Artificial Intelligence for Computational Pathology

Andrew H Beck MD PhD
CEO - PathAI

March 15, 2017

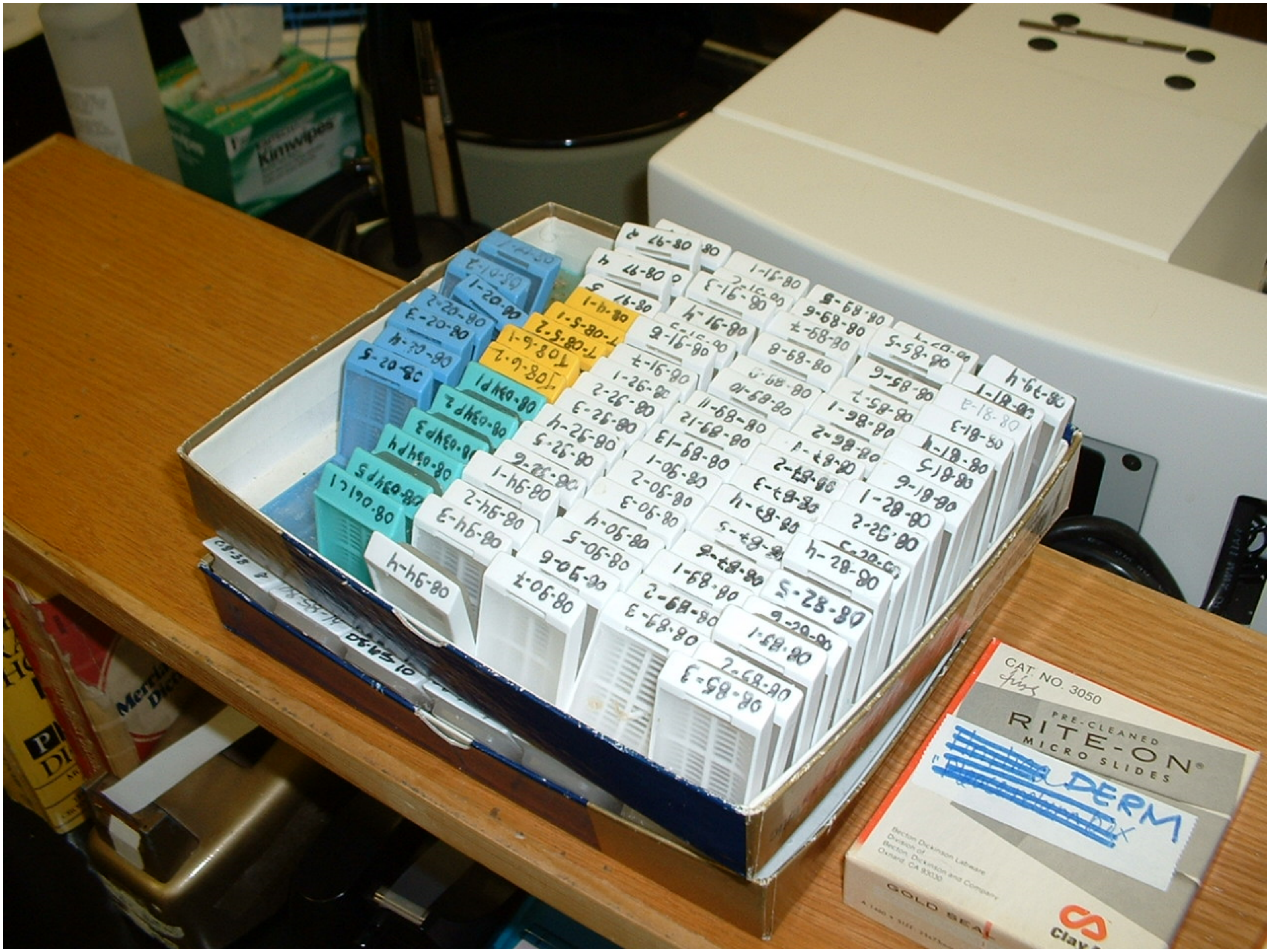
6.S897/HST.S53: Machine Learning for Healthcare

Typical “Gross” Specimen Received in Pathology


Formaldehyde
to fix structure
in place

-95 9
08-95 10

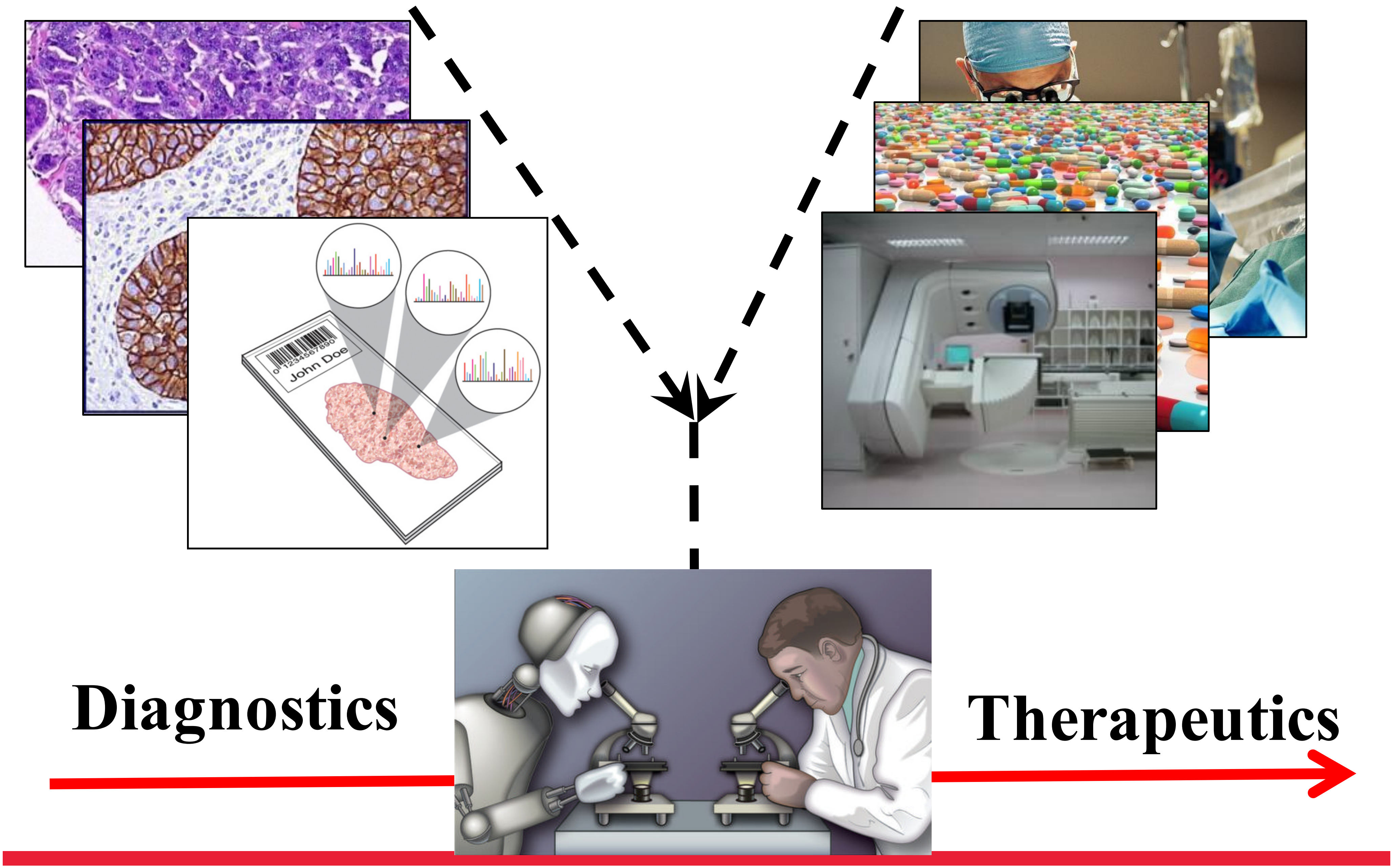

AUTOPSY
1000 ml
IMPORTANT:
RAISE HANDLE FULLY
UPWARD THEN
PUSH DOWN TO LATCH
Clay Stoddard


Kimwipes
CAT. NO. 3050
PRE-CLEANED
RITE-ON
MICRO SLIDES
DERM
GOLD SEAL

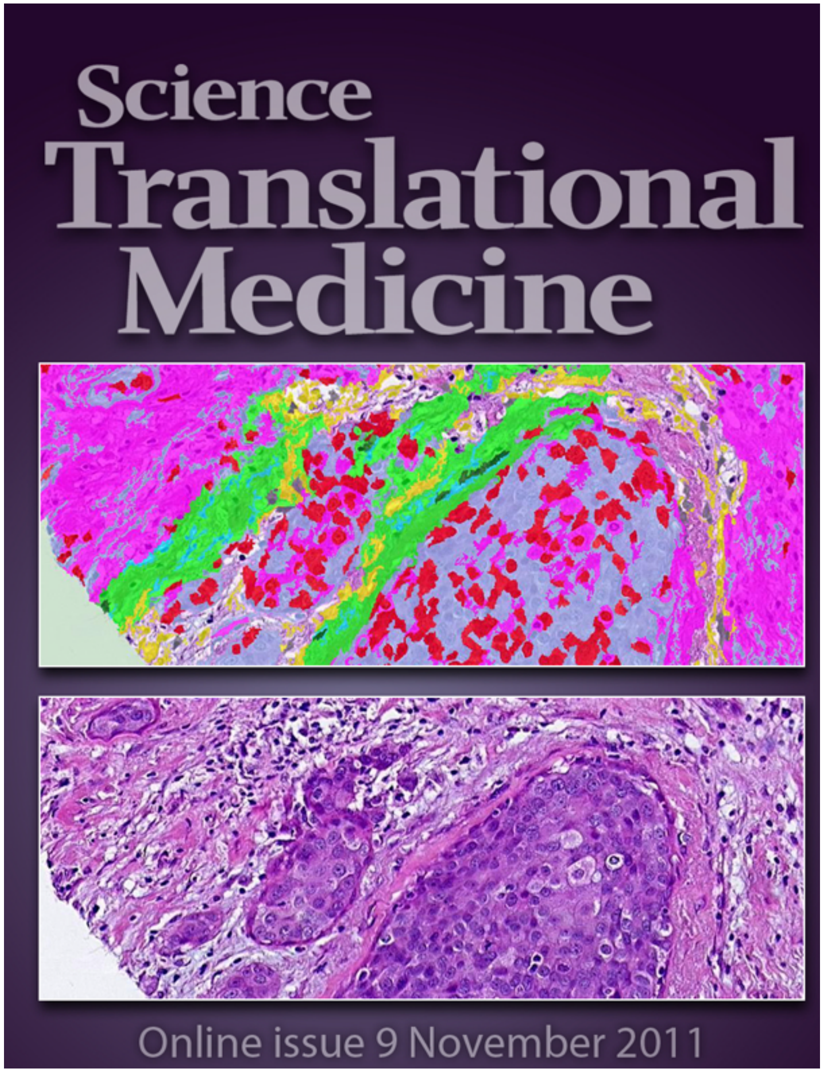

FINESSE
NEXT
CLEAR
RETRACT
RUN
STOP
MODE
MEMORY
AUTO
TRIM SECTION
ROCK
STOP
RUN

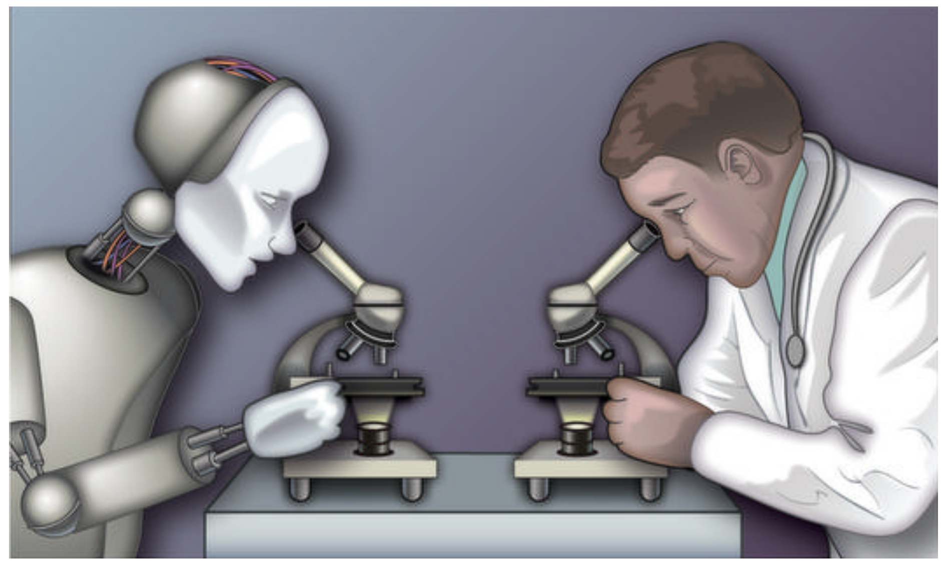
The microscope has remained the most essential tool used by pathologists from the 1900s to the present day

Pathology is critical for precision medicine



Development of a Computational Pathology (C-Path) System (2011)





Joint work with Daphne Koller PhD at Stanford University

THE POSITION OF

HISTOLOGY IN THE PROGNOSIS OF CARCINOMA OF THE BREAST.

BY D. H. PATEY, M.S. LOND., F.R.C.S. ENG.,
SURGICAL REGISTRAR, MIDDLESEX HOSPITAL;

AND

R. W. SCARFF, M.R.C.S. ENG.,
ASSISTANT PATHOLOGIST, BLAND-SUTTON INSTITUTE OF PATHOLOGY, MIDDLESEX HOSPITAL.

[APRIL 21, 1928 801
THE LANCET,]

Methods for Building Prognostic Model

Signs of Prognostic Value.

The present study was undertaken in an attempt to ascertain if there is any correlation between the histological appearance of the growth and the subsequent course of the disease, and to determine the value of such an analysis in giving a prognosis in an individual case when all the ascertainable factors have been taken into account.

largely followed, but chief importance has been attached to three factors—tubule formation, inequality in size of nuclei, and hyperchromatism.

Standardized Semi-Quantitative Elston-Ellis Grading Scheme (1991)

Table 1. Summary of semiquantitative method for assessing histological grade in breast carcinoma

Feature	Score
Tubule formation	
Majority of tumour (>75%)	1
Moderate degree (10–75%)	2
Little or none (<10%)	3
Nuclear pleomorphism	
Small, regular uniform cells	1
Moderate increase in size and variability	2
Marked variation	3
Mitotic counts	
Dependent on microscope field area (see Table 2)	1–3

3–5 points: grade I —well-differentiated

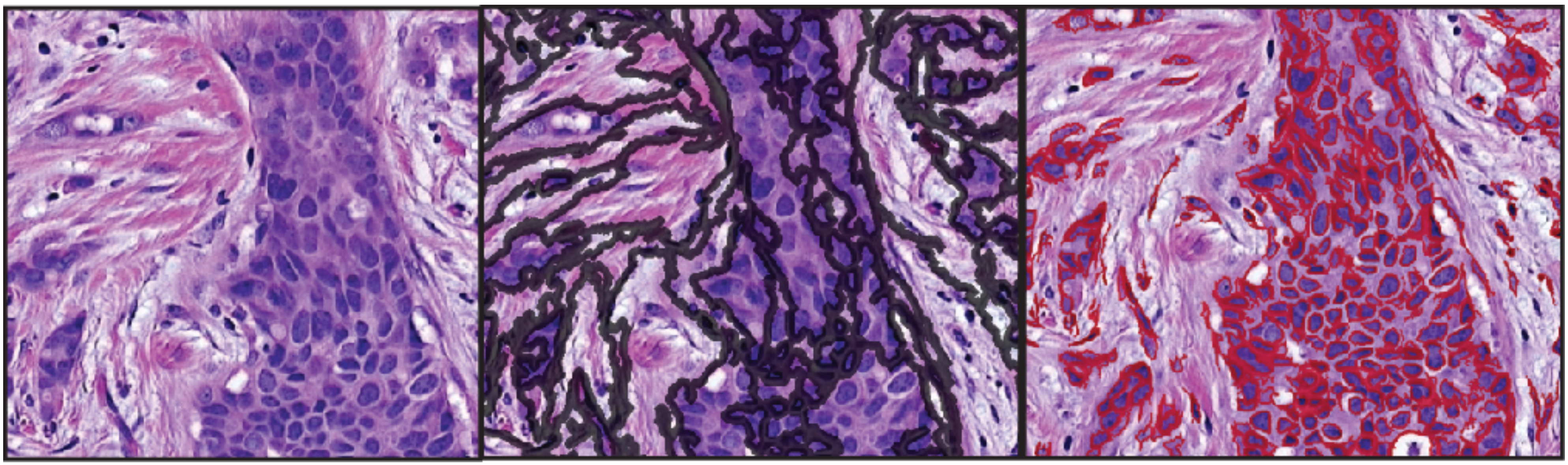
6–7 points: grade II —moderately differentiated

8–9 points: grade III—poorly differentiated

Problems with qualitative visual microscopic analysis for breast cancer grading

- Significant inter-observer variability
- Doesn't fully capture rich biology encoded in images
- Not well-suited to evolving landscape of biomedical research

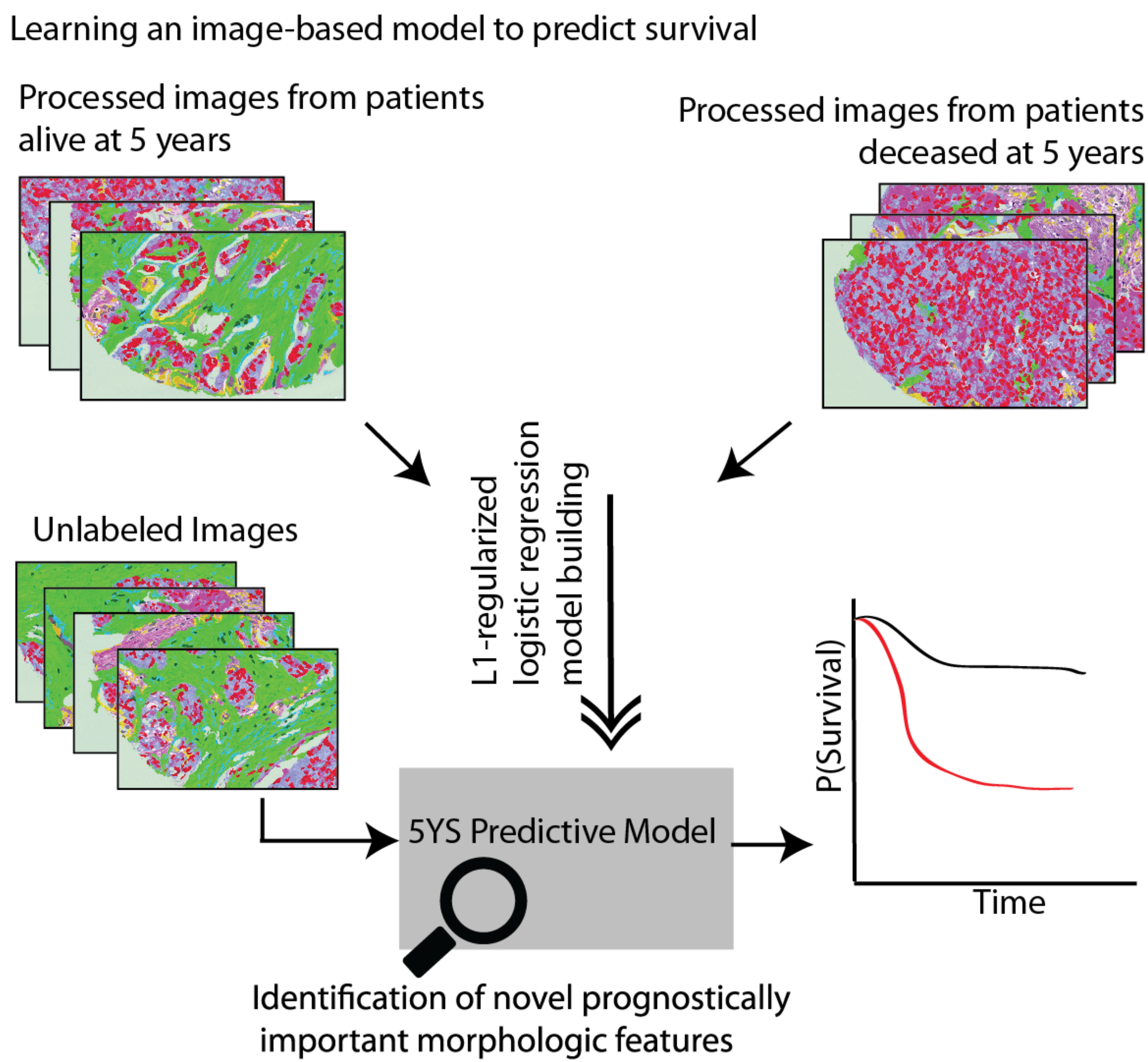
Basic image processing and feature construction



