SIGN Cutaneous Melanoma Consultation

COMMENTS RECEIVED FROM EXTERNAL REFEREES AND OTHERS

All reviewers submitted declarations of interests which were viewed prior to the addressing of comments.

Invited reviewers			Type of response and declared interests
AA	Dr Andrew Affleck	Consultant Dermatologist & Mohs Surgeon NHS Tayside	*Individual response.* **No doi submitted – email response.**
CP	Professor Charlotte Proby	Professor of Dermatology, University of Dundee & NHS Tayside	*Individual response.* *Non-personal financial interests (12 months)* - I received a £20K grant from Melanoma Focus to validate an SLN risk prediction algorithm that includes clinicopathological characteristics and an 8-gene expression profile. I have donated this money to the Nuffield Department of Surgery, Oxford to fund validation of this prediction algorithm on their melanoma tumours that had a SLNB biopsy and at least 5 years of follow-up. *Non-personal financial interests (topic specific)* - See above about our SLN Predict research project in collaboration with the Department of Plastic Surgery at Oxford University Hospitals NHS Trust.
CM	Dr Colin Moyes	Consultant Pathologist, Queen Elizabeth University Hospital, NHS GG & C	*Individual response.* Nothing declared.
GP	Dr Gregory Parkins	Consultant Dermatologist, NHS Greater Glasgow and Clyde	*Individual response.* Nothing declared.
JS	Mr John Scott	Consultant Plastic Surgeon, NHS Greater Glasgow and Clyde	*Individual response.* Nothing declared.

LS	Ms Leigh Smith	Chair/Trustee Volunteer. Ex stage 4 patient, retd RGN, commenting on behalf of MASScot - Melanoma action and support Scotland	*Group response.* *Nature and purpose of your group or organisation* - Patient support and advocacy group. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity?* - We hope the guidance will results in all patients across Scotland having access to best considered care. We would like to see more strength behind SIGN to ensure government take cognition of the recommendations particularly prevention. The need for adequate trained specialist staff to treat this fast increasing cancer and particularly the necessity of GPs to recognise melanoma early, refer appropriately and assist with prevention.
MN	Professor Marianne Nicolson	Locum Consultant Medical Oncologist, Raigmore Hospital, Inverness, NHS Highland	*Individual response.* Nothing declared.
MM	Dr Marie Mathers	Consultant Pathologist, NHS Lothian	*Individual response.* Nothing declared.
MMo	Dr Megan Mowbray	Consultant Dermatologist, Queen Margaret Hospital, NHS Fife	**Comments submitted by email – no DOI submitted**
PL	Professor Paul Lorigan	Professor of Medical Oncology, Christie NHS Foundation Trust, Manchester, UK	*Individual response.* *Personal financial interests (3 years)* - Consultancy and speaker fees: BMS, MSD, Pierre Fabre, Novartis, Amgen; Melagenix, Ultimovacs. *Non-personal financial interests (12 months)* - Research funding BMS and Pierre Fabre.
SR	Dr Senthil Kumar Arcot Ragupathy	Consultant Radiologist, Aberdeen Royal Infirmary, Aberdeen	*Individual response.*

			Nothing declared.
SW	Mr Stuart W Waterston	Consultant Plastic Surgeon, NHS Tayside	*Individual response.* Nothing declared.
Open consultation			**Type of response and declared interests**
AB	Dr Adrian Baker	GP, Nairn Healthcare Group	*Individual response.* Nothing declared.
GK	Mr Georgios Kontorinis	Consultant ENT Surgeon & Hon Ass. Professor, Queen Elizabeth university Hospital Glasgow	*Individual response.* Nothing declared.
JM	Ms Jane Meaney	Director, commenting on behalf of AMLo Biosciences Ltd.	*Group response.* *Nature and purpose of your group or organisation* - Medical Device manufacturer. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity?* - The draft SIGN inclusion of our novel dual antibody test for stratifying risk in early stage cutaneous melanoma; AMBLor, would promote uptake in NHS Scotland which would improve company performance and potentially reduce resource impact and improve patient experiences in Scotland.
KB	Dr Kashif Bhatti	GP with Extended Role & Specialty doctor in Dermatology, commenting on behalf of Primary Care Dermatology Society (PCDS)	*Group response.* Nothing declared.
MFM	Dr M. Firouz Mohd Mustapa	DIrector of Clinical Standards, commenting on behalf of British Association of Dermatologists' Therapy & Guidelines and Service Improvement sub-committees.	*Group response.* *Nature and purpose of your group or organisation* - Specialist society for UK dermatology www.bad.org.uk

YM	Yann Maidment	Dentist, commenting on behalf of the College of General Dentistry	*Group response.* *Nature and purpose of your group or organisation* - Professional group representing all dental professionals registered with the GDC. Purpose to support and promote highest standards of professionalism and patient care. *How might the statements and recommendations in the draft SIGN guideline impact on your organisation's functions/status/productivity?* - Draft guidelines will have no discernible impact on organisation function or productivity. Nor on the everyday practice of dental professionals. Awareness of (rapidly) changing diagnosis, treatment and management IS relevant to our groups - to support better patient care.

Section	Comments received		Development group response
	CP	This brings SIGN into line with the recent NICE guidelines which is helpful and necessary. Follow-up imaging using high resolution ultrasound of nodal basin in patients who were eligible, but did not have a SLNB is desirable, however this requires access to high resolution US which in Scotland is usually not available. This recommendation is probably aspirational rather than realistic, but it is what we should be working towards when work force issues allow. Future research should include prospective studies to validate the ability of SLN prediction tools to avoid unnecessary SLNB and to detect melanomas with negative SLNB (or low risk of SLNB) who go onto to relapse with nodal or distant metastases. There should be some comment under the sections on immunotherapy that point out that immune checkpoint inhibitors are contraindicated in patients with solid organ transplants because of the risk of rejection, however ICI are being investigated in otherwise lethal cases of melanoma and clinicians should seek expert opinion. It is essential that any treatment decisions are made in close collaboration with the relevant transplant clinicians.	Agree, thank you. Agree, prediction tools were included in the evidence review but there was insufficient research to support a recommendation. Further studies are needed before recommendations can be made. The following sentence has been added to the introduction of the section: Sentinel lymph node prediction tools are available to avoid unnecessary SLB, but further research into their accuracy is required before recommendations can be made on their use. A research recommendation has been added to section 13.2 The guideline group do not think it is necessary to include a list of contraindications in this guideline – this is one of many.
	SW	There is a section in melanoma in women. Should there be a specific section in Melanoma in Children? Although this is rare, there have been a number of cases discussed at the MDT's I am part of. Evidence is obviously limited due to the rarity. There are some difference with paediatric melanoma, particularly Spitzoid melanoma, where there is a high incidence of sentinel node positivity, but does not necessarily translate into the poor outcome that may be expected. The surgery to be undertaken (wide excision, lymph node surgery) is unusual in a Paediatric setting and may benefit from a	This is outwith the remit. This has been made more explicit in section 1.2.1 Overall objectives, and the sentence added with regard to discussion with the paediatric oncology MDT. This section also explains that the guideline specifically covers cutaneous melanoma.

