



## COMMENTARY TO HABILITATION THESIS

Thesis title: **Integrative Bioinformatics and Computational Modelling in Colorectal Cancer: Unveiling Tumor Heterogeneity through Multi-Omics Data**

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Colorectal cancer (CRC) represents a highly heterogeneous disease, with diverse molecular subtypes, distinct tumor microenvironments, and complex interactions with host factors, including the gut microbiome. Understanding this heterogeneity is essential for improving patient stratification, optimizing treatment selection, and identifying novel therapeutic targets.

My habilitation thesis summarizes key developments in this field, highlighting contributions from my research over the past years. My work has focused on refining CRC molecular classification, biomarker discovery, and the integration of multi-omics data for improved patient stratification and treatment selection.

I have selected 20 publications to contribute to this habilitation thesis illustrating my contributions across bioinformatics and computational method development, biomarker discovery and clinical translation. My specific roles in these works are summarized in the following tables, detailing my involvement.

The studies included in this thesis combine methodological innovations, large-scale clinical dataset analyses, microbiome research, and applications in preclinical models. A significant part of my work has been dedicated to developing computational approaches for biomarker identification, including novel feature selection methods, transcriptomic classifiers, and integrative multi-omics analyses. These methods have been instrumental in defining clinically relevant CRC subtypes, prognostic signatures, and predictors of therapy response. A key part of this work has been also in image-based analysis of histopathological slides, particularly focusing on tumor morphological heterogeneity. By combining quantitative histopathology with molecular profiling, I have explored how spatial tumor characteristics correlate with molecular subtypes and patient outcomes, offering novel insights into tumor aggressiveness and risk stratification. My research interest has guided me into exploration of the role of microbiome in the complex puzzle of the CRC heterogeneity and its involvement with tumour microenvironment. Beyond computational analyses, my research has contributed to preclinical model validation and translational applications. By applying molecular classifiers to genetically engineered mouse models and patient-derived xenografts, I have helped bridge the gap between computational predictions and experimental validation, ensuring that CRC models accurately reflect human disease.

Throughout my career, I have played a leading role in both method development and biological interpretation, working closely with interdisciplinary teams to translate computational insights into clinically meaningful applications. I have also contributed significantly to study design, data analysis, manuscript preparation, and research direction, shaping multiple high-impact studies in CRC molecular characterization.

By presenting results across these interconnected themes, this thesis provides a cohesive overview of CRC heterogeneity and demonstrates the role of integrative computational methods in advancing both basic and clinical cancer research in CRC.

## List of commented publications

[1] Popovici V, **Budinska E**, Tejpar S, Weinrich S, Estrella H, Hodgson G, Roth AD, Bosman FT, Delorenzi M. Rgtsp: a generalized top scoring pairs package for class prediction. *Bioinformatics*. 2011 Mar 15;27(6):812-3. doi:10.1093/bioinformatics/btr003.

Impact Factor (2011): 4.926

Quartile (2011): Q1 in Computer Science, Interdisciplinary Applications

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40%	10%	30%	20%

[2] Schimek MG, **Budinska E**, Kugler KG, Svendova V, Ding J, Lin S. TopKLists: a comprehensive R package for statistical inference, stochastic aggregation, and visualization of multiple omics ranked lists. *Stat Appl Genet Mol Biol*. 2015;14(3):311-6. doi:10.1515/sagmb-2014-0093.

Impact Factor (2015): 1.200

Quartile (2015): Q3 in Computational biology/Bioinformatics

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
80%	10%	40%	40%

[3] Ihnatova I, **Budinska E**. ToPASEq: an R package for topology-based pathway analysis of microarray and RNA-Seq data. *BMC Bioinformatics*. 2015; 16:350. doi:10.1186/s12859-015-0763-1.

Impact Factor (2015): 2.435

Quartile (2015): Q1 in Computer Science Applications

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10%	100%	30%	50%

[4] Ihnatova I, Popovici V, Budinska E. A critical comparison of topology-based pathway analysis methods. *PLOS ONE*. 2018;13(1):e0191154. doi:10.1371/journal.pone.0191154.

Impact Factor (2018): 2.776

Quartile (2018): Q1 in Multidisciplinary Sciences

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10%	90%	30%	70%

[5] Xie T, d'Ario G, Lamb JR, Martin E, Wang K, Tejpar S, Delorenzi M, Bosman FT, Roth AD, Yan P, Bougel S, Narzo AF, Popovici V, **Budinska E**, Mao M, Weinrich SL, Rejto PA, Hodgson JG. A Comprehensive Characterization of Genome-Wide Copy Number Aberrations

in Colorectal Cancer Reveals Novel Oncogenes and Patterns of Alterations. *PLoS One*. 2012 Sep 5;7(9):e42001. doi:10.1371/journal.pone.0042001.

