



Australian Government

Medical Services Advisory Committee

Public Summary Document

Application No. 1485 – Sentinel Lymph Node Biopsy (SLNB) for intermediate thickness and thick melanoma

Applicant: **Australian Society of Specialist General Surgeons**

Date of MSAC consideration: **MSAC 73rd Meeting, 26-27 July 2018**

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

1. Purpose of application

An application requesting Medicare Benefit Schedule (MBS) listing for sentinel lymph node biopsy (SLNB) in patients with intermediate thickness (>1 to 4 mm) and thick (>4 mm) melanoma was received from 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 comparative safety, clinical effectiveness and cost-effectiveness, MSAC deferred its advice on MBS funding for SLNB for intermediate thickness and thick cutaneous melanoma.

MSAC did not accept the rationale for a fee increase for a SLNB-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 SLNB compared to not using it.

While MSAC acknowledged the prognostic value of SLNB in staging of melanoma and the potential for this to determine patient access to adjuvant therapies, MSAC deferred its advice to request further clarification of the patient selection criteria for adjuvant treatment of melanoma and the role of SLNB in selecting patients for such treatment.

MSAC considered that it would be helpful to discuss this application further with the Oncology Clinical Committee of the MBS Review Taskforce, and to seek input from the Medical Oncology Group of Australia and melanoma surgeons.

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

MSAC noted that SLNB is performed with lymphoscintigraphy followed by lymphotropic dye injection and intraoperative gamma probe guidance. The procedure is performed as an

inpatient/day procedure (requiring surgeon and anaesthetist). MSAC noted that SLNB for melanoma is recognised as having prognostic value for patients with intermediate thickness and thick melanoma in a number of Australian and international evidence-based guidelines.

MSAC noted that SLNB is currently being performed for melanoma patients but is claimed against multiple existing MBS items for lymph node biopsy, excision and dissection (30075, 30329, 30332, 31420 and 31423). Lymphoscintigraphy items (61469, 61462, 61506) are also already funded. MSAC noted that the proposed fee is benchmarked to one of the existing items for SLNB in patients with breast cancer. The fee is set between the costs of lymph node biopsy and lymph node clearance. MSAC did not accept the rationale for a fee increase for a SLNB-specific MBS item, compared to the current non-specific MBS items under which this service is currently being claimed.

MSAC noted that SLNB for melanoma differs to SLNB for breast cancer. In breast cancer, SLNB is always performed in the axilla, but melanoma may involve multiple lymph node basins (which are difficult to predict for truncal and head-and-neck melanomas), so SLNB for melanoma could be performed in the neck, axilla and/or groin. MSAC proposed that there should be separate melanoma-specific SLNB items for each nodal region, and different fees for different nodal regions could reflect any differences in surgical complexity. MSAC noted that the current fees for biopsy and complete dissection items imply a gradient of increasing complexity from the groin or pelvis, to the axilla and to the neck. MSAC considered that the multiple operations rule should apply if more than one item is required for one episode of care.

MSAC noted that the assessment of this application sought to determine the comparative safety, effectiveness and cost-effectiveness of wide local excision (WLE) of the primary lesion and follow-up with and without SLNB.

MSAC noted that the Cancer Council Australia guidelines state that complication rates from SLNB are low compared to WLE and completion lymph node dissection (CLND). MSAC noted that the most concerning adverse event is lymphoedema, which is more common after inguinal than after axillary or cervical SLNB. MSAC noted that the applicant accepted that the addition of SLNB will add to the rate of adverse events compared to WLE alone, but that lymphoedema-related morbidity is usually minor and temporary, in contrast to CLND. MSAC suggested that consideration be given to limiting the procedure to centres with appropriate expertise. MSAC noted that complication rates are inversely related to procedure volume, particularly for primary lesions arising in the head and neck (CCA/MIA 2018).

MSAC noted that, for both intermediate thickness and thick melanoma:

- sentinel lymph node status is a significant predictor of melanoma-specific survival;
- compared to WLE alone, SLNB is associated with no significant improvement in overall survival, melanoma-specific survival or the cumulative incidence of non-sentinel lymph node metastases.

MSAC also noted that a positive SLNB followed by CLND is associated with improved regional disease-free survival, but no improvement in distant metastasis-free survival. CLND is also associated with a high risk of lymphoedema. MSAC noted, however, that clinical practice has changed following these trials, and CLND is no longer considered standard treatment after a positive SLNB.

