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ENDORISK-2: A personalized Bayesian network for preoperative risk stratification in endometrial cancer, integrating molecular classification and preoperative myometrial invasion assessment

Marike S. Lombaers [a], Casper Reijnen [b,*], Ally Sprik [a,1], Petra Bretová [c], Marcel Grube [d,e], Stephanie Vrede [a], Hege F. Berg [f], Jasmin Asberger [g], Eva Colas [h], Jitka Hausnerova [i], Jutta Huvila [j], Antonio Gil-Moreno [h,k], Xavier Matias-Guiu [l], Michiel Simons [m], Marc P.L.M. Snijders [n], Nicole C.M. Visser [o], Stefan Kommoss [d,e], Vit Weinberger [c], Frederic Amant [p], Peter Bronsert [g], Ingfrid S. Haldorsen [q], Martin Koskas [r], Camilla Krakstad [f,s], Heidi V.N. Küsters-Vandevelde [t], Gemma Mancebo [u], Louis J.M. van der Putten [v], Irene de la Calle [h], Peter J.F. Lucas [w], Arjen Hommersom [x], Johanna M.A. Pijnenborg [a]

[a] Department of Obstetrics and Gynecology, Radboud University Medical Center, Nijmegen, the Netherlands
[b] Department of Radiation Oncology, Radboud University Medical Center, Nijmegen, the Netherlands
[c] Department of Gynecology and Obstetrics, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czechia
[d] Department of Women's Health, University Hospital Tuebingen, Tuebingen, Germany
[e] Department of Obstetrics and Gynecology, Diak Klinikum Schwaebisch Hall, Schwaebisch Hall, Germany
[f] Department of Clinical Science, Center for Cancer Biomarkers CCBIO, University of Bergen, Norway
[g] Department of Obstetrics and Gynecology, Medical Center – University of Freiburg, Freiburg, Germany
[h] Biomedical Research Group in Gynecology, Vall Hebron Institute of Research, Universitat Autònoma de Barcelona, CIBERONC, Barcelona, Spain
[i] Department of Pathology, University Hospital Brno and Faculty of Medicine, Masaryk University, Brno, Czechia
[j] Department of Pathology, Turku University, Turku University Hospital, Turku, Finland
[k] Gynecological Department, Vall Hebron University Hospital, CIBERONC, Barcelona, Spain
[l] Department of Pathology and Molecular Genetics and Research Laboratory, Hospital Universitari Arnau de Vilanova, University of Lleida, IRBLleida, CIBERONC, Lleida, Spain
[m] Departpent of Pathology, Radboud University Medical Center, Nijmegen, the Netherlands
[n] Department of Obstetrics and Gynecology, Canisius Wilhelmina Hospital, Nijmegen, the Netherlands
[o] Department of Pathology, Eurofins PAMM, Eindhoven, the Netherlands
[p] Department of Obstetrics and Gynecology, University Hospital Leuven, Leuven, Belgium
[q] Department of Radiology, Haukeland University Hospital, Bergen, Norway
[r] Department of Obstetrics and Gynecology, Hospital Bichat, Paris, France
[s] Department of Gynecology and Obstetrics, Haukeland University Hospital, Bergen, Norway
[t] Department of Pathology, Canisius Wilhelmina hospital, Nijmegen, the Netherlands
[u] Department of Obstetrics and Gynecology, Hospital del Mar, Barcelona, Spain
[v] Department of Obstetrics and Gynecology, Jeroen Bosch Hospital, Den Bosch, the Netherlands
[w] Department of Data Science, University of Twente, Enschede, the Netherlands
[x] Department of Computer Science, Open University, Heerlen, the Netherlands

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ABSTRACT

Background: ENDORISK is a Bayesian network that can assist in preoperative risk estimation of lymph node metastasis (LNM) risk in endometrial cancer (EC) with consistent performance in external validations. To reflect state of the art care, ENDORISK was optimized by integrating molecular classification and preoperative assessment of myometrial invasion (MI).

* Correspondence to: Dept. of Radiation Oncology, Radboud University Medical Center, Geert Grooteplein Zuid 10, Nijmegen, GA 6525, the Netherlands.
E-mail address: casper.reijnen@radboudumc.nl (C. Reijnen).
[1] Affiliation at time of study

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Methods: Variables for *POLE*, MSI, and preoperative assessment of MI, either by expert transvaginal ultrasound or pelvic magnetic resonance imaging (MRI), were added to develop ENDORISK-2. The p53 biomarker, part of the molecular classification, was already included in ENDORISK. External validation of ENDORISK-2 for LNM prediction was performed in two independent cohorts from: Brno (CZ), (n = 581) and Tübingen (DE), (n = 247).
Findings: ENDORISK-2 yielded AUCs of 0·85 (95 % CI 0·80–0·90) (CZ) and 0·86 (95 % CI 0·77–0·96) (DE) for predicting LNM. In patients with low-grade histology, 83 % (CZ) and 89 % (DE) were estimated having less than 10 % risk of LNM, with false negative rates (FNR) of 4·3 % (CZ) and 2·2 % (DE). The previously defined set of minimally required variables, i.e.: preoperative tumor grade, three of the four immunohistochemical (IHC) markers, and one clinical marker, could be interchanged with the new variables, with comparable validation metrics, including AUC values of 0·79–0·87 for LNM prediction.
Interpretation. Incorporation of molecular data and preoperative MI improved the flexibility of ENDORISK with comparable diagnostic accuracy for estimating LNM as when based on low-cost immunohistochemical biomarkers. In addition, the high diagnostic accuracy in patients with low-grade EC demonstrates how ENDORISK-2 could aid clinicians in identifying patients in whom surgical lymph node assessment may safely be omitted. These results underline its power for clinical use in both high and low resource countries.