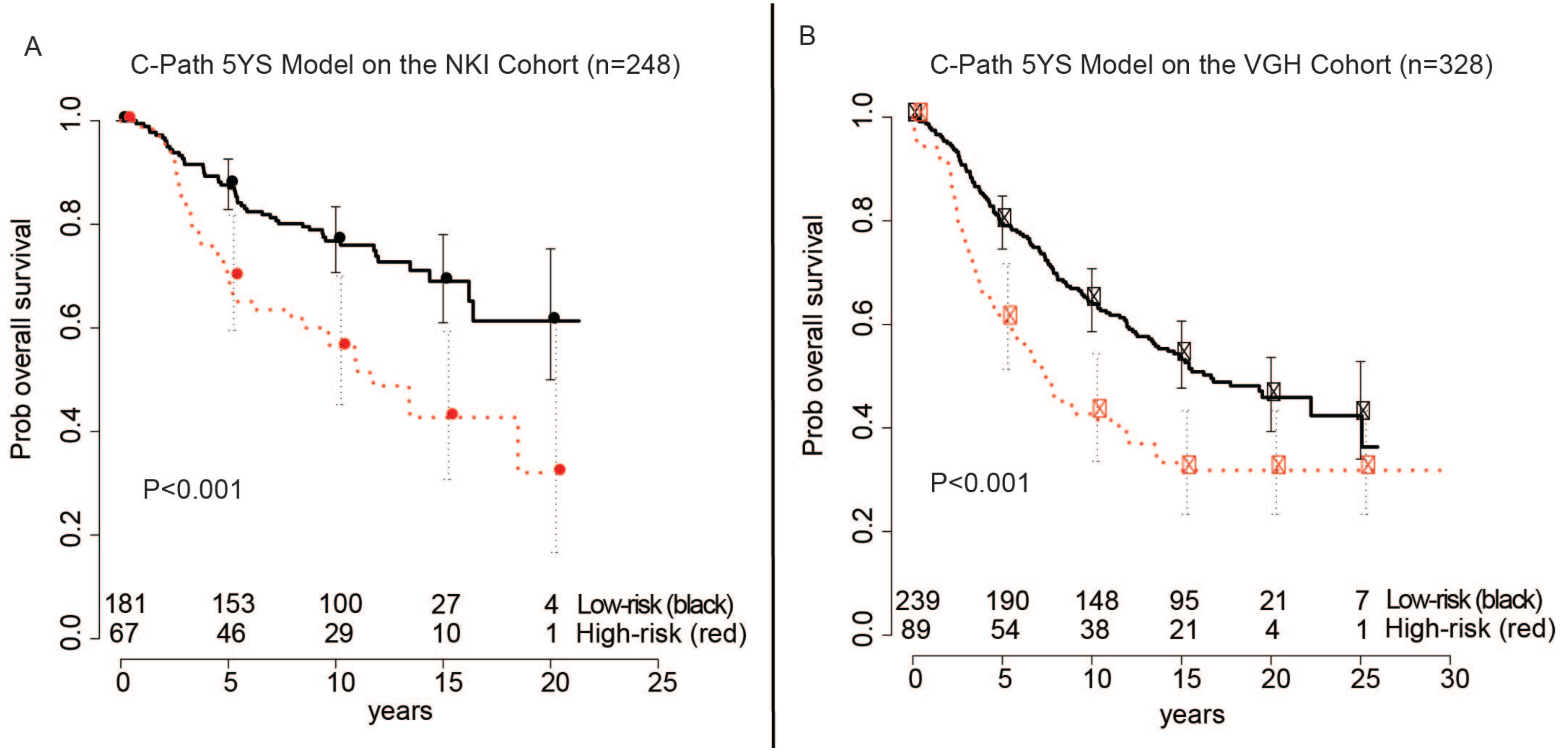
H&E Image

Image partitioned into superpixels

Nuclear objects identified within each superpixel

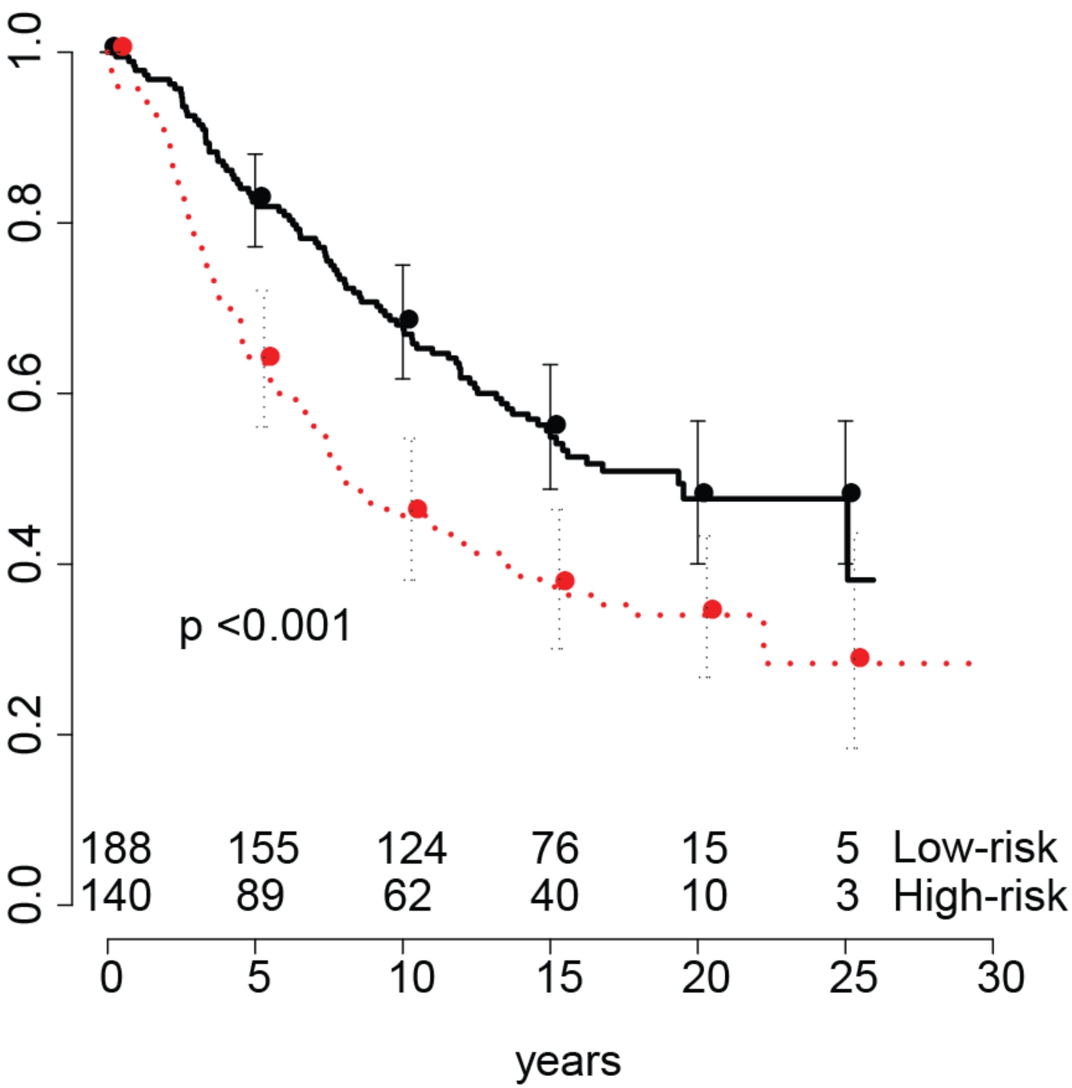

Learning an image-based model to predict survival
Processed images from patients alive at 5 years
Processed images from patients deceased at 5 years
L1-regularized logistic regression model building
Unlabeled Images
5YS Predictive Model
P(Survival)
Time
Identification of novel prognostically important morphologic features

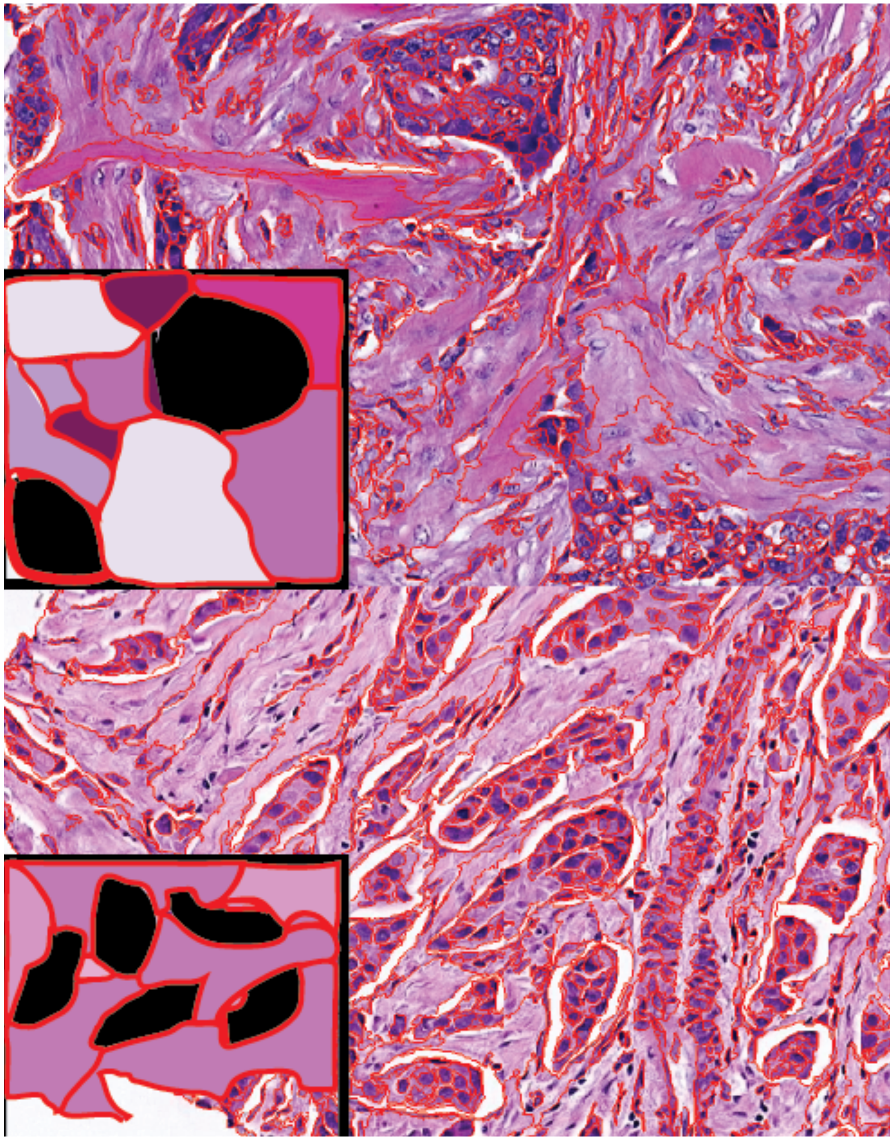
C-Path 5YS Score Significantly Associated with Overall Survival



Sci Transl Med. 2011 Nov 9;3(108):108ra113.

Data-driven discovery of prognostic stromal phenotypes





Training more effective systems requires more labeled data

- Obtaining within image annotations from pathologists is difficult

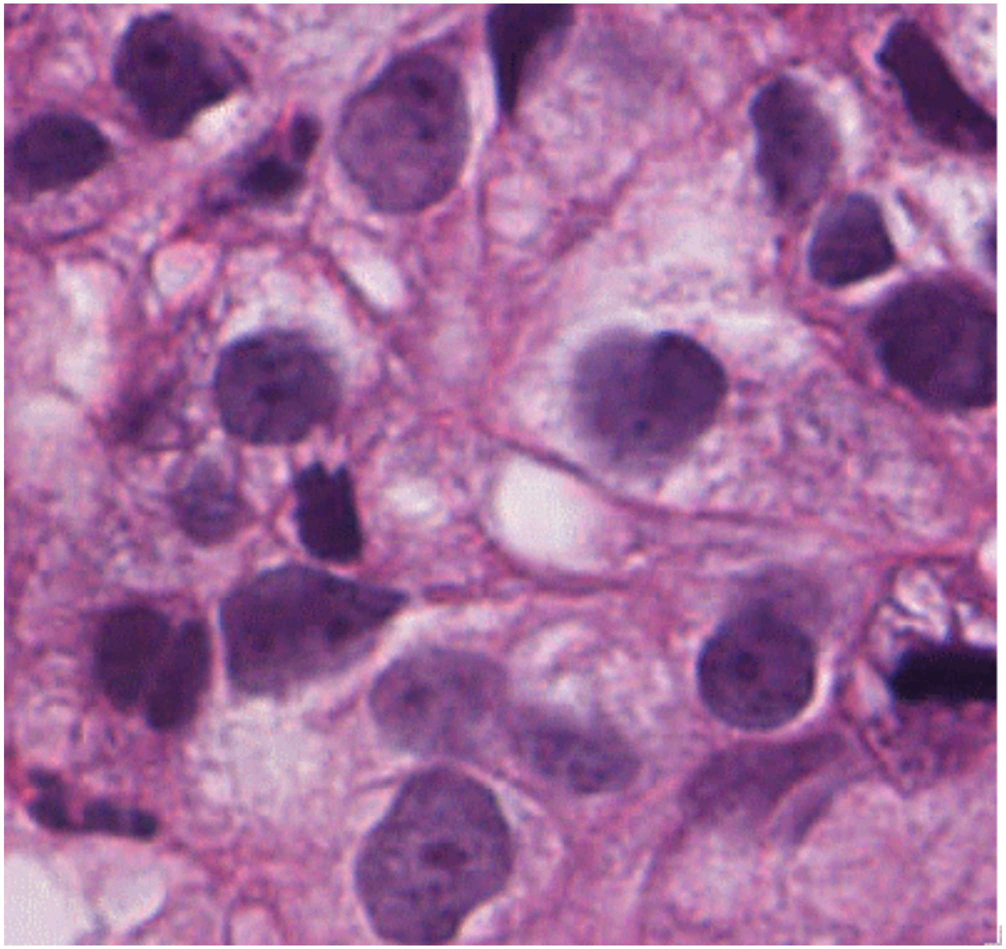
- No large-scale annotated pathology datasets exist for machine learning algorithm development and evaluation