MSAC noted that the applicant agreed there is no evidence that any nodal surgery improves overall survival for melanoma. MSAC noted that the applicant emphasised the prognostic value of SLNB, especially in light of the availability of new adjuvant systemic agents that

improve survival in patients with resected stage III melanoma. MSAC acknowledged that a number of immune therapies are available for unresectable stage III/IV melanoma, and that new melanoma indications for these agents, as well as new targeted and immune therapies, are in the pipeline. However, none of the available immune checkpoint inhibitors is PBS-funded for adjuvant therapy in resected stage III melanoma and one is not TGA approved for this indication.

MSAC noted that use of sentinel lymph node status to guide adjuvant systemic therapies for resected stage III melanoma is not currently justified. MSAC considered that SLNB may become a triage tool to determine the intensity of follow-up after WLE of intermediate thickness and thick melanomas, but this question has not been evaluated in trials.

MSAC concluded that the main value of SLNB for melanoma is for staging of disease, to determine prognosis and inform decisions regarding further regional node dissection. However, trial evidence indicates that SLNB does not currently modify patient management, and criteria for determining suitability for adjuvant therapy are not adequately established.

MSAC considered that recent clinical trial results suggested that adjuvant therapy may become the standard of care. However, patients entering these trials were not selected on the basis of SLNB results, so it is not clear whether effectiveness outcomes of these trials will be applicable for patients with a positive SLNB. If SLNB results were to be used to assess eligibility of patients for adjuvant therapy in practice, MSAC recommended establishing risk equivalence criteria (i.e. the SLNB result that equates to the same melanoma risk as for the patients in the adjuvant trials) that would qualify a patient for access to adjuvant treatment.

MSAC recommended consultation with the MBS Review Taskforce and other stakeholders (e.g. the Medical Oncology Group of Australia, the Royal College of Pathologists of Australasia, and melanoma surgeons) to establish such risk criteria as a possible basis for extrapolated evidence of predictive effect.

MSAC noted that the economic evaluation resulted in an ICER of \$22,237, and that the ICER was most sensitive to the probability of a positive SLNB. MSAC noted that ESC considered the revised ICERs to be unreliable. MSAC considered that there are issues in how the clinical evidence has been applied in the economic model, particularly relating to the reliance on CLND as the therapeutic intervention after a positive SLNB.

MSAC noted that the economic evaluation indicated SLNB is likely to be cost-effective for intermediate thickness (>1–4mm) melanoma but not for thick (>4mm) melanoma. However, out-of-pocket costs and Medicare Safety Net were not explored in the current assessment. MSAC also noted that the costs of follow-up appear to be underestimated in the model. In the clinical algorithm, follow-up for patients with negative SLNB is assumed to be provided by general practitioners, but published Australian data indicate that 76% of patients with melanoma ≥ 1 mm in thickness receive follow-up from specialists (Read et al 2018).

MSAC noted that the financial implications of listing melanoma-specific SLNB items are highly uncertain. MSAC commented that it is not possible to ascertain the current cost of SLNB for melanoma from current data. Direct costs to the MBS were estimated at approximately \$620,000, rising to approximately \$670,000 in year 5. However, it is difficult to estimate the extent of cost offsets associated with replacement of currently claimed MBS items, as current items may continue to be used. In addition, MSAC considered that the financial implications are overestimated because associated lymphoscintigraphy interventions are already funded.

Total costs for SLNB were calculated as \$12,375,259 in the first year up to \$13,369,081 in year 5. Although there would be cost savings to the MBS due to reductions in current SLNB items, it was not possible to estimate the proportion of current lymph node biopsy items that are used for intermediate thickness and thick melanoma.

MSAC noted that MBS data, provided by the Department, which attempted to measure the proportion of current claims for current lymph node biopsy items that are for melanoma patients, showed a wide range from 2% (based on biopsy/excision co-claims) to 27% (based on lymphoscintigraphy co-claims). Around \$100,000 in benefits was paid for lymph node biopsy/excision items in 2017. However, this excluded services in the public sector, so it may be an underestimate.

MSAC commented that better data are required on current and likely utilisation of SLNB items for melanoma. MSAC noted the PASC outcome that, while a melanoma-specific SLNB item will not impact patient clinical outcomes, it will reduce the variation in MBS rebates for patients and enable better data collection on melanoma procedures. Anatomical region-specific items for melanoma SLNB would provide more granularity for future review of utilisation.

