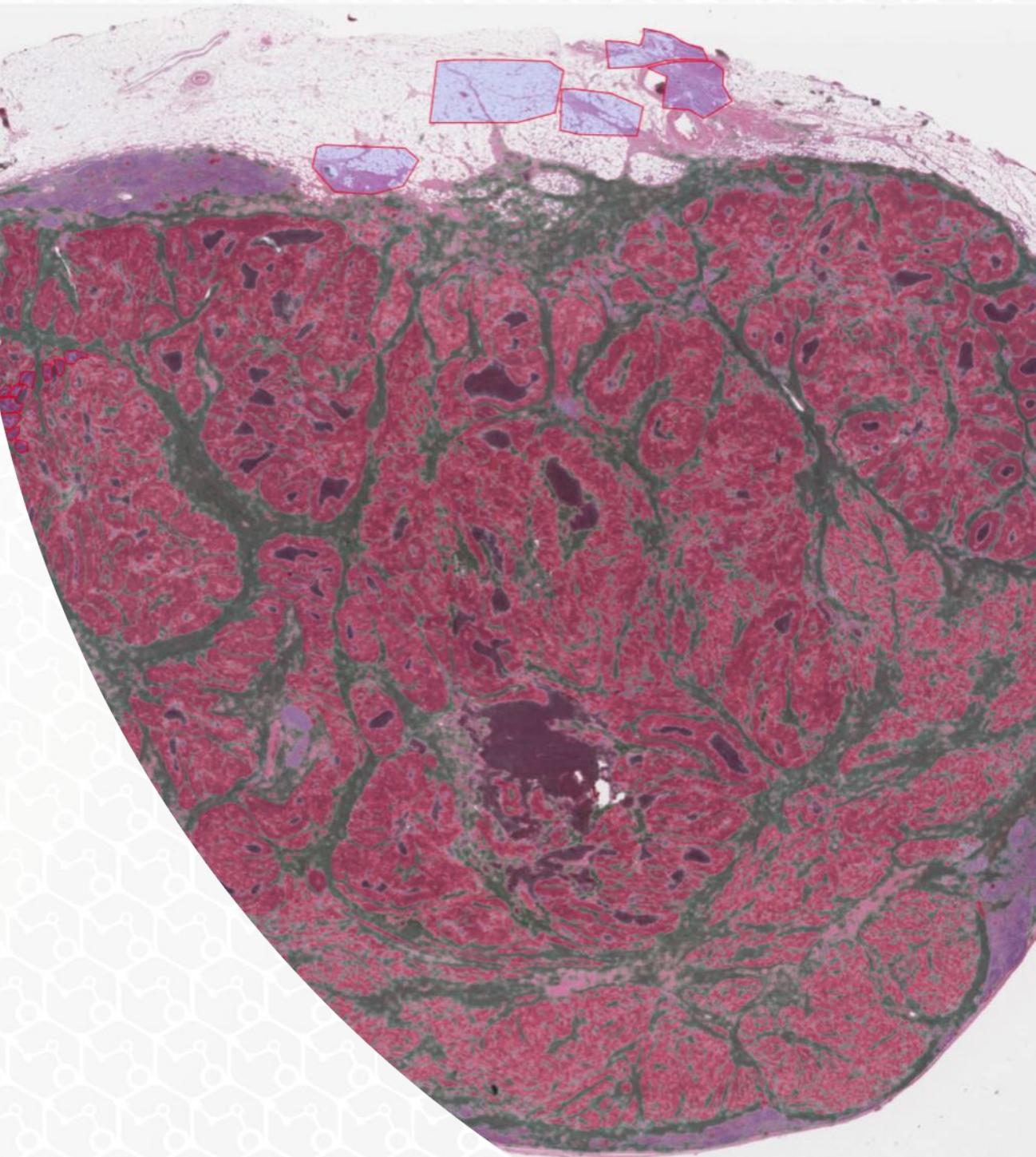


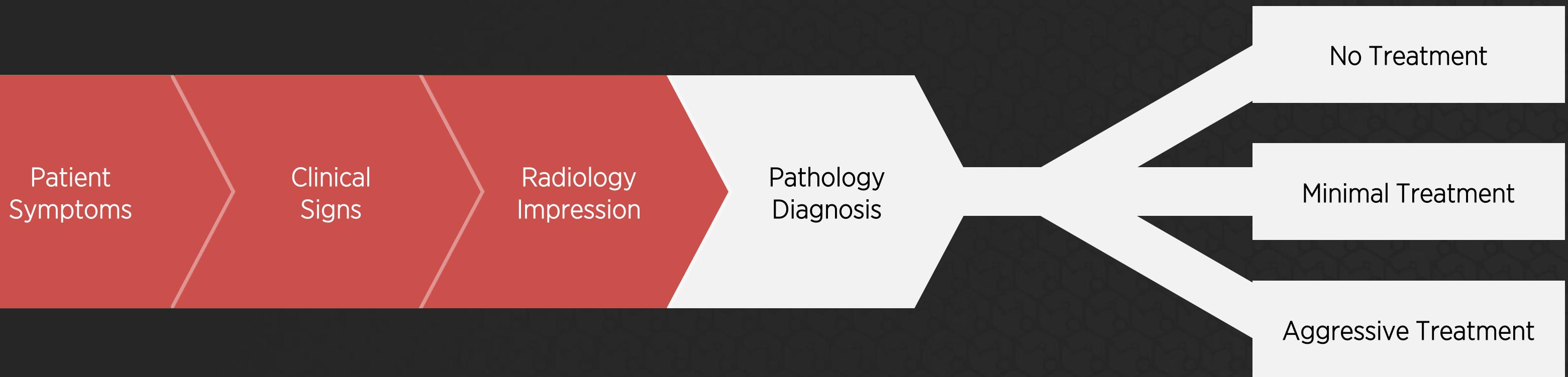
# Machine learning for Pathology

Andrew H Beck MD PhD  
CEO @ PathAI

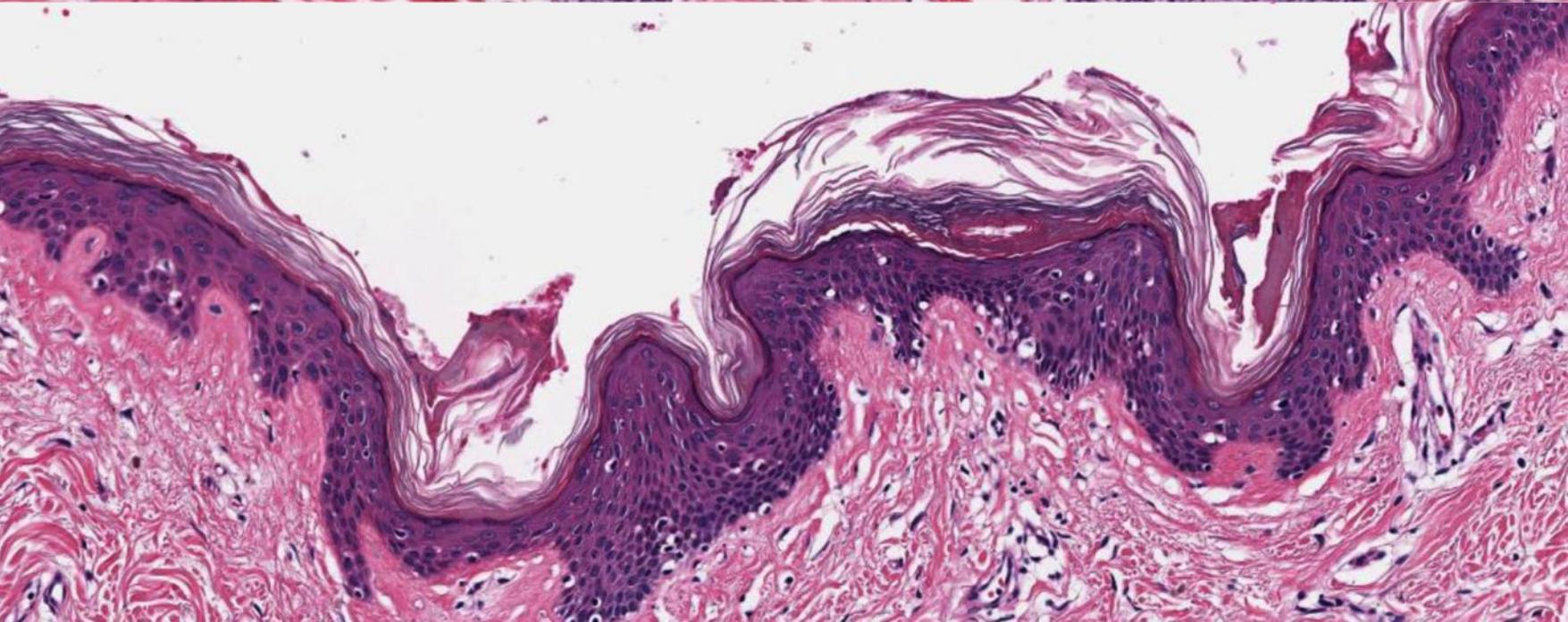
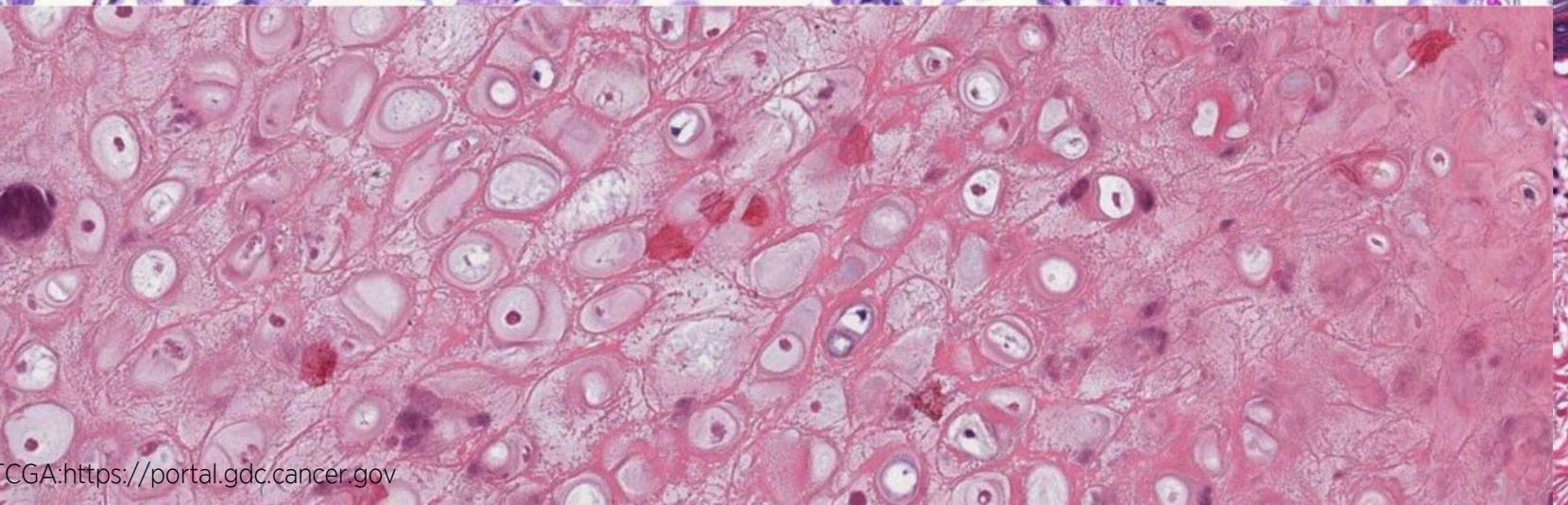
