



Australian Government
Medical Services Advisory Committee

Public Summary Document

Application No. 1485.1 – Sentinel Lymph Node Biopsy for intermediate thickness melanoma

Applicant: The Australian Society of Specialist General Surgeons

Date of MSAC consideration: MSAC 78th Meeting, 3 April 2020

Context for decision: MSAC makes its advice in accordance with its Terms of Reference, [visit the MSAC website](#)

1. Purpose of application

A resubmission requesting Medicare Benefits Schedule (MBS) listing for sentinel lymph node biopsy (SLNBx) in patients with primary melanomas ≥ 1.0 mm Breslow thickness, or those ≥ 0.8 mm with high-risk features (e.g. ulceration), was received from the Australian Society of Specialist General Surgeons by the Department of Health.

2. MSAC's advice to the Minister

After considering the strength of the available evidence in relation to its safety, clinical effectiveness and cost-effectiveness, MSAC supported public funding for sentinel lymph node biopsy (SLNBx) in patients with primary melanomas ≥ 1.0 mm Breslow thickness, or those ≥ 0.8 mm with high-risk features on the basis that, compared to wide local excision (WLE) plus follow-up, SLNBx provides important prognostic information, allows for improved local disease control, and provides for more effective selection of patients for adjuvant therapy.

The MSAC-supported descriptor reflected the advice of the MSAC-initiated stakeholder meeting:

SENTINEL LYMPH NODE BIOPSY OR BIOPSIES for cutaneous melanoma, where the primary lesion is greater than 1.0 mm in depth (or at least 0.8 mm in depth in the presence of ulceration), and appropriate excision of the primary melanoma has occurred, using preoperative lymphoscintigraphy and lymphotropic dye injection.

Limit to one lesion per patient per occasion.

Consumer summary

The Australian Society of Specialist General Surgeons applied for public funding through the Medicare Benefits Schedule (MBS) for sentinel lymph node biopsy (SLNBx) for patients with a certain type of skin cancer. The Society also asked for a fee increase for a new MBS item that is specific for SLNBx, compared with the non-specific MBS items that are used now.

Melanoma is a skin cancer in the skin pigment cells (melanocytes). Most patients are diagnosed at an early stage by looking at the lesion (skin damage) caused by the melanoma. The thickness of the lesion is important. The thinner the melanoma, the more chance the patient has of recovery. Also, the further the melanoma cells spread beyond the lesion, the harder the melanoma is to treat.

SLNBx is done to find out whether any melanoma cells have spread to the lymph nodes nearest the site of the original melanoma lesion. If so, they are called sentinel lymph nodes. Lymph nodes filter fluids from within the body and are where you find white blood cells that circulate through the body/bloodstream to help fight cancer and infections. If cancer cells reach the nearby lymph nodes, they can more easily spread further in the body.

The SLNBx procedure involves two steps. First, radioactive dye is injected around the site of the original melanoma so a camera can find the nearest lymph nodes: this is called lymphatic mapping. Second, these lymph nodes are then removed and examined under a microscope for evidence of melanoma cells.

MSAC considered that, because of new treatments available to treat some types of melanoma, it is important for SLNBx to be available to some patients with melanoma. This will help to determine sooner which patients will benefit from these treatments. The evidence shows that, when used in the right patients, there is an overall benefit to using SLNBx compared with other procedures.

MSAC's advice to the Commonwealth Minister for Health

MSAC supported the funding of a new MBS item for SLNBx in patients who have high-risk melanomas. MSAC considered that SLNBx is safe, clinically effective and cost-effective.

3. Summary of consideration and rationale for MSAC's advice

MSAC noted that this resubmission sought to address the July 2018 MSAC meeting request for further clarification of the patient selection criteria for adjuvant therapy of melanoma and the role of SLNBx in this patient selection.

MSAC noted that there has been no new direct evidence since the original application, but 22 studies were included in the resubmission as linked evidence.

MSAC noted that SLNBx is already being performed and is relatively safe, with the reported risk of adverse events being similar between wide local excision (WLE) with SLNBx versus WLE alone. However, given that SLNBx is an additional surgical procedure, doing SLNBx in addition to WLE means that there is an additional risk of adverse events compared with WLE alone.

MSAC recalled that clinical practice had changed after the initial submission because a recent study (MSLT-II) showed that there is no survival benefit for complete lymph node dissection (CLND) after a positive SLNBx. MSAC accepted the revised clinical claim for the application – that SLNBx would allow effective treatment selection by helping determine which patients are eligible for newly approved adjuvant therapies.

MSAC noted that nivolumab is now PBS-listed for patients with Stage IIIB, Stage IIIC or Stage IIID melanoma, as well as dabrafenib and trametinib for patients who are also *BRAF*-positive. Nivolumab was PBS-listed for this indication on 1 March 2020, so any SLNBx-positive patient who is diagnosed with Stage IIIB, Stage IIIC or Stage IIID melanoma could be offered this adjuvant therapy. MSAC considered this to be important because these adjuvant therapies have been demonstrated to improve cancer outcomes. However, MSAC considered that not all patients who will receive SLNBx would be eligible for adjuvant therapies on the PBS because the main purpose of SLNBx would be to help determine which of these patients have Stage IIIB, Stage IIIC or Stage IIID melanoma by identifying micrometastases in the sentinel lymph node(s) not identified clinically.

MSAC noted that these new treatments were not included in the simplified economic model presented. MSAC also agreed with ESC that the estimates of effectiveness in identifying which SLNBx-eligible patients would also be eligible for adjuvant therapy used in the base-case model (15% in SLNBx arm vs. 3.34% in WLE plus follow-up arm) were in the range that might be expected. Thus, MSAC accepted the inferred increased diagnostic yield of patients eligible for adjuvant therapy. MSAC also considered that PBAC's acceptance of the cost-effectiveness of these treatments supported the clinical utility of SLNBx for subsequent treatment planning. MSAC therefore considered overall that SLNBx was acceptably cost-effective compared with WLE plus follow-up with an incremental cost of about \$29,000 per extra patient eligible for adjuvant therapy.

Overall, MSAC supported SLNBx mostly as a staging procedure because there is relatively little direct therapeutic value associated with it. Given the basis of the PBAC's recommendations about which Stage III patients should be eligible for adjuvant therapy, reference to SLNBx results to inform the staging assessment will allow the selection of patients who will most benefit from this therapy. However, subsequent access to adjuvant therapy is also predicated on the patient having had a resected primary lesion.

MSAC also considered that SLNBx provides important prognostic information and allows for improved local disease control.