4. Background

SLNB for melanoma is already performed in Australia and is claimed using the non-specific MBS diagnostic biopsy item 30075, and other items relating to specific sites (MBS items 30329, 30332, 31420, 31423).

SLNB is currently MBS listed for breast cancer.

5. Prerequisites to implementation of any funding advice

SLNB for melanoma is already being claimed on the MBS.

6. Proposal for public funding

The procedure is targeted to two populations of patients with malignant cutaneous melanoma at high risk of nodal metastasis:

- Population 1: Patients with intermediate thickness malignant cutaneous melanoma (Breslow thickness >1.0 mm to 4 mm)
- Population 2: Patients with thick melanoma (>4 mm).

Table 1 Proposed MBS item descriptor

Category 3 – THERAPEUTIC PROCEDURES
SENTINEL LYMPH NODE BIOPSY OR BIOPSIES for cutaneous melanoma, where the primary lesion is 1.0 mm or greater in depth and appropriate excision of the primary melanoma has occurred, using preoperative lymphoscintigraphy and lymphotrophic dye injection. Limit of one lesion per patient per occasion* (Anaes.) (Assist.)
Fee: \$637.45

*The Applicant has requested consideration be given to allowing billing of the item for more than once per occasion, depending on the number of lymph node basins sampled.

7. Summary of public consultation feedback/consumer issues

A professional organisation supported the reimbursement and tracking of SLNB for patients with melanoma. They noted that SLNB “is an accurate diagnostic procedure that provides patients with genuine insights into their prognosis but that current evidence is not conclusive regarding overall survival benefit,” and that “accurate staging was required to access some treatments including those in the adjuvant setting.”

8. Proposed intervention’s place in clinical management

Melanoma is a malignancy arising from the skin pigment cells (melanocytes). Cutaneous melanoma is estimated to be the 4th most commonly diagnosed cancer in Australia, with 13,941 newly-diagnosed cases. Melanoma lesions are classified as thin (Breslow thickness <1 mm), intermediate thickness (1-4 mm), or thick (>4 mm). Most cases are diagnosed at an early stage (<1 mm thickness) where 5-year survival is >95%, but as Breslow thickness increases, survival decreases.

The proposed medical service is SLNB with excision of lymph node(s) identified by a combination of lymphoscintigraphy/gamma probe and blue dye (lymphotropic dye) injection in addition to WLE for use in patients with intermediate thickness (>1 mm to 4 mm) and thick (>4 mm) cutaneous malignant melanoma.

As the intervention is already in use, the clinical management algorithm is the same for both current management and proposed management. The only difference proposed is that there would be a new specific MBS item number for SLNB for melanoma, to distinguish it from other indications for lymph node biopsy.

9. Comparator

The comparator for both populations (intermediate thickness and thick melanoma) is WLE of the primary melanoma and follow-up.

10. Comparative safety

Eighteen studies were included in the assessment of safety of SLNB for melanoma. Three studies were RCTs, three were prospective cohort studies, eight were retrospective cohort studies, and four were cross-sectional studies.

Overall rates of adverse events were similar following WLE (18.9%) and SLNB alone (4.6-13.8%), whereas higher rates of adverse events were experienced after CLND (23.2-77.8%).

Most frequent adverse events related to SLNB were wound complications (0-8.3%), lymphoedema (0.4-11.4%), nerve dysfunction (0.1-31.7%), and pain (13.8%). Rare complications included functional limitations (0-0.4%), anaphylactic (0-0.7%) and allergic reactions (0.0-0.9%) to the blue dye, and skin discolouration from the blue dye (0.1-0.4%). SLNB procedures performed in the inguinal region appeared to carry higher rates of lymphoedema, wound complications, and nerve dysfunctions than those in the axilla.

Overall, the safety profile of SLNB without CLND was similar to that of WLE. However, CLND was found to cause more adverse events than SLNB alone.

11. Comparative effectiveness

Eleven studies and one systematic review were included in the evidence base for effectiveness of SLNB.

One randomised controlled trial (MLST-I, Morton DL et al 2014) reported that, relative to WLE and follow-up, SLNB in addition to WLE improved disease-free survival and nodal recurrence for melanoma >1 mm thickness (i.e. for both population 1 and 2: 1-4mm and >4mm). However, this RCT found no improvement in overall survival, melanoma-specific survival, or distant recurrence for melanoma >1 mm thickness (i.e. for both population 1 and 2: 1-4mm and >4mm).

