

The Contemporary Role of Sentinel Lymph Node Biopsy in the Era of Modern Systemic Therapy for Cutaneous Melanoma

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Abstract

MSLT-II and DeCOG-SLT have often been interpreted as the end of the therapeutic case for sentinel lymph node biopsy. The argument advanced here is more nuanced. Completion lymph node dissection has been retired; sentinel biopsy has not. Its contemporary value is prognostic rather than therapeutic, serving as a staging gateway to adjuvant systemic therapy whose decisional impact is greatest in intermediate-thickness disease. This review defends the thesis that SLNB retains an irreplaceable role because its function has been redefined by KEYNOTE-054, COMBI-AD, CheckMate 238, KEYNOTE-716, CheckMate 76K, PRADO, SWOG S1801, and NADINA. The procedure should be performed where its result will be acted upon and omitted where systemic therapy eligibility or biomarker criteria render it redundant. This principle must remain responsive to the evolving surgical standard: emerging studies, including MSLT-III, may support further surgical de-escalation even when nodal status is established after neoadjuvant therapy. Five propositions are examined: completion dissection offered no demonstrable survival benefit despite reducing basin recurrence; adjuvant anti-PD-1 and BRAF/MEK therapy have elevated accurate nodal staging; adjuvant anti-PD-1 in stage IIB/IIC disease has reduced SLNB's prescriptive function without eliminating its prognostic value; neoadjuvant checkpoint blockade is increasingly displacing SLNB in macroscopic stage III disease; and tissue-based gene-expression profiling should not be treated as a homogeneous category: CP-GEP and 31-GEP show divergent performance, particularly in their ability to reduce SLNB procedures without exceeding acceptable false-omission rates, while circulating tumor DNA remains a context-dependent and investigational adjunct whose sensitivity may be substantially lower for certain recurrence sites, including brain metastases, limiting its reliability because of site-specific false-negative results; neither approach has crossed the evidence threshold required for substitution. Strongest counter-arguments are addressed explicitly throughout. This review synthesises landmark randomised controlled trials, contemporary clinical practice guidelines (NCCN, ASCO-SSO, ESMO, and AIOM), and high-quality systematic reviews published between January 2000 and December 2025. Studies were identified through structured searches of

Date of Submission: 14-09-2026

Date of Acceptance: 25-09-2026

I. Introduction

The conventional evaluation of SLNB asks whether the procedure prolongs survival. The evidence suggests that with a narrow subgroup caveat from MSLT-I [1], it does not. That framing is evolving.

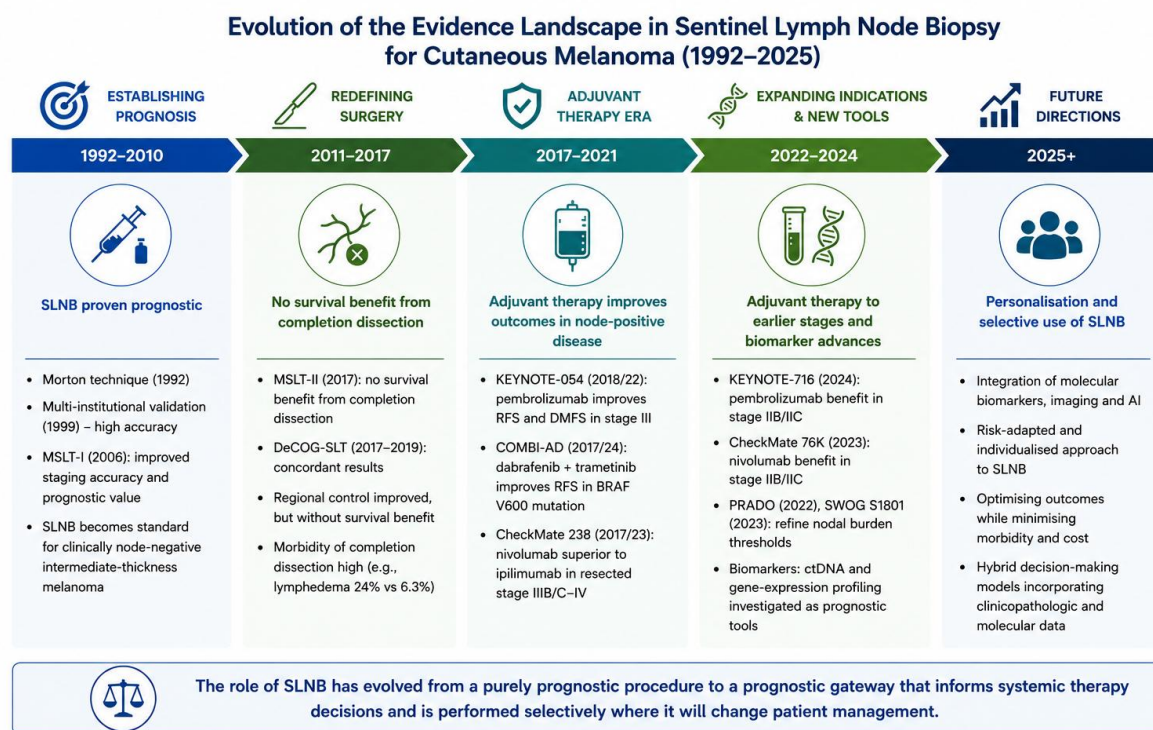
The contemporary question is whether the prognostic information SLNB provides alters a downstream management decision that meaningfully changes the patient's outcome. Three clinical settings demand this distinction. In intermediate-thickness melanoma, where the patient would accept adjuvant anti-PD-1 on a positive sentinel result, SLNB is decisive. In stage IIB/IIC disease, where the patient would accept adjuvant anti-PD-1 on the basis of primary-tumor features alone, as licensed by KEYNOTE-716 [2] and CheckMate 76K [3], SLNB remains prognostically informative but therapeutically optional in stage IIB/IIC disease. **This conclusion remains contested.** Although some surgical experts argue that SLNB continues to provide important regional staging and control, and that omission may permit delayed nodal recurrences requiring more morbid therapeutic lymph node dissection, others have advanced the opposite position. In a recent European Journal of Cancer perspective, van Akkooi and Eggermont [4] argued that SLNB may become largely redundant in stage IIB/IIC melanoma because adjuvant anti-PD-1 therapy is now recommended on the basis of primary tumour characteristics alone, reducing the procedure's role as the gateway to systemic treatment. The authors propose that patients with high-risk stage II disease may derive similar access to effective systemic therapy irrespective of sentinel-node status. However, this position remains controversial because prospective evidence demonstrating that omission of SLNB does not compromise regional disease control or long-term oncological outcomes is still lacking. In macroscopic stage III disease managed with neoadjuvant dual checkpoint blockade as in the NADINA trial [5], SLNB is no longer the staging operation; upfront pathologic response assessment is. The synthesis of the past decade's trials permits each

setting to be reasoned through distinctly. The challenge is not the absence of evidence but the integration of evidence into a coherent decision framework.

Clinical implication: Surgical decision-making should be reframed in terms of whether the sentinel result will change management, rather than whether the procedure improves survival in any absolute sense.

The evolution of surgical nodal staging in cutaneous melanoma is summarised in Figure 1, illustrating how the role of sentinel lymph node biopsy (SLNB) has evolved from a staging procedure linked to completion lymph node dissection into a selective prognostic tool integrated with modern systemic therapy.

Figure 1 — Historical Evolution of Surgical Nodal Staging for Cutaneous Melanoma



Abbreviations: SLNB, sentinel lymph node biopsy; MSLT, Multicenter Selective Lymphadenectomy Trial; DeCOG-SLT, Deutsche Cooperative Group–Sentinel Lymph Node Trial; RFS, relapse-free survival; DMFS, distant metastasis-free survival; ctDNA, circulating tumor DNA; AI, artificial intelligence.