MSAC noted that the financial estimates are likely to be an underestimate. Both the original application and the resubmission used a utilisation rate of 49.8% from van der Ploeg (2014). Since this data related to an older population and the guidelines have changed, this rate may now be much higher. In addition, the proportion of patients with more than one affected basin is more likely to be 20% as used in the sensitivity analysis rather than 0% as used in the base case calculations, which would increase the eligible rebate for these patients. However, the cost to the Medicare Benefits Schedule (MBS) would still be modest, with the total cost to the MBS estimated to be about \$641,000 in Year 1 rising to \$696,000 in Year 5 and an estimated 5-year cost of approximately \$3.3 million.

MSAC noted that SLNBx for melanoma is already being performed in Australia, but this procedure and the MBS items used (30075, 30329, 30332, 31420, and 31423) are general and not specific for melanoma. MSAC considered a separate MBS item for SLNBx in melanoma would facilitate collection of more informative utilisation data. A predicted versus actual

utilisation review should be conducted at two years, or earlier if coordinated with a Drug Utilisation Sub-Committee review of the adjuvant therapies.

MSAC noted that the applicant did not raise any issues in its pre-MSAC response, and that there was mixed support in the public consultation feedback.

MSAC supported the proposed fee increase for the new MBS item beyond the existing non-specific items to reflect benchmarking to the existing MBS item for breast SLNBx, and considered that the item should be restricted to specialist providers only that the multiple operations rule should apply, and that there should be no co-claiming of this item with existing general surgical items. MSAC noted that whether a patient is admitted as an in-patient is subject to clinical judgement, and concluded that the procedure should continue to be classified as Type A.

4. Background

This is the first resubmission of Application 1485.

At its July 2018 meeting, MSAC did not accept the rationale for a fee increase for a SLNBx-specific MBS item, compared to the current non-specific MBS items under which this service is currently being claimed, since there was insufficient evidence of a difference in patient health outcomes or clinical management as a consequence of using SLNBx compared to not using it. MSAC deferred its advice to request further clarification of the patient selection criteria for adjuvant treatment of melanoma and the role of SLNBx in selecting patients for such treatment (p1, [Public Summary Document \[PSD\] Application No. 1485](#), July 2018).

Following this, a stakeholder meeting including members of MSAC, clinicians with experience and expertise in clinical oncology, pathology, dermatology and clinical genetics, representatives of the applicant, consumers and Department of Health was held in November 2018 ([Stakeholder Meeting Minutes – Final](#), Sentinel lymph node biopsy for intermediate and thick melanoma 2018).

The resubmission was informed by a department-contracted assessment report (DCAR), which provided (Table 1) a detailed summary of previous MSAC issues from the previous submission (1485) and how they were addressed for the resubmission (Application 1485.1).

Table 1: Summary of MSAC's recommendations from MSAC 1485, and approach used for the resubmission

MSAC issues/recommendations from 1485	How these have been addressed for 1485.1
<p>Evidence assessing a difference in patient health outcomes or clinical management as a consequence of using SLNBx compared to not using it.</p> <p>MSAC deferred its advice to request further clarification of the patient selection criteria for adjuvant treatment of melanoma and the role of SLNBx in selecting patients for such treatment (p1, 1485 PSD). See Stakeholder Meeting Minutes below.</p>	<p>Clinical utility of SLNBx was determined to be identification of patients eligible for adjuvant therapy listed on the PBS. Treatment with adjuvant therapy improves overall and relapse-free survival of patients with Stage III melanoma.</p> <p>In response to the MSAC's request for further clarification of the patient selection criteria for adjuvant treatment of melanoma and the role of SLNBx in selecting patients for such treatment (p1, 1485 PSD), the following were notes in relation to patients with Stage III melanoma:</p> <p>PBS-subsidised patients must have resected Stage IIIB, IIIC or IIID melanoma.</p> <p>With regard to this requirement for patients to have Stage IIIB, IIIC and IIID melanoma, SLNBx plays a key role in accurately staging melanoma in this population of patients. Specifically:</p> <p>According to the American Joint Committee on Cancer (AJCC) 8th edition melanoma staging criteria, SLNBx is used to determine the presence or absence of lymph node involvement in patients who</p>

MSAC issues/recommendations from 1485	How these have been addressed for 1485.1
	do not have clinically apparent metastasis, in order to accurately determine the stage of melanoma (Gershenwald et al. 2017). Current Australian guidelines recommend SLNBx to be considered for all patients with melanoma greater than 1 mm in thickness and for patients with melanoma greater than 0.75 mm with other high-risk pathological features to provide optimal staging and prognostic information and to maximise management options for patients who are node-positive (Gyorki et al. 2017).
MSAC considered that the multiple operations rule should apply if more than one item is required for one episode of care (p2, 1485 PSD).	The applicant recommends the multiple operations rule be applied to reflect that a proportion of patients have drainage to two (2) or more nodal basins.
MSAC suggested that consideration be given to limiting the procedure to centres with appropriate expertise (p2, 1485 PSD).	In the original application, as well as the resubmission, it has been recommended that proceduralists be trained specifically to undertake SLNBx for melanoma. This is analogous to SLNBx in breast cancer where a minimum of 20 cases are recommended to acquire appropriate skills. Proceduralists who already perform SLNBx in breast cancer do not require further training as the skills are transferable. Similar to breast cancer, an increasing number of melanoma patients around Australia are discussed within a multidisciplinary clinic and this improves the quality of decision-making and also service. The application fully supports the local development of melanoma multidisciplinary discussions. Finally, it is recommended that a combination of blue dye and radioisotope be used for this procedure.
MSAC noted, however, that clinical practice has changed following these trials, and CLND is no longer considered standard treatment after a positive SLNBx (p2, 1485 PSD).	Clinical utility of SLNBx (relative to comparator) is now framed in relation to access to PBS-subsidised adjuvant therapy, which is informed by diagnostic performance of SLNBx.
Availability of, and eligibility criteria for, adjuvant therapies on the PBS (p1, 1485 PSD).	As of 1 March 2020, both nivolumab and the combination of dabrafenib and trametinib are listed on the PBS for patients with resected Stage IIIB, IIIC or IIID melanoma (the combination is further restricted to <i>BRAF</i> -positive patients). Other immunotherapy-based options have been submitted for PBAC consideration, but not recommended.
Applicability of effectiveness outcomes in adjuvant therapy trials for patients with a positive SLNBx (e.g. patients entering trials were not selected on the basis of SLNBx results). If SLNBx results were to be used to assess eligibility of patients for adjuvant therapy in practice, MSAC recommended establishing risk equivalence criteria (p3, 1485 PSD). See Stakeholder Meeting Minutes below.	Only patients with Stage IIIB, IIIC or IIID melanoma were considered eligible for adjuvant therapy. Melanoma-specific survival curves for Stage III subgroups (IIIA, IIIB, IIIC and IIID) were presented in clinical validity section. The proportion of patients in each subgroup was estimated for the base case using Australian data presented by Haydu et al. 2017.
Economic issues (p3, 1485 PSD): Underestimated follow-up costs in the model (e.g. proportion modelled for follow up with specialists) Out-of-pocket costs and Medicare Safety not explored	Follow-up cost: Addressed. It was assumed that all patients with a positive SLNBx would receive specialist follow-up, and the frequency of follow-up was determined based on Faries et al. 2017. This is also aligned with Australian guidelines. Out-of-pocket costs: Not addressed.
Highly uncertain financial estimates (p3, 1485 PSD): Cost of SLNBx from current data Extent of cost offsets	Improved data on current and likely utilisation is impossible with current MBS descriptors. Not addressed