Impact Factor (2012): 3.730

Quartile (2012): Q1 in Multidisciplinary Sciences

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
10%	0%	5%	0%

[6] Missiaglia E, Jacobs B, D'Ario G, Di Narzo AF, Sonesson C, **Budinska E**, Popovici V, Vecchione L, Gerster S, Yan P, Roth AD, Klingbiel D, Bosman FT, Delorenzi M, Tejpar S. Distal and proximal colon cancers differ in terms of molecular, pathological, and clinical features. *Ann Oncol*. 2014 Oct;25(10):1995-2001. doi: 10.1093/annonc/mdu275. Epub 2014 Jul 23. Erratum in: *Ann Oncol*. 2015 Feb;26(2):445. doi: 10.1093/annonc/mdu548. PMID: 25057166.

Impact Factor (2014): 7.040

Quartile (2014): Q1 in Oncology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
5%	0%	10%	0%

[7] Popovici V, **Budinska E**, Bosman FT, Roth AD, Delorenzi M, Tejpar S. Identification of a Poor-Prognosis BRAF-Mutant-Like Population of Patients With Colon Cancer. *J Clin Oncol*. 2012 Oct 1;30(28):128-43. doi:10.1200/JCO.2011.41.1607.

Impact Factor (2012): 18.038

Quartile (2012): Q1 in Oncology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50%	20%	40%	20%

[8] Popovici V, **Budinska E**, Bosman FT, Tejpar S, Roth AD, Delorenzi M. Context-dependent interpretation of the prognostic value of BRAF and KRAS mutations in colorectal cancer. *BMC Cancer*. 2013 Sep 12;13:439. doi:10.1186/1471-2407-13-439..

Impact Factor (2013): 3.319

Quartile (2013): Q1 in Genetics , Q2 in Oncology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50%	30%	33%	30%

[9] **Budinska E**, Popovici V, Tejpar S, D'Ario G, Lapique N, Sikora KO, et al. Gene expression patterns unveil a new level of molecular heterogeneity in colorectal cancer. *J Pathol*. 2013 Aug;231(1):63-76. doi:10.1002/path.4212.

Impact Factor (2013): 7.330

Quartile (2013): Q1 in Pathology and Forensic Medicine

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

[10] Belmont PJ, **Budinska E**, Jiang P, Sinnamon MJ, Coffee E, Roper J, Xie T, Rejto PA, Derkits S, Sansom OJ, Delorenzi M, Tejpar S, Hung KE, Martin ES. Cross-species analysis of genetically engineered mouse models of MAPK-driven colorectal cancer identifies hallmarks of the human disease. *Dis Model Mech*. 2014 Jun;7(6):613-23. doi: 10.1242/dmm.013904. Epub 2014 Apr 17. PMID: 24742783; PMCID: PMC4036469.

Impact Factor (2014): 4.973

Quartile (2014): Q1 in Cancer Research

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
40%	20%	30%	20%

[11] Byrne AT, Alférez DG, Amant F, Annibali D, Arribas J, Biankin AV, Bruna A, **Budinská E**, Caldas C, Chang DK, Clarke RB, Clevers H, Coukos G, Dangles-Marie V, Eckhardt SG, Gonzalez-Suarez E, Hermans E, Hidalgo M, Jarzabek MA, de Jong S, Jonkers J, Kemper K, Lanfrancone L, Mælandsmo GM, Marangoni E, Marine JC, Medico E, Norum JH, Palmer HG, Peeper DS, Pelicci PG, Piris-Gimenez A, Roman-Roman S, Rueda OM, Seoane J, Serra V, Soucek L, Vanhecke D, Villanueva A, Vinolo E, Bertotti A, Trusolino L. Interrogating open issues in cancer precision medicine with patient-derived xenografts. *Nat Rev Cancer*. 2017 Apr;17(4):254-268. doi: 10.1038/nrc.2016.140. Epub 2017 Jan 20. Erratum in: *Nat Rev Cancer*. 2017 Sep 15;17(10):632. doi: 10.1038/nrc.2017.85. PMID: 28104906. Interrogating open issues in cancer precision medicine with patient-derived xenografts. *Nature Reviews Cancer*. 2017;17:254–268. doi:10.1038/nrc.2016.140.

Impact Factor (2017): 53.029

Quartile (2017): Q1 in Oncology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
Not applicable (review)	0%	15%	5%

[12] Popovici V, **Budinská E**, Čápková L, Schwarz D, Dušek L, Feit J, Jaggi R. Joint analysis of histopathology image features and gene expression in breast cancer. *BMC Bioinformatics*. 2016 May 11;17(1):209. doi: 10.1186/s12859-016-1072-z. PMID: 27170365; PMCID: PMC4864935.

Impact Factor (2016): 2.448

Quartile (2016): Q1 in Computer Science Applications

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30%	0%	20%	30%

**[13]** Popovici V, **Budinska E**, Dusek L, Kozubek M, Bosman F. Image-based surrogate biomarkers for molecular subtypes of colorectal cancer. *Bioinformatics*. 2017;33(13):2002-2009. doi:10.1093/bioinformatics/btx027.