Clinical implication: The contemporary role of SLNB was not eliminated by MSLT-II; it was functionally transformed by the convergence of the completion-dissection verdict with the adjuvant anti-PD-1 programme.

II. Literature Search and Evidence Synthesis

This review synthesises evidence from landmark randomised controlled trials, contemporary clinical practice guidelines, and high-quality systematic reviews evaluating the role of sentinel lymph node biopsy (SLNB) in cutaneous melanoma. A structured search of PubMed/MEDLINE and relevant reference lists identified studies published between January 2000 and December 2025, with emphasis on practice-changing clinical trials and guideline-defining evidence, including recommendations from NCCN, ASCO–SSO, ESMO, and AIOM. Studies were selected based on their relevance to the evolving role of SLNB in contemporary melanoma management.

2. The Retirement of Completion Lymph Node Dissection

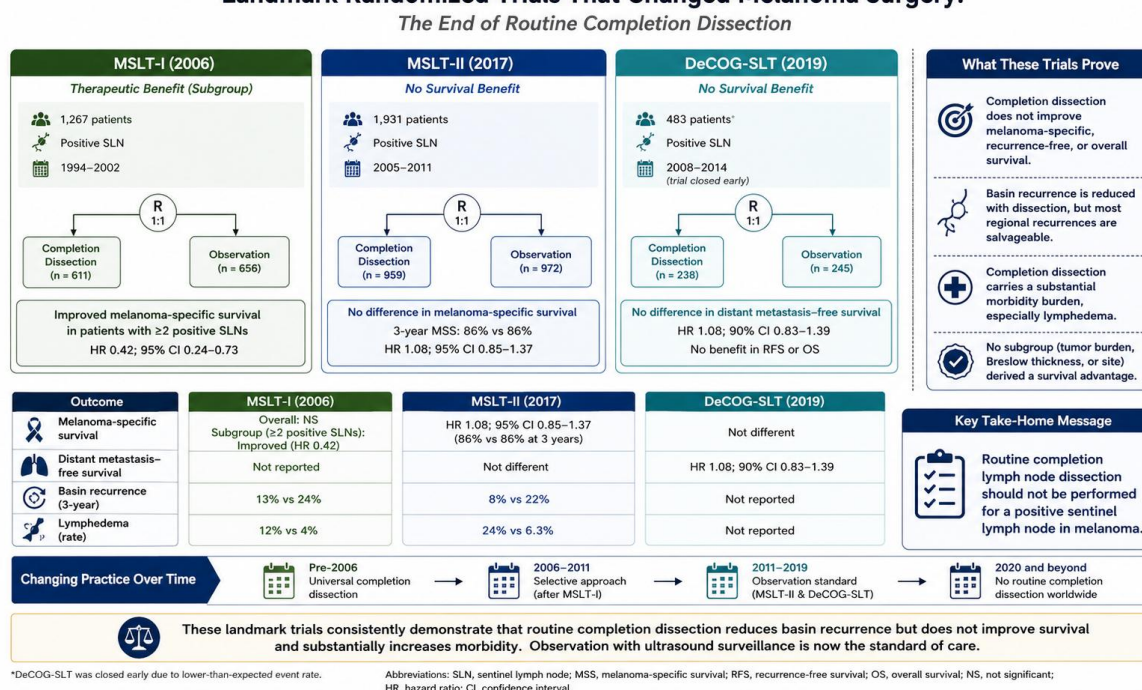
The strongest summary of modern melanoma surgery is that completion lymph node dissection has been retired. MSLT-II [6] randomised 1,931 sentinel-positive patients to immediate completion dissection versus ultrasound-guided observation. Three-year melanoma-specific survival was 86% in both arms (HR 1.08, 95% CI 0.85–1.37). DeCOG-SLT [7] randomised 483 sentinel-positive patients (enrolment curtailed for lower-than-projected events) and reported a distant-metastasis-free survival hazard ratio of 1.08, with no recurrence-free or overall survival benefit.

The two trials reached concordant conclusions through independent designs, different eras, and different surgical philosophies. Their findings also mandated a shift in postoperative surveillance: after a positive sentinel node, patients managed with observation rather than completion lymph node dissection require structured, basin-focused ultrasonography and clinical examination to detect nodal recurrence at a potentially salvageable stage. This approach transfers responsibility from prophylactic surgery to disciplined surveillance, requiring clear

imaging schedules, experienced ultrasonographers, prompt investigation of suspicious findings, and reliable patient follow-up. Thus, omitting completion dissection does not mean omitting regional management; it replaces routine surgery with active surveillance and timely therapeutic intervention. That convergence is what rendered the verdict inescapable. Their complementary contribution is also informative: MSLT-II [6] demonstrated that dissection reduced 3-year basin recurrence from 22% to 8%, indicating that regional control can be achieved, but it did not translate into a survival benefit because recurrence remained salvageable. DeCOG-SLT [7] further showed that no subgroup, including those stratified by sentinel tumour burden, derived a survival benefit from immediate dissection.

Two nuances temper the apparent clarity. First, the trials accrued before routine adjuvant anti-PD-1 therapy became standard, and whether integrating completion lymph node dissection with modern adjuvant treatment would alter the conclusion has not been tested directly. This limitation is partly addressed by the 2024 EADO/EDF/EORTC interdisciplinary guidelines, which integrate surgical staging with contemporary adjuvant treatment strategies; however, guideline-based recommendations do not substitute for direct randomised evidence evaluating completion dissection in the era of adjuvant checkpoint inhibition. Second, the morbidity penalty of completion dissection was substantial, with MSLT-II, a randomized controlled trial, reporting lymphedema in 24% of patients assigned to completion dissection versus 6.3% assigned to observation [6,8], whereas the retrospective Italian CNMR cohort reported a 6.9% rate of early wound complications after SLNB alone [8]. These are not directly comparable outcomes: lymphedema reflects a potentially chronic morbidity associated with the intervention, while early wound complications represent short-term postoperative events assessed in a non-randomized cohort. The verdict is unambiguous, but the question of how completion dissection interacts with current adjuvant practice remains open. The next phase of surgical de-escalation will be informed by the MSLT-III trial, launched in 2025, which is directly relevant to the future of regional nodal management. The landmark randomised trials that transformed regional nodal management are compared in **Figure 2**. Together, these studies demonstrate that while SLNB remains valuable for pathological staging, routine completion lymph node dissection does not improve melanoma-specific or overall survival.

Figure 2. Landmark Randomised Trials Defining Contemporary Nodal Surgery
Landmark Randomized Trials That Changed Melanoma Surgery:



Key elements: MSLT-I HR 0.56 in subgroup [1]; MSLT-II 3-year MSS 86% in both arms with basin recurrence 8% versus 22% [6]; DeCOG-SLT DMFS HR 1.08 [7].

Clinical implication: MSLT-I tested whether biopsy plus completion dissection improves survival and found subgroup benefit; MSLT-II and DeCOG-SLT tested whether completion dissection itself was the active component and answered no.

The principal characteristics and outcomes of the landmark randomised trials that reshaped regional nodal management are summarised in Table 1. Collectively, these studies established that while SLNB remains essential for pathological staging, routine completion lymph node dissection does not confer an overall survival advantage.