PBS = Pharmaceutical Benefits Scheme; SLNBx = sentinel lymph node biopsy
Source: Table 11, pp31-32 of the DCAR

Stakeholder meeting

Following the MSAC July 2018 meeting, a stakeholder meeting including members of MSAC, clinicians with experience and expertise in clinical oncology, pathology, dermatology and clinical genetics, representatives of the applicant, consumers and Department of Health was held in November 2018 (Stakeholder Meeting Minutes – Final, Sentinel lymph node biopsy for intermediate and thick melanoma 2018). The DCAR summarised this for Table 2.

Table 2: Summary of Stakeholder Meeting Minutes from MSAC 1485, and approach used for the resubmission

Minutes issues/recommendations based on 1485	How these have been addressed for 1485.1
Guidelines recommendations for SLNB	The indication for the resubmission was broadened to all melanoma greater than 1 mm thick, and melanoma at least 0.8 mm thick in the presence of ulceration as this was consistent with Australian and international guidelines.
Pathology: advice on method (immunohistochemistry or polymerase chain reaction [PCR]) of assessment of lymph nodes and the definition of positive (for each method)	Not addressed. SLNBx positivity was taken from the MLST-I trial (15.84%), which used immunohistochemically analysis (Morton et al. 2006).
Access, equity and education issues	The relevance of SLNBx in clinical management has changed because a positive SLNBx will now inform suitability for PBS-subsidised adjuvant therapy for some patients.
MBS item descriptor and proposed fee	The applicant suggested that the fee for melanoma SLNBx be equivalent to the fee for breast SLNBx. This was despite melanoma patients being more likely to have multiple sentinel nodes within a nodal basin than breast cancer patients. The applicant also expressed a preference for simplification of the MBS item(s) by not tying them to specific sites. SLNBx of the groin is potentially (but not always technically) simpler than other areas, however the aftercare following biopsy is often more involved. Similarly, within the neck, some areas are straightforward and others more technically complex. Finally, site-specific numbers do not take into account atypical nodal sites, for example, popliteal, epitrochlear, and scapular regions. The applicant would be willing to negotiate on this.
Risk equivalence	Only patients with Stage IIIB, IIIC and IIID melanoma would be considered eligible for PBS-subsidised adjuvant therapy. Melanoma-specific survival curves for Stage III subgroups (IIIA, IIIB, IIIC and IIID) were presented in the clinical validity section. The proportion of patients in each subgroup was estimated for the base case using Australian data presented by Haydu et al. 2017.
Trigger for access to adjuvant therapy	Sentinel nodes status is now a guide for adjuvant treatment. Patients who are determined to have Stage IIIB, IIIC or IIID melanoma would be eligible for PBS-subsidised adjuvant therapy. A negative sentinel node is a positive prognostic sign and thus patients intuitively require less intensive follow-up. There is a paucity of research in the area of melanoma follow-up and guidelines generally defer to expert opinion.

SLNBx = sentinel lymph node biopsy

Source: extended from Table 12, pp32-33 of the DCAR

5. Prerequisites to implementation of any funding advice

SLNBx for melanoma is already being claimed on the MBS.

6. Proposal for public funding

The proposed MBS item descriptor is summarised in Table 3.

Table 3: Proposed MBS item descriptor

Category 3 – Treatment of Malignant Melanoma and Locally Aggressive Skin Tumours
SENTINEL LYMPH NODE BIOPSY OR BIOPSIES for cutaneous melanoma, where the primary lesion is greater than 1.0 mm in depth (or at least 0.8 mm in depth in the presence of ulceration), and appropriate excision of the primary melanoma has occurred, using preoperative lymphoscintigraphy and lymphotropic dye injection.
Limit of one lesion per patient per occasion*
(Anaes.) (Assist.)
Fee: \$637.45 Benefit: 75% = \$478.00 85% = \$541.75

* The applicant recommended that the multiple operations rule be applicable in the situation of more than one lymph node basin being sampled

In its pre-ESC response, the applicant stated the proposed fee should be aligned with the existing MBS fee for SLNBx for breast cancer (MBS item 30299; \$647.65).

7. Summary of public consultation feedback/consumer issues

Targeted consultation was received from several sources:

- Two professional medical organisations and a patient support group provided supportive letters
- Two professional medical organisations did not support the resubmission for the following reasons:
 - SLNBx provided some limited information on prognosis, albeit not sensitive or accurate for most patients. This feedback also considered that the technique has been identified consistently over decades as a poor-quality test which causes patient harm. Furthermore, they raised concerns with the use of SLNBx as a gatekeeper to the current biological trial agents
 - SLNBx provides added prognostic advice that can be obtained more cheaply with less invasive methods. Further, this feedback highlighted that there are many concerns raised for SLNBx in the published literature
- One specialist did not support the resubmission as they considered that SLNBx had no therapeutic benefit, but rather is a prognostic test marginally better in some instances than Breslow thickness/ulceration – though this is disputed by many experts.

8. Proposed intervention's place in clinical management

Description of proposed intervention

The proposed medical service is SLNBx, in addition to wide local incision (WLE) of lymph node(s) identified by a combination of lymphoscintigraphy/gamma probe and blue dye (lymphotropic dye injection). The DCAR stated that SLNBx can identify micrometastases in sentinel lymph node(s) that cannot be identified by clinical examination.

SLNBx for melanoma is already being performed in Australia, but this procedure and the item numbers used (MBS 30075, 30329, 30332, 31420, 31423) are not coded on the MBS for melanoma.

Description of medical condition(s)

The proposed population for SLNBx is all patients with malignant cutaneous melanoma greater than 1 mm in depth (or at least 0.8 mm depth in the presence of ulceration). SLNBx is not indicated in patients with established lymph node involvement or distant metastases.

Place in clinical management

As the intervention is already widely used, the clinical management algorithm is the same for both current management and proposed management (Figure 1).

