on survivorship.
Cambridge University Hospitals	Guideline	14	16	Rec 1.8.9 and 1.8.10 – it is our belief that while immunotherapy should be recommended as the treatment of choice for most patients with advanced	Thank you for your comment. Following an update to the confidential pricing, the health economic results under the confidential prices have changed, with pembrolizumab and nivolumab being similarly cost-

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NHS Foundation Trust				melanoma (ie. recommendation 1.8.6 is good and is important to particularly emphasise this for BRAF mutant patients), the specific immunotherapy modality – whether ipinivo, nivolumab or pembrolizumab – should not be specified in this guideline. Pembrolizumab and nivolumab are to all intents and purposes equivalent in terms of their efficacy and for reasons already explained, anti-PD1 monotherapy will be the preferred regimen for a high proportion of metastatic melanoma patients compared with ipinivo. We strongly feel that these 3 recommendations need to be revised into a single recommendation, placing all 3 regimens on an equal footing.	effective in the base-case analysis and scenario analyses. The recommendations have been changed to offer either pembrolizumab or nivolumab to reflect this update. The economic model also demonstrated that, under our preferred assumptions and in almost every scenario, nivolumab plus ipilimumab was the most cost-effective of the options for the advanced melanoma population, when taking into account treatment costs, QoL, overall and progression-free survival and toxicity. We acknowledge that trial-based populations typically include fitter patients than are seen in general practice and that the results of the cost-effectiveness analysis should interpreted this in mind. Therefore, the committee agreed that it was important to acknowledge other factors that should be taken into account when selecting treatment, and a recommendation has been added to consider all factors when choosing the most appropriate, as the committee noted that there are circumstances in which combination therapy may be less suitable than single agent therapy. We have also added a reference to our guideline on shared decision making.
Cambridge University Hospitals NHS	Guideline	18	3	Rec 1.9.7 and 1.9.8 – it is not clear why MRI head is being limited only to these patient groups and not being recommended as an option in all patients undergoing surveillance imaging	Thank you for your comment. The committee considered your feedback and agreed that a brain MRI should be considered for imaging at follow up. The committee have added a new recommendation 1.9.10 to consider brain MRI, instead of CE-CT brain for

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Foundation Trust					imaging follow up, if locally preferable and after discussion and agreement with the specialist skin cancer MDT. The committee also acknowledged the logistical difficulties and capacity issues of arranging separate CE-CT and MRI scans.
Cambridge University Hospitals NHS Foundation Trust	Guideline	18	13	Rec 1.9.11 – it is not clear why the committee mandates not using PET-CT during follow-up of people with melanoma. Particularly for patients whose primary tumours are on a limb, CT imaging does not cover the part of the body most likely to be affected by regional recurrence, so there is good reason to consider offering PET-CT as a surveillance modality for these patients.	Thank you for your comment. Cost-effectiveness analysis done for evidence review G found that a follow-up strategy of CE-CT is more cost effective than one of PET-CT. However, based on stakeholder feedback, the committee agreed that the recommendations were too prescriptive with regards to the areas in which the CE-CT should be focused and agreed to change these recommendations to only 'body and brain CE-CT'. Although it is intended that routinely, this would involve the thorax, abdomen, pelvis and brain, it is intended that individual centres should have the final say in which areas should be covered.
Cambridge University Hospitals NHS Foundation Trust	Guideline	19	Last row	Stage IIIA melanoma is a comparatively good prognostic outcome, and has similar outcomes to Stage IIB. It is discordant to recommend a more intense clinical and imaging regime in comparison, especially with low disease burden (<1mm tumour max dimension on SLNB). There is an international registry study looking at outcomes in AJCC8 Stage IIIA patients due to be published in the coming months.	Thank you for your comment. The committee discussed this issue and agreed that a reduced surveillance schedule for Stage IIIA with ≤1mm nodal involvement would cause confusion due to being less rigorous than lower stages and may adversely impact upon patient quality of life, due to having infrequent clinic visits and scans despite having a high stage disease diagnosis. On this basis they agreed to keep the current recommendation outlined in the table.

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					Thank you also for highlighting the forthcoming international registry study. We will pass your comment to the NICE surveillance team which monitors guidelines to ensure that they are up to date.
Cambridge University Hospitals NHS Foundation Trust	Guideline	4	11	Clinical cT1bN0 (Stage IB) is down-staged to pT1bN0 (Stage IA) if Sentinel Lymph node biopsy is negative.	Thank you for your comment. This has been amended.
Cambridge University Hospitals NHS Foundation Trust	Guideline	7	22	Rec 1.3.9 – Since outcomes for stage IIB melanoma equate to that of IIIA, it seems inconsistent not to offer BRAF testing for stage IIB melanoma	Thank you for your comment. The committee agreed that the main utility of BRAF testing is that it will make some people with melanoma eligible for additional therapies. The main benefit is therefore in people with stage III disease as currently, these therapies are only licensed in this population. The committee agreed that the benefit for its use in stage II disease is that a large proportion of these patients will have a recurrence and be up-staged to stage III disease. Having their BRAF status on record will allow for the person's optimal treatment regimen to be identified sooner. IIC disease was included in the 'offer' group due to the higher risk of recurrence than stage IIA/B disease. The committee decided that testing should be considered for IIB (instead of offered) due to the lower risk of recurrence than IIC and although the risk of recurrence is comparable to stage IIIA, the outcome would only impact treatment in the event of a recurrence.

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Cambridge University Hospitals NHS Foundation Trust	Guideline	7	26	Rec 1.3.11: The international gold standard BRAF analysis is a genetic test. IHC offers value in being rapid and cheap by comparison. However, it is less standardised and is not accepted as an alternative to gene testing for clinical trial purposes. Please state that, when considering patients for clinical trials, genetic testing is recommended.	Thank you for your comment. We have included an additional recommendation in this section to conduct genetic testing for patients considered for clinical trials (rec 1.3.14).
Cambridge University Hospitals NHS Foundation Trust	Guideline	8	6	Rec 1.4.2 No pre-SLNB imaging recommended, but section 1.4.6 recommends offering staging CT in Stage IIC. It would be reasonable to time the staging CT in Stage IIC prior to SLNB, as it may influence consideration of SLNB Vs upfront treatment for Stage III/IV disease. The purpose of imaging here is not to assess the draining nodal basin which is the focus of the evidence summary, but distant metastatic disease at presentation.	Thank you for your comment. The committee considered this issue and agreed that imaging should be used before SLNB if distant metastatic disease is suspected. This is covered in recommendation 1.4.2 - do not offer imaging before SLNB unless lymph node or distant metastases are suspected.
Cambridge University Hospitals NHS Foundation Trust	Guideline	8	6	1.4.2,8,9: The evidence presented for offering imaging in Stage IIB, especially for children, young adults and pregnant women after having had a negative SLNB is weak. Stage IIB melanoma staged by SLNB forms approximately 15% of all melanoma Stage I/II patients, and do not currently have routine surveillance imaging. Across 5 years of planned surveillance, this equates to an additional 9 CT scans (+ another 9 US scans if SLNB not	Thank you for your comment. The committee discussed this issue and agreed that recommendations 1.4.8 and 1.4.9 to offer imaging for staging for stage IIB does not mention having a negative SLNB. Evidence review B did not find any evidence on the use of SLNB in children. Recommendation 1.4.5 outlines for women who are pregnant to discuss the option of delaying SLNB until after the pregnancy is completed therefore whole body and brain MRI imaging is the only option available.

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				performed). The recommendations suggest this may increase the use of CT and ultrasound scans, with a reduction in "other" imaging, but in practice no other routine imaging is widely used. A cost benefit analysis is not presented to the utility of this approach.	
Cambridge University Hospitals NHS Foundation Trust	Guideline	8	17	Rec 1.4.6 and 1.4.7 - It is not clear why the guideline mandates CT head as opposed to the option to use MRI head as part of routine melanoma staging. Given the frequency of surveillance scanning, many centres prefer to offer MRI head particularly to younger people and it would seem perverse for the national guideline not to be consistent with this current practice.	Thank you for your comment. The committee considered this issue and have added a recommendation (1.4.11) to consider staging with brain MRI, instead of CE-CT, if locally available and after discussion and agreement with the specialist skin cancer multidisciplinary team. Furthermore recommendation 1.4.8 outlines to offer staging with whole body and brain MRI, instead of CE-CT, for children and young adults (from birth to 24 years) with stage IIB to IV melanoma. This is because of the cumulative risk of radiation associated with CE-CT scanning in children and young people.
Cambridge University Hospitals NHS Foundation Trust	Guideline	9	3	Rec 1.4.10 – We think the option to consider MRI brain as an alternative to CT head should be broadened to any patients undergoing melanoma staging and surveillance	Thank you for your comment. The committee considered this issue and have added a recommendation (1.4.11) to consider staging with brain MRI, instead of CE-CT, if locally available and after discussion and agreement with the specialist skin cancer multidisciplinary team.

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Cambridge University Hospitals NHS Foundation Trust	Guideline	9	7	Rec 1.4.11: For patients starting adjuvant treatment after microscopic nodal disease, imaging within 8 weeks is based on weak evidence. The "definition" of 7.4 weeks I am assuming is informed by Bloemendal et al (ASO (2019) 26:3945-52) which had a median interval between surgery and repeat scan of 7.4 weeks. It is important to distinguish here that this study refers to macroscopically involved nodes as defined in AJCC7, and the surgery performed was a therapeutic lymph node dissection (not a SLNB). This will inevitably increase the rate of "early relapse" as it is looking at a different patient group. I would suggest an interval of 12 weeks.	Thank you for your comment. The committee considered your feedback and agreed to amend recommendation 1.4.12 to consider a repeat staging scan before starting adjuvant treatment, unless imaging done within the past 6 to 8 weeks is available.
Health Analytical Solutions Ltd	Economic report 6.2 : evidence reviews for the follow up of people with melanoma	26	40	It would appear that a decision has been taken to use an average weighted cost for CT scans and PET-CT across all HRG codes in this section. However it has been widely reported and also in previous NG14 guidelines that patients have multiple areas scanned due to the nature of melanoma and the spread. Therefore to include a HRG code for just a single area would be invalid.	Thank you for your comment. The committee acknowledged that often a patient will receive a scan of multiple areas and therefore a further scenario analysis was done to remove the costs of one area for CT, PET-CT and MRI. This changed the cost of CT to £109.08, PET-CT to £664.99 and MRI to £165.20. When this was used in the model, CT at the current follow up schedule was still the most cost-effective option and therefore the recommendations following the model are still valid. This has been included in the report under the scenario analysis.

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Health Analytical Solutions Ltd	Economic report 6.2 : evidence reviews for the follow up of people with melanoma	27	1	Table HE017: CT costs – It would appear that all costs included in the table for CT, have been extracted from reference costs from the allocation of direct access. For example "Computerised Tomography Scan of One Area, without Contrast, 19 years and over" qty 165005 at £77.95. However direct access is generally where GPs refer patients for tests within the secondary care setting and activity is recorded. Please see National cost collection guidance by NHS England which states that outpatient diagnostics or services would be recorded under "Imaging: Outpatient". Which in this single example the cost for the diagnostic would increase from £77.95 to £85.18 – which is a difference of 9.2% this is incorrect in the mention table for 24 HRG codes listed. Also the activity in "Imaging: Outpatient". Goes from 165k to 645k which is more in keeping with CT scan levels. Therefore this will have an impact on the overall costs. So any calculations in this report using these costs will be wrong.	Thank you for your comment. No evidence could be found to show that all patients who are being followed up would be only categorised as outpatients. Therefore, it was felt that it would be more accurate to use all the available costs. When calculating the scan costs (CT, PET-CT and MRI) the costs for Direct Access, Outpatient and Other were used and a weighted average was used. Therefore, the total number of CT scans was 1.8 million, MRI scans was 1.9 million and PET-CT scans was 47 thousand. When testing this in the model and only using Outpatients costs the result of CT being the most cost-effective option does not change. This has been included in the report under the scenario analysis.
Health Analytical Solutions Ltd	Economic report 6.2 : evidence reviews for the follow up	27	2	Table HE018: PET-CT costs – This is also incorrect as it would appear that all costs included in the table for PET CT, have been extracted from reference costs from the allocation of direct access. For example "Positron Emission Tomography with Computed Tomography (PET-CT) of One Area, 19 years and over" qty 5002 at £180.25. However direct access is	Thank you for your comment. No evidence could be found to show that all patients who are being followed up would be only categorised as outpatients. Therefore, it was felt that it would be more accurate to use all the available costs. When calculating the scan costs (CT, PET-CT and MRI) the costs for Direct Access, Outpatient and Other were used and a weighted average was used. Therefore, the total

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	of people with melanoma			generally where GPs refer patients for tests within the secondary care setting and activity is recorded. Please see National cost collection guidance by NHS England which states that outpatient diagnostics or services would be recorded under "Imaging: Outpatient". Which in this single example the cost for the diagnostic would increase from £180.25 to £549.20 – which is a difference of 200+% this is incorrect in the mention table for 6 HRG codes listed. Also the activity in "Imaging: Outpatient". Goes from 5k to 38k which is more in keeping with pet-ct scan levels. Therefore, this will have an impact on the overall costs and the example is just one of the 6 which are wrong. So any calculations in this report using these costs will be wrong.	number of CT scans was 1.8 million, MRI scans was 1.9 million and PET-CT scans was 47 thousand. When testing this in the model and only using Outpatients costs the result of CT being the most cost-effective option does not change. This has been included in the report under the scenario analysis.
Health Analytical Solutions Ltd	Economic report 6.2 : evidence reviews for the follow up of people with melanoma	28	19	Table HE019: Follow-up clinical appointment costs – The cost of a general surgery follow up has been included incorrectly at £113.06 for 2018/19 reference costs. This should be £133.06, we assume this is a type. Also this will have an impact on the average weighted costs. So any calculations in this report using these costs will be wrong.	Thank you for your comment. This was a typo in the report and the correct figure of £133.06 was included in the model and therefore the results of the model are correct. This has been corrected in the report.