Table 1. The Completion-Dissection Trials Converge on a Single Negative Verdict

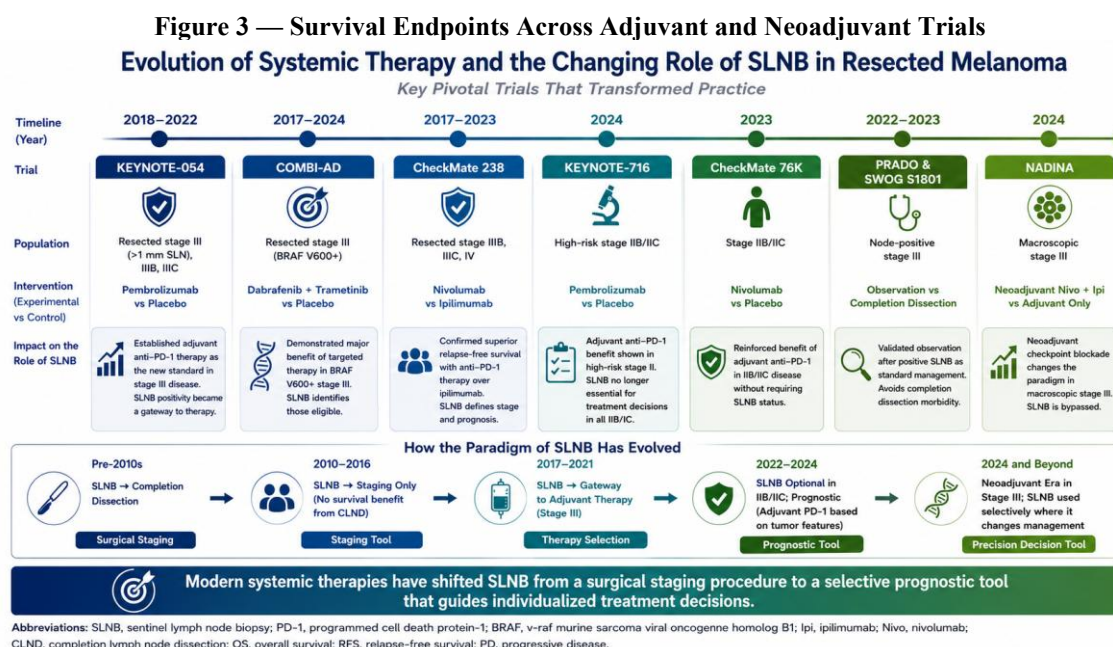
Trial	n	Endpoint	Hazard ratio	Interpretation
MSLT-II [6]	1,931	3-yr MSS, OS	HR 1.08 (CI 0.85–1.37) for dissection	Basin recurrence 8% vs 22%; no survival benefit; 4× lymphedema
DeCOG-SLT [7]	483 (closed early)	DMFS, RFS, OS	DMFS HR 1.08 (90% CI 0.83–1.39)	Concordant with MSLT-II; no subgroup benefit by sentinel burden

Clinical implication. Routine completion lymph node dissection after a positive sentinel node should not be performed; structured observation with ultrasonography and adjuvant therapy consideration is the contemporary standard.

III. The Adjuvant Therapy Imperative

Until 2017, a positive sentinel node obliged the surgeon to consider completion dissection. The same prognostic information now obliges the patient to consider adjuvant systemic therapy. The prognostic value did not change; the decision pathway to which it leads has been re-cabled. The evolution of modern adjuvant and neoadjuvant systemic therapy, and its impact on the contemporary role of SLNB, is illustrated in **Figure 3**. These landmark studies—KEYNOTE-054 [9,10], CheckMate 238 [11,12], and COMBI-AD [13,14]—demonstrate how SLNB has transitioned from directing further surgery to guiding personalised systemic treatment. Their strongest and most consistent benefits are improvements in relapse-free and distant-metastasis-free survival; in COMBI-AD, the overall-survival benefit remained directional but did not reach statistical significance [15].

Three pivotal randomised phase III trials support this re-framing (see Table 2). KEYNOTE-054 [9] randomised 1,019 patients with resected stage IIIA (>1 mm sentinel deposit), IIIB, or IIIC melanoma to pembrolizumab versus placebo. At 5 years [10], relapse-free survival was 55.4% versus 38.3% and distant-metastasis-free survival was 60.6% versus 44.5%. CheckMate 238 [11] randomised 906 patients with stage IIIB/IIIC/IV disease to nivolumab versus ipilimumab; 5-year relapse-free survival was 50% versus 39%, with directional but non-significant overall survival benefit [12]. COMBI-AD [13] randomised 870 patients with resected stage III BRAF V600-mutant melanoma to dabrafenib plus trametinib versus placebo. The final 10-year analysis of COMBI-AD represents the longest follow-up of any adjuvant targeted-therapy programme in resected stage III melanoma and supports the durability of relapse-free survival and distant metastasis-free survival gains first demonstrated at 3 and 5 years [16]. After a median follow-up of 100.0 months in the dabrafenib-plus-trametinib arm and 82.5 months in the placebo arm, median overall survival was not reached in either arm, with RFS (HR 0.52; 95% CI 0.43-0.63) and DMFS (HR 0.56; 95% CI 0.44-0.71) both favouring combination therapy [15]. **However, the OS analysis showed that the risk of death was 20% lower with dabrafenib plus trametinib than with placebo in the overall ITT population, an effect that did not reach statistical significance (HR 0.80; 95% CI 0.62-1.01; P = 0.063) [15].** Among patients with a *BRAF* V600E mutation the signal strengthened to a 25% reduction in death risk (HR 0.75; 95% CI 0.58-0.96), but this subgroup analysis cannot salvage the primary OS claim [14]. The loss of statistical significance on OS is plausibly attributable to crossover and effective post-progression therapies: 29% of patients in each arm received salvage immunotherapy, and 21% versus 37% (treatment vs placebo) received subsequent targeted therapy [15]. **Informed interpretation therefore requires explicit acknowledgement that the 20% ITT OS reduction did not reach statistical significance, even though RFS and DMFS gains remain robust at the 10-year horizon [15].**



Key elements: KEYNOTE-054 [10] 5-year RFS; CheckMate 238 [12] 5-year RFS; COMBI-AD [14] 10-year OS HR 0.80; SWOG S1801 [17] 2-year EFS HR 0.58.

Clinical implication: Across modalities, adjuvant and neoadjuvant trials converge on a recurring pattern: substantial relapse-free or event-free survival gain, with overall-survival benefit consistently directional rather than statistically definitive at conventional thresholds.

The major contemporary adjuvant and neoadjuvant melanoma trials are summarised in Table 2. Together, these studies demonstrate how the therapeutic implications of SLNB have evolved from guiding further surgery to directing personalised systemic treatment, while emerging strategies such as Index Lymph Node-guided surgical de-escalation after neoadjuvant therapy—being explored in the context of the forthcoming MSLT-III trial—may further redefine the future role of nodal surgery.

Table 2. Adjuvant Anti-PD-1 and BRAF/MEK Trials Redefine the Value of Sentinel Positivity

Trial	Regimen	n	Key endpoint	Interpretation
KEYNOTE-054 [9,10]	Pembrolizumab vs placebo	1,019	5-yr RFS 55.4% vs 38.3%	Clean placebo design; OS unresolved
CheckMate 238 [11,12]	Nivolumab vs ipilimumab	906	5-yr RFS 50% vs 39%	Active-control design; OS HR NS
COMBI-AD [13,14]	Dabrafenib + trametinib vs placebo	870	10-yr OS HR 0.80; 10-yr RFS HR 0.52	Sustained RFS gain; directional OS

In synthesis, the trials converge on a single conclusion: a positive sentinel node in an adjuvant-eligible patient yields a substantial reduction in relapse hazard. They do not establish cure on overall-survival endpoints, a limitation that warrants honest patient counselling, but relapse delay in melanoma is meaningful when the relapse event is itself morbid. The argument that SLNB does not produce cure is weaker than the premise that it produces fewer relapses; the latter is what the trials established.

Clinical implication. A positive sentinel node in a patient eligible for adjuvant anti-PD-1 or BRAF/MEK inhibitor therapy roughly halves the relapse hazard. SLNB is the procedure that establishes this eligibility, and its prognostic value is now anchored in the adjuvant trial evidence base rather than in any surgical demonstration of survival benefit.

