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Review Article

# Blind by Design: How Axillary Surgical De-escalation Left the Medical Oncologist Without a Map

**Enrique Díaz-Cantón***

*Instituto de Oncología, Instituto Universitario CEMIC; Postgraduate Program in Artificial Intelligence and Medicine, Academia Nacional de Medicina, Buenos Aires, Argentina*

***Corresponding Author:** Enrique Díaz-Cantón, Instituto de Oncología, Instituto Universitario CEMIC; Postgraduate Program in Artificial Intelligence and Medicine, Academia Nacional de Medicina, Buenos Aires, Argentina.

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## Abstract

**Background:** Three landmark phase III randomized trials—SOUND, INSEMA, and BOOG 2013-08—have demonstrated the oncological safety of omitting sentinel lymph node biopsy (SLNB) in select patients with clinically node-negative (cN0), hormone receptor-positive (HR+), HER2-negative early breast cancer. The 2025 American Society of Clinical Oncology (ASCO) guideline formally endorses SLNB omission in postmenopausal women aged ≥50 years with low-grade, small tumors undergoing breast-conserving therapy. This paradigm shift creates an unresolved clinical problem: the medical oncologist inherits a patient with unknown nodal status (Nx) precisely when adjuvant therapy options increasingly depend on pathological nodal information.

**Key Issues:** Nodal status remains central to eligibility for adjuvant abemaciclib (monarchE), ribociclib (NATALEE), and olaparib (OlympiA); to chemotherapy decisions in premenopausal women with node-positive disease (RxPONDER); and to extended endocrine therapy duration. The "blind axilla" paradox describes a scenario in which surgical de-escalation is evidence-based but may inadvertently limit access to survival-improving systemic therapies.

**Genomic Platforms and Artificial Intelligence:** Genomic assays (Oncotype DX, MammaPrint, Prosigna, EndoPredict, Breast Cancer Index) provide critical biological information but were not designed to replace nodal staging, and some explicitly require nodal input for their validated algorithms. Emerging artificial intelligence (AI) models—including deep learning applied to mammography, ultrasound, and MRI—show promise for non-invasive axillary risk estimation (AUCs 0.69–0.91) but lack prospective clinical validation.

**Therapeutic Implications:** A decision framework for Nx patients must integrate tumor biology, genomic risk, imaging-based AI risk scores, and shared decision-making within multidisciplinary teams. The OFSET trial (NRG-BR009) may resolve whether ovarian function suppression substitutes for chemotherapy in premenopausal N1 patients, but results are not expected before 2034.

**Conclusion:** The blind axilla represents a genuine clinical paradox demanding coordinated solutions spanning surgery, medical oncology, genomics, and artificial intelligence. Until non-invasive tools achieve sufficient accuracy for clinical implementation, a thoughtful individualized approach guided by multidisciplinary expertise remains the standard of care.

**Keywords:** Blind Axilla; Sentinel Lymph Node Biopsy Omission; Surgical De-Escalation; Breast Cancer; Adjuvant Therapy; Genomic Assays; Artificial Intelligence; Axillary Staging; CDK4/6 Inhibitors; Nodal Status

## Introduction

The management of the axilla in early breast cancer has undergone a century-long evolution mirroring shifting paradigms in cancer biology. Halsted's radical mastectomy, introduced in the 1890s, enshrined the axiom that breast cancer spreads in an orderly centrifugal pattern through lymphatic channels, mandating en bloc resection of the breast, pectoralis muscles, and all ipsilateral axillary lymph nodes. For nearly eight decades this anatomic dogma governed surgical practice. The NSABP B-04 trial, initiated by Bernard Fisher in 1971, challenged this paradigm by demonstrating that axillary lymph node dissection (ALND) conferred no survival advantage over observation in clinically node-negative patients at 25-year follow-up—a finding that fundamentally reframed the axilla as a marker of systemic disease rather than a waystation for orderly metastatic spread [1,2].