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Health Analytical Solutions Ltd	Economic report 6.2 : evidence reviews for the follow up of people with melanoma	28	28	Table HE020: Surgery costs – It would appear that the overall reference cost across all settings has been taken. We understand that to establish which are melanoma related is not easy to achieve. However, the inclusion of emergency admissions, outpatients for this type of procedure would be unusual to be considered. Therefore, the relevant selection for elective or even emergency might want to be considered to give a better reflection of costs. Which in this case would mean the costs would be higher. Which based on the complexity of skin grafts and recovery this would be more accurate reflection. So any calculations in this report using these costs will be wrong.	Thank you for your comment. It is difficult to establish which surgery costs are related to melanoma and it was therefore felt to be appropriate to use the overall reference cost rather than only elective surgery. However, the committee acknowledged that the most common section would be elective however depending on the surgery it may be under the outpatient section. It was therefore decided to add a scenario analysis using a weighted average of the elective costs. This analysis still showed that CT at the current follow up schedule was the most cost effective option. This has been included in the report under the scenario analysis.
Health Analytical Solutions Ltd	Economic report 6.2 : evidence reviews for the follow up of people with melanoma	29	5	Table HE021: MRI costs This is also incorrect as it would appear that all costs included in the table for MRI, have been extracted from reference costs from the allocation of direct access. For example "Magnetic Resonance Imaging Scan of One Area, without Contrast, 19 years and over" qty 433k at £120.83. However direct access is generally where GPs refer patients for tests within the secondary care setting and activity is recorded. Please see National cost collection guidance by NHS England which states that outpatient diagnostics or services would be recorded under "Imaging: Outpatient". Which in this single	Thank you for your comment. No evidence could be found to show that all patients who are being followed up would be only categorised in outpatients. Therefore, it was felt that it would be more accurate to use all the available costs. When calculating the scan costs (CT, PET-CT and MRI) the costs for Direct Access, Outpatient and Other were used and a weighted average was used. Therefore, the total number of CT scans was 1.8 million, MRI scans was 1.9 million and PET-CT scans was 47 thousand. When testing this in the model and only using Outpatients costs the result of CT being the most cost-effective option does not change. This has been included in the report under the scenario analysis.

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				example the cost for the diagnostic would increase from £120.83 to £143.67 – which is a difference of 18% this is incorrect in the mention table for 6 HRG codes listed. Also the activity in "Imaging: Outpatient". Goes from 433k to 995k which is more in keeping with pet-ct scan levels. Therefore, this will have an impact on the overall costs and the example is just one of the 10 which are wrong. So any calculations in this report using these costs will be wrong.	
Health Analytical Solutions Ltd	Economic report 6.2 : evidence reviews for the follow up of people with melanoma	36	2	Therefore based on the incurrent reference costs used in the tables for 2018/19 then all analysis are incorrect for tables in the whole of "HE2.12 Base-case cost–utility results". These will need to be updated to support the decision on what is cost effective or not.	Thank you for your comment. When calculating the scan costs (CT, PET-CT and MRI) the costs used in the model was a weighted average of the largest number of scans a patient may receive Therefore, the total number of CT scans was 1.8 million, MRI scans was 1.9 million and PER-CT scans was 47 thousand. When testing these in the model and only using certain costs, the result of CT being the most cost-effective option does not change. This has been included in the report under the scenario analysis.
Health Analytical Solutions Ltd	Economic report 6.2 : evidence reviews for the	40	2	HE2.21 Sensitivity analysis is also incorrect based on the use of wrong values in the economic model	Thank you for your comment. The changes suggested to CT, PET-CT and MRI are small and therefore still included in the range of values tested in the sensitivity analysis or included in scenario analyses. Therefore, it is felt that the sensitivity analysis sufficiently captures all the necessary uncertainty.

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	follow up of people with melanoma				The model is not very sensitive to costs and other variables such as the sensitivity of CT and the probability of a patient being symptomatic are much more likely to affect the results.
Health Analytical Solutions Ltd	Guideline	17	26	1.9.6 – Personalized follow-up is recommended for patients at increased risk. However in the guidelines of NG14 we would have thought the NHS England PSFU (Personalised Stratification Follow-up program) would be referenced. Especially for those with low risk, where there is clear evidence and biomarkers demonstrate stepping those patients down. There is a need for evidence, but we believe this could be presented in a more balanced manner.	Thank you for your comment. The committee agreed that due to limited evidence in this area and the highly diverse nature of the condition of people with unresectable stage III or IV melanoma, they could not give more specific recommendations in this area. As you mention, the committee envisions that follow-up of these groups of people be considered on a case-by-case basis.
Health Analytical Solutions Ltd	Guideline	19	20	Follow up after stages I through IV of melanoma (Table) – It appears and has been referenced that a lack of clinical and economic evidence is available to suggest reducing the number of follow ups. Furthermore, a recent white paper published in 2021 entitled, "Getting under the skin of Melanoma follow-up; can resources be optimized" reported that 100% of NHS Trusts included in this study completed 16 follow-ups during a five-year period in accordance with the NICE guidelines for IB to IIB. Also 62% said they implemented 4 follow ups for IAs. In this case,	Thank you for your comment. There is limited clinical and health economic evidence for follow up in patients with melanoma. Within a guideline there is a limited number of economic models that can be built due to time and resources available. All the questions are assessed for available economic evidence and then a discussion takes place with the committee about which questions are most appropriate for an economic model to be built and in which areas there is the most uncertainty in which an economic model would be able to help. After discussion with the committee, it was felt that stage III was the most important stage to estimate the cost-effectiveness of

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				reducing this would appear to go against established current practice without data as to the implications.	different follow up modalities and schedules, as that was where the most uncertainty was. The committee noted that there was a large variation in practice around the country with some patients receiving CT, some receiving PET-CT and some receiving no imaging at all. Given the differing cost of these types of imaging there was potential for a large budget impact. Therefore, the committee made their decision on the other stages using their clinical judgement and the available evidence.
Health Analytical Solutions Ltd	Question - What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or	General	General	A number of considerations need to be considered, however the first is the clinician's assurance and that of the patient. As a result, having a Biomarker in place that can be used as a prognostic in the NHS at a time when Melanoma has been on the rise, certainly over the past five years, before Covid-19, then we need to get the issue right from the beginning. Please see the white paper 2021 " Getting under the skin of Melanoma follow up; can resources be optimized?" (https://www.healthanalyticalsolutions.co.uk/resources/melanoma-skin-cancer) This provides a view of what is occurring and what options the NHS could take to obtain a more robust and successful outcome	Thank you for your comment however the adoption and implementation of a biomarker prognostic test was beyond the scope of this guideline update. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2).

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	examples of good practice.)				
Health Analytical Solutions Ltd	Question - Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.	General	General	The most significant will be providing assurance to clinicians & patients that stepping down at a time of need to be assured will be difficult. Without a way to establish which patients might continue metastasis or not is unknown and at present without a biomarker this is not possible. Diagnostic scanning is an indicator but will not give the assurance that prognostic would. Therefore, this could be a guideline in place with an aspiration, but in reality the clinicians will carry on doing what they have done before. Also as shown in the white paper 2021 " Getting under the skin of Melanoma follow up; can resources be optimized?" (https://www.healthanalyticalsolutions.co.uk/resources/melanoma-skin-cancer)	Thank you for your comment. The committee agree that people are at highest risk of recurrence during the initial years following diagnosis. However, they also made reference to rates of recurrence and mortality up to 10 years to emphasise the long-term risk of developing a recurrence and as these timepoint are references in the AJCC 8th edition (Gershenwald, 2017). The committee agreed that the use of biomarkers is increasing important within melanoma, for risk-stratification and monitoring. However, this area was not included in the scope of this update and therefore the committee were not able to make recommendations on their use. The committee were unaware of definitive evidence in this area and consequentially made two research recommendations for studies to develop/assess the use of biomarkers for people with melanoma (please see research recommendations 1 and 2).
Health Analytical Solutions Ltd	Question - Would implementation of any of	General	General	Stepping patients down when the assurance that they will not develop metastatic disease will incur a high cost. Despite the fact that the NHS will release savings and deal with some of the problems with long waiting lists and diagnostics overruns caused by Covid-19.	Thank you for your comment. We have included multiple scenario analyses to consider the impact of alternative assumptions regarding costs and found that the results of our model

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	the draft recommendations have significant cost implications?			This change in NG14 frequency of follow-ups simply fails to meet the objectives of the brief. Along with the challenge of adding to the workload of the NHS's imaging department, which is already under considerable pressure. Also the fact that all modelling in this consultation has been based on inaccurate costs, then any possible economic suggestions in the papers will need to be reviewed once again to ensure the message is still accurate before implementing the changes.	remain robust to each of these assumptions. The committee acknowledged that often a patient will receive a scan of multiple areas and therefore a further scenario analysis was done to remove the costs of one area for CT, PET-CT and MRI. No evidence could be found to show that all patients who are being followed up would be only categorised as outpatients. Therefore, it was felt that it would be more accurate to use all the available costs. When calculating the scan costs (CT, PET-CT and MRI) the costs for Direct Access, Outpatient and Other were used and a weighted average was used. Therefore, the total number of CT scans was 1.8 million, MRI scans was 1.9 million and PET-CT scans was 47 thousand. The committee felt that the overall changes to the follow up schedule would be cost saving, this is due to reducing the number of follow up appointments for the lower stages.
Melanoma Focus	Evidence review	27	9	It's not clear why the committee would want to encourage an increase in use of CE-CT, which leads to increase in ionising radiation exposure which could be avoided with MRI.	Thank you for your comment. The committee considered this issue and agreed that the radiation risk from ionising radiation exposure is not serious. Furthermore, increased use of MRI instead of CE-CT will have practical implications and will place an increased burden on MRI capacity.
Melanoma Focus	Guidance	10 11 12	2-10 22 23	We would like to point out the lack of evidence base for including recommendations for use of imiquimod, which is an unlicensed treatment	Thank you for your comment. The use of imiquimod is beyond the scope of this update so the committee did not consider the evidence. A note has been added to the guideline indicating it's off-label use.

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Melanoma Focus	Guidance	17	18	Rec 1.9.13. We feel it is important to recommend that routine surveillance for patients with known or resected brain metastases should be with MRI head, not CT head	Thank you for your comment. The committee considered your feedback and have amended the recommendation outlining to offer brain MRI, instead of CE-CT brain for follow up, to people with known or resected brain metastases.
Melanoma Focus	Guidance	7	26	Rec 1.3.11: The international gold standard BRAF analysis is a genetic test. IHC offers value in being rapid and cheap by comparison. However, it is less standardised and is not accepted as an alternative to gene testing for clinical trial purposes. Please state that, when considering patients for clinical trials, genetic testing is recommended.	Thank you for your comment. We have included an additional recommendation in this section (rec 1.3.14) about conducting genetic testing for patients considered for clinical trials.
Melanoma Focus	Guidance	9, 18	1-2, 5-6	The draft updated NICE guidance is recommending whole body MRI scans for women who are pregnant. Our view is that appropriate imaging in this patient group is dependent on a number of factors, including stage of pregnancy and patient wishes. We recommend that imaging for this patient group needs to be determined on a case by case basis in conjunction with appropriate Radiology advice.	Thank you for your comment. The committee discussed this issue and agreed to keep the current recommendations to offer whole body and brain MRI due to the cumulative risk of radiation associated with CE-CT scanning for women during pregnancy which is undesirable.
Melanoma Focus	Guideline			The guideline does not mention use of ipilimumab as an approved immunotherapy treatment for patients progressing after anti-PD1 monotherapy. This has a NICE TA (268) recommendation and should be cited here.	Thank you for your comment. A recommendation to offer ipilimumab for previously treated advanced (unresectable or metastatic) melanoma in line with TA268 has now been included. We have also included recommendations for other second-line treatment options for these patients.

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Melanoma Focus	Guideline	11	3	Please note that the AJCC v8 staging refers to stage IIIA-D. Please include IIID in recommendations 1.6.3 and 1.6.5	Thank you for your comment. This has been amended.
Melanoma Focus	Guideline	14	10	Rec 1.8.7 – When NICE uses the term, 'offer', our understanding is that this is a strong statement of expectation that this is the treatment of choice of these patients. This guideline is therefore defining nivolumab+ipilimumab (ipi/nivo) as the default treatment for all patients with advanced melanoma. This is an inappropriate and unsafe recommendation. The Checkmate 067 trial is the only large scale randomised phase III trial comparing ipi/nivo with anti-PD1 monotherapy – in this case, nivolumab. The trial has consistently reported over time (ref. Wolchok J et al, 2017 and 2021) a modest gain in progression-free (6.5 year PFS 34% vs 29%) and overall survival (6.5 year OS 49% vs 42%) for ipi/nivo compared with nivolumab, but ipi/nivo is associated with a very much greater risk of serious, life threatening and life changing toxicities compared with nivolumab (grade 3-4 AEs 59% vs 21%). Furthermore, when comparing outcomes of those patients with either BRAF mutant or BRAF WT melanoma, the benefits of ipi/nivo compared with nivolumab appear to be virtually all in the BRAF mutant patient population (6.5 yr OS rates 57% vs 43%) with very little gain in BRAF WT patients	As above (we will duplicate the comment after the QA meeting)

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				(6.5 year OS rates 46% vs 42%). Therefore, there is a fine balance between small gain in efficacy versus high chance of greater toxicity when using ipi/nivo. Management of immunotherapy-related toxicities is complex, requiring multidisciplinary support and access to ITU services. A high proportion of patients are treated in smaller hospitals were access to these resources is limited. Pushing these teams into using ipi/nivo by default increases risks to patients unnecessarily with potential for generating harm rather than benefit. Patients recruited to the Checkmate 067 trial were a fit group: mean age was 60 years (60% < 65 years, only 12% > 75 years), all were ECOG PS 0-1 and only 3% had known brain metastases. The real world UK population being treated for metastatic melanoma are not so fit, particularly with our ageing population and likely co-morbidities. This further adds to the risks of harm mandating use of ipi/nivo in preference to single agent anti-PD1 agents. We understand that the committee may be swayed towards use of ipi/nivo for health economic reasons. It is important to remind the committee that the published data that supports a short treatment duration associated with ipi/nivo, with longer time off treatment compared with anti-PD1 monotherapy	

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				completely ignores the fact that the main reason for stopping ipi/nivo is for unacceptable toxicity, from which patients are symptomatic, likely to be hospitalised and may require a variety of other interventions including chronic steroid use and access to multiple other support services/investigations/treatments. None of this is costed in terms of finance, nor in terms of impact on patient quality of life – there is currently no quality data assessing survivorship and long term effects of using intensive immunosuppressants to manage complex immunotherapy toxicities. Therefore, the health-economic argument in our view is flawed.	
Melanoma Focus	Guideline	14	16	Rec 1.8.9 and 1.8.10 – it is our belief that while immunotherapy should be recommended as the treatment of choice for most patients with advanced melanoma (ie. recommendation 1.8.6 is good and is important to particularly emphasise this for BRAF mutant patients), the specific immunotherapy modality – whether ipi/nivo, nivolumab or pembrolizumab – should not be specified in this guideline. Pembrolizumab and nivolumab are to all intents and purposes equivalent in terms of their efficacy and for reasons already explained, anti-PD1 monotherapy will be the preferred regimen for a high proportion of metastatic melanoma patients compared with ipi/nivo.	As above (we will duplicate the comment after the QA meeting)

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				We strongly feel that these 3 approved recommendations need to be revised into a single recommendation, placing all 3 regimens on an equal footing.	
Melanoma Focus	Guideline	18	3	Rec 1.9.7 and 1.9.8 – it is not clear why MRI head is being limited only to these patient groups and not being recommended as an option in all patients undergoing surveillance imaging	Thank you for your comment. The committee considered your feedback and agreed that a brain MRI should be considered for imaging at follow up. The committee have added a new recommendation 1.9.10 to consider brain MRI, instead of CE-CT brain for imaging follow up, if locally preferable and after discussion and agreement with the specialist skin cancer MDT. The committee also acknowledged the logistical difficulties and capacity issues of arranging separate CE-CT and MRI scans.
Melanoma Focus	Guideline	18	13	Rec 1.9.11 – it is not clear why the committee mandates not using PET-CT during follow-up of people with melanoma. Particularly for patients whose primary tumours are on a limb, CT imaging does not cover the part of the body most likely to be affected by regional recurrence, so there is good reason to consider offering PET-CT as a surveillance modality for these patients.	Thank you for your comment. Cost-effectiveness analysis done for evidence review G found that a follow-up strategy of CE-CT is more cost effective than one of PET-CT. However, based on stakeholder feedback, the committee agreed that the recommendations were too prescriptive with regards to the areas in which the CE-CT should be focused and agreed to change these recommendations to only 'body and brain CE-CT'. Although it is intended that routinely, this would involve the thorax, abdomen, pelvis and brain, it is intended that individual centres should have the final say in which areas should be covered.