		discussion with a clinician who regularly undertakes such procedures. If a section, even brief, were to be included, I think it would be important to say something like "all Paediatric melanomas should be discussed at a Paediatric Oncology MDT, ideally involving clinicians who have direct experience in the management of cutaneous melanoma"	
	GK	Well done to the people involved. High quality work.	Thank you. No action required.
	PL	Thank you for allowing me to review.	No action required.
	GP	Overall, I thought the guidelines were well laid out and very helpful	Thank you. No action required.
	CM	Not much change to pathology.	No action required.
	JM	Section 11 Page 40 – Section 11 Provision of information There is a need for robust, accessible evidence for all, considering the requirement for patient information to meet the needs of minority groups and those in areas of social deprivation. Information should be provided for patients by working with patient support groups involved in Melanoma care. Information will be required for the clinical team involved in melanoma care with particular emphasis on Pathology support as identified in Melanoma QPI 2-Pathology reporting. We feel there could be a further benefit of incorporating AMBLor into clinical practice here, making it explicit that biomarker prognostic tests are available and patient choice is considered. The NICE MedTech Innovation briefing MIB294 (AMBLor for identifying low-risk non-ulcerated early-stage cutaneous melanomas) includes a statement from patient organisation The British Skin Foundation acknowledging the patient benefits of AMBL or (Ref: https://www.nice.org.uk/advice/mib294/chapter/Patient-	Agree. Section 11.5 signposts to organisations which offer further information and support. This is outwith the remit of the guideline. Agree this is interesting but too early to recommend in routine practice as there is insufficient published trial data. The group looked at prognostic indicators and there was nothing specific to recommend.

		organisation-comments) This could be an assurance measure for the clinician to discuss with the patient, as would be done with breast cancer, for example Oncotype DX genomic testing and many others. Reflecting also in the quality-of-life measures, suggested to be recorded, as anxiety and personal behaviour could change. General statements The NHS in general is facing significant amounts of resource pressures, such as staff shortages, theatre time, bed capacity and outpatient availability. This has resulted in longer waiting lists, MDT time becomes a scarce commodity, the patient is left with possible later diagnosis and in some cases, challenges to get into clinic. Having a biomarker prognostic test such as AMBLor offers multiple opportunities for NHS Scotland and patients which are in keeping with the Once for Scotland approach and the National Cancer Recovery Plan. We respectfully suggest consideration of review of the levels of evidence submitted to NICE under the MIB program and their conclusions .. Ref: https://www.nice.org.uk/advice/mib294 Given the unprecedented pressures facing NHS Scotland and the need to recover from the prolonged disruption caused by COVID 19 there is a clear need to identify innovative technologies with a role to play in reducing system pressures without compromising patient care. AMBLor- The AMBRA 1 and Loricrin test identifies the risk of disease progression in early-stage no n ulcerated melanomas. The test is an immunohistochemical assay that uses two	

		antibodies. It is based on the identification of two proteins that are normally present in the upper layer of the skin (epidermis): AMBRA1 (Autophagy and Beclin 1 regulator) - a regulatory protein that plays a role in cell proliferation and differentiation and is a known tumour suppressor. Loricrin- a marker of epidermal terminal differentiation. Maintenance of one or both protein markers in the epidermis is associated with genuinely low-risk tumours, while loss of both proteins is associated with at-risk tumour subsets. The results of the test may be used to guide the appropriate management for patients with early-stage melanomas. AJCC stage 1 and 2 tumours represent 91% of all melanomas, these are all managed as having the same level of significant risk of progression, even though fewer than 5% of Stage 1 and 20% of Stage 2 melanomas do eventually result in metastases. Ref: Keung E and Gershenwald G. Expert Rev Anticancer Ther. 2018 August; 18(8): 775–784. There is an opportunity for a robust biomarker to aid further stratification of these patients into low risk and at-risk groups. The former perhaps benefiting from less invasive management enabling concentration of resource towards those identified as being at-risk. We suggest that the use of AMBLor allows better risk stratification and with credible biomarkers, a personalised approach to care which can play a part in reducing system pressures and reflects the drive for innovation in cancer care in Scotland.	
	MM	Thanks for all the work on this update	Thank you. No action required.

	LS	We would like to see this Guidance used more to inform Government – specifically education and PHS. All weather reports from March to end of September should have the UV Index and some time given to educating the general public and in particular children on sun safety on TV as it is the main source of information for most people. Might SIGN be able to influence this.	The guideline is distributed to the Scottish Government and Public Health Scotland. However, publicity of the UV Index is outside the remit of the guideline.
	MN	Most progress has been made in the systemic therapy arena so close attention to updating that section with recent publications is essential. Also important to omit therapies that are no longer offered eg ILP, adjuvant RT as per comments above.	Thank you, the systemic therapy section has been updated and other sections considered for removal.
	Mmo	Page 1 – 1.1 – Braf should be BRAF.	Amended
	AA	Thanks for all your efforts and time in this challenging task. There is little doubt that melanoma is by far the biggest topic of all skin cancers with the most publications and it is also the most rapidly evolving area in skin cancer management. I have read through the latest version of the guideline and made some suggestions which I hope you find constructive. I have concentrated on the areas of my clinical practice. I think we should recommend a daily OTC vitamin D supplement ie. Vitamin D3 capsules containing a vitamin D dose of 400 IU (10mcg) in all patients with a diagnosis of melanoma to take for 6 months of the year ie October to March. There is some evidence that Vitamin D supplementation may be beneficial to individuals with a new Dx of melanoma and no evidence that it could cause harm and so it is a pragmatic and realistic approach in my view. Further studies exploring this area are in progress. It is wrong in my opinion for SIGN to ignore this altogether and not to comment on this topic – the evidence should be appraised. 13.2 Research	Vitamin D was not included in the update as the evidence is still inconclusive. The review would have been resource intensive, possibly without resulting in a recommendation. This is on the radar for a future update. A recommendation for research has been added to section 13.3 Out of scope for this review. There is other research

		A prospective study of 5 v 10mm WLE of microinvasive melanoma (radial growth phase) looking at incidence of local recurrence and nodal mets and cosmetic outcome / complications from WLE. Annex1 5.3.2 Clark level is no longer reported and so it is no longer a predictor that "should be assessed" – please remove. PS It would be really useful if SIGN illustrate as an annex / appendix a "melanoma new diagnosis checklist" for use at clinic and MDT. A gold standard Scotland wide MDT proforma for melanoma would also be desirable which would in part incorporate all the melanoma QPIs to make sure all the desirable info is captured routinely.	ongoing. Perhaps for next update. Removed This is a helpful suggestion, which perhaps the MCNs could pick up. It is out of the scope for this update.
	KB	I see that advice on Vitamin D has not been mentioned. I think it may be because they haven't decided what should be done. There was discussion at the most recent WoScan meeting a few weeks ago about whether they could ask GPs to check Vit D levels or whether it should be prescribed or just otc and nothing has been decided but I'm surprised nothing at all was mentioned even just general advice.	Vitamin D was not included in the update as the evidence is still inconclusive. The review would have been resource intensive, possibly without resulting in a recommendation. This is on the radar for a future update.
	JS	1.2.5 refers to SCC guideline Page 10, Table 2: Risk factor – female: male incidence rates *Suggest that it contradicts statement in Section 4, paragraph 1 (p11). Is reference 27 correct?*	Section removed. Agree, in Scotland it is more common in males, and more recent literature suggests the female:male incidence varies dependent on geographic location, age and location of tumour. The statement has been removed.
3.5	LS	Addition of who should collect and record family history of potential genetic mutation would help in alerting to a possible diagnosis.	Out of scope of this review.