1. Introduction

For patients with endometrial carcinoma (EC), the most common gynecological cancer in western countries, a hysterectomy with bilateral salpingo-oophorectomy is the initial treatment of choice. Guidelines recommend risk stratification of EC patients based on tumor grade, histology, lympho-vascular space invasion (LVSI), depth of myometrial invasion (MI), lymph node (LN) status, and molecular classification [1,2]. For patients with verified lymph node metastases (LNM) after surgery, adjuvant radiotherapy and/or adjuvant chemotherapy is recommended to reduce the risk of recurrence [3]. While morbidity of surgical LN assessment has been decreased significantly by the sentinel lymph node (SLN) procedure, side-specific lymphadenectomy is still needed in about 25 % of EC patients in case of SLN biopsy failure, with subsequent risk for lymphedema [4,5]. Furthermore, this procedure increases surgical time with 33 min on average [6]. As only 10 % of EC patients has LNM, the majority may not benefit from surgical LN removal and will be exposed to an unnecessary extended surgical procedure and longer anesthesia time. Moreover, patients with EC are often obese, which is associated with increased prevalence of SLN mapping failure, underlining the relevance of improving risk estimation preoperatively [7]. We developed a Bayesian network (BN), named ENDORISK, integrating preoperative clinical and immunohistochemical biomarkers to estimate the risk of LNM and outcome in EC patients [8]. Variables incorporated in ENDORISK are tumor grade; immunohistochemical expression of estrogen receptor (ER), progesterone receptor (PR), p53, and L1 cell adhesion molecule (L1CAM); cancer antigen 125 (CA125) serum level; thrombocyte count; imaging results on lymphadenopathy; and cervical cytology. In external validation cohorts, ENDORISK yielded an area under the ROC Curves (AUC) for estimating LNM and 5-year disease-specific survival (DSS) ranging from 0·82–0·85 and 0·70–0·86 (6-8). ENDORISK could therefore be a valuable pretreatment tool in EC patients estimating the individual risk of LNM to guide tailored surgical treatment, and support shared-decision making.

BNs have the advantage of graphically representing conditional probability distributions and relationships between the variables. Moreover, BNs combine expert knowledge with machine learning from data, and can easily deal with missing variables making these models very suitable and intuitive for clinicians. Finally, the flexibility of BNs allows for integration of new variables according to revised guidelines or new evidence. While several studies have investigated the use of other machine learning techniques for risk estimation in endometrial cancer, the graphical representation of variables in BN such as ENDORISK is a unique quality which can support shared-decision making [9].

In recent years, molecular classification, identifying the prognostic subgroups *POLE* mutated, mismatch repair deficient or microsatellite instable (MMRd or MSI), p53 abnormal, and the copy number low, or non-specific molecular profile (NSMP) subgroup, has been incorporated in EC guidelines for postoperative risk stratification and adjuvant treatment stratification [1,10]. Several studies have shown that molecular subgroups have different risks of LNM, suggesting a possible role in the preoperative setting as well [11,12]. A low incidence of tumor invasiveness was found in *POLE* mutated tumors, which could partially be explained by the fact that ultra mutational burden may activate the immune system [13,14]. Yet, also patients with POLE mutations may present with LNM and recurrence [15]. On the other side, MSI leads to reduced government of DNA mismatch repair. While tumors with MSI status also have a higher mutational burden and illicit an increased immunogenic response, the prognosis of patients without *POLE* mutations but with MSI is worse than those with POLE mutations irrespective of MSI status, similar to those in the NSMP subgroup [16]. Yet, the impact of molecular subgroups in low-grade EC seems less significant than in high-grade patients [17]. Therefore, separate consideration of each molecular subgroup next to other histologic variables remains relevant.

In addition, recent guidelines recommend incorporating preoperative assessment of depth of MI by either magnetic resonance imaging (MRI) or expert transvaginal ultrasound (TVU) in the diagnostic workup [1]. Deep (≥ 50 %) MI has repeatedly been identified as an important predictor for LNM, recurrence, and survival [18–20].

To ensure ENDORISK maintains up-to-date with state of the art care, this study aimed to investigate and validate whether integration of the molecular classification and preoperative assessment of MI by TVU or MRI in the network improved accuracy and clinical usability of ENDORISK. In addition, we aimed to assess whether ENDORISK can correctly identify truly low risk of LNM in patients with low-grade EC in whom surgical lymph node assessment could be safely omitted.

2. Methods

2.1. Participants and source of data

A retrospective multicenter study was performed at the Radboud university medical center, Nijmegen, the Netherlands. Ethical approval was obtained by the Institutional Review Board of Radboud university medical center (Institutional Study Protocol 2019–5325). No informed consent was obtained as the data was pseudonymized. An overview of the inclusion process for this study is shown in supplement 1. Training data for the original ENDORISK network were derived from a previously published retrospective multicenter cohort study including patients from ten European Network for Individualized Treatment of Endometrial Cancer (ENITEC) centers treated between February 1995 and August 2013 for EC [21]. Patients diagnosed by an expert gynecological pathologist, with complete clinical and pathological data, and a follow-up of at least 36 months were included, resulting in a cohort size of 1·119. For the original ENDORISK training cohort, patients without sufficient preoperative tissue were excluded, resulting in a cohort consisting of 763 patients [8]. For this study, all 1·119 cases were reviewed

and cases with available hysterectomy specimens were included, as literature has shown excellent concordance between biopsy and hysterectomy specimen for molecular classification [22].

2.2. DNA-extraction and mutational analysis

For each case, four blank 10μm sections, or extracted DNA, were requested for (DNA-extraction and) mutational analysis. All analyses were performed in a single center (Radboud university medical center) to prevent batch effects between different testing methods. One slide was stained with hematoxylin and eosin to mark tumor areas and estimate tumor cell percentage. This area was microdissected. Using a TET-lysis buffer (10 mmol/L Tris/hydrochloride, pH 8·1, 1mmol/L ethylenediaminetraacetic acid, pH 8·0, and 0·01 % polysorbate 20 [Tween-20, Thermo Fisher]) at 56 °C, specimens were digested overnight with 5 % Chelex-100 (Bio-Rad) and 0·2 % proteinase K, with subsequent 10 min inactivation at 95 °C. After centrifugation and transferring the supernatant into a clean tube, DNA concentration was determined using the Qubit Broad Range Kit (Thermo Fisher Scientific).