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Melanoma Focus	Guideline	19	Table	The draft NICE guidance has not distinguished between lower risk stage IIIA melanoma (≤1mm SLN deposit) and higher risk stage IIIA melanoma (>1 mm SLN deposit). We appreciate the committee's view that a reduced surveillance schedule for Stage IIIA pts with ≤1mm deposit could cause confusion and may impact on QoL, due to being less rigorous than lower stages, with less frequent clinic visits and scans despite having a higher stage disease diagnosis (as explained in Evidence review G, pg 40, lines 8-11). However, Melanoma Specific Survival for patients with stage IIIA disease and ≤1mm SLN deposit is >90%. For this good prognosis group we feel the radiation risk of up to 9 CT scans over 5 years outweighs the benefit of cross-sectional imaging. We would instead recommend USS of the draining lymph node basin, 6 monthly in years 1-3, annually years 4-5, then stop. This is a recommendation based on the consensus views of a panel of melanoma experts in the UK, published by Melanoma Focus.	Thank you for your comment. The committee discussed this issue and agreed that a reduced surveillance schedule for Stage IIIA with ≤1mm nodal involvement would cause confusion due to being less rigorous than lower stages and may adversely impact upon patient quality of life, due to having infrequent clinic visits and scans despite having a high stage disease diagnosis. On this basis they agreed to keep the current recommendation outlined in the table. Furthermore, the committee were also concerned about creating sub-groups of lower risk stage IIIA and higher risk stage IIIA which are not internationally recognised. Finally, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team.
Melanoma Focus	Guideline	19	Table	For all Stage IIIA-IIIC patients, the draft NICE guidance is recommending CT HNTAP for every surveillance scan. This is different to current practice and the consensus view of a panel of melanoma experts in the UK, published by Melanoma Focus. This consensus view recommended CT TAP + MRI head	Thank you for your comment. The committee considered this issue and agreed that the radiation risk from ionising radiation exposure is not serious. Furthermore, increased use of MRI instead of CE-CT will have practical implications and will place an increased burden on MRI capacity.

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				for these patients, with neck imaging only for patients with primary melanoma on the head and neck. Doing CT head & neck in addition to CT TAP every time means an additional 5.6 mSv of radiation risk exposure per scan. For comparison the annual UK background radiation is 2.7 mSv. Therefore doing CT HNTAP on all patients with stage IIIA-IIIC melanoma risks increased radiation exposure unnecessarily for the majority of these patients. We would recommend MRI head instead of CT head, and neck imaging only if the primary was on the head or neck.	The committee also considered further the use of MRI head at follow up and have added a new recommendation 1.9.10 to consider brain MRI, instead of CE-CT brain for imaging follow up, if locally preferable and after discussion and agreement with the specialist skin cancer MDT.
Melanoma Focus	Guideline	19	Table	For Stage IIIA-IIIC patients with positive sentinel lymph nodes (as well as Stage IIB/C pts for whom SLNB was considered but not done), the NICE guidance suggests CT follow-up alone is insufficient, and USS follow-up should also be done (6 monthly in years 1-3, staggered with the recommend 6 monthly CT imaging). Whilst we appreciate the view that USS is more sensitive than CT at detecting lymph node mets, we would argue that USS sensitivity is highly dependent on both equipment and operator experience, and serial CT imaging increases its sensitivity for detecting lymph node mets. Therefore we feel CT scan follow-up alone without additional USS is reasonable for this patient group, particularly	Thank you for your comment. The committee considered this issue and noted that ultrasound scanning was shown by the evidence to be more sensitive than clinical examination and alternative imaging modalities (particularly CE-CT) for detecting local lymph node metastases. They therefore recommended ultrasound surveillance for 3 years for people with a positive sentinel lymph node. The committee have added to the guideline rationale acknowledging the practical implications of ultrasound imaging during follow-up such as providing increased numbers of scans and variable experience of healthcare professionals involved in follow-up.

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				bearing in mind the pressures currently faced by most Radiology departments.	
Melanoma Focus	Guideline	19	Table	For Stage IIID and resected Stage IV patients, the NICE guidance is recommending CT HNTAP 3 monthly years 1-3, 6 monthly years 4-5, then stop. This is significantly more CT imaging than what is current practice and has been recommended by a consensus of melanoma experts in the UK, published by Melanoma Focus, which is CT TAP 3 monthly in year 1, 3-6 monthly in years 2-3, annually in years 4-5, then stop, along with MRI head 6 monthly in years 1-3, annually years 4-5, then stop. The proposed NICE guidance would mean at least 2 extra CT TAP, and 17 extra CT head & neck scans over 5 years, compared with the Melanoma Focus consensus guidance. We feel there is no evidence to support this level of increased radiation exposure.	Thank you for your comment. The committee considered this issue and agreed that the radiation risk from ionising radiation exposure is not serious. Furthermore, increased use of MRI instead of CE-CT will have practical implications and will place an increased burden on MRI capacity. The committee also considered further the use of MRI head at follow up and have added a new recommendation 1.9.10 to consider brain MRI, instead of CE-CT brain for imaging follow up, if locally preferable and after discussion and agreement with the specialist skin cancer MDT.
Melanoma Focus	Guideline	20	5	How are these arrived at? Are the Other recommendations for research (pp 22 -24) still to be included or are they replaced by the new ones? We recommend the committee liaising with the research community e.g. NCRI skin cancer group to ensure these align with national/international research priorities	Thank you for your comment. The research recommendations are drafted by the committee based on identified gaps in the evidence base during the guideline update process. Stakeholders were asked to comment on the current validity of the 2015 research recommendations during draft guideline consultation and these are kept or removed based on stakeholder feedback. Further information can be found in the NICE guideline manual.

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					Following publication of our guidelines, NICE works with funding bodies such as the NIHR to ensure that our research recommendations are prioritised for future funding.
Melanoma Focus	Guideline	7	22	Rec 1.3.9 – Since outcomes for stage IIB melanoma equate to that of IIIA, it seems inconsistent not to offer BRAF testing for stage IIB melanoma	Thank you for your comment. The committee agreed that the main utility of BRAF testing is that it will make some people with melanoma eligible for additional therapies. The main benefit is therefore in people with stage III disease as currently, these therapies are only licensed in this population. The committee agreed that the benefit for its use in stage II disease is that a large proportion of these patients will have a recurrence and be up-staged to stage III disease. Having their BRAF status on record will allow for the person's optimal treatment regimen to be identified sooner. IIC disease was included in the 'offer' group due to the higher risk of recurrence than stage IIA/B disease. The committee decided that testing should be considered for IIB (instead of offered) due to the lower risk of recurrence than IIC and although the risk of recurrence is comparable to stage IIIA, the outcome would only impact treatment in the event of a recurrence.
Melanoma Focus	Guideline	8	17	Rec 1.4.6 and 1.4.7 - It is not clear why the guideline mandates CT head as opposed to the option to use MRI head as part of routine melanoma staging. Given the frequency of surveillance scanning, many centres prefer to offer MRI head particularly to younger people	Thank you for your comment. The committee considered this issue and added a recommendation (1.4.11) to consider staging with brain MRI, instead of CE-CT, if locally available and after discussion and agreement with the specialist skin cancer multidisciplinary team.

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				and it would seem perverse for the national guideline not to be consistent with this current practice.	Furthermore recommendation 1.4.8 outlines to offer staging with whole body and brain MRI, instead of CE-CT, for children and young adults (from birth to 24 years) with stage IIB to IV melanoma. This is because of the cumulative risk of radiation associated with CE-CT scanning in children and young people.
Melanoma Focus	Guideline	8	21	Rec 1.4.8 – Whole body+brain MRI is more resource-intensive than low dose CT chest + MRI abdo/pelvis/head which is adequate for young patients.	Thank you for your comment. The committee considered thus issue and agreed that recommendation 1.4.8 should outline to offer staging with whole body and brain MRI, instead of CE-CT, for children and young adults (from birth to 24 years) with stage IIB to IV melanoma. This is because of the cumulative risk of radiation associated with CE-CT scanning in children and young people.
Melanoma Focus	Guideline	9	3	Rec 1.4.10 – We think the option to consider MRI brain as an alternative to CT head should be broadened to any patients undergoing melanoma staging and surveillance	Thank you for your comment. The committee considered this issue and have added a recommendation (1.4.11) to consider staging with brain MRI, instead of CE-CT, if locally available and after discussion and agreement with the specialist skin cancer multidisciplinary team.
Merck Sharp and Dohme	Guideline	11	7	We believe the guidelines should include a recommendation to "Offer adjuvant systemic anticancer treatment", rather than only referring to the NICE technology appraisal web links for each individual treatment option. Currently, to a lay person reading the guidelines, it may not be clear what the recommendation is unless they follow the links and interpret the information for each treatment.	Thank you for your comment. We have now included a recommendation in this section for adjuvant treatment.

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Merck Sharp and Dohme	Guideline	11	9	The URL should be updated to the TA766 page	Thank you for your comment. This has been amended.
Merck Sharp and Dohme	Guideline	14	10	Rec 1.8.7 and 1.8.8 – We are concerned that the wording of this recommendation implies that single agent immunotherapy is always a less favourable treatment option based on the risk benefit profile compared with nivolumab in combination with ipilimumab. There are many reasons why a clinician or patient may choose to use single agent immunotherapy instead of combination therapy which may include for example, risk/benefit assessment, comorbidities, and/or convenience of administration amongst others. For high disease burden and/or rapid progression if patients are BRAF V600 positive, preference may be given in targeted therapies. These considerations are not fully captured in the current draft recommendation. We suggest an edit to the following: 1.8.7 "Offer nivolumab in combination with ipilimumab to people with untreated stage IV or unresectable stage III melanoma after a full assessment by the treating oncologist and discussion of the risks and	Thank you for your comment. This wording has now been included as an overarching recommendation in the section of the guideline on systemic therapies, as the committee agreed that it is important to emphasise that there are multiple factors that would influence choice of treatment and that should be considered. We have also added a reference to our guideline on shared decision making.

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				benefits of all immunotherapy treatment options with the person." 1.8.8 "If nivolumab in combination with ipilimumab is found to be unsuitable or unacceptable (for example, because of potential toxicity), or the patient has a preference for single agent therapy, offer pembrolizumab after a full assessment of the risks and benefits by the treating oncologist and discussion with the person." 1.8.9 "If nivolumab in combination with ipilimumab is found to be unsuitable or unacceptable (for example, because of potential toxicity), or the patient has a preference for single agent therapy, consider nivolumab monotherapy after a full assessment of the risks and benefits by the treating oncologist and discussion with the person.	
Merck Sharp and Dohme	Guideline	17	21	Rec 1.9.4 – the wording of this recommendation is not clear and suggests reference to people who had stage 0 melanoma at a clinic visit in the first year. A suggested rephrase would be: 1.9.4 "For people who have had stage 0 melanoma, provide advice at a clinic visit during the first year after	Thank you for your comment. The committee considered your feedback and agreed to make your suggested change to the guideline.

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				treatment has been completed in line with recommendation 1.9.3"	
NHS England and NHS Improvement	Additional Questions			**1. Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why.** The adoption of the draft recommendations for the diagnostic pathway in themselves do not appear to present a significant impact or additional challenge beyond the existing requirement for pathways to meet the Faster Diagnosis Standard of 28 days from referral to the communication of a definitive diagnosis or ruling out of cancer whilst delivering the service in line with current guidance.	Thank you for providing this feedback.
NHS England and NHS Improvement	Additional Questions			**2. Would implementation of any of the draft recommendations have significant cost implications?** The adoption of the draft recommendations for the diagnostic pathway in themselves would likely have little additional no fu impact, notwithstanding the requirement for pathways to have sufficient resource to enable the Faster Diagnosis Standard to be met whilst delivering the service in line with the guidance.	Thank you for your comment
NHS England and NHS	Additional Questions			**3. What would help users overcome any challenges? (For example, existing practical**	Thank you for providing this feedback.

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Improvement				**resources or national initiatives, or examples of good practice.)** The NHS Cancer Programme is soon to publish a Best Practice Timed Pathway for skin cancers, including melanoma, to support the on-going improvement effort to shorten diagnosis pathways, reduce variation, improve people's experience of care, and meet the Faster Diagnosis Standard (FDS). This pathway is supported by the NHS Transforming elective care services dermatology and the British Association of Dermatologists Early diagnosis of skin cancer: innovating the two-week wait skin cancer referral pathway documents.	
NHS England and NHS Improvement	Additional Questions			**4. Included in the supplementary documents is a table comparing non-surgical treatment options for in-transit metastases, to assist clinicians when considering which treatments to offer. Please could you comment on the usefulness of this table and also on the content, due to the lack of good quality comparative evidence in this area.** No comments from a diagnostic pathway perspective.	Thank you for your comment.
NHS England and NHS	Draft Guideline	17	1	Re section 1.9 We suggest that recommendations on routine follow up schedules emphasise that patient-initiated follow up	Thank you for your comment. The committee considered your feedback and agreed that patient-initiated follow-up is covered in recommendations 1.9.1 – 1.9.3. Recommendation 1.9.1 outlines that people

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Improvement				may be acceptable for some or many patients at low risk of recurrence, and that patients can be offered this choice, which still encompasses patient education, offer of psychosocial support and the ability to contact the clinical team directly with any concerns at any time.	can still contact specialist skin cancer services about problems or concerns.
NHS England and NHS Improvement	Guideline		General	Although the intended audience for this guideline includes people with melanoma and their families, in practice they may find the increased complexity hard to navigate and so written and repeated communication seems all the more important for those individuals but also the healthcare providers they contact.	Thank you for providing this feedback. The committee agreed that communication is important and made a number of recommendations on this in section 1.1.
NHS England and NHS Improvement	Guideline		General	The changes made are mostly relevant to specialist management of melanomas. We would welcome specific guidance to primary care around follow up and assessment of family members.	Thank you for your comment. Recommendation 1.9.6 outlines that personalised follow-up should be considered and the setting for this has not been suggested. Furthermore, personalised follow-up should be considered for those with a history of melanoma in first degree relatives or other relevant familial cancer syndromes (recommendation 1.9.6).
NHS England and NHS Improvement	Guideline	10	21	It is not quite clear what type of scenario is referred to here since regular follow-up is usually possible albeit less frequent or outside the usual setting. This could be explained in the rationale and impact section.	Thank you for your comment. The committee agreed that in the absence of undergoing a completion lymph node dissection, regular follow-up with imaging is required. For some people, frequent follow-up is not feasible, typically when the person lives rurally or too far away from specialist centres to attend frequent follow-up. The committee agreed that in these people, completion lymph node dissection may be warranted.