IV. Stage II Disease — When SLNB Becomes Optional

KEYNOTE-716 [2] and CheckMate 76K [3] licensed adjuvant anti-PD-1 for resected stage IIB/IIC melanoma on primary tumor features alone. KEYNOTE-716 achieved a 3-year relapse-free survival of 76.2% versus 63.4% in 976 patients with resected stage IIB/IIC melanoma [2]. CheckMate 76K achieved a 12-month relapse-free survival HR of 0.42 in 790 stage IIB/IIC patients. The immediate interpretation that SLNB is no longer required for adjuvant decision-making in stage IIB/IIC disease is technically correct in a narrow sense. Because

adjuvant systemic therapy can now be considered on the basis of primary-tumour features alone, omission of SLNB does not necessarily preclude access to treatment. However, this does not make SLNB clinically redundant. Sentinel-node staging may still provide prognostic information and, when a node is positive, permit timely regional management before nodal disease progresses to clinically apparent recurrence. Systemic therapy reduces, but does not eliminate, the risk of regional nodal relapse; omitting SLNB may therefore leave some patients vulnerable to a later, more morbid therapeutic lymph-node dissection. The most defensible interpretation is consequently that SLNB has become optional for adjuvant access but remains selectively valuable for regional control, prognostic refinement, and avoidance of delayed nodal surgery. The pivotal phase III trials that expanded adjuvant anti-programmed death-1 (PD-1) therapy into stage II melanoma are summarised in **Table 3**. These studies represent a major shift in melanoma management by demonstrating that selected patients with stage IIB/IIC disease may derive benefit from adjuvant immunotherapy irrespective of sentinel lymph node status, thereby reducing the exclusive role of SLNB as the gateway to systemic treatment.

Table 3. Stage II Adjuvant Anti-PD-1 Trials Decouple Sentinel Status from Adjuvant Access

Trial	Regimen	n	Key endpoint	Interpretation
KEYNOTE-716 [2]	Pembrolizumab vs placebo	976 (sentinel-negative)	3-yr RFS 76.2% vs 63.4%	Sentinel-negative enrolment; limits generalisability
CheckMate 76K [3]	Nivolumab vs placebo	790 (stage II)	12-mo RFS HR 0.42	Short follow-up; stage II revolution

The conceptual distinction, however, is essential. KEYNOTE-716 and CheckMate 76K established that adjuvant decision-making does not require SLNB; they did not demonstrate that prognostic integration does not benefit from SLNB. The defensible synthesis, supported by the Annals of Surgical Oncology 2024 practice guideline [18] and the Matteucci 2025 narrative review of contemporary lymphadenectomy practice across AIOM, ESMO, and NCCN guidelines [19], is that routine SLNB in stage IIB/IIC disease is no longer required for adjuvant access but remains viable for integrated prognostic staging. The procedure has moved from mandatory to selective in this population, but this shift remains contested because the available stage IIB/IIC systemic-therapy trials have not yet demonstrated a reduction in regional nodal recurrence. Accordingly, some surgeons continue to advocate SLNB for regional nodal staging and control, arguing that adjuvant-treatment access and the management of occult nodal disease are distinct clinical questions.

Clinical implication. In stage IIB/IIC melanoma, SLNB is no longer required for adjuvant access; it remains an option when integrated staging or trial eligibility benefits from nodal information.

V. The Neoadjuvant Disruption in Macroscopic Disease

The most consequential development for SLNB in macroscopic stage III disease is the neoadjuvant paradigm (see Table 4). PRADO [20] introduced response-directed surgery after two cycles of low-dose ipilimumab (1 mg/kg) plus nivolumab (3 mg/kg), demonstrating a reported 49% pathologic complete response rate and a 72% overall pathologic response rate [20]. SWOG S1801 [17] established that pembrolizumab sequenced before surgery produces superior 2-year event-free survival (72% versus 49%, HR 0.58) compared with adjuvant pembrolizumab alone. NADINA [5] extended the approach to dual checkpoint blockade in 423 patients and supports neoadjuvant ipilimumab plus nivolumab as a first consideration in macroscopic stage III disease. The principal neoadjuvant immunotherapy trials that have reshaped the management of macroscopic stage III melanoma are summarised in **Table 4**. Collectively, these studies demonstrate that neoadjuvant checkpoint blockade can achieve substantial pathological and event-free survival benefits, challenging the traditional sequence of SLNB followed by completion lymph node dissection in appropriately selected patients. The next frontier is surgical de-escalation after neoadjuvant systemic therapy. The forthcoming MSLT-III trial is expected to clarify the role of index lymph-node surgery and help establish definitive standards for managing the regional basin in stage III melanoma, potentially further reducing the need for conventional nodal surgery.

Table 4. Neoadjuvant Trials are Reshaping Surgical Decision-Making in Macroscopic Stage III Melanoma

Trial	n	Regimen	Key result	Interpretation
PRADO [20]	99	Response-directed surgery after Ipi/Nivo	49% pCR; 72% overall pathologic response	Single-arm; surrogate endpoint
SWOG S1801 [17]	313	Neoadjuvant then adjuvant pembro vs adjuvant-only	2-year EFS 72% vs 49%, HR 0.58	First sequencing RCT
NADINA [5]	423	Neoadjuvant Ipi/Nivo vs adjuvant nivo	EFS superiority for neoadjuvant arm	Adequately powered phase III

These three trials together demand a reinterpretation of the surgical algorithm, while the forthcoming MSLT-III trial, expected to launch in 2025, is designed to evaluate whether index lymph-node surgery can be safely de-

escalated after neoadjuvant therapy and may provide the definitive evidence needed to guide this evolving approach. In experienced centres, macroscopic stage III melanoma is increasingly being considered for neoadjuvant dual checkpoint blockade followed by response-directed surgery, although real-world adoption of index lymph node-guided surgical de-escalation remains limited; the SLNB-then-dissection pathway therefore remains common rather than no longer being the default. Two caveats are essential. Overall survival data continue to mature, and pathologic complete response as a cure surrogate, supported by International Neoadjuvant Melanoma Consortium pooled analyses, remains a hypothesis at 5- and 10-year horizons. Dual checkpoint blockade is associated with a high incidence of grade 3–4 immune-related adverse events, typically occurring in over 50% of patients in the neoadjuvant setting[20]. The neoadjuvant programme offers the strongest contemporary case against frontline SLNB in macroscopic disease; it does not yet establish cure.

Clinical implication. At experienced centres, macroscopic stage III melanoma should be referred for neoadjuvant dual checkpoint blockade assessment; SLNB-then-dissection is no longer the default pathway[5].

VI. Molecular Biomarkers — Adjuncts, Not Substitutes

A meaningful appraisal of molecular biomarkers for SLNB decision-making must distinguish between commercially available GEP platforms rather than treat them as a homogeneous class. Head-to-head modelling of the i31-SLNB and CP-GEP, including T1-T3 cohorts with comparable inclusion criteria, has demonstrated an **i31-SLNB false-negative rate of 3.9% in patients classified as low-risk (n = 233) — well below the NCCN 5% threshold for safely omitting SLNB — versus a 7.1% false-negative rate for CP-GEP in low-risk patients (n = 624), which exceeds that threshold [21].** This patterned difference persists across T-stage subgroups: in T1b tumours the i31-SLNB achieved a 2.8% false-negative rate compared with 5.1% for CP-GEP, and in T2a tumours the rates were 4.3% versus 7.3% respectively [21]. **Reanalysis of US-based cohorts confirmed a 96.1% NPV for i31-SLNB (n=1,152) versus 92.9% NPV for CP-GEP (n=1,761), with modelled false-omission-rates consistently lower for i31-SLNB across clinically relevant prevalence ranges [22].** Additional US cohorts further support i31-SLNB 100% NPV at 20.5% and 6.4% SLN-positivity prevalence, while CP-GEP reached only 93.8% NPV in a 21.2% prevalence cohort [22]. **In the largest GEP data set to date — the DECIDE prospective multicentre study — Class 1A 31-GEP patients had a 3.2% SLN-positivity rate (2/63) at 2-year median follow-up, with no recurrences documented regardless of SLNB status, supporting clinical utility of i31-SLNB rather than indiscriminate endorsement of all GEP platforms [23].** Conversely, CP-GEP (MERLIN_001) classified 37% of patients as low-risk, but in harmonised reanalyses this broader low-risk designation did not consistently achieve >95% NPV across simulated prevalence levels, raising concerns about whether SLNB omission can be safely guided by a CP-GEP-negative result alone [24]. A recent CP-GEP validation cohort of 879 low-risk out of 930 stage I/II patients showed significant RFS, DMFS and MSS stratification, but the population-based performance gap between platforms precludes their interchangeable use [4]. Clinicians should therefore adopt a platform-specific threshold — i31-SLNB Class 1A results appear to clear the <5% SLN-positivity benchmark, while CP-GEP low-risk predictions should not, in isolation, drive omission of SLNB. The leading molecular biomarker platforms currently under investigation as adjuncts or potential alternatives to SLNB are summarised in Table 5.