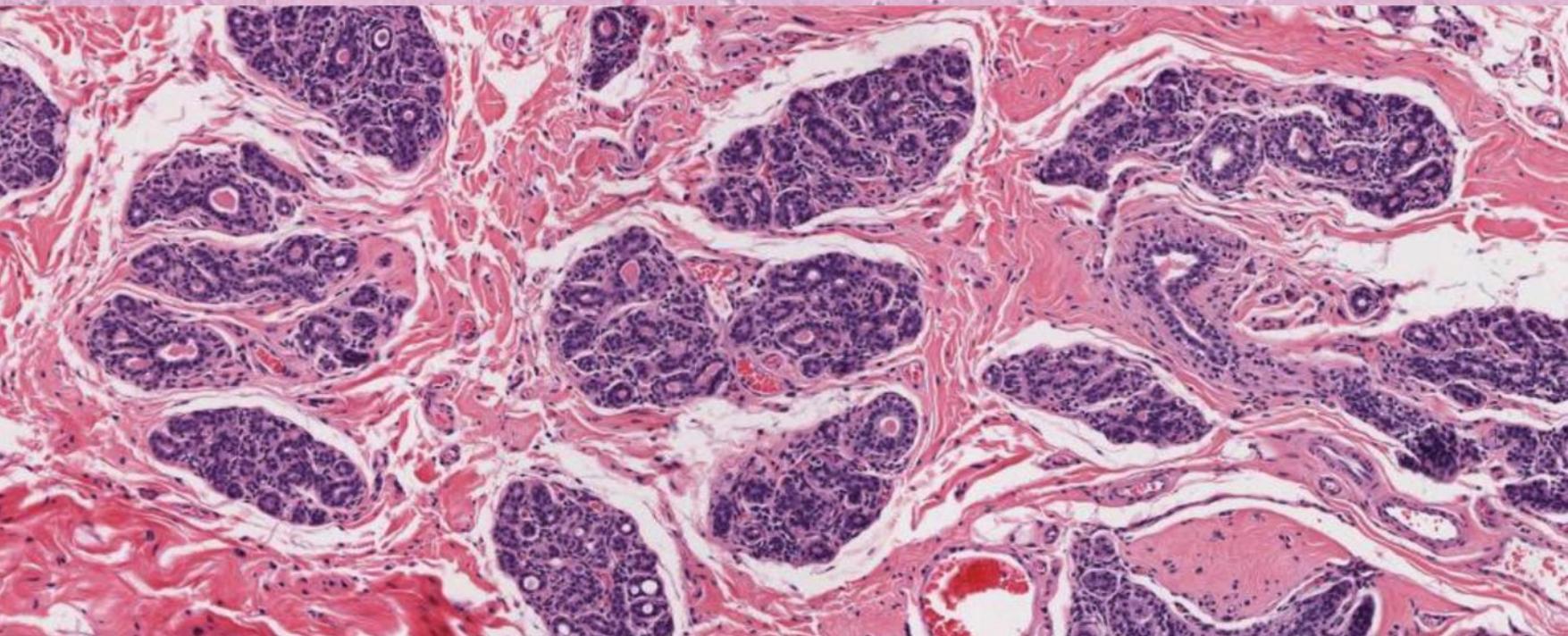
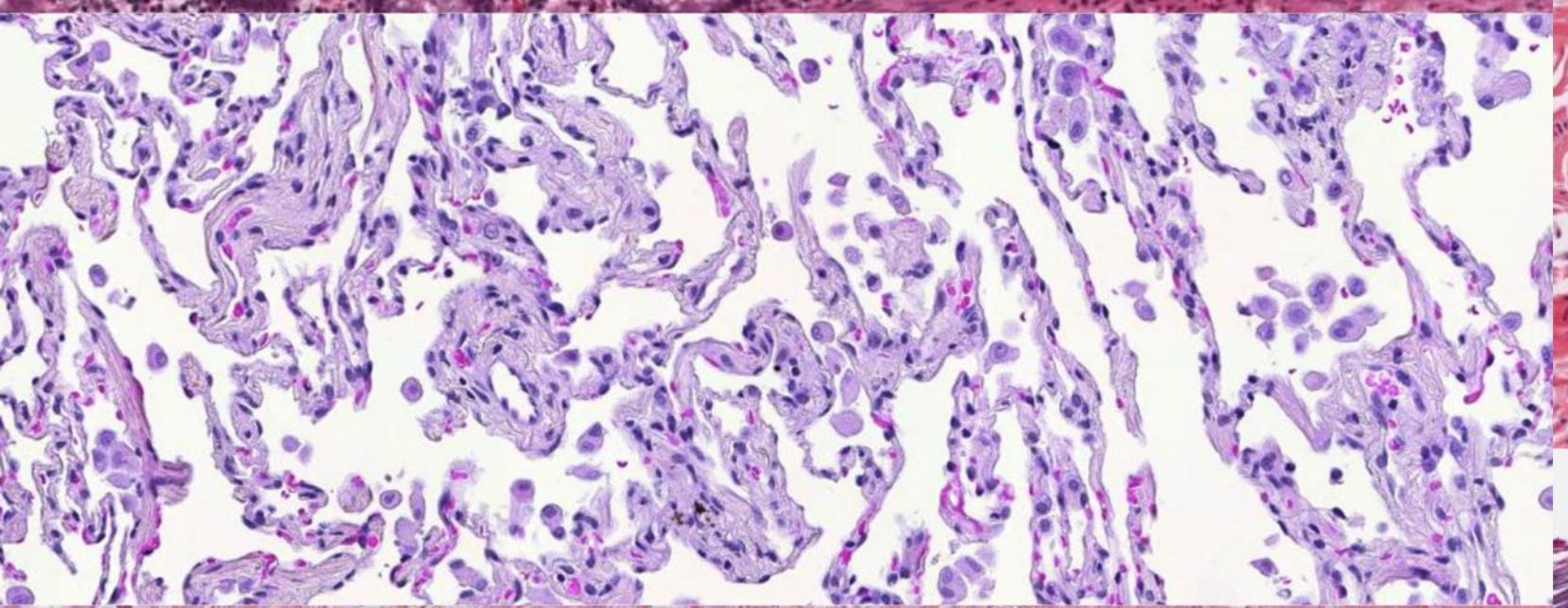
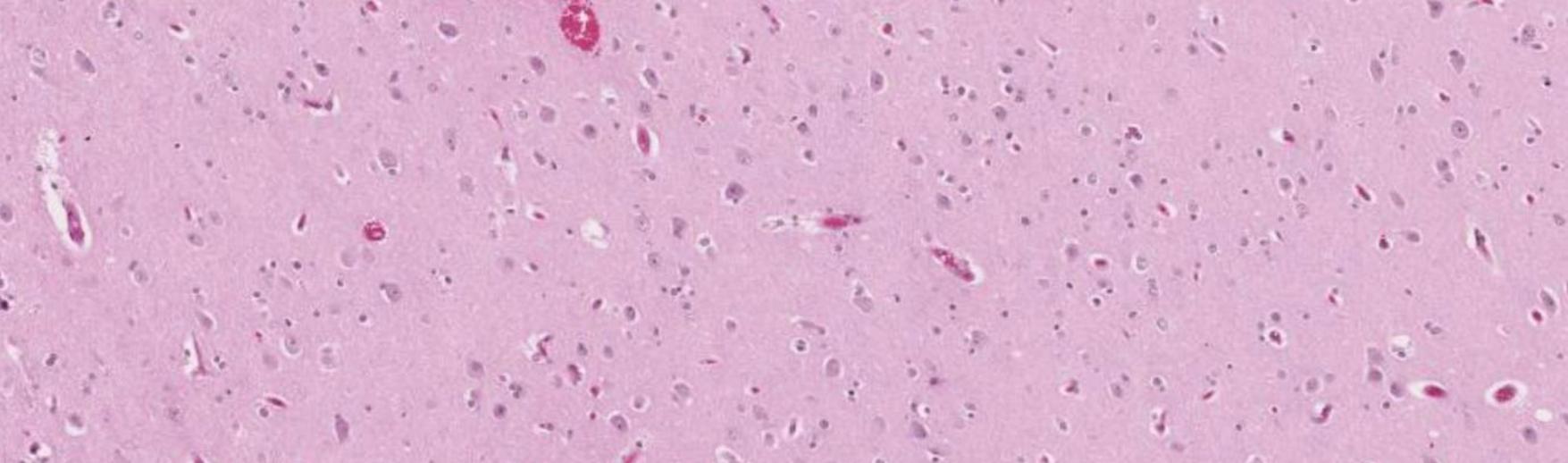
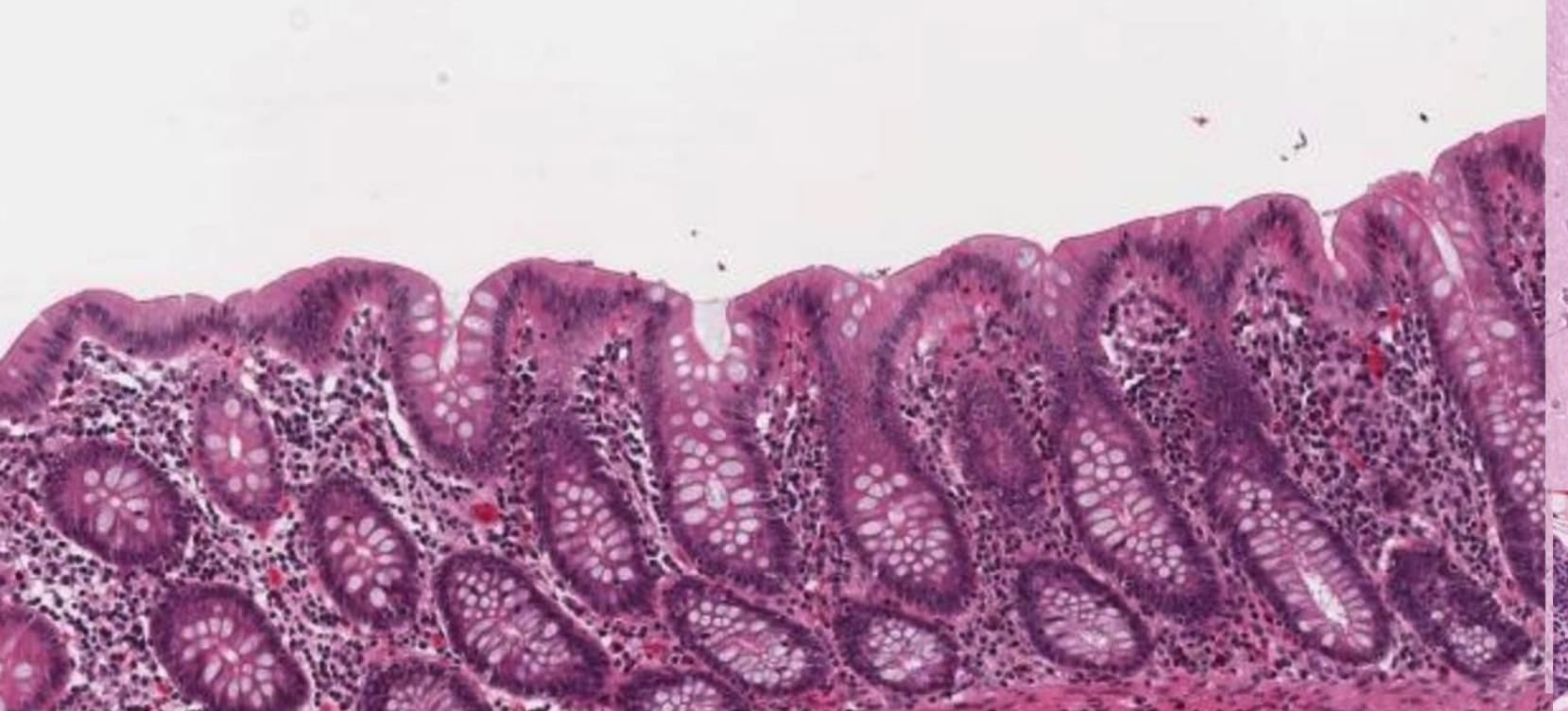
6.S897/HST.956: Machine Learning for Healthcare. MIT.  
March 19, 2019