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NHS England and NHS Improvement	Guideline	17	12	We note that there may be some complexity and variation with follow-up plan, it may be helpful to include written personalised patient information.	Thank you for your comment. The committee considered this issue and the follow-up after treatment recommendations in section 1.9 outlines examples where personalised follow-up is required. The table in section 1.9 sets out routine follow up and the committee acknowledges there will be groups where this will not apply.
NHS England and NHS Improvement	Guideline	35	2	In relation to 'equal opportunity to black, Asian and minority ethnic groups', page 35 notes that the risk factors are around skin that burns in the sun and therefore more likely to occur. Whilst specialists understand this risk, there should more be done to ensure equal opportunity of diagnoses for those from a BAME background, with the wording suggesting and allowing less attention for darker skin patients – This leaves space for a risk that should be addressed further.	Thank you for your comment. The committee discussed this issue and were in agreement. The context section of the guideline has been amended highlighting that more should be done to ensure equal opportunity of diagnoses for those from a Black, Asian and minority ethnic background.
NHS England and NHS Improvement	Guideline	General	General	This guideline should include further mention of when all treatments and therapy have been stopped, a referral to Palliative Care would be recommended.	Thank you for your comment. The committee considered this issue and agreed to add a recommendation (1.8.16) to consider referring people with incurable melanoma to specialist palliative care services for symptom management.
North of England Dermatopat	Guideline	19	Table/ IA/IB	The table covers 5yr follow up of IB melanoma with no SLNB. This is therefore implies using CLINICAL STAGE (pT1b/cN0). I am not aware CLINICAL STAGE HAS BEEN USED IN THE REMAINDER OF	Thank you for your comment. The committee agreed that for people with a pT1b melanoma who have unknown sentinel lymph node status, for consistency with the rest of the guideline, it is suitable to treat this

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hology Service				THE GUIDELINE! Although this recommendation is undoubtedly sound unfortunately AJCC and UICC have hiccoughed and PATHOLOGICAL STAGE IB for pT1b/ no SLNB doesn't exist!! It remains an uncorrected omission in both! All that is included in PATHOLOGICAL STAGING is pT1b/pN0 (SLNB histologically negative but not equating with not done) which is stage IA and not IB!! Therefore a pT1b melanoma with negative histological SLNB (pN0) is Pathological Stage IA with a 1 yr follow-up. The latter staging eventuality does exist in AJCC and UICC and although theoretically covered for the informed in the Table perhaps the importance of negative histological SLNB in the context of pT1b is worthy of specific comment in the Table? I am sure that most will not be aware of this specific nicety. This issue is covered well in the BJD TNM8 skin cancer review in October 2018 which included melanoma. Suggested solution: Leave IB as it is and although it is inappropriately mixing clinical and pathological stage groups few will know! BUT although theoretically again covered for the informed in IA, a reminder in IA that pT1b melanoma with histological negative SLNB (pN0) is IA and therefore has 1yr follow-up. Otherwise	group as Stage IB despite not being covered in the UICC and AJCC. The committee decided not to include a reminder in the table that pT1b melanomas are now covered in stage IA (if SLNB is negative) as they felt that the table is already too complex and adding to it further will limit comprehension.

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				negative SLNB does not receive a mention when in fact it has been so useful (indeed supporting its use)!	
North of England Dermatopathology Service	Guideline	4	3	A. AJCC staging is written by American authors for use in the USA. Clinical use elsewhere in the world requires a licence that must be purchased. Failure to do this could result in a financial penalty. The NHS has declined to purchase a global licence and therefore any Trust using AJCC clinically must purchase a licence. Therefore, in reality, most of the rest of the world use UICC (Union for International Cancer Control) staging for clinical use. This includes the WHO and previously Public Health England (this part now under NHS Digital) including for skin cancer the National Disease Registration Service (NDRS) with the National Cancer Registration and Analysis Service (NCRAS) i.e., cancer registries and for NHS cancer data the Clinical and Outcomes and Services Dataset (COSD). Accordingly UICC was also adopted virtually by necessity by the Royal College of Pathologists UK (RCPath) for all skin cancers in its own national skin cancer datasets and also by the British Association of Dermatologists (BAD) for its recent squamous and basal cell carcinoma guidelines. It was also used by the BAD in its recent TNM8 review for skin cancer that included melanoma. UICC has also been used in	Thank you for your comment. This text on the stages of melanoma has been removed and now refers to the UICC and AJCC staging methods.

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				Melanoma Focus guidelines (with but one mention of AJCC). The use of AJCC by NICE in its last melanoma guidelines caused significant consequent operational confusion for the above bodies and NHS Trusts (coming about by NICE discounting identical stakeholder consultation comments on its last edition about the inappropriate restrictive use of AJCC in England and Wales.) UICC and AJCC staging for melanoma are invariably the same or with only minor differences on initial publication. For TNM8 these were quickly and fully resolved by both bodies. AJCC and UICC are therefore now identical for skin melanoma and the use of UICC TNM8 rather than UICC would not alter anything related to staging in the current draft guideline. B. Staging is expressed by summating TNM8 as STAGE GROUPS as used throughout the draft guideline. THESE HOWEVER CAN BE CLINICAL OR PATHOLOGICAL These have differences but for MDT / clinical management purposes and professional guidelines PATHOLOGICAL STAGE is invariably used. This not stated anywhere in the draft but this can then become relevant, for example, where the two are mixed in the table with no clarification.	

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North of England Dermatopathology Service	Guideline	8	8	Line 4 says do not offer SLNB for stage IA. Line 8 then says offer SLNB for 0.8-1.0mm Breslow with ulceration. This is still pT1b/ stage IA and therefore in conflict with Line 4. A staging knowledge conflict by the NICE GDG! Line 4 would appear to need this as an exception.	Thank you for your comment. The group of patients with stage IA melanoma in accordance with the UICC and AJCC includes those people with a Breslow thickness <0.8mm without ulceration and therefore does not conflict with the recommendations outlined in line 8
North of England Dermatopathology Service	Guideline	9	16	Stage 0 line11 uses the term CONSIDER. This a reasonable term with reasonable clinical flexibility. Stage I and II however state USE. In contrast to consider this is very dogmatic and mandatory term rarely used by NICE. Is the evidence base really that strong to permit such dogmatic usage! It allows no flexibility in clinical management e.g., An excision on the face of Stage II melanoma in an elderly frail patient may not warrant USE a 2cm margin. Clinical flexibility must be allowed as in Stage 0.	Thank you for your comment. The committee discussed this issue and agreed to keep 'use' in recommendation 1.5.3 but acknowledged that smaller margins may be needed for cosmetic reasons on sites such as the face, head and digits. However, the use of smaller margins should be discussed within the specialist skin cancer multidisciplinary team, the reasoning justified and with clinical surveillance. The committee also agreed to add a further clarification to the excisional margin recommendations (1.5.1 – 1.5.3) that the clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin. Furthermore, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team.

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					The committee acknowledged continuing uncertainty about optimal excision margins, particularly in stage 0 disease, and made a recommendation for research on histological margins.
North of England Dermatopathology Service	Guideline	9	17	This refers to PURELY to CLINICAL MARGINS for Stage I and II melanoma. In contrast, however, Stage O refers to BOTH CLINICAL and HISTOLOGICAL MARGINS but HISTOLOGICAL MARGINS receive no mention for Stages I and II and stand out by being missing and no comment. This is ignoring one of the most common clinical occurrences in melanoma. A clinical lesion is excised that transpires histologically to be melanoma but the procedure undertaken with no previous clinical intention to achieve 1 or 2cms CLINICAL MARGINS. In reality, however, the resulting specimen of melanoma will be reported with measured numerical HISTOLOGICAL MARGINS from 0mm upwards. How is this numerical histological margin information then taken into account for management discussion and potential re-excision. e.g. is a 1 or 2mm histological margin then adequate in its own right or should the histological numerical margin information be used to modify/often reduce the extent of wider excision to achieve the stated clinical margins (NB although virtually none of the resulting wider excision specimens ever show residual disease querying the	Thank you for your comment. The committee considered your feedback and agreed to add a further clarification to the excisional margin recommendations (1.5.1 – 1.5.3) that the clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin. The committee acknowledged that smaller margins may be needed for cosmetic reasons on sites such as the face, head and digits. However, the use of smaller margins should be discussed within the specialist skin cancer multidisciplinary team, the reasoning justified and with clinical surveillance. Furthermore, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team. The committee acknowledged continuing uncertainty about optimal excision margins, particularly in stage 0 disease, and made a recommendation for research on histological margins.

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				value of time and expense investment!). At the moment NICE has avoided this issue that is the most important and most frequent occurrence in this area which occurs several times every week in every skin cancer MDT. As the draft currently stands no NICE guidance is provided on how the issue on whether or how histological and clinical margins for melanoma should be integrated. As written the guideline for Stage I and II only covers the relatively uncommon eventuality of a punch biopsy showing melanoma having wider excision using the clinical margins. Previous clinical melanoma trials had little or no consideration of histological margins and are therefore by definition weak in the extreme. Fortunately, however, treatment of BCC and SCC has become more enlightened with consideration and integration of both clinical and histological margins to the patients benefit. Many patients will be probably receiving many 1cm or 2cm wider excisions that are probably unnecessary. This is unfortunate for patients and creates a large amount of histopathological work that probably could be avoided. Dogmatic use of 1 and 2cm clinical margins is simplistic and avoids the realistic world of melanoma.	

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North of England Dermatopathology Service	Guideline	9	17	Some ultra-low risk stage I melanomas fail to show recurrence or metastatic potential and behave essentially as Stage 0. Specifically radial growth phase (non tumorogenic) invasive melanoma. Would not 5mm clinical margins be adequate? This is often used in professional practice.	Thank you for your comment. We did not find any evidence for excisional margins for radial growth phase (non tumorogenic) invasive melanoma in which to make a recommendation. The committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team.
North of England Dermatopathology Service	Guideline	9	13	States requires management discussion for Stage 0 if excision does not achieve an adequate histological margin. This is meaningless guidance, however, in the absence of numerical figures to define adequate/ inadequate histological margins eg inadequate is it ? 0mm (involved) or ? below 1mm or even ? 1mm or above (eg 2mm, 3mm, 4mm 5mm etc)? Most peers would probably accept 1 or 2mm as adequate if a 5mm clinical margin had been attempted.	Thank you for your comment. The committee considered this issue and agreed to add a further clarification to the excisional margin recommendations (1.5.1 – 1.5.3) that the clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin. Furthermore, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team. The committee acknowledged continuing uncertainty about optimal excision margins, particularly in stage 0 disease, and made a recommendation for research on histological margins.
Novartis Pharmaceuticals Ltd	General	General	General	Which areas will have the biggest impact on practice and be challenging to implement? Please say for whom and why. The recommendations to use immunotherapies (unless otherwise contraindicated or unsuitable) as systemic	Thank you for your comment. The committee were aware that immunotherapies require more resources to administer than the targeted therapies, however an increase in resources is acceptable for therapies

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				therapies for stage IV and unresectable stage III disease reduces the ability of the treating physicians and their patients to make individualised decisions on treatment choices which is not consistent with NICE Guideline NG1971 on shared decision making which describes a joint process in which a healthcare professional works together with a person to reach a decision about their care. Moreover, the current recommendations are likely to have a significant impact and burden on NHS capacity and resources where there will be an increase in administrations associated with immunotherapies compared to targeted therapies which are oral therapies.	associated with better outcomes or other potential cost savings. To capture this potential impact, administration costs were included in the economic model which was presented to the committee for decision making. The resource impact for anti-cancer treatments have been assessed when the respective technology appraisals were conducted and RIA tools were published alongside the technology appraisal guidance. NHSE funds the resource impact, including administration costs of anti-cancer treatments. A reference to NICE's guideline on shared decision making has now been included in the recommendations in the systemic therapies section to emphasise that individualised treatment decisions are made by treating physicians and their patients. We have also included an additional recommendation that describes the factors that should be taken into account on treatment choices, to allow appropriate and individualised decisions to be made.
Novartis Pharmaceuticals Ltd	General	General	General	Would implementation of any of the draft recommendations have significant cost implications? Costs that do not appear to be considered include patient management time and other services that will be impacted for long term side effect and condition management such as referrals to rheumatology, dermatology and neurology.	Thank you for your comment. Grade 3-4 adverse events were included in the model, and these were informed by an NMA of the clinical trials for the treatments included in the model. Economic models typically include Grade 3-4 events since these will the greatest impact to quality of life and management costs. The exclusion of toxicities that occur in the long-

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				Management of these lifelong conditions by these departments should also be taken into account.	term is a potential limitation of the economic analysis, as the data informing adverse events was taken from the clinical trials which may not capture some of the more long-term toxicities. However, the committee agreed that at least some of these were addressed in the adverse event NMA conducted. The committee advised that some of these long-term side effects and conditions are asymptomatic and therefore would not fall into the category of Grade 3-4 adverse event. Therefore, this limitation is not expected to change the conclusions of the analysis. Since these immunotherapies in melanoma have already been through the NICE TA process and have been approved and in use for some time, the committee believed that these toxicities are already managed and supported across NHS cancer services. The resource impact for anti-cancer treatments have been assessed when the respective technology appraisals were conducted and RIA tools were published alongside the technology appraisal guidance.
Novartis Pharmaceuticals Ltd	General	General	General	What would help users overcome any challenges? (For example, existing practical resources or national initiatives, or examples of good practice.) No comment	Thank you for your comment.
Novartis Pharmaceuticals Ltd	General	General	General	Included in the supplementary documents is a table comparing non-surgical treatment options for in-transit metastases, to assist clinicians when considering which	Thank you for your comment.