Three retrospective studies found a very small improvement in 5 year melanoma-specific survival in the SLNB group for population 1 (intermediate thickness melanoma).

One retrospective study found improved disease-free survival in the SLNB group and one other retrospective study found a reduced nodal recurrence and a higher distant recurrence in the SLNB group for population 2 (thick melanoma).

The remaining studies did not report findings separately for population 1 or 2.

Diagnostic performance

The diagnostic yield (defined as the number of positive SLNB/total number of SLNB) reported ranged from 11.3% to 50.0% and did not change notably depending on the site of the melanoma. However, the results indicated that the thicker the melanoma, the higher the diagnostic yield is likely to be.

Variations in the extent of follow-up across the included studies are likely to contribute to considerable uncertainty in identification of regional nodal recurrence. The false negative rate ranged from 8.5% to 39.6%. However, higher rates were observed for the studies reporting results from head and neck primary sites. Sensitivity and specificity were not calculated.

Clinical claim

The application's clinical claim is that SLNB in addition to WLE is non-inferior in safety and superior in clinical effectiveness to WLE and clinical follow-up.

The application claimed that SLNB provides important prognostic information, allowing for improved local disease control and more effective treatment selection in patients with intermediate thickness and thick melanoma. In SLN-positive patients, CLND may be considered or avoided, and in addition, these patients may be eligible for adjuvant biologic therapies. As a result, there may be an improvement in overall survival, melanoma-free survival, and/or disease-free survival, as well as health-related quality of life.

12. Economic evaluation

The application presented a cost-utility analysis using two microsimulation Markov models to estimate the incremental cost per quality-adjusted life year (QALY) gained of SLNB plus WLE compared with WLE alone in each of the patient populations proposed, and assuming that therapy in CLND SLNB positive patients is effective in extending survival. The clinical pathway of patients with intermediate thickness or thick melanoma was simulated in annual cycles over a 10-year time horizon to represent extrapolated disease progression and survival.

Table 2 Summary of the economic evaluation

Perspective	Australian Health System
Comparator	WLE alone
Type of economic evaluation	Cost-utility analysis
Sources of evidence	RCTs
Time horizon	10 years
Outcomes	QALYs
Methods used to generate results	Markov model
Health states	Disease free, SLN+ surveillance*, nodal metastases, distant metastases, unresectable stage III/IV, dead melanoma, dead other
Cycle length	12 months
Discount rate	5%
Software packages used	TreeAgePro 2017 R2.0.

The overall costs and outcomes, and incremental costs and outcomes as calculated for the test and comparator in the intermediate thickness melanoma model, with the base case assumptions, are shown in Table 3.

Table 3 Base case incremental cost effectiveness ratio – Intermediate thickness melanoma (Population 1: 1-4 mm)

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
SLNB+WLE	\$26,462.09	\$7483.83	6.19	0.3	\$25,237.40
WLE alone	\$18,978.25	-	5.89	-	-

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

The overall costs and outcomes, and incremental costs and outcomes as calculated for the test and comparator in the thick melanoma model, with the base case assumptions, are shown in Table 4.

Table 4 Base case incremental cost-effectiveness ratio – Thick melanoma (Population two: >4 mm)

	Cost	Incremental cost	Effectiveness (QALYs)	Incremental effectiveness	ICER
SLNB+WLE	\$43,503.00	\$11,267.74	6.68	-0.1	Dominated
WLE alone	\$32,235.26	-	6.78	-	

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

13. Financial/budgetary impacts

An epidemiological approach was used to estimate the financial implications of SLNB for patients with intermediate thickness and thick melanoma.

The estimated financial implications to the MBS resulting from the proposed listing of SLNB for patients with intermediate and thick melanoma are summarised in Table 5.