Table 5. Molecular Biomarker Platforms versus Sentinel Biopsy in 2025

Platform	Evidence base	Critical limitation
DecisionDx 31-GEP[25,26]	8,244-sample analytic validation; 523- and 782-patient validation	No randomised survival endpoint; not guideline-endorsed
Merlin CP-GEP[27]	Kött 2024 prospective cohort; MERLIN_001 in progress	Awaiting randomised validation
ctDNA[28]	100% relapse in untreated ctDNA-positive; lead-time detection	Modest early-stage sensitivity; poor intracranial sensitivity

DecisionDx-Melanoma 31-GEP [25] dichotomises primary tumours into Class 1 (low risk) or Class 2 (high risk), with intervening analytical validity and independent clinical validation in a 523-patient cohort [26] confirming risk stratification independent of Breslow thickness, ulceration, and mitotic rate. The Merlin clinicopathologic GEP platform[27] integrates an 8-gene signature with age and Breslow depth to predict sentinel-node positivity and is specifically designed to identify patients at sufficiently low risk who might safely avoid SLNB; prospective validation is ongoing. By contrast, the 31-GEP platform[25,26] primarily provides prognostic risk stratification for recurrence and melanoma-specific survival, with less direct evidence that it can guide SLNB omission. Accordingly, these platforms should not be treated as interchangeable: CP-GEP is the more directly relevant candidate for SLNB de-escalation, whereas 31-GEP remains principally a prognostic adjunct, and neither should currently replace SLNB outside prospective validation. Neither NCCN nor AJCC has formally endorsed either platform for primary treatment decisions [29], [18].

Circulating tumour DNA is detectable in approximately half to two-thirds of patients with metastatic melanoma, with rapid decline upon initiation of MAPK-targeted therapy [30] and lead-time detection of emergent resistance mutations before clinical progression. However, these findings should not be extrapolated uncritically to surveillance: ctDNA sensitivity for recurrence is strongly dependent on anatomical site and may be particularly low for intracranial metastases, creating a significant risk of false-negative results in high-stakes sites [31]. Accordingly, a negative ctDNA result should not be interpreted as evidence of the absence of disease or as a substitute for imaging and clinical assessment. Postoperative ctDNA identifies patients at the highest relapse risk: 100% of untreated patients with detectable postoperative ctDNA relapsed in published series [32]. Longitudinal monitoring identifies molecular relapse before imaging during adjuvant therapy [33], [34].

Both biomarker classes are credible adjuncts in 2025. For biomarkers proposed to support SLNB omission, the false-omission rate—the proportion of patients classified as low risk who would nevertheless have sentinel-node metastases—should be the primary safety metric, supplemented by sensitivity and negative predictive value. Neither platform has generated the randomised survival-endpoint data required for regulatory-grade substitution, and the evidence base does not yet establish an acceptable FOR for routine SLNB avoidance. Gene-expression profiling augments clinicopathological staging but does not replace SLNB; ctDNA complements surveillance but lacks the analytic maturity and intracranial sensitivity to substitute primary staging.

Clinical implication. Tissue-based gene-expression profiling and circulating tumour DNA are credible adjuncts to clinicopathological staging and SLNB; neither has a randomised survival endpoint sufficient for substitution.

VII. Where SLNB Remains Indispensable — And Cost-Effectiveness

Three clinical positions remain where SLNB is irreplaceable. In intermediate-thickness melanoma (1.0–4.0 mm), the survival discrimination between sentinel-positive and sentinel-negative disease exceeds 20% at 5 years, providing a clinically actionable staging signal that current molecular biomarkers do not yet reliably replace; however, CP-GEP and 31-GEP have distinct intended uses and performance profiles, and ongoing debate—particularly regarding false-omission rates—continues to determine whether CP-GEP can safely support SLNB de-escalation, and the 2017 ASCO-SSO guideline recommends routine SLNB [29]. In selected stage IIB/IIC patients, sentinel status remains informative for integrated staging and trial access; however, omission also raises a regional-control concern: systemic therapy has not definitively demonstrated that it can prevent nodal recurrence in lieu of identifying occult nodal disease, and patients who subsequently develop regional relapse may require therapeutic lymph node dissection, with associated morbidity [35,36]. Thus, the potential to avoid SLNB must be balanced against the possibility of delayed nodal intervention and its consequences. KEYNOTE-716 [2] restricted enrolment to sentinel-negative patients, leaving a residual indication. In patients requiring stage III designation for adjuvant trial eligibility, undocumented sentinel positivity limits therapeutic options.

Economic data support this synthesis. The Wilson Markov analysis [37] demonstrated that sentinel mapping followed by adjuvant therapy is cost-effective across reasonable willingness-to-pay thresholds, with an incremental cost-effectiveness ratio well below the \$50,000 per QALY threshold for stage II disease. Furthermore, the MSLT-II-derived analysis demonstrates that observation after a positive sentinel lymph node biopsy is the dominant strategy, yielding greater cumulative QALYs than immediate completion lymphadenectomy (5.379 versus 4.840 over 10 years) with a cost saving of approximately \$7,745 per patient [38]. The economic argument aligns with the clinical: SLNB is cost-effective when its result feeds an adjuvant decision and cost-inefficient when the result is informational only.

Clinical implication. SLNB should be performed in intermediate-thickness disease, in stage IIB/IIC patients whose adjuvant decision is contingent on sentinel status, and in patients requiring stage III designation for trial access. Economic data align with this clinical synthesis.

VIII. Critical Appraisal — Limits of the Argument

The thesis defended here rests on the validity of the adjuvant-trial evidence, and five vulnerabilities warrant acknowledgement.

First, the adjuvant anti-PD-1 trials have not crossed pre-specified overall survival thresholds. KEYNOTE-054 [10] has not demonstrated a curative effect, and CheckMate 238 [12] was not adequately powered for overall survival. Second, the neoadjuvant programme is recent, and long-term OS data for PRADO [20], SWOG S1801 [17], and NADINA [5] continue to mature. Whether pathologic complete response is a sufficient cure surrogate remains a hypothesis. Third, biomarker platforms — DecisionDx 31-GEP [26], Merlin CP-GEP [27] — lack randomised survival endpoint validation. Fourth, AI-augmented imaging and pathology applications in melanoma have documented promising performance but remain preliminary. The Valenti 2025 review of imaging technologies and AI for melanoma surveillance [39] and the Mansini 2025 SLNB overview [40] document the clinical maturation under way while flagging unresolved regulatory and validation gaps. Fifth, ctDNA sensitivity in early-stage disease is modest: recent 2025 data reported an overall sensitivity of 53.6% for recurrence or relapse, falling to 33.3% for brain metastases [31,32,41]. Intracranial sensitivity therefore remains poor, limiting ctDNA

as a standalone surveillance tool. The argument advanced survives these vulnerabilities by acknowledging them rather than ignoring them.