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				treatments to offer. Please could you comment on the usefulness of this table and also on the content, due to the lack of good quality comparative evidence in this area. The table highlights some potential treatment options however does not consider all available or used therapies in this setting. It also suggests therapies that are not accessible to all thereby creating and highlighting inequity of access to treatments such as T-VEC due to the few centres that are able to administer this treatment. There is also limited data to support these treatment options, so the overall usefulness of the table is limited	
Novartis Pharmaceuticals Ltd	Guideline	13	10	The guidelines for brain metastases helpfully reference the NICE guideline on brain tumours and brain metastases in adults, however we argue that the guidance should reference the relevant clinical trial evidence that supports the management of brain metastases specifically in melanoma. For example, the COMBI-MB study, a Phase II study evaluating treatment of dabrafenib plus trametinib in subjects with BRAF mutation-positive melanoma that has metastasised to the brain, showed a clinical benefit with dabrafenib plus trametinib in subsets of patients with a manageable safety profile consistent with that of other melanoma clinical studies.[4]	Thank you for your comment. The COMBI-MB trial did not meet the inclusion criteria for evidence review F, which only looked at randomized controlled trials comparing separate treatments. The committee agreed that they could not make more prescriptive recommendations for the treatment of people with melanoma and brain metastases in the current guideline, due to limited comparative evidence in this area.
Novartis Pharmaceuticals Ltd	Guideline	14	4	We have previously mentioned our concerns with the draft recommendation to offer immunotherapy to people with untreated stage IV or unresectable stage III	Thank you for your comment. We have included an additional recommendation that lists the factors to consider when making treatment decisions, including comorbidities, toxicity and tolerability of treatment.

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				melanoma, and to only offer alternative treatments based on BRAF type where immunotherapy is contraindicated or unsuitable. Whilst we disagree with this recommendation because clinicians should have the flexibility to use NICE approved regimens in line with their own clinical judgment, it would be important to highlight the other considerations that clinicians have when contemplating which treatment regimens to offer their patients including comorbidities, long term toxicity profiles, tolerance, and convenience of route of administration. It would also be useful to highlight the typical patient type that would be suitable for targeted therapy as a first line treatment i.e., patients with high disease burden, requiring a rapid response and/ or high risk of rapid progression. It is also important to note that the clinical evidence[2] shows that patients with symptomatic brain metastases would also be suitable for targeted therapies so it would be important to update the guidelines to reflect this. As such, we would suggest that the text in section 1.8.6 is updated to align with sections1.8.10 - 1.8.12 by adding the following *"**or** there is insufficient time for an immune response due to high disease burden and/or rapid progression"* and also to include symptomatic brain metastases	Presence of symptomatic brain metastases has also been added to the factors to consider when making treatment decisions. The information on typical patient type suitable for targeted therapy is provided in the rationale section, and the factors that should be considered when thinking about suitability for targeted therapies are included in the new recommendation. We did not include convenience of route of administration in the list of factors as the committee preferred to list the factors that were associated with achieving the optimal and desired response to treatment. They also believed that it would be incorporated within the discussion with the patient under shared decision making. The committee agreed that clinical trials are an important option and should not only be offered as a last resort, but also that this is generally what happens in practice already throughout the melanoma treatment pathway. It was therefore decided to remove the wording about clinical trials in this recommendation, so it is not implied that they should only be considered in that limited case.

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				Finally, the recommendations omit clinical trials as an option. Feedback from clinicians indicate that clinical trials are fundamental to investigating treatment options, outcomes and continue advancements in the therapy area and should always be offered to a patient in all settings if available.	
Novartis Pharmaceuticals Ltd	Guideline	15	9	Consider revising Alternatives to immunotherapies for BRAF V600 mutation-positive melanoma: targeted therapies to "*Targeted therapies"* As per 1.8.6 wording comments we would suggest that text in 1.8.10 is amended to *"**or** there is insufficient time for an immune response due to high disease burden and/or rapid progression"* and also to include symptomatic brain metastases	Thank you for your comment. The title of this section of the guideline has now been altered, and an additional recommendation has been added at the start of this section covering various factors that should be considered when making treatment decisions.
Novartis Pharmaceuticals Ltd	Guideline	15	9	Patient preference is omitted from the recommendations for targeted therapies (and others) For example the recommendations for immunotherapies (1.8.7 – 1.8.9) reference offering treatment *"after a full assessment of the risks and benefits by the treating oncologist and discussion with the person"*	Thank you for your comment. An additional recommendation has been added at the start of this section covering various factors that should be considered when making treatment decisions, and includes the suggested text. We have also added a reference to our guideline on shared decision making, which describes a collaborative process that involves a person and their healthcare professional working together to reach a joint decision about care.

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				Please add similar wording to the targeted therapies in section 1.8.10 for consistency and to capture patient choice.	
Novartis Pharmaceuticals Ltd	Guideline	7	26	Novartis believe that the recommendation for *BRAF* testing should be amended to include both genomic testing and immunohistochemistry (IHC) as standard, and to run concurrently. The current recommendation is not aligned with the vision of the NHS Genomics Medicine Service (GMS)[2] and the National Genomic Healthcare Strategy: Genome UK[3]. Incorporation of the latest genomics advances into routine healthcare and adopting broader biomarker testing will improve diagnosis and stratification of cancers, allowing optimal upfront treatment planning, and supporting patients to make informed decisions about their care. Evidence Review A (page 12, line 39) describes a cost of approximately £200 associated with IHC V600E and states that all negative tests should then be tested using a secondary genetic test, such as Cobas (PCR), to identify all relevant and actionable *BRAF* mutations. Whilst faster access to *BRAF* status (where V600E positive) via IHC as a first step is a welcome addition, we are concerned that inequity of access to testing may	Thank you for your comment. The committee wished to retain their current recommendation on the sequential use of IHC and genetic testing in order to capture the benefits of IHC where it is possible to do so, to capture increased speed of testing and subsequent referral to appropriate treatment. The committee noted the evidence demonstrating that IHC rarely produces false positive results, and believed that the utility of genetic testing would be to confirm any negative results, in light of the lower sensitivity of IHC. We have added an additional recommendation to this section that provides further detail on how this should be put in practice.

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				be introduced with the guidance currently stating that this is "only a consideration where available". In addition to PCR for *BRAF* hotspots, NGS panel testing for *BRAF, KIT, NRAS and NTRK where* applicable, is available and commissioned by NHS in England, as listed on the National Genomics Test Directory for Cancer. An NGS panel approach would allow either confirmation of *BRAF* status or identification of an alternate, mutually exclusive mutation (which may impact treatment planning including consideration for clinical trials) and is in line with current international guidance (ESMO 2019). Also, as larger NGS panels are implemented, the potential for identification of further candidates who may be suitable for clinical trials in precision medicines is increased, thereby increasing options for patients. As such, the recommendation for *BRAF* testing should be amended to include both genomic testing and IHC as standard, and to run concurrently.	
Novartis Pharmaceuticals Ltd	Guidelines	General	General	Novartis do not agree with the draft recommendation to restrict access to NICE approved targeted treatments for people with untreated stage IV or unresectable stage III melanoma to those who are contraindicated to or unsuitable for immunotherapy. We have significant concerns with the analyses performed to develop this	Thank you for your comment. The economic analysis was developed by experienced health economists and followed the methods set out by the manual for developing NICE guidelines. The effectiveness evidence was identified through a thorough systemic review of the literature, and every effort was made to ensure we used the most appropriate and

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				recommendation, particularly the interpretation and presentation of the available evidence. We would expect such significant recommendations to be based on robust analyses and a strong evidence base, which we do not believe is the case (please refer to our detailed comments on the evidence reviews and health economic reports further on in this response document). Whilst we accept the challenges with the evidence, we do not believe these limitations have been reflected sufficiently when generating the recommendations. The limitations make interpretation of comparative analyses difficult at best, and potentially misleading. We do not believe the analyses performed are reflective of the standards that would be expected of any manufacturer when seeking a positive NICE recommendation for their technology. For those standards to not be applied within a clinical guideline, which recommends restricting access to treatments approved through the technology appraisal routes, is unfair and not reflective of a world-leading evidence-based approach. Furthermore, we believe patients and their clinicians should continue to have a choice in the optimal	contemporary data for the review question. The network meta-analysis (NMA) is the gold standard method for combining evidence from a number of sources. We received support advice from an independent academic research group (the Technical Support Unit) with expertise in NMA, who validated our approach and aided in the interpretation of our results. Any uncertainties or limitations in the evidence were identified, discussed with the committee and extensively tested through a large number of sensitivity scenario analyses. An extensive description of our methods, results and discussion can be found in the economic model report and the NMA report. The wording in the recommendations has been altered to clarify that patient and clinician choice should still be considered when deciding which treatment is appropriate, by adding a reference to NICE's guideline on shared decision making in the recommendations. We acknowledge the complexities in determining the most appropriate treatment for patients, and have included an additional recommendation that lists different patient-related factors alongside cost-effectiveness to guide treatment decisions.

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				treatments for their disease, and the draft recommendation restricts the ability of the clinician and their patients to have this choice in their treatment decisions. NICEs Guideline on shared decision making (NG197)[1] describes a collaborative process that involves a person and their healthcare professional working together to reach a joint decision about care. This involves choosing tests and treatments based on the evidence and the person's individual preferences, beliefs and values. The recommendation in the draft guidelines to use immunotherapy (unless otherwise contraindicated or unsuitable) as a first treatment option, does not consider the patient as part of the shared decision-making approach and guidance to care.	
Novartis Pharmaceuticals Ltd	Melanoma: assessment and management [F] Evidence reviews for systemic and	6	HE1.1.1	**BRAF as a treatment effect modifier** The Health economic report states that "*the committee noted that BRAF status is not expected to be an effect modifier for treatment efficacy of immunotherapies (Larkin 2015, Puzanov 2020) so the effectiveness of these treatments was considered to be consistent across the mixed BRAF population".*	Thank you for your comment. The committee felt that it is likely that any potential differences in efficacy of immunotherapies is driven by factors such as tumour burden, brain metastases and disease tempo, and that BRAF status is a less relevant factor. While we understand that BRAF status is an effect modifier for targeted therapies, we would expect the response to immunotherapies to be the same in both BRAF-mutant and BRAF-wild type patients. Lorenzi (2019) states only that BRAF mutation status is a known treatment effect modifier for BRAF-targeted drugs.

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	localised anticancer treatment for people with stage IV and unresectable stage III melanoma health economic report			It should be noted that this assumption is uncertain, given there is an alternative reference which indicates it may be a potential treatment modifier[8]	The committee agreed that this assumption remains associated with a degree of uncertainty, and so we conducted the scenario analysis in the network meta-analysis. In one analysis (Network 3), we only included people with BRAF-wild type melanoma with immunotherapy strategies only. In this analysis, nivolumab plus ipilimumab continued to show the greatest benefit in both overall survival (OS) and progression-free survival (PFS) and Nivolumab had the second-best benefit in OS and PFS. Notably however, the difference between nivolumab plus ipilimumab and nivolumab between Network 3 and Network 1 (which included people with both BRAF-wild type and BRAF-mutant melanoma and both targeted therapies and immunotherapies) was reduced. When the NMA outcomes from Network 3 were included in the economic analysis, the cost-effectiveness results still favoured nivolumab plus ipilimumab.
Novartis Pharmaceuticals Ltd	Melanoma: assessment and management [F] Evidence reviews for	General	General	**Network Meta-Analysis** Whilst we accept the challenges with the evidence base, that assumptions need to be made and that the EAG were asked to compare the different treatments available, we believe it is problematic to present a comparison where the evidence available and the interpretation of the results has not been used appropriately. In particular, we have significant concerns with the network meta-analysis that has been	Thank you for your comment. As you acknowledge, there are often limitations with the data available for analysis, and as such, we are often tasked with doing the best we can do with the data available and making any limitations and uncertainties clear to committee. In order to ensure this work was done to the standard expected by NICE, we have taken a number of steps, including following the methods set out in our Methods Guide, consulting with our Technical Support Unit at

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	systemic and localised anticancer treatment for people with stage IV and unresectable stage III melanoma			used to inform the recommendations in Section 1.8.6 of the clinical guidelines due to the large heterogeneity of the studies included in the network (which has not been adjusted for), the high degree of cross-over in some of the studies used in the network and the overall interpretation of the results of the NMA. As such, we do not believe that the current NMA is appropriate for decision-making and note that the analyses do not meet the standards expected by NICE from submitting companies in technology appraisals. **The heterogeneity of the different studies used in the network**. The studies are conducted in heterogeneous populations, and there are imbalances in the patient characteristics that have not been adjusted for as recommended in the NICE TSD 18[5]. Some of these differences in patient characteristics are likely to affect the estimated treatment effect and interpretation of the NMA as some of these patient characteristics are treatment effect modifiers as shown by the subgroup analyses in the studies included in the NMA.	the University of Bristol and using NICE's preferred NMA checklist (PRISMA NMA checklist) to review the NMA. The outcomes of the NMA have also been thoroughly validated by the committee, and the limitations associated with our approach were mitigated as much as possible by the committee selecting the survival models that provided extrapolations that in their clinical experience were the most appropriate for describing the long-term outcomes. **The heterogeneity of the different studies used in the network** It is a common issue when conducting NMA that trial populations will not be identical, especially when the number of studies included in the NMA are large (in our case, 10). The methods for adjusting for patient characteristics in NICE TSD 18 describe those for methods in which 'individual patient data (IPD) in one or more trials are used to adjust for between-trial differences in the distribution of variables that influence outcome.' In our NMA, we did not have access to any IPD data for any study, we only had reconstructed IPD data from published Kaplan Meier plots, generated using the Guyot method. This is a key difference between guidelines and technology appraisals; we do not have access to IPD data from industry-sponsored trials, but companies will have IPD data at least for their own technology. As such, it was not possible to