	SR	No comments.	No action required.
	YM	No comment.	No action required.
	GK	The point/ recommendation that all patients diagnosed with CM should be discussed at an MDT is extremely important and accurate. It should probably also highlight that such cases should not be treated without MDT input. Tables 3 and 4 would provide an excellent, quick-to-read guidance for primary care; they should be widely distributed across Scotland.	This is covered by the QPI rather than SIGN. Thank you.
	GP	No comment	No action required.
	MM	Page 19 – in relation to the microscopic features which should be recorded in sentinel lymph node biopsy reports, the list of features includes “if parenchymal if deposits localised </=3 or multifocal >/=3”. This statement uses the greater than or equal to symbol for both options. This should be amended to “multifocal>3” (greater than 3).	Amended, thank you.
	MN	Should mention REFLEX testing for BRAF status in stage III and IV to avoid delay in systemic therapy.	The recommendation is to do BRAF testing, the guideline group feel it is up to local units to decide whether it is done automatically or on request.
	KB	4. 4.7.10 - interested to hear what others do locally in terms of the following advice "If the zone of regression is deeper than the deepest melanoma cell then this should not alter the formal Breslow thickness; Breslow thickness should be measured to the deepest tumour cell as per the original definition".	No action required. Outside scope.
4.1	MFM	Should have a sentence stating that although this is a guideline for cutaneous melanoma, melanomas can arise on mucosal surfaces and in the eye. Should subungal also be included as a distinct subgroup?	The guideline group think it is sufficient to state in the introduction that this guideline is specifically for cutaneous melanoma. The guideline group do not think this is necessary as it is treated in the same way.

4.1.5	PL	Desmoplastic melanoma: It would be worth including here that there is evidence that desmoplastic melanoma has a high response rate to checkpoint inhibitors.	A detailed review of predictive markers was not included in the scope of this update. A more extensive update will be considered for next time
	JS	However, a small single centre study described higher local recurrence rates in pure DM (28/118) compared with mixed DM (18/124)'. Suggest this is taken slightly out of context because it should refer only to thin lesions excised with 1cm margin (ref 37). Not sure reference 36 is relevant.	Thank you, we have replaced the reference with a more relevant review which cites studies showing higher recurrence rates with DM.
4.2	MMo	I suggest also mentioning the Georgia approach/Georgia criteria.	Thank you for the suggestion but this is one of various criteria and for consistency the group preference is to retain the table that has been in the guideline previously.
	AA	Similar to the update in 2017 when there was no update on the evidence for dermoscopy which I commented on, I am surprised and disappointed that again in the 2022 update, this section has not been updated. There are only 4 references to historical papers on dermoscopy – form 1995, 1999, 200 and 2001. A quick pubmed search for publications over the last 10 years using search terms "melanomand dermoscopy" generated 1846 publications including a recent Cochrane review in 2018 – see attached. I do find it odd that the SIGN group do not feel that up to date evidence in the diagnosis of melanoma is not an important part of the guideline.	Thank you but the update focused on areas where new evidence would change the current advice. The guideline already recommends that it should be used and it is unlikely this would change with a review of more recent evidence.
	KB	The EFG (evolving, fast growing; for nodules or rapidly growing lesions) rule should be a must.	Agree this is another option but for consistency the guideline group would prefer to keep with the original list of features in table 3.
	AB	At the bottom of page 12 in the guideline is the following statement. "GPs should refer urgently all patients in whom melanoma is a strong possibility rather than carry out a biopsy in primary care." I would prefer this statement to have a second sentence, along the lines of	The guideline group understand there may be regional differences but overall best practice is that the original statement still stands. Liaison is needed with the MDT and QPIs dictate that these should be managed by skin cancer specialists.

		"Local MDT guidelines may allow named GP's to biopsy suspicious lesions as part of a local agreements with Dermatology colleagues." The named GP addition would help with quality and clinical governance and ensure that a consistent approach is taken when lesions are biopsied in Primary Care. Local agreement and cooperation does improve patient care and I hope that this can be reflected in the guideline.	
4.3	JM	We support the drive in Scotland for rapid cancer diagnosis and treatment and suggest that the AMBLor test (AMBRA1 and loricrin dual antibody IHC) can support moves towards this aim. AMBLor is a novel dual antibody prognostic test for stratifying early-stage cutaneous melanoma into low risk and at-risk groups. The test is worthy of consideration in non-ulcerated AJCC stage 1A to 2B melanomas where stratification of risk of progression would be helpful and assist decision making with regard to more invasive/costly interventions. Ref: QPIs Melanoma -To ensure safe, effective and compassionate person-centred cancer care.	See response to this point in the general comments.
4.4	KB	Is skin cancer recognition part of the VTS? GPs should be encouraged to learn dermoscopy with the primary focus of screening out benign non-melanocytic lesions such as seborrhoeic keratosis.	This is out of scope for the guideline.
4.4/5	GK	Are very important for primary care. Perhaps a few points could be added to 4.4 with regards to what exactly this targeted education should include (videos, photos, magnification, booklets?)	Out of scope for this update.
4.5	SW	At the end of section 4.5 - biopsy of suspicious lesions, a statement appears about providing information to newly diagnosed patients. This appears mis-placed and should presumably appear in section 11 - provision of information?	We think it is important to highlight that patients should be provided with information at this stage. Section 11 provides more detail on what information should be shared. A reference to section 11 has been added to the good practice point.
	MFM	'Non-excisional biopsy may lead to inadequate histology' is probably not strong enough – it may give a false	Thank you for the comment. The guideline group disagree, and think what is stated is

		estimation of the Breslow depth of the tumour.	adequate.
	MMo	Last line - GPs should refer 'urgent suspicious of cancer' (to replace) 'urgently' all patients in whom melanoma is a strong possibility..... This would keep the SIGN guideline in line with Scottish skin cancer referral guidelines and government waiting time target data collection, 62 day data is only collected for suspected melanoma referred USC not urgent.	Good practice point changed to refer via the urgent suspected cancer (USC) cancer referral pathway.
	AA	The statement recommending an initial 2mm margin is not backed up by evidence. I agree that a definitive excision is best – ideally containing subcutis – a shallow layer would usually be enough. A “cuff” is an ambiguous term in my view. The initial peripheral margin can be individualised – up to 5mm is a good guide – this will adequately excise melanoma in situ in most cases and obviate the need for a re-excision so some flexibility is desirable in my view. I always try to predict the Breslow thickness – there are several publications on this. Taking only 2mm runs the risk of incomplete peripheral clearance which carries risk. Taking 3,4 or 5mm minimises the risk of incomplete clearance, may completely treat the melanomas in situ misdiagnosed as invasive melanoma and so remove the need for a re-excision and most importantly causes no harm. Acral lentignous melanoma – as for LM – role of initial scouting biopsies. Some GPs who have a special interest in skin cancer and links with the MDT eg in Highland and Grampian – can and do perform initial excision biopsy of suspected melanoma – there is no harm to patients and indeed possible benefit as excision is done quicker. SIGN guidance should reflect clinical practice in Scotland. There should be a section on the minimum clinical info on the path request form eg clinical dimensions, site etc.	Thank you for the comment. The consensus of the guideline group is that this is best practice for clinicians undertaking excision, and this is adequate, standard practice. The QPI has been removed. No action required. See previous comments.