Single-molecule molecular inversion probes (smMIP) analysis was used to determine *POLE, TP53,* and MSI status for obtained samples, using a previously published design and library preparation [17,23,24]. The purified libraries were then sequenced on a NexSeq500instrument (Illumina). The Sequence Pilot software (version 4·4·0; JSI Medical Systems) was used to demultiplex the bar-coded reads and create consensus reads minimizing sequencing errors. Variant calling was performed and variants were annotated as either benign, likely benign, unknown, likely pathogenic or pathogenic using publicly available databases: The Clinical Knowledgebase (https://www.jax.org/clinical-genomics/ckb), ClinVar (https://www.ncbi.nlm.nih.gov/clinvar/), Cancer Genome Interpreter (https://www.cancergenomeinterpreter.org/home), and the Catalog of Somatic Mutations in Cancer (cancer.sanger.ac.uk/cosmic). The latter three categories were considered relevant and consisted of known activating hotspot mutations for the oncogenes, and frameshift, nonsense, missense, and splice-site mutations for the TSGs.

2.3. Immunohistochemical staining and scoring

Blank 4μm sections on Superfrost slides were requested for immunohistochemical analysis. Mismatch repair (MMR) endonucleases PMS2 and MSH6 were immunohistochemically (IHC) stained [17]. A total loss of nuclear staining of PMS2 or MSH6 in the presence of a positive internal control was used to define MMR deficiency. Staining for p53 was already performed for ENDORISK and considered aberrant if more than 80 % of tumor cell nuclei showed intense staining, or when there was a complete absence of nuclear staining (null expression).

2.4. Selection of variables

An overview of variables incorporated in ENDORISK and ENDORISK-2 can be found in supplement 2**.** No significant difference was found for sensitivity of preoperative assessment of MI by TVU or MRI to identify deep MI, given that TVU is performed by an expert to ensure its accuracy [18,20]. Therefore, preoperative assessment of MI was defined as assessed either by expert TVU or by pelvic MRI.

2.5. BN structure optimization

The original ENDORISK network was first evaluated for possible changes that could improve the structure, by reviewing all causal relations and variables using expert knowledge.

After initial manual adjustment of the network, arc strengths (between zero and one), log likelihood, Aikake information criterion (AIC), and Bayesian information criterion (BIC) were computed for comparison of the new structure to the original network and previous adjustments.

2.6. Integration of additional variables and local training

Next, the network structure was reviewed for integration of nodes for preoperative assessment of MI and the molecular classification subgroups, using expert knowledge.

As the number of cases with preoperative assessment of MI was limited (n = 102), a literature search was performed to locally learn the conditional probability tables (CPT) of this node using data extracted from recent systematic reviews [18,20]. Pooled sensitivity and pooled specificity for 2D-transvaginal ultrasound (TVU) and for MRI from this review were used to calculate the CPT. For the nodes for *POLE* and MSI, local learning was used as well. For these nodes, only cases from the training dataset with full molecular classification, postoperative tumor grade, and lymph node status were included. *POLE* and MSI were added as separate variables as this enables modelling for potential 'double--classifiers', in which patients have, for example, both a *POLE* mutation and aberrant p53 expression.

As literature on performance of BNs in learning from censored survival data is limited, cases with limited follow-up for disease-specific survival (DSS), or patients who died due to other causes than EC, were defined event-free [25]. Multiple imputation was already performed in the original ENDORISK study to impute missing data in the training data, by calculating missing values using all the nodes in the BN as evidence in 500 random samples [8]. These were averaged for each new observation. By only using local learning for variable integration in ENDORISK-2, arcs between existing and new variables could be learning without requiring additional imputation.

2.7. BN validation

Validation of ENDORISK-2 was performed using only preoperative variables, by including cases with at least preoperative tumor grade, at least 3 immunohistochemical biomarkers, and at least one of the clinical preoperative markers available, similar to the original ENDORISK study [8,26,27]. For validation of LNM risk estimation, only patients who underwent surgical LN assessment, either by SLN procedure or LN dissection, were included. For validation of five-year DSS, only patients with at least five years of follow-up after surgery were included. The network performance was assessed for overall performance, calibration, and discrimination testing, including the Brier score and AUC.

Two external cohorts were used for validation: a retrospective cohort from Tübingen, Germany, including 247 EC patients, treated between 2003 and 2013 at the Tübingen University Women's Hospital [26]. The other retrospective cohort included 425 EC patients treated between January 2006 and May 2021 at the University Hospital Brno, Czechia [27].

2.8. Clinical usability

The impact of different risk thresholds on accuracy was investigated to review clinical usability, including a low-grade and high-grade subgroup analysis [28]. A major advantage of BNs is that evidence does not need to be entered for every variable to obtain accurate results. Therefore, multiple sets of minimal variables were defined and validated to aid flexible use in different clinical settings. First, an analysis was run to create all possible combinations of all preoperative variables to obtain a better understanding of the impact of the individual predictor variables. Next, minimal subsets were defined for a variation of clinical settings. For a clinical setting with limited resources, a minimal set of preoperative grade, three of the biomarkers ER, PR, p53 or L1CAM, and CA125 was tested. Next, a set was identified without the use of IHC biomarkers or molecular classification, which consisted of preoperative tumor grade, CA125, preoperative assessment of MI and one other clinical variable. For clinical settings with more extensive resources, a set including the preoperative tumor grade, CA125, *POLE*, MSI, and p53 was used.

R version 4·4·2 (packages bnlearn, Rgraphviz, and pROC), and Python version 3·10·8 (packages pandas, numpy and pyAgrum) were used for network construction and validation. Genie (version 4·0) was used to visualize the BN and for manual CPT adjustment.

This study followed the Transparent Reporting of a Multivariable Prediction Model for Individual Prognosis or Diagnosis + Artificial Intelligence (TRIPOD+AI) reporting guideline [29].

2.9. Role of the funding source

The funding organization of the study had no role in study design, data collection, data analysis, data interpretation, or the writing of the report. the funder had no role in any part of the study.

3. Results

3.1. Participants

Molecular data was obtained for 444 of 1·119 cases. Of these, 255 were included in the original ENDORISK training cohort (n = 763). As the additional cases lacked sufficient preoperative data to re-train the entire network, local re-learning was performed for the molecular classification nodes. Baseline characteristics for the training cohort and external validation cohorts are shown in Table 1. An overview of the cases with molecular classification is shown in supplement 3.

3.2. BN enhancement

The final BN (ENDORISK-2) is shown in Fig. 1. Arrows between variables depict the dependencies. Variables with multiple incoming arrows are indicated to be influenced by multiple other variables. To better represent natural tumor progression, the arc directions from MI to postoperative grade and from cervical cytology to postoperative grade were reversed. The node for adjuvant therapy was split up into a separate node for adjuvant chemotherapy and a node for adjuvant radiotherapy. The node for adjuvant radiotherapy was given a separate incoming arc from MI to reflect the diagnostic evidence used in clinical practice. Next, the arc between 5-year DSS and 1-year DSS was removed as these were already connected through 3-year DSS, to reduce complexity of the network. Finally, the nodes for preoperative MI assessment and for *POLE* and MSI were added.