Most pathologists do not enjoy labeling images

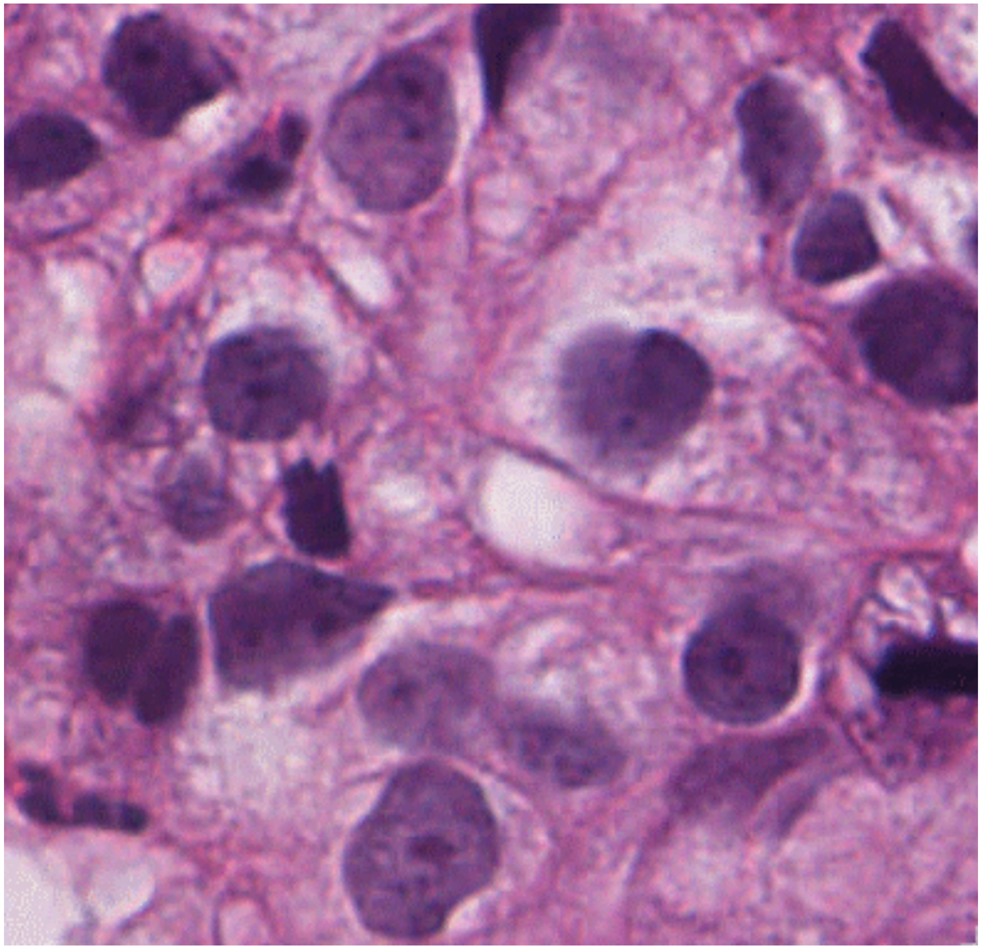
Some people may enjoy it

Crowdsourcing Micro-Tasks in Computational Pathology

Nuclei Detection



Nuclei Segmentation

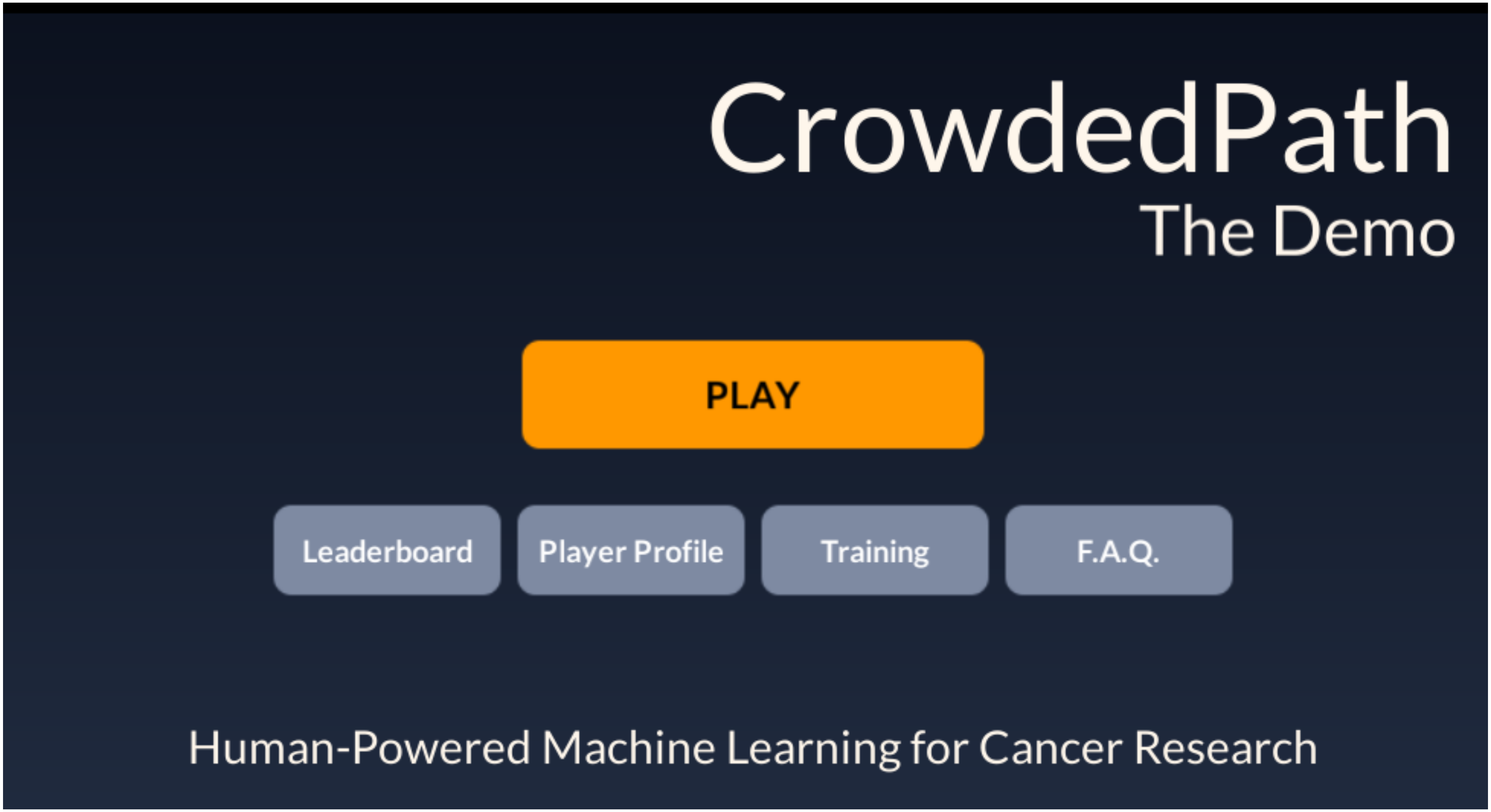


Project led by: Humayun Irshad PhD. Harvard Medical School and BIDMC

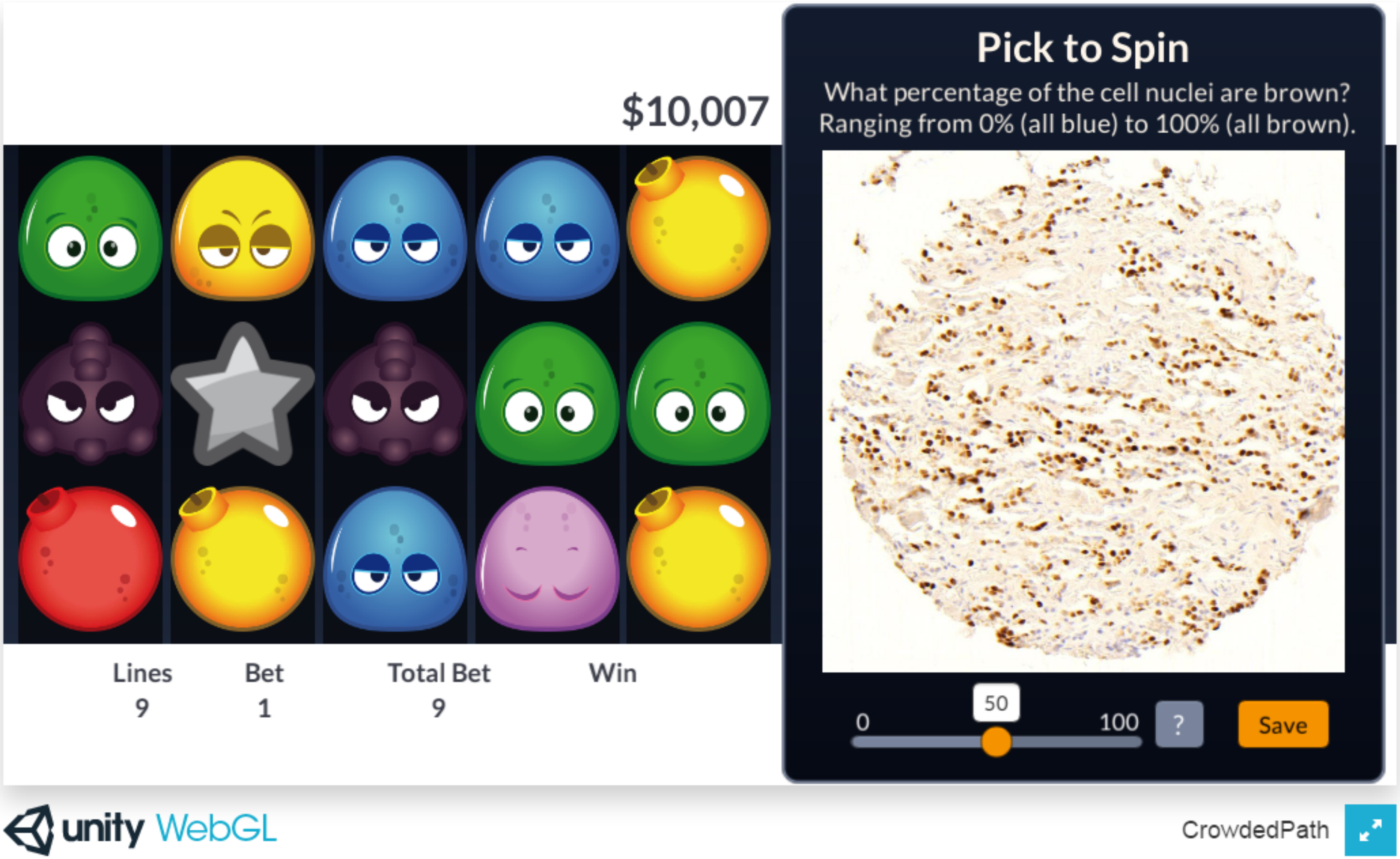
Human labelers produce annotations to train and evaluate computational algorithms

Nucleus Detection **Nucleus Segmentation**

Irshad et al. *Pac Symp Biocomput. 2015;20:294-305. Irshad et al. Scientific Reports (2017, In Press)*


CrowdedPath
The Demo
PLAY
Leaderboard
Player Profile
Training
F.A.Q.
Human-Powered Machine Learning for Cancer Research

The CrowdedPath slots

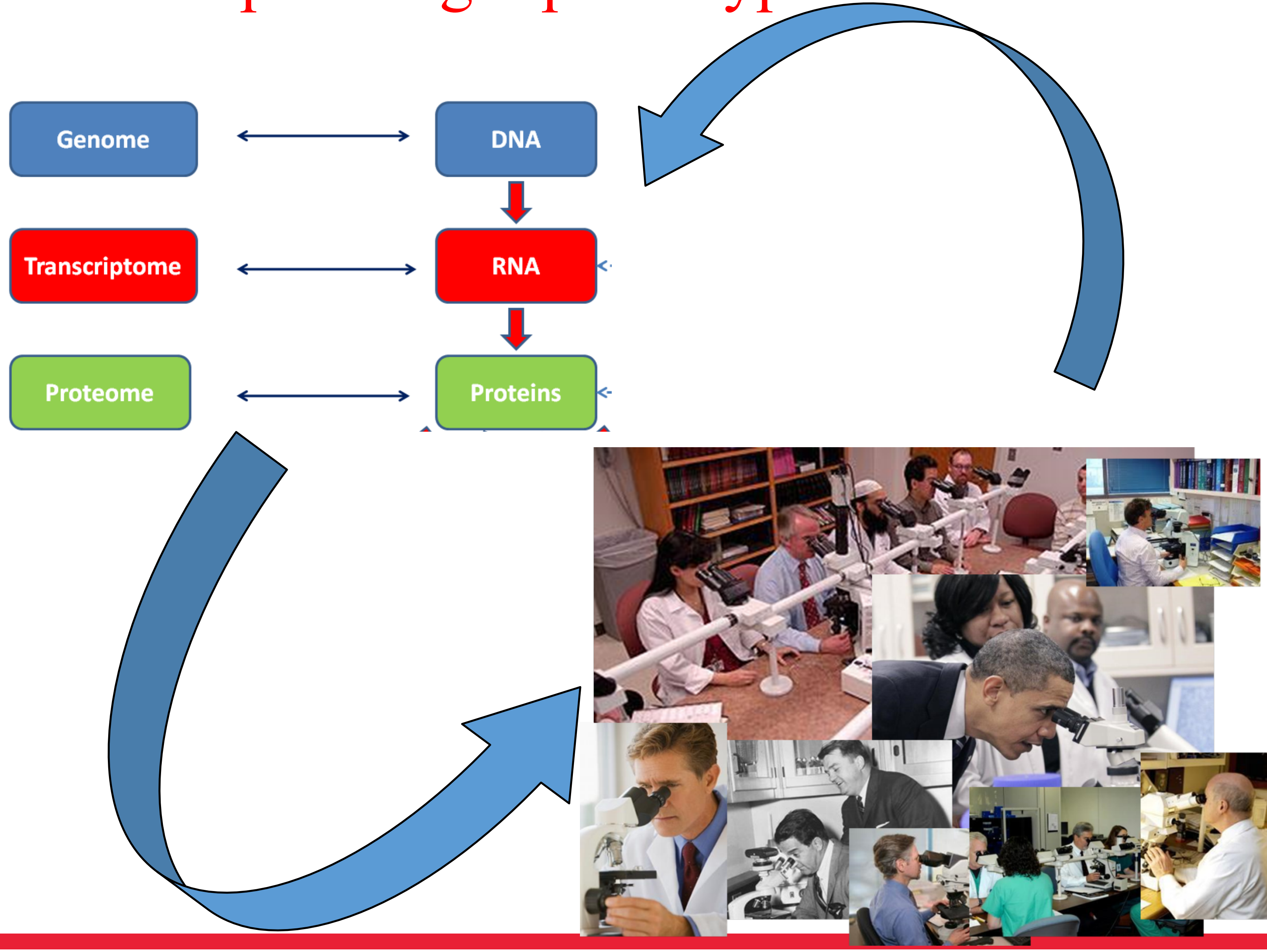


Crowdsourcing for computational pathology

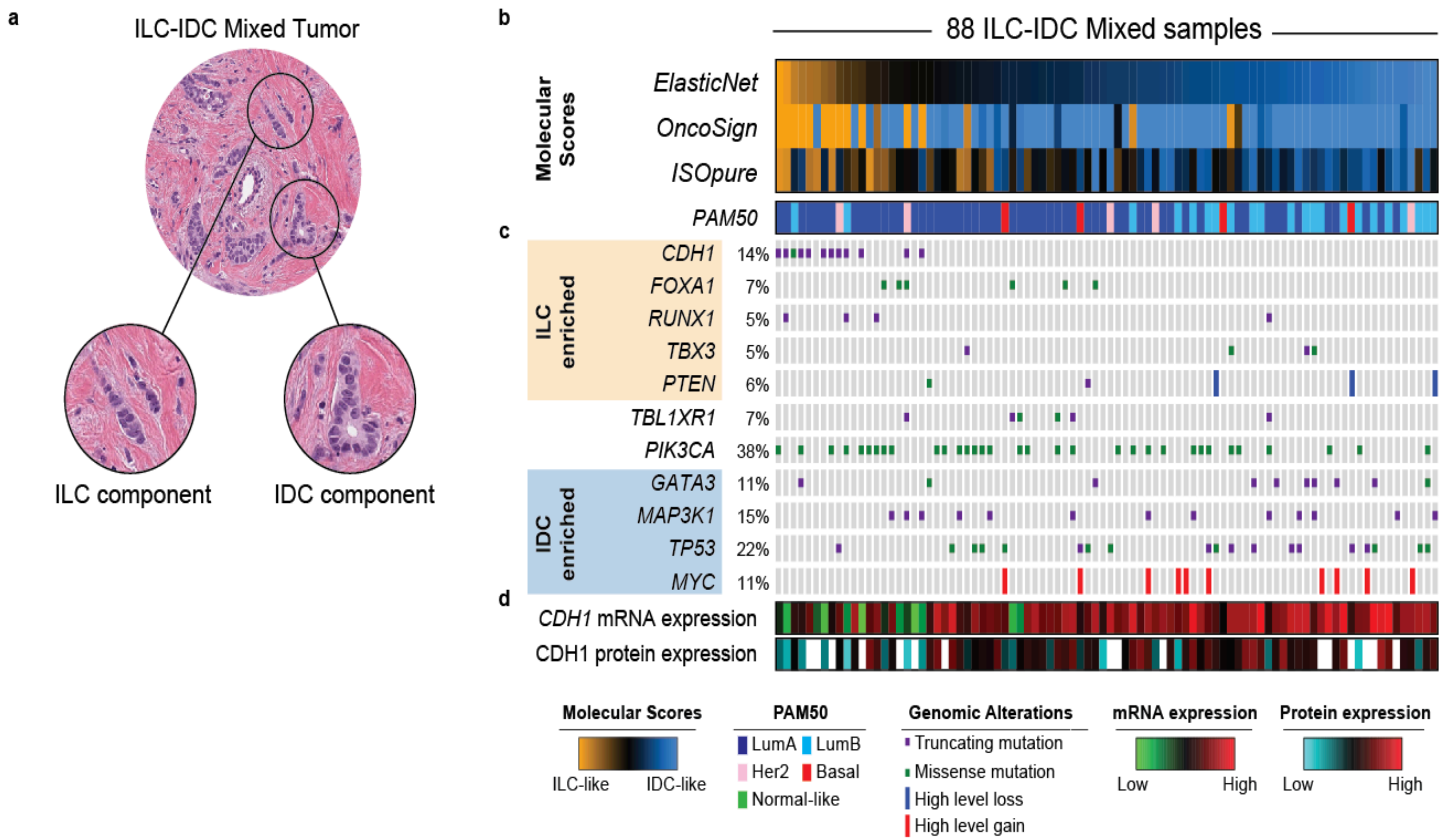
- Crowdsourcing and gamification are new approaches for generating large-scale annotated data sets for computational pathology

- Massive hand-annotated data should fuel the development of improved computational pathology tools

Computational Pathology to link Omics data with pathologic phenotypes

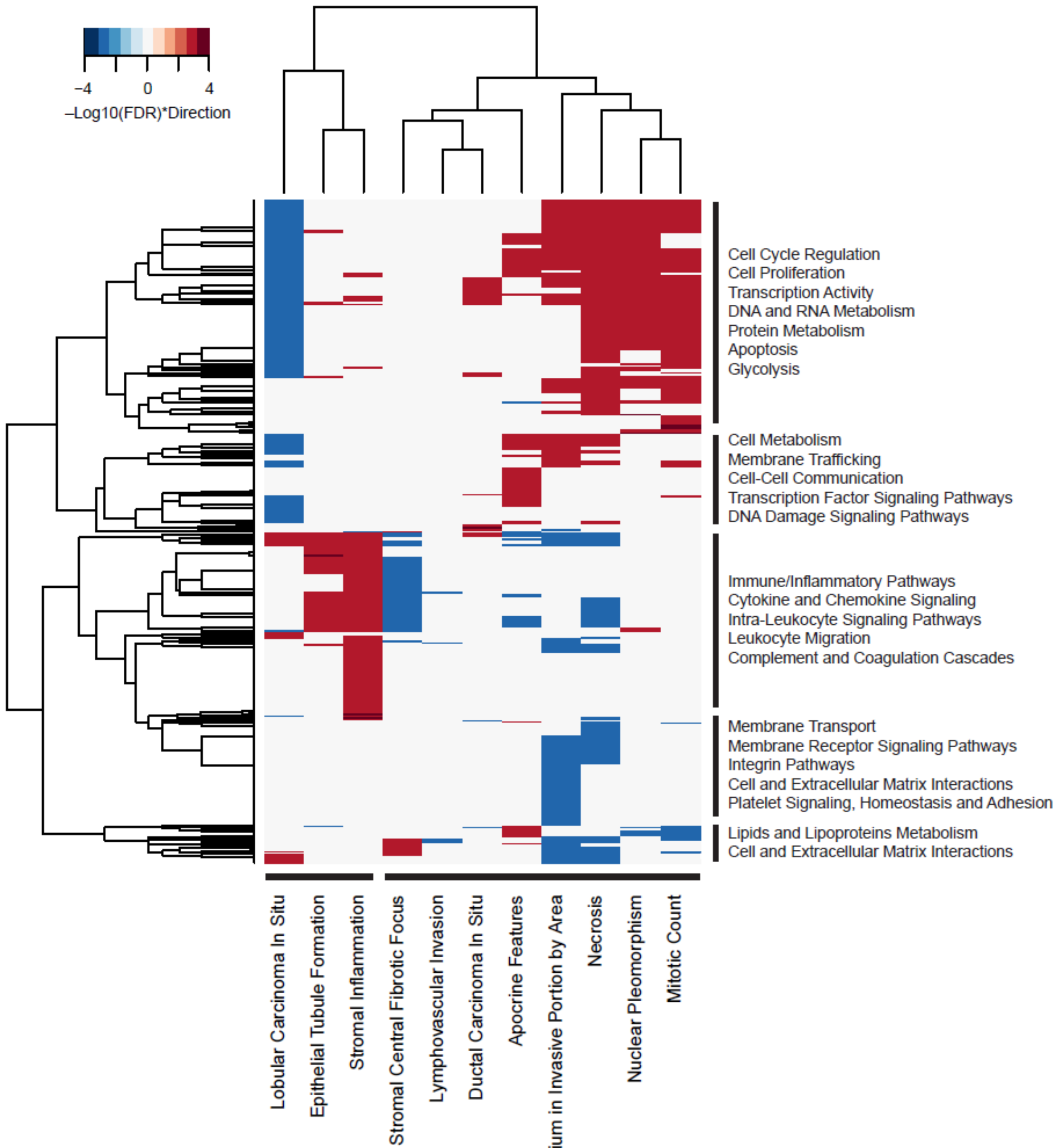


Comprehensive molecular portraits of invasive lobular breast cancer



Ciriello et al. *Cell 2015*

Comprehensive molecular portraits of 11 major pathologic phenotypes



Morpho-molecular analysis identifies novel prognostic signatures

	Coefficient (b)	Standard Error SE(b)	p-value	Hazard Ratio (e^b)	95% Confidence Interval for Hazard Ratio	
					Lower	Upper
Age at Initial Pathologic Diagnosis	**0.039**	**0.004**	**2.20E-16**	**1.040**	**1.031**	**1.048**
Tumor Size	**0.144**	**0.022**	**1.04E-10**	**1.155**	**1.105**	**1.206**
Metastasis (to Regional Lymph Nodes)	**0.437**	**0.084**	**2.23E-07**	**1.548**	**1.312**	**1.827**
Nuclear Pleomorphism Signature	**0.452**	**0.193**	**1.93E-02**	**1.572**	**1.076**	**2.297**
Epithelial Tubule Formation Signature	**0.291**	**0.131**	**2.66E-02**	**1.337**	**1.034**	**1.729**
Her2-Enriched	0.508	0.276	6.57E-02	1.662	0.968	2.854
Necrosis Signature	-0.233	0.136	8.73E-02	0.792	0.607	1.035
Luminal B	0.331	0.254	1.94E-01	1.392	0.845	2.292
Histologic Grade	-0.144	0.145	3.22E-01	0.866	0.651	1.151
OncotypeDx	0.111	0.129	3.92E-01	1.117	0.867	1.440
MammaPrint	-0.072	0.120	5.49E-01	0.930	0.735	1.178
Mitotic Count Signature	-0.076	0.181	6.75E-01	0.927	0.650	1.322
Histologic Grade (METABRIC)	0.029	0.073	6.87E-01	1.030	0.893	1.187
Luminal A	0.096	0.269	7.21E-01	1.101	0.650	1.866
Genome Grade Index	0.030	0.132	8.19E-01	1.031	0.796	1.334

Integrated morpho-molecular data enables discovery of novel molecular signatures

- Morpho-molecular approach enables the construction of non-redundant signatures that independently contribute to a prognostic model

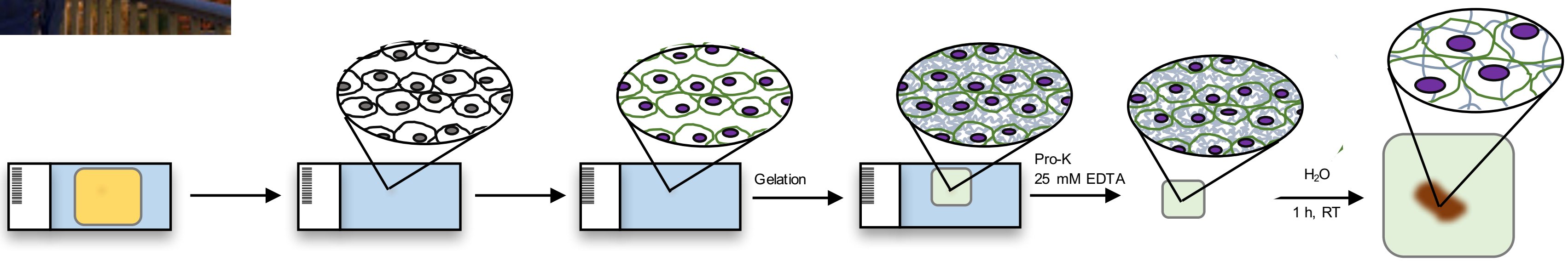
- Web resource at:

www.pathology.ai/tcga_breast

Jan Heng PhD. Harvard Medical School

Heng, TCGA Pathology Committee, Beck. (2016) Journal of Pathology

Expansion Pathology to Generate Massive Morpho-Molecular Data from Tiny Specimens

