

## COMMENTARY TO HABILITATION THESIS<sup>1</sup>

### Individualized Approach to Patients with Endometrial Cancer

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The habilitation thesis entitled “*Individualized Approach to Patients with Endometrial Cancer*” is presented as a thematically integrated collection of original scientific papers that collectively document the author’s systematic and long-term contribution to advancing personalized care in gynecologic oncology. With a focus on endometrial carcinoma, the thesis addresses key areas of modern patient management, including early diagnostics, molecular profiling, individualized surgical staging, and predictive modeling. The central aim of the work is to improve risk-adapted clinical decision-making by implementing biologically and clinically informed strategies that enhance diagnostic precision, optimize therapeutic planning, and ultimately contribute to better patient outcomes.

The methodologies employed across the included studies are diverse and appropriately selected for the posed research questions. They encompass both prospective and retrospective cohort designs, largely conducted at the Department of Obstetrics and Gynecology, University Hospital Brno, often in collaboration with leading European research centers, especially under the auspices of the ENITEC (European Network for Individualized Treatment in Endometrial Cancer) consortium. The author utilizes advanced ultrasound diagnostics, immunohistochemical and molecular-genetic analysis (including mismatch repair protein expression, *POLE* and *TP53* mutation testing), and statistical modeling approaches such as Bayesian networks and decision trees. Multicenter collaboration and large patient cohorts further strengthen the robustness and clinical relevance of the findings.

Among the most significant outcomes of the thesis is the clarification of the clinical role of ultrasound and endometrial biopsy in asymptomatic patients. The author’s work demonstrates that in the absence of bleeding or other risk features, the detection of polyps or hyperplasia on ultrasound should not be considered an automatic indication for biopsy. Furthermore, her data show that early detection of endometrial cancer in asymptomatic women does not translate into improved survival when adjusted for tumor stage and biology, supporting a more individualized, risk-adapted diagnostic approach.

In the area of molecular classification, the author demonstrates that routine application of immunohistochemistry for mismatch repair proteins and p53, supplemented by *POLE* sequencing where indicated, is both feasible and clinically impactful. Implementation of molecular stratification led to a reclassification of risk categories in a substantial number of patients and thus influenced

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<sup>1</sup> The commentary must correspond to standard expectations in the field and must include a brief characteristic of the investigated matter, objectives of the work, employed methodologies, obtained results and, in case of co-authored works, a passage characterising the applicant’s contribution in terms of both quality and content.

recommendations for surgical procedure and adjuvant therapy. The clinical relevance of traditional biomarkers such as estrogen and progesterone receptors is also revisited, with new evidence confirming their independent prognostic value even within molecular subtypes. Pilot study on serum biomarkers such as DJ1 and L1CAM suggests potential for treatment monitoring and early recurrence detection, although further validation is needed.

A particularly strong part of the thesis lies in its contribution to refining lymph node staging. The author has conducted both single-center and multicenter studies on sentinel lymph node biopsy using indocyanine green, identifying key predictors of mapping failure and supporting its adoption as the standard staging procedure. These findings are corroborated by her contribution to the international SENECA study, which examined the correlation between sentinel node involvement and molecular subtypes. Although p53-abnormal and MMR-deficient tumors had higher nodal positivity rates, molecular classification did not yet surpass histopathological criteria in predictive accuracy, emphasizing the complementary rather than substitutive role of molecular data in surgical planning.

In the final part of the thesis, the author explores predictive modeling as a tool for individualized care. She contributed to an external validation of the ENDORISK model, which uses clinical, histological, and molecular data to predict lymph node metastases and disease-specific survival. The model performed with high accuracy in low-risk patients, highlighting its value in preoperative planning. Another original study showed that incorporating immunohistochemical markers into existing diagnostic models significantly improved risk stratification, further supporting the integration of molecular pathology into daily practice.

MUDr. Petra Bretová, Ph.D., is either the first or corresponding author in half of the 16 included publications. Her contribution consistently includes the formulation of research hypotheses, design of methodology, clinical data collection, and manuscript preparation. In multicenter settings, she has assumed responsibility for coordinating data acquisition, ensuring methodological rigor, and participating in critical manuscript revisions.