The sentinel lymph node biopsy (SLNB) era began in the 1990s when Giuliano, Krag, and colleagues applied the sentinel node concept to breast cancer. The NSABP B-32 trial (n = 5,611) validated SLNB as equivalent to ALND in node-negative patients, establishing a less morbid staging procedure as the standard of care [3]. The subsequent ACOSOG Z0011 trial demonstrated that omission of completion ALND in patients with one or two positive sentinel nodes undergoing breast-conserving therapy yielded equivalent 10-year overall survival (OS) (86.3% versus 83.6%; hazard ratio [HR] 0.85) [4]. This finding was confirmed by IBCSG 23-01, AMAROS, and SENOMAC [5,6].

The current frontier goes further: the complete omission of any axillary surgery. Three pivotal phase III randomised trials have now demonstrated non-inferiority of foregoing SLNB entirely. The SOUND trial (n = 1,405) showed equivalent 5-year distant disease-free survival (DDFS) of 98.0% versus 97.7% (HR 0.84; 90% CI 0.45–1.54) in tumours ≤2 cm [7]. The INSEMA trial (n = 4,858 per protocol) confirmed equivalent 5-year invasive disease-free survival (iDFS) of 91.9% versus 91.7% (HR 0.91; 95% CI 0.73–1.14) [8]. The BOOG 2013-08 trial similarly met its non-inferiority endpoint for regional recurrence at 5-year follow-up [9]. Based on this evidence, the 2025 ASCO guideline issued a strong recommendation against routine SLNB in postmenopausal women aged ≥50 with grade 1–2, HR+/HER2-negative tumours ≤2 cm, undergoing breast-conserving therapy with negative axillary ultrasound [10].

Yet from the medical oncologist's vantage point, this surgical milestone creates a paradox. Pathological nodal status is not merely prognostic—it is the gateway to a growing arsenal of adjuvant therapies whose eligibility criteria and proven survival benefits hinge on knowing whether and how many lymph nodes harbour metastatic disease. The oncologist now faces a patient with an Nx axilla precisely when abemaciclib has demonstrated an OS benefit in node-positive disease, when chemotherapy decisions in premenopausal N1 patients depend on nodal information, and when extended endocrine therapy decisions are informed by nodal burden. This paradox was first framed from the medical oncologist's perspective in an editorial published in the Revista Argentina de Mastología in 2026 [55]. The present narrative review substantially expands that framework, incorporating a comprehensive review of current evidence on genomic platforms, artificial intelligence, and therapeutic implications, and proposing a structured decision algorithm for clinical practice.

### The cN0 scenario: Surgical evidence and its limits

The evidence base supporting SLNB omission rests on three randomised trials conducted across Europe, each enrolling cN0 patients with predominantly low-risk, HR+ disease. Understanding their design, populations, and rates of occult nodal disease is essential for appreciating what information is forfeited when axillary surgery is omitted.

The SOUND trial, published in JAMA Oncology in 2023, randomised 1,405 women with tumours ≤2 cm across 18 European centres [7]. Inclusion required negative axillary ultrasound; 88% had oestrogen receptor-positive, HER2-negative disease. At a median follow-up of 5.7 years, DDFS was virtually identical (98.0% versus 97.7%), with axillary recurrence of 0.4% in each arm. Critically, among patients who underwent SLNB, 13.7% had positive sentinel nodes, including 0.6% with pN2 disease—confirming a significant hidden nodal disease burden in the no-surgery arm.

The INSEMA trial, published in the New England Journal of Medicine in 2025, enrolled 5,502 eligible patients across 151 German and Austrian centres in a 1:4 randomisation ratio [8]. The per-protocol population of 4,858 patients was predominantly postmenopausal (median age 62 years), with 98.5% HR+ tumours and only 3.6% grade 3 disease. At 73.6 months of median follow-

up, iDFS was 91.9% versus 91.7% (HR 0.91; 95% CI 0.73–1.14), definitively meeting non-inferiority. In the SLNB arm, 14.9% had pathologically confirmed nodal metastases (3.5% micrometastases, 11.4% macrometastases). Quality-of-life data were compelling: persistent lymphoedema occurred in 1.8% without surgery versus 5.7% with SLNB; arm mobility restriction in 2.0% versus 3.5%; pain with arm movement in 2.0% versus 4.2%—all statistically significant.