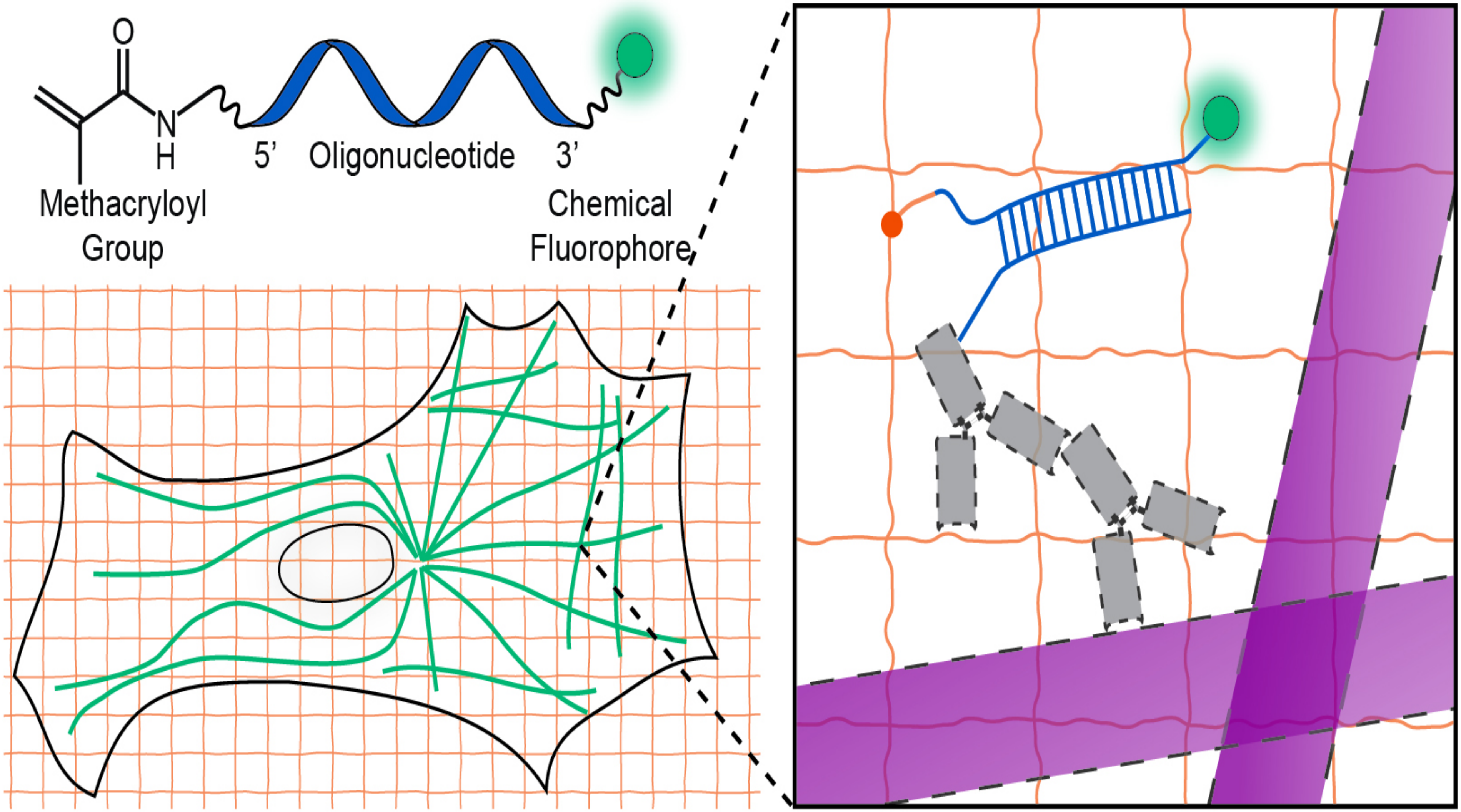


Joint work with Ed Boyden, Yongxin Zhao, Octavian Bucur (2017, *in revision*)

Expansion Microscopy (ExM)

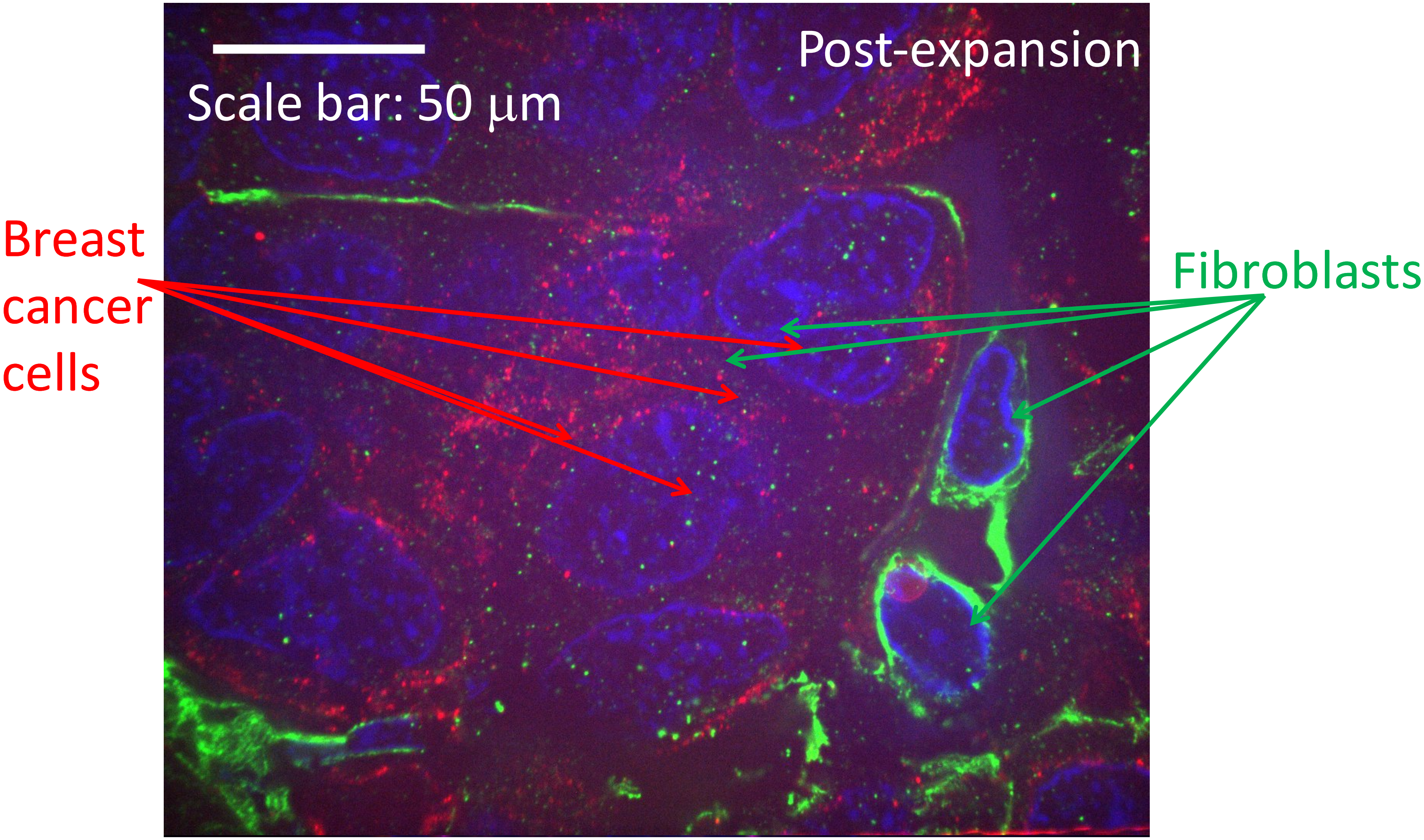
Applications in Diagnostic pathology?

Expansion Microscopy (ExM)



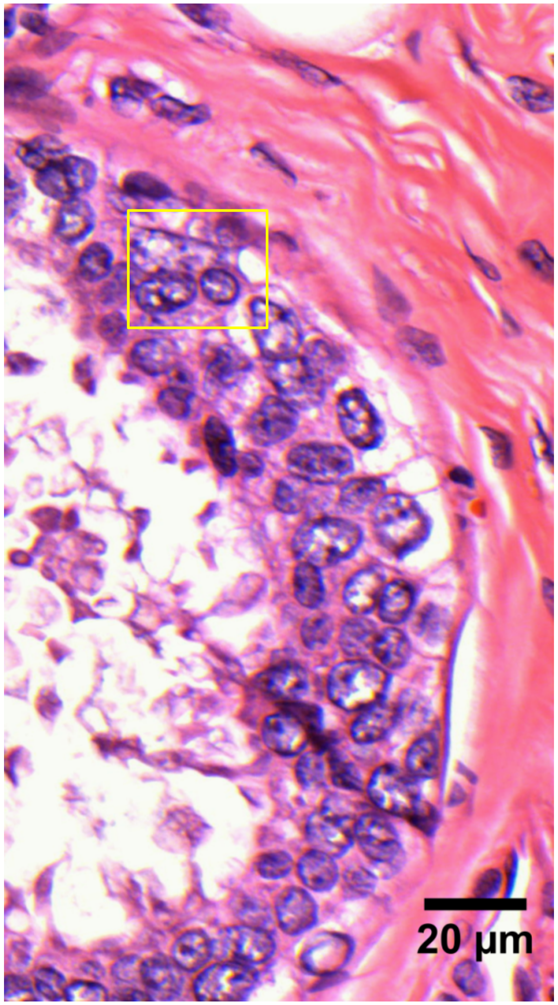
Chen, Tillberg, Boyden (2015) *Science* 347(6221):543-548. http://expansionmicroscopy.org

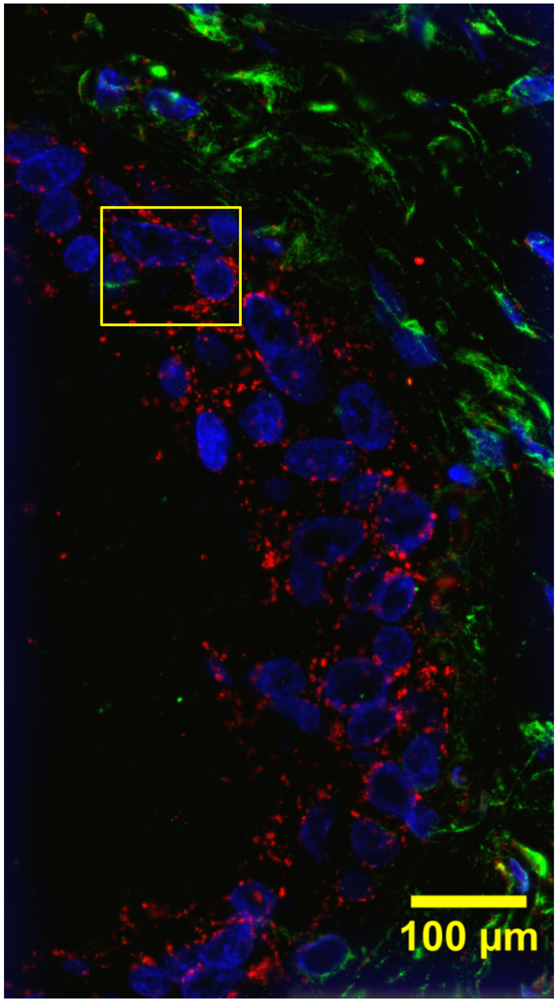
Expansion pathology of breast cancer



Nuclei-Epithelium-Stroma-Stroma

Expansion pathology performed on a pre-invasive breast lesion

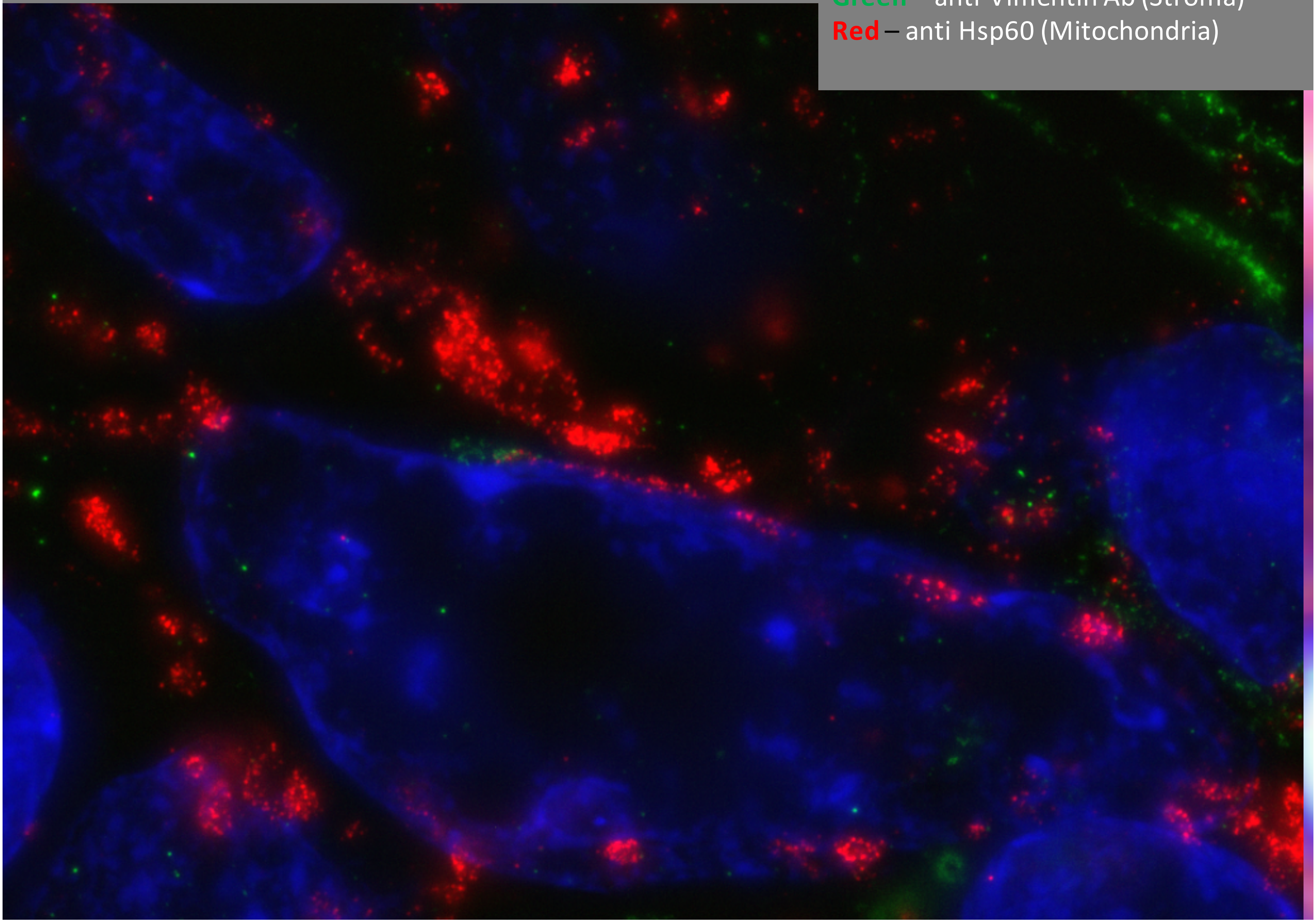


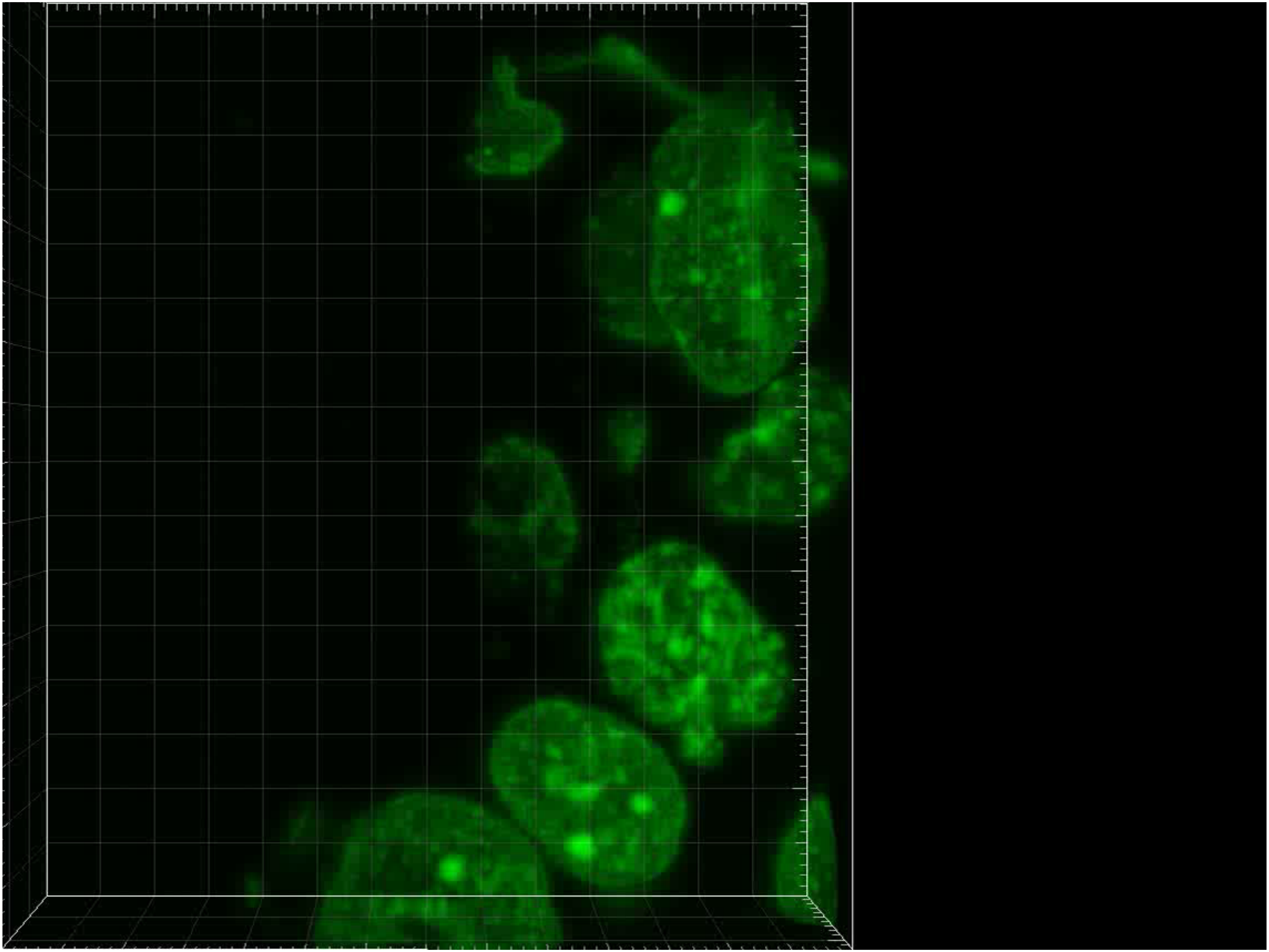


Blue –Dapi
Green – Vimentin
Red – anti Hsp60

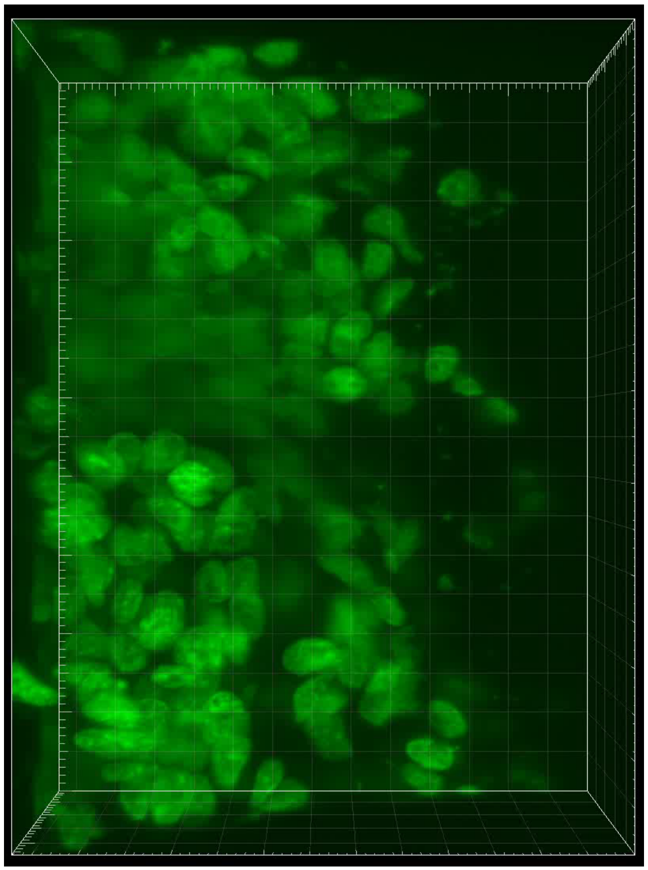
Post-expansion

Blue – nuclei with Dapi
Green – anti-Vimentin Ab (Stroma)
Red – anti Hsp60 (Mitochondria)