In conclusion, this habilitation thesis presents a comprehensive, methodologically rigorous, and clinically relevant body of work that significantly advances individualized management in endometrial cancer. The results are well-validated, thoroughly discussed, and directly applicable to clinical practice. The author's contributions meet all the criteria for independent scientific work and academic promotion.

**[1 ]<sup>2</sup> VINKLEROVA, P., M. FELSINGER, S. FRYDOVA, P. OVESNA, J. HAUSNEROVA and V WEINBERGER.** Is the finding of endometrial hyperplasia or corporal polyp a mandatory indication for biopsy? *Ceska Gynekologie-Czech Gynaecology*. 2020, **85(2)**, 84–93. ISSN 1805-4455.

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<sup>2</sup> Bibliographic record of a published scientific result, which is part of the habilitation thesis.

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	70	80	80

[2] KOBIZKOVA, M., P. BRETOVA\*(corresponding author)\*, M. FELSINGER, L. MINAR, M. BEDNARIKOVA and V. WEINBERGER. Ultrasound finding of an endometrial polyp and factors increasing the risk of malignancy. *Ceska Gynekologie-Czech Gynaecology* [online]. 2024, **89**(1), 44–51. ISSN 1805-4455. Available at: doi:10.48095/cccg202444

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	90	50	80

[3] VINKLEROVA, Petra, Petra OVESNA, Marketa BEDNARIKOVA, Lubos MINAR, Michal FELSINGER, Jitka HAUSNEROVA and Vit WEINBERGER. Does an Endometrial Cancer Diagnosis among Asymptomatic Patients Improve Prognosis?. *Cancers* [online]. 2022, **14**(1, Article 115). ISSN 2072-6694. Available at: doi:10.3390/cancers14010115

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	70	80	80

[4] HRSTKA, Roman, Filip ZAVADIL-KOKAS, Lucie MOUKOVA, Tamara KOLAROVA, Maryam SHAHIDIANAKBAR, Milan ANTON, Petra OVESNA, Dita MUNZOVA, Marketa BEDNARIKOVA, Petra BRETOVA, Lubos MINAR, Jitka HAUSNEROVA and Vit WEINBERGER. Genetic analysis of uterine lavage fluids to identify women at high risk of endometrial cancer. *Bmc Research Notes* [online]. 2025, **18**(1, Article 117). ISSN 1756-0500. Available at: doi:10.1186/s13104-025-07173-8

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	20	10	20

[5] BEDNAŘÍKOVÁ, M., J. HAUSNEROVÁ, L. MINÁŘ, R. TASLEROVÁ, P. VINKLEROVÁ, L. EHRlichOVÁ, J. TRIZULJAK, I. BLAHÁKOVÁ, D. PRINC, K. MATULOVÁ, P. OVESNÁ, O. SLABÝ and V. WEINBERGER. Molecular testing of endometrial carcinoma in real-world clinical practice [Molekulární testování karcinomu endometria – analýza prvních zkušeností z klinické praxe]. *Klinická Onkologie* [online]. 2023, **36**(3), 215–223. ISSN 0862-495X. Available at: doi:10.48095/ccko2023215

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	20	10	20

[6] CHACON, Enrique, Felix BORJA, R. RAJAGOPALAN LYER, Francesco FANFANI, Mario MALZONI, Petra BRETOVA, Ana LUZARRAGA AZNAR, Robert FRUSCIO, Marcin A.

JEDRYKA, Richard TOTH, Anna MYRIAM PERRONE, Athanasios KAKKOS, Ignacio CRISTOBAL QUEVEDO, Luigi CONGEDO, Vanna ZANAGNOLO, Sergi FERNANDEZ-GONZALEZ, Beatriz FERRO, Fabrice NARDUCCI, Tatevik HOVHANNISYAN, Elif AKSAHIN, Laura CARDENAS, M. REYES OLIVER, Gonzalo NOZALEDA, Marta ARNAEZ, Marcin MISIEK, Annamaria FERRERO, Flore ANNE PAIN, Janire ZARRAGOITIA, Cristina DIAZ, Lorenzo CEPPI, Shamsi MEHDIYEV, Fernando ROLDAN-RIVAS, Alberto Rafael GUIJARRO-CAMPILLO, Joana AMENGUAL, Nabil MANZOUR, Luisa SANCHEZ LORENZO, Jorge M. NUNEZ-CORDOBA, Antonio GONZALEZ MARTIN, Jose ANGEL MINGUEZ, Luis CHIVA and SENECA WORKING GRP. SENECA study: staging endometrial cancer based on molecular classification. *International Journal Of Gynecological Cancer* [online]. 2024, **34**(9), 1313–1321. ISSN 1525-1438. Available at: doi:10.1136/ijgc-2024-005711