Table 5 Total costs to the MBS associated with SLNB in patients with intermediate thickness (Population 1: 1-4 mm) and thick melanoma (Population 2: >4 mm)

	2019	2020	2021	2022	2023
SLNB					
Number of services	2,232	2,277	2,322	2,367	2,412
Sub-total cost	\$1,329,548.56	\$1,356,241.62	\$1,382,934.67	\$1,409,627.73	\$1,436,320.79
Associated interventions					
Interventions associated with SLNB (no CLND)	\$9,784,500.03	\$9,980,941.30	\$10,177,382.57	\$10,373,823.84	\$10,570,265.11
Interventions associated with SLNB + CLND	\$1,089,219.61	\$1,111,087.64	\$1,132,955.66	\$1,154,823.69	\$1,176,691.71
Interventions associated with mapping failure	\$442,107.63	\$450,983.73	\$459,859.82	\$468,735.92	\$477,612.02
Total services		-	-	-	-
SLNB no CLND	\$11,005,451.06	\$11,226,405.10	\$11,447,359.14	\$11,668,313.18	\$11,889,267.22
SLNB plus CLND	\$1,364,055.04	\$1,391,440.87	\$1,418,826.71	\$1,446,212.55	\$1,473,598.38
SLNB with mapping failure	\$502,541.65	\$512,631.07	\$522,720.49	\$532,809.91	\$542,899.33
Total cost	\$12,872,047.76	\$13,130,477.05	\$13,388,906.34	\$13,647,335.63	\$13,905,764.93

CLND: completion lymph node dissection, SLNB: sentinel lymph node biopsy

14. Key issues from ESC for MSAC

Key Issues from ESC to MSAC

ESC Key ISSUES	ESC ADVICE
Clinical guidelines	Sentinel Lymph Node Biopsy (SLNB) for intermediate-thickness & thick melanoma is considered “standard of care” in national & international guidelines and is included in AJCC staging. However, this may be based on simplistic biological assumptions re: spread of melanoma and the role of the SLN.
SLNB safety	SLNB appears to be a relatively safe procedure. However, since it involves an additional surgical procedure, it is implausible that SLNB + wide local excision (WLE) can be “as safe” as WLE.
SLNB effectiveness	<ul style="list-style-type: none"> • Diagnostic yield & FN rate highly variable and may depend on clinical experience. • SLN status appears to have <i>prognostic</i> value – it may be useful as a triage tool to determine intensity of follow-up, but this question has not been specifically addressed.
SLNB + CLND	<ul style="list-style-type: none"> • SLNB + completion lymph-node dissection (CLND) offer no benefit in overall survival, melanoma-specific survival or cumulative incidence of non-SLN metastasis. • It is associated with better regional DFS but no benefit in distant metastasis-free survival. • It is associated with a high (potentially prohibitive) risk of lymphoedema.

Descriptor

- 75% benefit applies (in-hospital procedure).
- Not restricted to one billing per occasion. Is the multiple operations rule applicable?
- Should there be separate items for intermediate-thickness & thick melanoma for monitoring usage?

ESC discussion

This submission is a new application to support the listing on the MBS of SLNB for cutaneous melanoma at high risk of nodal metastasis in two populations:

- patients with intermediate thickness malignant cutaneous melanoma of depth > 1.0–4.0 mm (population 1); and
- patients with thick malignant cutaneous melanoma of depth > 4.0 mm (population 2).

ESC noted that the comparator for both populations is WLE without SLNB.

ESC noted that SLNB is currently being performed in the proposed populations and claimed against existing MBS items 30075, 30329, 30332, 31420, and 31423. ESC noted that none of these items includes lymphoscintigraphy and lymphotropic dye injection, both of which are essential for this SLNB.

ESC noted that although these items relate to diagnostic biopsy of lymph nodes, glands, muscle or other deep tissue or organ, they are not specific to the diagnosis of particular cancers and it was not possible to distinguish the proportion of claims being made for SLNB, and hence the cost offsets attributable.

ESC noted that guidelines from the [Cancer Council Australia](#) had recently been updated and recommended SLNB be considered for all patients with melanomas > 1 mm and patients with melanomas > 0.75 mm with adverse pathological features (primarily ulceration). ESC noted that this was in line with international guidelines which also recommend consideration of SLNB for patients with melanomas of varying thickness and adverse pathological features ([American Joint Committee on Cancer \[AJCC\] Cancer Staging Manual 8th edition](#); [National Comprehensive Cancer Network Cancer Staging Guide](#)). ESC considered that although SLNB may be standard of care, this may be based on theoretical biological assumptions regarding the spread of melanoma and the role of the sentinel lymph nodes (SLN). ESC considered that the role of SLN as indicators of the spread of cancer was uncertain, noting that there are currently two hypotheses regarding the role of SLN in the process of lymphatic drainage and metastasis (the ‘incubator’ and ‘marker’ hypotheses).