3.3. BN validation

Results of external validation of ENDORISK-2 are shown in Fig. 2. Calibration plots for the validation cohorts can be found in supplement 4. The impact of different risk thresholds for LNM on the validation cohorts is shown in Fig. 3. Although the network has become more complex due to addition of new variables, the diagnostic accuracy remained comparable to the original ENDORISK network.

3.4. Clinical usability – stratifying based on tumor grade

As tumor grade is an important stratifying feature in current EC care, the performance of ENDORISK was evaluated in patients with low-grade EC and high-grade EC separately (supplement 6). In patients with low-grade EC in the Brno cohort, the false negative rate (FNR) ranged from 2 to 5·5 % for different risk thresholds up to 25 % for LNM, compared to 1·3–3·1 % in the Tübingen cohort. 83 % (Brno) and 89 % (Tübingen) of patients with low-grade EC were classified below a 10 % risk, with FNR of 4·3 % (Brno) and 2·2 %, respectively. For patients with high-grade EC, the FNR ranged from 0 to 16·7 % for risk thresholds up to 25 % for LNM for the Brno cohort, and 0–15·6 % in the Tübingen cohort.

3.5. Clinical usability – minimal variable set analysis

Three minimal sets of variables were selected to illustrate performance in varying clinical resource settings. In all three sets, CA125 and tumor grade were included because of their large impact on LNM prediction and availability. In addition, set one included IHC markers, set two included imaging markers (TVU/MRI), and set three included molecular subgroups.

The sets showed consistent performance with AUCs ranging between 0·79–0·87 (Table 2).

4. Discussion

This study demonstrated that by integration of state-of-the-art variables in ENDORISK, the accuracy and clinical usability of ENDORISK for preoperative risk estimation in patients with low-grade EC is high. In addition, clinical flexibility was improved as the added variables increase the options of minimal variable sets that can be entered while maintaining accuracy. Importantly, with this network almost 90 % of patients with low-grade EC could be classified as low-risk, with FNR of less than 5 %, identifying a relevant subgroup in which SLN mapping may safely be omitted.

4.1. Results in context of published literature

This study demonstrates how ENDORISK was enhanced in accordance with a defined framework investigating the benefit, credibility, accuracy, generalizability, usability and impact [28]. Compared to other published risk estimation models, ENDORISK performed similar or better: a systematic review by Ren et al. compared metrics of several machine learning models, including the original ENDORISK model, with pooled AUCs of 0·823 (95 % CI 0·757–0·890), for models using logistic regression, random forest, support vector machine, or a convolutional neural network [9]. The ENDORISK network was the only BN included in the study. For most other machine learning methods, the process from input to risk estimation is a black box, which can hinder trust and understanding of the model [30]. This black box does not exist for BN and regression models. Compared to regression models, benefits of BN are that BN can be learned from data, expert knowledge, or a combination, as demonstrated in ENDORISK-2, which enables them to fill in gaps in circumstances were data for certain variables are limited [31]. This allows for dynamic changes in subsets of a Bayesian network, as connections between variables can be learned from a combination of data, previous studies and (medical) expert knowledge.As the purpose of ENDORISK is supporting shared-decision making, the explainability of the model is a vital advantage compared to other machine learning approaches, as Bayesian networks can be shown as a graphical structure providing immediate insight in connections between different variables in the network.

Based on the risk estimation qualities of ENDORISK, it could be used in preoperative counseling to determine optimal surgical treatment. Surgical LN assessment is important to define EC stage and adjuvant treatment. The SLN procedure is increasingly implemented in clinical practice, and is associated with significantly less complications and side-effects compared to LN dissection [32]. However, the SLN procedure reportedly increases the average operation time by 33 min, exposing patients to additional time under anesthesia [6]. SLN mapping failure occurs in 20–25 % [4]. For these patients, additional (bi)lateral lymph node dissection might still be needed, increasing risk of complications. In addition, a systematic review found a FNR of 4 % (95 % CI 3 %-5 %) for the SLN procedure [33]. By comparison, ENDORISK is non-invasive and is able to accurately stratify low risk patients in a preoperative clinical setting: in patients with low-grade EC it was able to stratify 83–89 % of the validation cohorts below an estimated risk of 10 % for LNM, with FNRs of only 2·2 %-4·5 %. This is lower or comparable to the SLN procedure. Therefore, ENDORISK could be used to accurately

Table 1
Baseline characteristics of the training and validation cohorts.