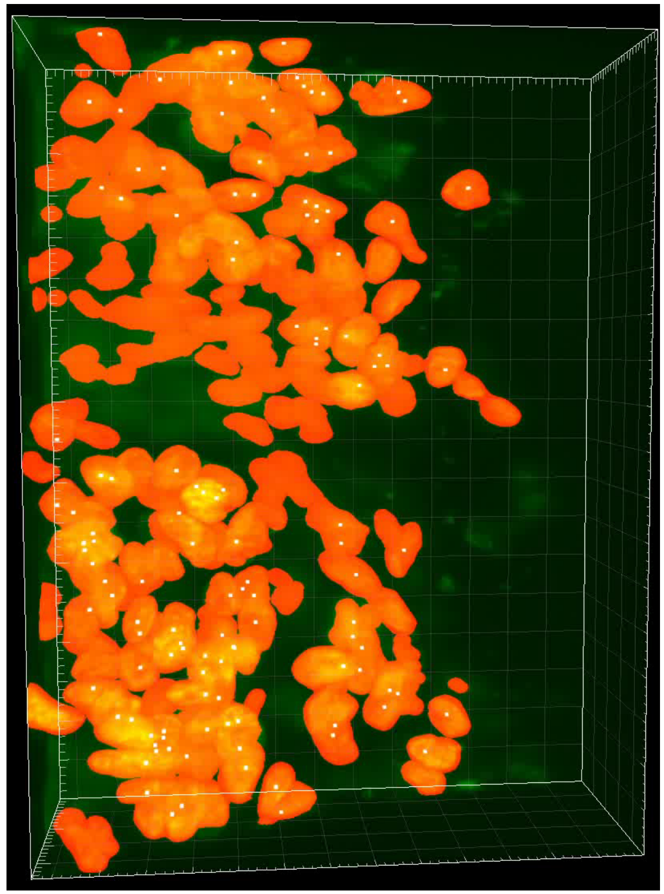




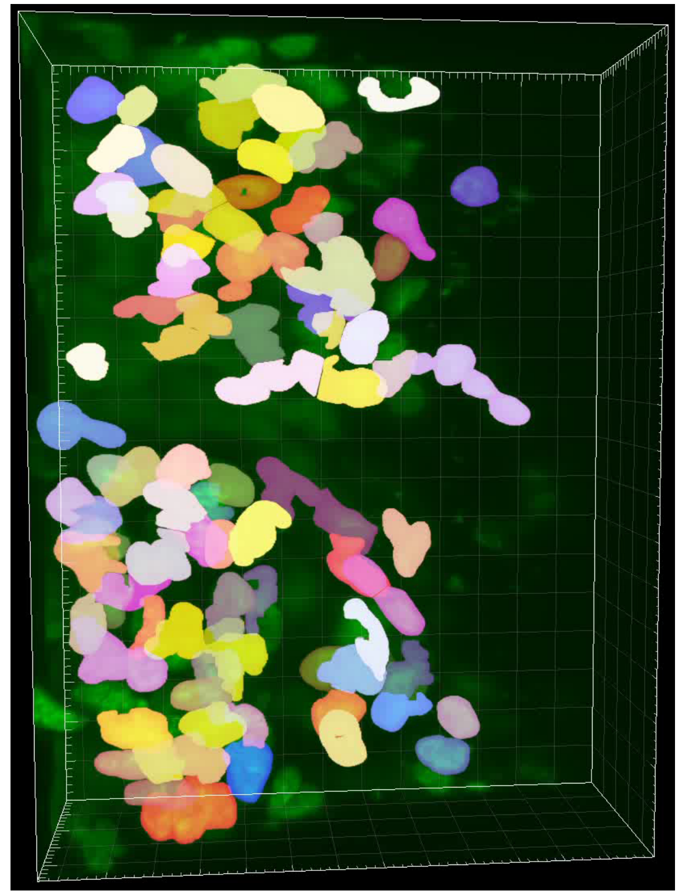
3D Expansion Pathology –Nuclear Detection and Segmentation



Lightsheet Microscopy

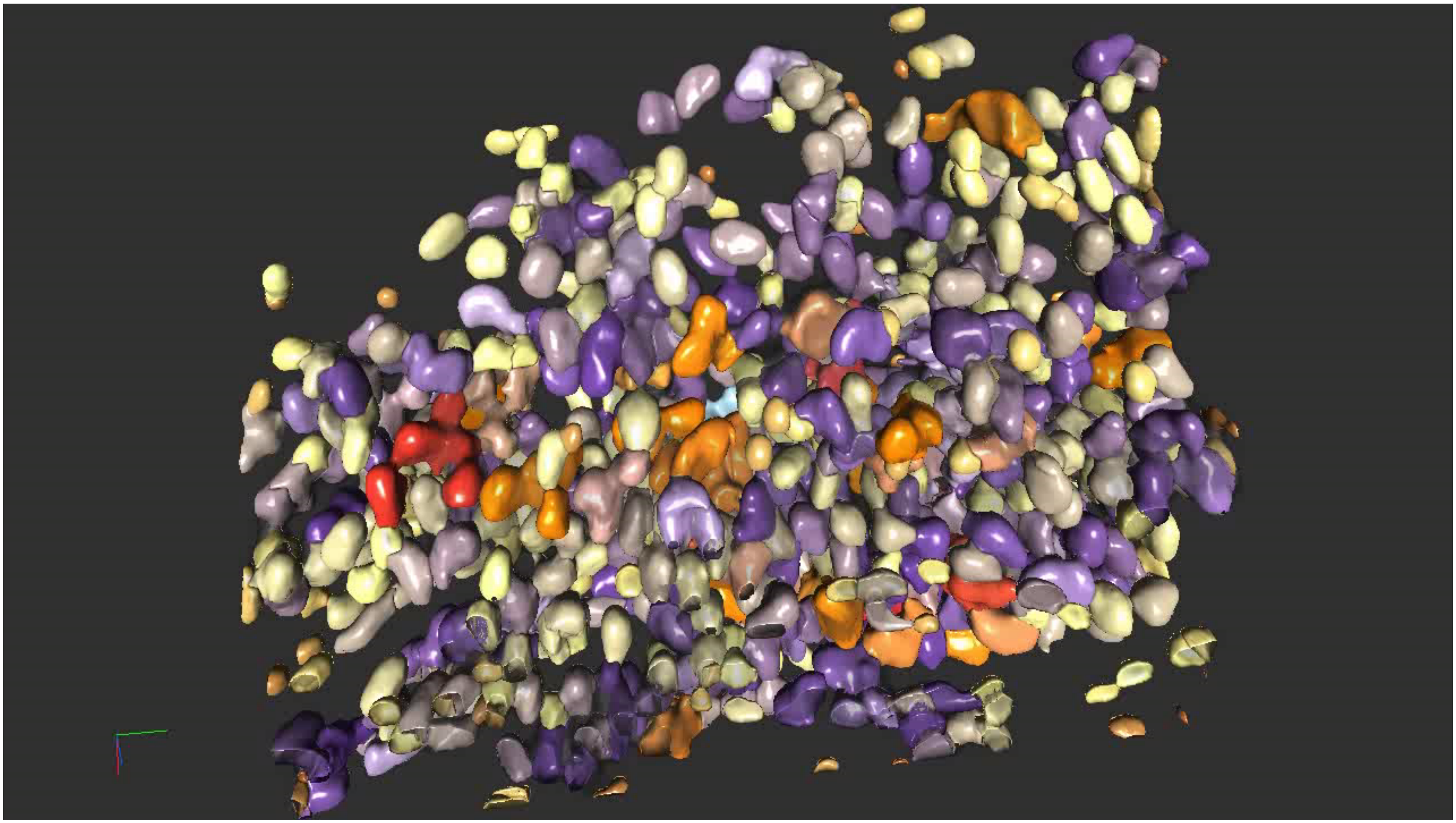


Foreground and nuclear seed-point detection

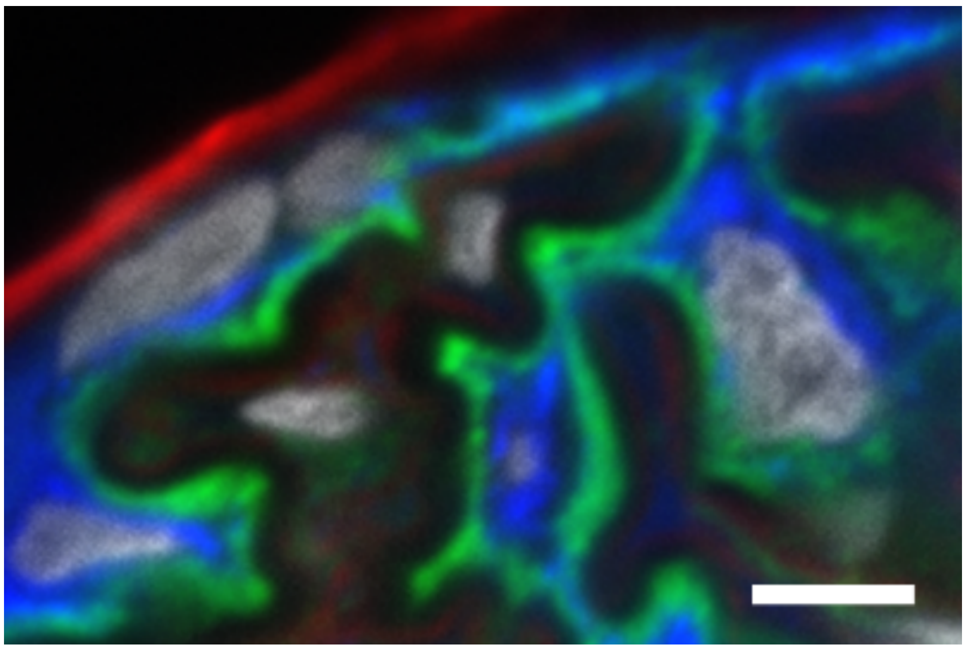


3D Nuclear Segmentation

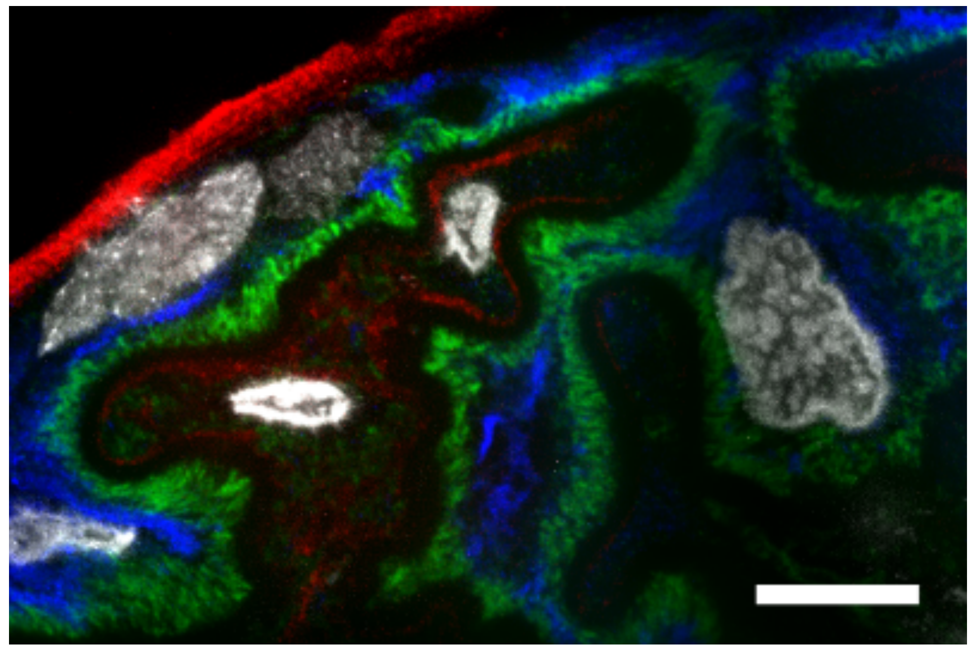
3D Nuclear Classification



Expansion pathology enables visualization of renal podocytes



Pre-expansion

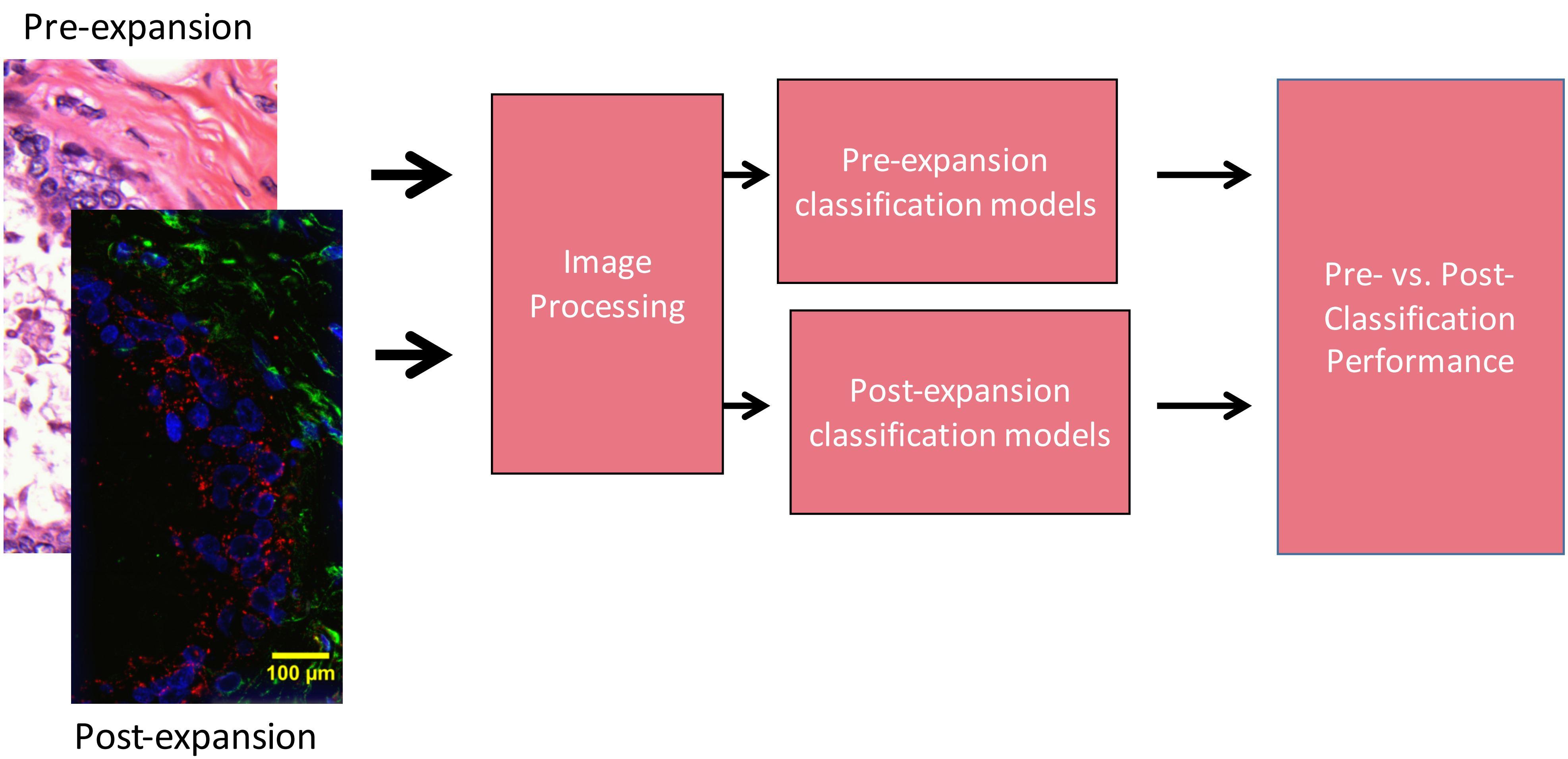


Post-expansion

Red = Collagen IV
Blue = Vimentin (Primary and Secondary foot processes)
Green = Tertiary foot processes

Joint work with Astrid Weins MD PhD

Does expansion improve computational pathology classifiers?



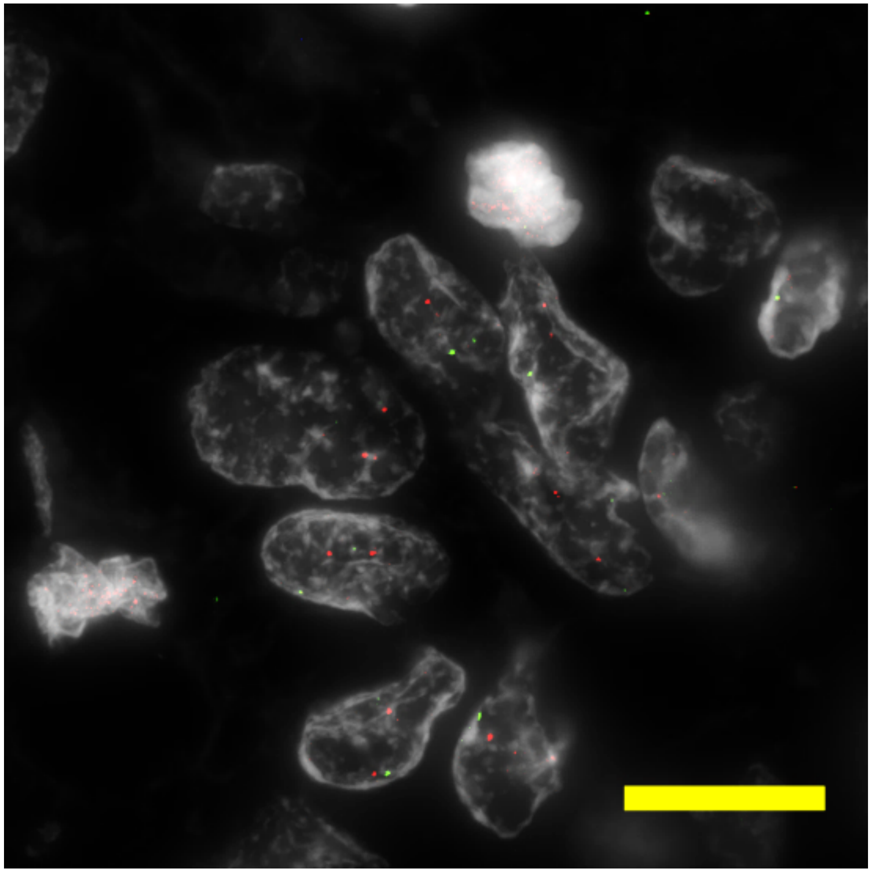
Expansion Pathology Produces More Accurate Classification Models

	Pre-Exp	Exp-Path
Normal vs Usual Ductal Hyperplasia	0.89	**0.94**
Normal vs Atypical Ductal Hyperplasia	0.89	**1**
Normal vs Ductal Carcinoma in Situ	0.74	**0.81**
Usual Ductal Hyperplasia vs Atypical Ductal Hyperplasia	0.75	**0.94**
Usual Ductal Hyperplasia vs Ductal Carcinoma in Situ	0.71	**0.75**
Atypical Ductal Hyperplasia vs Ductal Carcinoma in Situ	0.75	**0.86**

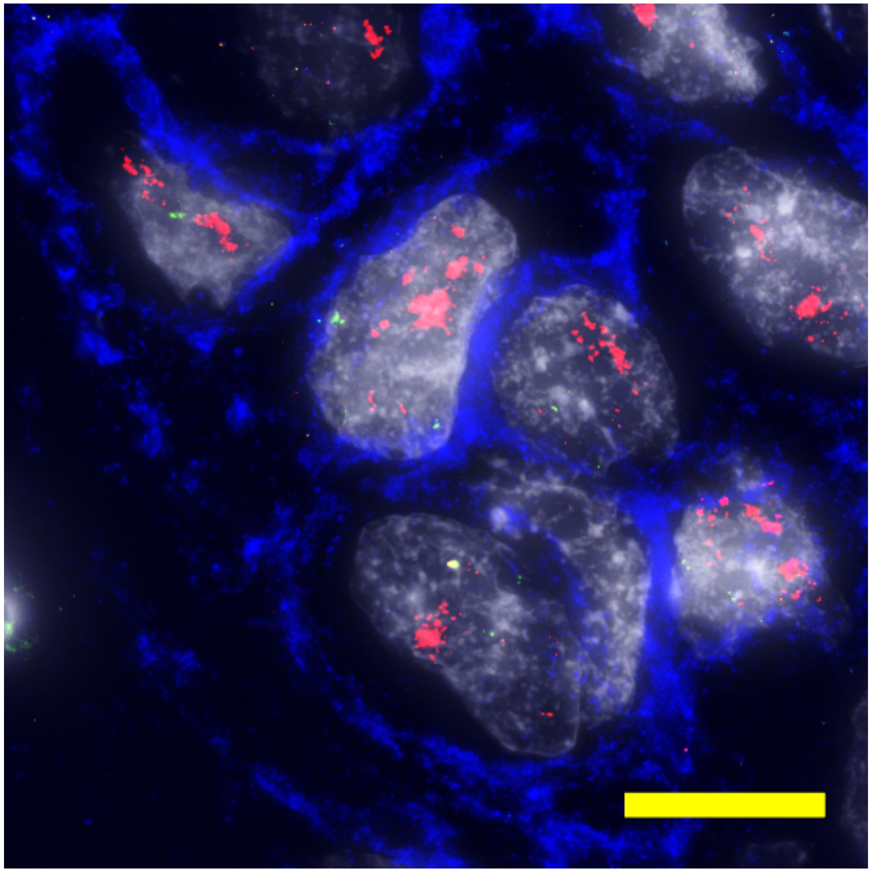
Area under the Receiver Operator Curve in Cross-Validation of L1-Regularized Logistic Regression Classifier