The clinical management algorithm presented by the applicant was similar to the previous consideration, with modifications to include melanoma >0.8 mm with ulceration and an option for PBS-subsidised adjuvant therapies. The proposed algorithm was somewhat simplistic and was modified in the DCAR (Figure 1). This figure does not specify how patients receiving therapeutic complete lymph node dissection (CLND) are then determined to be eligible for adjuvant therapy or surveillance, including by reference to Stage III sub-categories.

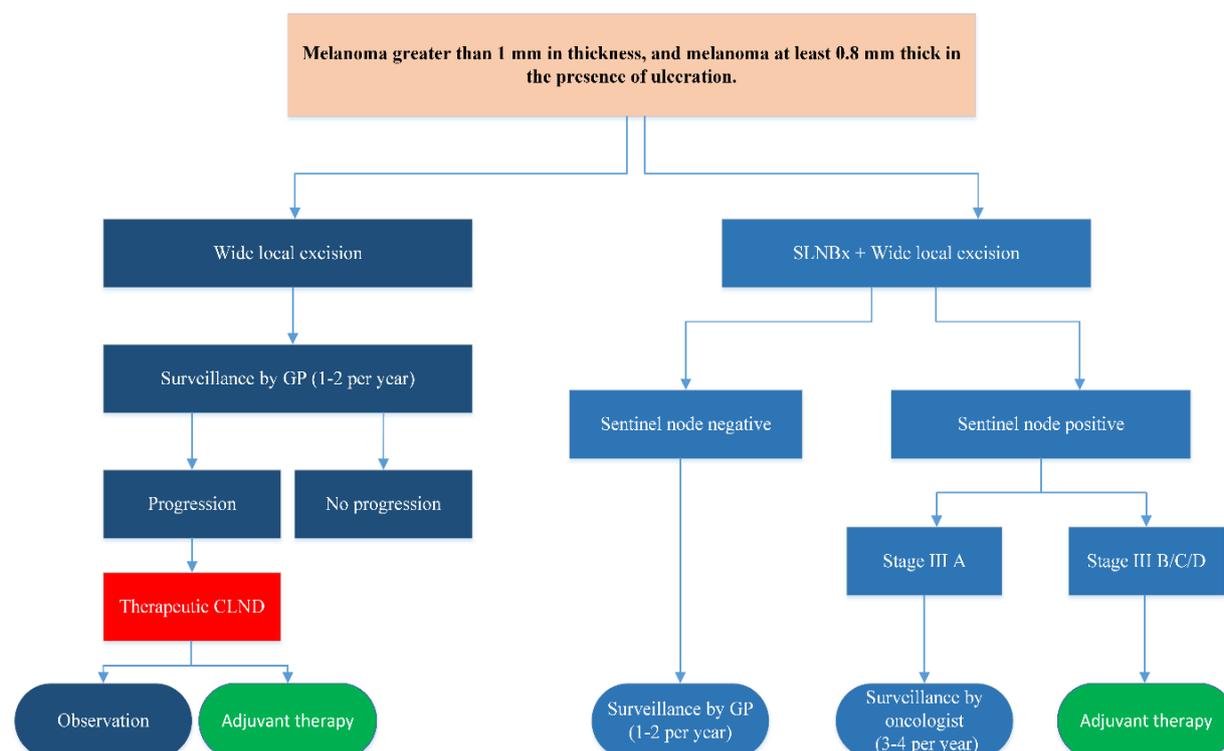


Figure 1: Clinical management algorithm of SLNBx relative to current clinical practice

CLND = complete lymph node dissection; GP = general practitioner; SLNBx = sentinel lymph node biopsy

Source: modified from the previous DCAR

The applicant noted that the clinical management algorithm for cutaneous melanoma has changed since the results of MSLT-II were published. Previously, all patients who were SLNBx positive underwent immediate CLND. Due to lack of survival benefits for CLND based on results of the MSLT-II trial, now CLND is no longer recommended for patients with positive SLNBx results. More recently, in light of the emerging role of adjuvant therapy in melanoma management and associated benefits for survival and recurrence free survival, it is becoming important to stratify patients including with reference to the information retrieved from SLNBx (Verver et al. 2018).

9. Comparator

The comparator for SLNBx remained WLE plus follow-up (i.e. surveillance), where follow-up includes regular observation and surveillance for disease progression. Generally, clinical surveillance of the regional lymph nodes is performed by the General Practitioner (1-2 per year). If patients develop clinical or imaging evidence of nodal melanoma during follow-up

(approximately 20% of patients), a therapeutic lymph node dissection is offered to those patients, providing no distant metastases have been detected.

10. Comparative safety

No new studies were identified on direct evidence; the DCAR used a linked evidence approach. Of the eligible studies, one study (that was presented in Application 1485) provided evidence on diagnostic performance, two new studies on clinical validity, two new studies on clinical utility, and 17 studies on safety of SLNBx (without CLND) that was presented in Application 1485 (Table 4).

Table 4: Key features of the linked evidence

Type of evidence	Description	Number of studies used	Number of patients (n) in each study
Diagnostic performance of SLNBx	The diagnostic performance of SLNBx is relevant to the proportion of patients undergoing SLNBx who are shown to have Stage IIIB, IIIC or IIID melanoma, and who would then be eligible for PBS-subsidised adjuvant therapy.	1 study	Morton et al. 2014 (from MSLT-I): Intermediate thickness melanoma (1.2-3.5 mm), n=1270 Thick melanoma (>3.5 mm), n=290
Clinical validity of SLNBx	Proportion of patients identified by SLNBx as being eligible for PBS-subsidised adjuvant therapy in Australian population.	2 studies	Haydu et al. 2017, n=4,540; Gershenwald et al. 2017, n>46,000
Clinical utility of SLNBx and impact on patient management and health outcomes	SLNBx results inform subsequent treatment and management of patients, including those who may benefit from adjuvant therapy and frequency of follow up.	2 studies	COMBI-AD trial by Long et al. 2017, dabrafenib plus trametinib n=438, placebo n=432; CA238 trial by Weber et al. 2017, nivolumab n=453, placebo n=453
Impact of repeat testing (if appropriate)	It is likely that patients who are SLNBx positive would receive additional monitoring (specialist follow-up three times per year).	1 study	Faries et al. 2017, n=931
Relative safety of SLNBx	The overall safety profile of SLNBx (without CLND) was similar to that of WLE.	17 studies	Study details are provided in Table 24 (p56) of the DCAR

CLND = complete lymph node dissection; PBS = Pharmaceutical Benefits Scheme; SLNBx = sentinel lymph node biopsy; WLE = wide local excision

Source: Table 2, p19 of the DCAR

Overall, the DCAR stated that rates of adverse events were similar following WLE (18.9%) and SLNBx alone (4.6-13.8%) (p5, 1485 PSD). ESC previously indicated that SLNBx appears to be a relatively safe procedure. However, since it involves an additional surgical procedure, it is implausible that SLNBx plus WLE can be “as safe” as WLE. (p8, 1485 PSD).