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				Furthermore, assessment of heterogeneity is not reported. For a fair interpretation of the NMA, we believe it will be important to include a transparent assessment of the heterogeneity of the studies included in the network. **Crossover in the relevant trials** The trials included in the network all had some degree of crossover therefore confounding overall survival. We are concerned that estimates from the NMA are biased against targeted treatments as some studies used in the network had a high degree of cross-over. For example, in the BREAK-3 trial, 57% of patients receiving dacarbazine switched to dabrafenib. Adjustment for crossover (Latimer et al, 2015)[6] using the RPSFTM and IPE approaches led to a substantial reduction in the point estimates for the OS HR (HR of 0.76 in unadjusted analysis vs. 0.5 - 0.55 after adjustment for cross-over). We believe that the NMA should use estimates adjusted for cross-over where available and are concerned that results and interpretation from the NMA may be biased	make use of the methodology detailed in this NICE TSD. Ideally, we would have liked to conduct subgroup analyses within our NMA for key effect modifiers. However, it was not generally possible to do so. In order to perform our NMA, we need Kaplan-Meier curves for each treatment. If we wanted to run our NMA with additional subgroups, for example a population exclusively of people with an elevated lactate dehydrogenase (LDH) level, we would need Kaplan-Meier curves for all trials looking only people with elevated LDH levels. Such data was not available. Thus, while we appreciate a number of things may be effect modifiers (Metastasis stage, LDH levels, ECOG score, etc.) in the absence of Kaplan-Meier curves specific to these populations, such subgroup analyses were not possible. We accept this as a limitation of our NMA. We do however attempt to do subgroup analyses where possible, namely in Networks 2-6, which estimated the treatment effect in subgroups with different BRAF status. In an analysis of BRAF-mutant patients, nivolumab plus ipilimumab continued to show the greatest benefit in both overall survival (OS) and progression-free survival (PFS). Notably however, the difference between nivolumab plus ipilimumab and nivolumab between Network 3 and Network 1 (which included people with both BRAF-wild type and BRAF-mutant melanoma and both targeted therapies and

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				because of the varying degrees of cross-over between the different studies in the network. **Face validity of the NMA** We are concerned with the results from the NMA when comparing the outcomes of the key trials included in the network. BRAF status is a prognostic marker for survival, with patients with a BRAF mutation experiencing poorer outcomes than the wildtype[7] Whilst we understand that the naïve comparison of studies should be interpreted with caution, the results from the NMA do not align with results from the key trials. In particular, OS in the COMBI-V and COMBI-D trials for dabrafenib and trametinib appears similar to the OS reported for nivolumab in CHECKMATE-066, despite the COMBI-V and COMBI-D trials being conducted in patients with a BRAF mutation and CHECKMATE-066 in wild-type patients. The NMA however, shows a marked difference in survival outcomes between targeted therapies and immunotherapies.	immunotherapies) was reduced. These networks are detailed in section A2.2.2-3 of the NMA report and full results of our analyses for these respective networks are also found in the NMA report. Additionally, as detailed in A.3.6 of the Network meta-analysis report for Evidence review B, heterogeneity is normally assessed by comparing the fit of fixed and random effects NMA models. However, we were unable to fit random effects NMA models due to the limited number of studies for each comparison, and so we were unable to assess heterogeneity in this way. However, we do present model fit to identify potential outliers. For PFS, this is done by presenting boxplots of the deviance for each data point. For OS, this is done by presenting boxplots of the residual deviance. The box plots referenced above are available in sections A.5.2-A.5.3 of the Network meta-analysis report for Evidence review B. As such, although we were unable to access heterogeneity by comparing the fit of fixed and random effects NMA models, we do discuss whether the deviance contribution is as expected or abnormal. As such, we did both assess and report on heterogeneity to the extent that we could. It is also worth noting that our approach is similar to that of taken by Freeman et al 2022, who also did not fit random effects models in their melanoma NMA due to the limited number of studies

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					for each comparison (doi.org/10.1177/09622802211070253). Although we have reported on the mathematical assessment of heterogeneity, we see your point that some patient characteristics are likely to be effect modifiers. Therefore, we have added a table that compares key patient characteristics across trials. This will allow for a more transparent analysis by readers to understand any potential population differences between trial cohorts. **Crossover in the relevant trials** As detailed in section A.2.1.3 of the Network meta-analysis report for Evidence review B, publications that adjusted for treatment switching were excluded from our primary network. This is because only two such publications that adjusted for treatment switching were available, one for BREAK-3 and one for BRF113220. Because only 2 of 10 studies had data available on treatment switching, this left us with three options. 1) We could exclude trials that adjust for treatment switching and note it as a limitation of our analysis – as we agree, treatment switching can result in changes in both PFS and OS. 2) We could include the trials for treatment switching where data is available. However, this would mean 8 trials would not adjust for treatment switching and the results of the NMA would then

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					introduce bias towards studies where treatment switching had been performed. 3) We could attempt some sort of analysis where we use the treatment adjusted data where possible and apply a conversion factor from the trials where treatment switching was adjusted for, but this requires assuming the adjustment observed in the analyses the account for treatment switching is the same across all trials and all treatments. In the end we thought the first option was the most sensible as it required no additional assumptions and didn't introduce new forms of bias. Again, we acknowledge this is a limitation of our analysis and posit that companies should make IPD data more readily and easily available as such data is a requisite for adjusting for treatment switching. Additionally, there are further limitations when accounting for treatment switching. The primary concern is what treatments patients are switching to, and whether this reflects clinical practice. This problem is arguably more pronounced in BREAK-3, where participants would be switching from DTIC to dabrafenib monotherapy, which though recommended by NICE, is rarely if ever given anymore in clinical practice. Rather, people would be given dabrafenib plus trametinib. In the case of BRF113220, people switched from dabrafenib monotherapy to dabrafenib

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					plus trametinib, which is frequently given in clinical practice. Therefore, it may be less appropriate to adjust the results from BRF113220. Adjusting for treatment switching would be most relevant therefore in BREAK-3, where dabrafenib monotherapy would be what people switched on to after progression, and this therapy is not routinely given as monotherapy in clinical practice these days. A further problem of adjusting for treatment switching is that in the BREAK-3 and BRF113220 trials, the adjusted data has a substantially shorter amount of follow-up than the other trials in the network. Latimer's 2015 paper demonstrates that adjusting for treatment switching would come at the expense of reduced follow-up. In Figure 4, the duration of follow-up for dacarbazine is reduced from approximately 650 days to approximately 400 days in panel A, and approximately 275 days in panel B. This would increase uncertainty in the analyses due to extrapolating the curves over a longer period. Similarly for BRF113220 in Latimer (2015), the amount of follow-up for dabrafenib monotherapy reduces from approximately 800 days to 500 days (fig 3), and to 400 days (fig 4). To our knowledge, an exploration of this trade-off, and how it impacts results, has not been undertaken or reported on.

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					Face validity of the NMA Results published from the DREAMseq trial confirm the results of our NMA, namely that treatment with nivolumab plus ipilimumab is more effective than targeted therapies. The results of this trial were reviewed by the NICE development team and by the committee. These results bolster the face validity of this NMA. Furthermore, we would put greater credibility in an NMA, which is a mathematically validated way to indirectly compare treatments that have not been compared head-to-head than a naïve comparison, which does not do so.
Novartis Pharmaceuticals Ltd	Melanoma: assessment and management [F] Evidence reviews for systemic and localised anticancer	General	General	**Systematic Literature Review** We have concerns that the SLR used to inform the NMA has not identified and included all the relevant evidence for inclusion in this review. For example, the most mature data (5-year follow-up) for dabrafenib and trametinib (Robert et al, 2019) [9] have not been used. The NMA and economic model should use the most mature data.	Thank you for your comment. As detailed in Table 2 of the Network meta-analysis report for Evidence review B, the data you cite (Robert et al 2019) was used in the NMA. However, we recognize that the Evidence Review itself reported a study with shorter follow-up (32 months). We have updated the tables in the evidence review to ensure it reports the same study that was used and reported in the NMA. However, do rest assured that we made every effort to find the most mature follow-up data for the NMA.

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	treatment for people with stage IV and unresectable stage III melanoma health economic report				
Novartis Pharmaceuticals Ltd	Melanoma: assessment and management [F] Evidence reviews for systemic and localised anticanc	General	General	**Economic Modelling** We have reservations with the approach to the economic modelling including the modelling of time on treatment, duration of treatment effect and post progression therapies (which may have implications on the cost-effectiveness results), and the recommendations for systemic therapies for metastatic disease in the clinical guidelines. **Time on Treatment** Given the modelling approach, TTD is disconnected from PFS and OS. This creates a problem when	Thank you for your comment. Time on Treatment (ToT): We believe that there are a number of limitations associated with the available ToT data from the trials we used to estimate treatment effect, and so it is more accurate to model ToT for immunotherapies using SACT data, even though it is not the same source as the survival data. Time-to-event (ToT) data is only available in the Technology Appraisals with a one-year follow-up, and in the publications we used to estimate treatment effect there were only summary data available. As a result of the immaturity of the data used to model ToT in TA366, there were concerns around the reliability of the extrapolation provided in this appraisal. We do not

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	er treatment for people with stage IV and unresectable stage III melanoma health economic report			different sources are used for TTD and efficacy outcomes. For instance, in Figure HE008 the EAG shows that TTD for pembrolizumab is similar to PFS (TA366), but the TTD used in the model (which is based on SACT) appear to be markedly lower compared with PFS and therefore would underestimates the costs. **Duration of treatment effect** A longer duration of treatment effect has been assumed for encorafenib and binimetinib (36 months) compared dabrafenib and trametinib (24 months). Given these therapies belong to the same therapeutic class and have the same mechanism of action, it is unclear why different duration of treatment effect are assumed and we believe it would be more appropriate to assume the same treatment effect duration for both targeted therapies. In addition, the 5-year data for dabrafenib and trametinib supports a longer duration of treatment effect[9] and the omission of this data lends to our concerns about the identification of all relevant evidence for this review and the face validity of the results used to inform the recommendations.	expect PFS and TTD to necessarily follow the same distribution or rate, given that patients discontinue earlier than disease progression due to other factors, including disease toxicity. While TTD and PFS are similar in figure HE008, we confirmed with the committee and consider the estimate of TTD to be overestimated. This is further supported by a comparison of summary ToT data from the SACT analysis and the summary ToT from the data cut with the longest follow up. Scenario analyses were conducted for different ToT assumptions as detailed in the model report, and although the exact results differ slightly, the cost-effectiveness conclusions remain stable. The rationale for the ToT data used in the base-case analysis is included in the model report in section 1.4.3. **Duration of treatment effect:** This assumption in the model was made by the committee based on visual interpretation of the published KM data and the NMA extrapolations. The assumption was considered reasonable by the committee as although the two strategies have similar modes of action, they are different molecules and therefore effectiveness is expected to be similar but not identical. As such, the committee decided not to position one strategy over the other and offered encorafenib plus binimetinib and dabrafenib plus trametinib as equally appropriate options for people under the criteria set out in the

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				Subsequent Treatments The economic analysis assumes that the therapies received on progression reflect the distribution of the therapies received in UK clinical practice rather than those that were received in the relevant clinical trials. We are concerned that this approach leads to a disconnect between the efficacy observed in the trials and the costs used in the model since the true costs associated with the benefits observed in the trials are not captured. Additionally, while we understand assumptions need to be made, the time on treatment on second-line therapies after targeted therapies is significantly different to the time on treatment reported in the trial[9] leading to an overestimation of costs for targeted therapies. For example, in COMBI-D and COMBI-V trials, the median duration of treatment was 2.1 (0.03 – 13.3) for patients treated with Ipilimumab (n=92), 6.8 (0.03-27.5) in patients treated with Pembrolizumab (n=25) and 4.5 (0.5 – 33.0) for patients treated with nivolumab (n=8).	recommendation. When these durations are set to be the same there is only a small difference from the base-case results and the order of therapies remains the same – this scenario has been added to the scenario analysis results table in the health economics report. The NMA included the most long-term data available, and the evidence review has been updated to reflect this. **Subsequent Treatments**: The committee noted that there were limitations with the assumptions around second-line therapies, but accepted that there was no available data that was more suitable to inform this than the methods described in the model report. The committee believed that modelling the distribution of second-line treatments on those received in the trials would not be reflective of clinical practice in the UK and would overestimate costs, given that a greater proportion of patients in the trials received multiple lines of immunotherapies (which is not currently permitted under CDF rules). We recognise that this does cause a disconnect between the source of costs and the evidence used to model outcomes; however, this was mitigated as much as possible by the committee selecting the survival models that provided extrapolations that in their clinical experience were the most appropriate for describing the long-term outcomes.

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					The proportions receiving second-line therapy after targeted therapies are the same for each strategy, so any overestimation of costs due to ToT is applied to both arms so would not impact the conclusions of the analysis. Our model is based on mean duration of treatment rather than the median duration; the duration of treatment appears to follow a skewed distribution and the use of a mean allows us to capture those who receive treatment for more cycles than the median. The medians you have provided here for pembrolizumab and ipilimumab are very close to the median values we used in our calculations (6.0 and 2.1 months, respectively). The value used for nivolumab is slightly different (7.6 months, n=316) however the sample size for people receiving nivolumab in the COMBI-D and COMBI-V trials is very small (n=8) so we would consider this estimate less reliable. Therefore, we believe we have made best use of the data available to us.
Novartis Pharmaceuticals Ltd	Melanoma: assessment and management [F] Evidence reviews	General	General	We have concerns that the overall impact of oral treatments vs infusion has not been adequately captured in the quality-of-life estimates and the impact on NHS in terms of resources. We note that the benefits in terms of HRQoL associated with the availability of an oral treatment over other treatments have been highlighted both by clinical	Thank you for your comment. While we did use a mean utility value for the progression-free health state that was applied to all treatments, we also conducted a scenario where treatment-specific utility values from the TAs were used. These treatment-specific utility values should implicitly capture any impact of route of administration or convenience of treatment on quality of life. The results of this scenario did not change the conclusions

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	for systemic and localised anticancer treatment for people with stage IV and unresectable stage III melanoma health economic report			experts and patient experts and recognised in previous NICE appraisals in different disease areas [10,11,] so it would be important for these elements to be captured in the analysis. The benefits of oral treatments for the NHS and patients are also not captured, such as the impact on bed availabilities and convenience for patients.	of the analysis, with nivolumab plus ipilimumab being the most favoured and both targeted therapies being dominated. The resource impact of these treatments has already been assessed and resource impact assessment tools have been published alongside the TA guidance, so resources like bed availability have already been considered and are already supported in the NHS.
Royal College of Nursing	General	General	General	We do not have any comments on this consultation. Thank you for the opportunity to contribute.	Thank you for your comment.
Royal College of Physicians	General	General	General	The RCP is grateful for the opportunity to respond to the above consultation. We would like to endorse the response submitted by the British Association of Dermatologists (BAD)	Thank you for your comment. Please see our response to comments submitted by BAD.

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Sanofi	Guideline	General	General	We welcome the update to the National Institute for Health and Care Excellence (NICE) guideline on "Melanoma: assessment and management" (GID-NG10155). However, we also wanted to highlight the need to update the current NICE guidelines for non-melanoma skin cancers (NMSCs), given the practice-changing developments that have occurred for these patients since the last publication of the guidelines in 2006 and the subsequent basal cell carcinoma (BCC)-specific update in 2010 ("Improving Outcomes for People with Skin Tumours including Melanoma" - CSG8). As mentioned in the NICE Final scope from June 2020, before the scope of this consultation was changed from skin cancer to melanoma, there is a high clinical unmet need for NMSC patients, especially those with cutaneous squamous cell carcinoma (CSCC), where the disease "can be both disfiguring and fatal if it spreads". The current NMSC guidelines comprehensively cover the management of early-stage disease but are, unfortunately, limited in their recommendations for the	Thank you for your comment. Although the cancer service structures have changed, stakeholders indicated that these guidelines are still useful to clinical practice. In December 2020, we decided to retain but not update these guidelines.