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	10	10	10

**[7]** BRETOVA, Petra, Munachiso Itheme NDUKWE, Jan LACO, Hana VOSMIKOVA, Tatana RESLOVA, Denisa POHANKOVA, Klara BALCAROVA, Jiri HAVIGER, Jana Marie HAVIGEROVA and Igor SIRAK. Preoperative risk stratification in endometrial cancer using ESGO/ESTRO/ESP 2021 guidelines: accuracy with and without molecular classification. *Bmc Cancer* [online]. 2025, **25**(1, Article 1302). ISSN 1471-2407. Available at: doi:10.1186/s12885-025-14741-5

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50	90	80	80

**[8]** VREDEA, Stephanie W., Willem Jan VAN WEELDEN, Johan BULTEN, C. Blake GILKS, Steven TEERENSTRA, Jutta HUVILA, Xavier MATIAS-GUIU, Antonio GIL-MORENO, Jasmin ASBERGERJ, Sanne SWEEGERS, Louis J. M. VAN DER PUTTEN, Heidi V. N. KUESTERS-VANDEVELDE, Casper REIJNEN, Eva COLASI, Jitka HAUSNEROVA, Vit WEINBERGER, Marc P. L. M. SNIJDERS, **Petra VINKLEROVA**, Antonella RAVAGGI, Franco ODICINO, Eliana BIGNOTTI, Jessica N. MCALPINE, Roy KRUITWAGEN and Johanna M. A. PIJNENBORG. Hormonal biomarkers remain prognostically relevant within the molecular subgroups in endometrial cancer. *Gynecologic Oncology* [online]. 2025, **192**, 15–23. ISSN 1095-6859. Available at: doi:10.1016/j.ygyno.2024.10.028

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	10	20	20

**[9]** MEIJS-HERMANNNS, Puk, Henrica M. J. WERNER, Loes KOOREMAN, **Petra BRETOVA**, Vit WEINBERGER, Stephanie VREDE, Luthy S. M. ALCALA, Frederic AMANT, Jasmin ASBERGER, Marketa BEDNARIKOVA, Dorry BOLL, Carolien M. BRONKHORST, Johan BULTEN, Antonio GIL-MORENO, Ingfrid S. HALDORSEN, Jitka HAUSNEROVA, Jutta HUVILA, Martin KOSKAS, Camilla KRAKSTAD, Heidi KUESTERS-VANDEVELDE, Gemma Mancebo MORENO, Xavier MATIAS-GUIU, Huy NGO, Brenda M. PIJLMAN, Maria SANTACANA, Marieke SMINK, Jone TROVIKO, Viola M. J. VERHOEF, Koen VAN DE VIJVER, Dennis VAN HAMONT, Anneke A. M. VAN DER WURFF, Johanna M. A.

PIJNENBORG and Nicole C. M. VISSER. Improving pre-operative binary grading: relevance of p53 and PR expression in grade 2 endometrioid endometrial carcinoma. *International Journal Of Gynecological Cancer* [online]. 2025, **35**(4, Article 101682). ISSN 1525-1438. Available at: doi:10.1016/j.ijgc.2025.101682

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	20	20	20

**[10]** BEDNARIKOVA, Marketa, **Petra VINKLEROVA**, Jana GOTTWALDOVA, Petra OVESNA, Jitka HAUSNEROVA, Lubos MINAR, Michal FELSINGER, Dalibor VALIK, Zdenka CERMAKOVA and Vit WEINBERGER. The Clinical Significance of DJ1 and L1CAM Serum Level Monitoring in Patients with Endometrial Cancer. *Journal Of Clinical Medicine* [online]. 2021, **10**(12, Article 2640). ISSN 2077-0383. Available at: doi:10.3390/jcm10122640

