Instructions for use NILS

1 About NILS

NILS (Non-Invasive Lymph Node Status) is a web-based tool that calculates the probability of a healthy axilla in women with primary breast cancer. By analysing entered patient data and tumour characteristics, NILS enables a non-invasive assessment of lymph node status in the axilla. The tool serves as a decision support and facilitates the decision of whether sentinel node biopsy (SLNB) should be performed in patients undergoing primary breast cancer surgery.

Note that NILS is intended to be used in the context of clinical and usability studies. During this validation phase, the tool is not intended to provide specific medical advice regarding the treatment of breast cancer. The results from the web-based calculator will therefore not be shared with either the patient or the attending physician during this validation phase. Please note that NILS is currently not CE-marked and shall not be used in clinical decision-making.

1.1 Instructions for use

The instructions for use (this document) must be read before using the product.

1.2 General information

Name of the device	NILS
UDI-DI	*Not yet assigned*
UDI-PI	*Not yet assigned*
Intended use	NILS is a web-based calculator that uses artificial intelligence to calculate the probability that the sentinel node(s) are healthy (benign) in women with a clinically node-negative axilla who are scheduled for primary surgery for invasive breast cancer. NILS is intended to be used preoperatively by attending physicians, surgeons and oncologists, to facilitate risk-benefit analysis and patient stratification prior to decisions on performing SLNB. In women with a high calculated probability of having benign axillary lymph nodes, NILS should be used as a complementary clinical decision support and not as a stand-alone tool for the decision to forgo SLNB.
Warnings and precautions	No warnings or precautions have been identified.
Patient population	Women aged 24 to 100 years, who are planned for primary surgery due to invasive breast cancer and are clinically axillary node negative.
Version of NILS	R1a
Indications	Primary invasive breast cancer.
Contraindications	The device is not intended for male patients. The device is not intended for patients scheduled for neoadjuvant therapy.

	The device is not intended for patients that have previously undergone ipsilateral surgery in the breast and/or axillary surgery due to invasive breast cancer or ductal carcinoma in situ DCIS). The device is not intended for patients with biopsy verified ductal carcinoma in situ (DCIS) without primary invasive breast cancer. The device is not intended for patients with clinical axillary node positive disease (palpable or ultrasound positive). The device is not intended for patients with biopsy verified axillary lymph node metastasis. The device is not intended for patients with T3/T4 tumours (tumours larger than 5 cm).
Intended user	Professional use only: attending physician
Limits of accuracy	The probability (percentage without decimals) of healthy axillary lymph nodes is calculated using a cutoff chosen based on the same accepted false-negative rate as for SLNB (<10%).
Specification of the population the AI algorithm is trained on	Dihge et al. BMC Cancer 2019.
Residual risks and side-effects	No residual risks or side-effects have been identified. The risk analysis will be updated after the usability study.
Clinical benefit	Act as a decision support to identify patients at low risk of axillary lymph node metastases, and thereby contribute to the abstaining of SLNB and subsequently reduce the negative consequences of the procedure.

1.3 Technical description

To use NILS, a stable internet connection is required. The website is adapted for use with a tablet or mobile phone.

1.4 Address

NILS is developed by Region Skåne.

Region Skåne
291 89 Kristianstad

1.5 Explanation of symbols

Instructions for use (this document) shall be read before using the device.

Date of the last update of the device.

Version number of the device.

2 How to use NILS

1. Open the browser and go to https://nils.cec.lu.se/
2. Click ’Log in’.
3. Enter your personal username and password and click ’Log in’.
4. Choose ’To calculator’ to get to the calculator.

5. Enter patient and tumour information in the intended fields (see details below).

   Note that you actively have to choose a value in all fields. However in some fields the value 'Unkown' is an option if the value is not available.

Variables	Allowed values	Comments
Age at diagnosis (years)	Integer: 24 – 92	For example, a person is considered to be 54 years old until the day they turn 55 years.
Screening detected	No / Yes	-
Multifocality	No / Yes	-
Placement of the largest tumour		
Laterality	Right / Left	Refers to the patient´s right / left breast
Central in the breast	No / Yes	-
Position in the breast	Integer: 1–12	This option can only be chosen if 'Central in the breast = No' has been selected in the previous step. Clock 1 to 12 is used to localise the tumours position in the breast from the clinician's perspective when observing the patient.
Size of the largest tumour (mm)	0.5 – 50.0	Note! only T1-T2 (50 mm or smaller)
Core biopsy data		
Histopathological type	Ductal (NST) Lobular Other/Mixed	-
Vascular invasion	No / Yes / Unknown	-
ER status	Negative Positive (≥ 1%) Unknown	Note – the threshold of the calculator is set to ≥ 1%, as opposed to the threshold of ≥ 10% that is used in Swedish clinical practice.
PR status	Negative Positive (≥ 1%) Unknown	Note – the threshold of the calculator is set to ≥ 1%, as opposed to the threshold of ≥ 10% that is used in Swedish clinical practice.
Ki67 (%)	0 – 100	-

3 Interpretation of results

The calculated probabilities, along with whether the result fall below or exceed the cutoff, can serve as a foundation for discussions with the patient regarding her individual likelihood of having healthy lymph nodes. The results can help clarify the risk profile and support informed decisions about the necessity of SLNB.

The NILS model is designed to handle missing (lympho)vascular invasion (LVI) information by imputing this value. In the validation study (Dihge et al., Front Oncol 2024), the model reached an AUC of 0.735 (95% CI, 0.704–0.764) when information on other variables was available. Furthermore, the model is adapted to perform predictions when information on

ER status, PR status, and/or Ki67 is missing, in which the predictive performance of healthy lymph nodes only marginally decreased to AUC = 0.718 (95% CI, 0.687–0.748).

3.1 The histogram

Red colour indicates that the estimated probability of healthy axillary lymph nodes is **lower** than the cutoff.

Green colour indicates that the estimated probability of healthy lymph nodes is **higher** than the cutoff.

4 Support and contact

If you need help, contact Professor Lisa Rydén at lisa.ryden@med.lu.se

5 References

Dihge L, Ohlsson M, Edén P, Bendahl PO, Rydén L. Artificial neural network models to predict nodal status in clinically node-negative breast cancer. *BMC Cancer*. 2019 Jun 21;19(1):610. doi: 10.1186/s12885-019-5827-6. PMID: 31226956; PMCID: PMC6588854.

Skarping I, Ellbrant J, Dihge L, Ohlsson M, Huss L, Bendahl PO, Rydén L. Retrospective validation study of an artificial neural network-based preoperative decision-support tool for noninvasive lymph node staging (NILS) in women with primary breast cancer (ISRCTN14341750). *BMC Cancer*. 2024 Jan 16;24(1):86. doi: 10.1186/s12885-024-11854-1. PMID: 38229058; PMCID: PMC10790472.

Hjärtström M, Dihge L, Bendahl PO, Skarping I, Ellbrant J, Ohlsson M, Rydén L. Noninvasive Staging of Lymph Node Status in Breast Cancer Using Machine Learning: External Validation and Further Model Development. *JMIR Cancer*. 2023 Nov 20;9:e46474. doi: 10.2196/46474. PMID: 37983068; PMCID: PMC10696498.