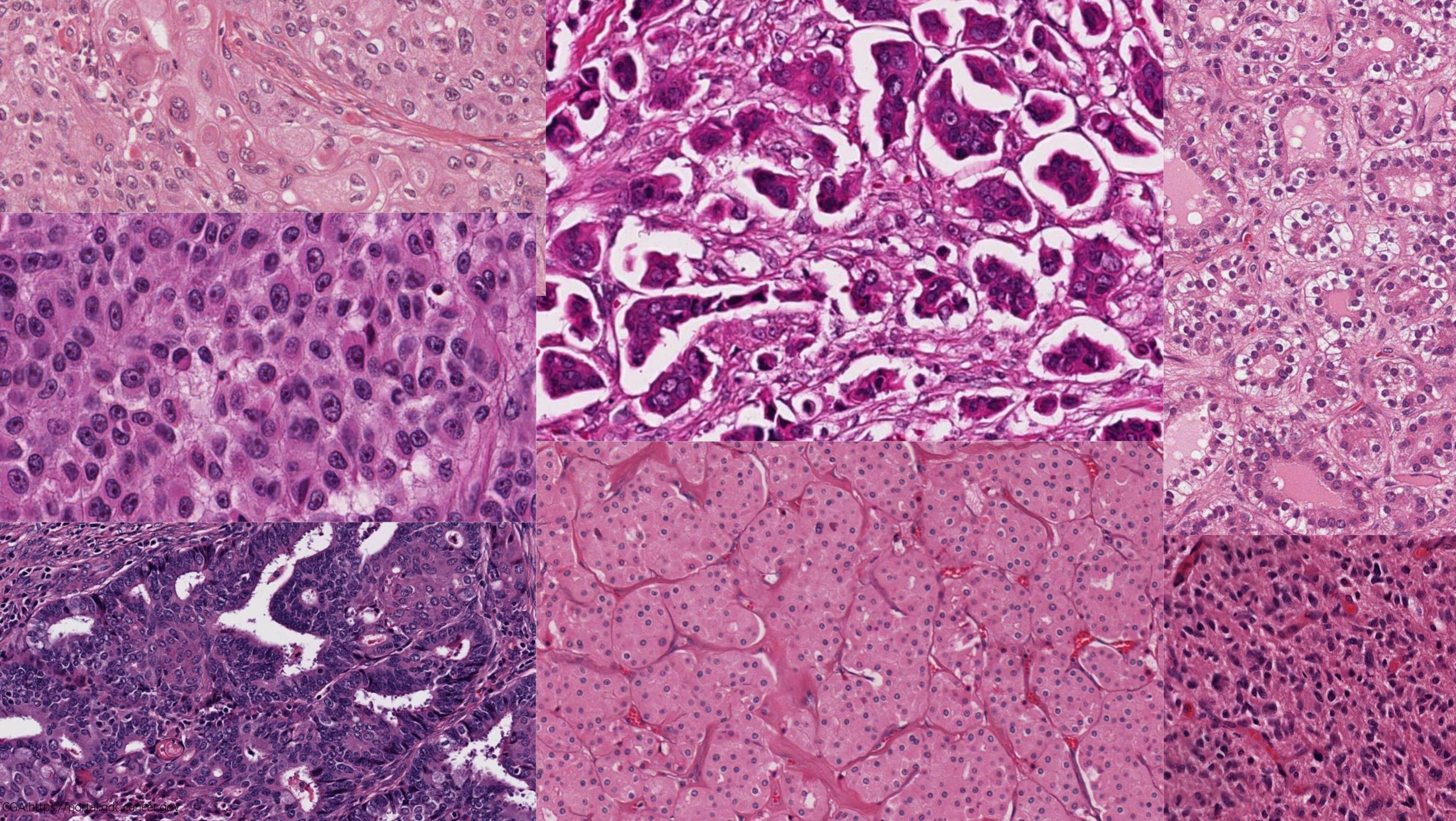


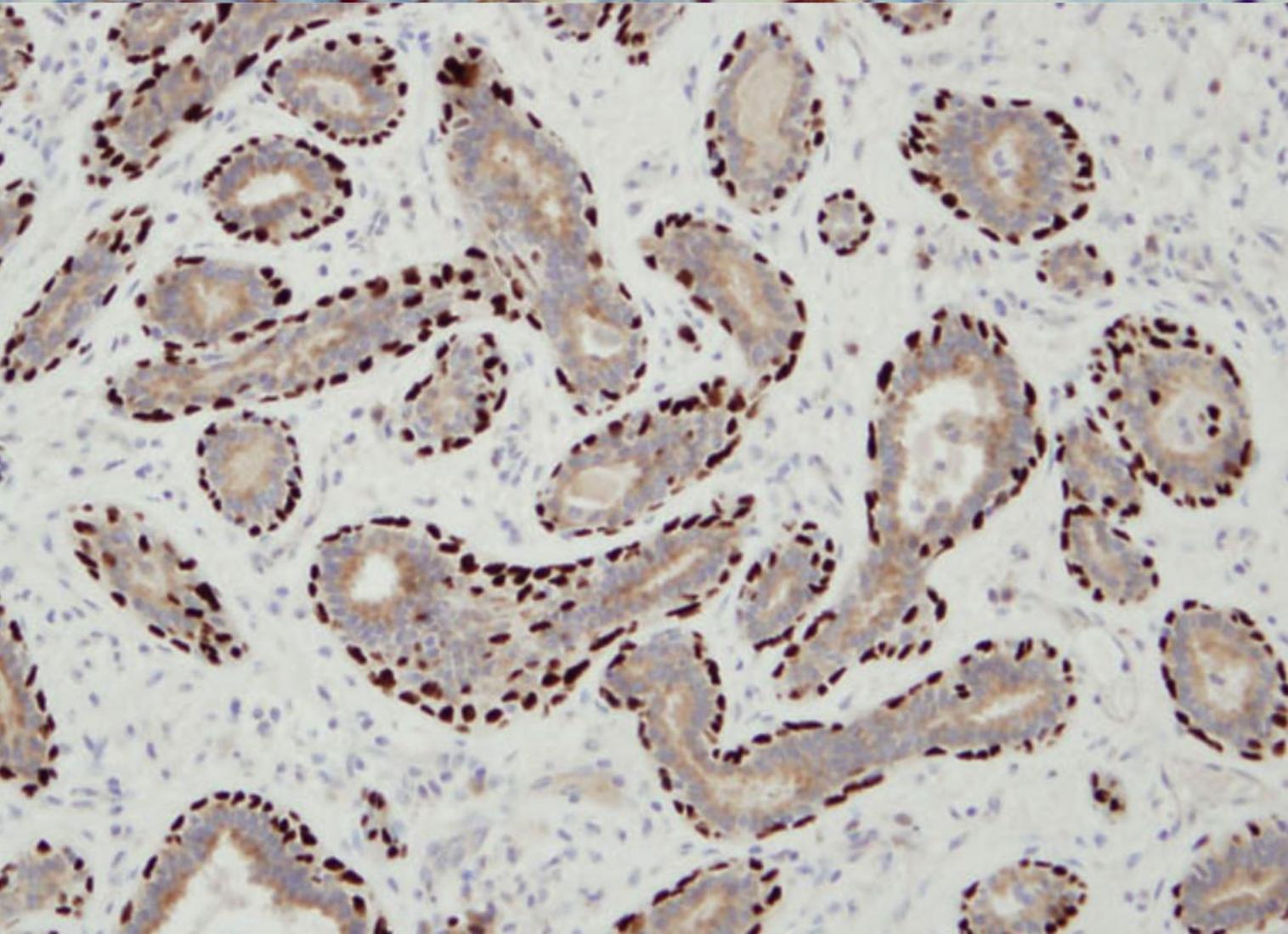
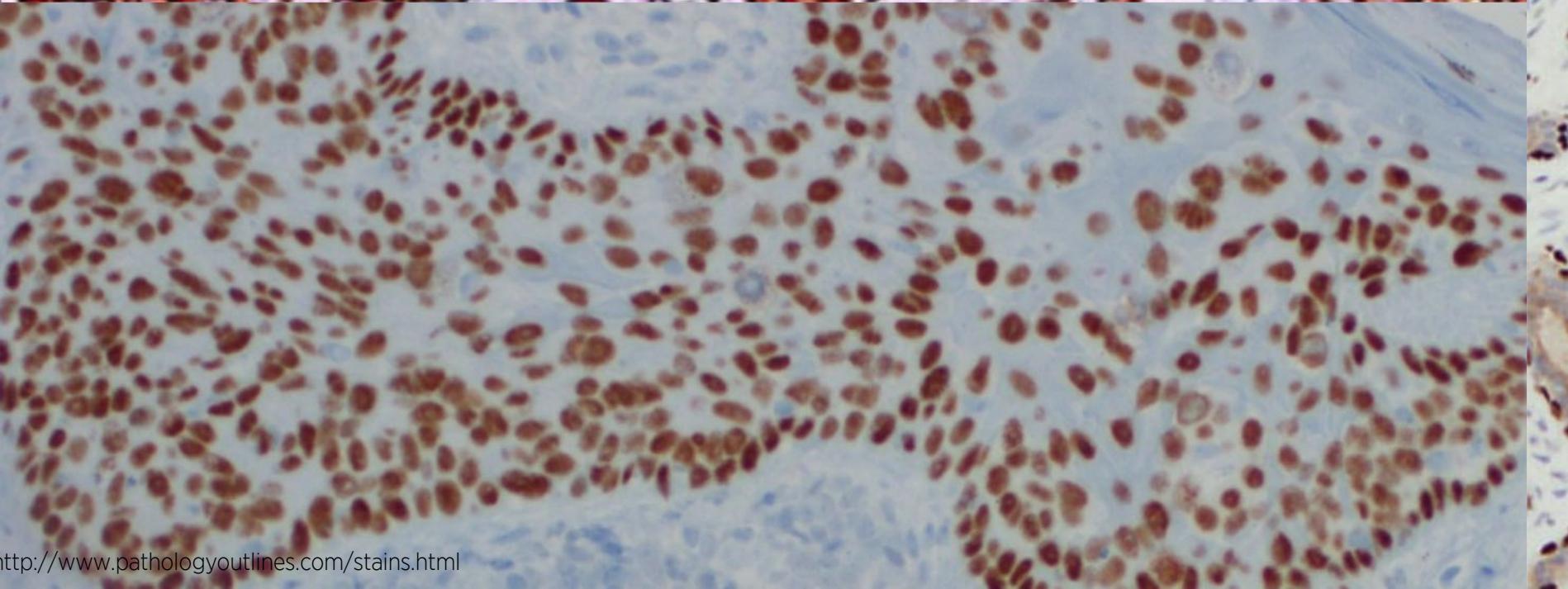
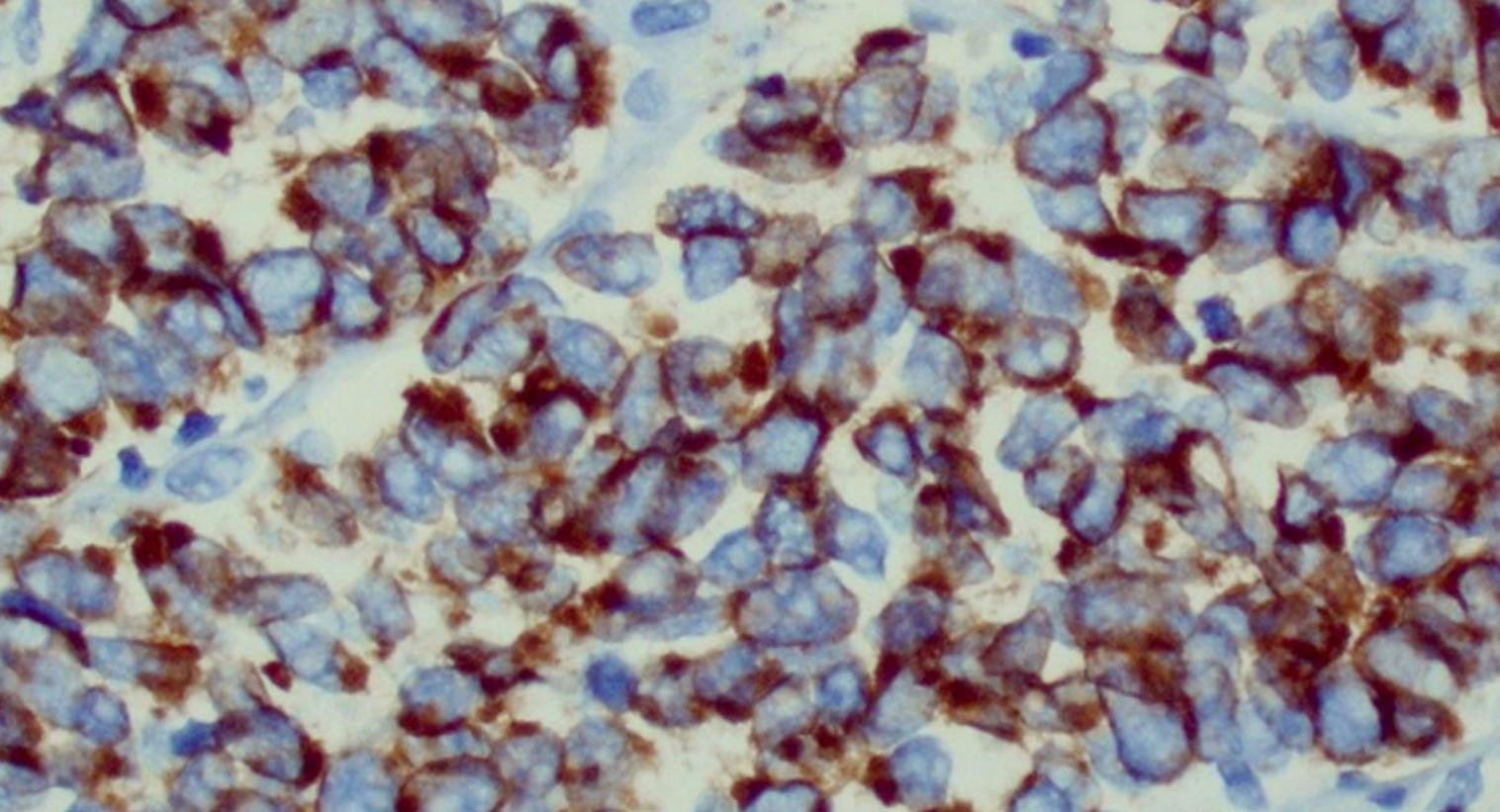
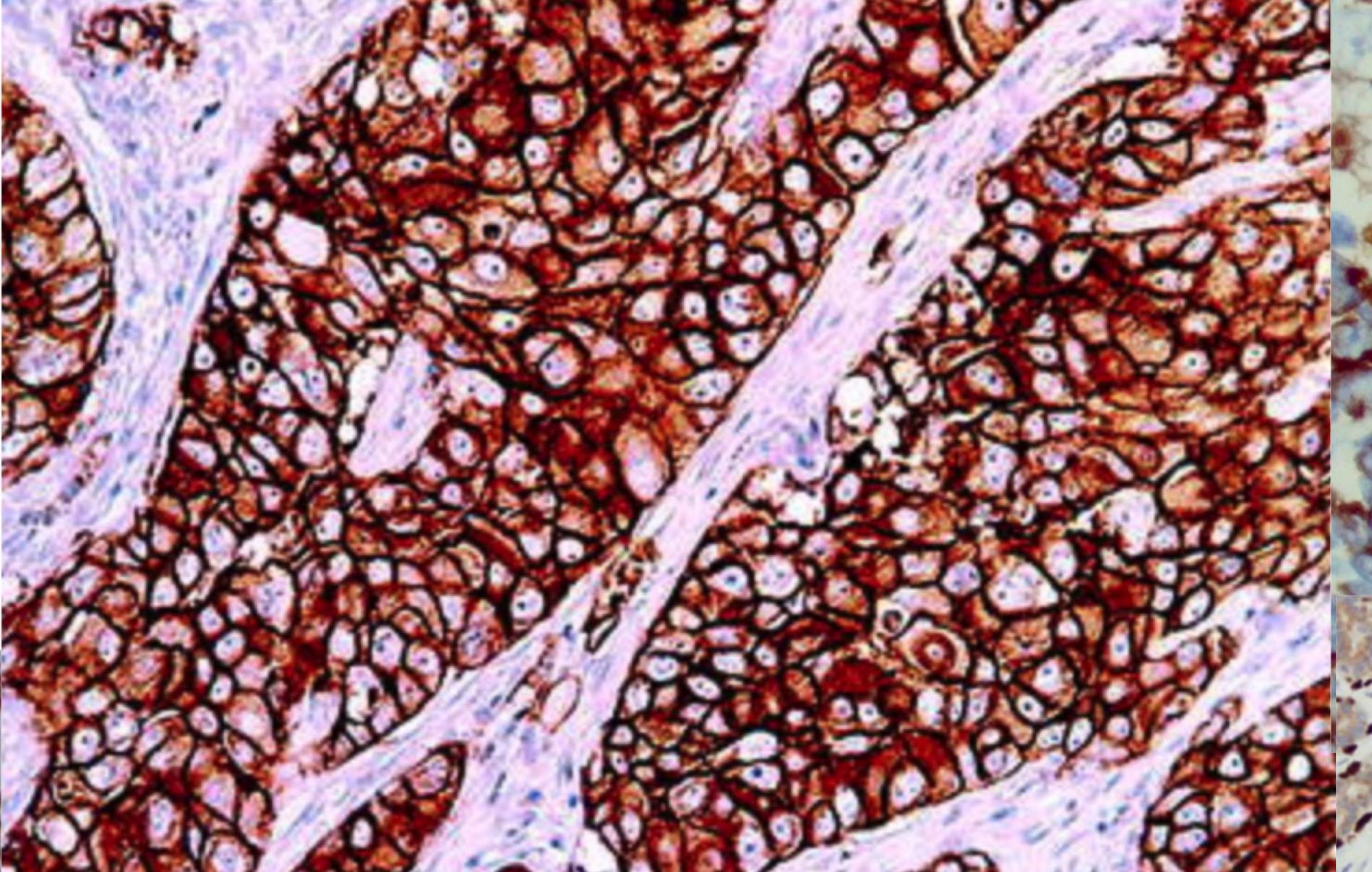
# Pathology