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	10	10	10

**[11]** **VINKLEROVA, P.\*(corresponding author)\***, L. MINAR, V. WEINBERGER, M. FELSINGER and M. KOBLIZKOVA. Change in the trend of surgical treatment and staging of lymph nodes in endometrial cancer - results of the Oncogynecology Center, Department of Gynecology and Obstetrics, University Hospital Brno and Masaryk University in the years 2012-2021. *Ceska Gynekologie-Czech Gynaecology* [online]. 2022, **87**(5), 308–316. ISSN 1805-4455. Available at: doi:10.48095/ccccg2022308

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	70	90	80

**[12]** **BRETOVA, Petra**, Lubos MINAR, Petra OVESNA, Vit WEINBERGER, Michal FELSINGER, Michaela KOBLIZKOVA, Jitka HAUSNEROVA, Eva JANDAKOVA and Tatiana STUPKOVA. Predictors for sentinel lymph node mapping failure using indocyanine green injection in apparent early stages of endometrial cancer: A single-center prospective study. *International Journal Of Gynecology & Obstetrics* [online]. 2025. ISSN 1879-3479. Available at: doi:10.1002/ijgo.70123

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30	70	80	70

**[13]** BORIA, Felix, Enrique CHACON, R. Rajagopalan IYER, Francesco FANFANI, Francesca FALCONE, **Petra BRETOVA**, Ana Luzarraga AZNAR, Robert FRUSCIO, Marcin JEDRYKA, Richard TOTH, Artem STEPANYAN, Gurkan KIRAN, Cecilia DARIN, Agnieszka RYCHLIK, Ester MIRALPEIX, Meriem KOUAL, Roberto BERRETTA, Natalia Anna PALASZ, Duska BERIC, Dimitrios TSOLAKIDIS, Soledad FIDALGO, Richard SCHWAMEIS, Somashekhar SP, Ibrahim YALCIN, Radovan PILKA, Cagatay TASKIRAN, Despoina MYOTERI, Estibaliz Iza RODRIGUEZ, Dariusz G. WYDRA, Silvia CATOT, Mathias FEHR, Frederic GOFFIN, Maria Ercilia IBARRA, Stamatios PETOUSIS, Enrique Moratalla

BARTOLOME, Mareike BOMMERT, Alfonso QUESADA, Shamistan ALIYEV, Jose Angel MINGUEZ and Luis CHIVA. Sentinel SENECA risk factors for unsuccessful bi-lateral sentinel lymph node mapping in endometrial cancer. *International Journal Of Gynecological Cancer* [online]. 2025, **35**(5, Article 101771). ISSN 1525-1438. Available at: doi:10.1016/j.ijgc.2025.101771

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10	10	10	10

[14] MUNZOVA, D., **P. BRETOVA\*(corresponding author)\***, J. HAUSNEROVA, M. BEDNARIKOVA, L. MINAR and V. WEINBERGER. Low-volume regional lymph node metastasis in endometrial cancer-2024 update. *Ceska Gynekologie-Czech Gynaecology* [online]. 2025, **90**(2), 158–162. ISSN 1805-4455. Available at: doi:10.48095/cccg2025158

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	90	60	80

[15] WEINBERGER, Vit, Marketa BEDNARIKOVA, Jitka HAUSNEROVA, Petra OVESNA, **Petra VINKLEROVA**, Lubos MINAR, Michal FELSINGER, Eva JANDAKOVA, Marta CIHALOVA and Michal ZIKAN. A Novel Approach to Preoperative Risk Stratification in Endometrial Cancer: The Added Value of Immunohistochemical Markers. *Frontiers In Oncology* [online]. 2019, **9**(265, Article 265). ISSN 2234-943X. Available at: doi:10.3389/fonc.2019.00265

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20	10	30	20

[16] **VINKLEROVA, Petra**, Petra OVESNA, Jitka HAUSNEROVA, Johanna M. A. PIJNENBORG, Peter J. F. LUCAS, Casper REIJNEN, Stephanie VREDE and Vit WEINBERGER. External validation study of endometrial cancer preoperative risk stratification model (ENDORISK). *Frontiers In Oncology* [online]. 2022, **12**(939226, Article 939226). ISSN 2234-943X. Available at: doi:10.3389/fonc.2022.939226

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
60	70	80	80