			This requires a full evidence review, which was not part of this selective update.
	JS	Page 12 (4.5): Elliptical excisions should be performed along the long axis in the line of a natural skin crease or longitudinally in limbs. Suggest: 'Elliptical excisions should be orientated in the long axis of the natural skin crease'. No evidence that I am aware of or reason to place longitudinally in limbs. Page 16: 'A study of 140 patients with thick melanomas reported that the identification of lymphatic invasion was associated with an increased risk of metastasis but not with overall survival'. *Ref 88 suggests this is vascular invasion not lymphatic invasion.* Page 16: 'In the AJCC8 staging system the presence of satellites upstages the tumour to pN1C (assuming no regional nodal metastasis).83' *This is a repetition of second paragraph from in same subsection 4.7.6 on Page 15*	This was not part of the update and there is mixed opinions on the optimum orientation with no evidence to guide it, so it should not be changed. Amended, thank you Thank you. The repeated sentence has been removed.
4.7	GK	Recommendations in 4.7 are clear and important	Thank you
	AA	Please add a section on when PTx should be used in melanoma reporting – we have had some debate on this locally. Thanks.	In practice this is rarely used – the approach 'at least pT if only part of the melanoma is sampled' is preferred. Discussion of this issue, while interesting, is out of scope of this guideline.
4.7.8	MFM	Radial versus vertical growth phase- in the studies quoted have these tumours been correlated with their Breslow depth as well as growth phase. It is important to state explicitly that even though a tumour maybe in radial growth phase their management should be dictated by the Breslow depth as per AJCC/UICC 8 staging. Should the controversary surrounding management of atypical Spitz, STUMP etc be addressed?	This section has not been reviewed for this update.
4.7.10	JS	There is an adverse association between histological evidence of regression and outcome, but the strength of	The first sentence has been removed and the following sentence has been added:

		this relationship is disputed.78,79,90 *In my opinion the statement suggesting an adverse association cannot be made because the presented evidence suggests the relationship is not proven.* Page 19: 'Microscopic features which should be recorded • if parenchymal if deposits localised </=3 or multifocal >/=3' *? </ & >/ typo error* Page 20: 'Lentigo maligna, (variant of melanoma-in-situ), should also be surgically removed, given…..' *Suggest; 'Lentigo maligna, (variant of melanoma-in-situ)- given the risk of invasion, surgical excision should be offered to patients if their comorbid status permits surgical intervention'.* Page 20: Excision margin recommendations *Suggest addition of 'The clinical margin should be around the histological biopsy scar and take into account the primary melanoma margin'. This would be similar to the NICE guidance referenced 46*.	It is unclear whether histological evidence of regression is associated with adverse or favourable outcomes. Amended to localised ≤3 or multifocal >3 Text amended to provide a caveat on fitness for surgery. Whilst the updated NICE guideline states this, on deeper inspection of their analysis it is not clear the evidence base for this change. Whilst many agree, clinical practice varies here and there is no evidence to justify formally changing the guidelines to stipulate including the pathological margin. MelMart does not include the pathological margins.
4.7.11	CP	I believe all pT4b melanomas (and above) should be subject to BRAF/NRAS/CKIT testing. Currently the clinically relevant test is BRAF testing, however most laboratories in Scotland are introducing molecular testing that will allow all 3 to be tested for no additional expense. In the future when/if new therapeutic agents are introduced, it may be important to explore and/or validate such approaches using archival melanoma tissue with known mutation status. Molecular atlas studies have shown melanoma to be basically 3 types: BRAF, RAS, NF1 mutant or 'Triple Wildtype'. The more we understand molecularly about melanoma, the better we will manage this cancer in the future so if it is easy to do, I would recommend more rather than less molecular testing.	Added

	CM	In GGC we now perform BRAF/NRAS and ckit - please refer to oncologists if these need to now be mandatory Nationally and whilst these should be done on stage 111 and 1V - please note that patients with lower stages but high risk primaries may now be offered adjuvant therapy so this may need to be modified too.	Agree – IIB and IIC have been added.
4.8	CM	Add in EQA - ... (CPD) and EQA (external quality assurance) activity	Added to the good practice point.
	JM	Introduction of the AMBLor test may assist in relation to QPI3 - MDT meeting by providing personalised, prognostic information to support subsequent treatment decisions. In combination with appropriate patient information, 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 National Cancer Recovery plan and Remobilisation and Recovery of cancer services while supporting the 'Once for Scotland' approach. https://www.gov.scot/publications/scotlands-national-cancer-plan-report-progress-actions-31-august-2022/	See response to this point in the general comments.
	SR	Use of USG in evaluating non palpable lymph nodes is not mentioned. I am not advocating use of USG in this patient group, however it might be prudent to insert a paragraph to say why use of ultrasound and biopsy does not change the outcome (page 42/46 of NICE guidelines - https://www.nice.org.uk/guidance/ng14/resources/melanoma-assessment-and-management-pdf-1837271430853)	This is covered in section 8 under follow up imaging.
	CP	We need to await the outcome of the MelMart-II RCT to understand the benefit (or not) of 2 cm WLE versus 1 cm surgical margins. Unfortunately, this will not report for a number of years as it includes 7 years follow-up. In the meantime, the current guideline recommendation seems	Agree. No change needed.

		sensible and appropriate. The surgical margin at WLE should take into account the pathological margin shown to be clear in the primary excision. I agree with the statements and recommendation for SLNB and CLND. Where there are clinically palpable LNs, a histological diagnosis is needed (FNA or core biopsy) as this could be lymphoma rather than melanoma metastasis. Where an FNA/core biopsy fails (or is considered too technically difficult) refer for an US-guided core biopsy.	Whilst many agree, clinical practice varies here and there is no evidence to justify formally changing the guidelines to stipulate including the pathological margin. MelMart does not include the pathological margins. This is covered in section 5.3.1. The first good practice point has been amended to include ultrasound to make this clearer: If there is palpable lymphadenopathy FNAC should be used to obtain cytological confirmation of metastases, with ultrasound guidance if required.
	YM	No comment.	No action required.
	GK	Recommendations under this section provide a clear guidance and will be of help for the involved surgical teams	Thank you. No action required.
	GP	Thanks for asking me to review. On the whole I think they are very helpful and well laid out, but I wanted to make a couple of points/observations regarding the management of in-situ disease. Management of lentiginous in-situ disease in the head and neck area often requires a completely different approach than non-lentiginous in-situ disease on the trunk. Various cosmetic and functional factors need to be taken into account that can alter/reduce the clinical margin taken and I wonder if this could be stated more clearly in the guideline. The clinical margin of 0.5cm for in-situ disease is widely misinterpreted as patients requiring a 0.5cm wide local excision even though this is not suggested by the guidelines. Again a bit more clarity regarding this point could result in a reduction in patient morbidity and health	We agree that the nuances around the management and appropriate margins for in-situ disease are complex and widely debated. It was out with the scope of this limited review to formally review the literature on this.