The BOOG 2013-08 trial, presented at SABCS in December 2025, enrolled 1,733 patients across 25 Dutch centres, with 1,574 evaluable [9]. Using a cortical thickness cut-off of 2.3 mm on axillary ultrasound, the trial met its non-inferiority criterion for regional recurrence-free survival (1.1% versus 0.6%; absolute difference 0.5%).

| Parameter | Sound [7] | INSEMA [8] | BOOG 2013-08 [9] |
|---|---|---|---|
| Publication | JAMA Oncol 2023 | N Engl J Med 2025 | SABCS 2025 |
| Evaluable patients (N) | 1,405 | 4,858 (per protocol) | 1,574 |
| Tumour eligibility | ≤2 cm | ≤5 cm (90% T1) | T1–T2 |
| HR+/HER2− (%) | 88% | 98.5% | ~82% |
| Primary endpoint | 5-yr DDFS | 5-yr iDFS | Regional recurrence |
| HR (no SLNB vs SLNB) | 0.84 (90% CI 0.45–1.54) | 0.91 (95% CI 0.73–1.14) | Non-inferiority met |
| Axillary recurrence, no-surgery arm | 0.4% | 1.0% | 1.1% |
| pN1 rate in SLNB arm | ~13% | ~15% | ~14% |
| Median follow-up | 5.7 years | 6.1 years | 5.0 years |

**Table 1:** Comparison of SLNB omission randomised trials.

The false-negative rate of axillary ultrasound is fundamental to this discussion. Meta-analyses report pooled sensitivity of approximately 66% (range 31%–82%) and specificity of approximately 73% [11]. False-negative rates increase with tumour size, reaching 31% for T2 tumours. Across all three omission trials, approximately 14–15% of patients classified as cN0 harboured occult nodal disease. This occult disease did not translate into excess axillary recurrences—rates remained below 1% at 5–6 years—likely reflecting the sterilising effect of whole-breast radiotherapy, which delivers ~80% of the prescription dose to the level I axilla in roughly half of patients, combined with systemic therapy effects [10].

The critical unresolved issue is the Nx status problem. These approximately 14–15% of patients with occult nodal disease represent a population whose systemic treatment decisions may be materially altered by knowledge of their pathological stage—a population rendered invisible when SLNB is omitted.

## Decisions in the dark: The medical oncologist's perspective

The medical oncologist confronting an Nx patient faces a clinical scenario without precedent in modern breast cancer care. Evidence-based surgical practice may now systematically withhold information that the oncologist's therapeutic armamentarium increasingly demands. The scope of affected decisions spans chemotherapy, CDK4/6 inhibitor selection, PARP inhibitor eligibility, endocrine therapy optimisation, and treatment duration.

## Adjuvant chemotherapy: the RxPONDER dilemma

The RxPONDER trial (SWOG S1007) crystallised the importance of nodal status for adjuvant chemotherapy decisions [12,13]. Among 5,083 women with HR+/HER2-negative breast cancer with 1–3 positive nodes and Oncotype DX Recurrence Scores (RS) ≤25, the impact of adding chemotherapy diverged dramatically by menopausal status. Postmenopausal women derived no chemotherapy benefit (5-year iDFS 91.9% versus 91.6%; HR 0.97; P = 0.82). In contrast, premenopausal women experienced a 5.2

percentage-point absolute improvement in 5-year iDFS (94.2% versus 89.0%), representing a 40% relative reduction in recurrence events—observed across all RS subgroups within 0–25. Whether this benefit reflects cytotoxic chemotherapy or chemotherapy-induced ovarian function suppression (OFS) is being addressed by the OFSET trial (NRG-BR009) [14]. For the Nx patient who is premenopausal, unknown nodal status means this potentially substantial benefit may go unrealised.