11. Comparative effectiveness

Linked evidence

The DCAR identified no direct trial evidence for role of SLNBx in risk stratification and access to adjuvant drug therapy, a linked evidence approach was used to explore the possible benefits of SLNBx in identifying patients who are would be eligible for adjuvant therapy.

Diagnostic accuracy

The DCAR did not provide any comparative evidence assessing diagnostic accuracy of SLNBx vs. WLE + follow-up; rather it provided the following narrative:

- the diagnostic performance that would be most relevant to the clinical utility relates to the proportion of patients undergoing SLNBx who would then be eligible for adjuvant

therapy. However, the DCAR identified no reference standard to relate the diagnostic yield of SLNBx to the number of patients identified as eligible for adjuvant therapy

- the eligibility for adjuvant therapy is a function of three factors:
 - the need for complete resection
 - the need to have Stage IIIB or Stage IIIC or Stage IIID melanoma
 - uniquely for the combination dabrafenib plus trametinib, the need also to be *BRAF* positive. The proportion of patients with *BRAF V600* positive melanoma calculated using a prevalence rate (44.5%) was previously accepted by the MSAC when it considered the funding of *BRAF* mutation testing in patients with locally advanced or metastatic melanoma for eligibility for dabrafenib treatment (1172 PSD, April 2013 MSAC meeting).

The DCAR stated that SLNBx positivity was obtained from the MSLT-I trial (presented in Application 1485). From the MSLT-I trial, Morton et al. 2014 reported the number of patients who underwent SLNBx and were then determined to be sentinel node positive (122/770; 15.84%). However, this trial did not directly report the proportion of patients who are eligible for SLNBx according to the proposed patient population definition who would then be diagnosed with Stage III melanoma based on the AJCC 8th edition staging system, before then breaking this estimate down into the proportion of these patients with Stage IIIB, Stage IIIC or Stage IIID melanoma. In other words, the issues rising are whether (a) the population in the MSLT-I trial matches the proposed population from the stakeholder meeting, and (b) being sentinel node positive from the MSLT-I trial can be accepted as being the same as having Stage III melanoma.

Clinical validity

The DCAR did not provide any comparative evidence assessing clinical validity; however, the DCAR identified two studies (Haydu et al. 2017 and Gershenwald et al. 2017) which estimated the proportion of patients with Stage III melanoma based on the AJCC 8th edition staging system (Table 5).

Table 5: Key features of included evidence

Study	Population	Diagnosis	Year of diagnosis	Sample size (n)	AJCC staging system
Haydu et al. 2017	Patients with Stage III melanoma in Australia	The study included all patients with Stage IIIA, IIIB, IIIC or IIID melanoma who have been diagnosed by SLNBx and clinical surveillance.	1970-2013	4,540	8 th edition
Gershenwald et al. 2017	Patients with Stages I, II or III melanoma from 10 centres worldwide (United States, Europe, and Australia)	Patients who were treated in the pre-SLN era (i.e., before the 1990s) and in the early SLN era (early through mid-1990s) were deliberately omitted. However, it is still not clear whether the patients with Stage IIIA, IIIB, IIIC or IIID melanoma have been diagnosed by SLNBx or clinical surveillance.	Since 1998	>46,000	8 th edition

SLN = sentinel lymph node; SLNBx = sentinel lymph node biopsy

Source: compiled from Table 31, p69; Table 45, p92; and Table 46, p94 of the DCAR

The breakdown of Stage III melanoma for each study is provided in Table 6, which was used to inform the DCAR's economic model for the SLNBx arm. However, the DCAR acknowledged that there was considerable variation across these two sources for this key piece of information to estimate the proportion of patients with Stage III melanoma based on the AJCC 8th edition melanoma staging system who are determined to have Stage IIIB, Stage IIIC or Stage IIID melanoma also based on the AJCC 8th edition melanoma staging system. This variation was particularly notable for the proportions of patients with Stage IIIA melanoma (5% vs. 22%), i.e., the subgroup excluded from PBS-subsidised adjuvant therapy.

Table 6: Breakdown of Stage III melanoma subcategory based on Haydu et al. 2017 vs. Gershenwald et al. 2017

	Haydu et al. 2017	Gershenwald et al. 2017
Subcategory	Number of patients (% in each subcategory)	Number of patients (% in each subcategory)
IIIA	220 (5.4%)	1,006 (21.96%)
IIIB	2,007 (49.7%)	1,170 (25.53%)
IIIC	1,709 (42.3%)	2,201 (48.04%)
IIID	104 (2.6%)	205 (4.47%)
Total	4,040^a	4,582

^a Patients with undefined subcategory were excluded from the analysis

Source: compiled from Table 32, pp69-70 and Table 33, p70 of the DCAR

Clinical utility

The DCAR did not provide any comparative evidence assessing clinical utility; rather it provided the following narrative outlining a linked evidence approach.

In response to the MSAC's request for further clarification of the patient selection criteria for adjuvant treatment of melanoma and the role of SLNBx in selecting patients for such treatment (p1, 1485 PSD), the DCAR noted the following in relation to patients with Stage III melanoma:

- As noted above, a patient must have resected Stage IIIB, IIIC or IIID melanoma in order to access PBS-subsidised adjuvant therapy: combination dabrafenib plus trametinib (patient must also have a *BRAF V600* mutation) or nivolumab. The DCAR noted that access to these therapies is also available for patients with Stage IV melanoma, however this was not considered relevant to this assessment, as patients are assigned to Stage IV regardless of lymph node involvement and therefore SLNBx is unlikely to be required in these patients.
- With regard to the requirement for patients to have Stage IIIB, IIIC and IIID melanoma, SLNBx plays a key role in accurately staging melanoma in this population of patients. Specifically:
 - according to the AJCC 8th edition melanoma staging criteria, SLNBx is used to determine the presence or absence of lymph node involvement in patients who do not have clinically apparent metastasis, in order to accurately determine the stage of melanoma (Gershenwald et al. 2017)
 - current Australian guidelines recommend SLNBx to be considered for all patients with melanoma greater than 1 mm in thickness and for patients with melanoma greater than 0.75 mm with other high-risk pathological features to provide optimal staging and prognostic information and to maximise management options for patients who are node-positive (Gyorki et al. 2017).

For therapeutic effectiveness, the DCAR presented the safety and effectiveness outcomes showing incremental health benefit for patients treated with PBS-listed or PBAC-recommended adjuvant therapies:

- dabrafenib plus trametinib (COMBI-AD trial; Dabrafenib and trametinib PSDs, March and July 2019 PBAC meetings)
- nivolumab monotherapy (CA238 trial; Nivolumab PSDs, March, July and November 2019 PBAC meetings).