		care costs associated with patients receiving procedures that are not recommended. Perhaps a position statement on histological clearance? I am happy to discuss further if needed.	
	MM	Page 25 - The first recommendation states "Sentinel lymph node biopsy should be considered as a staging technique in patients with IB-IIC melanoma with a Breslow thickness of ≥1mm." I wonder if this should be >1mm (greater than) rather than greater than or equal to for this statement, as the second recommendation listed on this page gives advice for melanomas of 0.8 to 1.0 mm.	Thank you for pointing this out. It should be greater than 1 mm, consistent with AJCC and NICE. This has been amended.
	LS	Information on SLNB might be better given by the surgeon rather than dermatologist as there can be conflicting views. Patients find a change in pathway very disconcerting. Potential diagnosis should not be given by GPs.	Thank you for the comment. Normal practice is the concept of SLNB is introduced at the first consultation post diagnosis (often in dermatology) and formal discussion and consent is undertaken by a surgeon fluent in the SLNB procedure. Hopefully these guidelines will clarify the cohort of patients in whom SLNB should be considered and minimise patient upset.
	KB	Also in point 4 - all patients suspected of having melanoma should have a full cutaneous examination (secondary care)	We agree that this is sensible suggestion, but is out with the scope of this evidence review and would not sit appropriately in section 5.
5.1	SW	In section 5.1, there is a brief comment on the management of lentigo maligna, stating that it should be surgically removed "given the risk of invasion". I wonder if this needs to be quantified and put into context, given that many of the patient population presenting with lentigo maligna are elderly, and that lesions are frequently large and in a head & neck site, therefore resection can be challenging and often incomplete. There is a cancer registry review on an Australian patient cohort (Menzies et al, Melanoma Research 2020; 30(2): 193-197) suggesting a 3.5% per annum risk, but an average time to transformation of approximately 28 years.	The risk of invasion refers not only to the rate of malignant transformation in true in-situ disease as outlines but also the rate of finding foci of invasion when the full lesion is examined histologically (range 5–67%). There is no consensus on either of these rates in the literature.

	MFM	Clarification is needed as to whether the excision margins are the total margin taken i.e. initial biopsy margin + wide local excision margin The last sentence of section 5.1 on page 20: "No evidence was identified on optimal timing of wide excision in patients with melanoma." This statement is incorrect. Surgery delayed by more than 3-5 months is associated with significantly increased melanoma-specific mortality, and more than 1 month with significantly increased overall mortality. Reference: Delays in the surgical treatment of melanoma are associated with worsened overall and melanoma-specific mortality: A population-based analysis J Am Acad Dermatol 2022	See response to comment CP on p18 above. Thank you for drawing our attention to this recent article. It was not part of the literature review for the specific topics investigated in this update, but it would seem sensible to remove the sentence as a result of this article.
	AA	"LM should also be surgically removed, given the risk of invasion" This is too strong a statement – the risk is very low – should be discussed in the guideline – circa 5% - often older frail people so active non-treatment is a legitimate management option +/- follow-up surveillance or use of imiquimod cream as a primary treatment. There are several new studies of the use of 5% imiquimod in primary LM – these should be summarised and referenced – the results are encouraging eg the study by Cliff Lawrence in 2019 (see attached) R I find the wording odd and too vague Mis – a 5mm peripheral margin is recommended (or 5-10mm) but "at least" is open to interpretation 10mm margin for stage 1 (not any more) Stage IIA and above – a 2cm wide radial margin is recommended – not any more "at least" is too vague and you may get people taking 3cm when no evidence.	See response to comment SW under section 5.1 above. The sentence has been amended to provide a caveat regarding fitness for surgery. Treatments for lentigo maligna and an evidence review were out with the scope of this restricted update. A full review of the surgical margins was outwith the scope of this restricted update. The recommendations are consistent with the recently updated NICE guidelines.

		There is evidence that excision of facia in scalp melanoma improves prognosis and reduces local recurrence – please look at this and summarise and reference it thanks. Please state that the clinical margin should be around the scar and take into account the clinical margin around the primary melanoma.	Please see response to comment CP under section 5 above.
5.2	AA	Worth stating that a stage IB with a –ve SLNB is then down-staged to a stage IA.	Thank you for pointing this out. While it changes the pathological staging it does not change the clinical staging.
5.3.1	JS	Page 23 (5.3.1): Management of palpable lymph nodes *Suggest addition of u/s guided FNAC or core biopsy.* Page 25, para 1 R: "Sentinel lymph node biopsy should be considered as a staging technique in patients with IB-IIC melanoma with a Breslow thickness of ≥1mm. *? typo. Suggest should be >1mm.* Page 24, Sentinel lymph node biopsy: *Suggest additional discussion of colloid only detection (no blue dye) and near-infrared fluorescence imaging.* *Refs:* *1)Systematic review and meta-analysis concerning near-infrared imaging with fluorescent agents to identify the sentinel lymph node in oncology patients* *B. Jeremiasse a , C.H. van den Bosch a , M.W.H.A. Wijnen a , C.E.J. Terwisscha van Scheltinga a , M.F. Fiocco b, c, d , A.F.W. van der Steeg. EJSO 46 2020 2011-20222) Isotope-Only Localization for Sentinel Lymph Node Biopsy - Medium-Term Oncological Outcomes Aikaterini Micha,1 Muhammad Asad Parvaiz,1,2 Liz O'Riordan,1,3 Fiona MacNeill,1 Jennifer E Rusby1,4.* *Clinical Breast Cancer, Vol. 22, No. 5, e636–e640* *3)* *A systematic review and meta-analyses of sentinel lymph*	We have updated the good practice point to include ultrasound guidance if needed. Thank you, this has been amended. Thank you for these references. An evidence review of the technical aspects of SLNB procedure was out with the scope of this restricted update- which was to review the criteria for SLNB.

		node identification in breast cancer and melanoma, a plea for tracer mapping *M.G.Niebling[ae]R.G.Pleijhuis[ae]E.Bastiaannet[bc]A.H.Brouwers[d]G.M.van Dam[a]H.J.Hoekstra[a]* *EJSO Volume 42, Issue 4, April 2016, Pages 466-473* Page 28 R – Consider adjuvant radiotherapy for patients with completely resected ……. *Suggest:* *R - adjuvant radiotherapy for patients with completely resected stage IIIB or IIIC melanoma should be offered with caution after discussion of the risk of local recurrence, the benefits and risks of adjuvant radiotherapy therapy including the risk of significant adverse effects. Adjuvant radiotherapy, in the setting of adjuvant immunotherapy and targeted therapy, has yet to be assessed.* Page 28: *Consider Roman numerals for all stage annotation for consistency with presented tables.* In a large multicentre RCT of adjuvant nivolumab versus ipilimumab nivolumab showed a significant improvement in RFS in patients with resected stage 3B–4 *stage IIIB to stage IV* disease (RFS at 4 years: 51.7% v 41.2%, HR 0.71, 95% CI 0.60 to 0.86).146 Adjuvant nivolumab is accepted for use by the SMC for patients with resected stage 3–4 *stage III to stage IV* disease. A large RCT of adjuvant pembrolizumab versus placebo showed a significant improvement in RFS in patients with resected stage 3A–3C *stage IIIA to stage IIIC* (HR 0.59, 95% CI 0.49 to 0.73) at 5 years. 147 Adjuvant pembrolizumab is accepted for use by the SMC for patients with resected stage 3 disease. Page 30: IIIA imaging *? typo* Ultrasound of nodal basin (if available) Every *every* 6 months for years 1–3 Annually for years 4–5 (if not	This is covered in Section 7.1 and has been revised to: Adjuvant radiotherapy for patients with completely resected stage IIIB or IIIC melanoma should not be routinely recommended. It may be considered following multidisciplinary team discussion in individual patients after discussion of the risk of local recurrence and the benefits and risk of adjuvant therapy including risk of significant adverse effects. This has been amended to use roman numerals throughout.