## CDK4/6 inhibitors: the monarchE and NATALEE eligibility problem

The monarchE trial enrolled 5,637 patients with node-positive, high-risk, HR+/HER2-negative early breast cancer [15,16]. The primary cohort required ≥4 positive axillary lymph nodes, or 1–3 positive nodes combined with grade 3 histology, tumour size ≥5 cm, or Ki-67 ≥20%. At a median follow-up of 76.2 months, abemaciclib plus endocrine therapy achieved a statistically significant OS benefit (HR 0.842; 95% CI 0.722–0.981; P = 0.027), with 7-year OS of 86.8% versus 85.0% [17]. This represents the first novel agent to demonstrate an adjuvant OS benefit in HR+ breast cancer since aromatase inhibitors. The critical constraint for Nx patients is absolute: 100% of monarchE participants were required to be node-positive. A patient whose axilla harbours undetected disease meeting monarchE criteria—estimated at 14.5–21.8% of all HR+/HER2-negative early breast cancers—would be denied access to a survival-improving therapy.

The NATALEE trial enrolled 5,101 patients across a broader risk spectrum, including select node-negative patients with high-risk features (~12% of the study population) [18]. At 5-year follow-up, ribociclib plus a nonsteroidal aromatase inhibitor yielded an iDFS HR of 0.716 (95% CI 0.618–0.829), representing a 4.5 percentage-point absolute improvement (85.5% versus 81.0%) [19]. Real-world analyses demonstrate that 91.8% of N1 patients meet NATALEE criteria versus only 9.5% of N0 patients—confirming that nodal burden drives most of the eligible population.

## Olaparib: Nodal burden as a high-risk criterion

The OlympiA trial demonstrated that adjuvant olaparib in patients with germline BRCA1/2 mutations and high-risk HER2-negative breast cancer improves OS (HR 0.68; 95% CI 0.50–0.91; P = 0.009) [20,21]. For HR+ patients in the adjuvant setting, the high-risk definition requires ≥4 positive lymph nodes—information entirely absent in Nx patients. For triple-negative disease, eligibility requires node-positive status or a primary tumour ≥2 cm, offering an alternative pathway somewhat less dependent on nodal information.

## Extended endocrine therapy: duration guided by nodal burden

The EBCTCG meta-analysis of 62,923 women demonstrates that 20-year cumulative recurrence risk varies from 13% in T1N0 disease to 34% in T1-N4-9 disease [22]. Node-positive patients are the strongest candidates for extended therapy beyond 5 years. The MA.17 trial showed the greatest OS benefit from extended letrozole in the node-positive subgroup (HR 0.61; 95% CI 0.38–0.98). MA.17R confirmed that an additional 5 years of letrozole after ~10 years of prior endocrine therapy reduced disease-free survival events by 34% (HR 0.66; P = 0.01) [23]. NSABP B-42 demonstrated a 28% reduction in distant recurrence with extended aromatase inhibitor therapy [24]. Without nodal status, clinicians cannot appropriately stratify patients for these consequential duration decisions.

A recent National Cancer Database analysis found that 7.9% of postmenopausal and 13.7% of premenopausal women with cT1N0 HR+ breast cancer would have at least one adjuvant decision impacted by the absence of lymph node pathology [25]. The 2025 ASCO guideline explicitly acknowledges that introduction of CDK4/6 inhibitors in the adjuvant setting has raised concerns about potential undertreatment in patients with undetected positive nodes [10].

| Therapy | Trial | Nodal requirement | Key benefit at risk |
|---|---|---|---|
| Abemaciclib | monarchE | All patients node-positive | OS HR 0.842; P = 0.027 [17] |
| Ribociclib | NATALEE | N1+ or N0 high-risk features | iDFS HR 0.716 [18,19] |
| Olaparib (HR+) | OlympiA | ≥4 positive nodes (HR+) | OS HR 0.68 [20,21] |
| Chemotherapy (premenopausal) | RxPONDER | N1 determines benefit | 5.2% absolute iDFS gain [12,13] |
| Extended endocrine therapy | MA.17R, B-42 | N+ strongest candidates | OS HR 0.61 in N+ [23,24] |
| OFS + AI vs tamoxifen | SOFT/TEXT | N+ derives greatest benefit | 10–15% absolute DRFS gain [26,27] |

**Table 2:** Systemic treatment decisions critically affected by unknown nodal status (Nx).

## Genomic platforms as a bridge in the nx setting

Multigene expression assays have transformed adjuvant decision-making in HR+ breast cancer over the past two decades. Their potential to partially compensate for the information gap created by SLNB omission deserves careful evaluation, including an honest assessment of fundamental limitations in the Nx context.