IX. Current Controversies — Balanced Synthesis

Stage IIB/IIC: routine SLNB? Pro-routine: integrated staging at stage III-comparable recurrence risk. Anti-routine: KEYNOTE-716 [2] and CheckMate 76K [3] licensure of adjuvant anti-PD-1 based on primary-tumor features. **Synthesis:** SLNB is permissive rather than mandatory in stage IIB/IIC disease, but omission may compromise regional control: systemic therapy has not definitively been shown to prevent nodal recurrence in lieu of identifying occult nodal disease, and patients who later develop regional relapse may require more morbid therapeutic lymph node dissection [35,36]

Elderly patients. Pro-omission: lower sentinel positivity rates, higher morbidity, and smaller adjuvant-eligible pool. **Synthesis:** SLNB is best omitted in elderly patients with comorbidities precluding adjuvant therapy and retained in those who would accept it.

Can biomarkers replace SLNB? Pro-replacement: DecisionDx Class 2B identifies high-risk patients[42], and Merlin CP-GEP is in prospective validation[42]. Anti-replacement: neither platform has randomised survival endpoint data. **Synthesis:** biomarkers augment, but do not substitute [18,29].

Can ctDNA replace nodal staging? Pro-substitution: high risk of relapse in ctDNA-positive patients[31] and lead-time detection of molecular relapse. Anti-substitution: ctDNA has modest sensitivity in low-volume disease and poor sensitivity for certain anatomical sites, including brain metastases (33.3%) and skin, mucosal, or muscle recurrences (37.5%) [31,41]. Consequently, a negative ctDNA result does not reliably exclude relapse in these sites and should not replace clinical assessment or site-appropriate imaging. **Synthesis:** ctDNA complements surveillance; it does not substitute primary staging.

Can AI replace pathologists? Not in 2025. AI applications in melanoma are approaching clinical maturity but lack pathologist-equivalent regulatory-grade validation [39,40]. **Synthesis:** AI is best deployed as a decision-support adjunct with explicit quality control.

Is SLNB becoming prognostic rather than therapeutic? Yes, and this is the central claim of this review: the procedure is performed because its prognostic information drives downstream decisions in systemic therapy, not because the surgery itself improves survival.

X. Practical Clinical Decision Algorithm

The following algorithm distils the preceding synthesis into a clinically actionable workflow. The evidence presented throughout this review can be synthesised into a practical clinical decision pathway (**Figure 4**). This algorithm integrates tumour stage, contemporary guideline recommendations, and modern systemic treatment pathways to support evidence-based use of SLNB.

Perform SLNB when:

Intermediate-thickness melanoma in a patient eligible for adjuvant therapy.

Sentinel-equivocal status after prior wide local excision; hybrid radioactive-fluorescent mapping and SPECT/CT are preferred [43].

Patient requires stage III designation for trial access.

Consider omitting SLNB when:

Low-risk clinicopathologic features and a favorable gene-expression profile are present, such as a CP-GEP/Merlin low-risk classification, provided the result is incorporated into shared decision-making rather than used as an automatic substitute for SLNB [42].

The estimated risk of sentinel-node positivity is below the accepted omission threshold, typically less than 5%, and the patient understands the residual risk of occult nodal disease.

The false omission rate, defined as $1 - \text{NPV}$, is acceptably low for the relevant population; FOR should be reported alongside sensitivity, specificity, negative predictive value, and the proportion of patients classified as low risk, rather than used as the sole measure of clinical utility [24].

Consider SLNB when:

T1b or T4 disease, individualised to patient preference.

Stage IIB/IIC in whom integrated staging will inform surveillance or trial access.

Omit SLNB when:

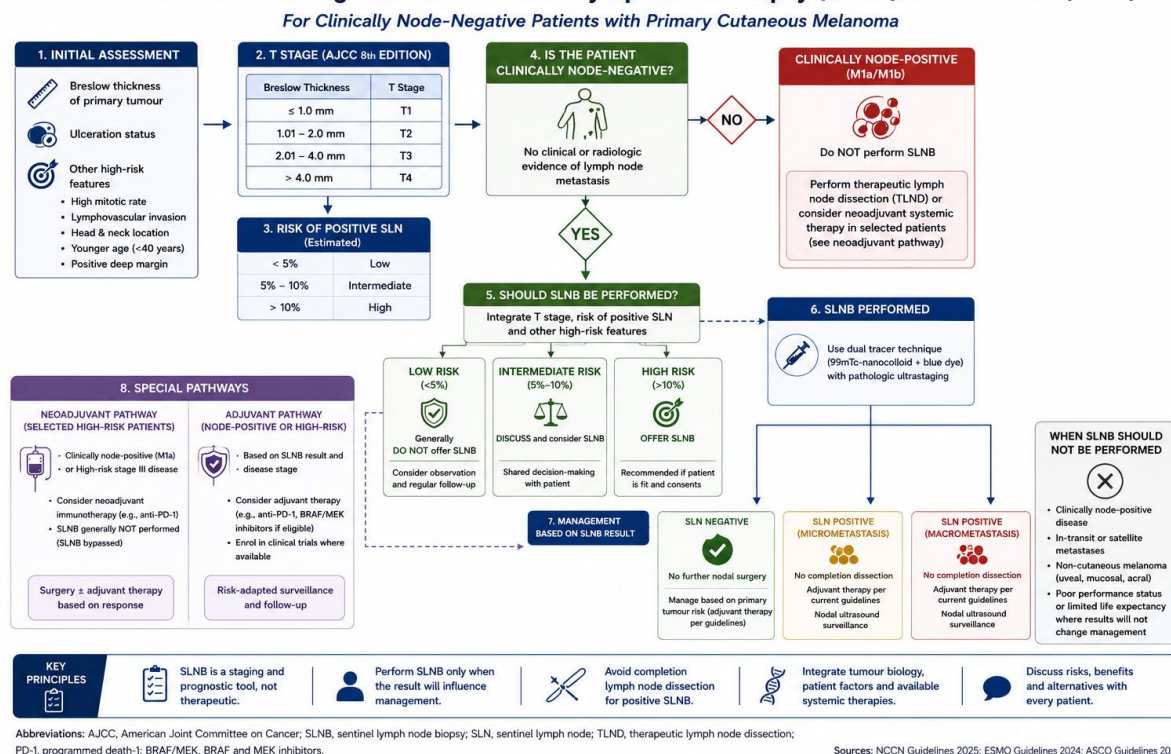
T1a melanoma (<0.8 mm, non-ulcerated).

Elderly or comorbid patients in whom adjuvant therapy is infeasible.

Macroscopic stage III melanoma suitable for neoadjuvant dual checkpoint blockade at an experienced centre.

Stage IIB/IIC patients who would accept adjuvant anti-PD-1 regardless of sentinel status.

Figure 4 — Practical Clinical Decision Algorithm for SLNB in 2025
Clinical Decision Algorithm for Sentinel Lymph Node Biopsy (SLNB) in Melanoma (2025)



Key elements: T1a omit; T1b discuss if therapy-eligible; T2/T3 recommend; T4 individualised; stage IIB/IIC selective or omitted based on adjuvant access; macroscopic stage III refer to experienced centre for neoadjuvant; sentinel-equivocal after prior wide local excision recommend with hybrid mapping.
Clinical implication: SLNB is performed where its result will be acted upon, considered where it may be, and omitted where it will not.

XI. Evidence Gaps and Research Priorities

Eight areas of uncertainty constrain the thesis advanced here.

