Applications of deep learning in computational pathology

Geert Litjens
Assistant professor
Department of Pathology
Radboud University Nijmegen Medical Center, The Netherlands

Radboudumc

The business case for digital pathology?

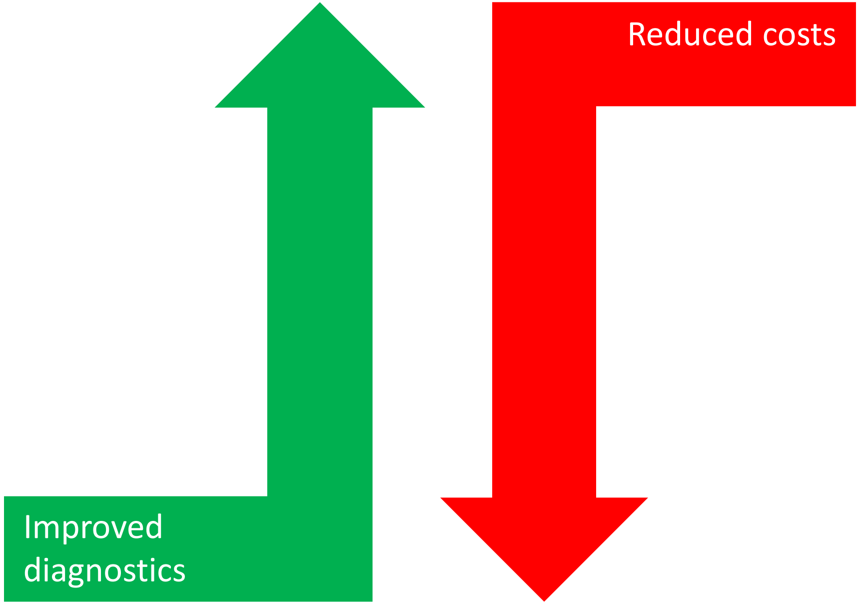
The business case for digital pathology?

Scanners

Storage

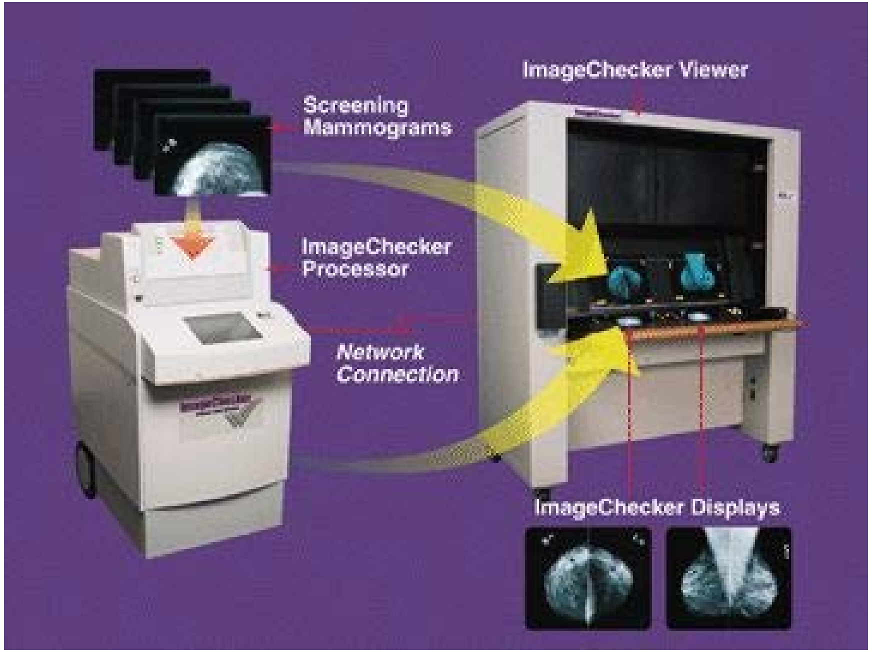
Computers

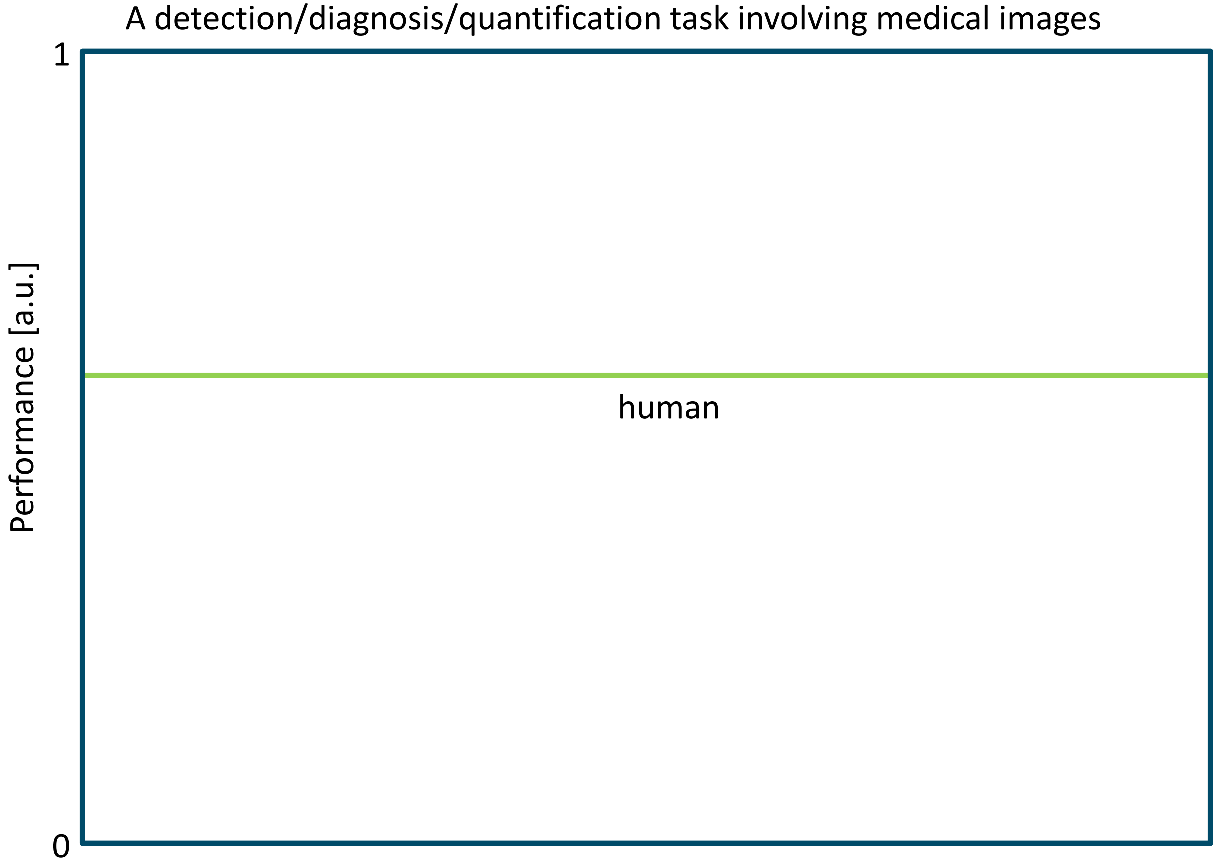
The business case for digital pathology?



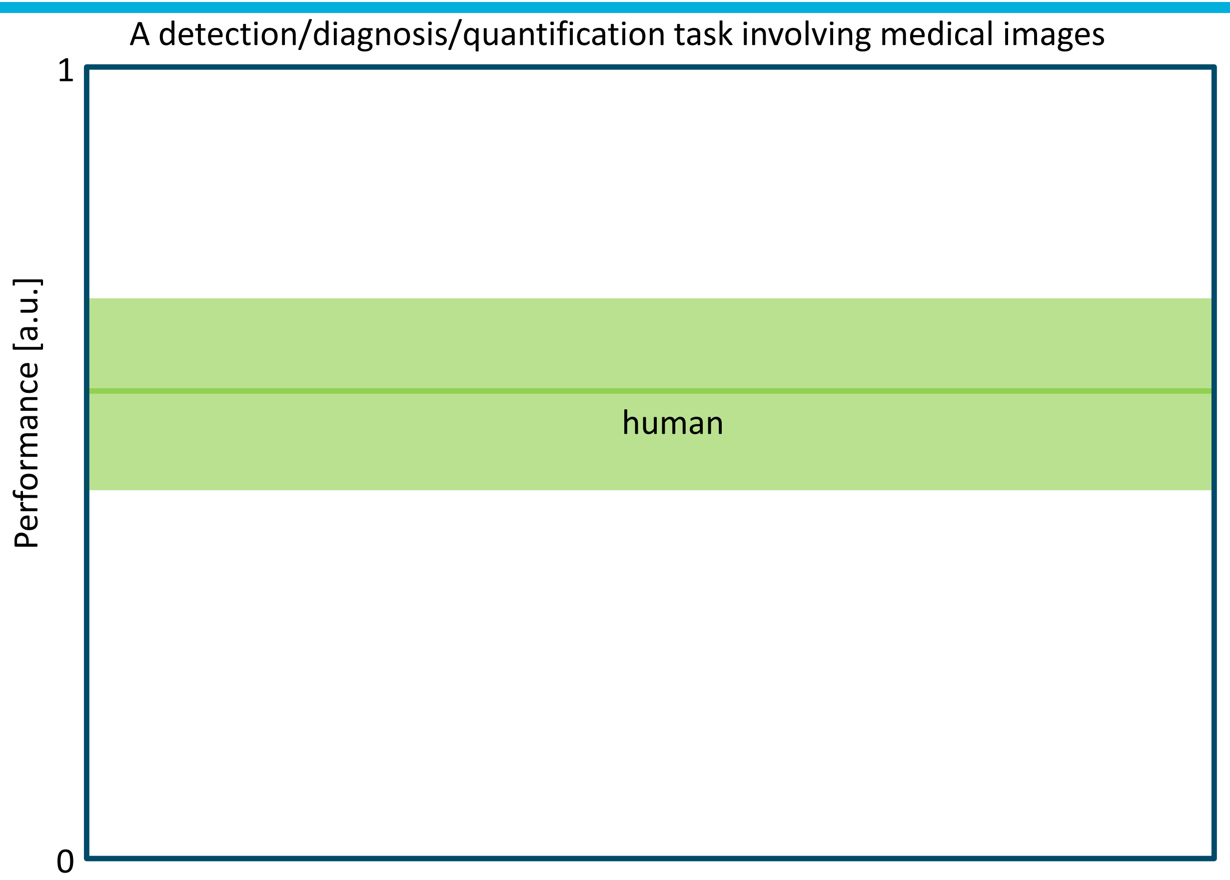
Computer Aided Diagnosis

The promise of computerized analysis?

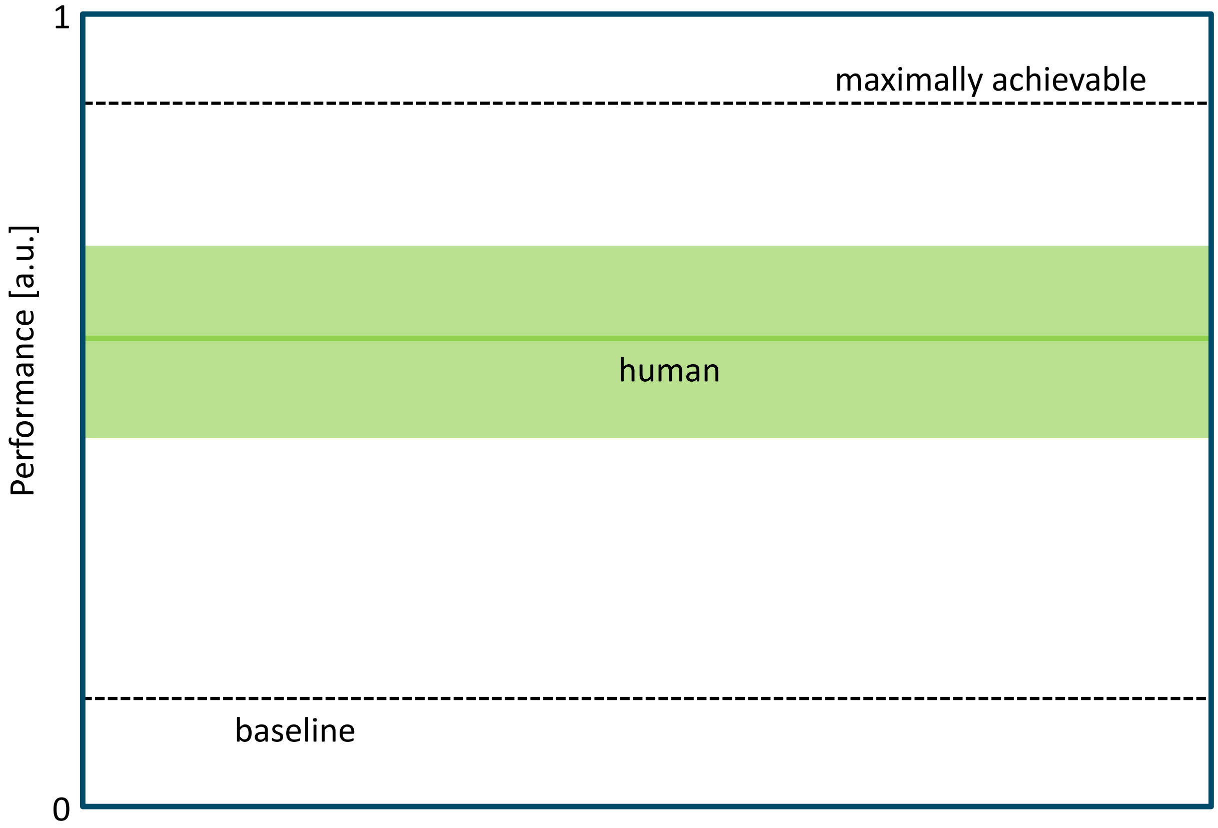


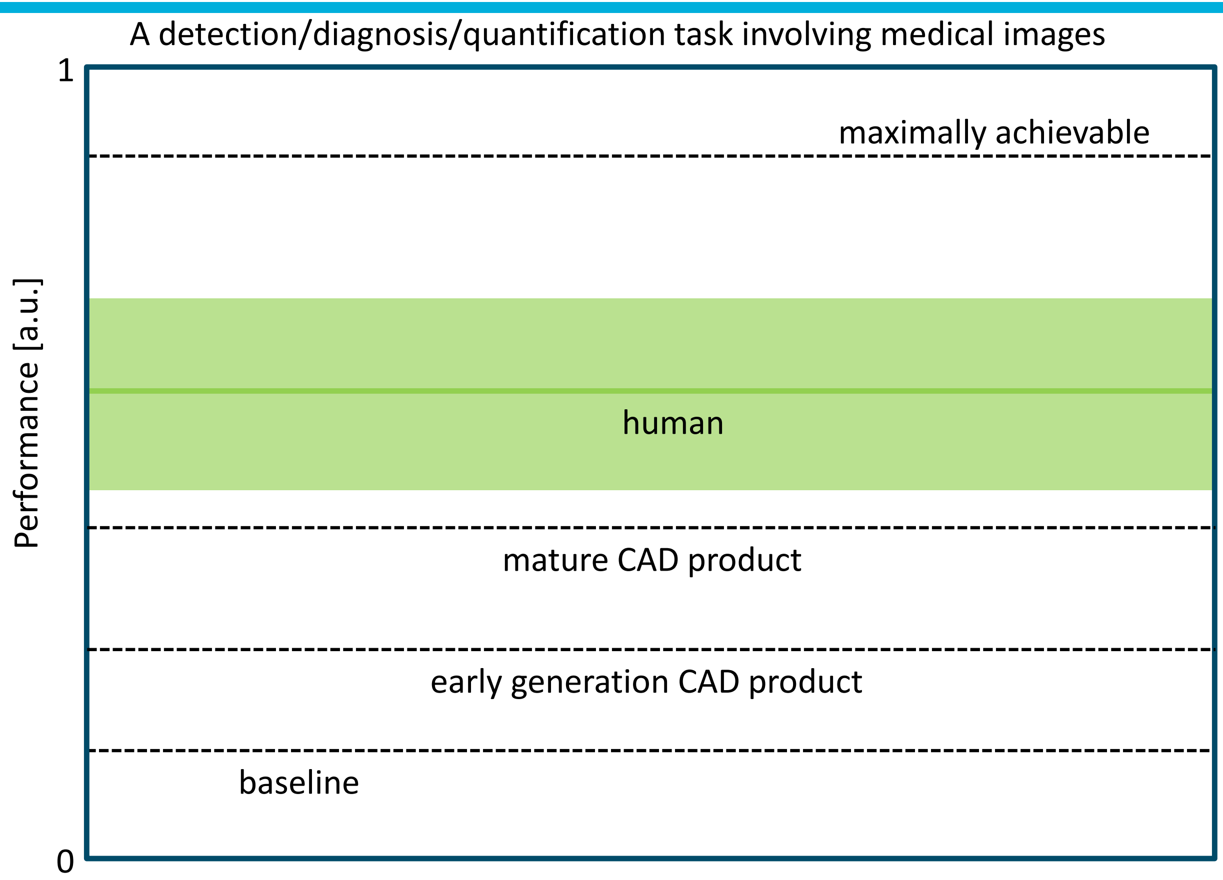


A detection/diagnosis/quantification task involving medical images
1
0
Performance [a.u.]
human


A detection/diagnosis/quantification task involving medical images
1
0
Performance [a.u.]
human

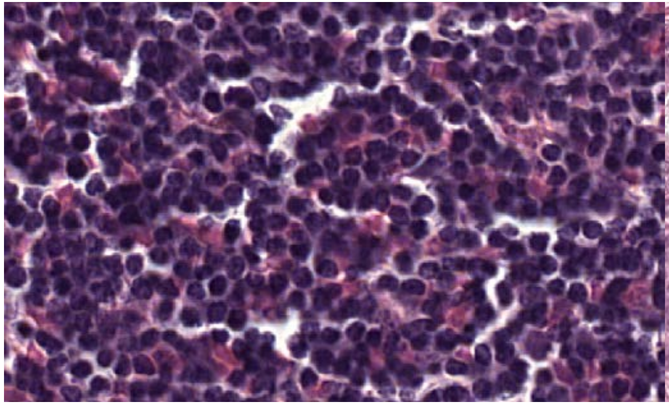
A detection/diagnosis/quantification task involving medical images



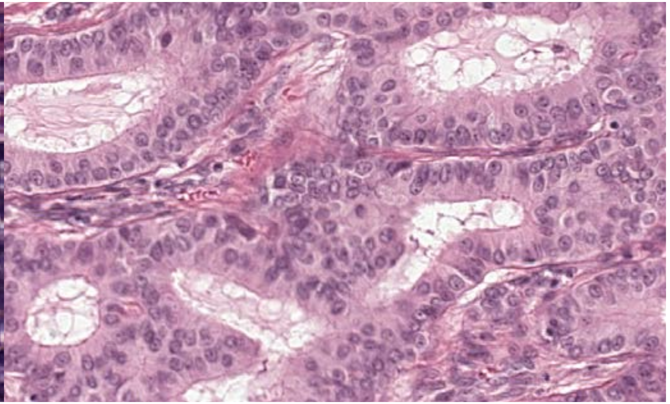

A detection/diagnosis/quantification task involving medical images
1
maximally achievable
Performance [a.u.]
human
mature CAD product
early generation CAD product
baseline
0

Radboudumc

How to build a traditional CAD system?



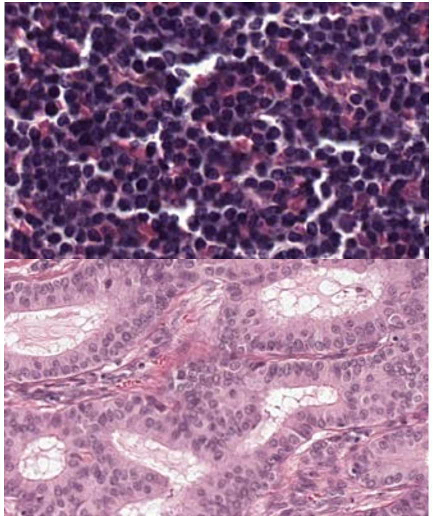
Normal lymph node tissue



Breast cancer metastasis

How to build a traditional CAD system?