## Oncotype DX (21-gene Recurrence Score)

The TAILORx trial (n = 10,253) demonstrated that endocrine therapy alone was non-inferior to chemoendocrine therapy for RS 11–25 (HR 1.08; 95% CI 0.94–1.24) in node-negative patients, with an age-dependent interaction favouring chemotherapy in women ≤50 years with RS 16–25 [28,29]. The RxPONDER trial extended these findings to node-positive disease, demonstrating no chemotherapy benefit in postmenopausal N1 patients with RS ≤25 [12,13]. The RS itself does not require nodal input—a significant advantage in the Nx context. However, the therapeutic algorithm derived from these data explicitly differs by nodal status: in premenopausal N1 patients, the same RS range still confers chemotherapy benefit. Without knowing nodal status, the correct treatment algorithm cannot be selected.

## MammaPrint (70-gene signature)

MammaPrint offers a unique advantage in the Nx scenario. The MINDACT trial enrolled 6,693 patients with 0–3 positive lymph nodes, making it one of the few assays prospectively validated across both node-negative and node-positive populations [30,31]. Among clinically high-risk but genomically low-risk patients, 5-year distant metastasis-free survival without chemotherapy was 95.1%, exceeding the predefined 92% threshold. Updated analyses at 8.7 years showed that chemotherapy benefit in genomically low-risk patients was not enhanced by nodal positivity—a finding with direct relevance to the Nx scenario, suggesting that MammaPrint low-risk patients may be safely spared chemotherapy regardless of unknown nodal status. MammaPrint does not incorporate nodal status into its genomic score.

## Prosigna (PAM50 Risk of Recurrence)

Prosigna presents a challenging scenario for Nx patients. While the intrinsic subtype classification does not require nodal input, the Risk of Recurrence (ROR) score uses different cut-off thresholds depending on nodal status [32,33]. For node-negative patients, low-risk encompasses ROR 0–40; for 1–3 positive nodes, the low-risk threshold drops to 0–15. Without knowing nodal status, the clinician cannot assign the correct risk category, rendering the quantitative ROR score uninterpretable within its validated framework.

## EndoPredict (EPclin)

EndoPredict presents the most critical limitation among commercial platforms. The EPclin score—the clinically validated composite measure—explicitly requires nodal status and tumour size as algorithmic inputs [34,35]. Without nodal information, EPclin literally cannot be calculated. The molecular EP score alone (12-gene expression) provides independent prognostic information, but with substantially less discrimination than EPclin.

## Breast Cancer Index (BCI)

BCI offers a distinctive niche in the Nx context. The H/I ratio component predicts benefit from extended endocrine therapy independent of its prognostic score. In the Trans-aTTom study, BCI H/I-high node-positive patients experienced a 10.2 percentage-point absolute risk reduction with extended tamoxifen (HR 0.35; P = 0.027), while H/I-low patients derived no benefit [36]. The IDEAL trial confirmed this pattern with extended letrozole (HR 0.42; P = 0.011) [37]. BCI does not require nodal status as input, making it particularly valuable when nodal information is unavailable for guiding duration decisions.