First, the overall survival benefit of adjuvant anti-PD-1 in stage III disease remains unresolved. KEYNOTE-054 [10] has not crossed pre-specified OS thresholds, and CheckMate 238 [12] was underpowered for OS. Extended 10-year follow-up of KEYNOTE-054, CheckMate 238, and COMBI-AD [14] will determine whether relapse-free benefit translates into documented cure.

Second, the optimal standardisation of surgical management after neoadjuvant therapy remains unresolved. Although response-directed strategies may reduce the extent of lymph-node surgery in selected patients, the appropriate indications, timing, and extent of sentinel-node biopsy, therapeutic lymph-node dissection, and completion surgery remain uncertain across response categories. The role of the MSLT-III trial will be particularly important in defining whether surgical management can be safely standardised after neoadjuvant treatment.

Third, pathologic complete response as a cure surrogate in neoadjuvant-treated macroscopic disease is supported by International Neoadjuvant Melanoma Consortium pooled analyses but not yet validated at 5- and 10-year OS endpoints. Long-term OS follow-up of PRADO [20], SWOG S1801 [17], and NADINA [5] will determine whether pathologic complete response is sufficient.

Fourth, biomarker-driven SLNB omission is largely hypothetical. The MERLIN_001 randomised trial of CP-GEP-defined low-risk patients [27] is a prominent biomarker-driven study in the pipeline.

Fifth, ctDNA-guided adjuvant decision-making lacks randomised evidence despite compelling observational data on postoperative relapse prediction [32] and lead-time detection [33,34]. Randomised ctDNA-guided intensification or de-escalation trials are warranted.

Sixth, the anatomical limitations of ctDNA sensitivity constrain its use in surveillance. Detection is substantially less reliable for low-shedding or anatomically compartmentalised recurrences, including brain, skin, mucosal, and muscle disease [31,41]. Consequently, a negative ctDNA result cannot exclude relapse and should not replace clinical assessment or site-appropriate imaging. Future studies should report sensitivity by recurrence site and establish surveillance pathways that integrate ctDNA with examination and imaging rather than treating it as a standalone test.

Seventh, AI-augmented imaging, surveillance, and pathology in melanoma have promising observational performance but lack regulatory-grade randomised validation [39], with documented concerns regarding algorithmic bias across skin tones.

Eighth, international guideline divergence persists in stage IIB/IIC disease and thin melanomas [18,19,29]. International consensus-building anchored on prospective biomarker-driven trials will likely be required.

First, the overall survival benefit of adjuvant anti-PD-1 in stage III disease remains unresolved. KEYNOTE-054 [10] has not crossed pre-specified OS thresholds, and CheckMate 238 [12] was underpowered for OS. The final 2024 results of COMBI-AD [14] demonstrate sustained relapse-free survival benefit, but the overall survival benefit did not reach statistical significance; therefore, whether relapse-free benefit translates into a definitive cure remains uncertain.

Second, pathologic complete response as a cure surrogate in neoadjuvant-treated macroscopic disease is supported by International Neoadjuvant Melanoma Consortium pooled analyses but not yet validated at 5- and 10-year OS endpoints. Long-term OS follow-up of PRADO [20], SWOG S1801 [17], and NADINA [5] will determine whether pathologic complete response is sufficient.

Third, biomarker-driven SLNB omission is largely hypothetical. The MERLIN_001 randomised trial of CP-GEP-defined low-risk patients [27] is a prominent biomarker-driven study in the pipeline.

Fourth, ctDNA-guided adjuvant decision-making lacks randomised evidence. Although observational studies suggest potential utility for postoperative relapse prediction and lead-time detection [32–34], current surveillance sensitivity remains limited: one 2025 study reported an overall sensitivity of 53.6%, with lower sensitivity for brain metastases (33.3%) and skin, mucosal, or muscle recurrences (37.5%) [31]. Accordingly, a negative ctDNA result cannot exclude relapse and should not replace clinical assessment or site-appropriate imaging. Randomised ctDNA-guided intensification or de-escalation trials are warranted.

Fifth, AI-augmented imaging, surveillance, and pathology in melanoma have promising observational performance but lack regulatory-grade randomised validation [39], with documented concerns regarding algorithmic bias across skin tones.

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XII. Future Directions

Three trends may reshape practice by 2035. Current evidence suggests, but has not established, that biomarker-driven de-escalation will determine whether biomarker-defined stage II patients can be managed without SLNB or with selective SLNB alone; this depends on the maturation of NivoMela and MERLIN_001 [4,27]. Current evidence further suggests that neoadjuvant dominance in macroscopic disease will mature as the MSLT-III trial clarifies Index Lymph Node-guided surgical de-escalation and as PRADO [20], SWOG S1801 [17], and NADINA [5] report extended OS follow-up; if pathologic complete response proves a sufficient cure surrogate, response-directed surgery will likely become the standard at experienced centres., SWOG S1801 [17], and NADINA [5] report extended OS follow-up; if pathologic complete response proves a sufficient cure surrogate, response-directed surgery will likely become the standard at experienced centres. Finally, AI-augmented imaging and surveillance will likely enter routine workflows, but whether these platforms achieve substitute rather than adjunct status depends on regulatory-grade validation [39].

A likely future trajectory is that SLNB will remain standard for intermediate-thickness melanoma, become selective for stage II disease only when supported by a validated biomarker platform and clinically acceptable metrics such as the false-omission rate, and be substantially displaced by upfront neoadjuvant immunotherapy in macroscopic stage III disease. Because genomic platforms do not perform equivalently in identifying patients who may safely forgo SLNB[21,24], platform selection and prospective validation will be critical. The extent of surgical de-escalation after neoadjuvant therapy also remains uncertain; the forthcoming MSLT-III trial, launching in 2025, should help clarify the surgical follow-up required for patients who achieve a pathologic complete response [44]. ctDNA and AI-assisted surveillance will probably complement radiologic surveillance without displacing it: current ctDNA sensitivity is modest overall (53.6%) and particularly limited for brain (33.3%) and skin, mucosal, or muscle recurrences (37.5%), creating a clinically important risk of false-negative results and delayed intervention [31]. Further validation is required before any of these directions can be regarded as definitive. The anticipated evolution of melanoma staging over the next decade is summarised in **Figure 5**. The roadmap illustrates how SLNB is expected to become increasingly integrated with molecular

biomarkers, circulating tumour DNA, artificial intelligence, and personalised treatment strategies as these technologies mature.

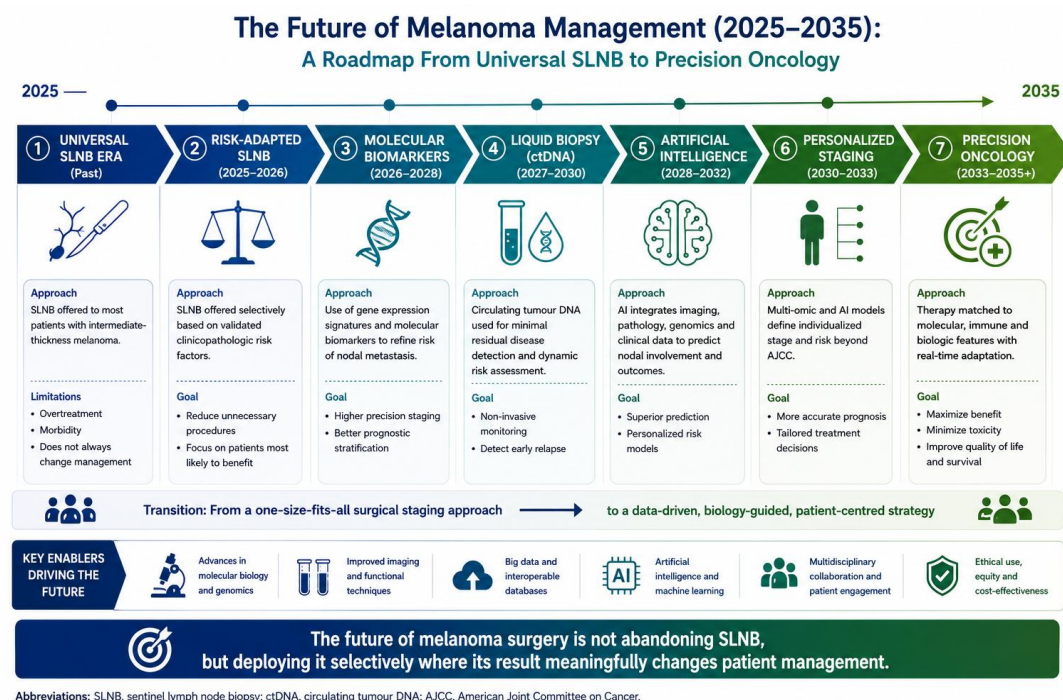


Figure 5 — Projected 2025–2035 Melanoma Staging Pathway. Clinical implication: The next decade will retain SLNB as a prognostic gateway for intermediate-thickness disease, render it selective for stage II disease guided by biomarkers, and substantially displace it by neoadjuvant immunotherapy in macroscopic stage III disease.