Examples

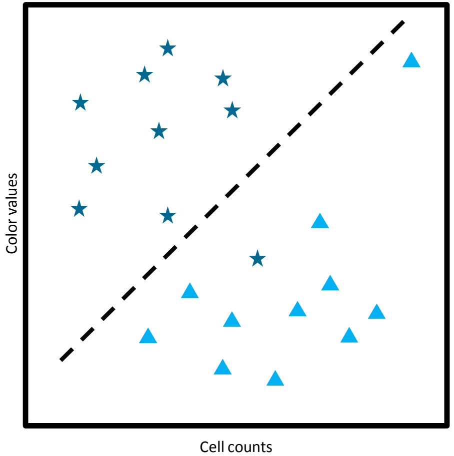


Features

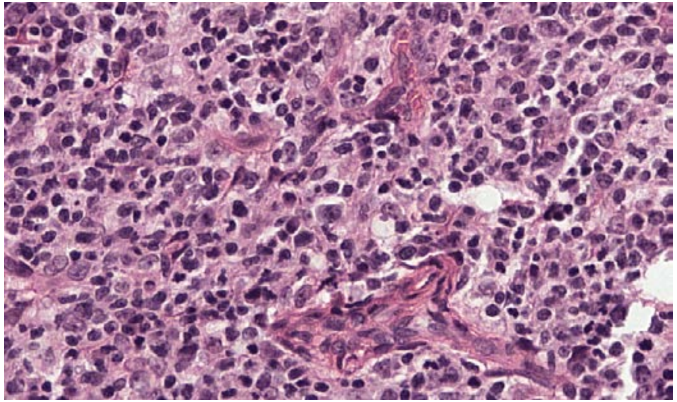
Color values

Cell counts

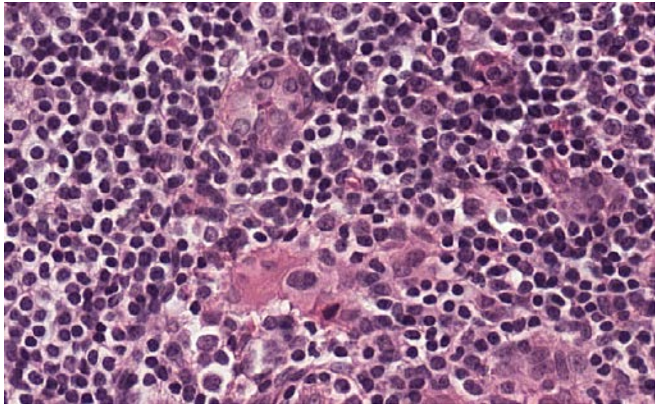
Classification



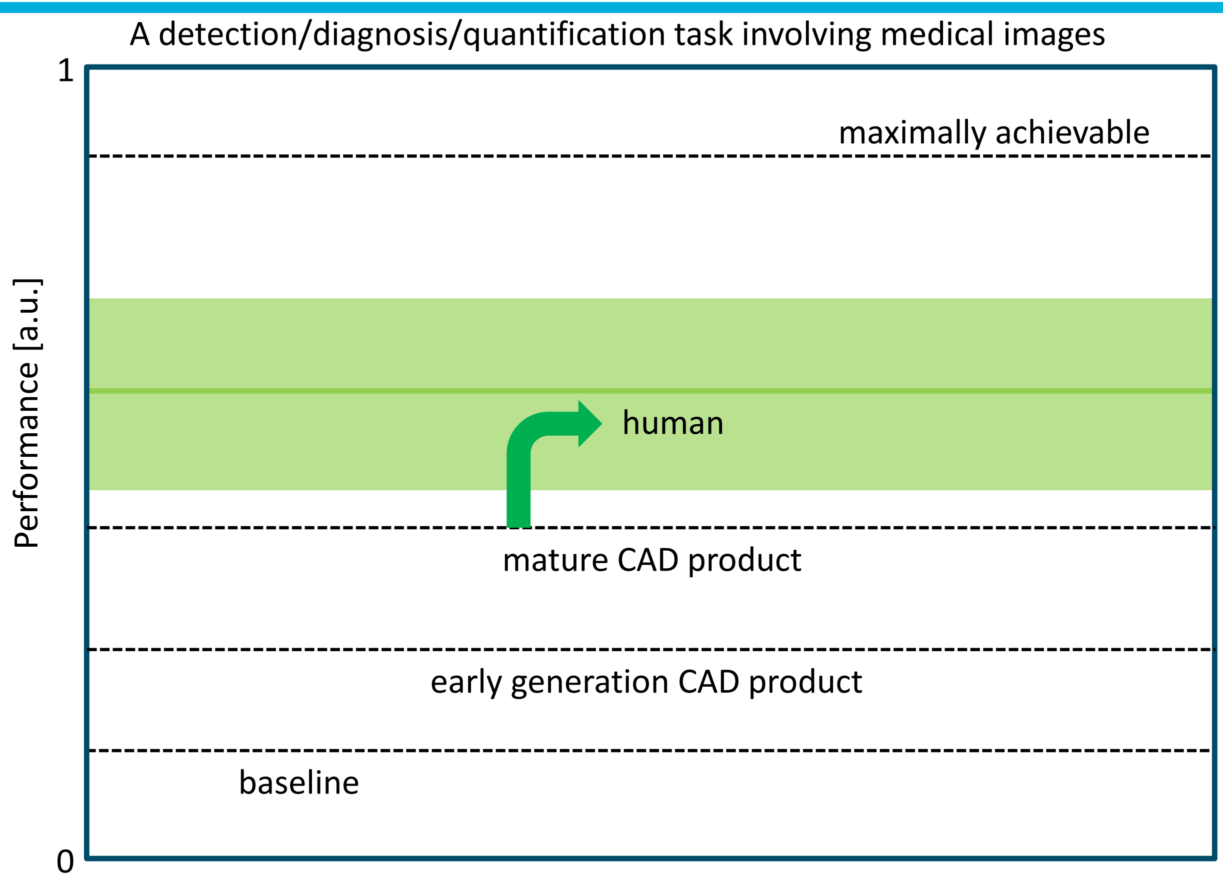
How to build a traditional CAD system?



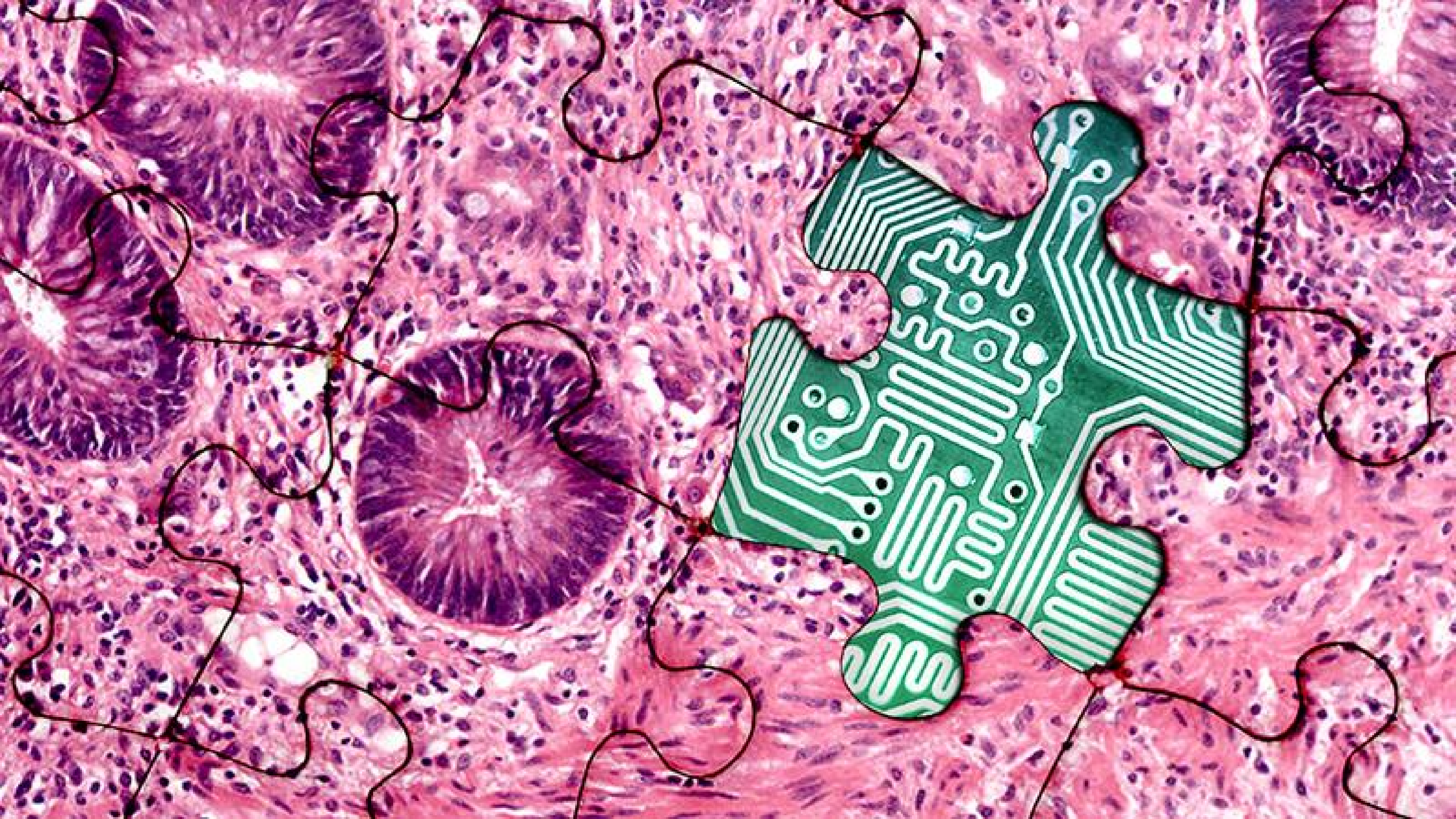
Normal lymph node tissue



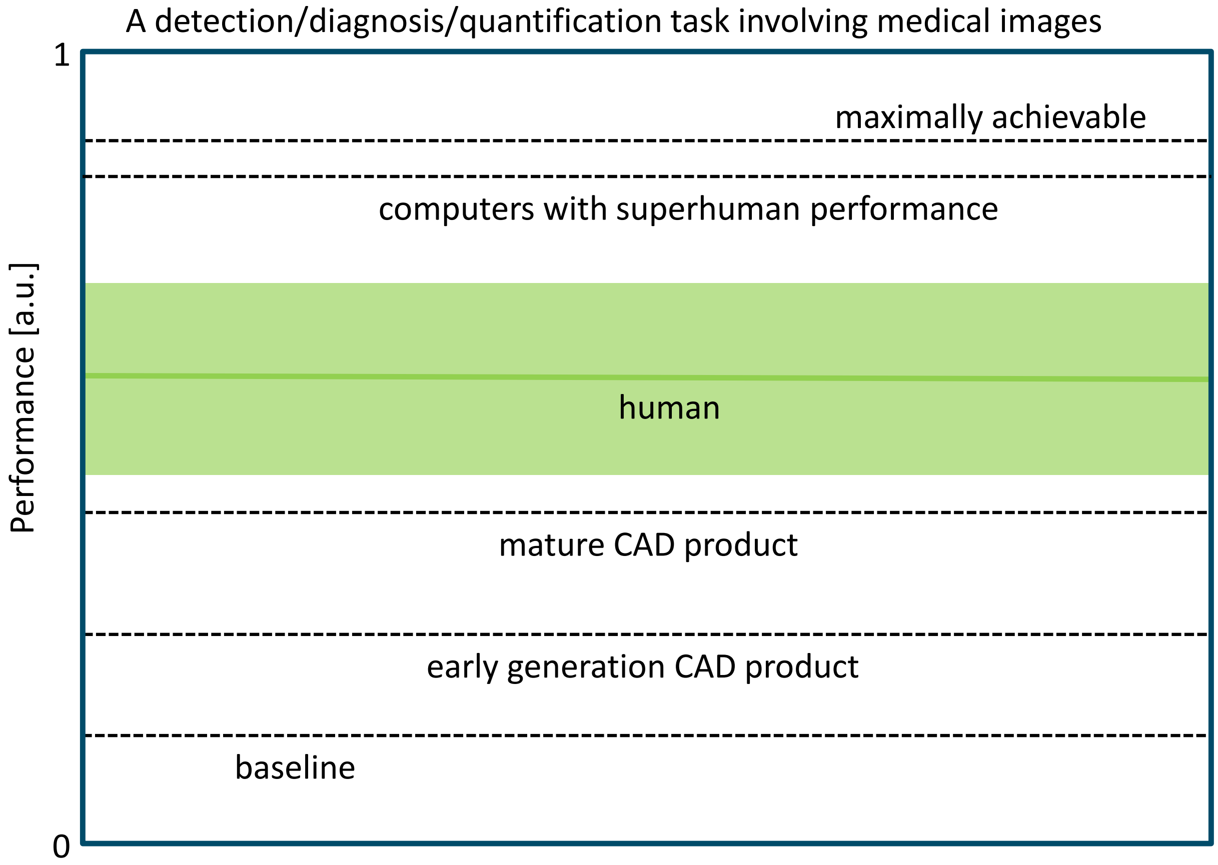
Breast cancer metastasis



A detection/diagnosis/quantification task involving medical images
1
maximally achievable
Performance [a.u.]
human
mature CAD product
early generation CAD product
baseline
0

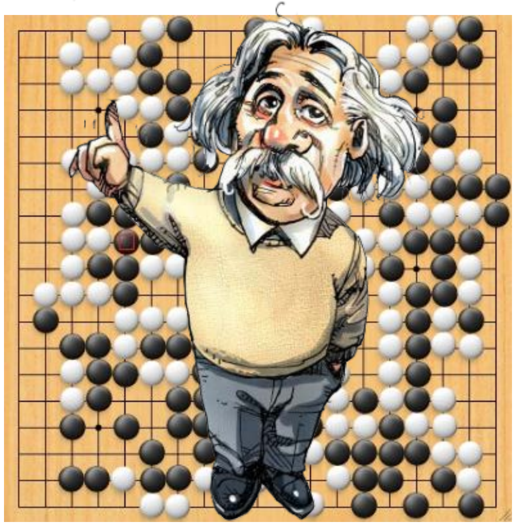



nature
THE INTERNATIONAL WEEKLY JOURNAL OF SCIENCE
At last — a computer program that can beat a champion Go player PAGE 484
ALL SYSTEMS GO
CONSERVATION
SONGBIRDS À LA CARTE
Illegal harvest of millions of Mediterranean birds
PAGE 452
RESEARCH ETHICS
SAFEGUARD TRANSPARENCY
Don't let openness backfire on individuals
PAGE 459
POPULAR SCIENCE
WHEN GENES GOT 'SELFISH'
Dawkins's calling card forty years on
PAGE 462
NATURE.COM/NATURE


A detection/diagnosis/quantification task involving medical images
1
maximally achievable
computers with superhuman performance
Performance [a.u.]
human
mature CAD product
early generation CAD product
baseline
0

Deep learning

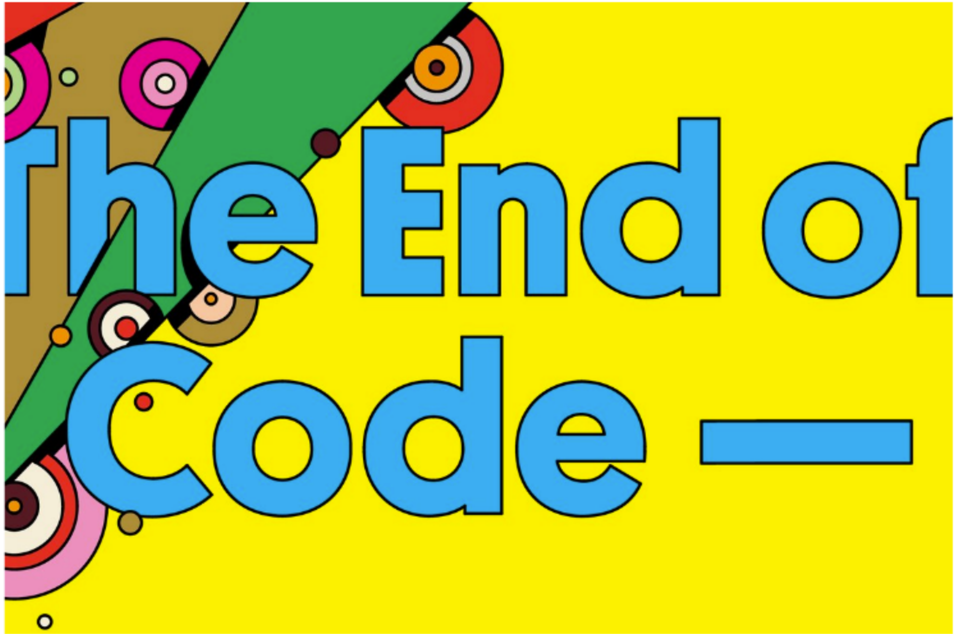
30 options per turn
40 turns per game



250 options per turn
150 turns per game

JASON TANZ IDEAS 05.17.16 06:50 AM

SOON WE WON'T PROGRAM COMPUTERS. WE'LL TRAIN THEM LIKE DOGS



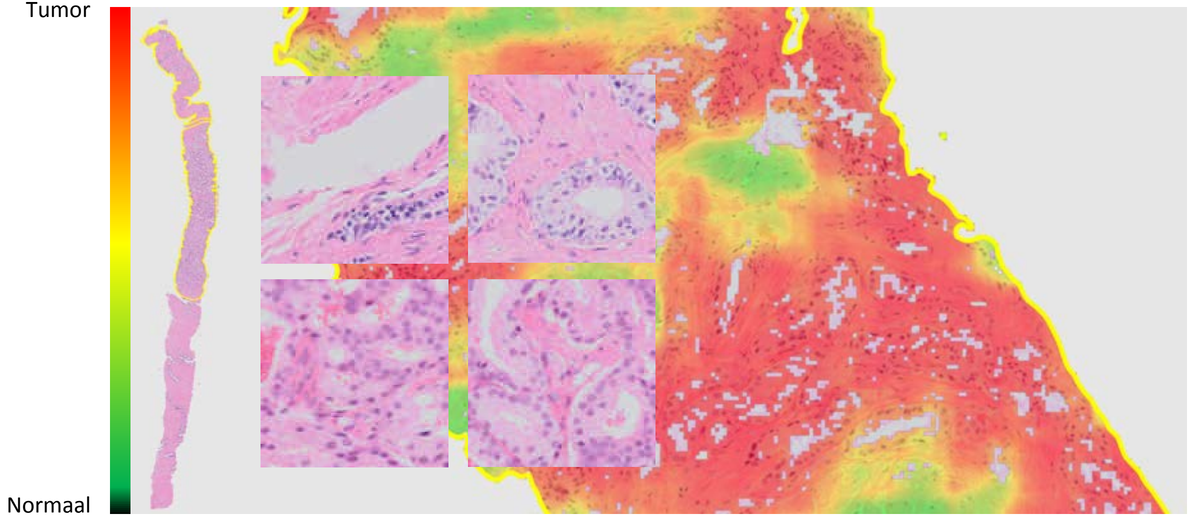
EDWARD C. MONAGHAN

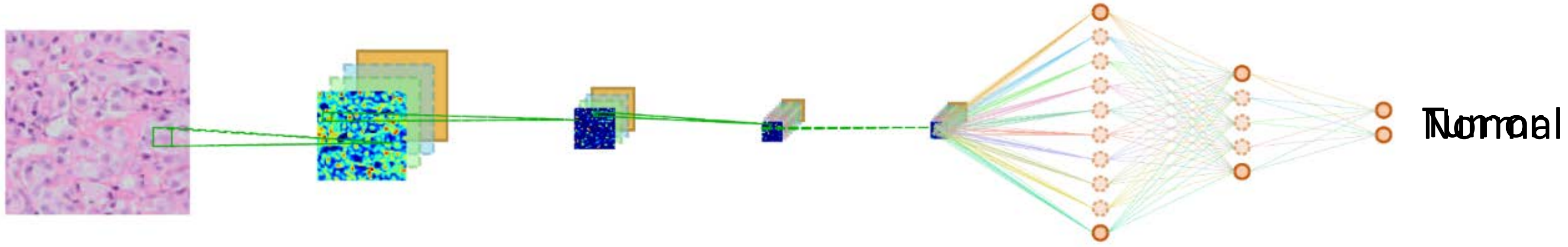
BEFORE THE INVENTION of the computer, most experimental psychologists thought the brain was an unknowable black box. You could analyze a subject's behavior—*ring bell, dog salivates*—but thoughts, memories, emotions? That stuff was obscure and inscrutable, beyond the reach of science. So these behaviorists, as they called themselves, confined their work to the study of stimulus and response, feedback and reinforcement, bells and saliva. They gave up trying to

JASON TANZ IDEAS 05.17.16 06:50 AM

SOON WE WON'T PROGRAM COMPUTERS. WE'LL TRAIN THEM LIKE DOGS

How to build CAD systems at (super-)human level?