		having CLND and not having cross-sectional imaging follow up)	Resolved, thank you Duplication of every has been removed, thank you.
5.3.2	JM	Para States “Evidence identified in the NICE meta-analysis showed that melanomas with a Breslow thickness of ≤0.8 mm have a very low risk of positivity”. However, this does not mean no risk. AMBLor is a rule-out test for non - ulcerated AJCC stage 1 and 2A-B melanomas, to identify tumours at low risk of progression. This risk stratification could potentially offer personalised, prognostic information for clinicians and reduce pressure on healthcare systems Ref: Ellis et al. British Journal of Dermatology (2020) 182, pp156–165 Ref: QPIs Melanoma statement-"To ensure safe, effective and compassionate person-centred cancer care" Pg 25 - The recommendations for sentinel lymph node biopsy are clear. However, SLNB is not without its attendant complications, which are acknowledged in Section 5.3.2 - Para 3 ‘it is invasive, potential risks also need to be considered (e.g. allergic reaction to dye, nerve damage and lymphoedema). It should only be performed in patients at high risk of developing metastatic disease.’ The AMBLor test (AMBRA1 and loricrin dual antibody IHC) could aid stratification of early-stage non-ulcerated cutaneous melanomas for SLNB by identifying those at low risk of progression. Thereby potentially relieving these low-risk patients from the burden of SLNB and reducing unnecessary costs and risks to health economy.	See response to this point in the general comments.

	MFM	The title of this section doesn't emphasise the pivotal role SLNB has in the management of patients with melanomas eligible for the technique. In NICE NG14 SLNB was in a section entitled: Staging with Sentinel lymph node biopsy and imaging.	The subheading has been amended to "Staging with sentinel node biopsy", and the first sentence revised to: SLNB is a key staging procedure in patients considered at risk of occult metastases, potentially upstaging these patients and making them eligible for consideration of adjuvant treatments.
	AA	SLNB has been offered to stage 1A (pT1b - < 0.8mm but with ulceration and > 0.8mm – 1mm with or without ulceration or with LVI or mitotic rate >/= 2). The > 1mm thick reference is from 2001. What are the publications that prompted the change to 0.8mm cut-off? Again there are many important new refs and guidelines published in this area. It says that this section has been "completely revised" but apart from the NICE papers – which I do not think SIGN should reference as SIGN is supposed to do its own independent evidence assessment using the primary publications - the refs 120-130 are all very dated – 20 years+. Please update this – the UK consensus statement on the current role of SLNB from 2020 is a good starting point (H Peach et al. JPRAS 73; 36-42). A 10% risk of a +SLNB is a reasonable threshold. Use of a SLN metastasis risk calculator is helpful to aid the decision - https://www.melanomarisk.org.au/SNLForm Completion lymphadenectomy Please state the relative indications where this may be	SLNB has historically been offered to these patients but there has been a move away from this (accelerated due to practice changes induced by COVID). The NICE update excluded these pT1b <0.8 mm patients from access to SLNB. So as not exclude early stage melanomas entirely from SLNB we added the good practice point that allows such cases to be offered SLNB at the MDM's discretion. The group reviewed the evidence along with the recently published NICE updated analysis and were happy to accept this. The recommendations are in line with current accepted best practice. We agree and undertook a separate analysis (not undertaken by NICE) investigating the evidence for the use of the tools/risk calculators. We had hoped to be able to have a concrete recommendation about thresholds and tools but the evidence was not definitive. Hence the good practice point references above. We do not think there is a need to detail criteria where CLND might be considered. It is subject to MDT discussion and given there will usually be questions of patient fitness

		offered eg Dewar criteria – multifocal or extensive - size of micromet > 1mm,extracapsular spread >/= 3 involved sentinel nodes Lower threshold for H+N completion lymphadenectomy especially if adjuvant SACT contraindicated or regular follow-up not possible – these factors make recurrent head and neck nodal disease more likely and this can be difficult to manage.	and suitability for adjuvant treatment that is probably the best guidance. We are unaware of any published evidence suggesting that particular tumour features may be better with CLND than not.
	SR	I would encourage the use of CE-CT (Contrast enhanced CT), as head CTs can be performed without contrast and ambiguity to be avoided.	Agree, contrast has been added to the recommendation.
	CP	MRI is often (usually) a better imaging investigation for brain metastases. I presume it has not been recommended first line because MRI is not consistently available across the whole of Scotland. It would be good to introduce some flexibility into the current wording of 6.1.2. Such as, "Where the MDT and clinicians involved in delivering patient care believe that MRI Head would be more appropriate, this can be used first line." Consider imaging for Stage IIB melanoma.	The previous recommendations have been replaced with the good practice point: MRI should be considered for patients after discussion with the specialist multidisciplinary team (MDT). Clinical situations where MRI is generally considered include patients with indeterminate findings on CT or patients being considered for locoregional treatment of brain metastases in order to identify further lesions which may alter management.
	YM	No comment.	No action required.
	GP	No comment	No action required.
	MM	No comments	No action required.
	LS	It is hoped that adequate resources will be provided for further genetic research to guide treatment choices - or none where treatment would not be of value. While a decision not to treat may be heart breaking at the time, it will prevent coping with quite dreadful ADRs instead of enjoying quality time with family and friends. A new test has been developed but as yet not accepted for use, it assess the potential of stage 1 melanoma to metastasize, thereby potentially preventing the need for SLNB	Thank you for the comment, this is out of scope for the update.

6.1	AA	I do think and recommend that MRI brain should be considered as part of staging instead of CT brain in the following cases – Scalp primary, mitotic index > / = 5, children and young adults, and pregnant women Repeat staging should be done before adjuvant SACT if a delay > 8 weeks.	Indications for MRI brain have been updated in section 6.1.2 but we agree that there may be other clinical situations where this could be considered, and that this is a resource issue for Scotland. We agree that this is good practice. As it is already embedded as standard practice we do not think it needs to be included in the guideline.
6.1.1	GK	The recommendation would benefit from including exactly what areas the CT staging should include (H+C+A+P)	This is included in the good practice point below the recommendation.
	PL	PET CT has a higher sensitivity and specificity than CT. However it is correct that this may not result in improved outcomes. The comment that PET should only be offered in limited circumstances is misleading. If it is available, it is reasonable to use. If it is not available routinely for all patients, then CR is sufficient. It's an availability/resource issue. PET CT is superior for imaging intransit metastases on the limb treated as CT does not routinely image the limbs.	The indications for PET have been updated to include patients with in-transit disease on limbs.
	MMo	Page 26 - the wording in the Scottish melanoma fu guideline and this SIGN guideline are subtly different and lead to a potentially different action. Regarding neck CT, the melanoma focus guideline suggests as neck CT for all patients with a primary melanoma on the head or neck. Scottish melanoma fu guideline suggests neck CT if primary drainage of the melanoma is into the head and neck. Given the recent discussions we have had within SCAN, I prefer the melanoma focus stance. Page 26 - 2nd to last paragraph, remove the word 'melanoma' from the end.	The wording has been discussed and agreed by the Scottish melanoma follow up group and the preference of the SIGN group is to retain their recommendation. Removed.
6.1.2	PL	MR brain is superior to CT for detection of brain metastases. It also reduces radiation exposure. The only reasons to recommend CT over MRI are cost,	Thank you for the comment. We acknowledge the utility of MRI and that the reason for being unable to recommend it for all patients is access and capacity.