XIII. Conclusion

What has changed. MSLT-II [6] and DeCOG-SLT [7] retired completion dissection. KEYNOTE-054 [9,10], CheckMate 238 [11,12], and COMBI-AD [13,14] elevated the prognostic value of sentinel-positive disease by transferring the next decision to systemic therapy. KEYNOTE-716 [2] and CheckMate 76K [3] decoupled sentinel status from adjuvant access in stage II disease. PRADO [20], SWOG S1801 [17], and NADINA [5] displaced sentinel biopsy in macroscopic stage III at experienced centres. DecisionDx-Melanoma 31-GEP, Merlin CP-GEP, and ctDNA remain credible adjuncts rather than substitutes for SLNB. However, these platforms should not be treated as interchangeable: recent comparative analyses report that CP-GEP may identify patients eligible to forgo SLNB more effectively than 31-GEP, although prospective validation is still required before either platform can guide routine SLNB omission [24,27,33,41].

What remains true. SLNB remains the dominant prognostic variable in intermediate and thick melanoma[45]; its morbidity is modest, with a 6.9% rate of early wound complications [8]; the 24% lymphedema rate of completion dissection has been retired as the cost of regional control without survival benefit [6].

What remains uncertain. Whether pathologic complete response in neoadjuvant-treated disease is a sufficient cure surrogate; whether biomarker-driven de-escalation can replace SLNB in stage II; whether AI-augmented pathology can substitute for histopathological reporting [39,40]; whether ctDNA can achieve primary staging status.

What clinicians should do today. Perform SLNB in intermediate and thick melanoma when the result will inform an adjuvant therapy decision. Offer SLNB selectively in stage IIB/IIC disease for integrated prognostic staging, while acknowledging the counterargument that omission—even when adjuvant systemic therapy remains available—may increase the risk of subsequent regional nodal recurrence and necessitate a more morbid therapeutic lymph node dissection than timely SLNB. The decision should therefore incorporate the patient’s risk of nodal disease, fitness for subsequent surgery, preferences, and access to structured nodal surveillance. Omit SLNB in elderly patients with comorbidities precluding adjuvant therapy and in macroscopic stage III patients suitable for neoadjuvant dual checkpoint blockade at an experienced centre.

What may change within ten years.

The forthcoming MSLT-III trial, launching in 2025, is poised to provide definitive evidence on nodal de-escalation after neoadjuvant therapy and may help establish whether Index Lymph Node-guided surgery can replace current institution-specific approaches for selected patients who achieve a favourable

pathological response [44]. Current evidence suggests that SLNB will probably remain standard for intermediate-thickness melanoma, become optional in selected stage II patients with favourable gene-expression profiles, and be substantially displaced by upfront neoadjuvant immunotherapy in macroscopic stage III disease. ctDNA and AI-assisted surveillance are likely to complement radiologic surveillance without displacing it. However, recent evidence indicates that ctDNA has substantial anatomical sensitivity limitations, particularly for brain and skin, mucosal, or muscle recurrences, which limit its use as a robust standalone surveillance tool [31].

The procedure has been functionally transformed. It is now worth more than it was in the completion-dissection era and used more selectively than it has ever been [46]. The thesis defended here, that SLNB should be performed where it matters and omitted where it does not, is supported by the best currently available evidence and is consistent with contemporary consensus recommendations, including the 2024 EADO/EDF/EORTC interdisciplinary guideline [47] and current guideline recommendations [29]. In stage II disease, however, omission remains debated: although systemic therapy may reduce recurrence risk, it has not definitively replaced the staging and regional-control functions of SLNB. Omission may therefore allow a regional nodal recurrence to present later and require more morbid therapeutic surgery, making the decision dependent on nodal-risk estimates, patient fitness, preferences, and access to structured surveillance [6,36]. Biomarker-guided substitution should not be treated as a single unresolved proposition: recent prospective evidence indicates that CP-GEP can identify appropriately selected patients with less than a 10% risk of sentinel-node metastasis and may support shared decision-making [48]. Nevertheless, broader implementation, outcome-based substitution, and the performance of other assays require further validation, alongside longer follow-up of adjuvant and neoadjuvant trials, before this approach can be regarded as definitive.

Key clinical implications

Completion lymph node dissection should not be performed routinely after a positive sentinel node; MSLT-II [6] and DeCOG-SLT [7] demonstrated absence of survival benefit and a four-fold lymphedema penalty.

SLNB remains the prognostic gateway to adjuvant systemic therapy in intermediate and thick melanoma; sentinel-node positivity identifies patients at substantially higher risk of relapse [45]. However, the cited adjuvant trials demonstrate relative reductions in relapse risk of approximately 20–40%—for example, hazard ratios of 0.61 with pembrolizumab and 0.80 with dabrafenib plus trametinib—rather than a roughly 50% reduction [10],[14].

In macroscopic stage III disease, neoadjuvant dual checkpoint

blockade is increasingly preferred at experienced centres; PRADO [20], SWOG S1801 [17], and NADINA [5] support the response-directed surgery paradigm, with the forthcoming MSLT-III trial, expected to launch in 2025, serving as a critical test of index lymph node-guided surgical de-escalation after neoadjuvant therapy [44].

In stage IIB/IIC disease, SLNB has moved from mandatory to selective; KEYNOTE-716 [2] and CheckMate 76K [3] licensure of adjuvant anti-PD-1 on primary-tumour features has decoupled sentinel status from adjuvant access, although omission may increase the risk of subsequent regional nodal recurrence—a concern distinct from systemic recurrence risk and one that may necessitate more morbid therapeutic lymph node dissection.

Tissue-based gene-expression profiling platforms should not be treated as interchangeable: available assays, including Merlin/CP-GEP and 31-GEP, have different performance characteristics. Clinical utility should therefore be assessed using the false-omission rate, rather than generic accuracy alone. Circulating tumour DNA (ctDNA) may complement surveillance, but its current sensitivity is insufficient to support an unqualified claim that it is a robust adjunct: overall sensitivity was 53.6%, falling to 33.3% for brain metastases and 37.5% for skin, mucosal, or muscle recurrence [31]. Neither GEP nor ctDNA is yet an accepted substitute for histopathological or radiological assessment, and both require further outcome-based validation.

The operational rule for SLNB in 2025 is to perform the procedure where its result will be acted upon, consider it where it may be, and omit it where it will not.

Long-term OS benefits of adjuvant and neoadjuvant therapy remain directionally favourable but below pre-specified thresholds at current follow-up; patients should be counselled that these therapies produce relapse delay rather than yet-established cure on mortality endpoints.

AI-augmented imaging, surveillance, and pathology applications will probably complement but not substitute for radiology and pathology over the next decade; further validation across diverse populations is required [39,40].