Litjens et al. *Sci Rep.* 2016

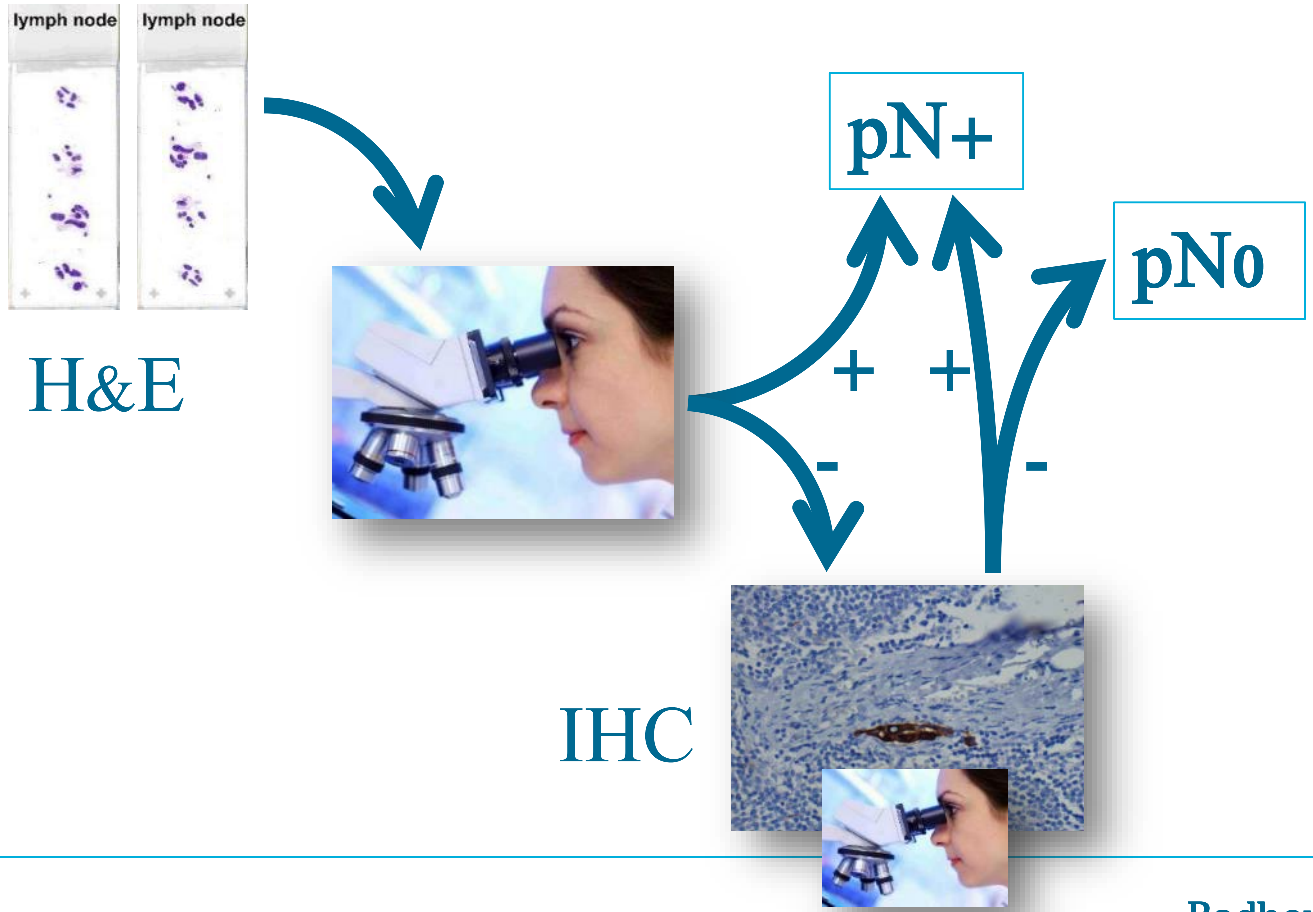
Applications of computational pathology

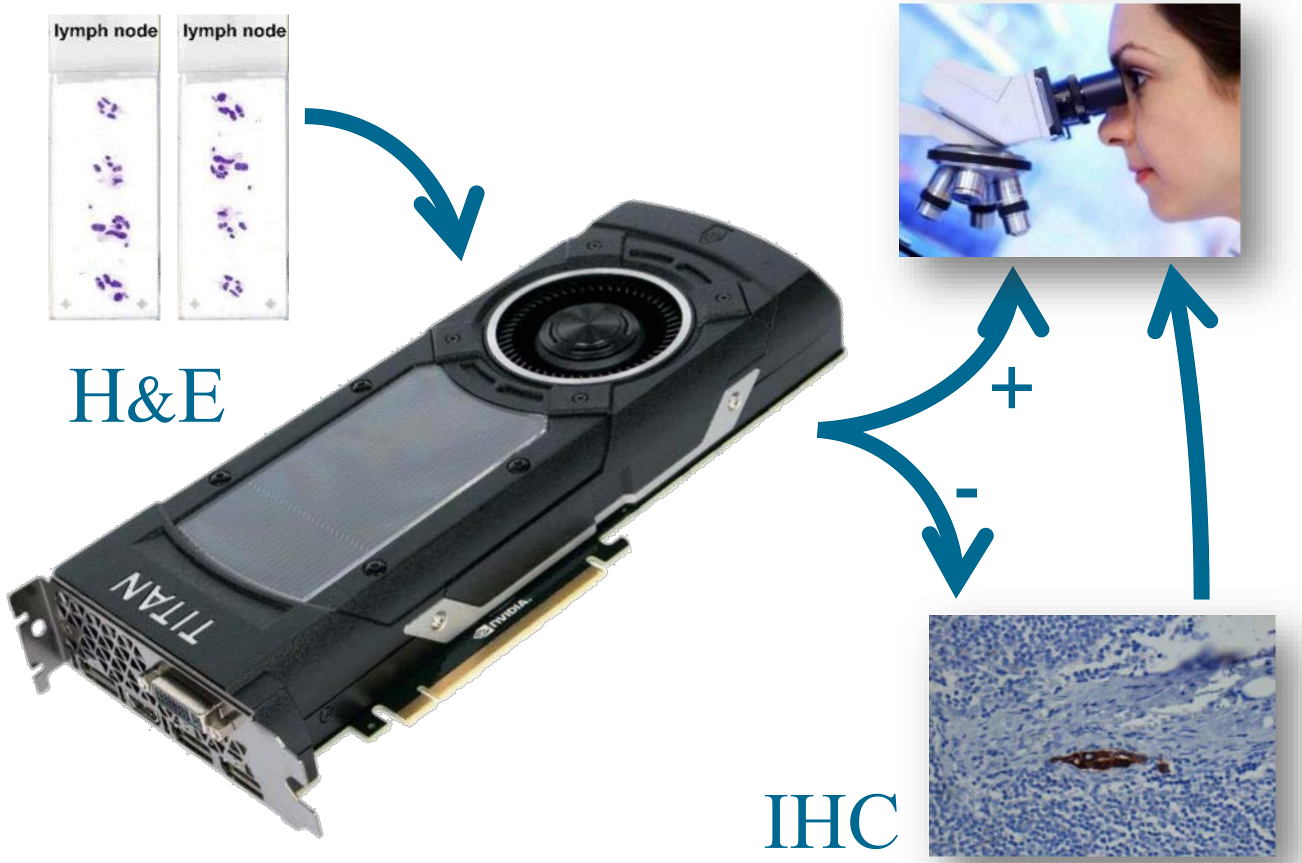
Clinical applications

Detection of metastases in lymph nodes	Automated counting of mitoses
Quantification of multiplexed immunohistochemistry	Quantification of tumor-associated stroma

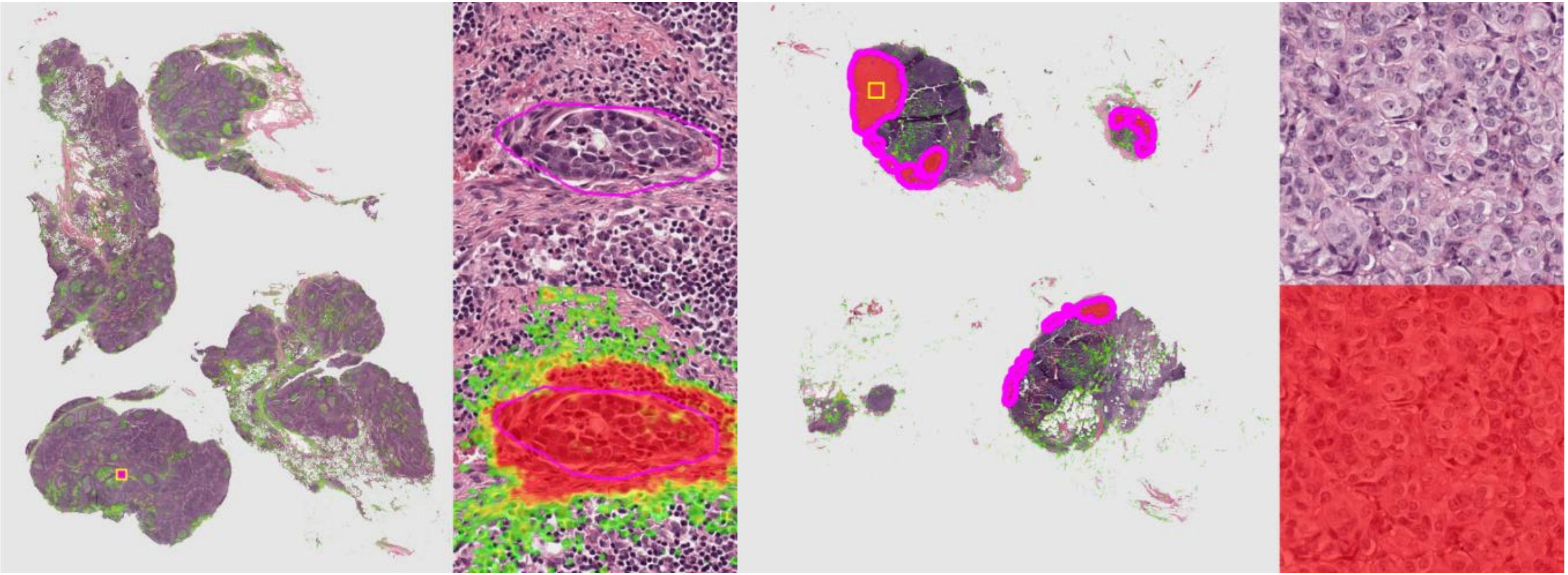
Biomarker research

Detection of metastases in lymph nodes


lymph node
lymph node
H&E
pN+
pN0
+
+
-
-
IHC


lymph node
lymph node
H&E
TITAN
+
-
IHC

Detection of metastases in lymph nodes



Data

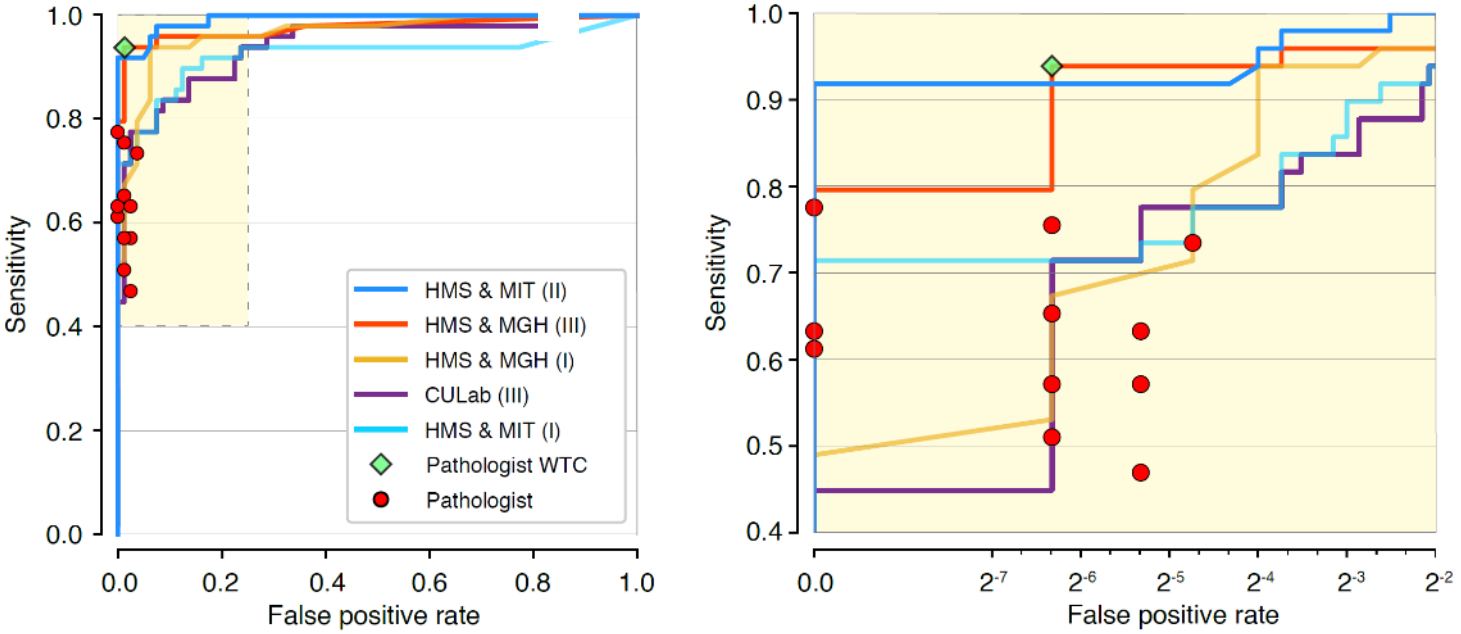
Center	Number of slides
CWZ (Nijmegen)	200
LabPON (Hengelo)	200
Rijnstate (Arnhem)	200
Radboudumc (Nijmegen)	439
UMCU (Utrecht)	350
Total	**1399**


CAMELYON16

CAMELYON17

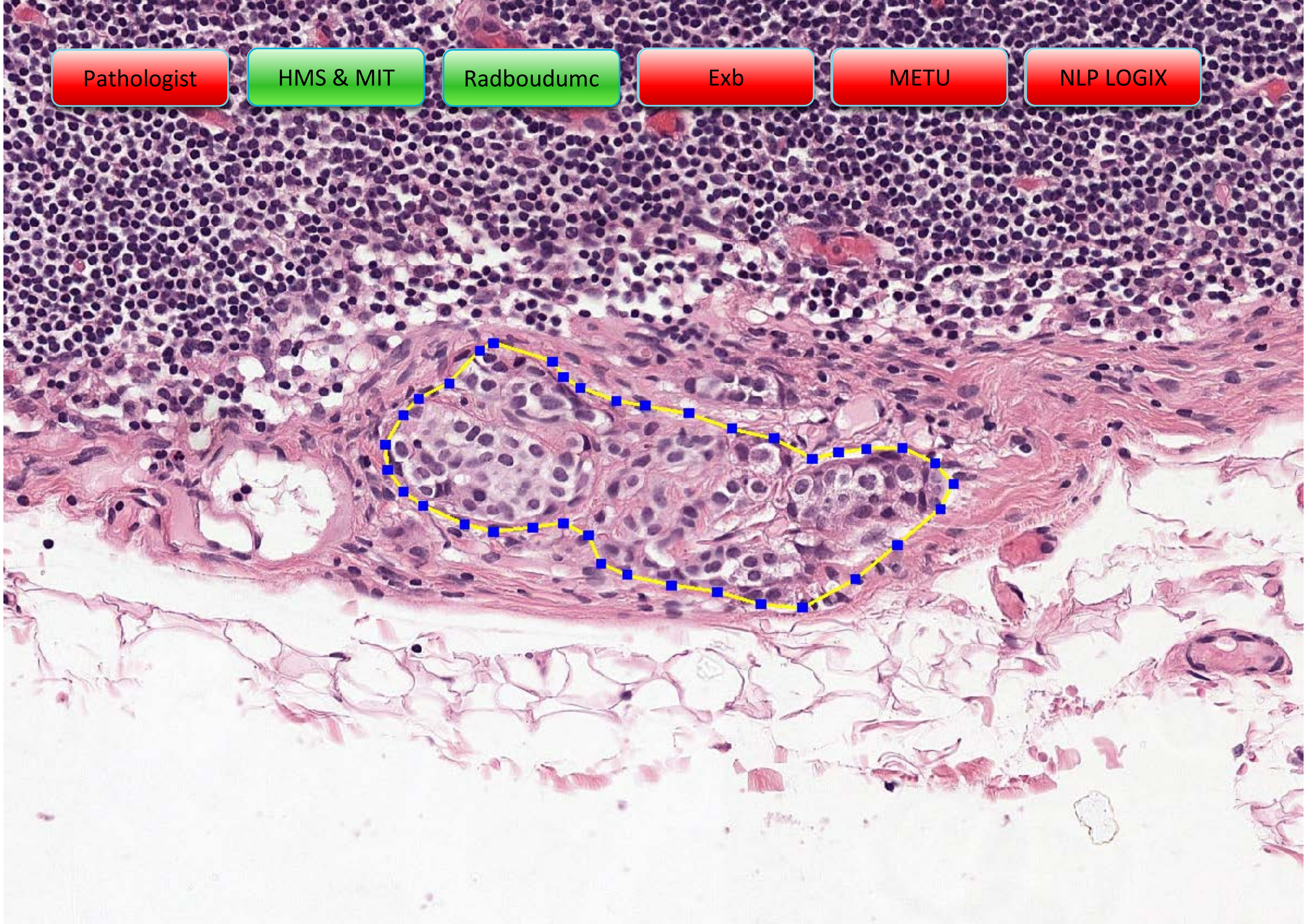
Rank	Team	AUC	Description
01	**Harvard Medical School (BIDMC) and Massachusetts Institute of Technology (CSAIL), USA**	**0.9250**	
02	ExB Research and Development co., Germany	0.9173	
03	Independent participant, Germany	0.8680	
04	Health Sciences Middle East Technical University, Turkey	0.8669	
05	NLP LOGIX co., USA	0.8332	
06	University of Toronto, Electrical and Computer Engineering, Canada	0.8181	
07	The Warwick-QU Team, United Kingdom	0.7999	
08	Radboud University Medical Center, Diagnostic Image Analysis Group, Netherlands	0.7828	
09	HTW-BERLIN, Germany	0.7717	
10	University of Toronto, Electrical and Computer Engineering, Canada	0.7666	