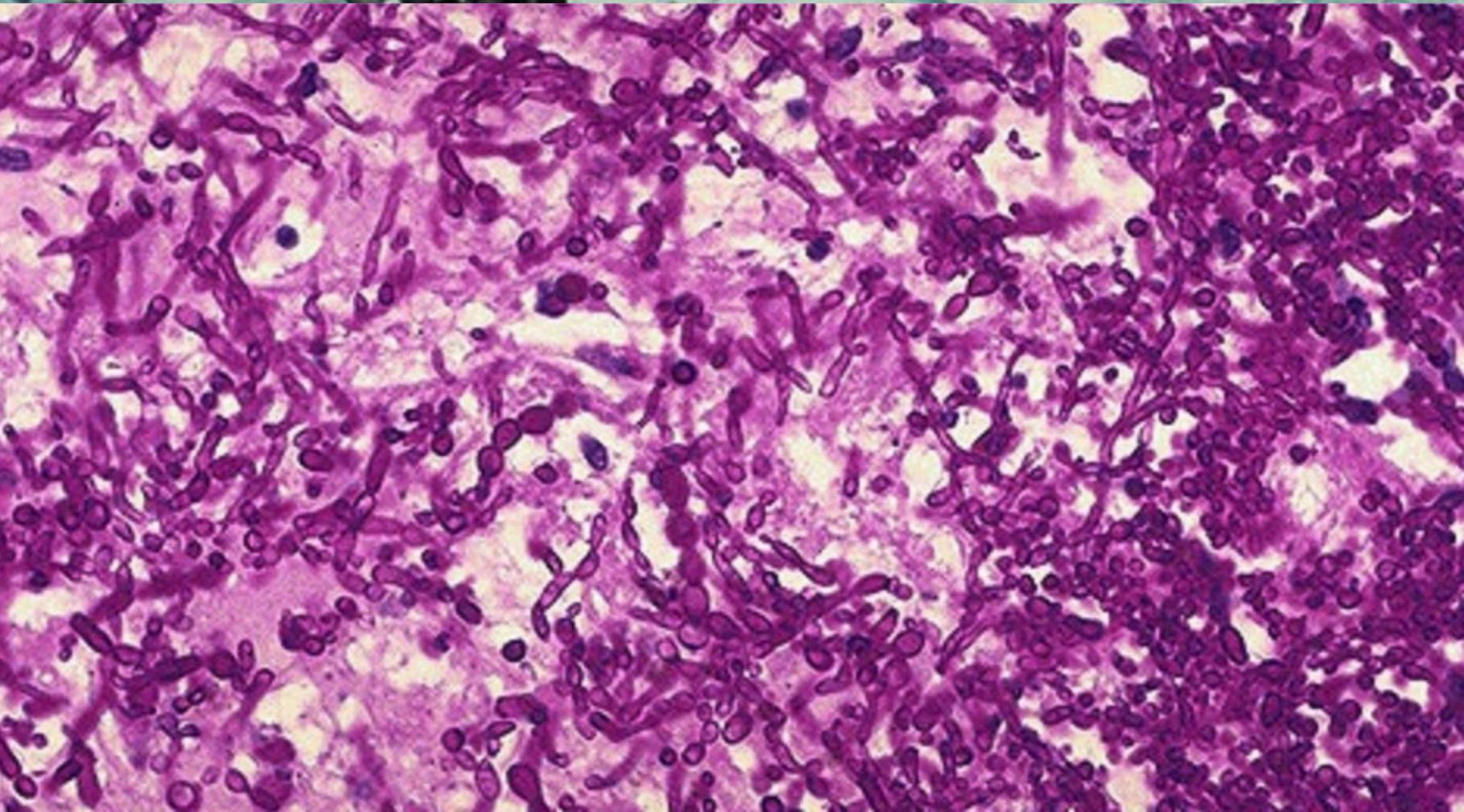
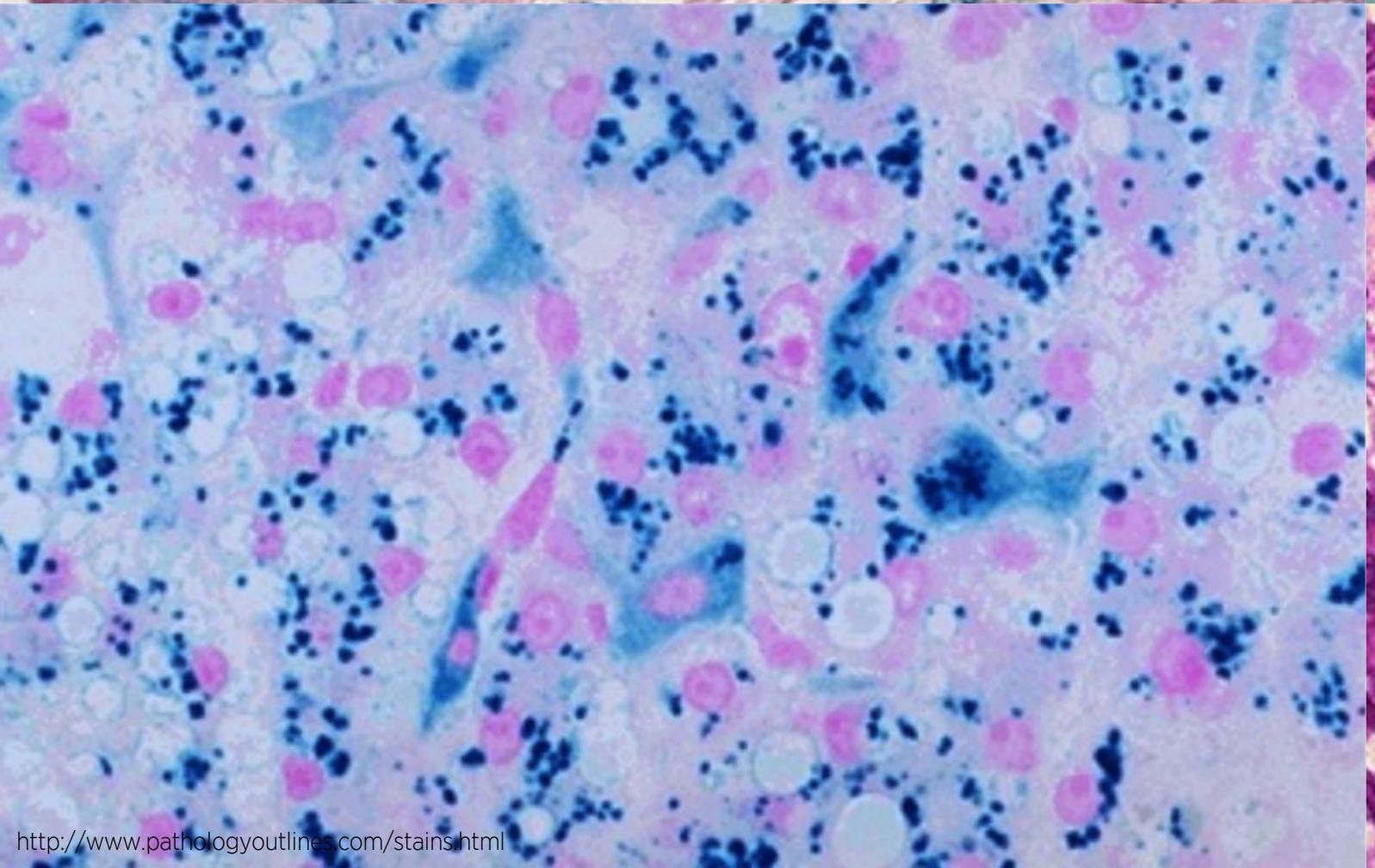
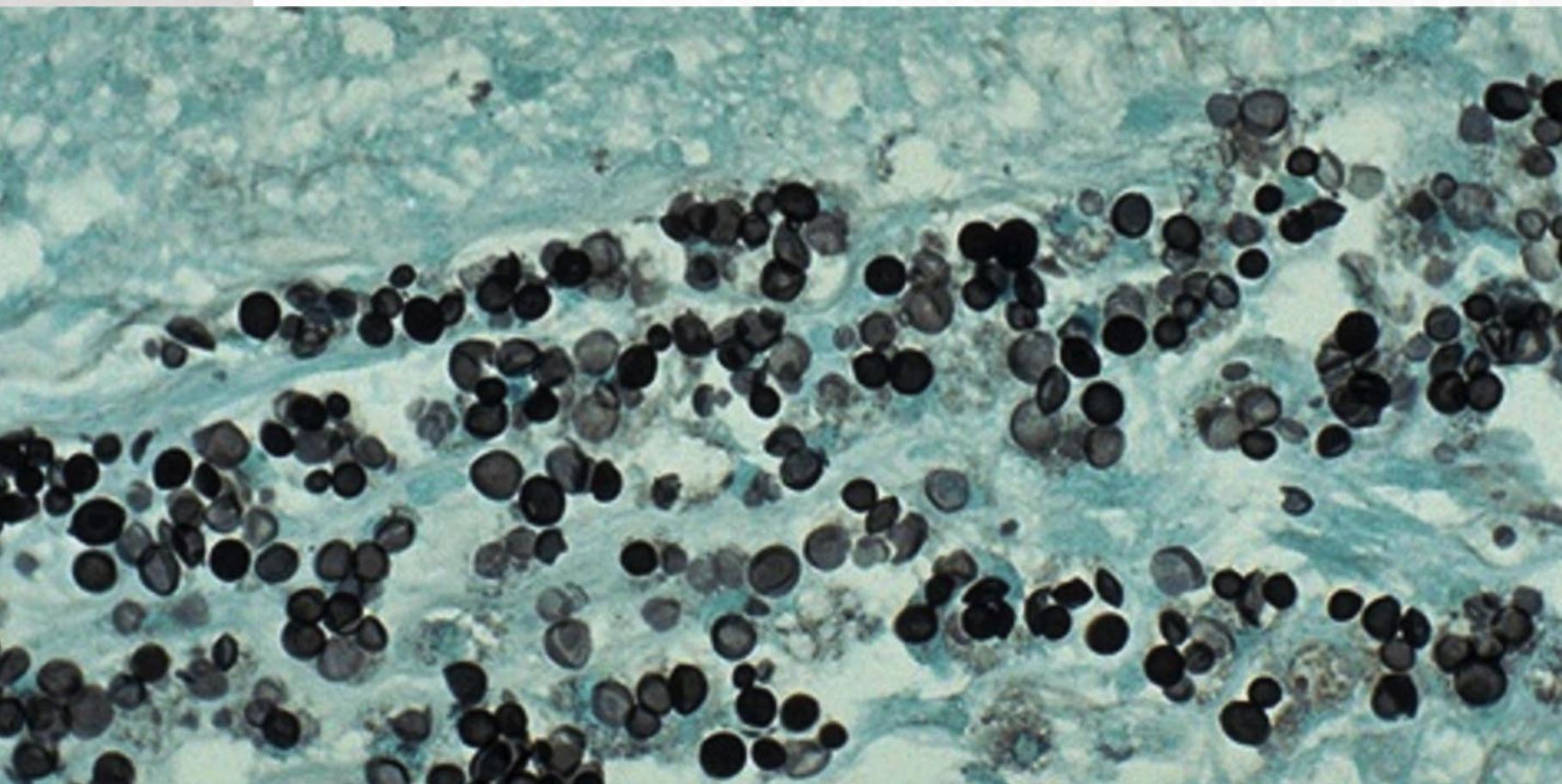
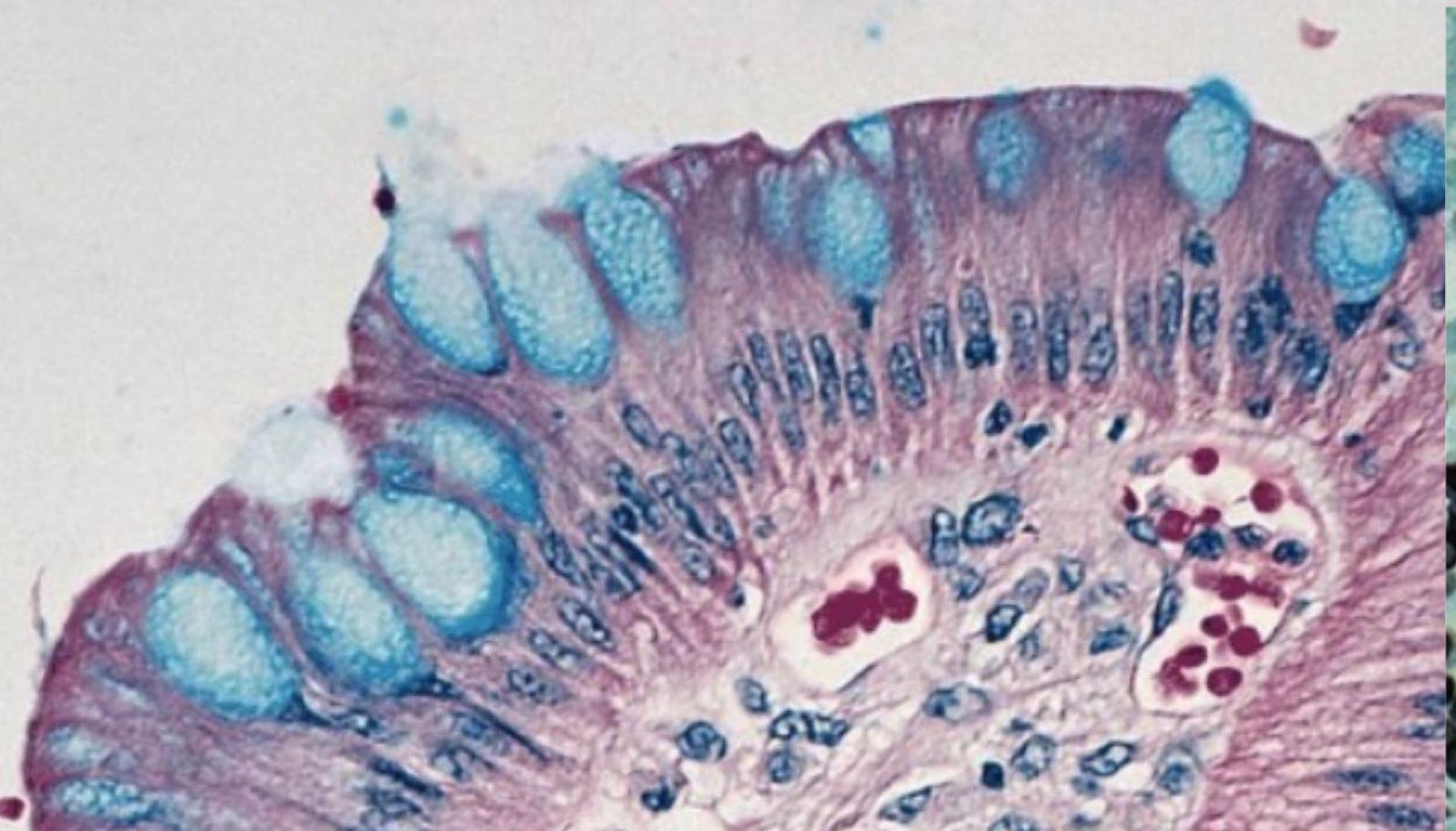


Pathologic diagnosis is a central determinant of therapeutic decisions.









# Emergence of early computational approaches in Pathology (1981)

## MORPHOMETRY FOR PROGNOSIS PREDICTION IN BREAST CANCER

SIR,—Some workers have found a correlation between prognosis and microscopical features of the primary tumour in breast cancer<sup>1-3</sup> but in one large prospective study the significance of the nuclear and histological grade for prognosis was weak.<sup>4</sup> Disagreement in grades assigned to the same tumours by different pathologists may range up to 40%,<sup>5,6</sup> and this disagreement may be due to the subjective nature of histopathological assessment. In contrast, the advantages of morphometry are objectivity and high reproducibility.<sup>7</sup>

PERCENTAGE CORRECTLY PREDICTED PROGNOSSES			
Method	Total (n = 78)	Learning set (n = 38)	Test set (n = 40)
ANS	59	65	54
TNM	64	67	56
Morphometry	87	92	78

Baak et al. Lancet 1981



# Artificial Neural Nets in Quantitative Pathology (1990)

[Anal Quant Cytol Histol. 1990 Dec;12\(6\):379-93.](#)  Paperpile

**Artificial neural networks and their use in quantitative pathology.**

Dytch HE<sup>1</sup>, Wied GL.