The DCAR stated the basis for the linked evidence was conditional on applying the transferability assumption; its assessment assumed that SLNBx identifies patients with Stage IIIB, IIIC or IIID melanoma, who would be eligible for adjuvant therapy, and there is PBAC-accepted evidence that adjuvant therapies (such as combination dabrafenib and trametinib)

sufficiently improve the health outcomes of these patients. The DCAR suggested that there was a lack of direct comparative evidence in relation to the role of SLNBx in risk stratification and access to adjuvant therapy as patients enrolled in the adjuvant therapy trials considered by the DCAR had also undergone complete resection. Relevant to this, in its consideration of dabrafenib plus trametinib, PBAC commented that as ‘CLND was no longer standard of care for all patients with a positive sentinel lymph node, the PBAC considered that “completely resected disease” would, in practice, include all patients with a wide excision of the primary tumour and either CLND or sentinel lymph node biopsy (or both). (p6, dabrafenib plus trametinib PSD, March 2019). As such, SLNBx is required for all patients eligible for treatment with this adjuvant therapy, as it is accepted in practice as resecting the nodal involvement irrespective of whether this proceeds to complete lymph node biopsy.

Clinical claim

On the basis of the benefits and harms reported in the evidence base (summarised above), the DCAR suggested that, relative to surveillance and WLE, SLNBx has non-inferior safety and superior effectiveness.

Translation issues

The DCAR summarised the key translation issues in Table 7. The DCAR did not discuss the translation issue associated with the probabilities used to inform the diagnostic accuracy of SLNBx and WLE plus follow-up.

Table 7: Key translation issues

Issue	Research question	Pre-modelling study
Population	Is the population in the clinical trials applicable to the proposed listing on the MBS or PBS?	Data from COMBI-AD and CA238 trials was based on the AJCC 7 th edition melanoma staging system. Patients with Stage IIIA, IIIB, IIIC or IIID melanoma enrolled in these clinical trials based on this now outdated staging system are not representative of the current PBS-subsidised population. Moreover, all patients enrolled in the selected adjuvant therapy trials had also undergone complete resection.
Treatment of melanoma	Are there changes in clinical practice in Australia that may differ from those described in the trial?	Adjuvant therapies were recently recommended in Australia for the PBS-subsidised treatment of selected melanoma patients (patients with Stage IIIB, IIIC or IIID melanoma). Recent guidelines recommend the consideration of observation vs. immediate CLND as an option in patients with a positive sentinel lymph node. Now patients with Stage IIIB, IIIC or IIID melanoma are eligible for PBS-subsidised adjuvant therapies that would improve their health outcomes.
Costing of resource use	What are the most appropriate cost inputs to quantify the cost implications of the included health resource use?	Cost inputs included in the cost-effectiveness evaluation from the previous DCAR considered by MSAC were updated for the resubmission DCAR using AR-DRGs and MBS items.

AJCC = American Joint Committee on Cancer; AR-DRG = Australian Refined Diagnosis Related Groups; CLND = complete lymph node dissection; MBS = Medicare Benefits Schedule; PBS = Pharmaceutical Benefits Scheme

Source: derived from Table 5, p24 of the DCAR

12. Economic evaluation

The DCAR modelled a cost-effectiveness analysis comparing SLNBx plus WLE *vs.* surveillance plus WLE (Table 8).

Table 8: Summary of the economic evaluation

Perspective	Australian health system
Intervention	SLNBx + WLE
Comparator	Surveillance + WLE
Type of economic evaluation	Cost-effectiveness analysis (CEA)
Sources of evidence	Haydu et al. 2017, Morton et al. 2014, Faries 2010, Faries et al. 2017
Time horizon	12 months
Benefit	Number of additional patients eligible for adjuvant therapy
Methods used to generate results	Expected cohort analysis using decision tree model
Discount rate	Not applicable
Software packages used	Microsoft Excel 2016

CLND = completion lymph-node dissection; SLN = sentinel lymph node; SLNBx = sentinel lymph node biopsy; WLE = wide lymph node excision

Source: Table 6, pp24-25 of the DCAR

Key structural assumptions of the DCAR's model are:

- It was assumed that all patients with a positive SLNBx had a true positive result and patients with a negative SLNBx had a true negative result, as the diagnostic accuracy of SLNBx could not be established. The proportion of false negative results could only be determined through clinical follow up.
- It was assumed that the proportion of patients who would be eligible for potential adjuvant therapy after undergoing SLNBx are those identified with Stage IIIB, Stage IIIC or Stage IIID melanoma. However, the proportion of patients with a *BRAF* mutation was not considered by the DCAR.
- It was assumed that all patients who developed a nodal metastasis within the first year of surveillance and underwent therapeutic CLND in the surveillance arm (comparator) would be eligible for adjuvant therapy. Although a sensitivity analysis was considered for this by lowering this parameter, the results were not reported in the DCAR.

The DCAR's estimation of the incremental cost effectiveness ratio (ICER) per additional patient eligible for adjuvant therapy for SLNBx over surveillance is presented in Table 9.

Table 9: Base case incremental cost-effectiveness ratio

Description	Cost	Incremental cost	Effectiveness (number of patients eligible for adjuvant therapy)	Incremental effectiveness (number of patients)	ICER
SLNBx + WLE	\$593,870.31	\$333,075.47	15	11.64	\$28,622.80
Surveillance + WLE	\$260,794.84	-	3.34	-	

ICER = incremental cost-effectiveness ratio; SLNBx = sentinel lymph node biopsy; WLE = wide local excision

Source: Table 8, p26 of the DCAR

The DCAR stated the modelled results were most sensitive to probability of nodal metastases (surveillance) and SLNBx positivity (Table 10).

Table 10: Key drivers of the economic model

Description	Estimate value	ICER	Impact
SLNBx positive (BC = 15.84%, Morton et al. 2014)	21% ^a	\$20,168.60 (more costly and more effective)	Low
Nodal metastases (after surveillance + WLE) (BC = 3.34%, Morton et al. 2009)	15.8% ^b	\$10,609.45 (less costly and less effective)	High, favours comparator
Stage III melanoma subgroups based on Gershenwald et al. 2017 study (BC = Haydu et al. 2017)	See Table 6	\$36,917.11 (more costly and more effective)	Low

BC = base case; ICER = incremental cost-effectiveness ratio; SLNBx = sentinel lymph node biopsy; WLE = wide local excision
^a upper limit sensitivity analysis obtained from Morton et al. 2014; ^b upper limit sensitivity analysis obtained from Morton et al. 2009
Source: Table 9, p26 of the DCAR

The DCAR relied on the following estimates derived from the MSLT-I trial as a basis for estimating the proportions of patients who have Stage III melanoma:

- for patients receiving SLNBx, proportion who are SLNBx positive = 15.84%
- for patients receiving surveillance, the annualised proportion who developed nodal metastases = 3.34%.