		convenience or if patient can't have MR (pacemaker, claustrophobia etc). MR be considered the standard of care.	
	SR	No comments.	No action required.
	YM	No comment.	No action required.
	GK	Points are clear	No action required.
	GP	No comment	No action required.
	MM	No comments	No action required.
	LS	Having begged SMC for these therapies, our experience is that the ADRs seem to be more common and worse than the pre SMC acceptance suggested. People do live longer - maybe around 5 - 10 years, PFS but it is not a normal life, nor normal life span. We hope that all ADRs, admissions, and long term effects are recorded and considered at regular intervals. Not all stage 2 & 3 died from lack of immunotherapy, nor progressed. Surveillance may be kinder and cheaper? PLEASE consider collection of sperm before treatment.	All adverse events from SACT are recorded and managed according to national agreed protocols within the oncology service to ensure that these drugs are delivered as safely as possible. This is standard so does not need to be included in the guideline. We also acknowledge that some patients choose not to proceed with adjuvant SACT due to concerns regarding toxicity. Sperm storage is discussed where clinically appropriate. This is not a common side effect with these therapies, so we don't think this needs to be added to the guideline.
7.1	CP	I would leave in this section on adjuvant radiotherapy. Although adjuvant immunotherapy is preferable in almost all situations, there will be cases where immune checkpoint inhibitors cannot be used (e.g., solid organ transplant recipients) and where there is a high risk of local or nodal relapse in a BRAF-negative melanoma. In these situations, adjuvant RT may be appropriate.	The recommendation has been revised to state that it is not recommended routinely but may be considered for individual patients following MDT discussion.
	PL	Adjuvant radiotherapy is not associated with a survival benefit and is associated with significant morbidity in the axilla and groin. The majority of local recurrences can be dealt with surgically and/or with systemic therapy. Adjuvant RT to axilla or groin is now very rarely used and should not be routinely considered as a treatment option. The statement should say that it is not recommended for the majority of patients.	The recommendation has been revised to state that it is not recommended routinely.

		This area is changing very quickly. Adjuvant pembrolizumab is now approved by EMA and NICE for resected Stage 2b and 2c melanoma, need to discuss this and comment on whether it is approved in Scotland. There are also emerging data on neoadjuvant and perioperative immunotherapy that are likely to change clinical practice in the next year. This is particularly relevant for adjuvant pembrolizuman. The SWOG 1801 presented at ESMO 2022 showed a major improvement in event free survival if 3 cycles of treatment were given before treatment. This does not change the indication for Stage 3, just a change in the timing of how the treatment is administered. Given that this does not change amount of drug given or risk of toxicity, but dramatically increases outcomes, this is likely to be accepted without a change in the license for the drug, in the same way that neoadjuvant therapy was accepted in breast cancer.	The SMC advice was published in April and has been included. We acknowledge the importance of the emerging data on neoadjuvant immunotherapy but the lack of published evidence at the time of the initial guideline search meant it was outwith the scope of this update.
	MN	Better to lay out by stage? This allows inclusion of dat on adj immunotherapy in stage II with NICE having approved Pembrolizumab in October 2022. SMC considers it in Feb 2023 meeting and most likely to be in favour given the positive results of clinical trials. Adjuvant radiotherapy can be mentioned but full paragraph not now necessary; perhaps state that since associated with morbidity but no improvement in time to relapse or overall survival, adj RT has been superceded by the improved systemic therapies. Definitely remove the recommendation.	We have amended the chapter heading to make it clearer what stages are included and restructured the recommendations to make the stage easier to read. The new SMC advice has been incorporated now. Other reviewers suggested retaining this section but revising the recommendation. The recommendation has been revised to say that it is not recommended routinely.
	MMo	I would suggest keeping this section as the R paragraph is very explanatory of the situation.	Thank you. The recommendation has been revised to state that it is not recommended routinely but may be useful in specific circumstances.
	AA	I think this should stay in as it is as adjuvant RT still has a role in individual cases after discussion at MDT.	Thank you. The recommendation has been revised to state that it is not recommended routinely but may be useful in specific circumstances.

7.2	MN	I understand the need to mention published data on single agent Ipilimumab but it is redundant as single agent Nivo and Pembro are approved. It is important to include the data (with recommendation) on the longer term benefit of adjuvant immunotherapy over targeted therapy in BRAF positive patients in view of the follow up in the clinical trial.	Thank you for your comment. We agree that single agent ipilimumab is now rarely used but given that it is still approved and recommended by SMC we plan to keep this section in. Thank you for your comment. We are unaware of any data where adjuvant immunotherapy and targeted therapy were directly compared.
7.3	MN	This section all belongs in section 3, surely?	This has been moved to section 3.5
	SR	In the foot note section - HCAP - may I suggest to use CE CT.	Thank you, this has been added.
	CP	Happy with the recommendations. They basically follow the recommendations of the SLWG which was recently discussed and debated at the Scottish Skin Cancer Annual Meeting prior to publication.	Thank you for your comment.
	YM	No comment.	No action required.
	GK	Points are clear. The recommendation on the holistic approach is highly relevant.	No action required.
	GP	No comment	No action required.
	MFM	Clarification of follow up and imaging required for Stage 1b tumours where a SLNB was considered but not done. Stage IIIa tumours with <1 mm SLN deposit justification needed for just us/s of draining basin as imaging follow up – variance from NICE NG14 and NCCN 2022 guidance.	Thank you for your comments. This will be discussed with the follow-up guidelines group. The SIGN guideline will be revised if the Follow up guidance is changed.
	MM	No comments	No action required.
	LS	Particularly in view of the lack of senior and junior grades, more CNSs, with advanced training are required. When we campaigned for CNSs, we hoped they would be available for advice, information and explanation of	Thank you for your comments. We agree that more CNSs are required.

		results. Instead they are undertaking tasks originally performed by doctors. While we are very glad of their support we recognise that many more are needed to provide the service envisaged to fill what we hope is a temporary gap.	
	MN	Why does follow-up come before stage IV disease is discussed? Is this because it is assumed that all metastatic patients will always be followed up by oncology? I think better to discuss all stages before the follow-up section.	Thank you, the structure has been amended so that follow up comes after the sections on treatment.
	AA	3-monthly FU for stage IA and IB is not realistic or evidence-based. The chance of recurrence is less than 1% in the first year. Less frequent FU in these very low risk groups will free up capacity to see higher risk patients. Patient self-exam should be encouraged and a rapid access route back to clinic if any concern / queries. I suggest 2 x 6-monthly appts for IA and 4-monthly with a 3 year FU for IB rather than 5 years.	Thank you for your comments. We'll feedback these suggestions to the working group that formulated the follow up guidelines.
8.1	JM	Page 30/31 – Follow-up Section 8.1 – table 10. Currently all AJCC stage 1 - 2B melanomas are followed up as shown in the table. We would submit that where the AMBLor test is utilised there may be an opportunity to offer both reassurance and reduced follow up in 20% of the stage 1-2B melanoma patients. The NPV of AMBLor demonstrates the test is very effective at identifying melanomas that are genuinely at low risk of progression (Ref: Ewen T, et al. Validation of AMBLor as a prognostic biomarker for non-ulcerated cutaneous AJCC stage I/II Melanoma. Presented at the 18th International Congress of the Society for Melanoma Research Congress. 28–31 October 2021. Pigment Cell Melanoma Res. 2022;35(1):97–184). We suggest that the test may provide support to the clinician in treatment planning.	Thank you for your comments. See previous response in earlier section.