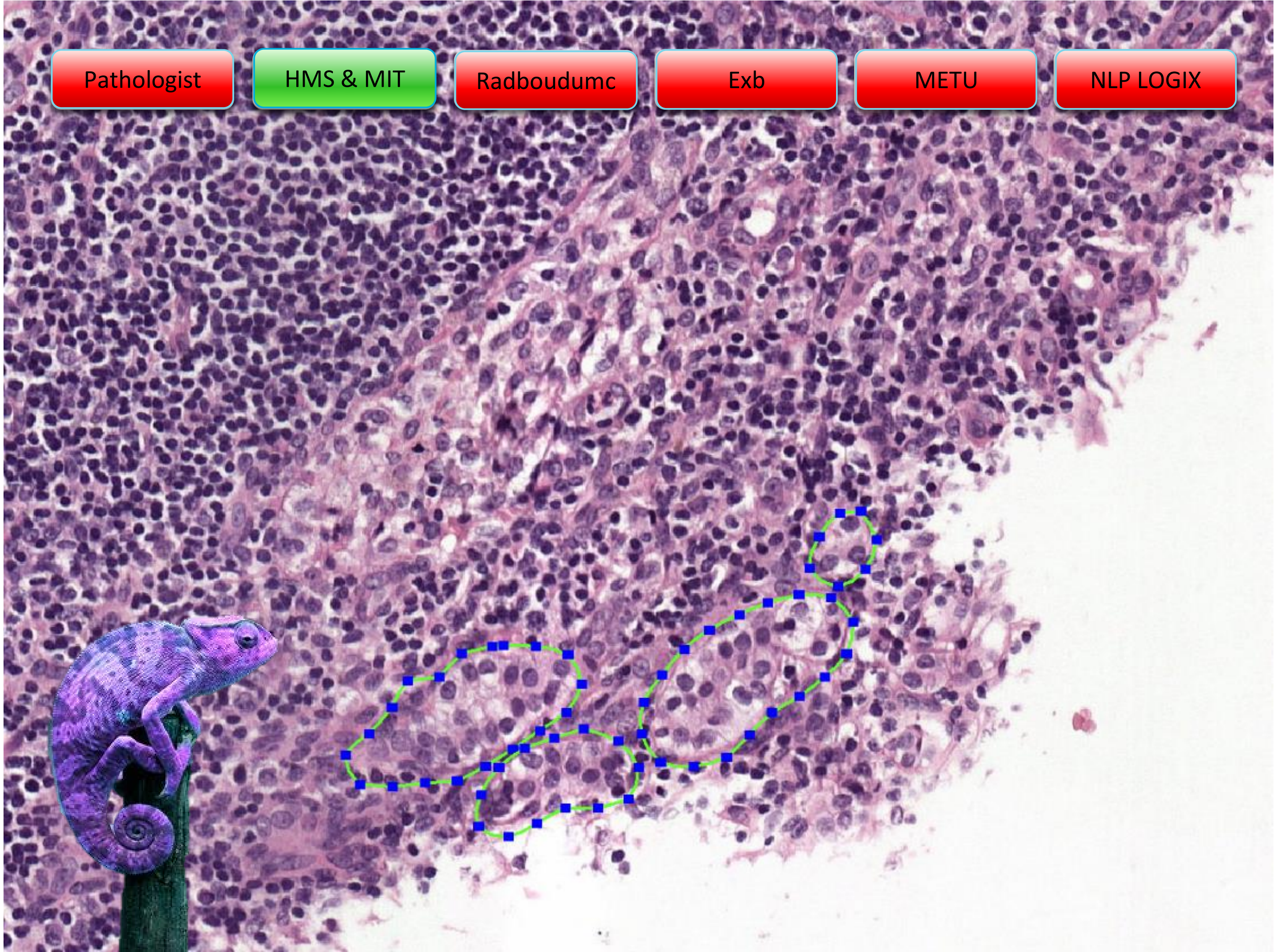
Comparison to human experts

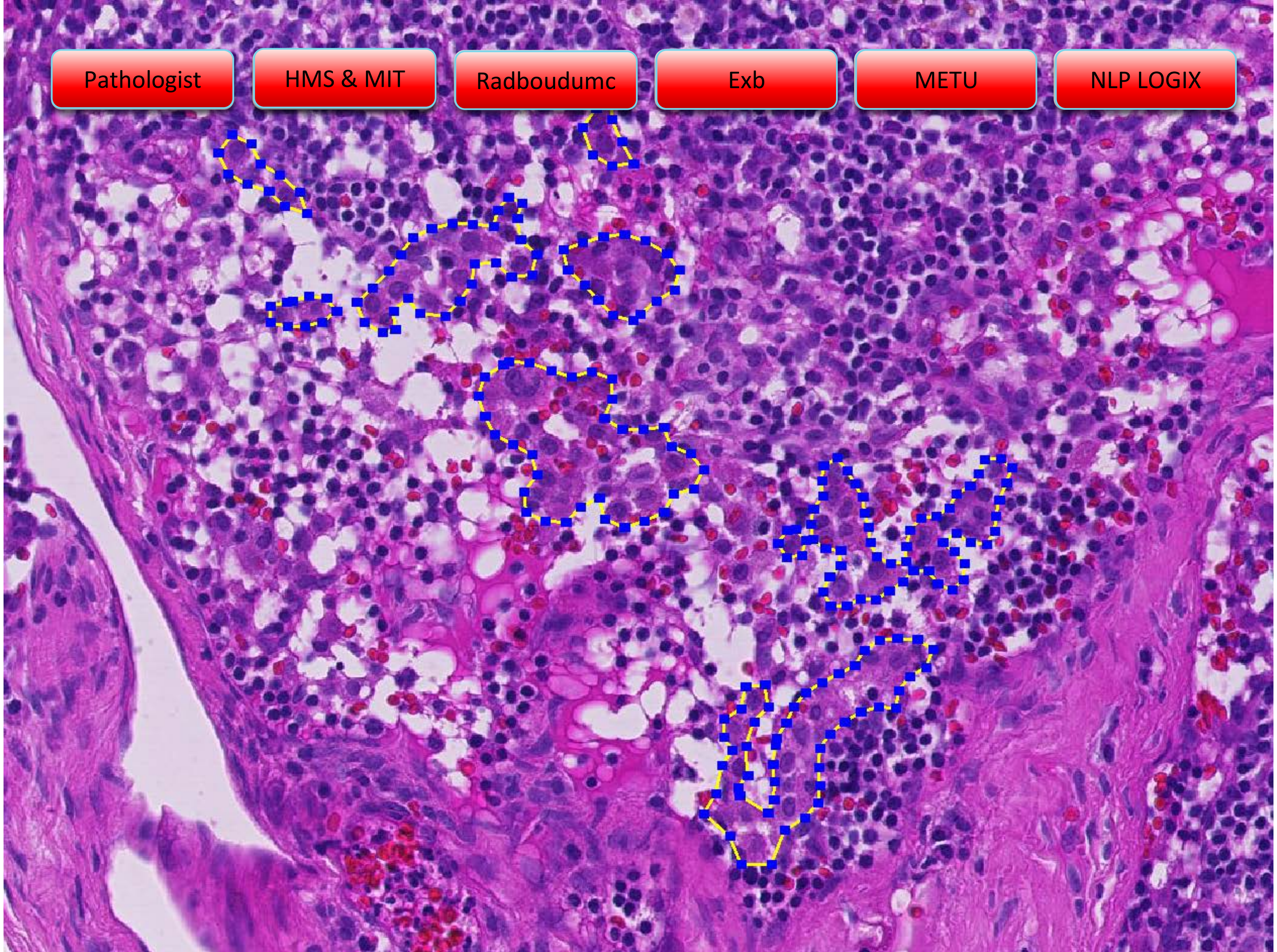


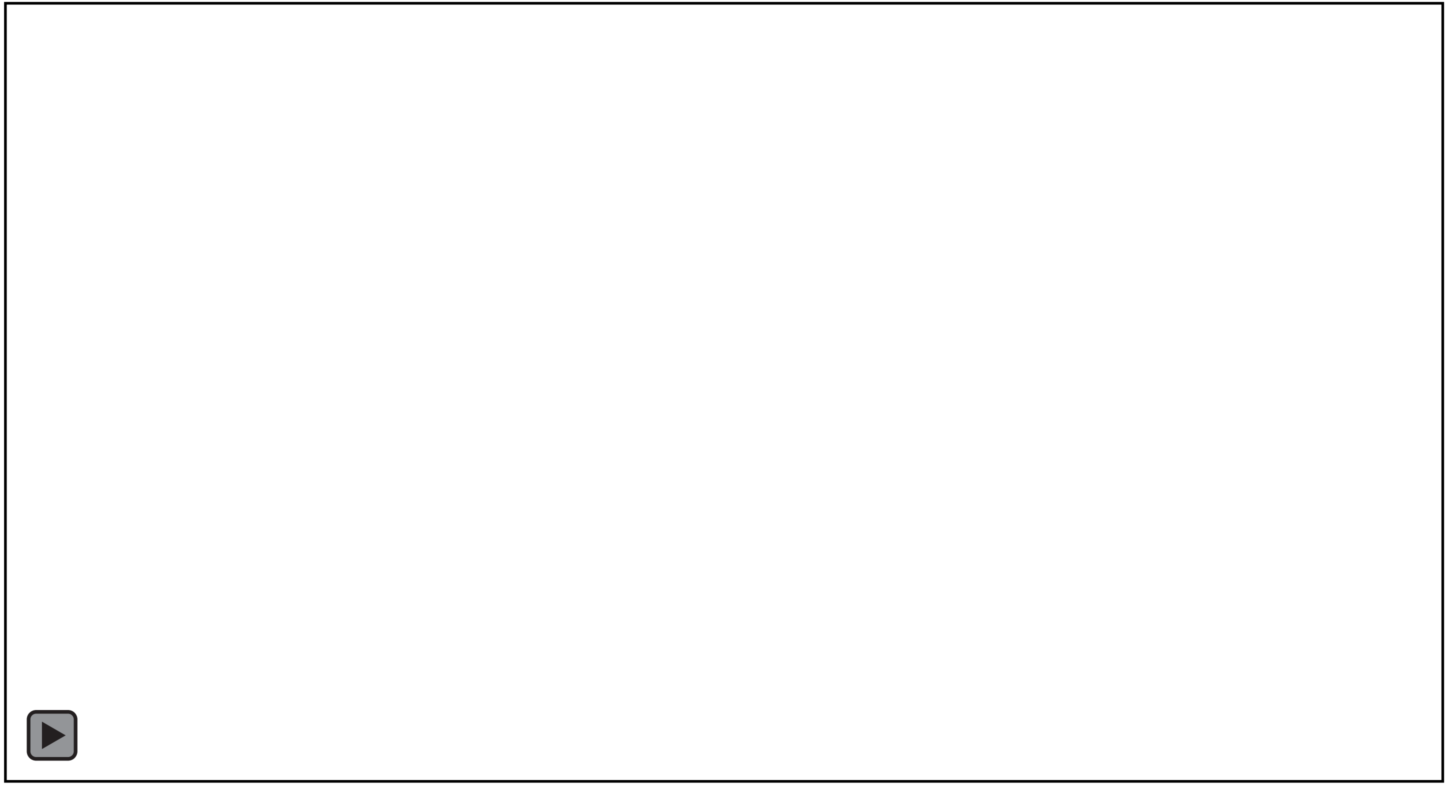
Ehteshami et al. *JAMA. 2017*

Radboudumc


Pathologist
HMS & MIT
Radboudumc
Exb
METU
NLP LOGIX


Pathologist
HMS & MIT
Radboudumc
Exb
METU
NLP LOGIX


Pathologist
HMS & MIT
Radboudumc
Exb
METU
NLP LOGIX



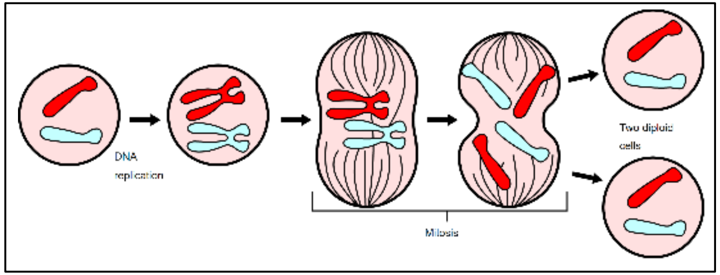
Applications of computational pathology

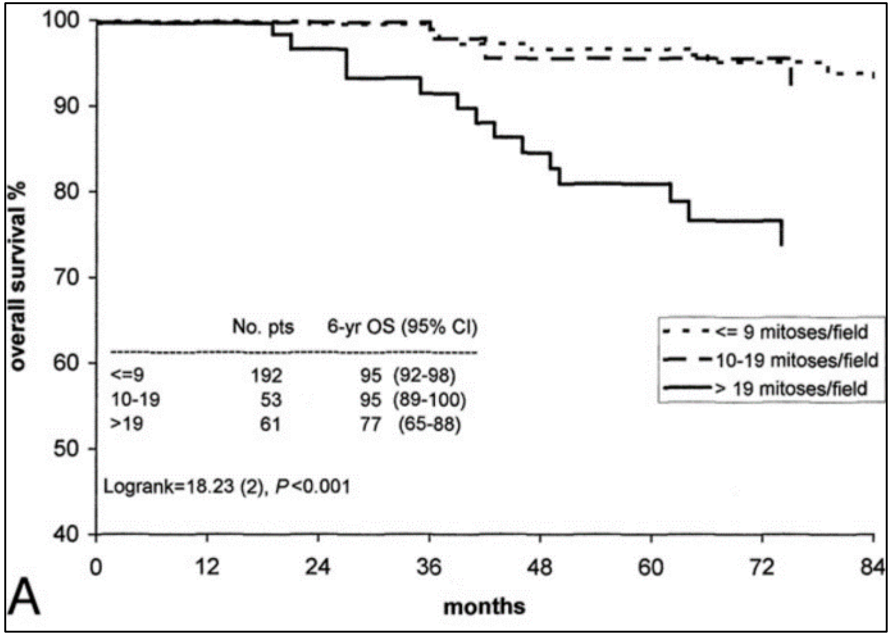
Clinical applications

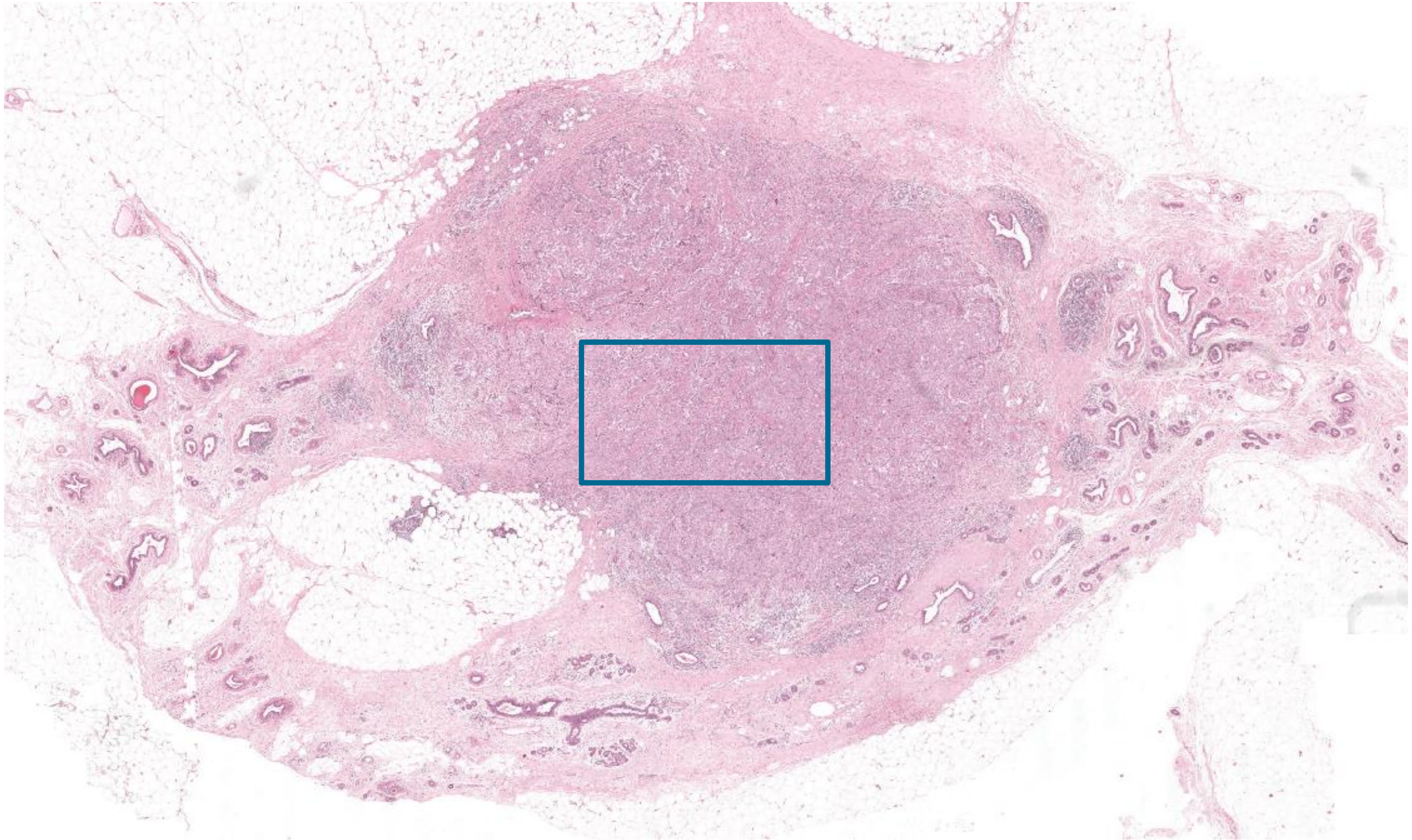
Detection of metastases in lymph nodes	Automated counting of mitoses
Quantification of multiplexed immunohistochemistry	Quantification of tumor-associated stroma

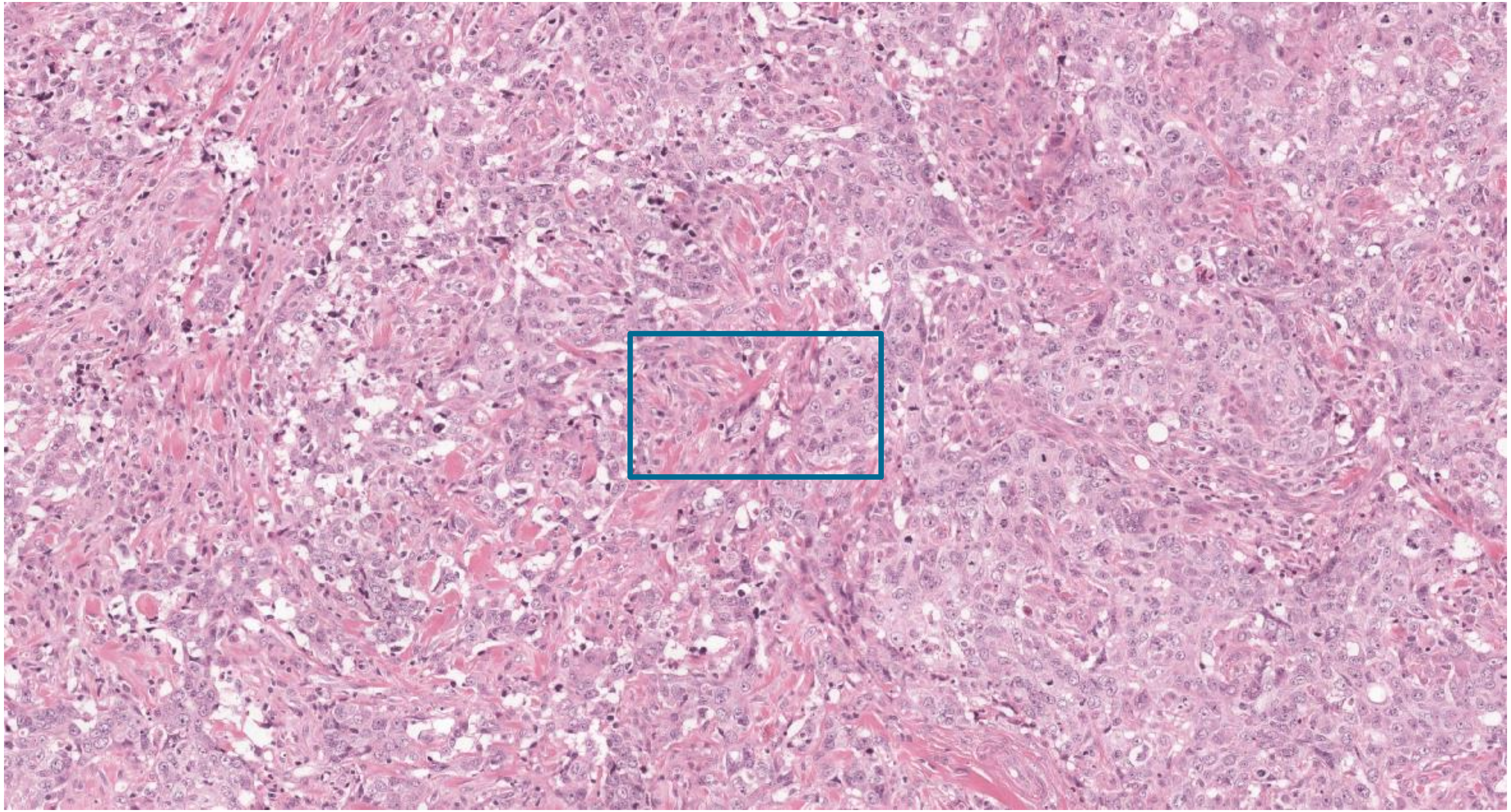
Biomarker research

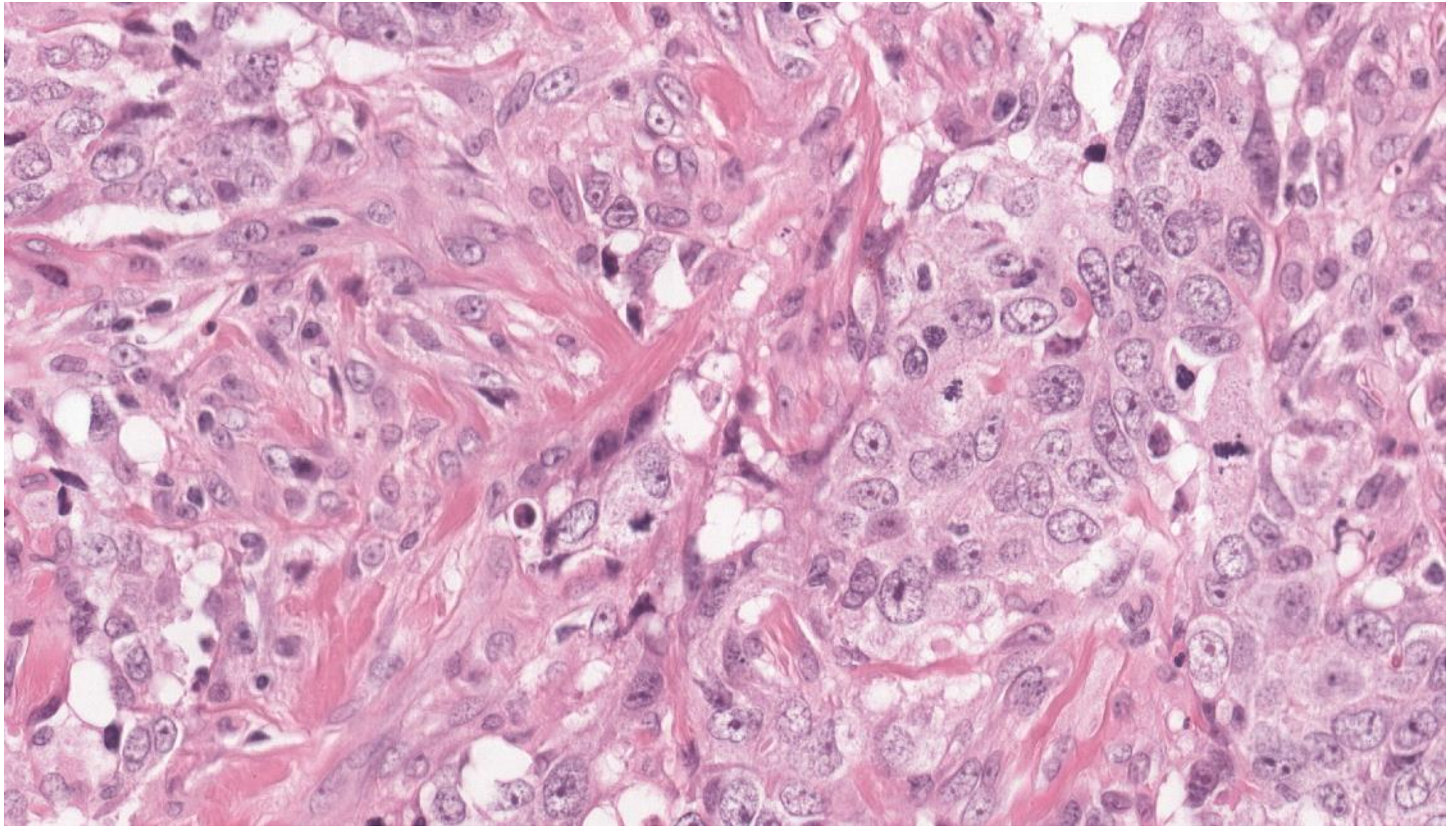
Automated counting of mitoses











Automated counting of mitoses

Assessment of Mitosis Detection Algorithms 2013
AMIDA13 | MICCAI Grand Challenge

D. C. Cireşan, A. Giusti, L. M. Gambardella, and J. Schmidhuber, "Mitosis detection in breast cancer histology images with deep neural networks," in *International Conference on Medical Image Computing and Computer-assisted Intervention*. Springer, 2013, pp. 411–418.

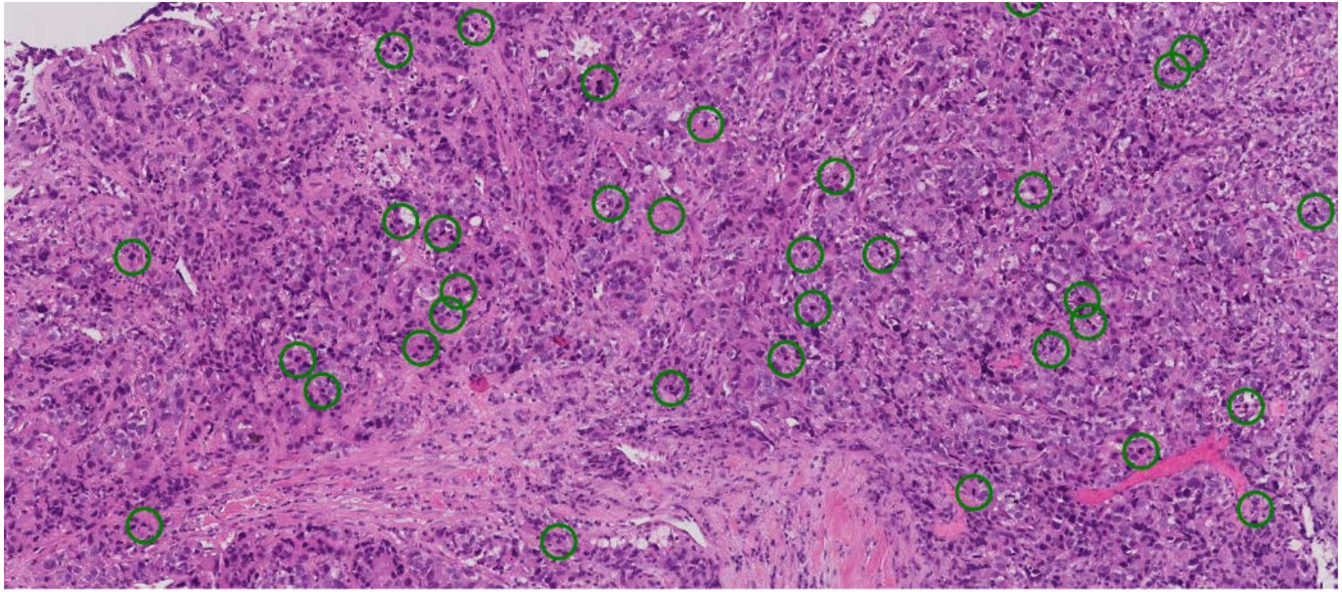
M. Veta, P. J. van Diest, M. Jiwa, S. Al-Janabi, and J. P. Pluim, "Mitosis counting in breast cancer: Object-level interobserver agreement and comparison to an automatic method," *PloS one*, vol. 11, no. 8, p. e0161286, 2016.