Variables		Training (N = 952)	Brno (N = 581)	Tübingen (N = 247)
Age (years)	median (range)	64 (35−93)	65 (30−87)	64 (33−90)
BMI (kg/m^2)	median (range)	29 (16−70)	31 (17−53)	-
Preoperative tumour grade	1	372 (56.8 %)	161 (27.8 %)	78 (31.6 %)
	2	172 (26.3 %)	291 (50.1 %)	115 (46.6 %)
	3	111 (16.9 %)	127 (21.9 %)	52 (21.5 %)
	Unknown	297	2	0
ER expression	Negative (<10 %)	76 (10.0 %)	44 (7.6 %)	27 (11.0 %)
	Positive (≥ 10 %)	686 (90.0 %)	537 (92.4 %)	219 (89.0 %)
	Unknown	190	0	1
PR expression	Negative (<10 %)	140 (18.5 %)	74 (12.8 %)	45 (18.2 %)
	Positive (≥ 10 %)	617 (81.5 %)	506 (87.2 %)	202 (81.8 %)
	Unknown	195	1	0
L1CAM expression	Negative (<10 %)	665 (87.2 %)	476 (83.5 %)	192 (77.7 %)
	Positive (≥ 10 %)	79 (10.4 %)	94 (16.5 %)	55 (22.3 %)
	Unknown	208	11	0
p53 expression	Wildtype	585 (83.9 %)	480 (86.0 %)	209 (84.6 %)
	Aberrant	112 (16.1 %)	78 (14 %)	38 (15.4 %)
	Unknown	257	23	0
CA125	< 35 IU/mL	318 (77.9 %)	420 (72.3 %)	197 (87.2 %)
	≥ 35 IU/mL	90 (22.1 %)	109 (18.7 %)	29 (12.8 %)
	Unknown	544	52	21
Platelet count	< 400.10^{9}1/L	557 (95.7 %)	553 (97.4 %)	225 (91.5 %)
	≥ 400.10^{9}1/L	25 25 (4.3 %)	15 (2.6 %)	21 (8.5 %)
	Unknown	370	13	1
MSI (training) or MMRd (validation cohorts)	No	352 (79.2 %)	89 (64.0 %)	170 (68.8 %)
	Yes	92 (20.7 %)	50 (36.0 %)	77 (31.2 %)
	Unknown	508	442	0
POLE mutation	No	409 (92.1 %)	137 (98.6 %)	218 (88.3 %)
	Yes	35 (7.9 %)	2 (1.4 %)	29 (11.7 %)
	Unknown	508	442	0
Imaging myometrial invasion (MRI or TVU)	< 50 %	65 (63.7 %)	384 (69.4 %)	
	≥ 50 %	37 (36.3 %)	169 (30.6 %)	
	Unknown	850	28	247
Lymphadenopathy on imaging	No lymphadenopathy	460 92.4 %) (94.5 %)	543 (97.6 %)	
	Lymphadenopathy	38 (7.6 %%)	13 (2.3 %)	
	Unknown	454	25	247
Cervical cytologyEndometrial cells	Benign	560 (94.6 %)	411 (96.3 %)	
	Malignant	32 (5.4 %)	16 (3.7 %)	
	Unknown	360	154	247
Postoperative histological subtype	EEC	688 (94.5 %)	512 (88.1 %)	193 (78.1 %)
	NEEC	40 (5.5 %)	69 (11.9 %)	54 (21.9 %)
	Unknown	224	0	0
Postoperative tumour grade	1	383 (40.3 %)	148 (25.5 %)	84 (46.0 %)
	2	365 (38.4 %)	296 (50.9 %)	110 (35.2 %)
	3	203 (21.3 %)	137 (23.6 %)	45 (18.8 %)
	Unknown	1	0	8
Myometrial invasion	< 50 %	606 (63.7 %)	314 (67.5 %)	165 (66.8 %)
	≥ 50 %	345 (36.3 %)	189 (32.5)	82 (33.2 %)
	Unknown	1	78	0
FIGO stage (surgical)	IA	544 (57.2 %)	343 (59.0 %)	156 (63.2 %)
	IB	234 (24.6 %)	94 (16.2 %)	52 (21.1 %)
	II	65 (6.8 %)	68 (11.7 %)	12 (4.9 %)
	IIIA	23 (2.4 %)	18 (3.1 %)	23 (9.31 %)
	IIIB	6 (0.6 %)	6 (1.0 %)	1 (0.40 %)
	IIIC	55 (5.8 %)	45 (7.7 %)	1 (0.40 %)
	IVA	2 (0.2 %)	0	1 (0.40 %)
	IVB	22 (2.3 %)	7 (1.2 %)	
	Unknown	1		
LVSI	No	821 (86.6 %)	463 (83.7 %)	213 (86.2 %)
	Yes	127 (13.4 %)	90 (16.3 %)	34 (13.8 %)
	Unknown	4	28	0
Lymph node metastasis	No	554 (89.1 %)	302 (84.4 %)	227 (91.9 %)
	Yes	68 (10.9 %)	56 (15.6 %)	20 (8.1 %)
	Unknown	330	223	0
Treatment	None	464 (49.8 %)	308 (63 %)	104 (42.1 %)
	Radiotherapy	380 (40.8 %)	108 (22.1 %)	119 (48.2 %)
	Chemotherapy	41 (4.4 %)	20 (4.1 %)	12 (4.9 %)
	Chemoradiation	46 (4.8 %)	53 (10.8 %)	12 (4.9 %)
	Unknown	21	92	0
Recurrence	No	803 (84.3 %)	520 (91.5 %)	205 (83.0 %)
	Yes, local	27 (2.8 %)	18 (3.2 %)	
	Yes, regional	11 (1.2 %)	8 (1.4 %)	
	Yes, distant	86 (9.0 %)	22 (3.9 %)	
	Yes, location unknown	0	0	42 (17.0 %)

(*continued on next page*)

Table 1 (*continued*)

Variables		Training (N = 952)	Brno (N = 581)	Tübingen (N = 247)
	Unknown	4	13	
1-year DSS	No	17 (2.2 %)		
	Yes	742 (97.8 %)		
	Unknown	4		
3-year DSS	No	44 (6.1 %)		
	Yes	682 (93.9 %)		
	Unknown	37		
5-year DSS	No	484 (87.5 %)	38 (11.4 %)	30 (12.2 %)
	Yes	69 (12.5 %)	295 (88.6 %)	215 (87.8 %)
	Unknown	399	248	2

BMI, body mass index; CA125, cancer antigen 125, DSS, disease-specific survival; ER, estrogen receptor; FIGO, International Federation of Gynaecology and Obstetrics; L1CAM, L1 Cell Adhesion Molecule; LVSI, lymphovascular space invasion; MMRd, mismatch repair deficiency; MRI, magnetic resonance imaging; MSI, microsatellite instability; POLE, polymerase epsilon; PR, progesterone receptor; TVU, transvaginal ultrasound.