		Page 31 – Section 8.1 Recommendations. Under the following recommendation which states 'Patients should have a holistic needs assessment at regular intervals during follow up to support their physical and mental wellbeing ', we suggest that the AMBLor test has a part to play in reassurance and therefore physical and mental wellbeing for some melanoma sufferers and may in some part aid the rationalisation of the workload of Cancer Nurse Specialists for Melanoma. As identified in the National Cancer Plan -Progress report Action 49- enhance the cancer nurse specialist role.	
9.1	MN	I think you should take out 'recent years' as it dates easily.....	Recent years has been removed.
9.2	MN	References for surgery in stage IV ie metastasectomy are from 1994-2000 and really are redundant as systemic treatments have improved. I think this should be removed. The exception is for isolated, accessible brain metastases. Treatment of brain metastases covered in 9.6.4; metastasectomy section should cross reference to this section. References should be updated to include 2020 and 2021 papers.	Thank you for your suggestion. This section has been removed.
9.3	SR	No comment.	No action required.
	CP	I agree with the recommendations made.	No action required.
	YM	No comment.	No action required.
	GK	This section highlights the importance of MDT in the management of these cases; no case should, ideally, be managed without MDT discussions.	Thank you for your comment.
	GP	No comment	No action required.
	MM	No comments	No action required.
	MN	Again, inclusion of 'novel' dates the guidance; immunotherapy has been available since 2011! Also, my comment above re giving detail on single agent Ipilimumab pertains - we don't give that so of historical interest only and better to concentrate on the randomised	The language in this section has been changed to reflect that these treatments are no longer novel. (now section 8.2) We accept that ipilimumab is rarely used as a single agent but it is difficult to remove from the guideline completely as it

		trials that clearly demonstrate superiority of combination - and of single agent Nivo over single agent Ipi. Mention immunotherapy less effective on patients who are on steroids before IO start; iimportant practice point. Mention better toxicity profile (and therefore compliance) of Enco and Bini over Dab and Tram? Mention need for careful monitoring of LVEF with regular (3-monthly) ECHO?	is still licensed and accepted for use by SMC. It is also used as a comparator in studies. We agree that there are some important clinical factors that can be associated with lower chance of response to immunotherapy but a detailed review of this was outwith the scope of the selective update. We are not aware of any data that directly compares different BRAF/MEK inhibitor combinations LVEF is one of a number of things that require monitoring and the group feel that to cover them all would be too detailed and therefore out of scope for the guideline.
	LS	At this stage patients will grasp at any straw particularly those who are parents or carers. A real understanding of the potential ADRs will not dissuade many but with good guidance they will be able to prepare better than often currently. Again help from further genetic research to advise on potential benefits is required.	Thank you for your comments.
9.4	SW	Section 9.4 - ILP: ILP is not available in Scotland, is a more significant surgical undertaking and has a considerable adverse effect profile when compared to treatments such as laser ablation or electrochemotherapy - I wonder if the ILP section would be better moved to the end of the section on palliative techniques e.g. ECT, laser, ILP.	This section has been removed.
	MN	Isolated prefusion is no longer available in Scotland, and certainly not in the adjuvant setting.	This section has been removed.
	AA	As far as I know – this is not done anywhere in Scotland so odd that it is in a Scottish guideline. It should be stated that patients would have to travel to England for this. Where is the nearest centre?	This section has been removed.
9.5.1	SW	Carbon dioxide laser ablation - CO2 laser is not the only ablative laser modality that is useful. Tayside use Er:YAG and CO2 laser. Should this section be changed simply to	Thank you for your response, the changes have been made. (now section 8.3)

		'laser ablation' without mentioning a specific type of laser, and perhaps adding the caveat that "laser ablation should be undertaken in a specialist setting by clinicians with experience of the technique and who are in a position to undertake appropriate post-treatment care or offer alternative treatments if laser ablation is not appropriate".	
9.5.2	SW	ECT is not technically an 'ablative' therapy as it does not immediately destroy the metastatic lesion - perhaps it would be better under its own heading rather than as an ablative therapy? I do not agree with the wording of the recommendation on Electrochemotherapy, in particular the line "when other treatment options have been exhausted". In my experience, this position results in patients only being referred for ECT as a last resort when the disease is out of control or with large bulky lesions. ECT is less likely to be effective in such situations and therefore the patient has missed the potential effect of ECT at an earlier stage. ECT can be useful as part of a combined treatment approach for patients on SACT. Although much of the evidence surrounding ECT is of poor quality, studies have suggested some predictors of response to ECT - metastatic deposits <3cm in size, <20 in number, and limb location (see Campana et al, Br J Surg 2012; 99:821. Could the ECT statement read: Electrochemotherapy should be considered as a treatment option for patients with cutaneous melanoma metastases after MDT discussion and careful consideration of treatment options. Electrochemotherapy can be combined with other anti-cancer therapies, is repeatable and has a low risk profile when compared to other palliative therapies such as ILP.	This has been given its own heading, under section 9.4 ‘when other treatment options have been exhausted’ has been removed from the recommendation.
9.6.2	MN	Need to be specific that RT to bone mets is for attempted palliation of pain ie update recommendation	This has been added to the recommendation. (now section 8.5.2)

9.6.4	PL	This section needs to be revised as the information is inaccurate and does not reflect the modern management of brain metastases. Important points to include are • Patients with brain metastases potentially suitable for treatment should be discussed with neuro-oncology MDT • Stereotactic radiosurgery is not experimental (as written), it is a standard of care given with curative intent. There are agreed criteria for number/volume of metastases. However all cases need to be discussed by neuro-oncology MDT as other factors are also relevant – presence of visceral disease, treatment options for systemic disease. • The outcomes for surgery and SRS are similar and the choice of treatment depends on a number of factors including need for histological confirmation, site of disease, patient fitness etc. • SRS may be indicated after incomplete resection of brain metastases, • For patients with asymptomatic brain metastases not requiring steroids, combination immunotherapy with ipilimumab and nivolumab has similar response rate, PFS and OS to those without brain metastases and should be considered as treatment for these patients. The optimum way to deliver has not yet been shown e.g. upfront concurrent SRS and IO or give 2 cycles of IO and reassess, then add SRS if not responding. • Immunotherapy can be given concurrently with SRS. There is evidence of a higher response rate but also higher risk of radiation necrosis.	(now section 8.5.4) Thank you for the comments. A review of the evidence for this section was not included in the scope of this update, however, we have removed the sentence stating that it is experimental and amended the recommendation to include a good practice point that stereotactic radiotherapy should be considered for patients when surgery is not possible.

		• Targeted therapy is associated with high response rate in patients with brain metastases from BRAF mutated melanoma. However the median PFS is only 6 months. Therefore immunotherapy is the preferred option for patients with asymptomatic disease not requiring steroids. • There is little benefit from whole brain radiotherapy and it should not routinely be offered.	
	MMo	Page 37 - last paragraph, insert 'be'. should be tested.	Amended, thank you.