Tumor Proliferation Assessment Challenge 2016
TUPAC16 | MICCAI Grand Challenge

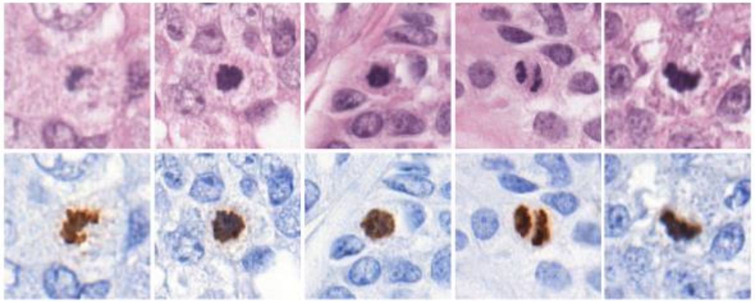
E. Zerhouni, D. Lányi, M. Viana, and M. Gabrani, "Wide residual networks for mitosis detection," in *Biomedical Imaging (ISBI 2017), 2017 IEEE 14th International Symposium on*. IEEE, 2017, pp. 924–928.

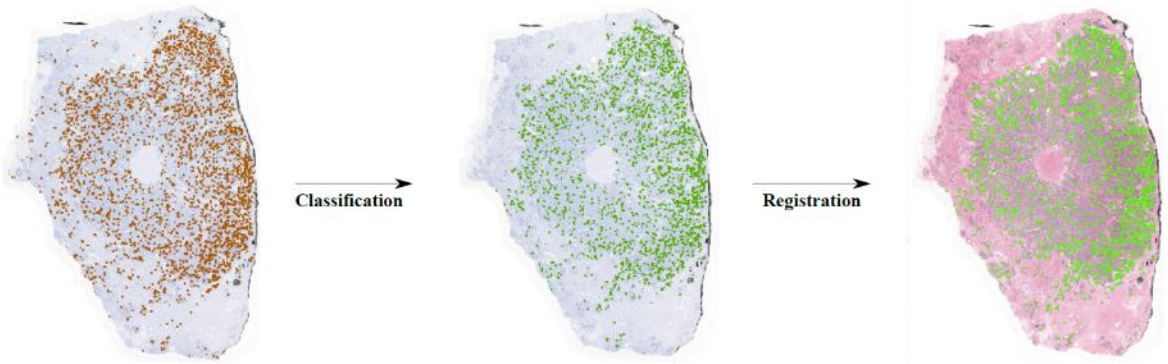
K. Paeng, S. Hwang, S. Park, M. Kim, and S. Kim, "A unified framework for tumor proliferation score prediction in breast histopathology," *arXiv preprint arXiv:1612.07180*, 2016.