Impact Factor (2017): 5.481

Quartile (2017): Q1 in Computational Biology/Bioinformatics

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30%	0%	20%	40%

**[14]** **Budinská E**, Hrivňáková M, Ivkovic TC, Madrzyk M, Nenutil R, Bencsiková B, Al Tukmachi D, Ručková M, Zdražilová Dubská L, Slabý O, Feit J, Dragomir MP, Borilova Linhartova P, Tejpar S, Popovici V. Molecular portraits of colorectal cancer morphological regions. *Elife*. 2023 Nov 13;12:RP86655. doi: 10.7554/eLife.86655. PMID: 37956043; PMCID: PMC10642970.

Impact Factor (2023): 6.4

Quartile (2023): Q1 in Biology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
50%	60%	80%	70%

**[15]** Zwinsová B, Brychtová V, Hrivňáková M, Zdražilová-Dubská L, Bencsiková B, Šefr R, Nenutil R, Vídeňská P, **Budinská E**. Role of the Microbiome in the Formation and Development of Colorectal Cancer. *Klin Onkol*. 2019 Summer;32(4):261-269. English. doi: 10.14735/amko2019261. PMID: 31426641. [in Czech]

Impact Factor (2019): 0.184

Quartile (2019): Q4 in Oncology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
Not applicable (review)	80%	20%	30%

**[16]** Videnska P, Smerkova K, Zwinsova B, Popovici V, Micenikova L, Sedlar K, **Budinska E**. Stool sampling and DNA isolation kits affect DNA quality and bacterial composition following 16S rRNA gene sequencing using MiSeq Illumina platform. *Sci Rep*. 2019 Sep 25;9(1):13837. doi: 10.1038/s41598-019-49520-3. PMID: 31554833; PMCID: PMC6761292.

Impact Factor (2019): 4.011

Quartile (2019): Q1 in Multidisciplinary Sciences

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20%	50%	30%	50%

**[17]** Zwinsová B, Petrov VA, Hrivňáková M, Smatana S, Micenková L, Kazdová N, Popovici V, Hrstka R, Šefr R, Bencsiková B, Zdražilová-Dubská L, Brychtová V, Nenutil R, Vídeňská P, **Budinská E**. Colorectal Tumour Mucosa Microbiome Is Enriched in Oral Pathogens and Defines Three Subtypes That Correlate with Markers of Tumour Progression. *Cancers* (Basel). 2021 Sep 25;13(19):4799. doi: 10.3390/cancers13194799. PMID: 34638284; PMCID: PMC8507728.

Impact Factor (2021): 6.35

Quartile (2021): Q1 in Oncology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
20%	80%	30%	80%

**[18]** Stenvang J, **Budinská E**, van Cutsem E, Bosman F, Popovici V, Brünner N. An Explorative Analysis of *ABCG2/TOP-1* mRNA Expression as a Biomarker Test for FOLFIRI Treatment in Stage III Colon Cancer Patients: Results from Retrospective Analyses of the PETACC-3 Trial. *Cancers* (Basel). 2020 Apr 15;12(4):977. doi: 10.3390/cancers12040977. PMID: 32326511; PMCID: PMC7226226

Impact Factor (2020): 6.639

Quartile (2020): Q1 in Oncology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30%	5%	20%	0%

**[19]** Pardini B, Ferrero G, Tarallo S, Gallo G, Francavilla A, Licheri N, Trompetto M, Clerico G, Senore C, Peyre S, Vymetalkova V, Vodickova L, Liska V, Vycital O, Levy M, Macinga P, Hucl T, **Budinska E**, Vodicka P, Cordero F, Naccarati A. A Fecal MicroRNA Signature by Small RNA Sequencing Accurately Distinguishes Colorectal Cancers: Results From a Multicenter Study. *Gastroenterology*. 2023 Sep;165(3):582-599.e8. doi: 10.1053/j.gastro.2023.05.037. Epub 2023 May 30. PMID: 37263306.

Impact Factor (2023): 25.7

Quartile (2023): Q1 in Gastroenterology & Hepatology

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

**[20]** **Budinská E**, Čarnogurská M, Ivković TC, Macháčková T, Boudná M, Pifková L, Slabý O, Bencsiková B, Popovici V. An invasion front gene expression signature for higher-risk patient selection in stage IIA MSS colon cancer. *Front Oncol*. 2024 Apr 19;14:1367231. doi: 10.3389/fonc.2024.1367231. PMID: 38706608; PMCID: PMC11066151.

Impact Factor (2024): 3.5

Quartile (2023): Q2 in Oncology

Experimental work (%)	Supervision (%)	Manuscript (%)	Research direction (%)
30%	20%	60%	50%