## Can tumour biology predict nodal involvement?

A fundamental question underlies the Nx genomic platform discussion: can tumour biology predict lymph node involvement? The evidence is sobering. The SCAN-B study, profiling 3,023 tumours by RNA sequencing, found that mixed models integrating gene expression with clinicopathological features achieved a maximum AUC of only 0.72 for predicting nodal metastasis; gene expression alone reached only 0.58–0.67 [38]. MammaPrint was specifically found to be ineffective in predicting lymph node status. These findings suggest that lymphatic and haematogenous metastatic pathways are driven by partially independent molecular mechanisms—a biological reality that limits the ability of any genomic platform designed to predict distant recurrence from serving as a surrogate for nodal staging.

| Platform | Requires nodal input? | Validated in N1? | Nx impact | Key limitation |
|---|---|---|---|---|
| Oncotype DX (RS) | No (score itself) | Yes — RxPONDER | RS calculable; algorithm differs by N status | Premenopausal N1 treatment cannot be determined |
| MammaPrint | No | Yes — MINDACT (N0–N1) | Fully applicable; G-low safe irrespective of N | Limited to 0–3 nodes in validation |
| Prosigna (ROR) | Yes — risk cut-offs | Yes — TransATAC, DBCG | Risk category unassignable; subtype valid | Cut-offs shift dramatically by N status |
| EndoPredict (EPclin) | Yes — explicit input | Yes — ABCSG, GEICAM | EPclin cannot be calculated | Most vulnerable platform in Nx |
| Breast Cancer Index | No | Yes — TransaTTom, IDEAL | Fully applicable for prognosis and H/I benefit | N0 subset underpowered for H/I |

**Table 3:** Genomic platforms evaluated in the Nx context.

## Artificial intelligence: From image analysis to clinical decision support

The convergence of computational power, large medical imaging datasets, and advanced deep learning architectures has generated intense interest in AI as a tool for non-invasive axillary staging. While none of these technologies has achieved regulatory clearance for this indication, the trajectory of research offers a plausible path toward reducing the information deficit of the blind axilla.

### AI applied to axillary ultrasound

Axillary ultrasound represents the most clinically intuitive application for AI. Liu and colleagues developed a deep learning radiomics nomogram validated across four hospitals in 883 patients, achieving AUCs of 0.914, 0.929, and 0.952 in three external validation cohorts for predicting axillary lymph node metastasis [39]. The model combined DenseNet deep learning features with handcrafted radiomics and four clinical parameters. A separate multicentre study using a graph convolutional network in 820 patients achieved AUCs of 0.88 and 0.84 in two validation cohorts [40]. Sun and colleagues demonstrated that combining intratumoral and peritumoral convolutional neural network features achieved an AUC of 0.912 with a negative predictive value of 94.4%—reducing the false-negative rate to approximately 6–10%, a substantial improvement over the ~14–15% rate of conventional ultrasound [41].

### AI applied to mammography

Zhang, Dihge, and colleagues published a multicentre study of 1,265 cN0 patients from three Swedish institutions in npj Digital Medicine in 2025 [42]. Incorporating full-breast mammogram deep learning features with clinical variables improved the ROC AUC from 0.690 (clinical variables alone) to 0.774 for predicting lymph node metastasis. At a sensitivity threshold of ≥90%, the model achieved an estimated SLNB reduction rate of 41.7% (95% CI 13.0%–62.6%). Crucially, full-breast images outperformed tumour-focused region-of-interest approaches, suggesting that peritumoral and global breast parenchymal patterns contain relevant biological information about metastatic propensity. Dihge and colleagues, in a related study of 755 women, achieved AUCs of 0.705–0.747 for preoperative nodal prediction using commercially available AI systems [43].

### AI applied to MRI

MRI-based AI models were evaluated in a systematic review and meta-analysis by Lee and colleagues, published in Cancer Imaging in 2025, encompassing 10 studies [44]. Pooled sensitivity was 0.76 (95% CI 0.67–0.83) and specificity was 0.81 (95% CI 0.74–0.87), with a summary AUC of 0.788. Individual studies have achieved considerably higher performance, with one group reporting an AUC of 0.91 for a convolutional neural network applied to breast MRI, outperforming experienced radiologists.

### Radiomics and multimodal integration

Radiomics consistently demonstrates that peritumoral microenvironment features contain significant predictive information for nodal involvement [45]. Wang and colleagues demonstrated that multi-modality radiomics combining MRI and mammography outperformed both single-modality models and

radiologists for axillary lymph node metastasis prediction [46]. The METACANS model, published in npj Precision Oncology in 2025, integrated whole-slide pathology images with clinicopathological features in 1,991 training cases, externally validated across five cohorts (n = 2,166), achieving an AUC of 0.733, sensitivity of 0.820, and a negative predictive value of 0.846 [47].