Problem 1: reference standard

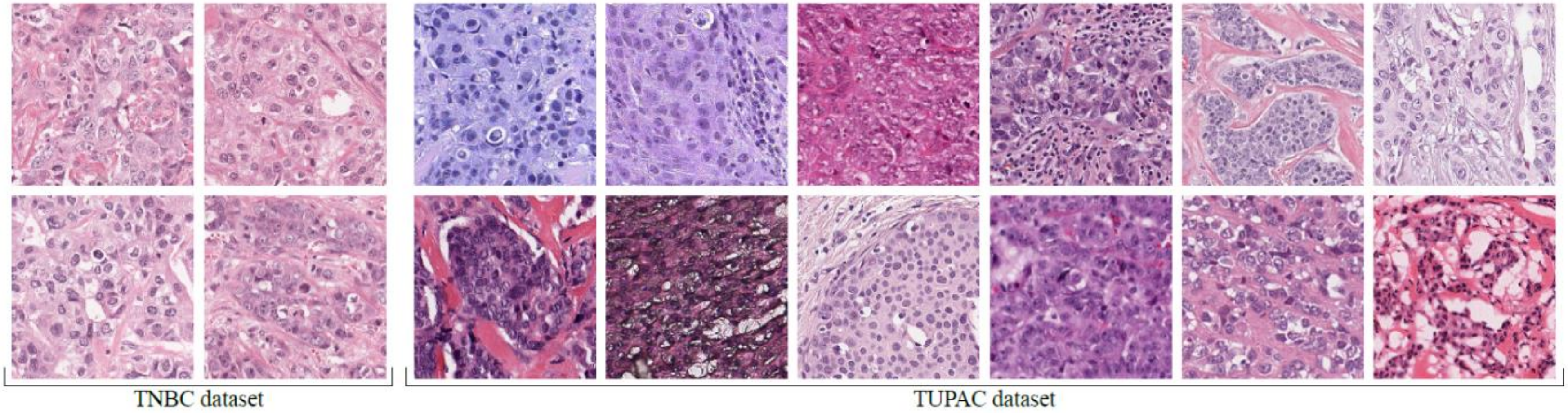


Solution: PHH3 IHC

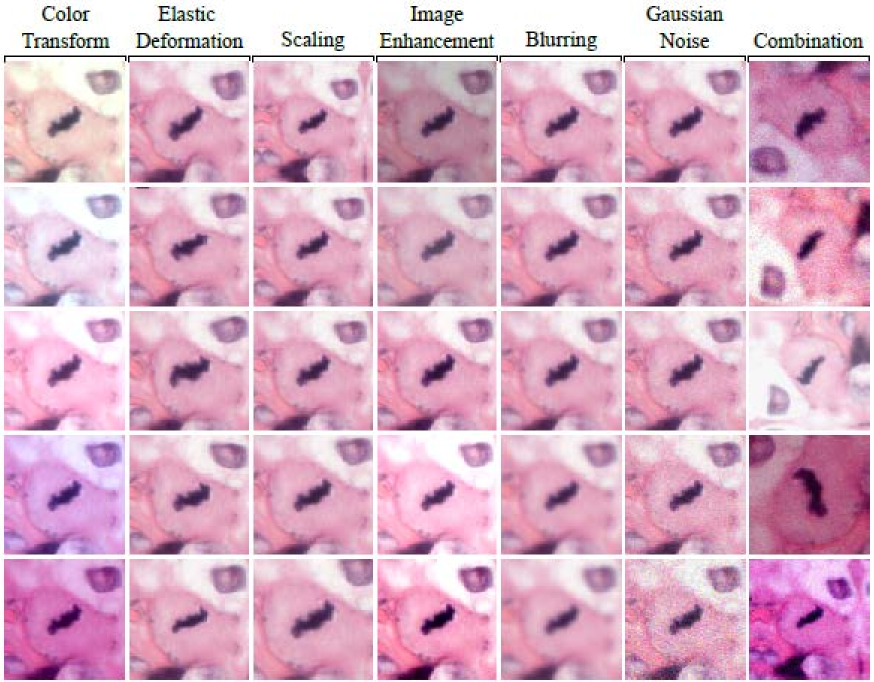


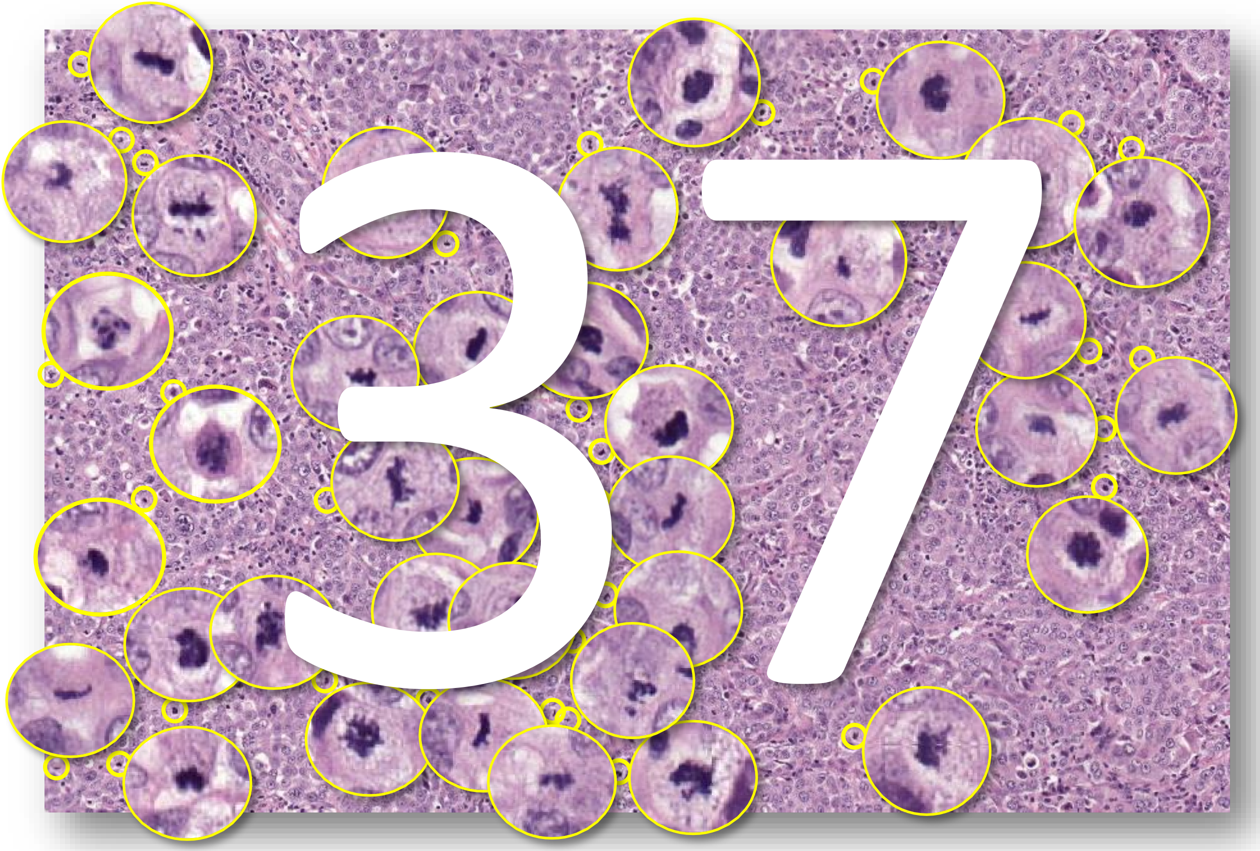


Problem 2: staining variation



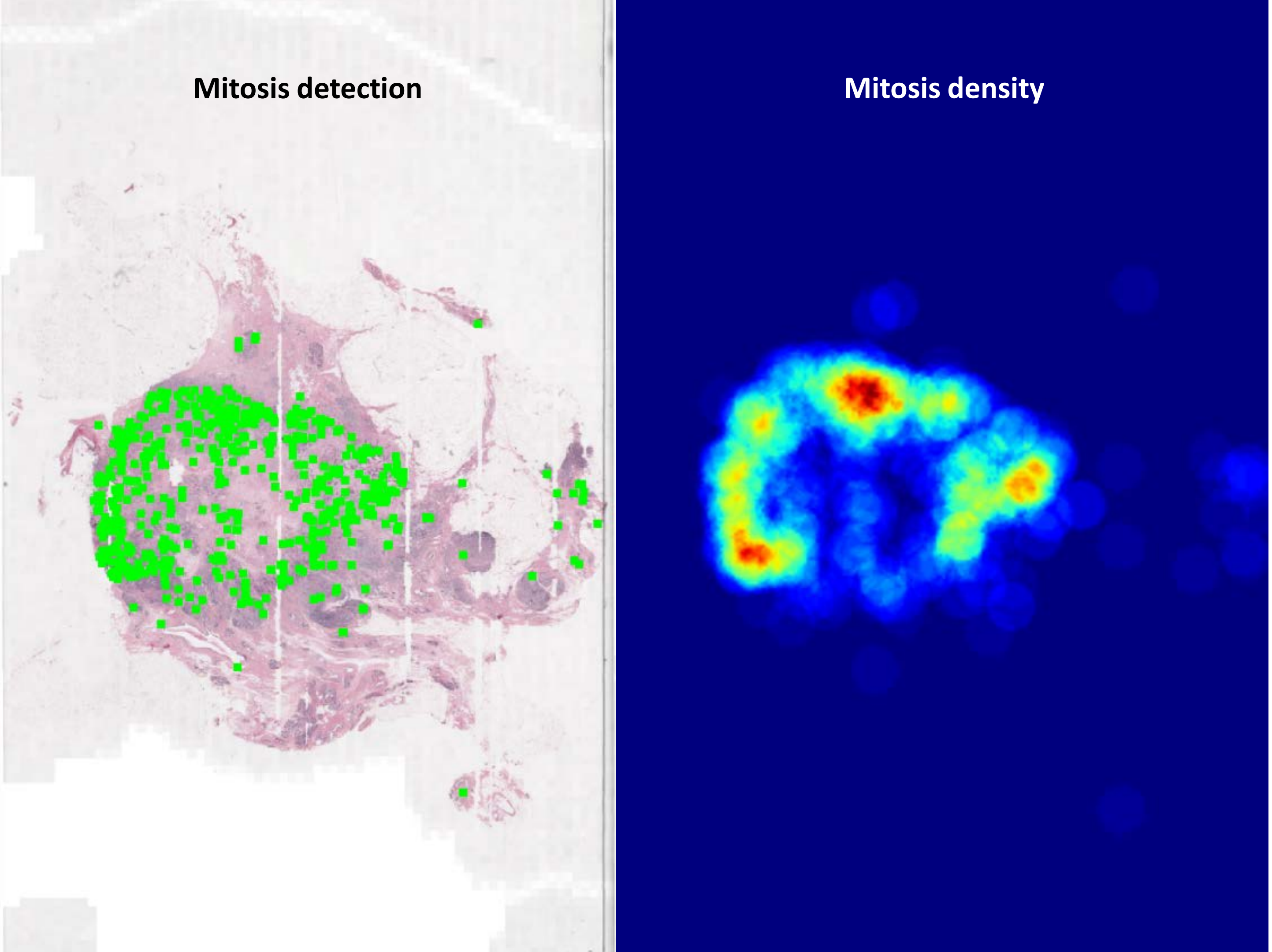
Solution 2: Data augmentation

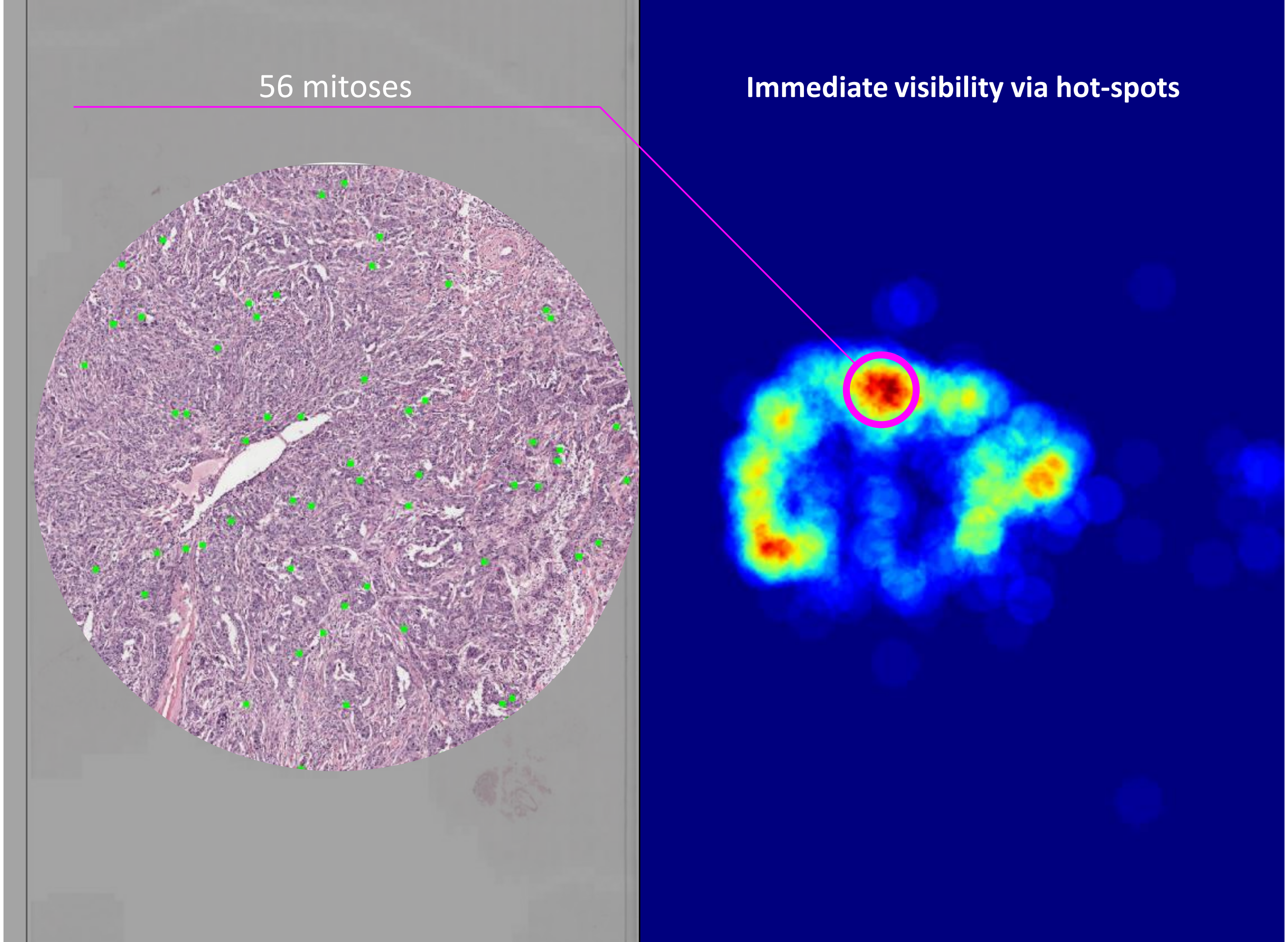


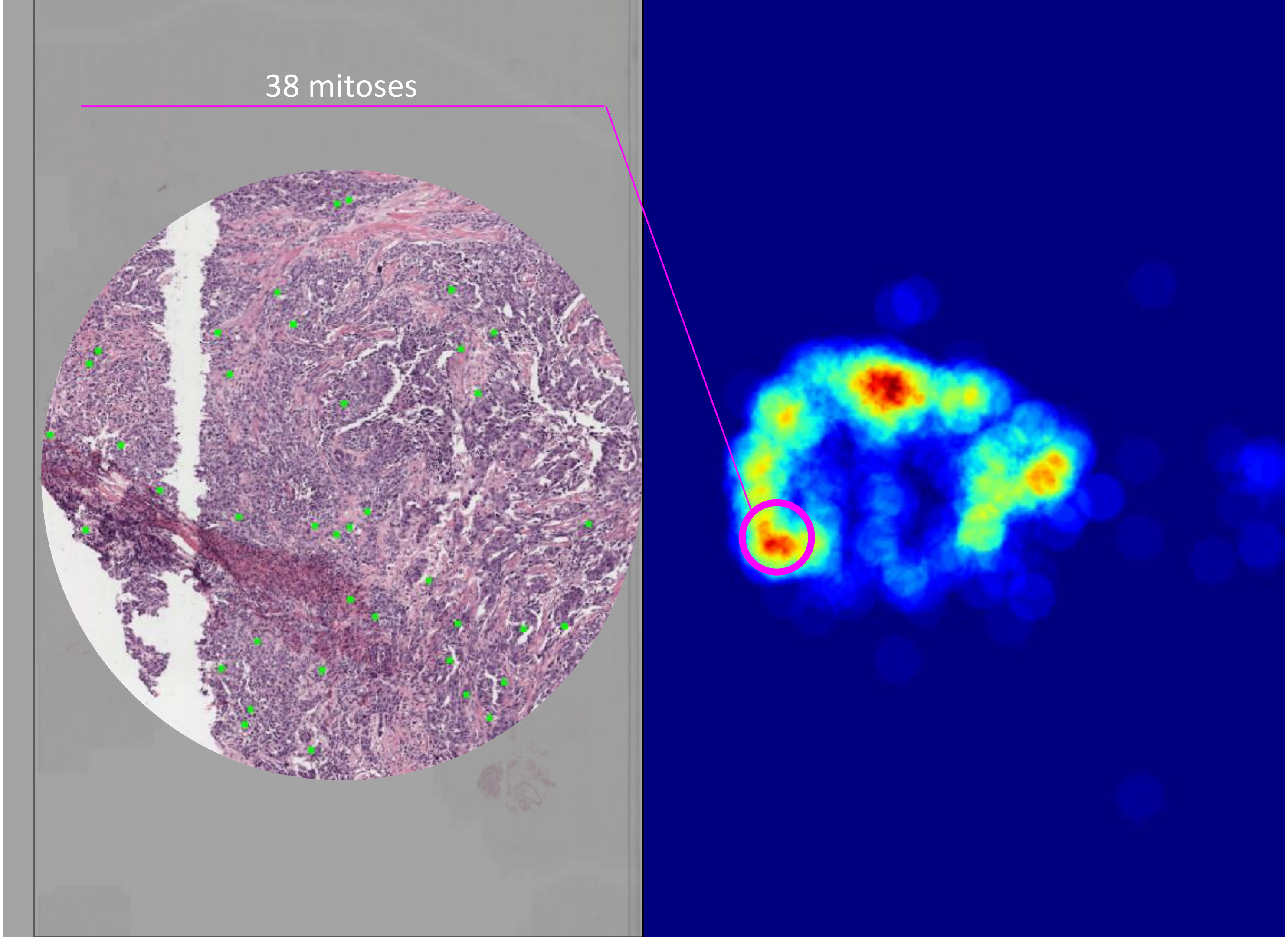


Tellez et al. *IEEE Transactions on Medical Imaging.* Accepted

Radboudumc


Mitosis detection
Mitosis density


56 mitoses
Immediate visibility via hot-spots


38 mitoses

Applications of computational pathology

Clinical applications

Detection of metastases in lymph nodes

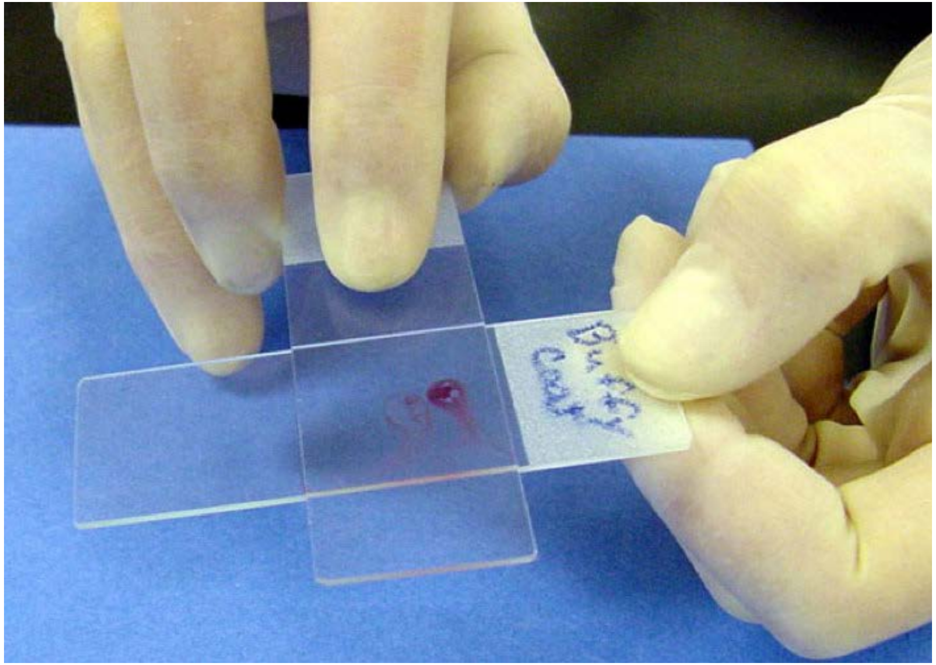
Automated counting of mitoses

Quantification of multiplexed immunohistochemistry

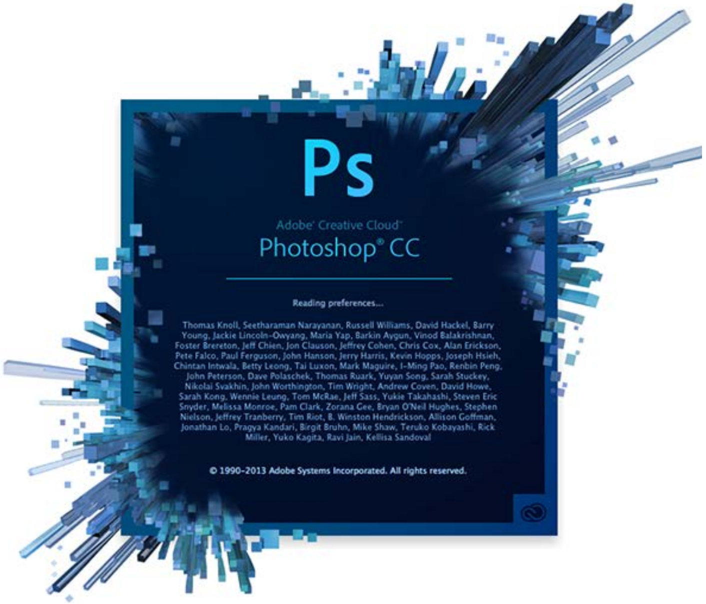
Quantification of tumor-associated stroma

Biomarker research

Multiplexing in routine...



Current multiplexing strategies in research…



- **A novel immunohistochemical sequential multi-labelling and erasing technique enables epitope characterization of bone marrow pericytes in primary myelofibrosis.** Madelung et al. *Histopathology.* 2012

- **Prediction of survival in diffuse large B-cell lymphoma based on the expression of genes reflecting tumor and micro-environment.** Alizadeh et al. *Blood, 2011*

- **Distribution Patterns of Dendritic Cells and T Cells in Diffuse Large B-Cell Lymphomas Correlate with Prognoses**. Chang et al. *Clin Canc Res*, 2007

- Many others...

Current literature focusses on ideal situations

Idealized setting

- Consecutive sections
- Similar stains
- No major tissue artifacts
- Rough alignment present

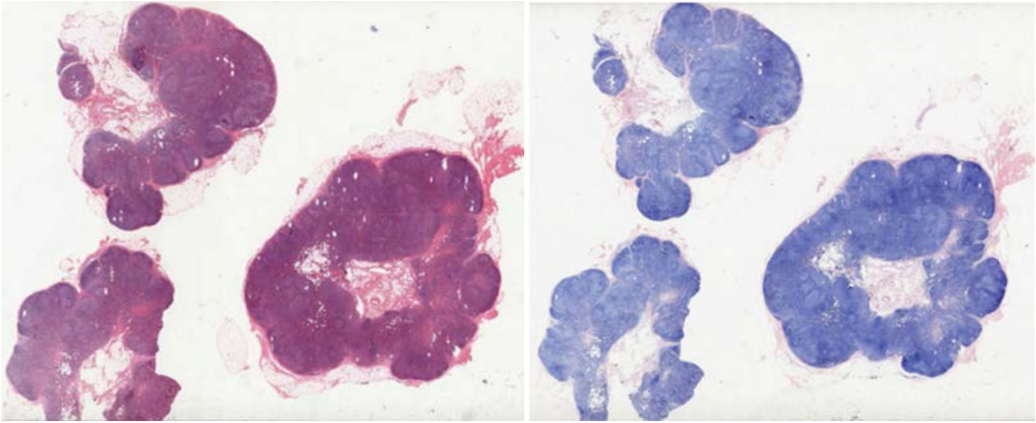


Image from Mueller et al. *Computerized Medical Imaging and Graphics.* 2011

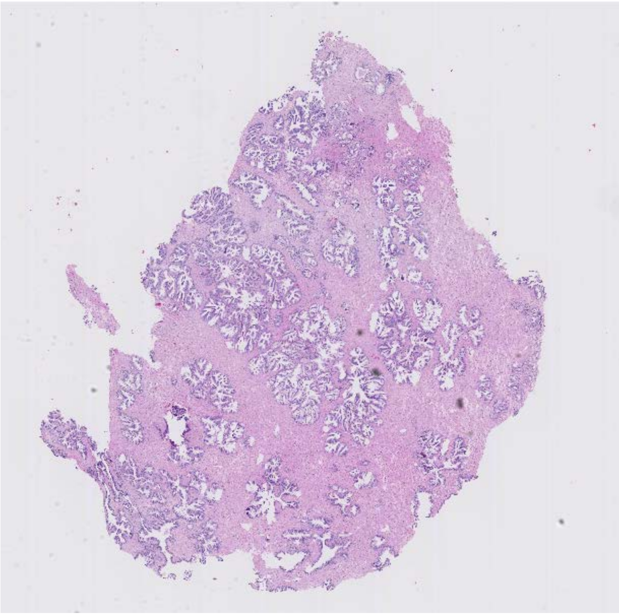
Deviations from idealized setting have huge impact

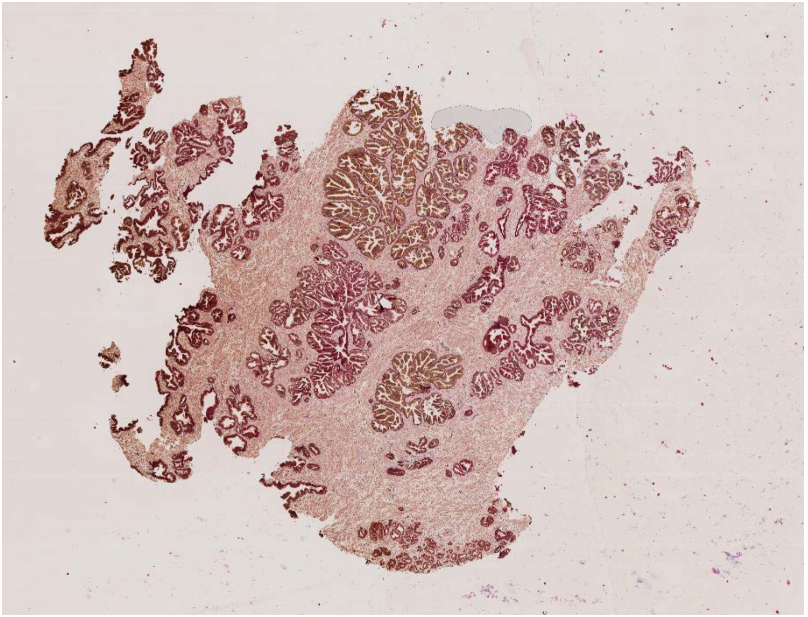
- Median Hausdorf distance between landmark points triples (25 microns to 75 microns)[1]

[1]Song et al. *IEEE Transactions on Biomedical Engineering.* 2014

Radboudumc

Most studies don’t have ideal data





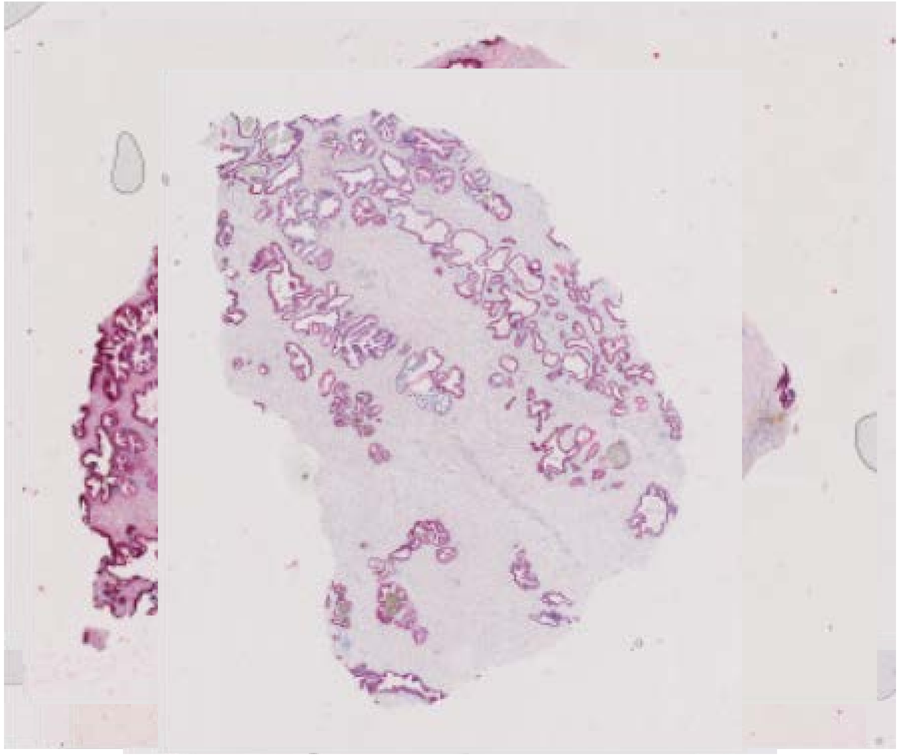
Litjens et al. *SPIE Medical Imaging. 2016*