**“It is concluded that artificial neural networks, used in conjunction with other nonalgorithmic artificial intelligence techniques and traditional algorithmic processing, may provide useful software engineering tools for the development of systems in quantitative pathology.”**

# Emergence of Digital Pathology (2000)

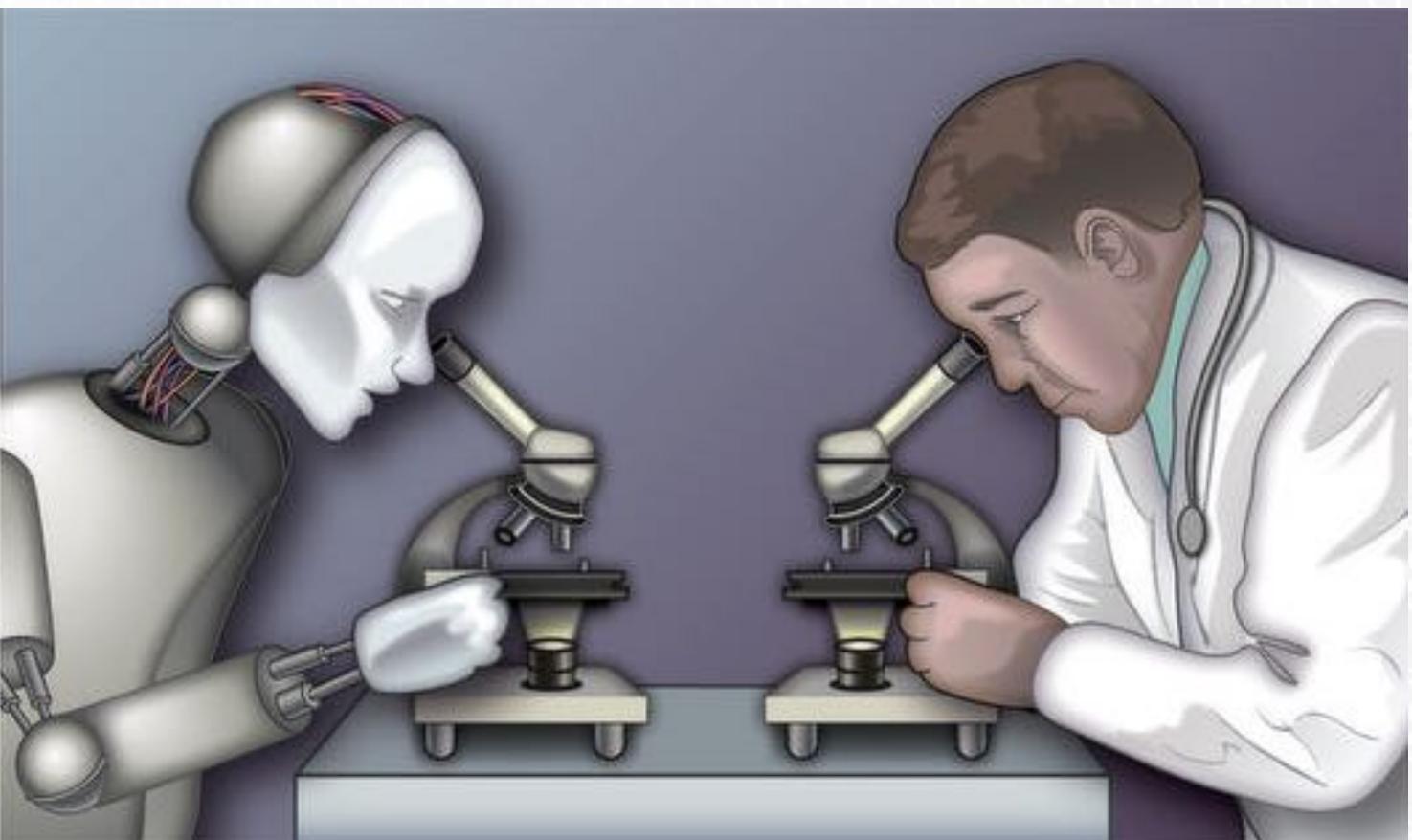
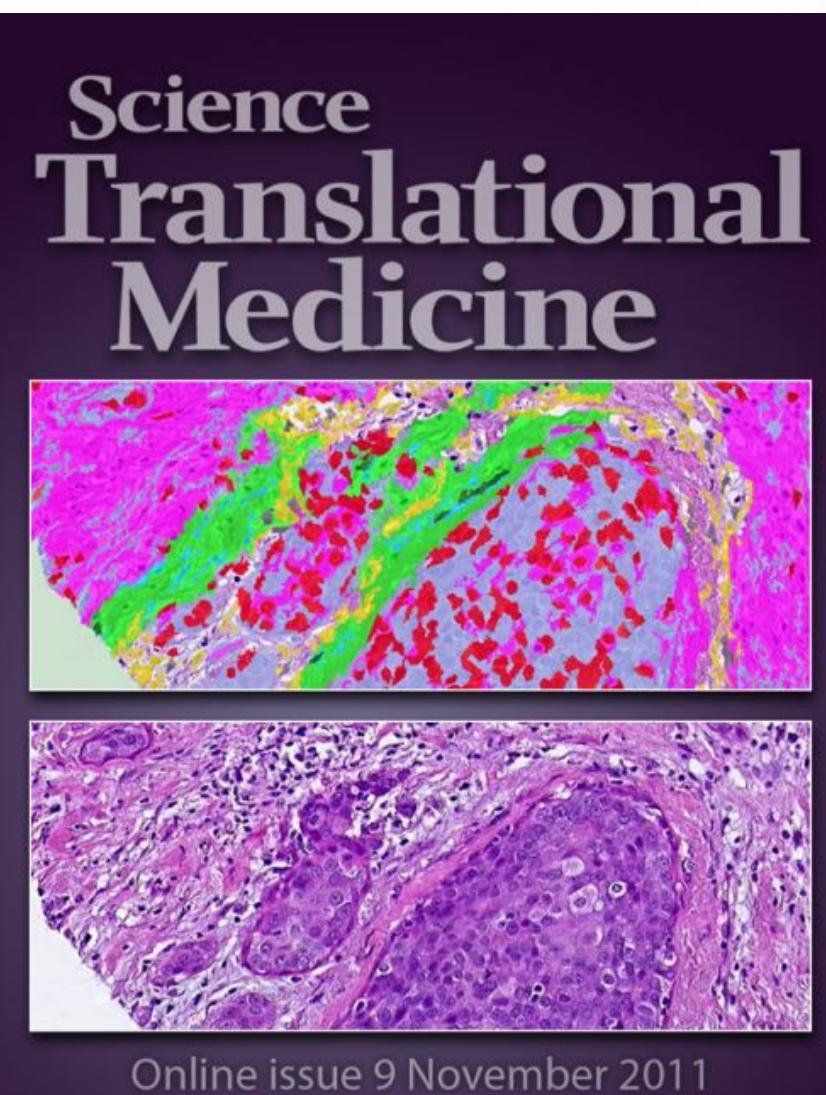
International Journal of Surgical Pathology 8(4):261–263, 2000

## Digital Pathology: Science Fiction?

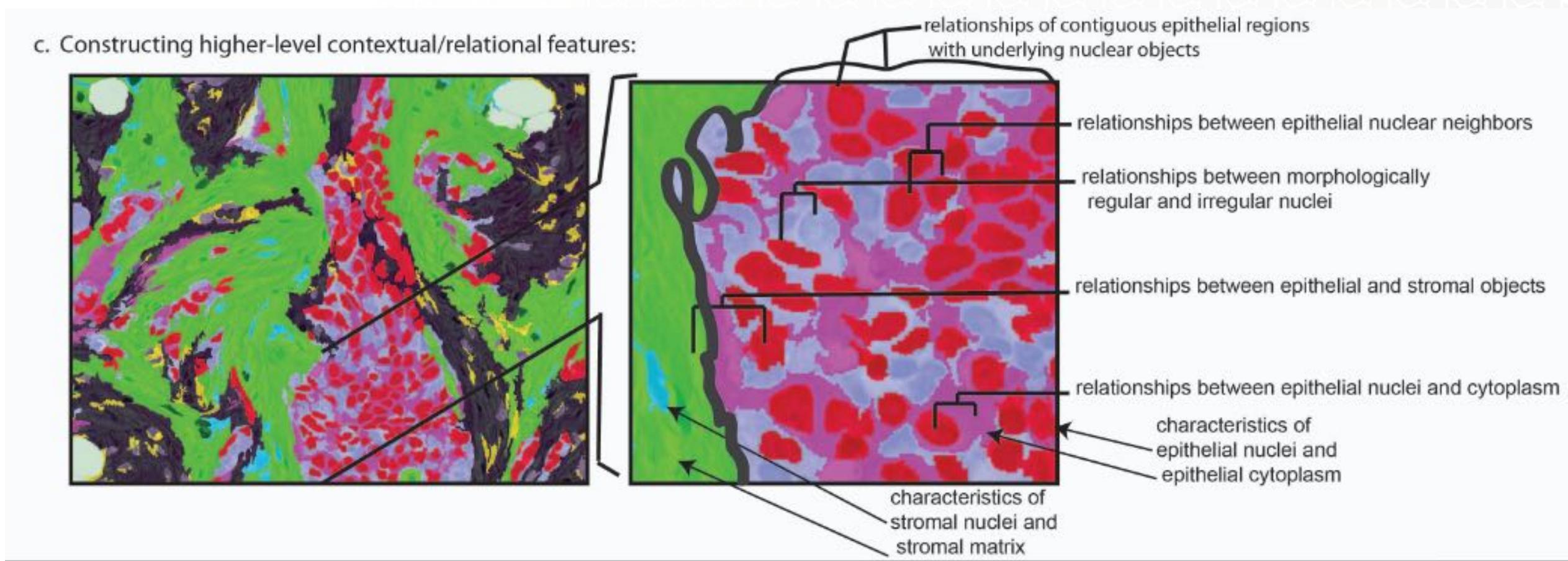
Mattia Barbareschi,\* Francesca Demichelis,† Stefano Forti,†  
and Paolo Dalla Palma\*

But what will come next? Is it possible to hypothesize that VC will completely substitute our traditional glass slides? Maybe yes, and let us describe the “science fiction” new millennium *digital pathology* laboratory, which we will call “DIGIPATH.”

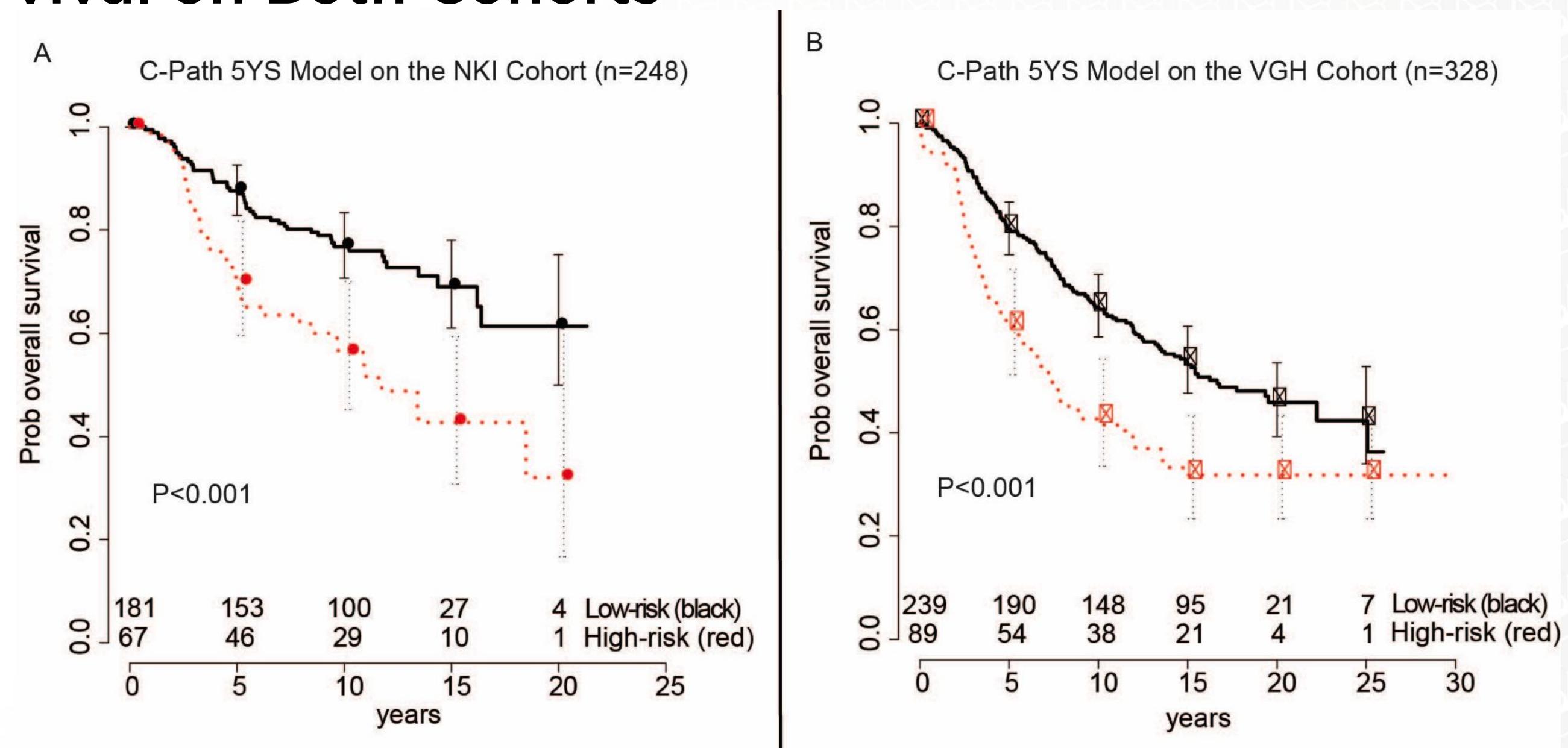
# The emergence of machine learning-based approaches for cancer histopathology