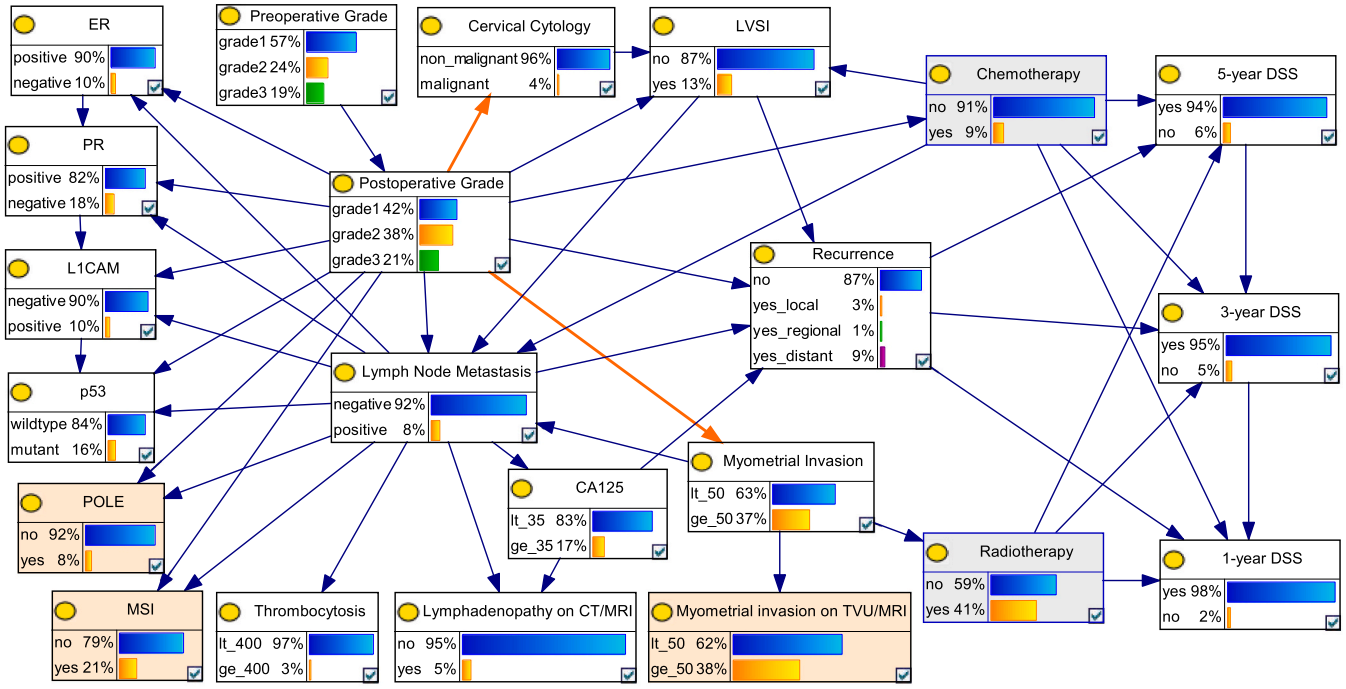


Fig. 1. Arrows between variables depict the dependency. Variables with multiple incoming arrows are indicated to be influenced by multiple other variables. Orange nodes include the variables added within the current study. The orange arrows were changed direction. The node for adjuvant therapy was split up into separate nodes for chemotherapy and radiotherapy (grey).

identify patients with low-grade EC in whom surgical LN assessment could be safely omitted. This could be especially useful in low-resource countries in which SLN procedures are not available or in patients who might be at higher risk of peri-surgical complications due to comorbidities.

Usage of ENDORISK provides a continuous risk estimation percentage as opposed to classifying patients in a risk group [1,2]. Research has shown that use of a continuous risk allows for more refined shared-decision making [34]. Therefore, clinical implementation of ENDORISK could positively impact shared-decision making and information provision to both clinicians and patients.

4.2. Strengths and limitations

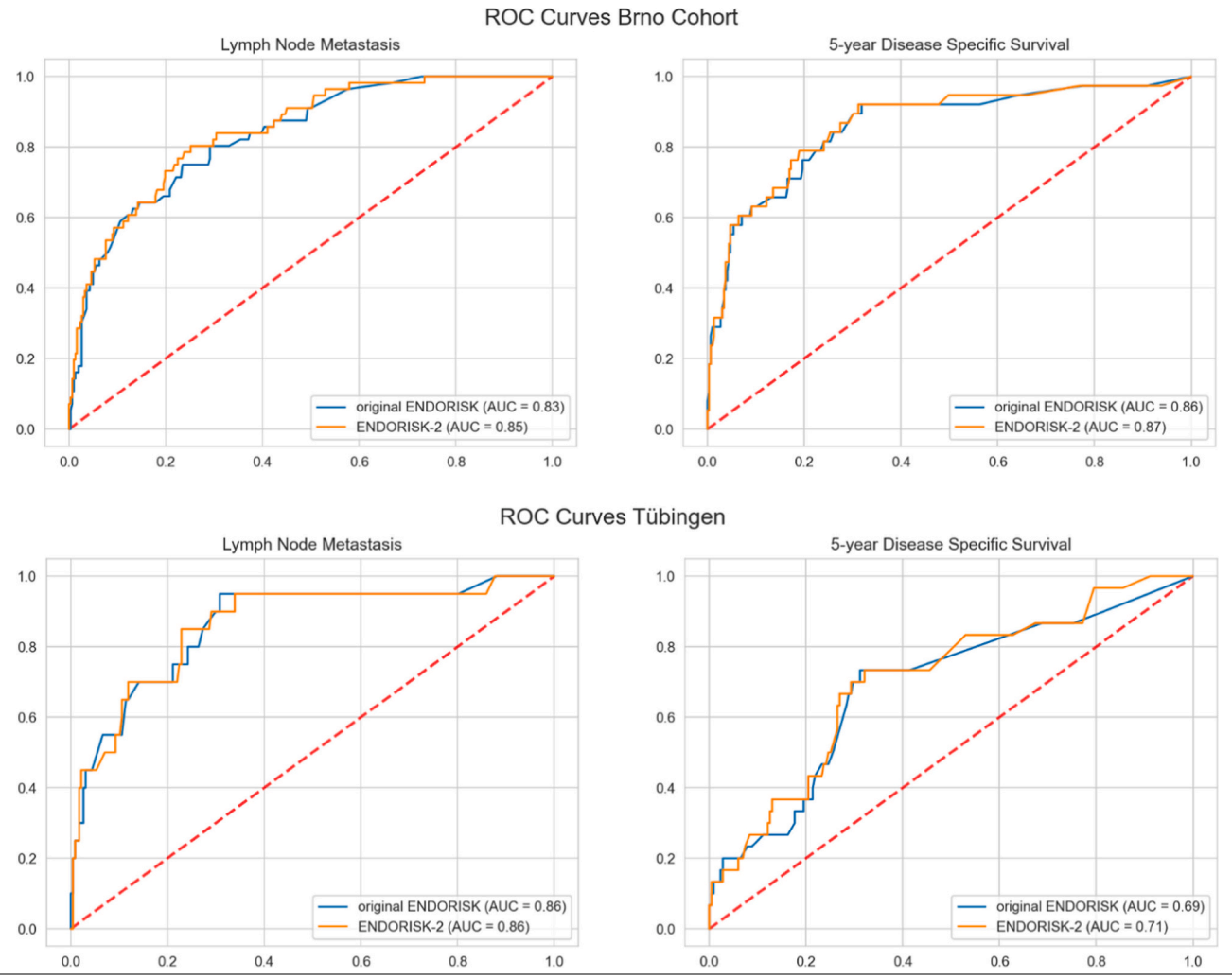
While an increasing amount of AI models are developed and published within the field of oncology and specifically within gynecologic oncology, literature on such models is limited for EC [35]. With this study we optimized one of the first preoperative risk estimation networks for EC. As ENDORISK is a graphical probabilistic model, this provides users with a unique insight into the rationale behind the output of the network. This has been demonstrated by research to support trust by users in AI models [36].