Radboudumc

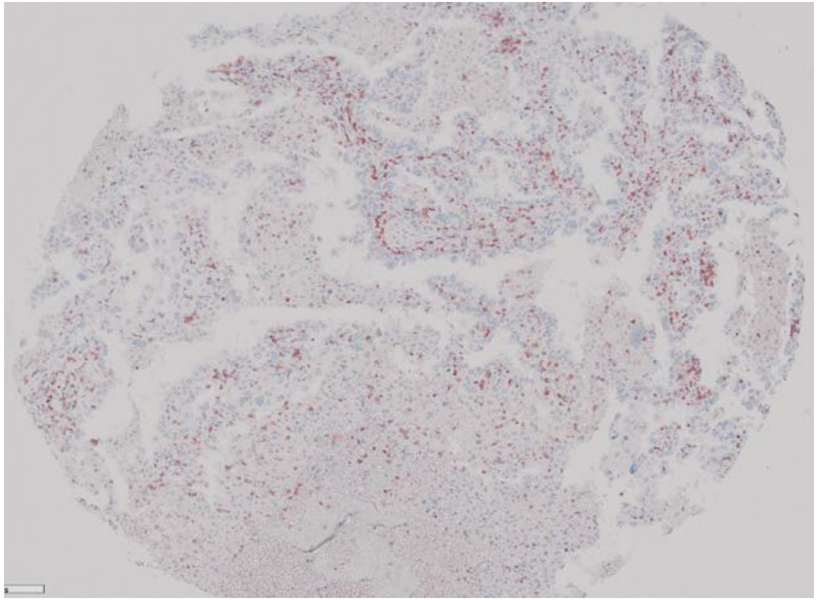
‘Real’ data

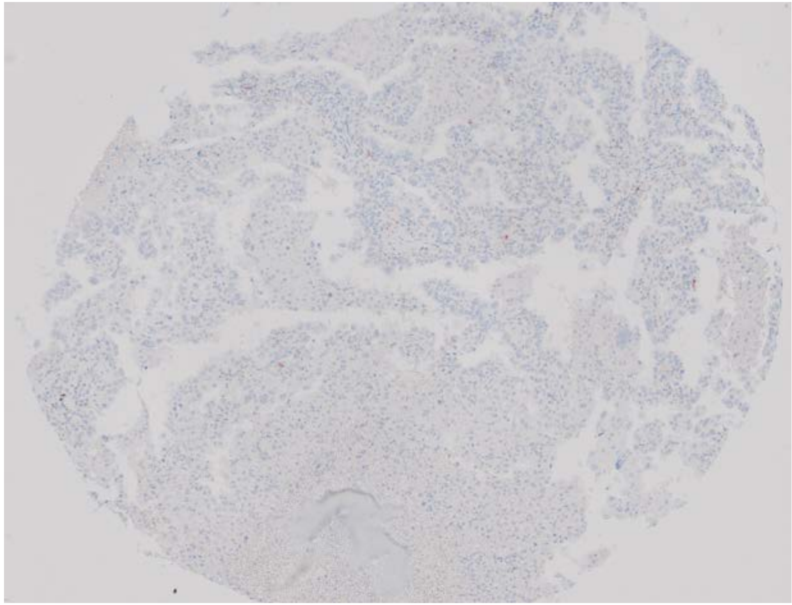
Clinical trial for immunotherapy

- 31 stains per section
- 0.48 microns per pixel

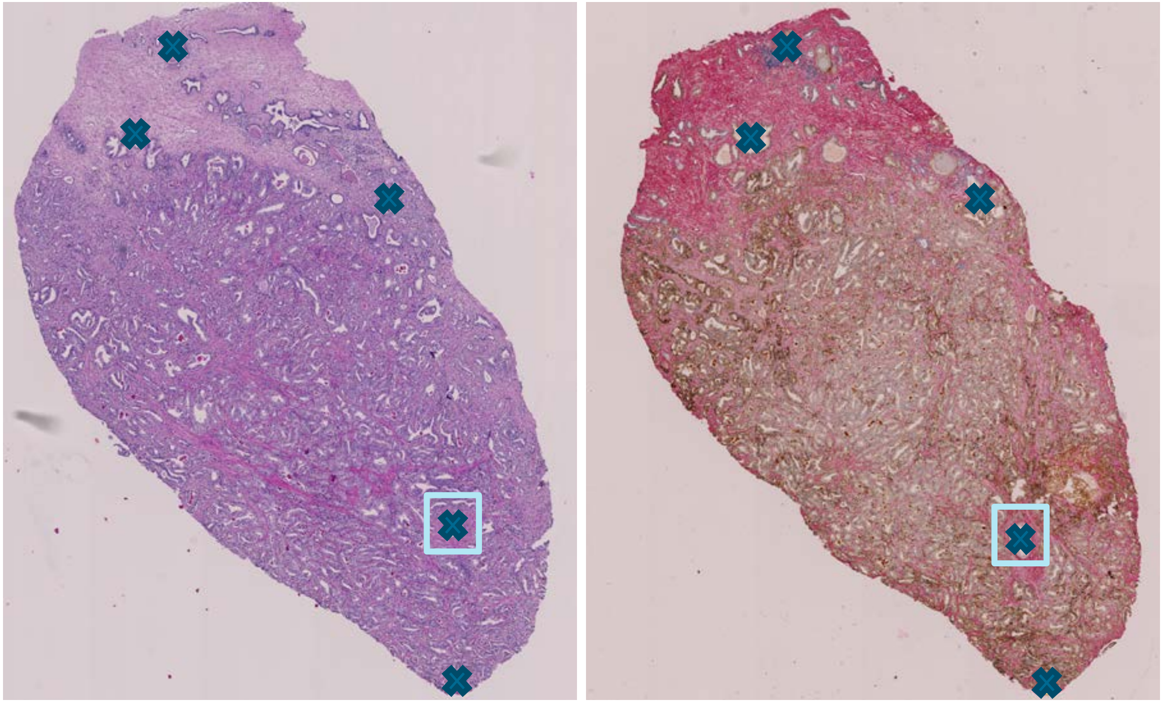


‘Ideal’ data

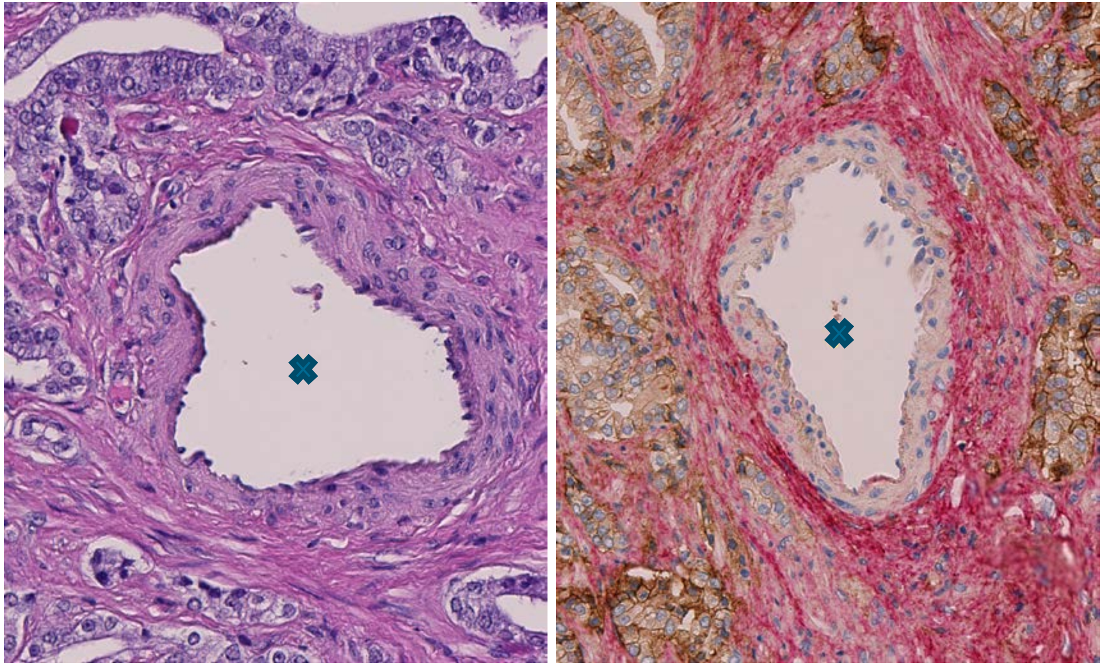




Experimental design

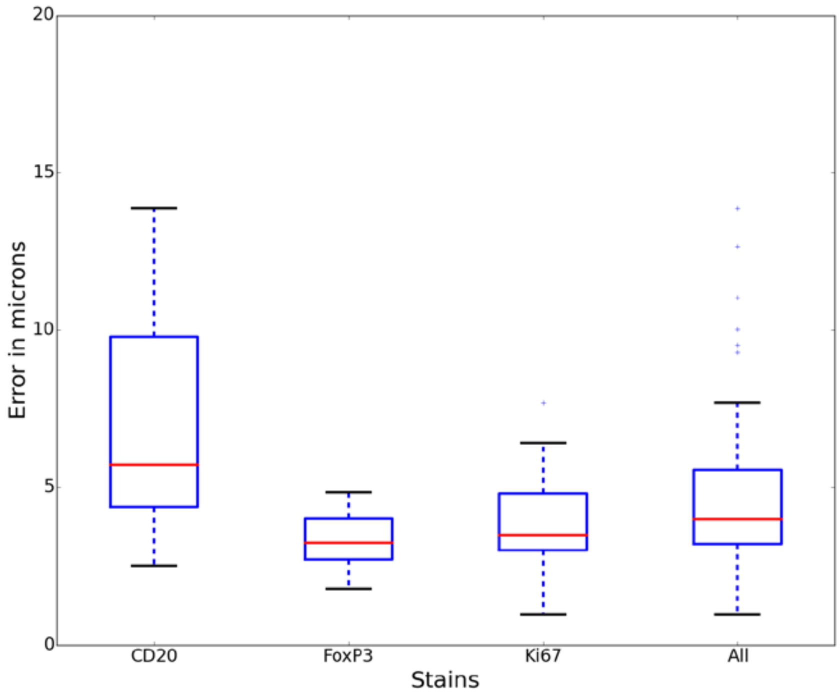


Experimental design

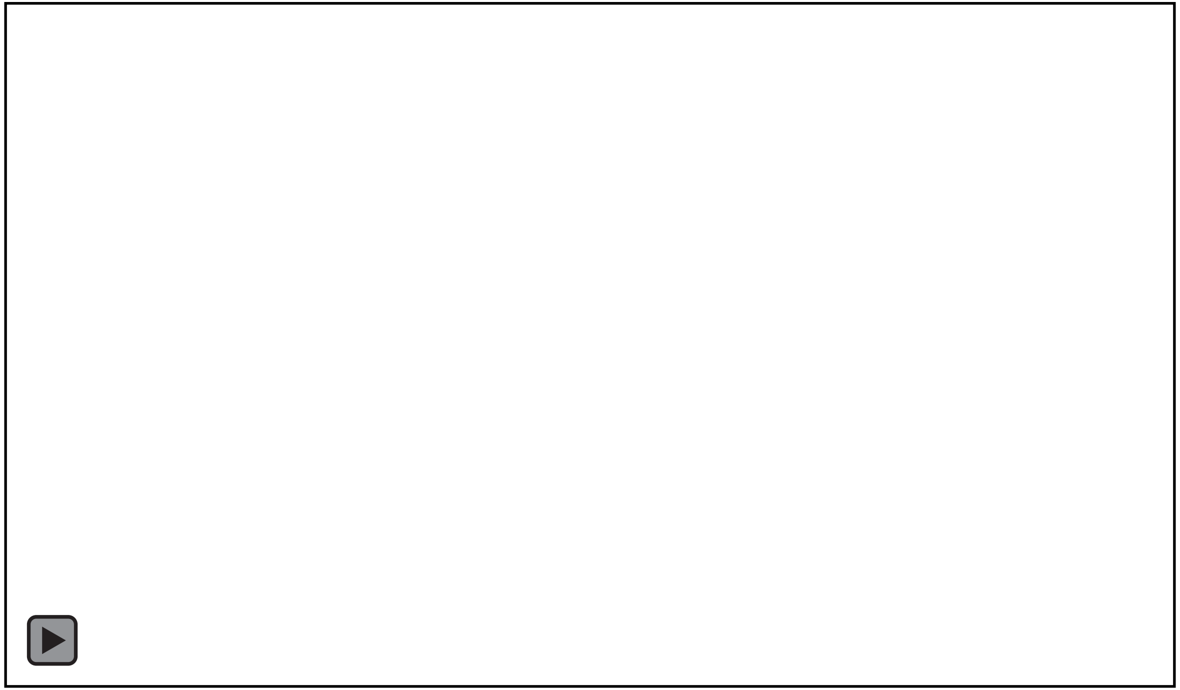


Quantitative results – ‘Ideal’ data

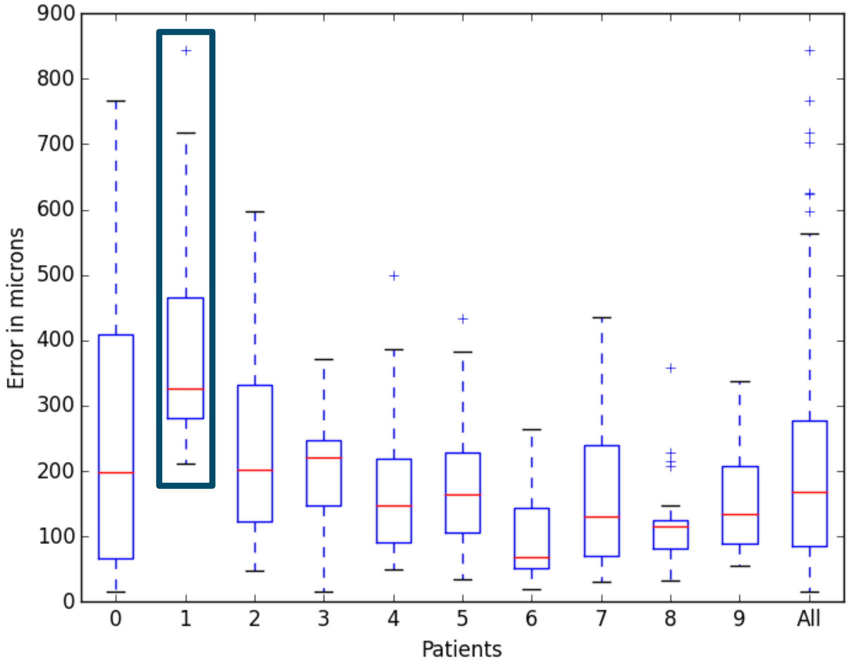
- Median registration error across all stains is 4 micron
- Maximum registration error is 14 micron



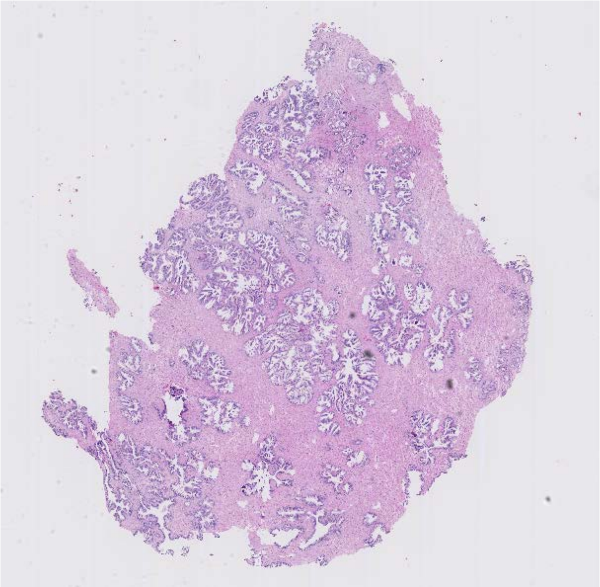
Qualitative results

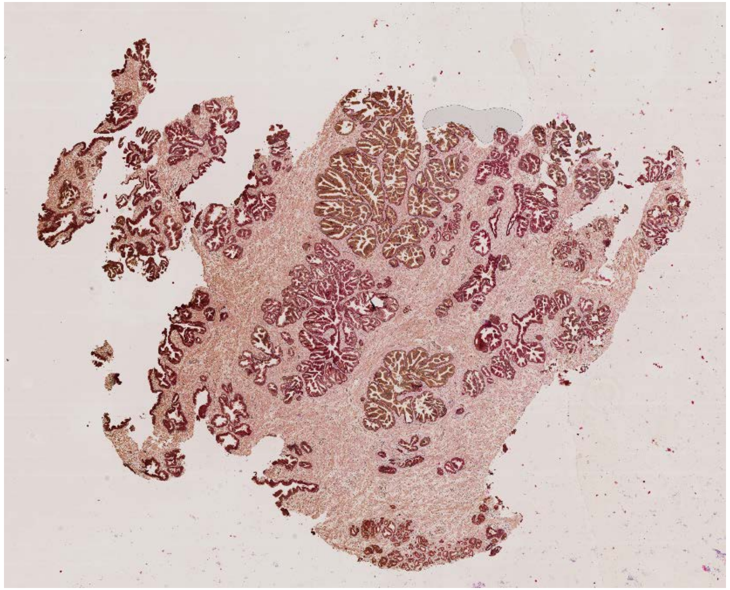


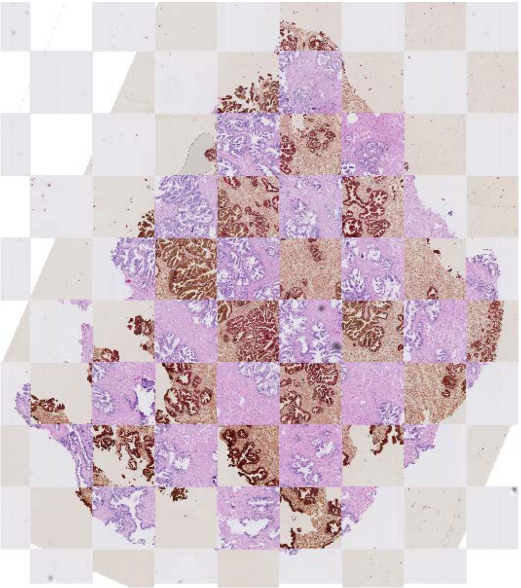
Quantitative results – ‘Real’ data

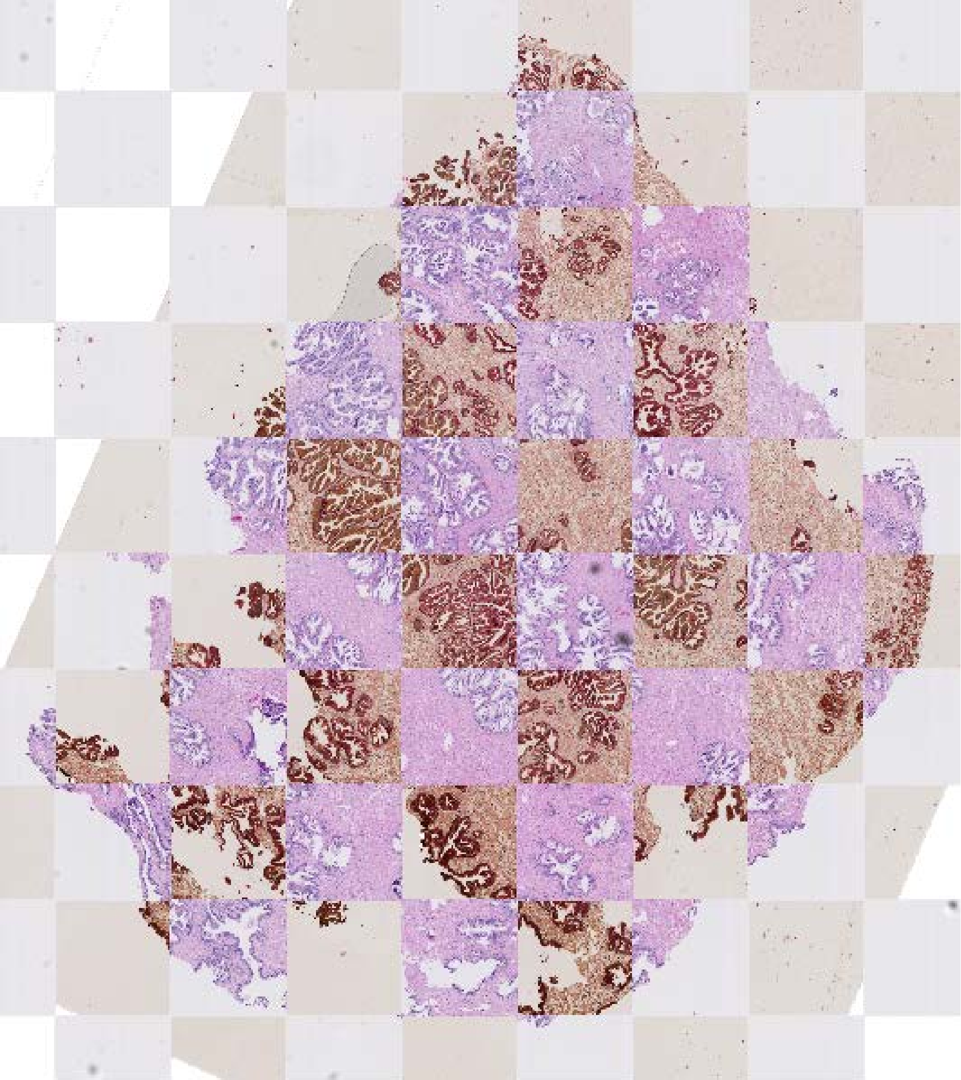


Qualitative results: Patient 1

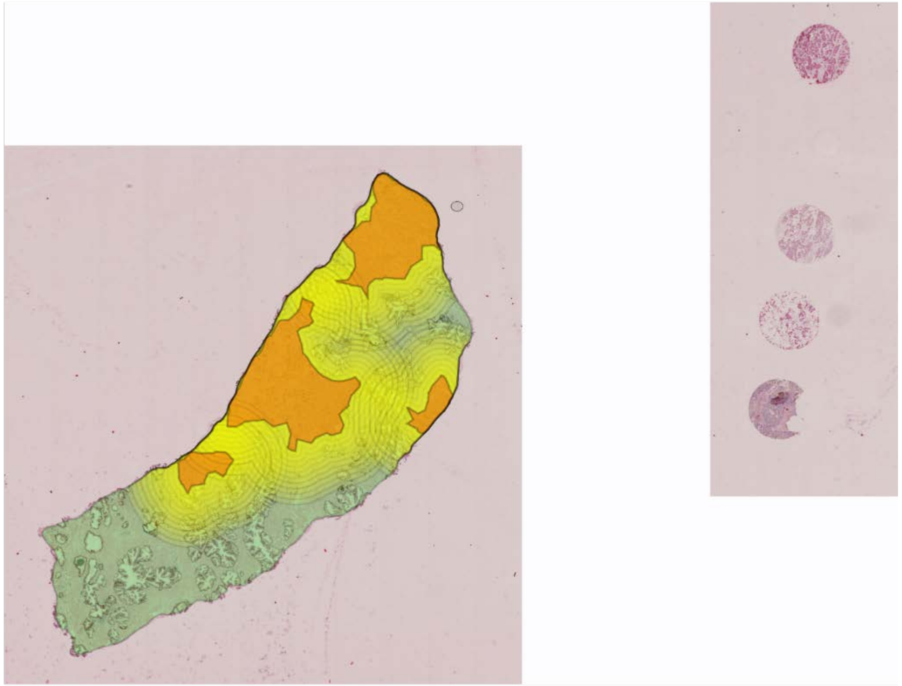


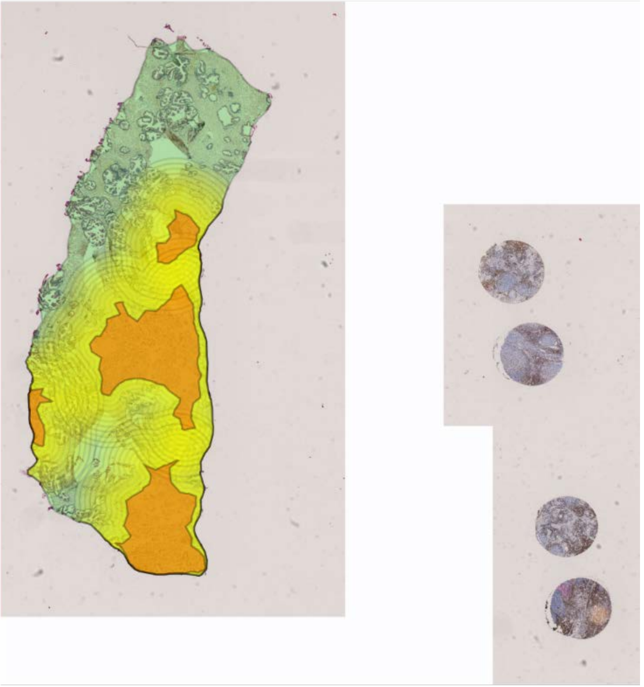




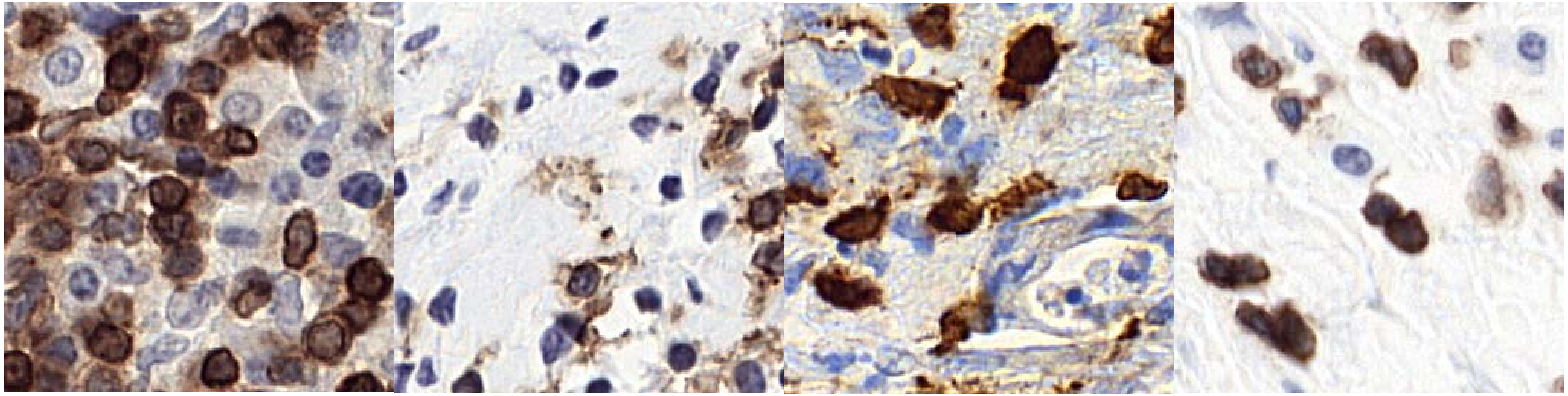


Qualitative results

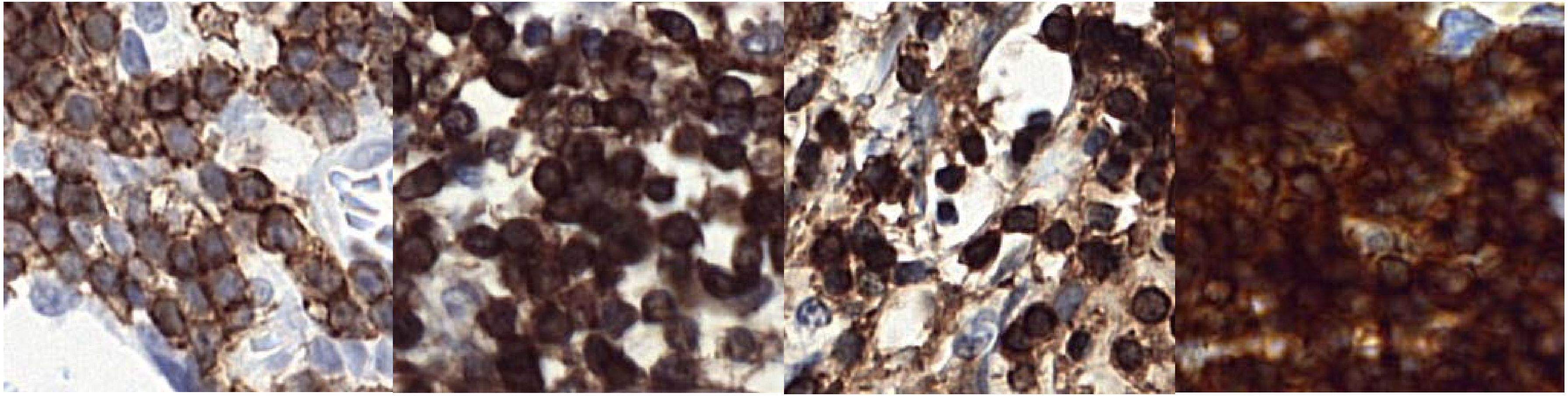




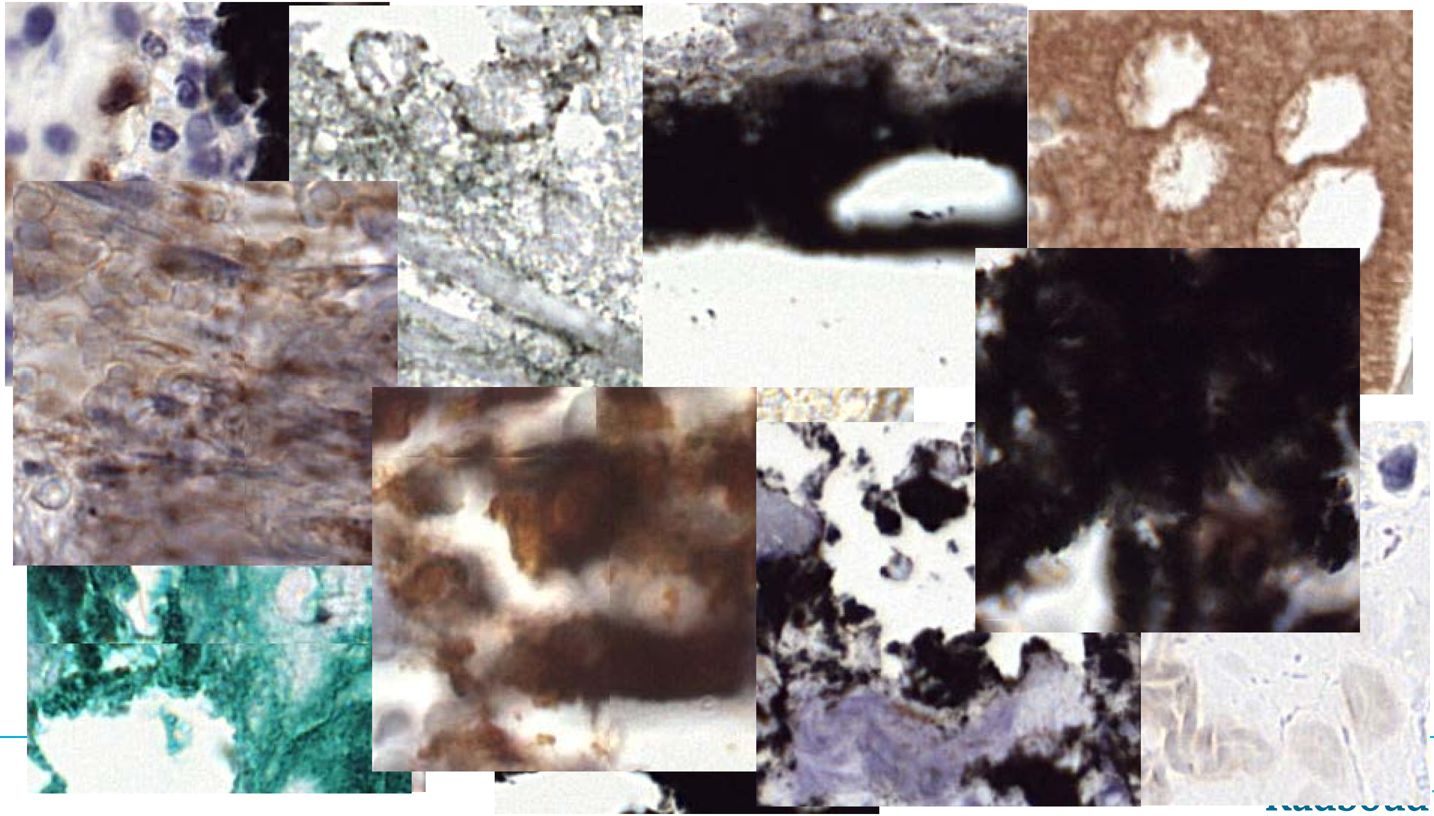
Quantification of IHC



Quantification of IHC



Quantification of IHC

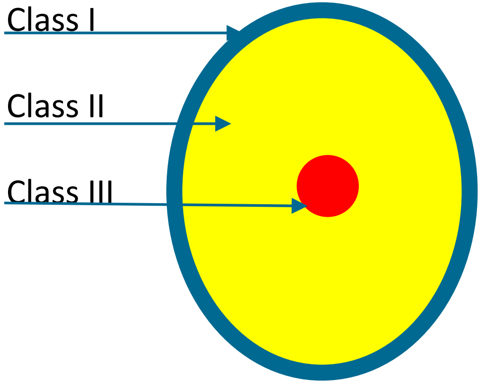


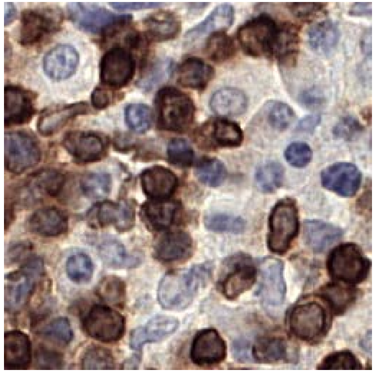
Lymphocytes detection by…

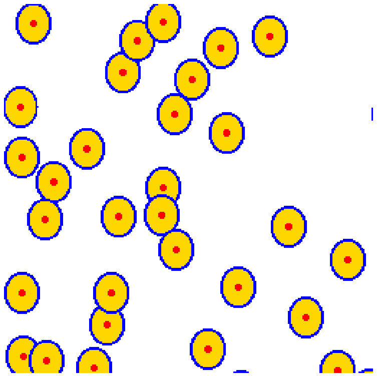
Classification	Bounding box	Center point	Semantic Segmentation
FCNN	YOLO	locality sensitive method	U-NET
Hans	Mart	Francesco	Zaneta