As noted above in relation to the 15.84% estimate for SLNBx, this trial did not directly report the proportion of the proposed patient population definition who patients who do not receive SLNBx but would be diagnosed with Stage IIIB, Stage IIIC or Stage IIID melanoma based on the AJCC 8th edition melanoma staging system. In other words, the issues rising are whether (a) the population in the MSLT-I trial matches the proposed population from the stakeholder meeting, and (b) developing nodal metastases over a year from enrolment in the MSLT-I trial can be accepted as being the same as having Stage IIIB, Stage IIIC or Stage IIID melanoma.

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of the introduction of SLNBx for patients with malignant cutaneous melanoma greater than 1 mm in depth or at least 0.8 mm depth in the presence of ulceration (Table 11). The DCAR stated that the uptake of SLNBx after WLE was based on the same study (van der Ploeg et al. 2014) as was used in the previous DCAR (MSAC 1485). However, there is some limitation to this study as the cohort is old (1992 – 2008) and guidelines have been modified since then, which may affect the proportion of patients undergoing SLNBx.

The DCAR stated that costs to MBS were calculated based on a 75% MBS benefit and one basin sampling. The DCAR estimated the cost offsets (reduction in items already in use for SLNBx: MBS items 30329, 30332, 31240, 31243) using the average 75% benefit (\$235.55) of the currently listed MBS items.

Table 11: Net costs to MBS associated with sentinel lymph node biopsy for melanoma

Description	2020	2021	2022	2023	2024
Total number of patients undergoing SLNBx	2,113	2,159	2,204	2,250	2,295
Total direct costs of SLNBx	\$1,010,395	\$1,032,107	\$1,053,818	\$1,075,529	\$1,097,241
Total cost offsets due to reduction in use of other MBS items	\$428,071	\$437,270	\$446,468	\$455,667	\$464,865
Net cost to MBS	\$582,324	\$594,837	\$607,350	\$619,863	\$632,376

MBS = Medicare Benefits Schedule; SLNBx = sentinel lymph node biopsy
Source: compiled from Table 10, p27; Table 62, p108 of the DCAR

The DCAR presented a sensitivity analysis estimating the impact for 20% of patients undergoing SLNBx having two basins affected, and therefore including the multiple operations rule (Table 12).

Table 12: Sensitivity analysis

Description	2020	2021	2022	2023	2024
Overall net cost base case	\$582,324	\$594,837	\$607,350	\$619,863	\$632,376
20% patients have two basins affected	\$640,556	\$654,321	\$668,085	\$681,849	\$695,613

Source: Table 65, p110 of the DCAR

The DCAR stated the listing of the proposed item for SLNBx would not have any additional impact on government health budgets, as it is already conducted as normal practice.

14. Key issues from ESC for MSAC

Table 13: Summary of key issues from ESC for MSAC

ESC key issue	ESC advice to MSAC
Safety	ESC considered SLNBx to be a safe procedure with a low risk of adverse events and a similar safety profile as WLE.
Effectiveness	ESC noted that SLNBx provides an important prognostic marker for cutaneous melanoma, and has been established as yielding critical information to guide clinical management. Most patients with nodal metastases achieve regional lymph node control through SLNBx alone and there is convincing evidence that proceeding to CLND in isolation does not confer additional survival benefit.
MBS fee	ESC considered that the proposed fee of \$637.45 appeared to be reasonable for the degree of complexity required in relation to undertaking the intervention of SLNBx using both radioisotope and lymphotropic dyes, and would be similar to the range of costings used in the breast cancer sentinel node biopsy item numbers. Although SLNBx for melanoma might involve multiple nodal basins, ESC was of the view that it would be simpler to have one item number that did not specify the sites to be biopsied, and considered that the degree of complexity of the intervention for the various sites is not sufficiently different to warrant different fees.
Base case ICER	ESC considered that the estimates of effectiveness in identifying SLNBx-eligible patients as also eligible for adjuvant therapy used in the base-case ICER (15% vs 3.34%) were in the range that might be expected.
Economic model	ESC noted that the economic model may be out of date, as new adjuvant therapies are PBS-listed that were not reimbursed when the model was developed.
Different financial estimates than in the original submission	It is unclear why the financial estimates were lower than the previous submission.
Separate MBS item	ESC advised that having a melanoma-specific MBS item would make it easier to track use of SLNBx for this indication.

ESC discussion

ESC noted that this was a resubmission of an application for MBS listing for SLNBx for intermediate thickness melanoma.

ESC noted that SLNBx for melanoma is already being performed in Australia, but this procedure and the MBS items used (30075, 30329, 30332, 31420, and 31423) are general and not specific for melanoma. This makes it difficult to track the costs and the number of procedures being performed specifically for melanoma. ESC considered that it would be reasonable to have a separate item to track its use.

ESC noted that the MBS fee requested by the applicant of \$637.45 is greater than the fees for the five current items used. ESC also noted that the pre-ESC response stated that the fee of \$637.45 was suggested in the original application and that the fee for the proposed benchmark MBS item 30299 (SLNBx for breast cancer) has increased to \$647.65. The applicant requested that the fee for SLNBx for melanoma be equivalent to the MBS fee for SLNBx for breast cancer, noting that melanoma patients are more likely to have multiple sentinel nodes within a nodal basin than breast cancer patients. ESC considered that this fee was likely to be reasonable for the degree of complexity required in relation to undertaking the intervention of SLNBx using both radioisotope and lymphotropic dyes.

ESC considered that, although SLNBx for melanoma might involve multiple nodal basins, it would be simpler to have one MBS item that does not specify nodal basins. ESC considered that the degree of complexity of the intervention for the various sites is unlikely to be sufficiently different to justify different fees. ESC noted the DCAR did not include the cost of SLNBx across more than one basin, implicitly assuming the invoking of the multiple operations rule, except in the sensitivity analysis (20% of patients having two basins affected, resulting in a 10% increase in costs).

ESC noted that the applicant had changed the focus of the application in the resubmission, claiming that SLNBx provides important prognostic information, allows for improved local disease control, and provides for more effective selection of patients with intermediate thickness and thick melanoma for adjuvant therapy.