ESC noted that overall rates of adverse events were similar following WLE (18.9%) and SLNB alone (4.6–13.8%). However, ESC queried the applicant’s claim of non-inferior safety as the additional surgical procedure involved introduced an added measure of risk.

ESC noted that no studies of diagnostic performance for SLNB in melanoma had used an ideal reference standard - that is CLND for all SLNB positive patients and all SLNB negative patients followed by histopathology of all resected nodes. ESC noted follow-up was used as the reference standard instead. ESC considered that variations in the extent of the follow-up used across the included studies contributed to considerable uncertainty in the definition and significance of regional nodal recurrence.

ESC noted that diagnostic yield in SLNB positive patients varied between 11.3% and 50% and was higher in melanomas of increasing thickness, independent of the primary site of the tumour. ESC noted that the false negative rates (defined as SLNB negative patients who had

regional recurrence on follow-up) ranged from 8.5% to 39.6%, but were uniformly higher in patients with melanomas of the head and neck. ESC considered that the variation in the rates of false negatives may also be related to clinical experience.

ESC noted that effectiveness data were presented from the MLST-I randomised controlled trial (Morton DL et al 2014), 10 retrospective cohort studies and one systematic review. ESC noted that the MLST-I trial was assessed to be at low risk of bias, whereas the cohort studies were at high risk of bias.

ESC noted that in the MLST-I study patients were randomised to WLE+SLNB or WLE+surveillance (hereafter WLE alone). ESC noted that patients in the WLE+SLNB arm who tested positive underwent immediate CLND.

ESC noted that in the MLST-I trial SLNB (+ CLND) was not associated with improvement in overall survival, melanoma-specific survival, or cumulative incidence of non-sentinel lymph node metastases in either population. ESC noted that an intention-to-treat analysis of the same data (Kyrgidis A et al 2015) came to similar conclusions.

ESC noted that in a per-protocol analysis of the MLST-I data, disease-free survival was significantly higher at 10 years in the WLE+SLNB group compared to the WLE alone group, but that the difference was almost entirely attributable to lower regional lymph node recurrences in patients with positive SLNB in the WLE+SLNB group who underwent CLND following SLNB.

ESC noted two RCTs of CLND following a positive SLNB that provided additional information but did not meet the inclusion criteria from the submission. In the DeCOG-SLT study survival curves were identical for patients who did or did not have CLND after a positive SLNB (Leiter U et al 2016). Similarly, the MLST-I study also found no difference in survival rates. ESC noted that there were limitations associated with both these studies; the DeCOG-SLT study excluded patients with head and neck melanomas (that is those at highest risk of false negative biopsies); and in both studies, approximately two thirds of patients had very small SLN tumour burden. ESC considered that this introduced uncertainty as to the applicability of the findings to patients with higher SLN burden.

ESC noted the proposed clinical management algorithm whereby patients with a positive SLNB finding have specialist follow-up (every four months for two years, then annually) and considered that this is less intensive than current recommendations. ESC noted that regarding surveillance of patients who test negative for SLNB and those who have had WLE alone, it was likely that a greater proportion of patients were actually followed up by specialists (76%) than the figure assumed in the algorithm, and that this had implications for estimated costs.

ESC noted that in both populations, SLN status is a significant predictor of melanoma-specific survival. As such, ESC considered that SLNB may have prognostic value and have a potential role in the triage of patients to determine the intensity of follow-up treatment, but that this question had not been specifically addressed in the application.

Despite the evidence that SLNB is in practice guidelines and seems to have become standard of care, ESC thought that considerable uncertainty regarding the clinical effectiveness evidence remains. ESC considered that this then had implications for the economic evaluation. ESC also noted recent trials of the adjuvant use of BRAF/MEK and immune checkpoint inhibitors in patients with resected stage III melanoma, and that SLNB positivity may in future become an eligibility criterion for use of these agents, but that all published studies to date required positive CLND as an entry criterion.

ESC noted that a cost utility analysis had been undertaken, with separate models for intermediate thickness and thick melanomas. ESC noted that cost inputs included in the Australian cost-effectiveness evaluation on which the pre-modelling study was based (Morton RL et al 2009) had been updated. However, ESC noted that some of the unit costs applied had inadequate reporting and were consequently difficult to assess. ESC noted that the cost attributed to lymphoedema was excessive at \$24,000 based on current treatment.