Expansion Pathology with DNA-FISH and Protein-IF

Negative for HER2 Amplification



HER2 Amplified

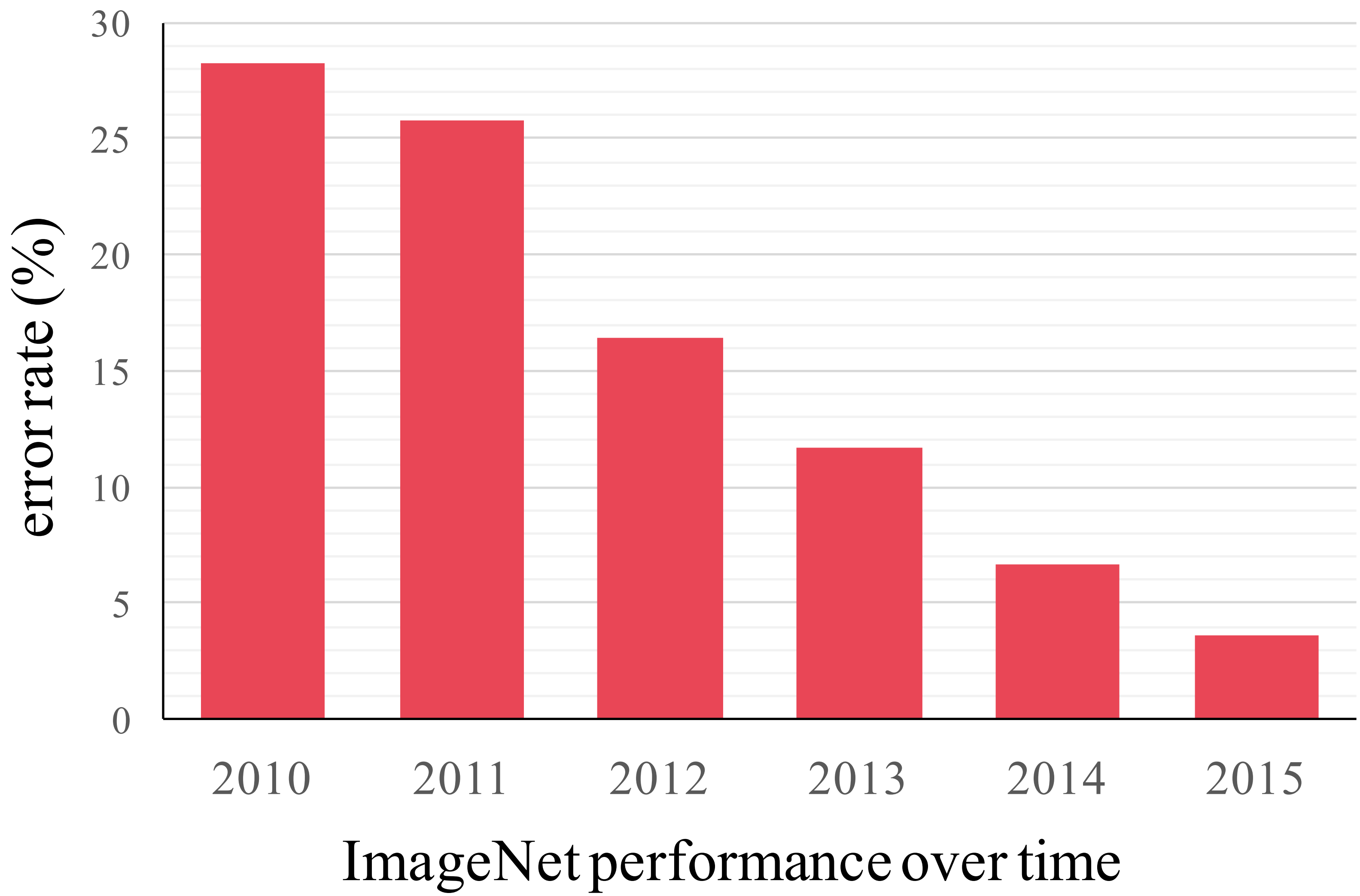


Blue = HER2 Protein
Red = HER2 Amplicon
Green = Centromeric probe

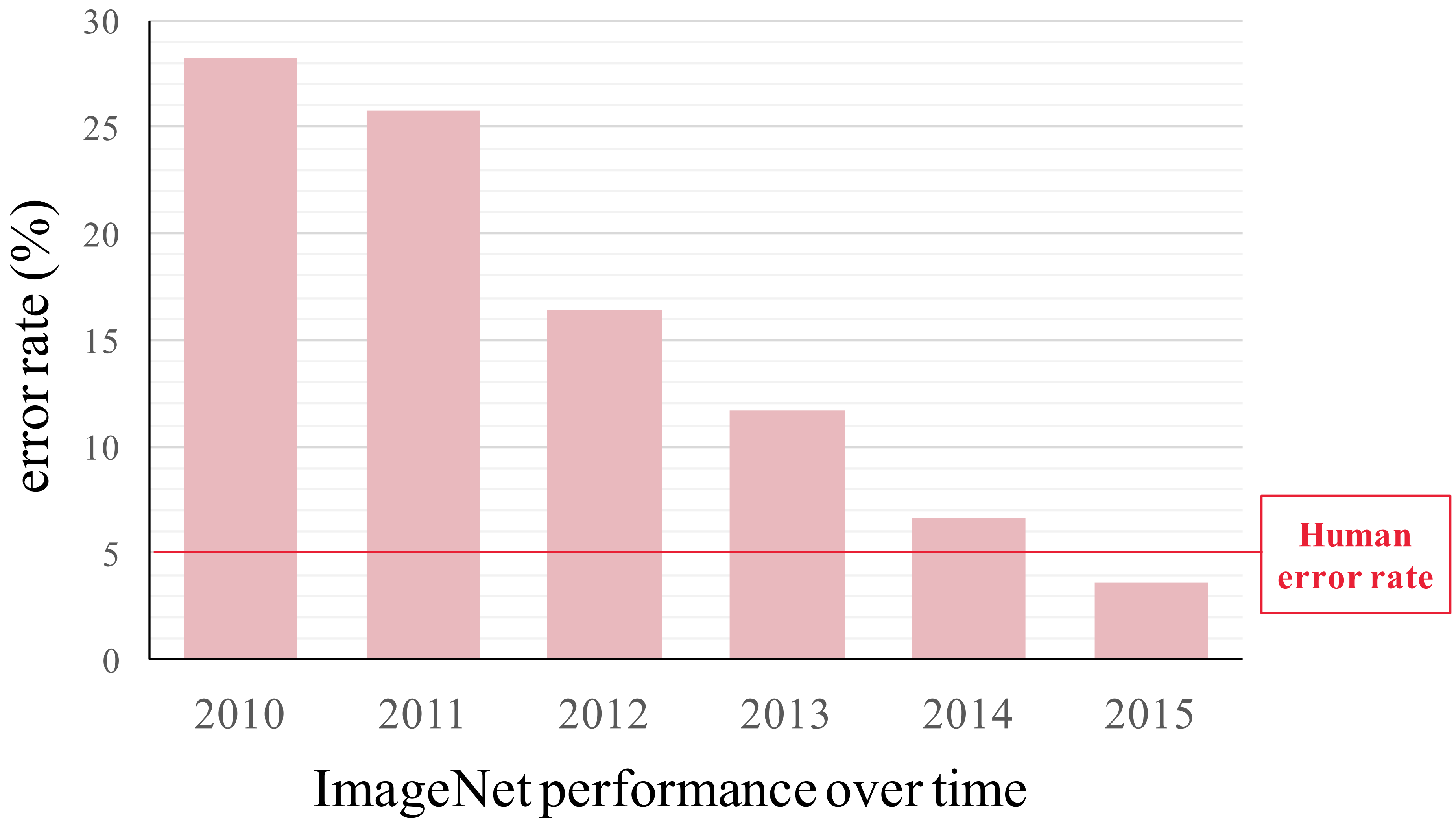
Expansion Pathology

- New approach for physically expanding pathology specimens
- Very high resolution analysis of morphology
- Multiplexed in situ molecular assays with very little autofluorescence
- Generates extremely large and complex morpho-molecular pathology data from tiny biopsy specimens

Deep learning is the solution



Deep learning is the solution



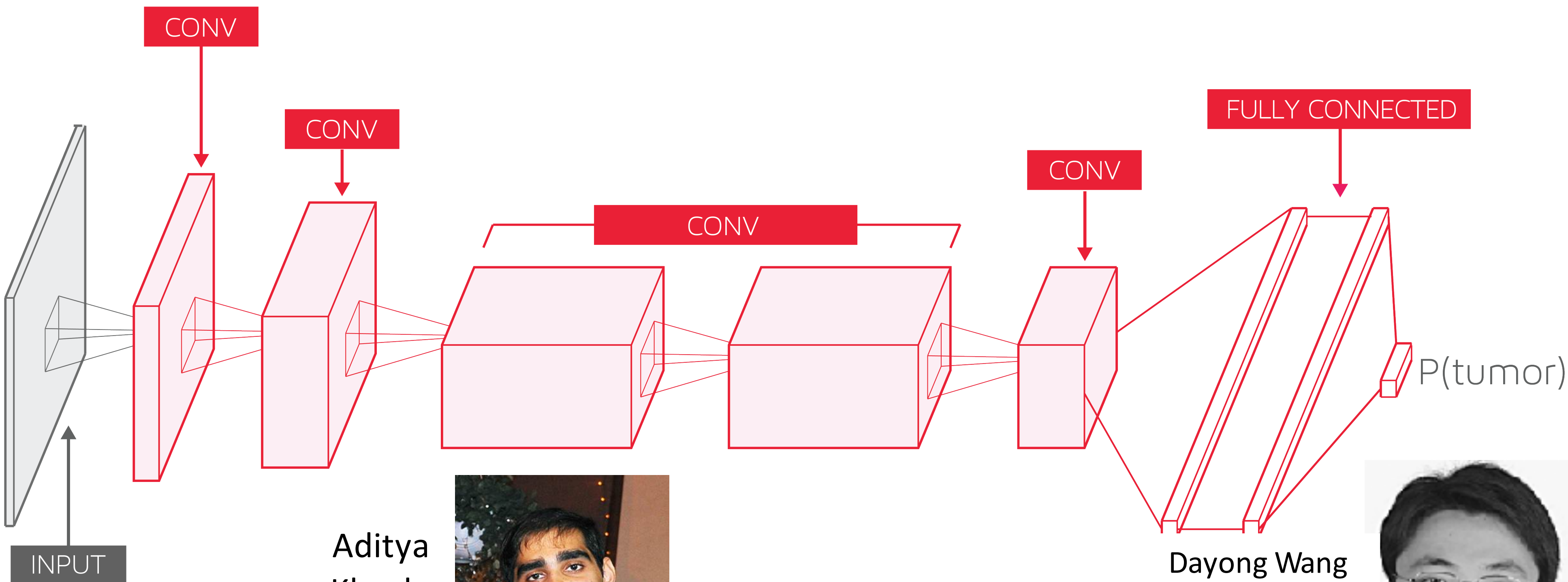
Deep learning has made incredible real-world advances in 2016

Google DeepMind's Alpha Go Defeats GO Champion Lee Sedol (March, 2016)

Uber deploys autonomous driving taxis on the streets of Pittsburgh (September 2016)

Deep Learning for Pathology: Cancer Metastasis Detection

PathAI CONVOLUTIONAL NEURAL NETWORK



Aditya Khosla
PhD
MIT

Dayong Wang
PhD
Harvard Medical School

ISBI Grand Challenge on
Cancer Metastases Detection in Lymph Node

Radboudumc
university medical center

UMC Utrecht

TU/e Technische Universiteit Eindhoven University of Technology
Where innovation starts

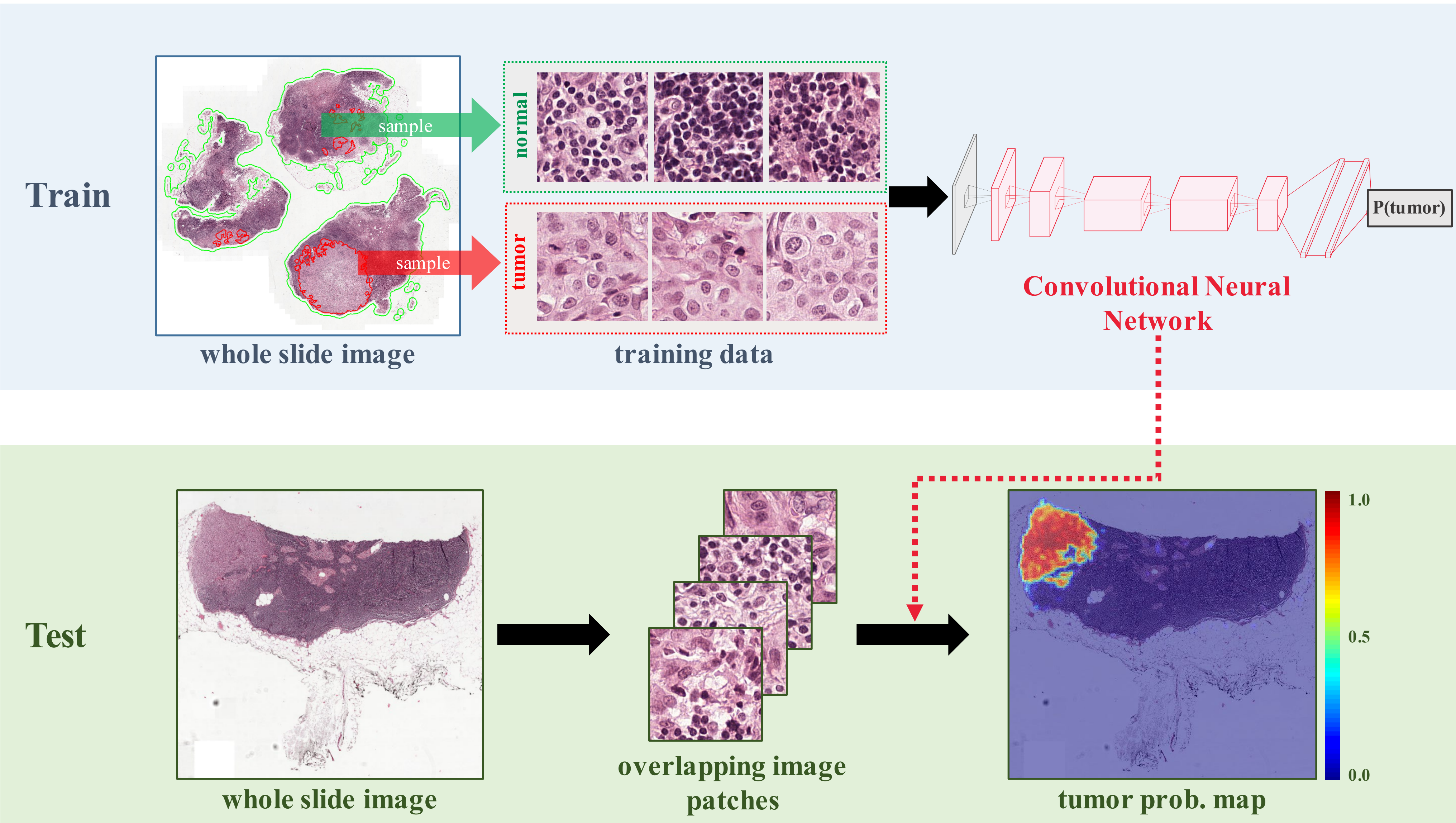
PHILIPS innovation + you

trait
a ctmm project

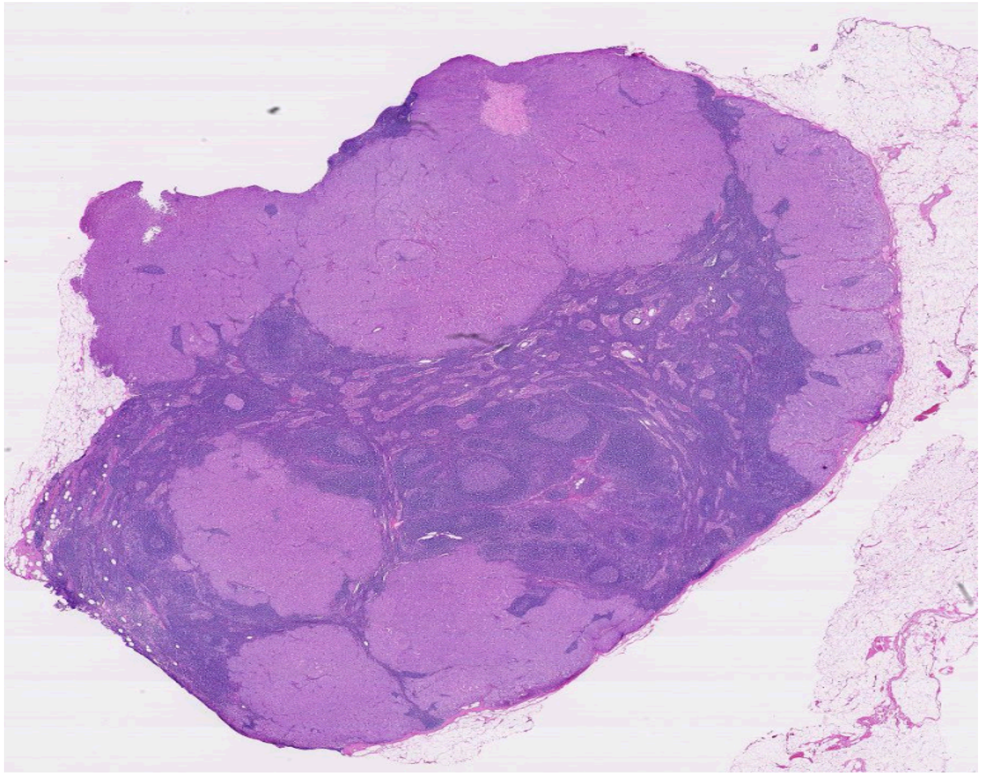
ST IT PRO

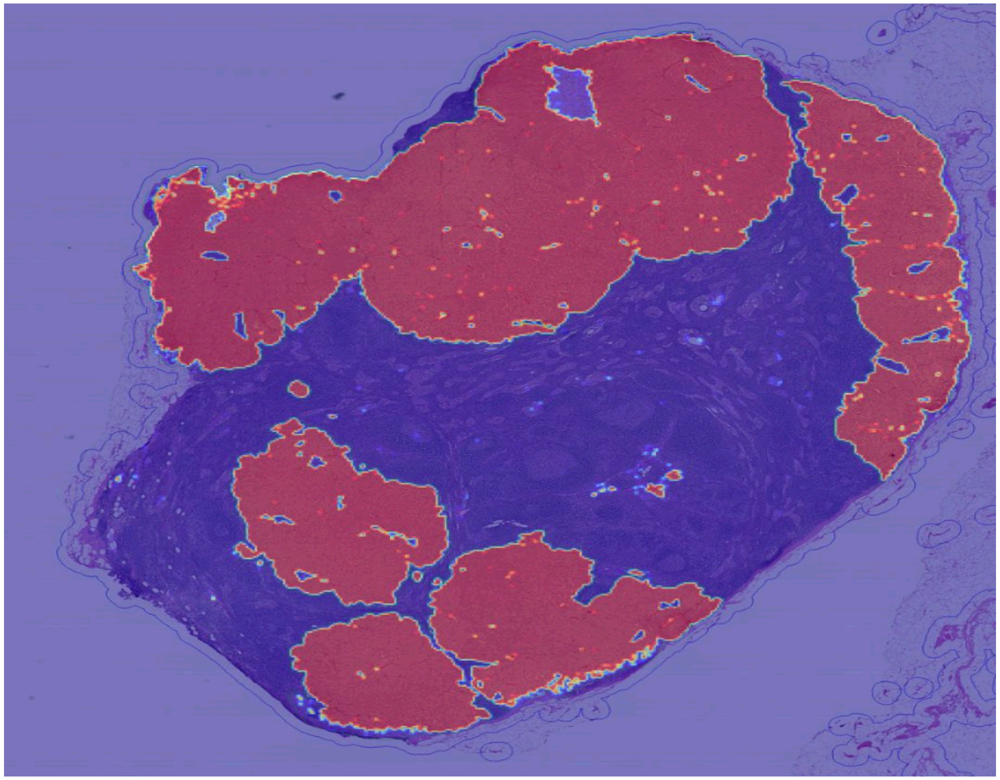
Camelyon16 (>200 registrants)