In addition, by investigating several sets of minimal variables, this study highlighted how a BN enhances clinical usability. The consistent accuracy across different minimal variable sets and different thresholds demonstrates the robustness of the network. By investigating the impact of several risk thresholds, this study provides clinicians a concrete guidance on how the use of ENDORISK could impact clinical practice.

By using local learning to integrate new variables, the impact of missing variables was reduced as much as possible.

The training cohort contains a relatively low prevalence of patients with non-endometrioid carcinoma, which could explain why the ENDORISK network is less accurate in external validation subgroups of patients with high-grade tumors.

In addition, the new International Federation of Gynaecologic Oncology (FIGO) 2023 classification reintroduced the category of 'no MI' for pathological staging, which could not be incorporated in the current model due to lack of available literature for local learning. This makes the enhanced network slightly less applicable to postoperative clinical situations [10]. However, as the main purpose of ENDORISK



External validation of ENDORISK-2

	Training cohort		Brno cohort		Tübingen cohort	
	LNM	5-year DSS	LNM	5-year DSS	LNM	5-year DSS
AUC (95% CI)	0.82 (0.75-0.88)	0.83 (0.78-0.89)	0.85 (0.80-0.90)	0.87 (0.80-0.93)	0.86 (0.77-0.96)	0.71 (0.61-0.81)
Brier score	0.06	0.14	0.10	0.09	0.06	0.12
Predicted / Observed N of Events	59 / 53	711 / 707	42 / 56	307 / 295	20 / 20	227 / 215
Predicted / Observed Ratio	1.12 (0.76-1.31)	1.01 (0.93-1.08)	0.75 (0.77-1.3)	1.04 (0.89-1.12)	1.02 (0.65-1.56)	1.06 (0.87-1.14)

Fig. 2. ROC for both validation cohorts, showing the original ENDORISK network and ENDORISK-2.

currently is use in a preoperative setting (clinical staging), this was deemed less relevant.

Finally, some heterogeneity exists between the two external validation cohorts. This is mainly based on a different proportion of high- and low grade tumors, with the Brno cohort having high-grade patients in 23.6 %, compared to 18.8 % in the Tübingen cohort. On the other hand, use of adjuvant treatment was higher in the Tübingen cohort, with 57.9 % compared to 37 % in the Brno cohort. This could explain a difference in performance of ENDORISK-2 for estimation of 5-year DSS. However, molecular analysis in both cohorts was based on the ProMisE criteria [24]. In addition, diagnostic accuracy for lymph node estimation was similar for both external cohorts, which underlines the broad applicability of the model in other cohorts.

4.3. Future research, stakeholders and implications for clinical practice

The ENDORISK network was trained with data from EC patients treated between 1995 and 2013 in several European countries. In addition, external validation was performed in multicenter European data cohorts. With current enhancements to the network, the next steps have been made towards the use of ENDORISK as a clinical decision support tool in a preoperative setting. Updating the training cohort with more recently treated patients, and with patient populations outside of European countries, could further improve accuracy and generalizability.

All patients in the training cohort underwent LN dissection. Therefore, incorporation of training data from patients who underwent a SLN procedure is needed to train the network on low volume metastases (micrometastasis) as well. In addition, multi-omics technologies are

A. Brno cohort

Threshold	1%	5%	10%	15%	20%	25%
						
N at risk (%)	58.4%	36.9%	27.1%	20.1%	19.3%	17.9%
FNR	2%	4%	6.9%	7.4%	8%	8.2%
PPV	25.4%	35.6%	39.2%	46.7%	47.8%	50%
NPV	98%	96%	93.1%	92.6%	92%	91.8%
Sensitivity	94.6%	83.9%	67.9%	62.5%	58.9%	57.1%
Specificity	48.3%	71.9%	80.5%	86.8%	88.1%	89.4%

B. Tübingen cohort

Threshold	1%	5%	10%	15%	20%	25%
						
N at risk (%)	68%	34%	19.8%	18.2%	11.3%	7.7%
FNR	1.3%	1.2%	3%	3%	4.6%	4.8%
PPV	11.3%	21.4%	28%	31.1%	35.7%	47.4%
NPV	98.7%	98.8%	97%	97%	95.4%	95.2%
Sensitivity	95%	90%	70%	70%	50%	45%
Specificity	34.4%	70.9%	84.1%	86.3%	92.1%	95.6%

Fig. 3. (A)Brno external validation cohort – influence of different ENDORISK risk thresholds for LNM on population (B)Tübingen external validation cohort – influence of different ENDORISK risk thresholds for LNM on population.

increasingly being applied in cancer prediction models, as well as in endometrial cancer specifically [37]. While the first steps of incorporating biomarkers into ENDORISK have been taken, integrating multi-dimensional data, such as specific molecular pathways, could improve predictive accuracy for survival. The successful integration of new variables in ENDORISK-2 by local learning demonstrates how separate variables of the network are easily adjustable. Further research towards accuracy of survival prediction is required to increase usability of ENDORISK for stratification of optimal adjuvant treatment and follow-up.

Literature has shown that involvement of stakeholders, the so-called 'end-users' of a risk estimation model, is important to facilitate successful implementation [38,39]. Since development of the original ENDORISK network, patients and clinicians have been actively involved in determining what is needed to create a clinically relevant and trustworthy risk estimation tool. Qualitative studies were performed with end-users in the form of focus groups with clinicians, and interviews with EC patients and patient advocacy groups [40,*publicationinpreparation*]. Results were used to identify clinically useful enhancements to ENDORISK, and to identify barriers and facilitators for implementation. In addition, a user interface for ENDORISK was developed and user-tested in close collaboration with gynecologists [41,42].