### Foundation models and multi-agent AI systems

Foundation models—large neural networks trained on broad corpora—represent an emerging paradigm with potentially transformative implications. Li and colleagues, in a review published in Cancer Letters in 2026, described how foundation models can reduce labelling requirements, fuse imaging, pathology, electronic health records, and omics data for individualised risk estimates, and operationalise clinical guidelines at scale [48]. Ferber and colleagues, in Nature Cancer in 2025, described an autonomous clinical AI agent leveraging GPT-4 with multimodal precision oncology tools that improved decision-making accuracy from 30.3% (GPT-4 alone) to 87.2% (integrated agent), approaching multidisciplinary tumour board performance [49]. Goh and colleagues developed a large language model augmented with NCCN guidelines via retrieval-augmented generation for adjuvant breast cancer therapy recommendations—the first pilot study of generative AI integrated with evidence-based oncological guidelines [50].

Federated learning addresses the critical barrier of training on large, diverse datasets without compromising patient privacy. A systematic review found federated learning outperformed centralised machine learning in 15 of 25 oncology studies [51]. Ogier du Terrail and colleagues demonstrated its effectiveness for predicting histological response to neoadjuvant chemotherapy in triple-negative breast cancer across multiple institutions [52].

### Current limitations

Despite considerable promise, the limitations of AI for axillary staging remain substantial. Most studies are retrospective and single-institution; multicentre prospective validation is limited. No regulatory-cleared AI tool exists specifically for preoperative axillary lymph node staging prediction. Performance variability across studies (AUC 0.73–0.91) may be insufficient for replacing surgical staging with the confidence required in clinical practice. Dataset bias, particularly the predominance of East Asian institutional data in many studies, limits generalisability. The concept of an "axillary risk score"—an AI-derived probability of nodal involvement that could directly inform systemic therapy decisions in Nx patients—remains theoretical, with no registered prospective trial evaluating such an approach for treatment decision support.

### Integrating the evidence: A decision framework for the medical oncologist

No validated algorithm exists specifically for the Nx patient, but the available evidence supports a structured five-principle approach.

- **First:** Risk stratification using clinicopathological features. Tumour grade, Ki-67, receptor expression levels, HER2 status, histological type, and lymphovascular invasion define a biological risk profile independent of nodal status. The population rendered Nx by guideline-concordant practice is predominantly low-risk by design—the information gap predominantly affects a defined, identifiable minority.
- **Second:** Genomic platform selection tailored to the Nx context. For postmenopausal women, Oncotype DX and MammaPrint provide the most robust guidance. RxPONDER demonstrated that postmenopausal N1 patients with RS ≤25 derive no chemotherapy benefit, making the decision essentially nodal-status-independent. MammaPrint's validation across node-negative and node-positive populations makes it particularly suitable for Nx patients. For extended endocrine therapy decisions, BCI H/I ratio can guide duration independent of nodal information. Prosigna's risk categories and EndoPredict's EPclin score cannot be accurately applied in the Nx setting.
- **Third:** Empirical escalation in high biological-risk cases. Consideration of CDK4/6 inhibitor therapy—particularly ribociclib, given NATALEE's broader inclusion criteria—may be warranted for patients with grade 3 histology, high Ki-67, or high genomic risk scores even without confirmed nodal positivity. For premenopausal patients with high RS (16–25) and Nx status, the RxPONDER data support strong consideration of OFS with an aromatase inhibitor as a default escalation strategy, pending OFSET results.
- **Fourth:** Transparent communication with patients. The shared decision-making conversation should explicitly address that SLNB omission trades a small surgical morbidity

reduction against a small probability of missing information that could influence treatment selection. Patients should understand that overall prognosis remains excellent (5-year DDFS >97% in trial populations) and that most decisions can be made on tumour biology alone.