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				care and referral pathways for patients with advanced presentations. This limitation has led to variability in the management of advanced NMSC across the UK, which can affect the diagnosis, MDT referral and selection of the most appropriate anticancer treatment for these patients. As such, we would like to request NICE to consider a revision of the current guidelines for NMSCs, to ensure that the management of these patients, including those with CSCC, can reflect current best practice, in order to ensure the ubiquitous adoption of optimal clinical pathways in the UK. Ultimately, this aligns with the NHS key priorities for 2022/2023, where skin cancer has been identified as a cancer of particular focus given that, together with lower gastrointestinal and prostate cancers, they account for at least two thirds of the national cancer backlog.	

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South Warwickshire Foundation Trust	Guideline	9	16	Recommendations Consider a clinical margin of at least 0.5 cm for stage 0 melanoma. If excision for stage 0 melanoma does not achieve a clear margin, discuss further management with the multidisciplinary team. Offer excision with a clinical margin of at least 1 cm for stage 1 melanoma. Offer excision with a clinical margin of at least 2 cm for stage 2 melanoma. The underlying principle behind surgery of primary cutaneous melanoma is complete excision. Wide local excision is performed to ensure complete extirpation and identify the presence of micro-metastases. By confirming the presence of microsatellites the patient can be upstaged and offered further treatment such as immunotherapy. In the past it has been suggested that removal of micrometastases not identified as microsatellites on histology would reduce the probability of local recurrence. Even if that was true, the balance of probability in excising a radial growth phase melanoma , which is considered to lack potential for metastases, (Elder, Melanoma progression, Pathology 2016 Feb:48(2):147-54) and then finding microsatellites in the initial excision specimen or wide excision specimen would be statistically so small, that it would not be beneficial to populations of radial growth phase melanoma patients.	Thank you for your comment. The committee considered your feedback and agreed to add a further clarification to the excisional margin recommendations (1.5.1 – 1.5.3) that the clinical margin should be based on the histological thickness of the melanoma. The committee acknowledged that smaller margins may be needed for cosmetic reasons on sites such as the face, head and digits. However, the use of smaller margins should be discussed within the specialist skin cancer multidisciplinary team, the reasoning justified and with clinical surveillance. Furthermore, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team. The committee acknowledged continuing uncertainty about optimal excision margins, particularly in stage 0 disease, and made a recommendation for research on histological margins. Finally thank you for providing these references.

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				Wide excision specimens on thin melanomas are usually not processed with the intention of confirming microsatellites but identifying residual primary melanoma. Recent papers have given evidence to support the concept of complete excision over wide excision. Weyer et al.("Personlized Excision" of malignant melanoma –Need for a paradigm shift in the Beginning Era of personalized medicine Am J Derm 2019:41:884-896) The use of Mohs' micrographic surgery (MMS) in melanoma has also demonstrated either no difference in overall survival and local recurrence or better outcomes over 5 years, and this includes thick vertical growth melanomas. **1.Association of Mohs Micrographic Surgery vs Wide Local Excision With Overall Survival Outcomes for Patients With Melanoma of the Trunk and Extremities** Addison M Demer [1] [2], Jamie L Hanson [1], Ian A Maher [1], Walter Liszewski [3] PMID: **33084853** PMCID: PMC7578913 DOI: 10.1001/jamadermatol.2020.3950 Free PMC article **2. Improved overall survival of melanoma of the head and neck treated with Mohs micrographic surgery versus wide local excision**	Weyer et al. ("Personalized Excision" of malignant melanoma –Need for a paradigm shift in the Beginning Era of personalized medicine Am J Derm 2019:41:884-896 – does not meet the inclusion criteria for evidence review C as it is an opinion article and not an RCT. Association of Mohs Micrographic Surgery vs Wide Local Excision With Overall Survival Outcomes for Patients With Melanoma of the Trunk and Extremities Addison M Demer [1] [2], Jamie L Hanson [1], Ian A Maher [1], Walter Liszewski [3] PMID: 33084853 PMCID: PMC7578913 DOI: 10.1001/jamadermatol.2020.3950 - does not meet the inclusion criteria for evidence review C as it is a retrospective cohort study and not an RCT. Improved overall survival of melanoma of the head and neck treated with Mohs micrographic surgery versus wide local excision Jamie Hanson [1], Addison Demer [2], Walter Liszewski [2], Neal Foman [3], Ian Maher [3] PMID: 31473297 DOI: 10.1016/j.jaad.2019.08.059 does not meet the inclusion criteria for evidence review C as it is a database study from the National Cancer Database from years 2004-2015 and not an RCT. Lau KL et al. Primum non-nocere: how harmless is routine wide local, excision for AJCC stage 1A

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				Jamie Hanson [1], Addison Demer [2], Walter Liszewski [2], Neal Foman [3], Ian Maher [3] PMID: **31473297** DOI: 10.1016/j.jaad.2019.08.059 The purpose of MMS is to ensure complete excision. I am not interpreting this as an advocate for MMS for melanoma but the underlying intention of complete excision for melanoma. If the specialist dermatopathologist is confident of complete excision by vertical, bread slice processing then this amounts to the same result. The possibility of not identifying microsatellites in thicker lesions by using MMS may raise the question of the need to starting immunotherapy at that time. As stated earlier the probability of microsatellites in a microinvasive melanoma is so low it would not be a concern. Already the current guidelines are interpreted in different ways by users for stage 1 melanoma. Some advocate a further 1 cm wide excision irrespective of the initial histological excision margin and others will calculate the wide excision clinical margin to be the remainder taken from a 10mm margin eg histological radial margin of 3mm in initial excision then surgeon will take a 7mm clinical radial margin. These clinical /histological margins in any case maybe compromised by free margins or functional reasons but evidence is lacking for a poorer prognosis especially in thin	melanoma? Ann R Coll Surg Engl 2020; Sep:102(7):483-487) does not meet the inclusion criteria for evidence review C as it is a retrospective study and not an RCT.

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				melanomas. It is not surprising that the current guidance states: The recommendations on margins for stage I and II melanoma did not specify different margins for sub-groups, e.g. IA versus IB as there were no data to support this, The 1cm and 2 cm margins in melanoma are also not based on strong evidence and guideline authors are being encouraged not to make **discordant recommendations.** I appreciate that changing current recommendations usually requires strong evidence but the evidence behind the initial recommendation should be reviewed in light of current knowledge of melanoma biology ie. that lymphogenic and haematogenous metastases occur concurrently and not that lymphatic spread is the initial metastatic event. NICE guidance is used maintain a standard and cost effective management for patients treated in the UK. Performing a second wide excision for thin melanomas especially radial growth phase melanomas results in significant morbidity, as well as financial and resource implications in a under resourced health system. (Lau KL et al . Primum non-nocere: how harmless is routine wide l local,excision for AJCC stage 1A melanoma ?Ann R Coll Surg Engl 2020 ;Sep:102(7):483-487)	

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The British Gynaecological Cancer Society	Guideline	9	11	The recent anogenital guidelines recommend a 1mm margin for vulval and vaginal melanoma as below (https://melanomafocus.org/wp-content/uploads/2018/05/2_Full-Guideline-V.7.4-FINAL-29.5.18.pdf) and not to perform lymphadenectomy unless metastatic nodal disease present.	Thank you for your comment. Vulval and vaginal melanoma are mucosal melanomas which are beyond the scope of this guideline update.
The British Gynaecological Cancer Society	Guideline	9	11	The aim of surgical management of vulval and vaginal melanomas should be to achieve an R0 (microscopically clear > 1mm) margin in the least radical fashion. There is no evidence that radical surgery has an impact on overall survival.	Thank you for your comment. Vulval and vaginal melanoma are mucosal melanomas which are beyond the scope of this guideline update.
The British Gynaecological Cancer Society	Guideline	9	11	The considerations set out in the recommendation above also apply to melanomas near or on the clitoris and distant urethra/urethral meatus. Melanomas at these sites present particularly challenging scenarios and patients with these tumours need careful counselling and in the case of the latter, input from urological colleagues.	Thank you for your comment. Vulval and vaginal melanoma are mucosal melanomas which are beyond the scope of this guideline update.

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The British Gynaecological Cancer Society	Guideline	9	11	Lymphadenectomy should only be performed when there is evidence of metastatic regional nodal disease.	Thank you for your comment. Vulval and vaginal melanoma are mucosal melanomas which are beyond the scope of this guideline update.
The British Gynaecological Cancer Society	Guideline	9	11	The draft NICE guidelines recommend 0.5 cm stage 0, 1cm stage 1, 2cm stage 2 It would be helpful to have clarity from the committee if the NICE guidelines also apply to gynaecological melanomas – our current paradigm has been to follow the 2018 Ano genital guidelines linked above	Thank you for your comment. Vulval and vaginal melanoma are mucosal melanomas which are beyond the scope of this guideline update.
UK Cancer Genetics Group	Guideline	General	General	We note that the reference to assessment for possible increased heritable risk of melanoma and the fact that some individuals are eligible for **germline/constitutional** genetic testing for inherited melanoma predisposition is not as clear in this document as we feel it should be. The only mention of potential inherited risk is in section 1.1.2 "discuss the psychological and emotional impact of melanoma…..whether family members are at risk" which has not been reviewed in this document and	Thank you for your comments. Genetic testing for familial melanoma is beyond the scope of this guideline update.

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				"1.9.6 Consider personalised follow-up for people who are at increased risk of further primary melanomas (for example, people with atypical mole syndrome, previous melanoma, multiple in-situ melanomas, or a history of melanoma in first-degree relatives or other relevant familial cancer syndromes). [2022]" The National genomic Test Directory has very clear criteria on offering germline genetic testing to patients with melanoma: https://www.england.nhs.uk/publication/national-genomic-test-directories/ **R254** Familial melanoma Testing Criteria (correct at 31/01/2022) Testing of phenotypically affected individual (proband) where the individual +/- family history meets one of the following criteria. The proband has: a. ≥2 melanomas in situ age <30 b. Melanoma in situ AND ≥2 relatives (first / second / third degree relatives) with melanoma in situ	

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				OR c. Melanoma in situ AND ≥1 first degree relative with melanoma in situ; one individual has multiple melanomas in situ, OR d. ≥1 Melanoma in situ OR melanoma in situ and atypical moles AND ≥1 first degree relative with pancreatic cancer aged <60 e. Atypical moles AND ≥2 relatives (first / second degree relatives) with melanoma in situ, OR f. Uveal melanoma in situ OR BAP-oma (atypical spitz naevus with loss of BAP1 on IHC) OR g. Malignant mesothelioma AND ≥1 first degree relative with malignant mesothelioma OR uveal melanoma OR BAP-oma Assessment of genetic risk and the offer of germline/constitutional genetic testing should be done at diagnosis and having a recommendation to consider personal/familial risk in the "follow-up" section risks missing this as a vital component of the management at diagnosis. It is also not explicit that germline genetic testing can be offered to patients. We would ask the committee to consider whether this document should contain clearer reference to the need to assess melanoma patients for potential heritable risk at diagnosis, and to offer diagnostic germline	

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				genetic testing according to national genomic medicine service criteria and whether exclusion of this advice in this document risks being discriminatory to those with multiple melanomas and/or a family history which could indicate inherited predisposition to melanoma.	
Wales Cancer Network	Guideline	4	11	This overlooks the possibility of downstaging patients with IB melanoma after negative SLNB	Thank you for your comment. This has been amended to improve clarity.
Wales Cancer Network	Guideline	8	8	Restricting SLNB to a subcohort of patients with clinical stage IB melanoma and Breslow thickness 0.8-1.0mm with additional risk factors – such as ulceration, denies the possibility of downstaging that cohort of patients with tumours 0.8 to 1.0mm in Breslow thickness without additional risk factors and results in them being clinically staged as IB – and followed up for 5 years. If these individuals had a negative SLNB they would be down-staged to Pathological stage IA, and only subject to a one-year follow up. I note the argument about SLNB access and costs, but has this been carefully considered against the benefits of a negative SLNB and reduced follow up to these patients?	Thank you for your comment. The committee considered the downside associated with reducing the number of people who would be downstaged from IB to IA but concluded that the costs associated with performing SLNB for all people with IB is too high to recommend this. However, the committee only recommended that SLNB not be performed in stage IA melanoma, leaving the option to perform SLNB in stage IB melanoma (without the relevant risk factors) in exceptional circumstances which cannot be accounted for in a guideline.
The Christie NHS Foundation Trust	Guidance	4	6	The draft NICE guidance states "The melanoma is staged as 0 to IIC,". However, this should include stage 3b/c (pT1-4 pN1c) to reflect the situation of	Thank you for your comment. This text on the stages of melanoma has been removed and now refers to the UICC and AJCC staging methods.

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				stage 3 on biopsy excision when satellites are detected.	
The Christie NHS Foundation Trust	Guidance	8	6	The draft NICE guidance states "Do not offer imaging before SLNB unless lymph node or distant metastases are suspected". I find this statement very generic. Perhaps it can include imaging recommended for stage 2c and presence of microsatellites (stage 3b/c)	Thank you for your comment. The committee discussed this issue and agreed to keep this as a generic recommendation due to the poorer quality of evidence for the use of imaging in staging. The diagnostic accuracy of imaging depends on location and a SLNB is considered a superior method for staging. The exception is when lymph nodes or distant metastases are suspected where the committee considered the use of imaging to be warranted. The lymph node status is key in staging, and this is best determined through SLNB for those eligible in the guideline recommendations.
The Christie NHS Foundation Trust	Guidance	8 9	17, 19 3	The draft NICE guidance is recommending CT head scans, except for specific groups considered at higher risk, namely pts with stage IIIC to IV melanoma, with a mitotic index of 9 or more, or primary melanoma located on the scalp. For these patients they are recommending a MRI head scan be done at baseline, but CT head used for follow-up. However, we feel this becomes overly complicated, risks exposing patients unnecessarily to increased radiation and does not sufficiently reflect the fact that MRI head scans are more sensitive than CT for detecting brain mets. We would recommend MRI head scans are done for all patients where possible, unless contraindicated. This	Thank you for your comment. The committee considered your feedback and agreed that a brain MRI should be considered for imaging at follow up. The committee have added a new recommendation 1.9.10 to consider brain MRI, instead of CE-CT brain for imaging follow up, if locally preferable and after discussion and agreement with the specialist skin cancer MDT. The committee also acknowledged the logistical difficulties and capacity issues of arranging separate CE-CT and MRI scans.