The next step will be to externally validate ENDORISK in a prospective clinical implementation study (ClinicalTrials.gov number NCT07200466), to evaluate clinical usability, verify accuracy and to provide more extensive data for a cost-effectiveness analysis. In this study, the ENDORISK model will be part of the preoperative work up by gynecologists after performance of the relevant diagnostic tests within multidisciplinary tumor boards and as part of the shared decision making process. ENDORISK estimates a personalized risk for LNM, which will be incorporated in preoperative counseling of patients to determine whether or not surgical lymph node staging will be performed

Table 2
External validation of minimal evidence sets for LNM estimation.

Minimal variables:		Brno cohort (LNM)	Tübingen cohort (LNM)
Set 1: Preoperative grade, CA125, 3 of 4 biomarkers (ER/PR/P53/L1CAM)	AUC Sensitivity* Specificity*	0.822–0.85 67.3–68.6 % 78.4–83.6 %	0.824–0.849 61.1–72.2 % 82.2–89.4 %
Set 2: Preoperative grade, CA125, preoperative assessment of MI by expert TVU/MRI, one biomarker (ER/PR/p53/L1CAM)	AUC Sensitivity* Specificity*	0.845–0.866 68.0–75.0 % 83.5–87.2 %	[no imaging in cohort]
Set 3: Preoperative grade, molecular classification (*POLE*, MSI and p53), CA125 and thrombocytes	AUC Sensitivity* Specificity*	[limited molecular classification in cohort]	0.787–0.803 66.7–73.7 % 76.7–84.1 %

*at 10 % risk threshold
AUC, area under the curve; CA125, cancer antigen 125; ER, estrogen receptor, L1CAM, L1 Cell Adhesion Molecule; LN< , lymph node metastasis; MRI, magnetic resonance imaging; MSI, microsatellite instability; POLE, polymerase epsilon; PR, progesterone receptor; TVU, transvaginal ultrasound

or can be safely omitted. In addition, counseling patients with their personalized risk estimation will contribute to more involvement of the patients' perspectives on whether or not patients would be willing to undergo adjuvant chemo- and/or radiotherapy in case of LNM. The results of the ENDORISK implementation study will contribute to the proper defining on how and for whom ENDORISK would be beneficial in daily clinical practice.

As part of this study a minimal set of required variables is defined: histologically confirmed endometrial cancer, preoperative tumor grade (1−2−3), CA-125 and three out of four biomarkers (ER, PR, P53 and/or L1CAM). In future studies, postoperative use of ENDORISK will be further explored to predict treatment response (chemo-and/or radiotherapy) and patients' outcome (recurrence/survival and quality of life).

5. Conclusion

With this study, we demonstrated improved clinical usability of ENDORISK-2. Integration of the molecular classification and preoperative assessment of MI have improved flexibility, and subgroup analysis showed that ENDORISK can be used to accurately and non-invasively stratify patients with low-grade EC in whom surgical lymph node staging can be omitted. This study illustrates how Bayesian networks such as ENDORISK can be used in preoperative information provision and individualized shared-decision making for clinicians and patients in varying clinical settings.

CRediT authorship contribution statement

Irene de la Calle: Writing – review & editing, Resources, Data curation. **Marcel Grube:** Writing – review & editing, Validation, Resources, Data curation. **Stephanie Vrede:** Writing – review & editing, Investigation, Data curation. **Gemma Mancebo:** Writing – review & editing, Resources, Data curation. **Ally Sprik:** Writing – review & editing, Writing – original draft, Software, Investigation, Formal analysis. **van der Putten Louis J. M.:** Writing – review & editing, Resources, Data curation. **Petra Bretová:** Writing – review & editing, Validation, Resources, Data curation. **Amant Frédéric:** Writing – review & editing, Resources, Data curation. **Peter Bronsert:** Writing – review & editing, Resources, Data curation. **Stefan Kommoss:** Writing – review & editing, Resources, Data curation. **Vit Weinberger:** Writing – review & editing, Validation, Resources, Data curation. **Camilla Krakstad:** Writing – review & editing, Resources, Data curation. **Marike S. Lombaers:** Writing – review & editing, Writing – original draft, Visualization, Validation, Software, Project administration, Methodology, Investigation, Data curation. **Küsters-Vandevelde Heidi V. N.:** Writing – review & editing, Resources, Data curation, Conceptualization. **Casper Reijnen:** Writing – review & editing, Writing – original draft, Visualization, Validation, Supervision, Software, Methodology, Data curation, Conceptualization. **Ingfrid S. Haldorsen:** Writing – review & editing, Resources, Data curation. **Martin Koskas:** Writing – review & editing, Resources, Data curation. **Visser Nicole C. M.:** Writing – review & editing, Resources, Methodology, Conceptualization. **Michiel Simons:** Writing – review & editing, Resources, Data curation. **Marc P.L.M. Snijders:** Writing – review & editing, Resources, Data curation, Conceptualization. **Johanna M.A. Pijnenborg:** Writing – review & editing, Writing – original draft, Validation, Supervision, Project administration, Methodology, Funding acquisition, Conceptualization. **Asberger Jasmin F.:** Writing – review & editing, Resources, Data curation. **Eva Colas:** Writing – review & editing, Resources, Data curation. **Peter J.F. Lucas:** Writing – review & editing, Validation, Supervision, Software, Methodology, Conceptualization. **Arjen Hommersom:** Writing – review & editing, Validation, Supervision, Software, Methodology. **Hege F. Berg:** Writing – review & editing, Resources, Data curation. **Antonio Gil-Moreno:** Writing – review & editing, Resources, Data curation. **Xavier Matias-Guiu:** Writing – review & editing, Resources, Data curation. **Jitka Hausnerova:** Writing – review & editing, Resources, Data curation. **Jutta Huvila:** Writing – review & editing, Resources, Data curation.

Data sharing

Data, protocols, and other metadata of the ENDORISK study are available for sharing within the scientific community. Bona fide researchers interested in accessing the data can apply to the corresponding author.

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Declaration of Competing Interest

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2025.116058.

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