# Extracting a rich quantitative feature set



# C-Path 5YS Score Significantly Associated with Overall Survival on Both Cohorts



Proprietary & Confidential

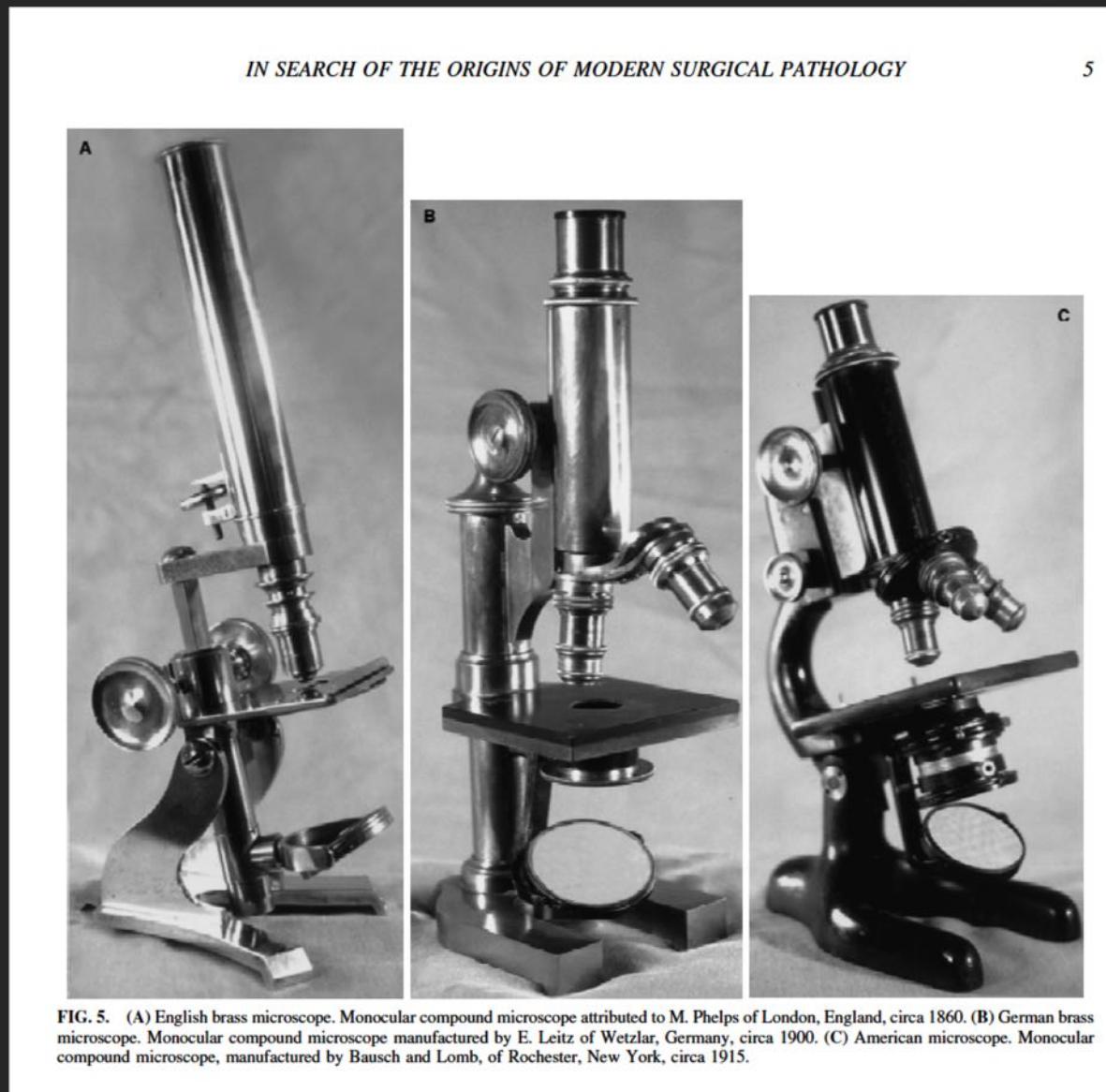
# Even today, the anatomic path lab has been largely unchanged for routine diagnostics



PathAI

Proprietary & Confidential

# And core technology breakthroughs in routine use are from the 19<sup>th</sup> century



## Histochemical Stains

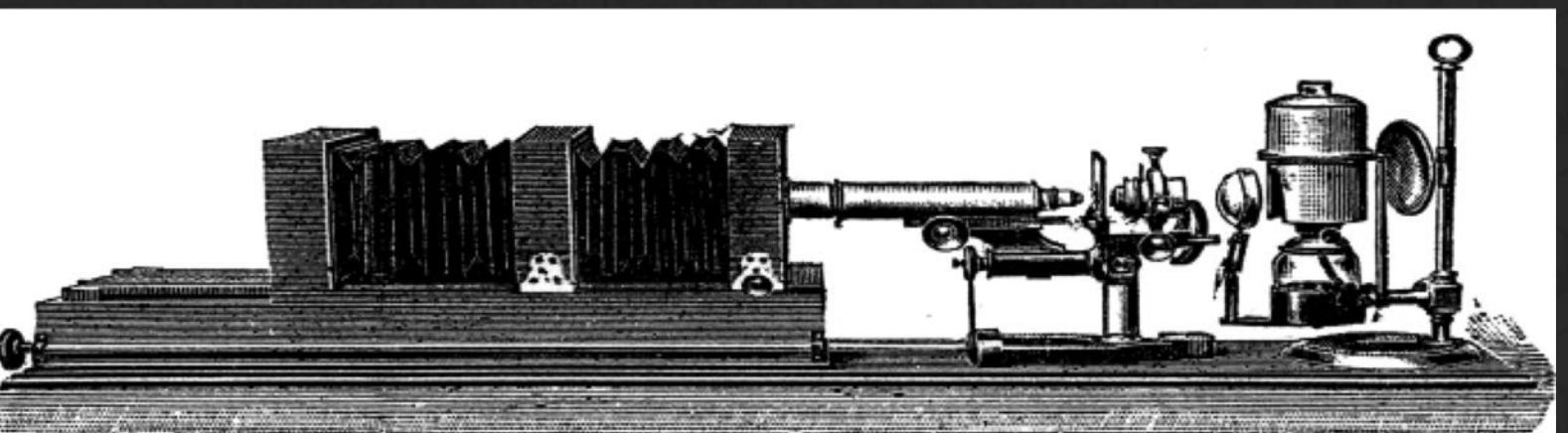
Developed from combinations of analine and natural dyes  
in the later half of the 19<sup>th</sup> century

- Mallory
- Van Gieson
- Congo red
- Gram
- Ziehl-Neelsen
- Methylene blue
- Hematoxylin & eosin
- Hematoxylin
- Carmine

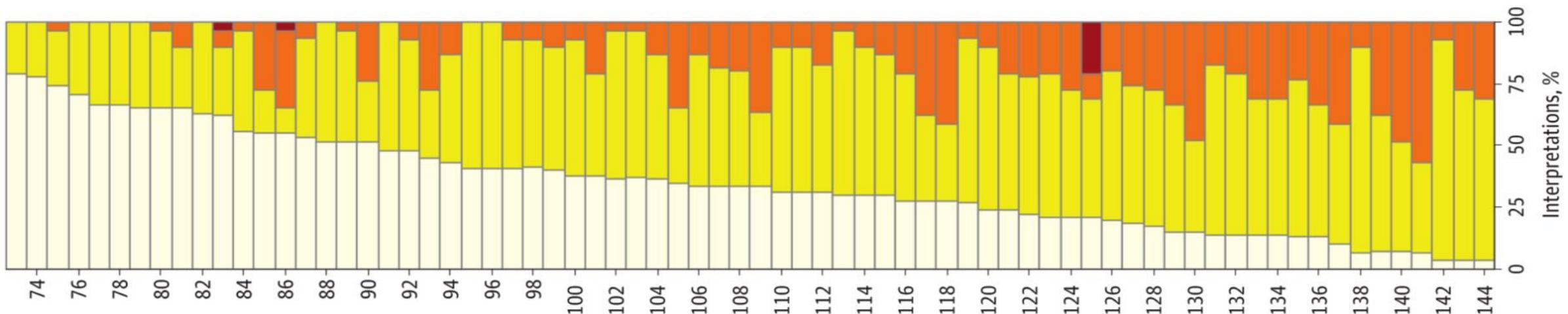
1850    1860    1870    1880    1890    1900

## Photomicroscope

Horizontal apparatus with camera, microscope, and light source, 1895.



# Discordance among pathologists is common in interpretation of breast biopsies

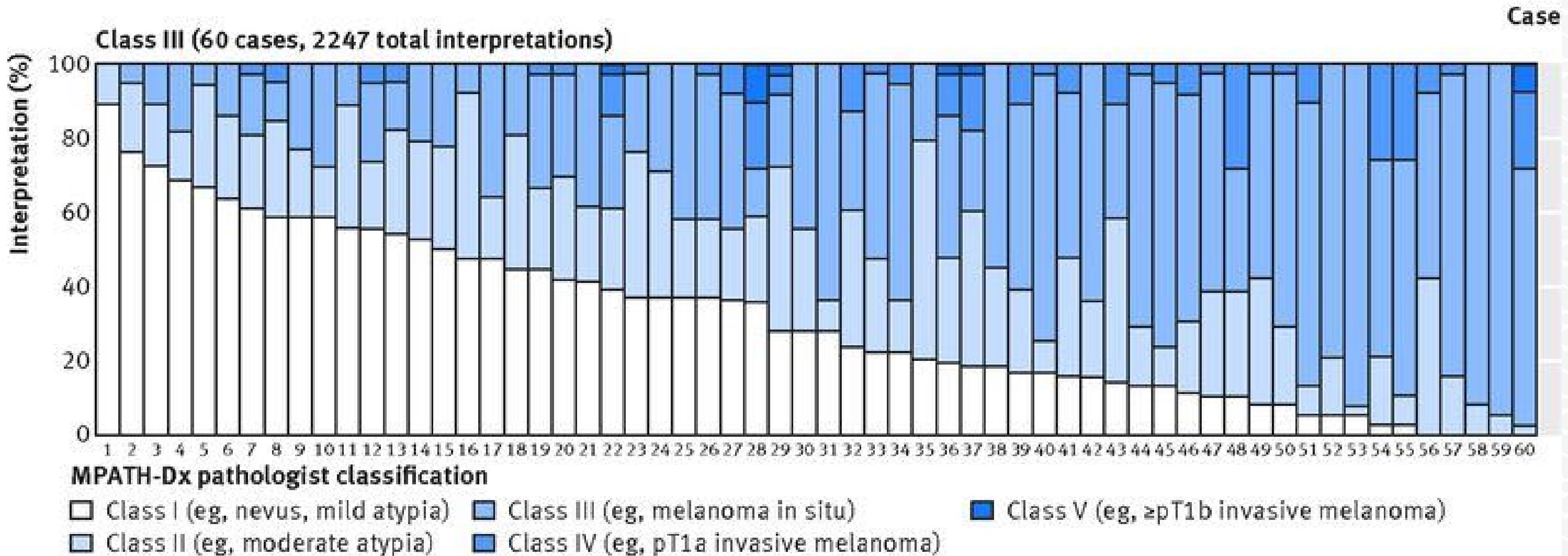


	Phase II Interpretation of Same Individual Pathologist					Agreement rates of phase I and II interpretations, % (95% CIs)
	Benign without atypia	Atypia	DCIS	Invasive	Total	
Phase I Interpretation of Individual pathologist						
Benign without atypia	947	137	41	5	1130	84 (81-86)
Atypia	157	303	109	2	571	53 (47-59)
Ductal Carcinoma <i>in situ</i> (DCIS)	43	94	792	14	943	84 (81-87)
Invasive Breast Cancer	8	4	11	273	296	92 (88-95)
Total	1155	538	953	294	2940	79 (77-81)

\*The same slide was interpreted on two different occasions separated in time by 9 or more months

Pathologists in individual practice setting  
Overall concordance rate of 75% on breast biopsies.  
Inter-observer concordance rate of only 48% for a diagnosis of atypia.  
Intra-observer concordance is only 79% overall and 53% for atypical lesions

# Discordance among pathologists is common in interpretation of melanocytic neoplasms on skin biopsies



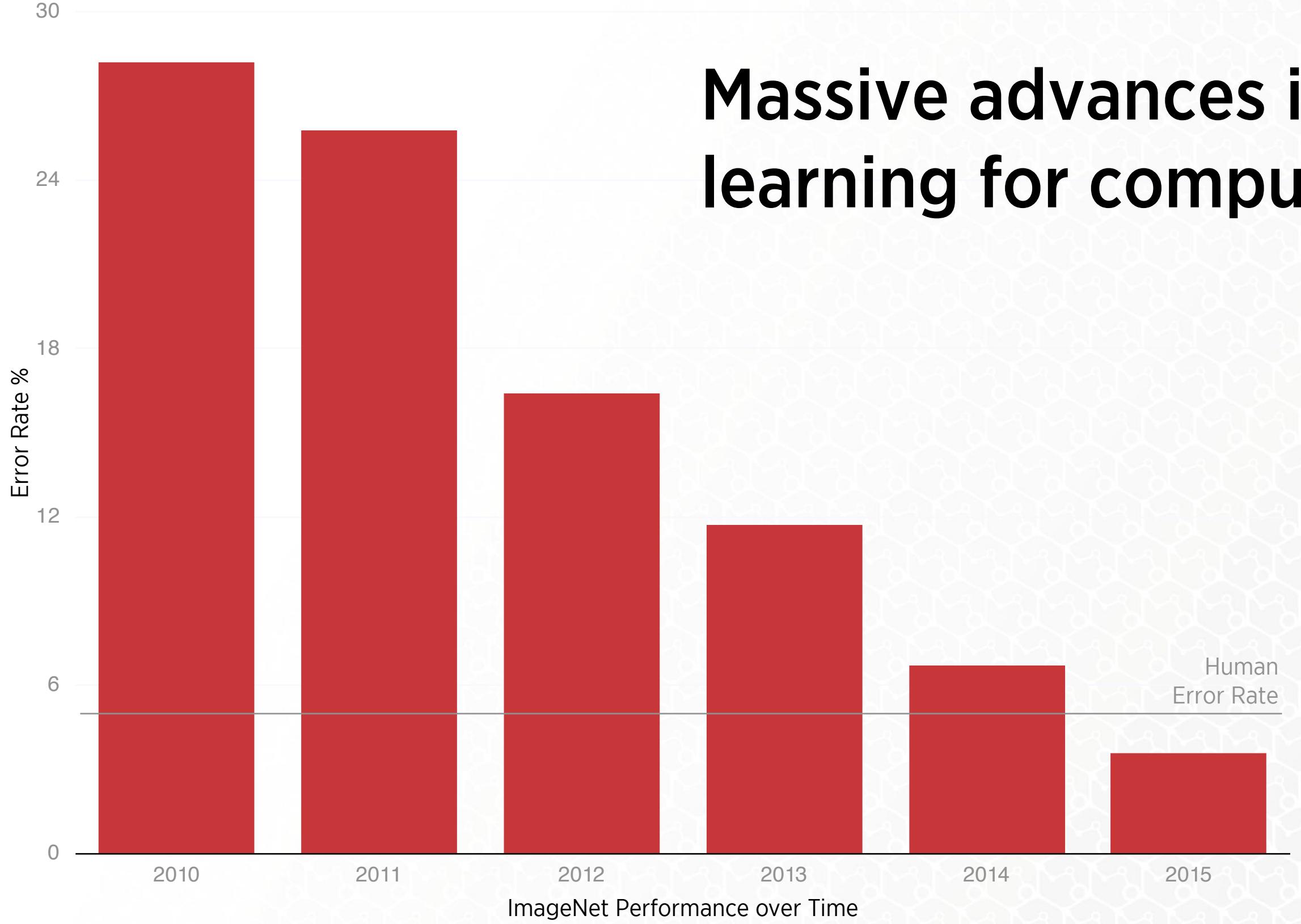
- 187 pathologists interpreted skin lesion biopsies, resulting in an overall discordance of 45%
- 118 pathologists read the same samples 8 months apart, and had an intraobserver discordance of 33%