- **Fifth:** Preoperative multidisciplinary team (MDT) discussion before SLNB omission—explicitly recommended by the 2025 ASCO guideline [10]. This represents a fundamental departure from traditional practice, in which the surgeon and pathologist complete staging before the medical oncologist enters the process. In the blind axilla era, the medical oncologist must participate in the surgical planning decision, identifying patients for whom nodal information would meaningfully alter systemic therapy recommendations—particularly premenopausal women, patients with high Ki-67 or grade 3 tumours, and germline BRCA mutation carriers.

### Future directions and open questions

The OFSET trial (NRG-BR009), activated in August 2023 and enrolling toward a target of 3,960 premenopausal women [14] directly tests whether OFS plus endocrine therapy is sufficient compared with chemotherapy plus OFS plus endocrine therapy in patients with pN0 (RS 16–25) or pN1 (RS 0–25) disease. If OFSET demonstrates that OFS renders chemotherapy unnecessary in premenopausal N1 patients, the treatment information lost by SLNB omission becomes substantially less consequential—the optimal endocrine strategy (aromatase inhibitor plus OFS) would be recommended regardless of nodal status. Results are not expected before 2034.

The ALLIANCE A011202 trial will provide Level I evidence on whether axillary radiation can replace ALND in patients with residual node-positive disease after neoadjuvant chemotherapy. The TAXIS trial evaluates tailored axillary surgery plus axillary radiation versus standard ALND in clinically node-positive patients, with primary results expected around 2029–2030 [53].

Liquid biopsy as a surrogate for nodal staging remains conceptually appealing but empirically premature. A cfDNA promoter profiling classifier achieved an AUC of 0.897 in 330 patients for preoperative nodal staging, but this remains retrospective and unvalidated prospectively [54]. The biology of circulating tumour DNA may not perfectly correlate with lymphatic dissemination, paralleling the observation that genomic assays designed for distant recurrence prediction are poor predictors of nodal metastasis [38].

The prospective validation of AI axillary risk models represents the most pressing near-term priority. The path from retrospective AI models to clinical decision tools requires standardisation of imaging protocols, external validation across diverse populations, regulatory clearance, and workflow integration—estimated at three to five years under favourable conditions [48]. Future trial designs should explicitly include Nx strata and integrate AI-derived axillary risk assessments as stratification variables, thereby generating the evidence needed to manage this growing patient population.

## Conclusion

The blind axilla represents a genuine paradox at the intersection of surgical progress and medical oncological need. The evidence supporting SLNB omission in carefully selected patients is robust, reproducible, and clinically meaningful. The 2025 ASCO guideline's strong recommendation endorsing this practice is well supported by Level I evidence from SOUND, INSEMA, and BOOG 2013-08.

Yet the medical oncologist inherits the consequences of this surgical advance in the form of an Nx status that, for a definable subset of patients, limits access to survival-improving therapies. Abemaciclib's demonstrated OS benefit, the chemotherapy signal in premenopausal N1 patients from RxPONDER, and the role of nodal burden in extended endocrine therapy decisions collectively establish that pathological nodal information retains therapeutic relevance even as its surgical acquisition is being abandoned.

Genomic platforms—particularly MammaPrint and Oncotype DX—provide a meaningful partial bridge. Artificial intelligence offers a plausible future pathway toward non-invasive axillary risk estimation, but prospective validation remains an absolute prerequisite for clinical adoption.

The immediate practical solution lies not in technology but in process: preoperative multidisciplinary discussion that positions the medical oncologist's informational needs alongside the surgeon's de-escalation goals before the axillary staging decision is finalised. Recognising patient heterogeneity—rather than applying a uniform policy—is the essence of personalised medicine in the era of surgical de-escalation.

## Conflicts of Interest

The author declares no conflicts of interest related to this article.

## Artificial Intelligence Use Declaration

Claude (Anthropic, 2026) was used as a research assistance and writing support tool during the preparation of this manuscript. All intellectual content, critical analysis, clinical interpretation, and conclusions are entirely the responsibility of the author.

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