ESC noted that the clinical management algorithm for cutaneous melanoma had changed since the results of the MSLT-II trial were published. Previously, patients who were SLNBx positive underwent immediate CLND. Due to a lack of additional survival benefits for CLND based on results from MSLT-II, CLND is no longer supported for patients with positive SLNBx results. More recently, in light of the emerging role of adjuvant therapy in melanoma management and associated benefits for survival and recurrence-free survival, it is becoming important to stratify patients based on the information retrieved from SLNBx to help select patients as eligible for these new adjuvant systemic therapies.

ESC noted that there was no new direct evidence linking SLNBx to improved survival outcomes. The key study for the previous submission, the MSLT-I trial, showed no therapeutic advantage, but subgroup analysis validated a prognostic role for the technique, as single lymph node status was a significant prognostic factor. There was also no new data to change the previous conclusion of comparative safety.

ESC noted that patients needed to be stage III under the previous American Joint Committee on Cancer (AJCC) 7th edition melanoma staging criteria to be eligible for the adjuvant therapy trials, and that SLNBx played an important role in selecting eligible patients. ESC considered this to be important because these adjuvant drug therapies have been demonstrated to improve cancer outcomes. As SLNBx is not itself associated with an overall survival benefit, its role is more appropriately viewed as a staging procedure to inform treatment planning, not a therapeutic intervention in and of itself.

ESC noted the pre-ESC response, which stated that nivolumab is now PBS-listed for patients with Stage IIIB, Stage IIIC or Stage IIID melanoma, as well as dabrafenib and trametinib for patients who are also *BRAF*-positive. Nivolumab was PBS-listed for this indication on 1 March 2020, so SLNBx-positive patients who are diagnosed with Stage IIIB, Stage IIIC or Stage IIID melanoma could be offered adjuvant therapy, and ESC agreed that it was likely that most patients would accept such treatment.

ESC noted that these new treatments were not included in the simplified economic model presented. The benefit was the number of additional patients diagnosed as eligible for adjuvant therapy as a result of SLNBx identifying nodal micrometastases in those patients for whom this would be essential for diagnosing Stage IIIB, Stage IIIC or Stage IIID melanoma according to the current AJCC 8th edition melanoma staging criteria. The model assumed that, of those patients who received SLNBx according to the proposed MBS item descriptor, the proportion testing positive according to the MSLT-I trial equals being diagnosed as having Stage III melanoma (15.84%, with an assumption of no false positives). The model then removed the estimated proportion of these patients who would have Stage IIIA melanoma (5.4% from Haydu et al. 2017, see Table 6), leaving 15% diagnosed with Stage IIIB, Stage IIIC or Stage IIID melanoma eligible for adjuvant therapy following SLNBx. This estimate would reduce to 12% if the proportion of patients with Stage IIIA melanoma from Gershenwald et al. 2017 (21.96%, see Table 6) were used instead. For the comparison arm, the model assumed that the annualised estimate of the proportion of patients who did not receive SLNBx in the MSLT-I trial who then developed a nodal metastasis during surveillance (3.34%) equals the proportion of SLNBx-eligible patients who would have been diagnosed with Stage III melanoma without SLNBx.

ESC considered that these estimates were in the range that might be expected, although the comparator arm ignored the likelihood that ultrasound could also help identify patients with Stage IIIB, Stage IIIC or Stage IIID melanoma. However, given the uncertainties involved with applying these derived estimates to the proposed eligible population for MBS-funded SLNBx and the proposed increased diagnostic yield of patients eligible for adjuvant therapy, ESC suggested the following approach should MSAC require a more confident basis for these estimates:

- contact those Australian experts with access to the dataset of patients contributing to the Haydu et al. 2017 and Gershenwald et al. 2017 publications and who have the capacity and likely motivation to address the following requests
- for those patients in the dataset who can be shown to meet the proposed population criteria (i.e. the primary lesion is greater than 1.0 mm in depth or at least 0.8 mm in depth in the presence of ulceration), identify:
 - what proportion had clinically detectable disease as the basis for being shown to have Stage IIIB, Stage IIIC or Stage IIID melanoma according to the current AJCC 8th edition melanoma staging criteria
 - what proportion received SLNBx (whether or not they were also in the previous proportion)
 - what proportion of this SLNBx-receiving population were shown to have Stage III melanoma according to the current AJCC 8th edition melanoma staging criteria
 - what proportion of this SLNBx-receiving population were shown to have Stage IIIB, Stage IIIC or Stage IIID melanoma according to the current AJCC 8th edition melanoma staging criteria
- and thus calculate the incremental diagnostic yield from the patients meeting the proposed population criteria who are shown to have Stage IIIB, Stage IIIC or Stage IIID melanoma according to the current AJCC 8th edition melanoma staging criteria due to the use of SLNBx.

ESC noted that, for the financial estimates, the same epidemiological approach was taken as the original application. However, without justification, the numbers of eligible patients and financial estimates were less than in the original submission. ESC queried these changes given that the eligible population has slightly increased from the previous submission by also including patients with a primary lesion at least 0.8 mm in depth in the presence of ulceration.

ESC noted that the SLNBx utilisation rate of 49.8% was taken from van der Ploeg (2014); however, considered that this data related to an older population and practice guidelines have since changed. ESC considered that the utilisation rate might be higher in practice, which led to uncertainty in the financial estimates.

ESC noted that, unlike the previous submission, the DCAR did not include other costs of surgery in the net cost to MBS (Section E.4 of the DCAR), as this is already being performed as part of excision. ESC was uncertain whether this was reasonable, as CLND may still occur in response to a positive SLNBx, even though the definition of “complete resection” for the purposes of adjuvant therapy would include wide excision of the primary skin lesion and sentinel node biopsy.

The re-submission claimed that it is likely there would be no additional impact on government health budgets. However, ESC considered that if more patients become eligible for adjuvant therapy, it would have a relatively large impact and so this should have been included in the financial estimates.

ESC noted the consultation feedback gave variable support for SLNBx as current standard of care.

15. Other significant factors

Nil.

16. Applicant comments on MSAC’s Public Summary Document

The applicant notes the positive recommendation and is grateful for the support of MSAC throughout the process. The applicant would like to explore a possible clarification of the wording of the item descriptor such that:

1. Appropriate excision of the primary melanoma can be at the same occasion (acknowledging the multiple procedure rule) or at a previous procedure.
2. Multiple sentinel node basins may be involved in lymphatic drainage, and each separate lymphatic basin biopsy is a separate procedure (again, where the multiple procedure rule will apply). Multiple sentinel nodes within the same lymphatic basin do not qualify as separate procedures.
3. Limit to one primary melanoma being assessed with sentinel lymph biopsy per patient per occasion.

The applicant believes that clarification of the descriptor will help with the roll out to the medical practitioners involved, and will minimise confusion.

17. Further information on MSAC

MSAC Terms of Reference and other information are available on the MSAC Website: [visit the MSAC website](#)