Discordance rates across a broad set of specimen types is fairly high with little improvement over past several decades



**Table 3. Summary of Studies That Express a Discrepancy or Major Discrepancy Rate**

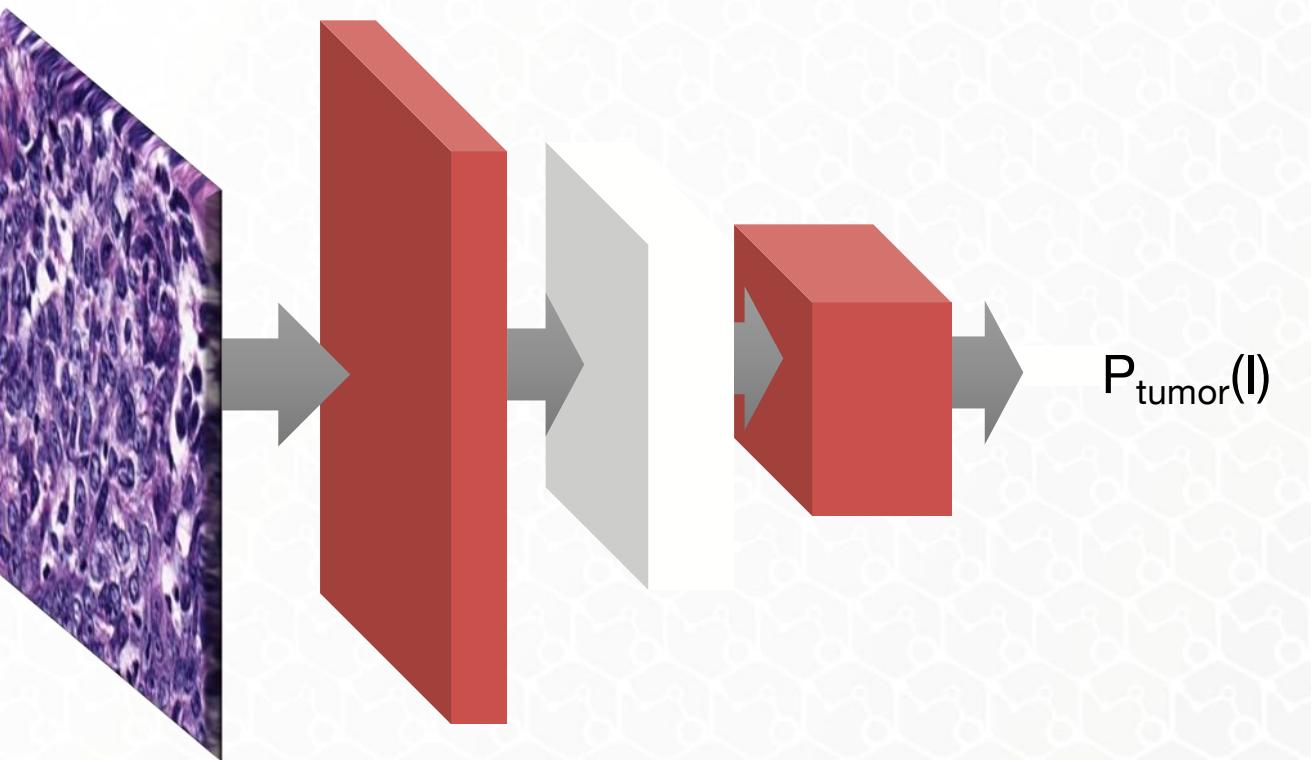
Study Type	Discrepancy Rates, %		Major Discrepancy Rates, %	
	No. of Studies	Median (25th–75th Percentile)	No. of Studies	Median (25th–75th Percentile)
All studies	116 <sup>c</sup>	18.3 (7.5–34.5)	78 <sup>d</sup>	5.9 (2.1–10.5)
Surgical pathology	84 <sup>e</sup>	18.3 (7.5–37.4)	63 <sup>f</sup>	6.3 (1.9–10.6)
Cytology		24.8 (17.4–38.8)	11 <sup>h</sup>	4.3 (2.8–7.5)
Both		9.1 (6.7–15.8)	11 <sup>i</sup>	5.9 (3.3–8.7)
Multiorgan		9.1 (3.8–18.7)	42 <sup>j</sup>	3.9 (1.1–7.4)
Single-organ <sup>a</sup>	73 <sup>m</sup>	25.2 (14.0–43.7)	36 <sup>n</sup>	8.0 (3.7–15.8)
Internal <sup>b</sup>	35 <sup>o</sup>	10.9 (3.8–17.6)	22 <sup>p</sup>	1.2 (0.30–3.1)
External	79 <sup>q</sup>	23.0 (10.6–40.2)	56 <sup>r</sup>	7.4 (4.6–14.7)



# Massive advances in deep learning for computer vision...

# What does AI mean at PathAI?

- Models which learn how to make decisions and predictions by recognizing patterns in data.
- These can be traditional machine learning models or, more commonly, deep convolutional neural networks.



**The human defines the data, the data defines the algorithm.**

**Traditionally, the human defines the algorithm**

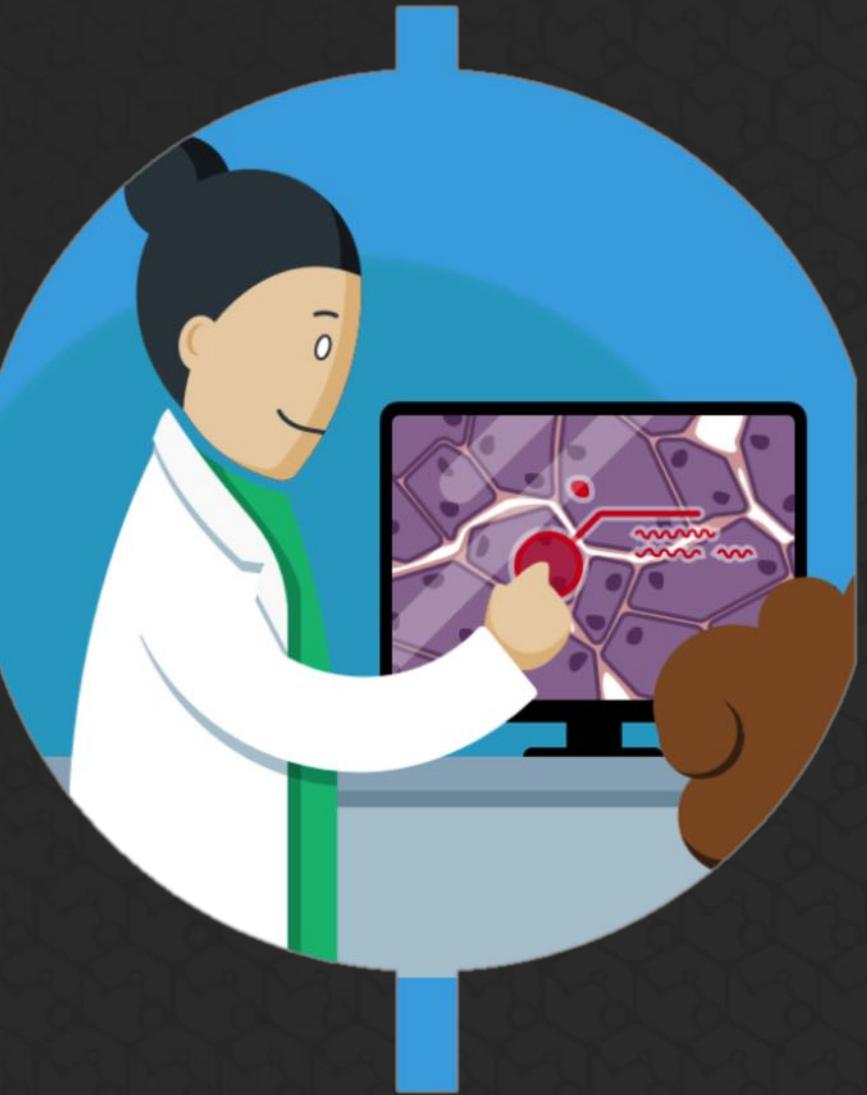
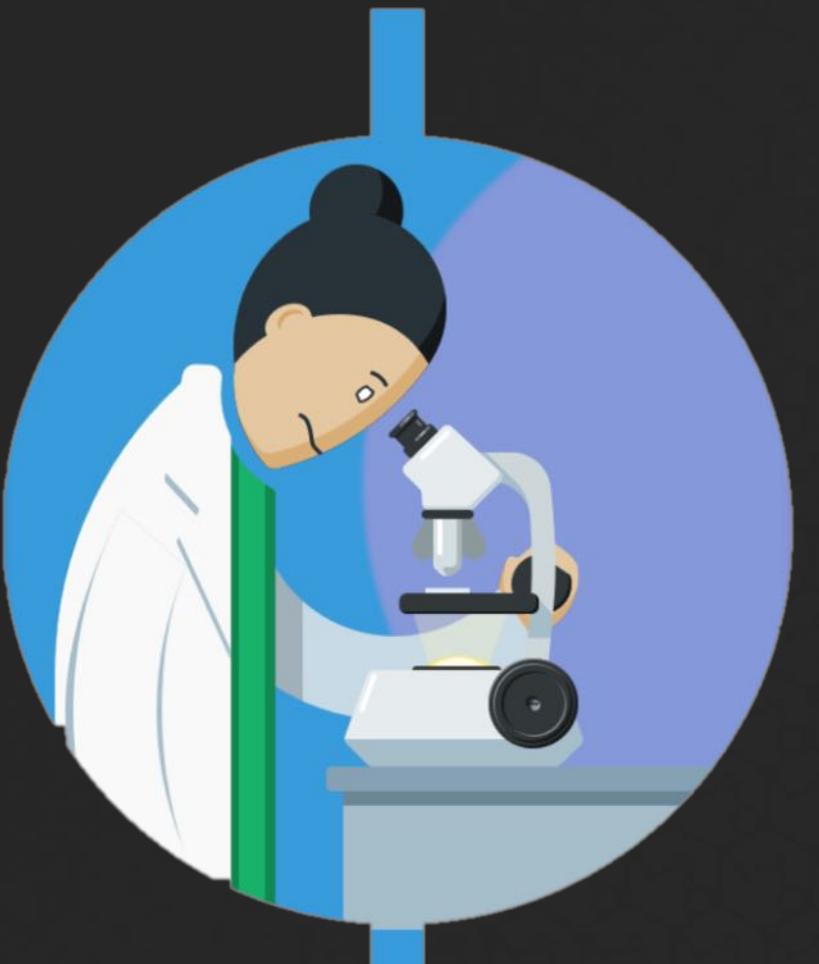
# What can AI do for pathology?

## A (somewhat) *practical* treatment

- Exhaustive - the model is tireless and is not distracted
- Quantitative - the model is reproducible and objective
- Efficient - massive parallelization for speedy processing
- Exploratory - learn relationships in a purely data-driven manner

# What AI *can't* do for pathology

Replace pathologists!