H&E Image Processing Framework

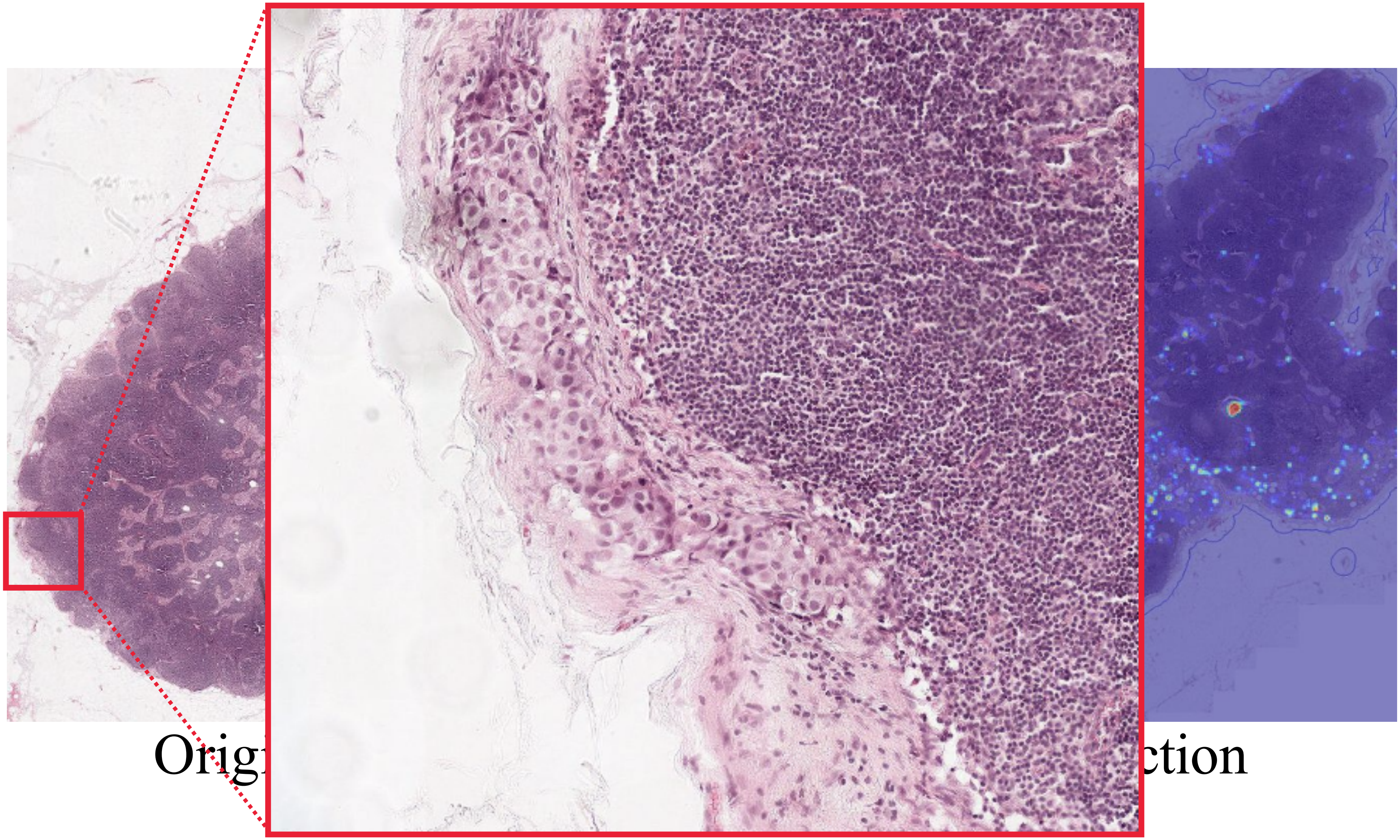


H&E Image Processing Results


Original image


Tumor prediction

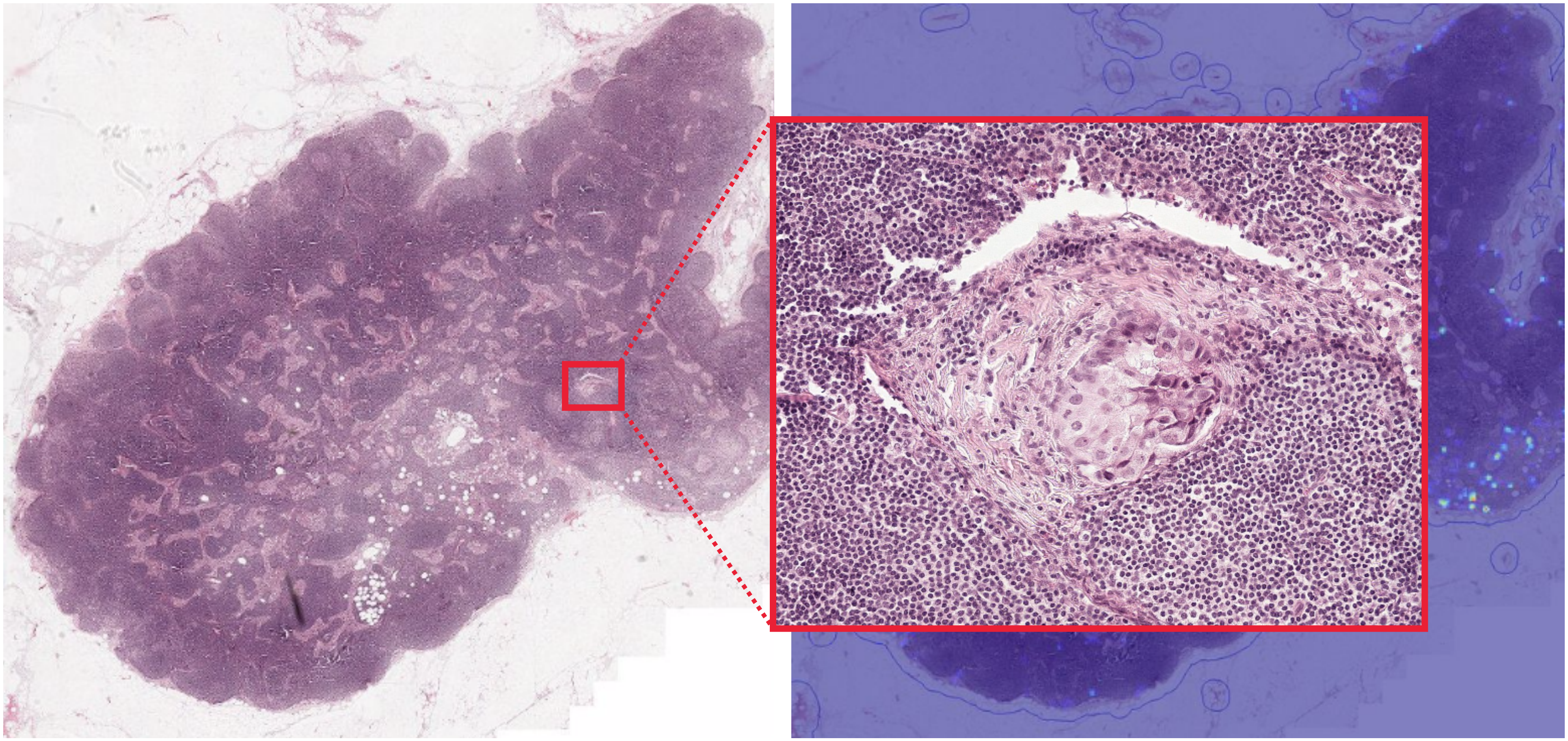
H&E Image Processing Results



Origi

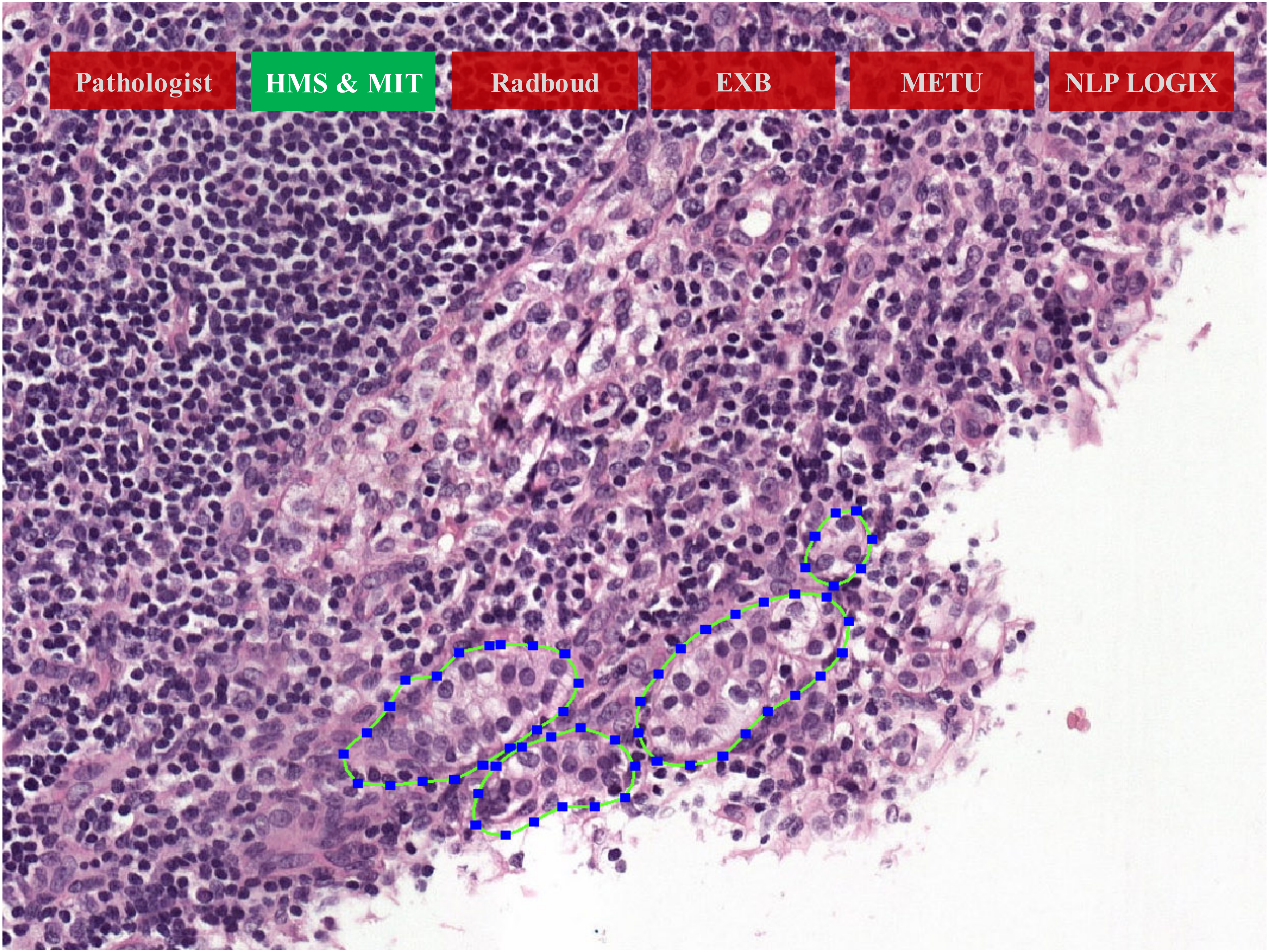
ction

H&E Image Processing Results

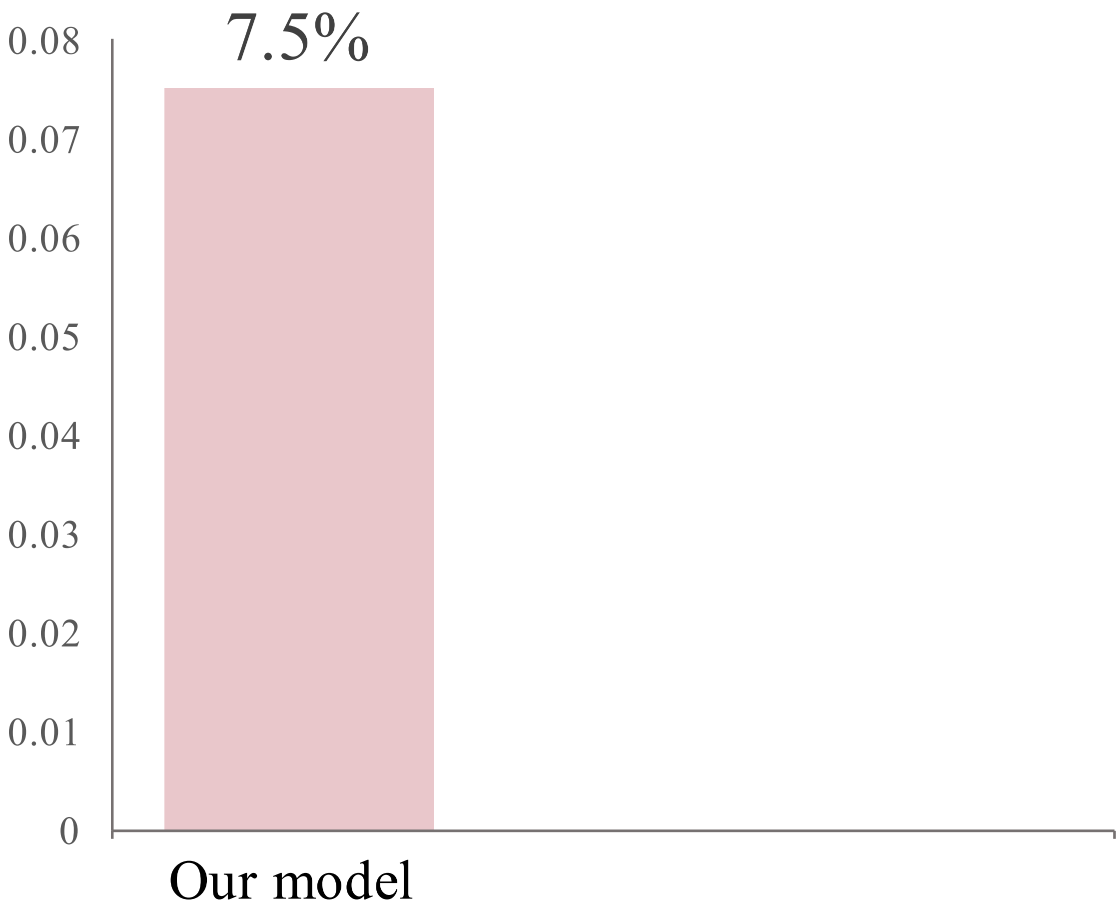


Original image

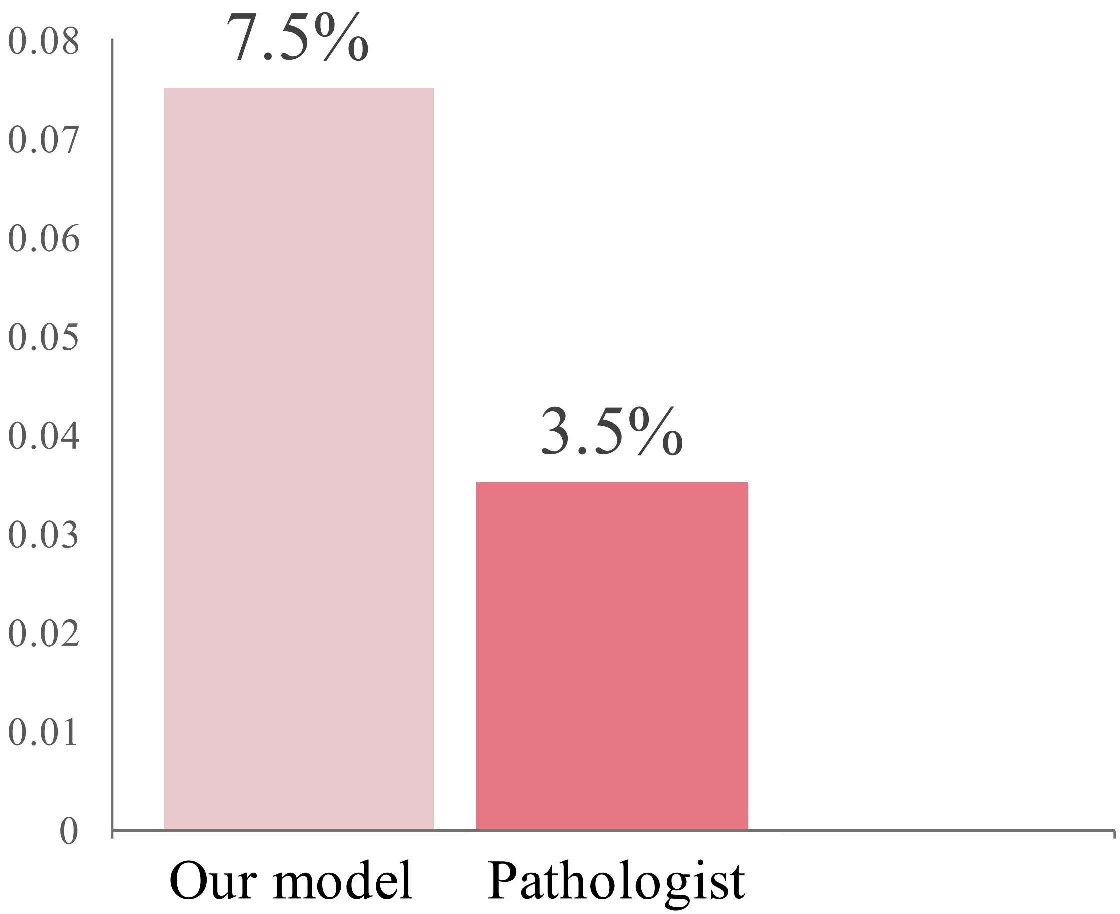
Tumor prediction


Pathologist
HMS & MIT
Radboud
EXB
METU
NLP LOGIX

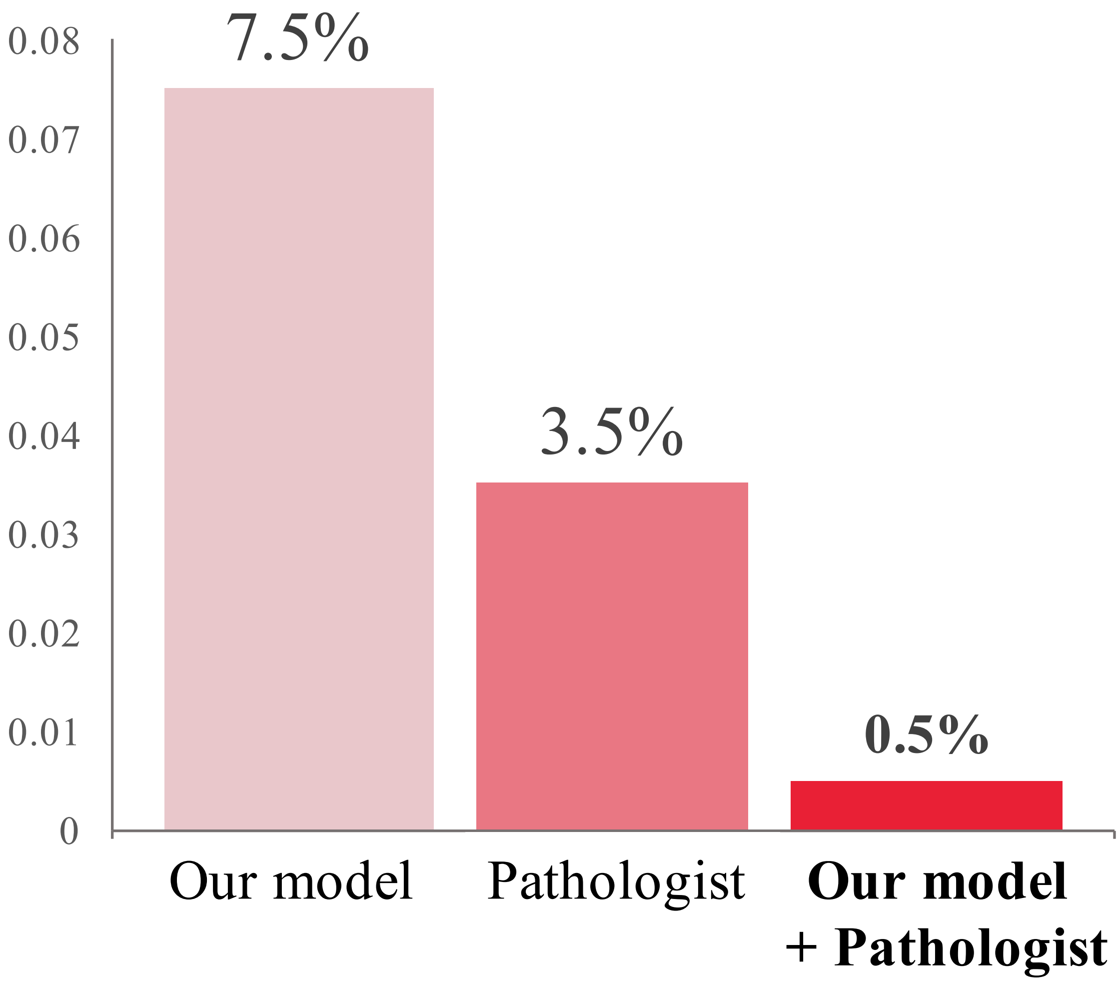
Deep Learning vs Pathologist



Deep Learning vs Pathologist



Deep Learning vs Pathologist



The **combination** of a pathologist and the Beck Lab deep learning system **reduces error rate** by 85% **to 0.5%.**

www.camelyon16.grand-challenge.org/results/

Clinical study on ISBI dataset

Beck Lab's deep learning model now outperforms pathologist

	Error Rate
Pathologist in competition setting	3.5%
Pathologists in clinical practice (n = 12)	13% - 26%
Pathologists on micro-metastasis (small tumors)	23% - 42%

Beck Lab Deep Learning Model	**0.65%**

Our Team Won the 2016 ISBI Grand Challenge for Metastatic Cancer Detection

Featured in the report "**Preparing for the Future of Artificial Intelligence**" prepared by the Executive Office of the President of the United States

"The fact that computers had almost comparable performance to humans is way **beyond what I had anticipated**. It is a clear indication that **artificial intelligence is going to shape the way we deal with histopathological images in the years to come**."