ESC considered that the economic modelling was too unreliable to be useful for decision-making. ESC considered that:

- the model had used transition probabilities based on digitised estimates from disease-free survival curves in the Morton DL et al 2014 study, rather than calculating the transitional probabilities from the digitised estimates; this resulted in a large degree of variation between the initial and revised model outcomes (following rectification of the error);
- modification of the Morton RL et al model to microsimulation to estimate the incremental cost per quality-adjusted life year (QALY) gain of WLE+SLNB compared with WLE alone was unnecessary and standard cohort analysis would have been sufficient;
- the addition of extra health states to the model had increased the complexity, which had not been adequately justified;
- there was no pathway in the model to test the specificity of SLNB, which ESC considered to be a major driver of effectiveness, although this pathway had been included in the Morton RL et al model where patients with intermediate thickness melanoma and a false negative finding on SLNB had poorer melanoma-specific survival outcomes;
- the same utilities had been applied for both populations, irrespective of the effect of melanoma thickness on quality of life, and the use of multiple sources for the utility estimates resulted in logical inconsistencies; for example, the lower boundary of the utility values for Stage II melanoma was lower than that for Stage IV;
- although in the MSLT-I trial all patients with a positive SLNB had undergone immediate CLND, around 20% of patients would now have this procedure, whereas in the model half the patients in the cohort underwent the surgery.

In summary, ESC considered that although the economic evaluation in the revised submission suggested that WLE+SLNB was cost-effective compared with WLE alone for patients with intermediate thickness melanoma, the findings were unreliable due to the difference in model outcomes between the initial and revised submissions; and the difference in the findings between the submissions and the evaluation performed in the critique.

ESC noted that an epidemiological approach had been taken to estimate the financial implications of the introduction of SLNB on the MBS.

ESC noted that as current data on utilisation rates had not been located, two studies were used to estimate utilisation rates in the Australian population (van der Ploeg IM et al 2014 and Varey AHR et al 2017). SLNB utilisation data from van der Ploeg IM et al (2014) were selected for the base case (55% for intermediate melanoma; 51% for thick melanoma) and a rate of 45% (Varey AHR et al 2017) was used in the sensitivity analysis. ESC considered that the rates were a source of uncertainty, and that listing of the item could potentially increase use.

ESC noted that the number of services had been estimated at ~2200 to ~2400 cases per year over a five year period, resulting in total direct costs of ~\$1.1 million to ~\$1.2 million and total costs to the MBS of ~\$12 million to ~\$13 million. ESC noted that several MBS funded medical services are already in use in association with SLNB, and that the financial estimates had not identified a potential reduction in use of these items which had likely overestimated the financial costs to the MBS.

ESC noted that the item descriptor currently states that SLNB should be performed following excision of the primary lesion. ESC considered that this should be modified to clarify that SLNB should be performed at the time of WLE to avoid potential disruption of lymphatic drainage.

ESC noted that the proposed item descriptor limited the procedure to one lesion per patient, and considered the claim by the applicant that this limit was unreasonable as it is not uncommon for positive SLNB to be found in more than one location in a patient. ESC noted the estimates in the revised assessment (20% of patients would have two basins affected). ESC considered that the item should not be restricted to one billing per occasion, and that consequently the multiple operations rule might be applicable.

ESC considered separate items for intermediate and thick melanoma might be helpful for monitoring usage and might also allow a comparison of fees for consumers. ESC noted that the proposed fee is the same as for patients undergoing SLNB for breast cancer (MBS item 30299). ESC also considered that a 75% (\$478.10) benefit would apply to the item as it is an in-hospital procedure, which is the same as for MBS item 30299.

ESC noted that although the procedure provides prognostic information it does not impact outcomes, and could potentially raise consumer expectations about improved survival.

15. Other significant factors

The 2008 Clinical Practice Guidelines for the Management of Melanoma in Australia and New Zealand (Cancer Council Australia and Australian Cancer Network 2008) were recently updated (Gyorki, Teddy et al. 2017), and their recommendations regarding SLNB are expected to directly affect the utilisation of the service and associated interventions.

16. Applicant's comments on MSAC's Public Summary Document

The applicant had no comment.

17. Further information on MSAC

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