Approach II -multi-class mask







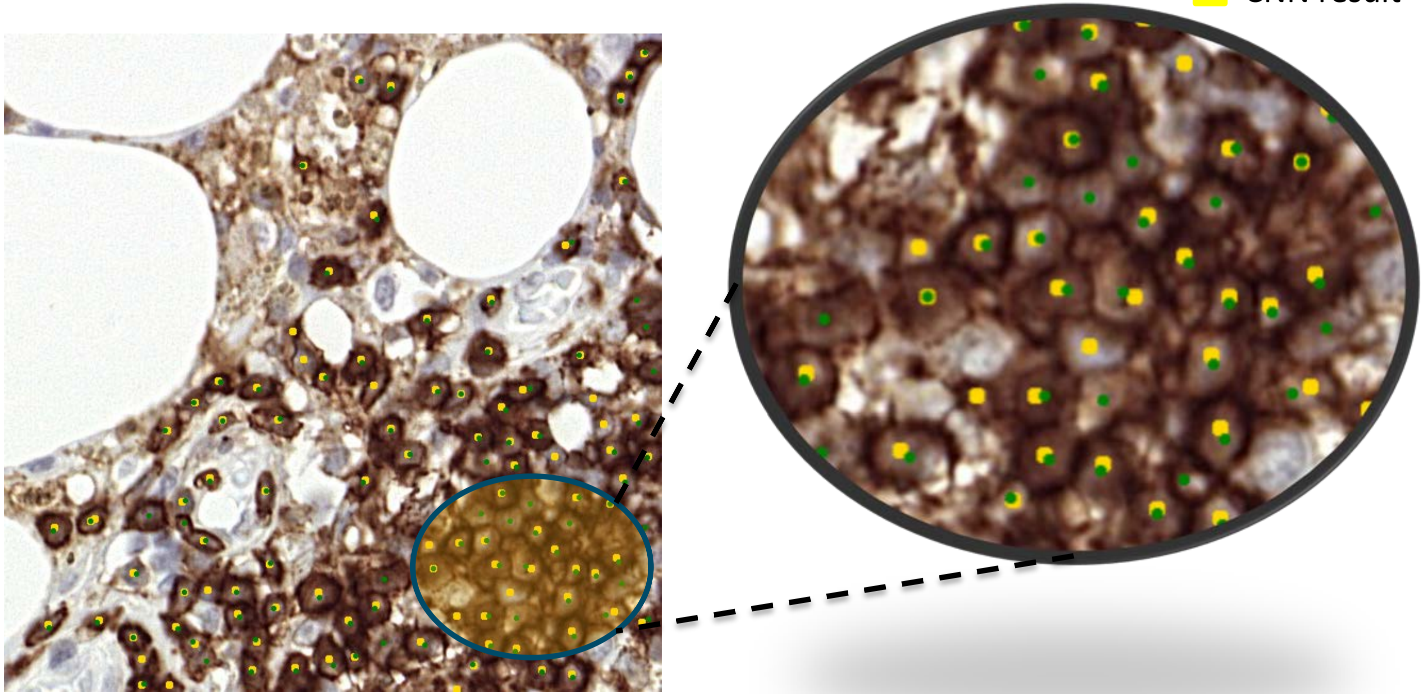
Quantitative results

		Test set		
Area type	Method	F1-score	Precision	Recall
Regular tissue	FCNN	0.721	0.753	0.810
	LSM	0.669	0.554	0.846
	YOLO	**0.780**	0.750	**0.810**
	Unet	0.762	0.785	0.740
	Unet-E	0.778	**0.756**	0.781

Qualitative results - clusters

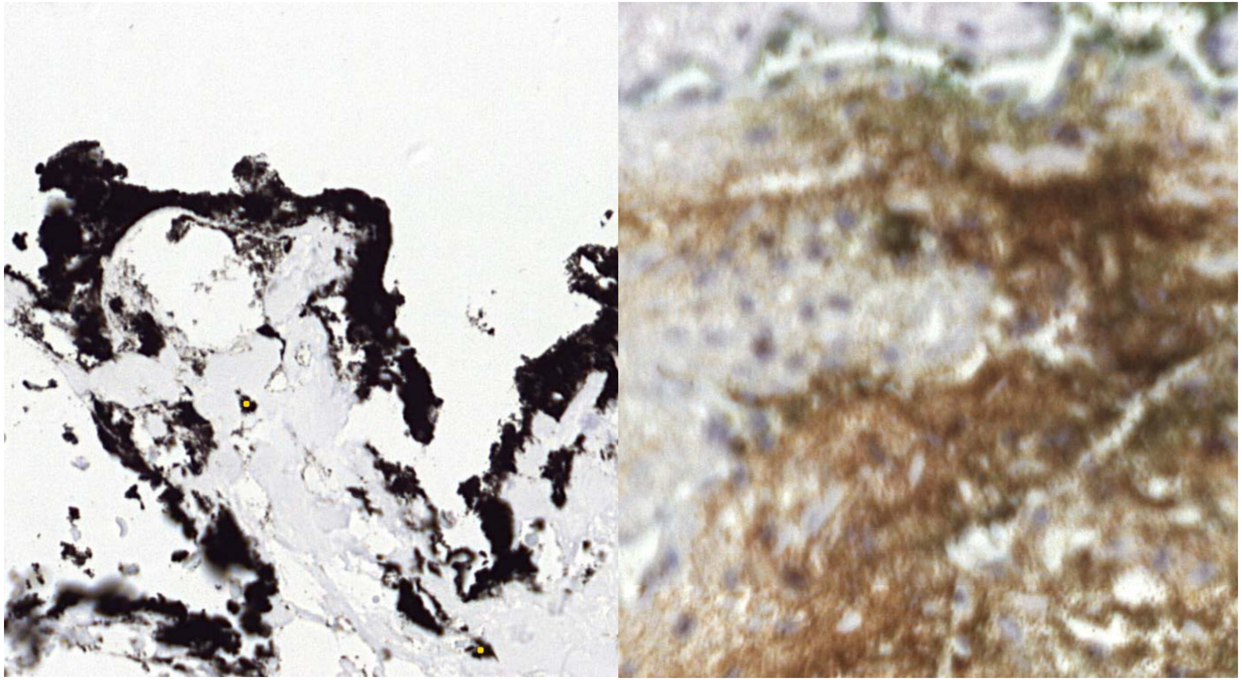
Manual annotation

CNN result



Radboudumc

Qualitative results - artifacts



Swiderska et al. *MIDL.* Accepted

Radboudumc

Applications of computational pathology

Clinical applications

Detection of metastases in lymph nodes

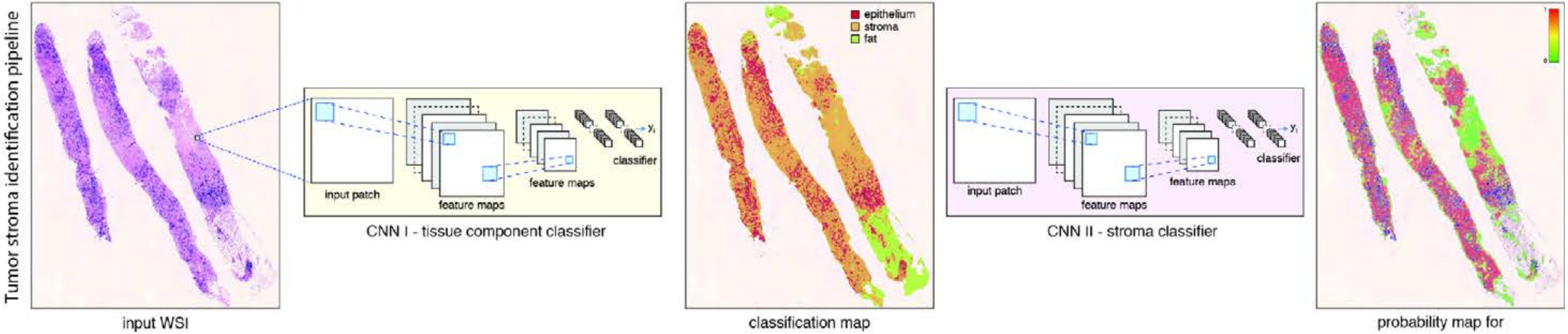
Automated counting of mitoses

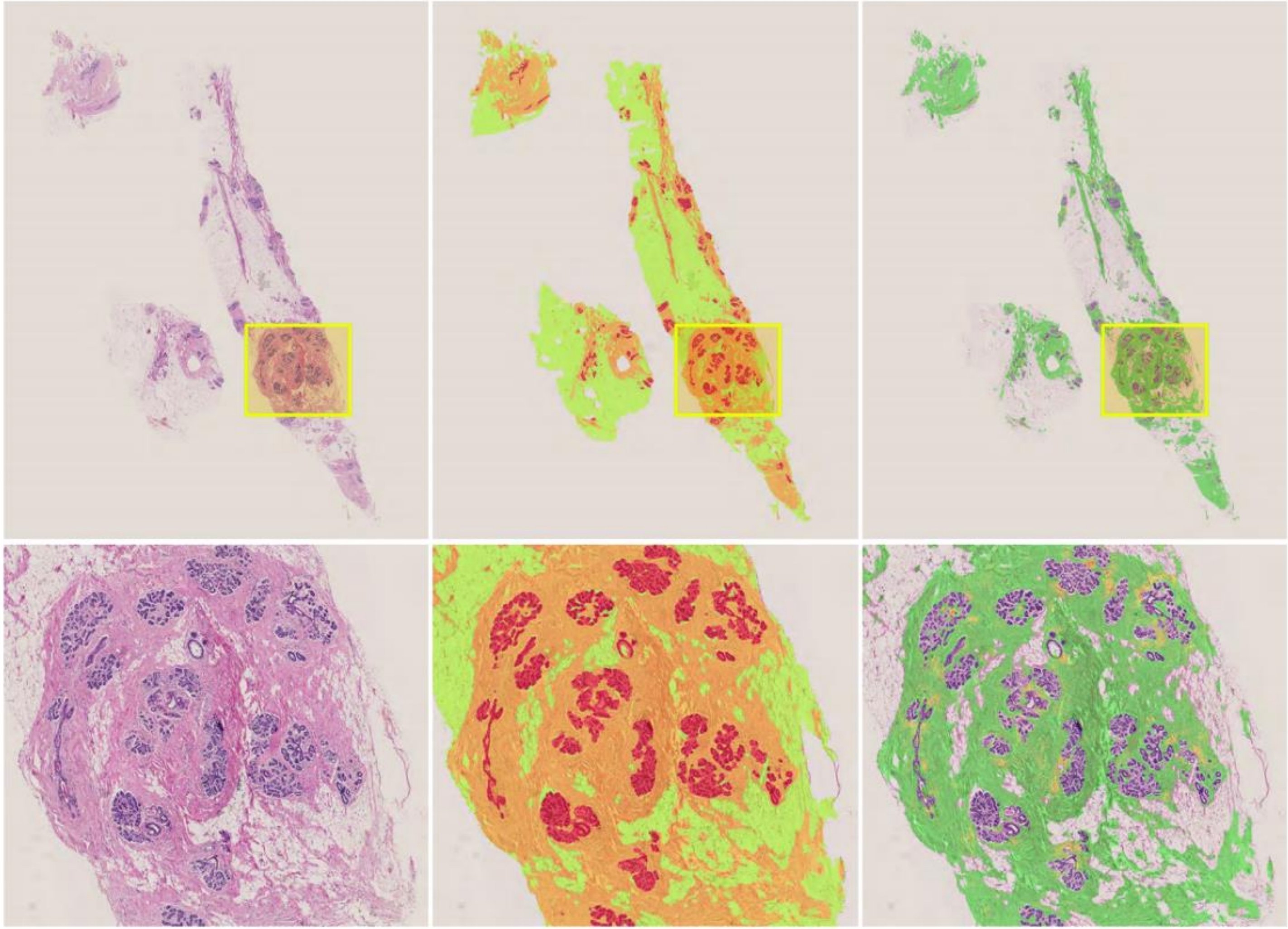
Quantification of multiplexed immunohistochemistry

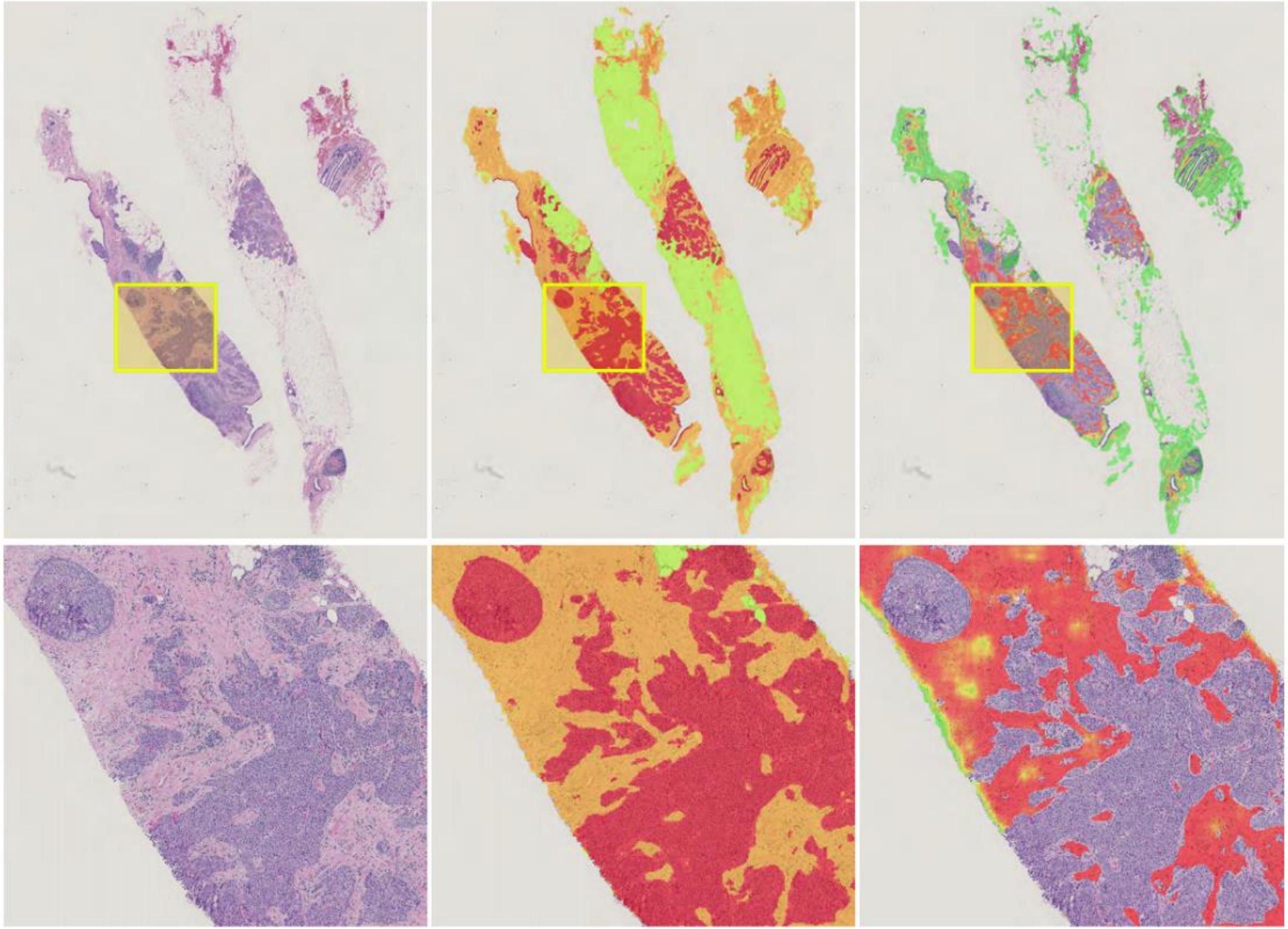
Quantification of tumor-associated stroma

Biomarker research

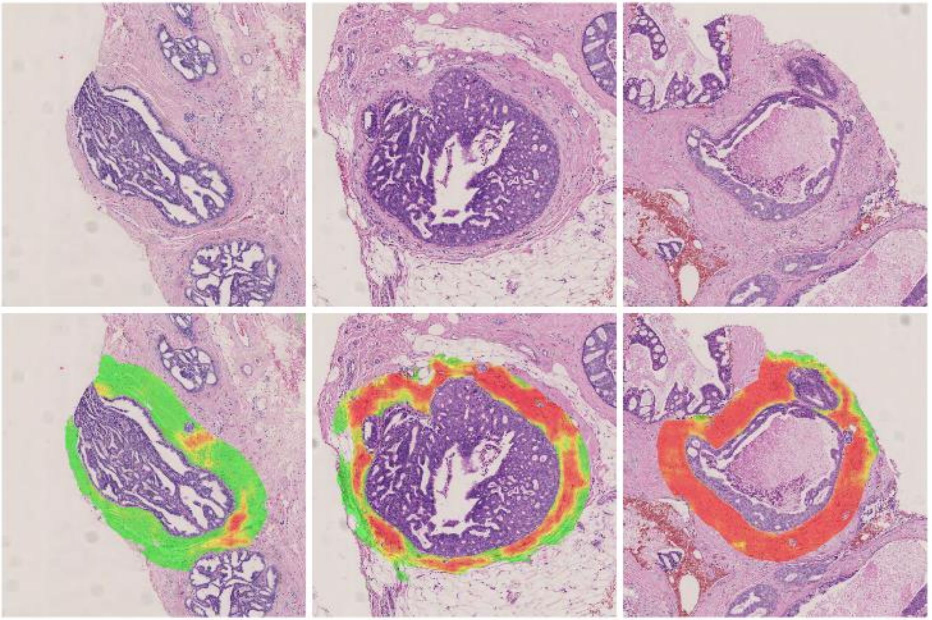
Tumor-associated stroma

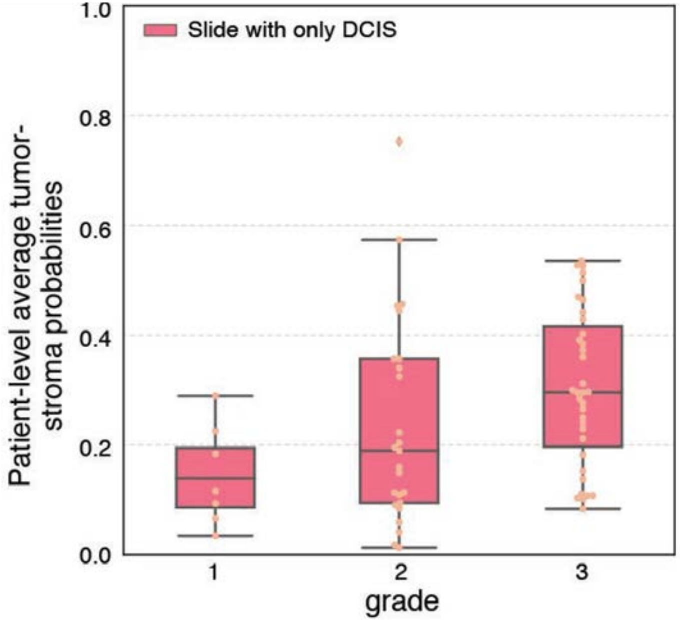






Tumor-associated stroma





Ehteshami et al. *Modern Pathology. Accepted*

Radboudumc

Other areas of research

Oncology

Breast	Prostate	Colorectal	Cancer metastases
Classification	Segmentation	Tumor/stroma-ratio	Detection
Mitosis counting	Prognosis	Tumor budding	
Prognosis			
Impact of tumor infiltrating lymphocytes			
Quantification of immunohistochemistry			
Stain normalization			

Other

Kidney transplants	Software development

Faculty


Jeroen van der Laak


Geert Litjens


Francesco Ciompi

Technicians


Karel Gerbrands


Rob van de Loo

Researchers


Maschenka Balkenhol


Péter Bándi


Thomas de Bel


John-Melle Bokhorst


Wouter Bulten


Oscar Geessink


Meyke Hermsen


Hans Pinckaers


Zaneta Swiderska-Chadaj


David Tellez

Students


Marjolijn den Boer


Mart van Rijthoven