- *Jeroen van der Laak, Radbound University Medical Center*

Artificial Intelligence Gets an A+ for Accurately Diagnosing Breast Cancer

- *Breast Cancer News (Jun 29, 2016)*

THE HUFFINGTON POST

NVIDIA

engadget

DIGITAL TRENDS

BREAST CANCER NEWS

livescience

Daily Mail

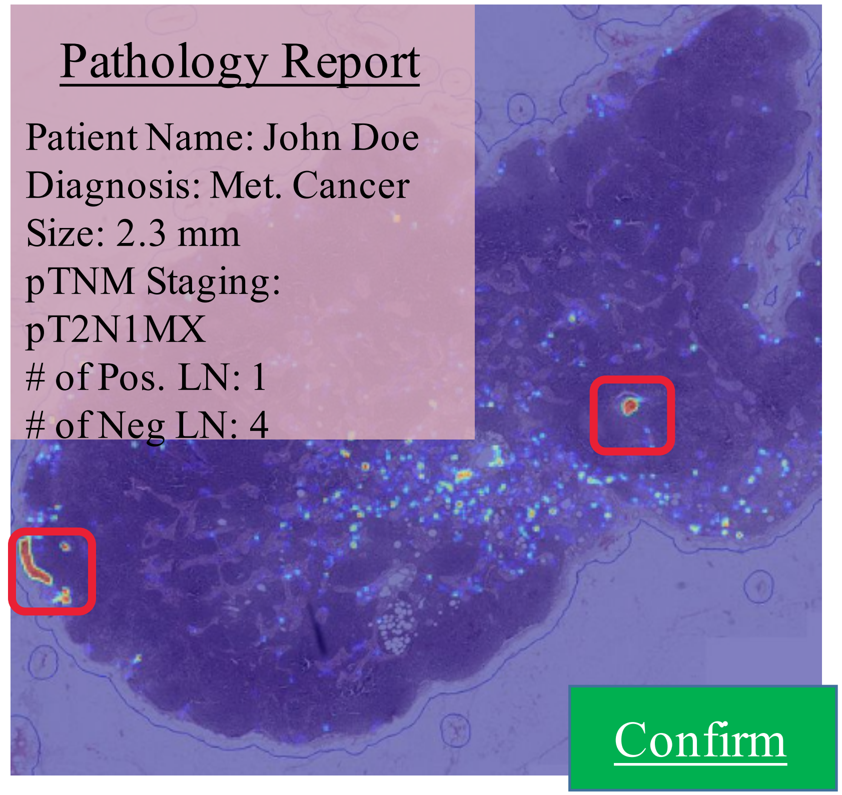
Deep Learning in the Clinical Workflow

Before

- microscope field of view

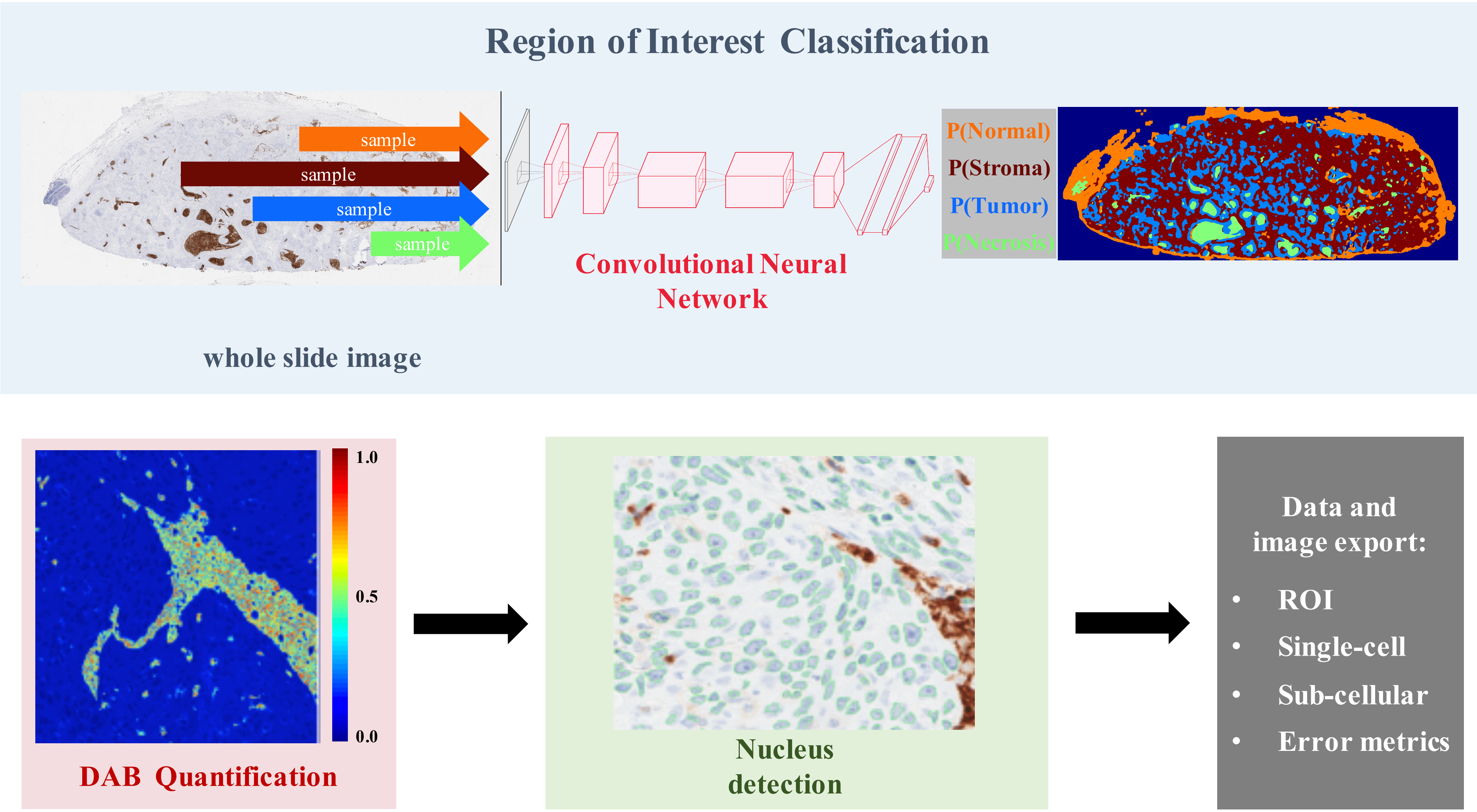
- Labor Intensive
- Error-prone
- Poor standardization

After

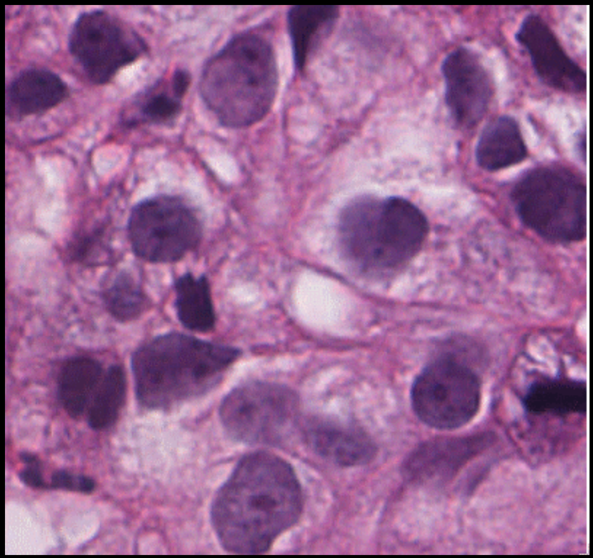


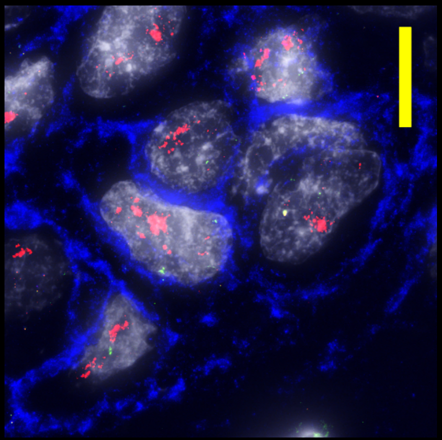
- Fast
- Accurate
- Standardized

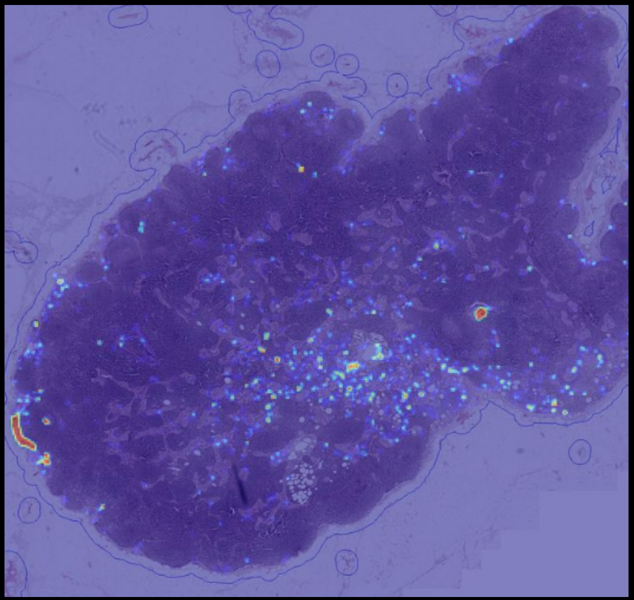
Immunohistochemistry Image Processing Framework

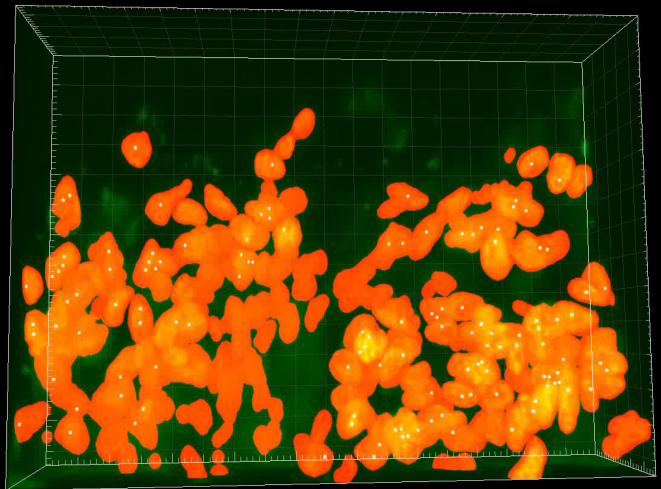


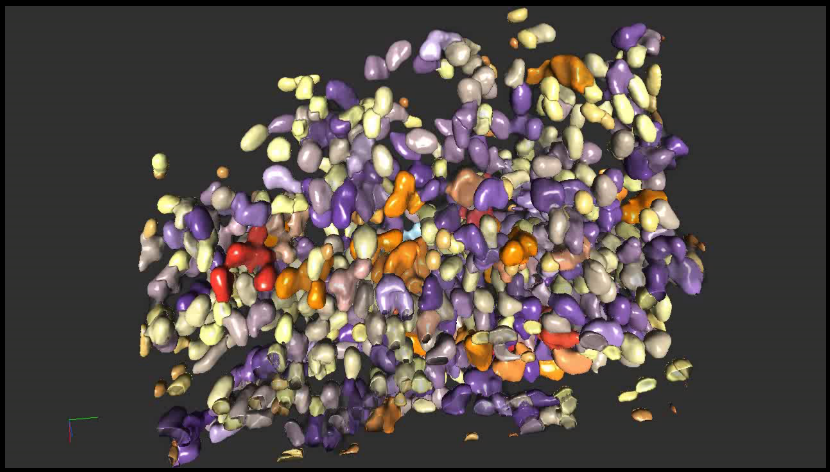
Deep Learning for Computational Pathology



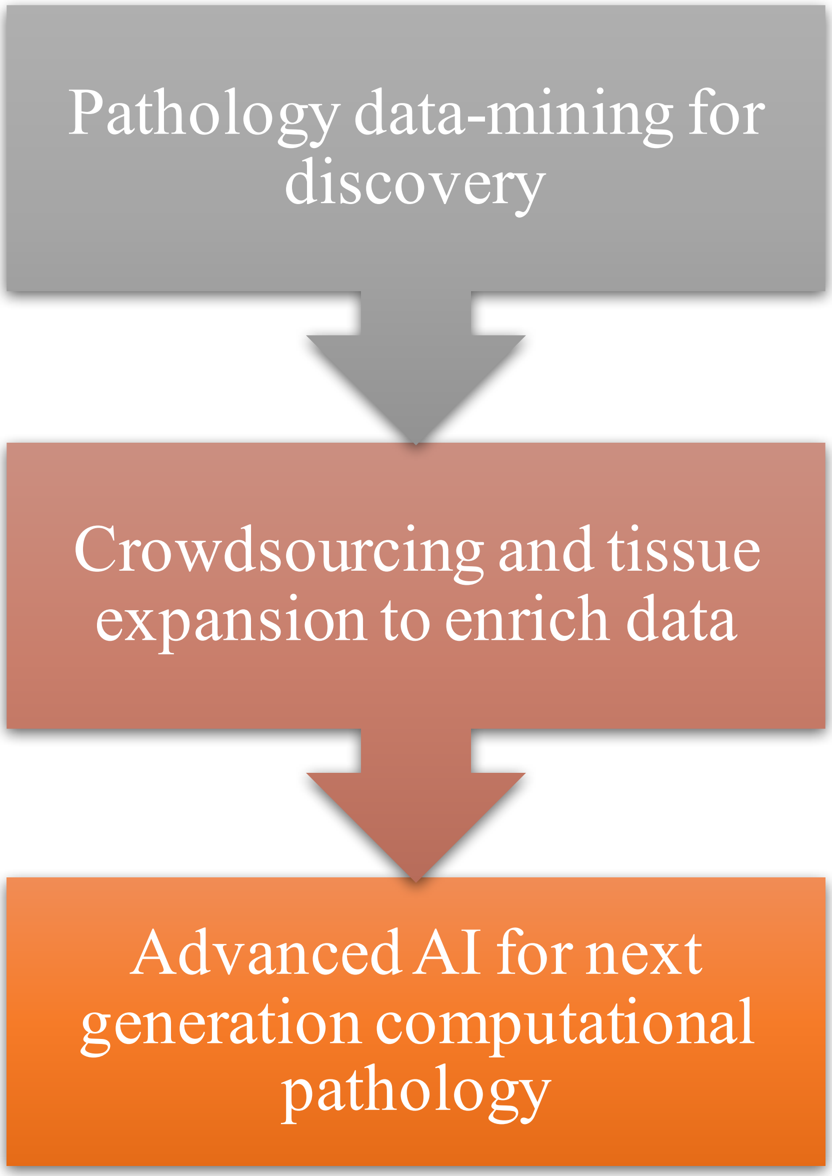


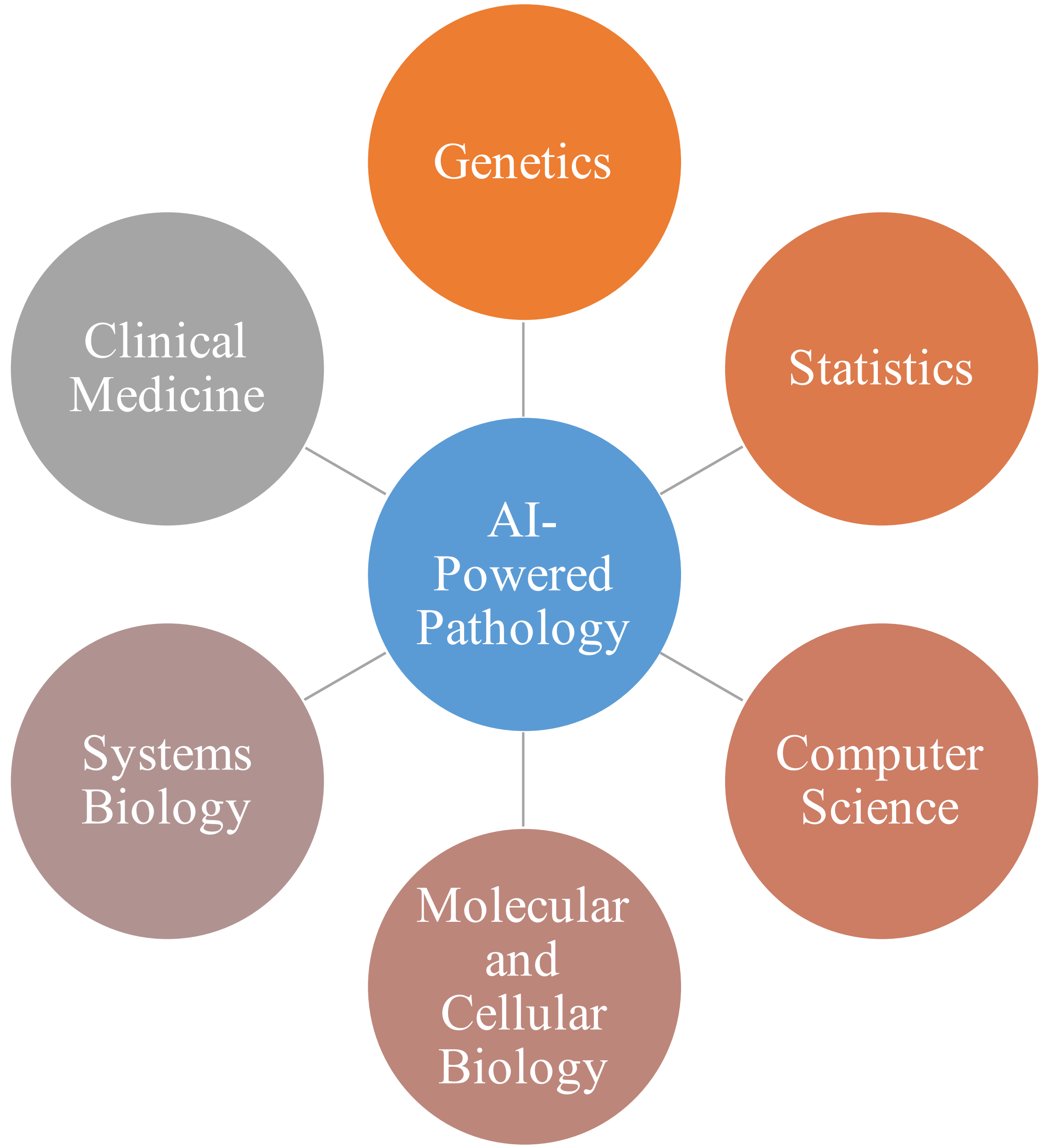






AI-Powered Computational Pathology at the center of bio-medicine and healthcare





Acknowledgements

- **BIDMC:**
  - Nick Knoblauch
  - Laleh Montaser
  - Marco Hefti
  - Eun-Yeong Oh
  - Dan Xia
  - Humayun Irshad
  - Jonathan Nowak
  - Fei Dong
  - Octavian Bucur
  - Jong Cheol Jeong
  - Sindhu Ghanta
  - Jan Heng
  - Dayong Wang
- **Nurses Health Study**
  - Rulla Tamimi
- **TCGA Breast Cancer Expert Pathology Working Group**
- **MIT**
  - Ed Boyden
  - Yongxin Zhao

Support

- Klarman Family Foundation
- NIH/NCI
- NIH/NLM
- Susan G Komen Foundation
- DFHCC
- Harvard Catalyst
- BIDMC
- Harvard Ludwig Center

Thank you!

- Contact: Andy.Beck@PathAI.com