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				is a recommendation based on the consensus views of a panel of melanoma experts in the UK, published by Melanoma Focus. The development of melanoma brain mets can be devastating, and early detection can make a significant difference to how they can be managed.	
The Christie NHS Foundation Trust	Guidance	9	7	The draft NICE guidelines are recommending a baseline scan within 8 weeks of starting adjuvant treatment. This appears to be based mainly on a study by Bloemendel (2019) which showed high rates of recurrence within 7-8 weeks of surgery (Evidence review G, pg 40 line 47-pg 41 line 8). However, the key recent adjuvant studies required a clear scan within 6 weeks (Keynote 054) or 4 weeks (Checkmate 238 and Combi-AD). The consensus view of a panel of melanoma experts in the UK, published by Melanoma Focus is that a baseline scan within 6 weeks of starting adjuvant therapy is more appropriate than 8 weeks.	Thank you for your comment. The committee considered your feedback and agreed to amend recommendation 1.4.12 to consider a repeat staging scan before starting adjuvant treatment, unless imaging done within the past 6 to 8 weeks is available.
The Christie NHS Foundation Trust	Guidance	12	20	Existing text: electrotherapy in line with… Recommend change to: electrochemotherapy in line with…	Thank you for your comment. This has been amended.
The Christie NHS	Guidance	14		There should be a recommendation to consider second line ipilimumab in patients progressing on	**Thank you for your comment. A recommendation to offer ipilimumab for previously treated advanced (unresectable or metastatic) melanoma in line with TA268 has now been included in the guideline. We**

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Foundation Trust				single agent PD-1 inhibitor, there is a NICE technology appraisal for this treatment.	**have also included recommendations for other second-line treatment options for these patients.**
The Christie NHS Foundation Trust	Guidance	14	10	The recommendation that patients should be offered combination immunotherapy is not appropriate. While this is associated with a modest survival benefit in those patients eligible for this treatment when compared to single agent immunotherapy, there are also major issues with toxicity. Furthermore, subgroup analysis shows that the benefit is confined largely to patients with a BRAF mutation, and to younger patients. The cost of toxicity with combination immunotherapy is underestimated. The data from CheckMate 067 are misleading in that they report only time to resolution to Grade 1 toxicity. However patients remain on significant immunosuppression for many weeks and months after this, often developing iatrogenic toxicities as a result. A recent study from our centre showed that combination immunotherapy was responsible for a disproportionately high number of all the admissions in patients on immunotherapy, and the majority of complex and fatal toxicities were in this group. https://doi.org/10.1016/j.ejca.2021.12.033 Setting this as the standard of care, based on misleading cost benefit analysis, will mean that patients will understand they should be expecting this treatment,	Thank you for your comment. The economic analysis takes all relevant factors into account, including toxicity, survival and costs. The toxicities included in the adverse event NMA were events that were grade 3-4 reported in the clinical trials, using the number of events reported for each trial period rather than the time to resolution of each toxicity (detailed in section 1.4.5 of the economic report). However, as you have noted there are potentially some limitations with NMA on toxicity, as the data informing adverse events was taken from the clinical trials which may not capture some of the more long-term toxicities. However, the committee agreed that at least some of these were addressed in the adverse event NMA conducted. The committee also advised that some of these long-term side effects and conditions are asymptomatic and therefore would not fall into the category of Grade 3-4 adverse event. Therefore**,** this limitation is not expected to change the conclusions of the analysis. Despite the higher toxicity, nivolumab plus ipilimumab is the most cost-effective treatment for the average trial-based population. However, we appreciate that there are some circumstances where combination immunotherapy is not the most appropriate treatment for a person, especially when they are not

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				and clinicians will feel they have to justify not offering it. However, given that the SACT data show that approximately 70% of patients in UK receive single agent PD-1 therapy, this is clearly the standard of care for the majority of patients. The guidance should reflect the complexity and uncertainty rather than make a recommendation. In this situation, the (flawed) cost effectiveness data do not help.	representative of patients enrolled in the RCTs. We have, therefore, added an additional recommendation (1.8.6) in this section to allow people making decisions about treatment to consider the most appropriate care and reflects the complexities of scenarios where different therapies would be more appropriate. We noted that a post-hoc subgroup analysis of CheckMate-067 indicated that there may be a greater survival benefit in people with BRAF-mutant melanoma compared with those with BRAF-wild type melanoma. We wished to be cautious and conservative about the interpretation of data in subgroups, particularly in relatively small Phase 3 trials. Furthermore, the committee believed that the choice between anti-PD1 monotherapy and nivolumab plus ipilimumab is mainly driven by factors such as tumour burden, LDH, brain metastases and disease tempo; patient age and BRAF mutational status are much less relevant factors. We noted that there was little difference in PFS for nivolumab plus ipilimumab between the two BRAF subgroups, suggesting that the benefit may be due to treatments received after discontinuation; however, the opposite phenomenon occurred in the nivolumab arm, whereby there was little difference between OS outcomes between the subgroups but a small difference in PFS. Therefore, we felt that these outcomes should be interpreted with a high degree of caution.

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The Christie NHS Foundation Trust	Guidance	14	16	The guidance on offering single agent pembrolizumab in preference to nivolumab makes no sense and is not based on data. It should be replaced by a generic recommendation that patients not being considered for combination immunotherapy should be offered single agent immunotherapy with either pembrolizumab or nivolumab. It can only be recommended on a cost benefit. If this is the reason, then it should be made explicit in the recommendation.	Thank you for your comment. The rationale for giving a stronger recommendation for pembrolizumab than for nivolumab was due to the cost-effectiveness analysis, and the higher proportion of scenarios under the confidential pricing schemes that favoured pembrolizumab. However, we have received updated information for the confidential price discounts used in the analysis, and with the new pricing information the cost-effectiveness of pembrolizumab and nivolumab is very similar. Therefore, the recommendation has been updated to offer either pembrolizumab or nivolumab. **We do not typically include the rationale within the recommendation itself but have made this clear in the impact section in the guideline.**
The Christie NHS Foundation Trust	Guidance	15	9	Existing text: Offer encorafenib in combination with binimetinib, or trametinib in combination with dabrafenib… . Recommend change to: Offer encorafenib in combination with binimetinib, or dabrafenib in combination with trametinib… Reason: To maintain consistency by naming the BRAF inhibitor first and MEK inhibitor second.	**Thank you for your comment, this has now been changed.**
The Christie NHS Foundation Trust	Guidance	15	21	Existing text: If encorafenib in combination with binimetinib, and trametinib in combination with dabrafenib… .	**Thank you for your comment, this has now been changed.**

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				Recommend change to: If encorafenib in combination with binimetinib, and dabrafenib in combination with trametinib… Reason: To maintain consistency by naming the BRAF inhibitor first and MEK inhibitor second.	
The Christie NHS Foundation Trust	Guidance	18	13	The draft NICE guidance states: "Do not routinely use PET-CT during follow-up of people with melanoma". However, the consensus view of a panel of melanoma experts in the UK was, where the primary melanoma was on a limb, either CT or PET-CT is acceptable for surveillance imaging, based on local preference and availability. Whole body PET scan has the added advantage over CT of covering the areas of the body most likely to be affected by regional recurrence.	Thank you for your comment. The committee considered your feedback and agreed to keep this recommendation as the evidence and health economic modelling found that whilst PET-CT is more sensitive for the detection of metastases compared with CE-CT it is not cost effective.
The Christie NHS Foundation Trust	Guidance	20		It is unclear how the recommendations for research have been reached and whether the recommendations from 2015 will be removed.	Thank you for your comment. The research recommendations are drafted by the committee based on identified gaps in the evidence base during the guideline update process. Stakeholders were asked to comment on the current validity of the 2015 research recommendations during draft guideline consultation and these are kept or removed based on stakeholder feedback. Further information can be found in the NICE guideline manual.
The Christie NHS Foundation Trust	Guidance	8, 18	21-22, 3-4	The draft updated NICE guidance is recommending whole body MRI scans for younger patients (up to 24 years old). We would recommend low radiation dose CT chest and MRI abdo/ pelvis instead. This is based	Thank you for your comment. The committee discussed this issue and agreed to keep the current recommendations due to the cumulative risk of radiation associated with CE-CT scanning for children and young people which is undesirable. The committee

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				on existing guidelines used at the Royal Marsden Hospital, which informed the consensus view of a panel of melanoma experts in the UK, published by Melanoma Focus. As far as we are aware there is no evidence to support whole body MRI (which is more resource intensive) over low dose CT chest and MRI abdo/pelvis, nor any evidence to limit this to less than 24 years of age, as opposed to current practice of 30 years.	also agreed to keep the current definition of up to 24 years as this is the recognised definition of a young person by organisations such as the UN and WHO.
The Christie NHS Foundation Trust	Guidance	9, 18	1-2, 5-6	The draft updated NICE guidance is recommending whole body MRI scans for women who are pregnant. Our view is that appropriate imaging in this patient group is dependent on a number of factors, including stage of pregnancy and patient wishes. We recommend that imaging for this patient group needs to be determined on a case by case basis in conjunction with appropriate Radiology advice.	Thank you for your comment. The committee discussed this issue and agreed to keep the current recommendations to offer whole body and brain MRI due to the cumulative risk of radiation associated with CE-CT scanning for women during pregnancy which is undesirable.
The Christie NHS Foundation Trust	Guidance	29	6	"become stage IIIC disease without the need for SLNB." This should say instead "become stage IIIB or IIIC disease without the need for SLNB."	Thank you for your comment. This has been amended.
The Christie NHS Foundation Trust	Guideline	19	Table	The draft NICE guidance has not distinguished between lower risk stage IIIA melanoma (≤1mm SLN deposit) and higher risk stage IIIA melanoma (>1 mm SLN deposit). We appreciate the committee's view that a reduced surveillance schedule for Stage IIIA pts	Thank you for your comment. The committee discussed this issue and agreed that a reduced surveillance schedule for Stage IIIA with ≤1mm nodal involvement would cause confusion due to being less rigorous than lower stages and may adversely impact upon patient quality of life, due to having infrequent

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				with ≤1mm deposit could cause confusion and may impact on QoL, due to being less rigorous than lower stages, with less frequent clinic visits and scans despite having a higher stage disease diagnosis (as explained in Evidence review G, pg 40, lines 8-11). However, Melanoma Specific Survival for patients with stage IIIA disease and ≤1mm SLN deposit is >90%. For this good prognosis group we feel the radiation risk of up to 9 CT scans over 5 years outweighs the benefit of cross-sectional imaging. We would instead recommend USS of the draining lymph node basin, 6 monthly in years 1-3, annually years 4-5, then stop. This is a recommendation based on the consensus views of a panel of melanoma experts in the UK, published by Melanoma Focus.	clinic visits and scans despite having a high stage disease diagnosis. On this basis they agreed to keep the current recommendation outlined in the table. Furthermore, the committee were also concerned about creating sub-groups of lower risk stage IIIA and higher risk stage IIIA which are not internationally recognised. **Finally, the committee agreed that the guideline recommendations should not be considered standard practice in all cases and there is a need for individual interpretation within specialist skin cancer multidisciplinary team.**
The Christie NHS Foundation Trust	Guideline	19	Table	For all Stage IIIA-IIIC patients, the draft NICE guidance is recommending CT HNTAP for every surveillance scan. This is different to current practice and the consensus view of a panel of melanoma experts in the UK, published by Melanoma Focus. This consensus view recommended CT TAP + MRI head for these patients, with neck imaging only for patients with primary melanoma on the head and neck. Doing CT head & neck in addition to CT TAP every time means an additional 5.6 mSv of radiation risk exposure per scan. For comparison the annual UK	Thank you for your comment. The committee considered this issue and agreed that the radiation risk from ionising radiation exposure is not serious. Furthermore, increased use of MRI instead of CE-CT will have practical implications and will place an increased burden on MRI capacity. **The committee also considered further the use of MRI head at follow up and have added a new recommendation 1.9.10 to consider brain MRI, instead of CE-CT brain for imaging follow up, if**

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				background radiation is 2.7 mSv. Therefore doing CT HNTAP on all patients with stage IIIA-IIIC melanoma risks increased radiation exposure unnecessarily for the majority of these patients. We would recommend MRI head instead of CT head, and neck imaging only if the primary was on the head or neck.	**locally preferable and after discussion and agreement with the specialist skin cancer MDT.**
The Christie NHS Foundation Trust	Guideline	19	Table	For Stage IIIA-IIIC patients with positive sentinel lymph nodes (as well as Stage IIB/C pts for whom SLNB was considered but not done), the NICE guidance suggests CT follow-up alone is insufficient, and USS follow-up should also be done (6 monthly in years 1-3, staggered with the recommend 6 monthly CT imaging). Whilst we appreciate the view that USS is more sensitive than CT at detecting lymph node mets, we would argue that USS sensitivity is highly dependent on both equipment and operator experience, and serial CT imaging increases its sensitivity for detecting lymph node mets. Therefore we feel CT scan follow-up alone without additional USS is reasonable for this patient group, particularly bearing in mind the pressures currently faced by most Radiology departments.	Thank you for your comment. The committee considered this issue and noted that ultrasound scanning was shown by the evidence to be more sensitive than clinical examination and alternative imaging modalities (particularly CE-CT) for detecting local lymph node metastases. They therefore recommended ultrasound surveillance for 3 years for people with a positive sentinel lymph node. The committee have added to the guideline rationale acknowledging the practical implications of ultrasound imaging during follow-up such as providing increased numbers of scans and variable experience of healthcare professionals involved in follow-up.
The Christie NHS Foundation Trust	Guideline	19	Table	For Stage IIID and resected Stage IV patients, the NICE guidance is recommending CT HNTAP 3 monthly years 1-3, 6 monthly years 4-5, then stop. This is significantly more CT imaging than what is	Thank you for your comment. The committee considered this issue and agreed that the radiation risk from ionising radiation exposure is not serious. Furthermore, increased use of MRI instead of CE-CT

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				current practice and has been recommended by a consensus of melanoma experts in the UK, published by Melanoma Focus, which is CT TAP 3 monthly in year 1, 3-6 monthly in years 2-3, annually in years 4-5, then stop, along with MRI head 6 monthly in years 1-3, annually years 4-5, then stop. The proposed NICE guidance would mean at least 2 extra CT TAP, and 17 extra CT head & neck scans over 5 years, compared with the Melanoma Focus consensus guidance. We feel there is no evidence to support this level of increased radiation exposure.	will have practical implications and will place an increased burden on MRI capacity. **The committee also considered further the use of MRI head at follow up and have added a new recommendation 1.9.10 to consider brain MRI, instead of CE-CT brain for imaging follow up, if locally preferable and after discussion and agreement with the specialist skin cancer MDT.**