# A diagnosis/detection example: Breast cancer metastases

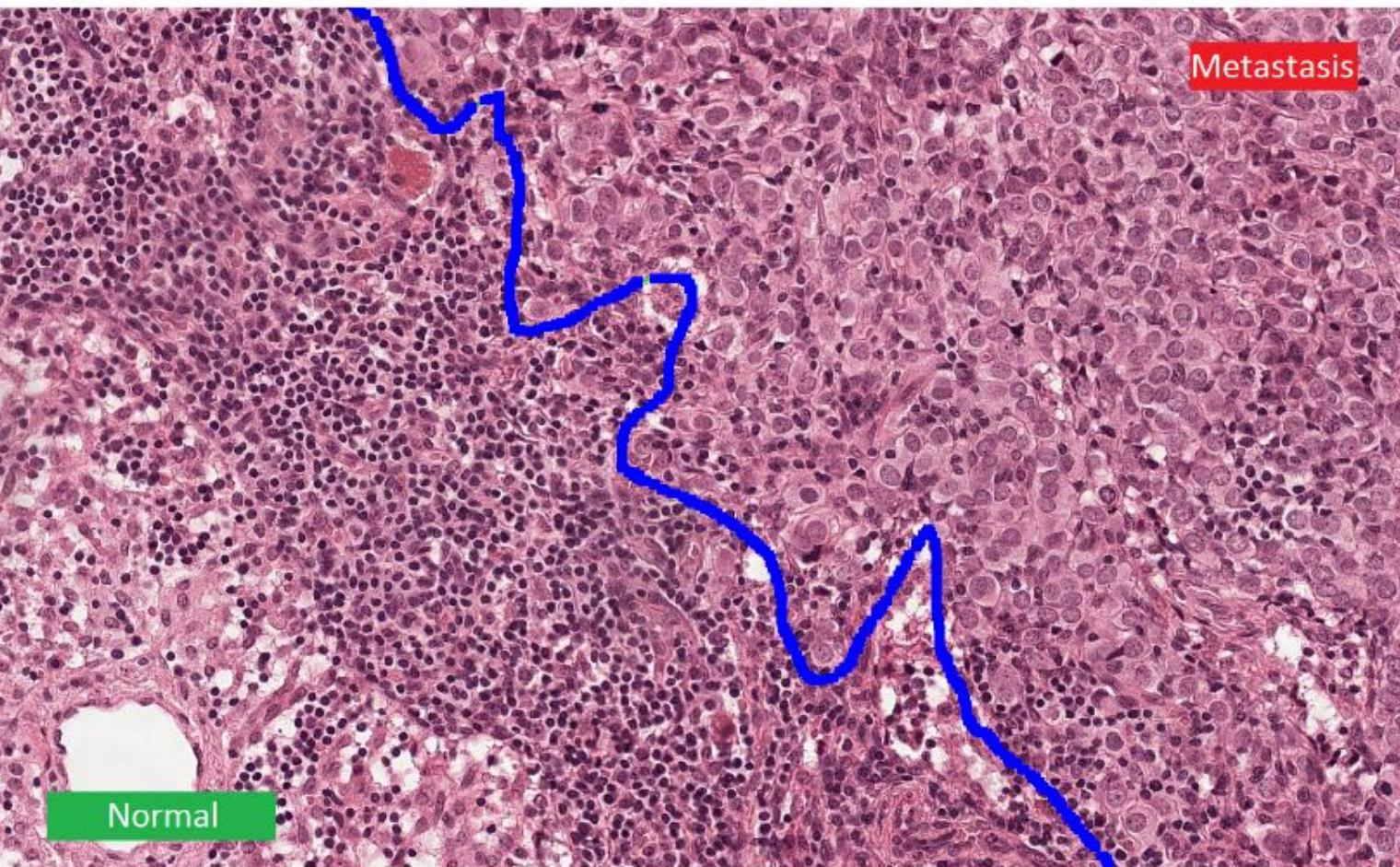
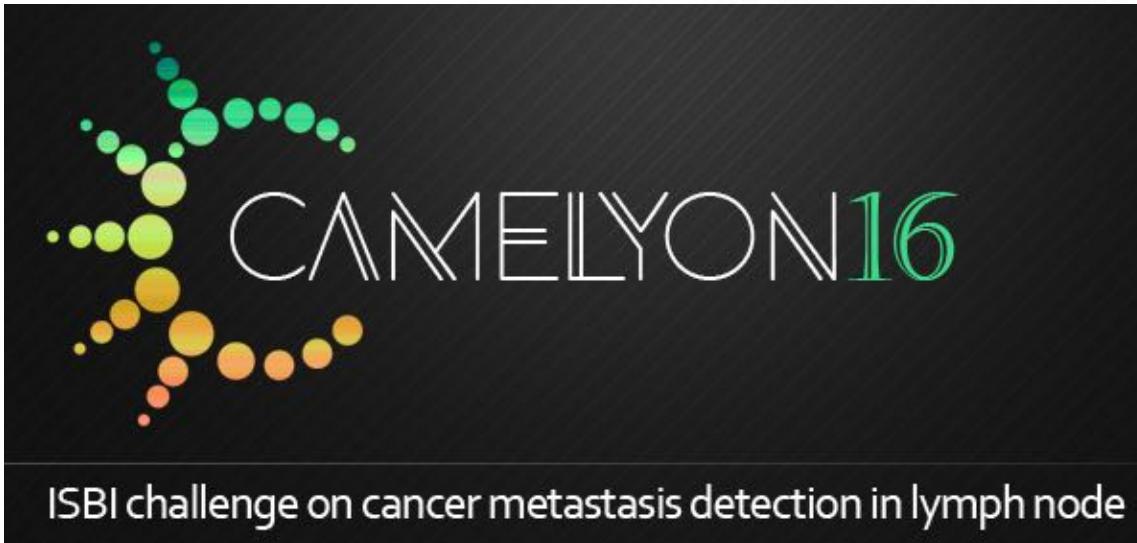


- After a primary mass discovered, lymph nodes are biopsied
- Pathologists check these for metastases
- Non-zero failure rate: a retrospective study found a 24% disagreement rate<sup>1</sup>

<sup>1</sup>Vestjens JHMJ, Pepels MJ, de Boer M, et al. Relevant impact of central pathology review on nodal classification in individual breast cancer patients. *Ann Oncol.* 2012;23(10):2561-2566.

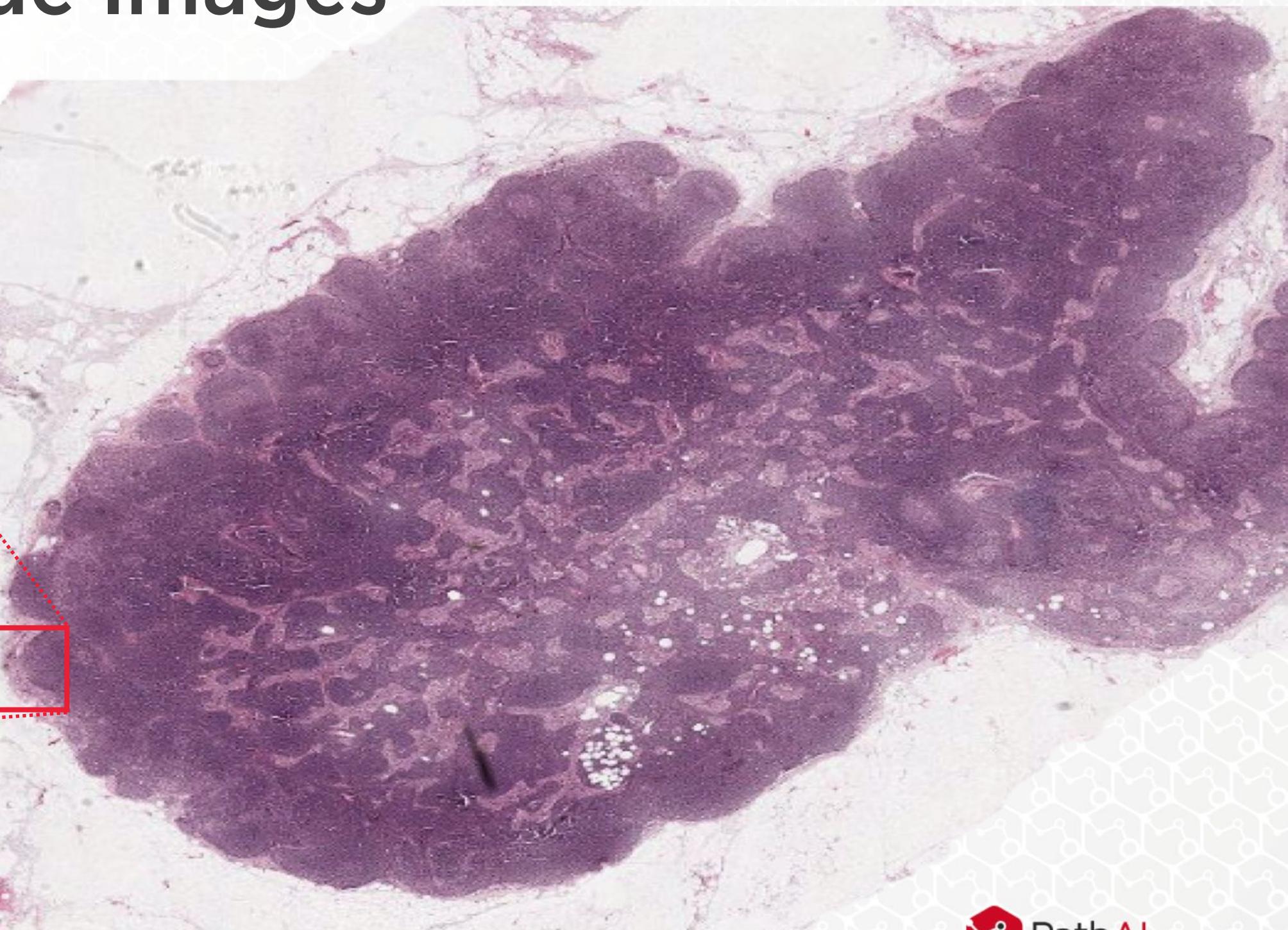
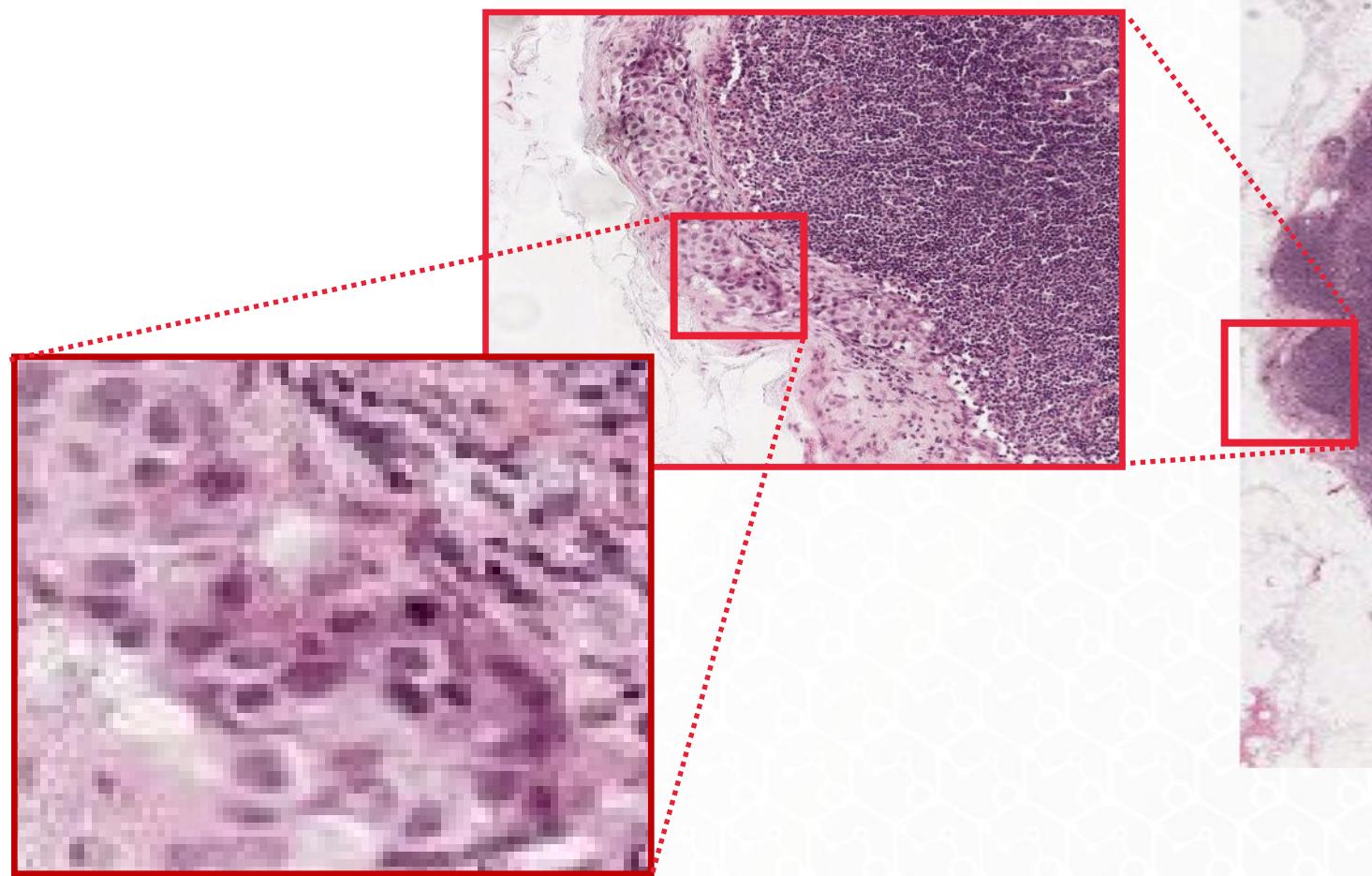
# The data - CAMELYON

- H & E stained, Formalin-Fixed Paraffin-Embedded (FFPE)
  - 270 training slides, 129 test
- Annotated by a panel



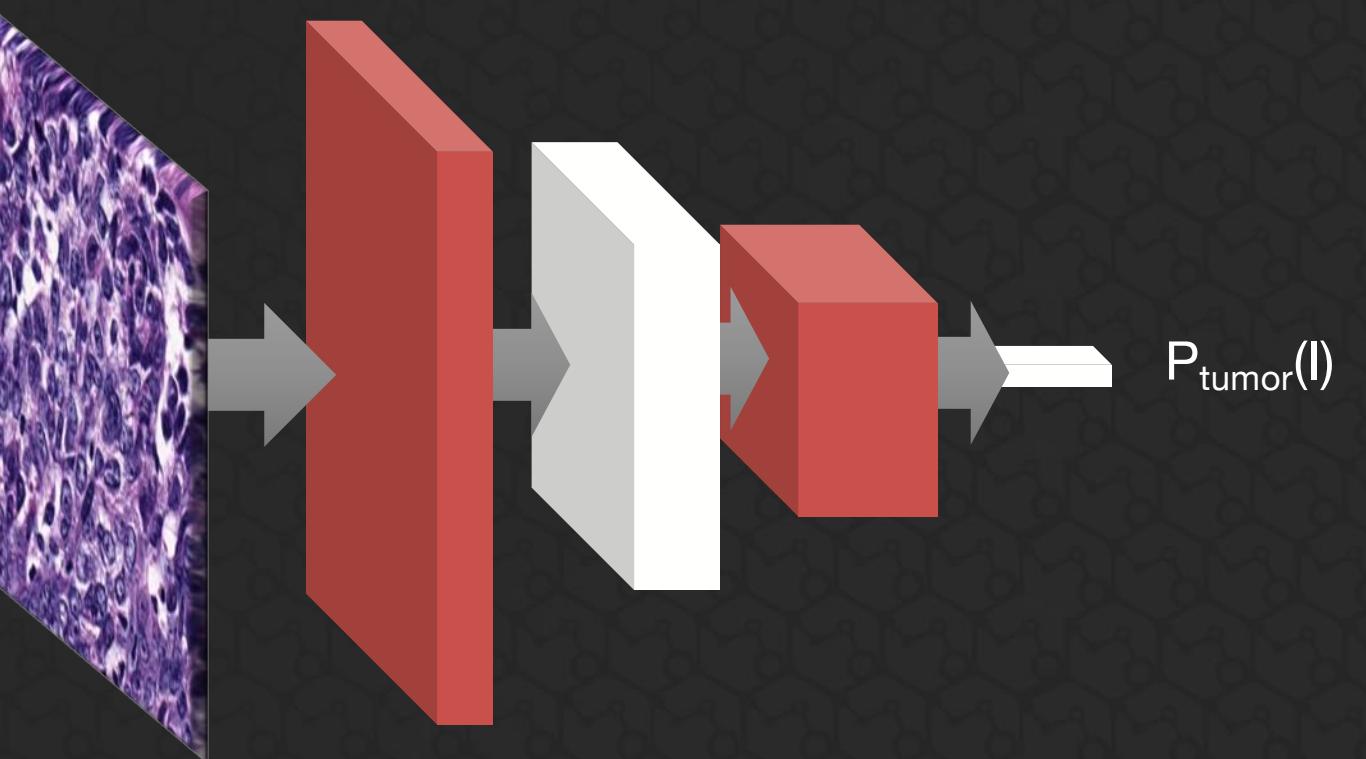
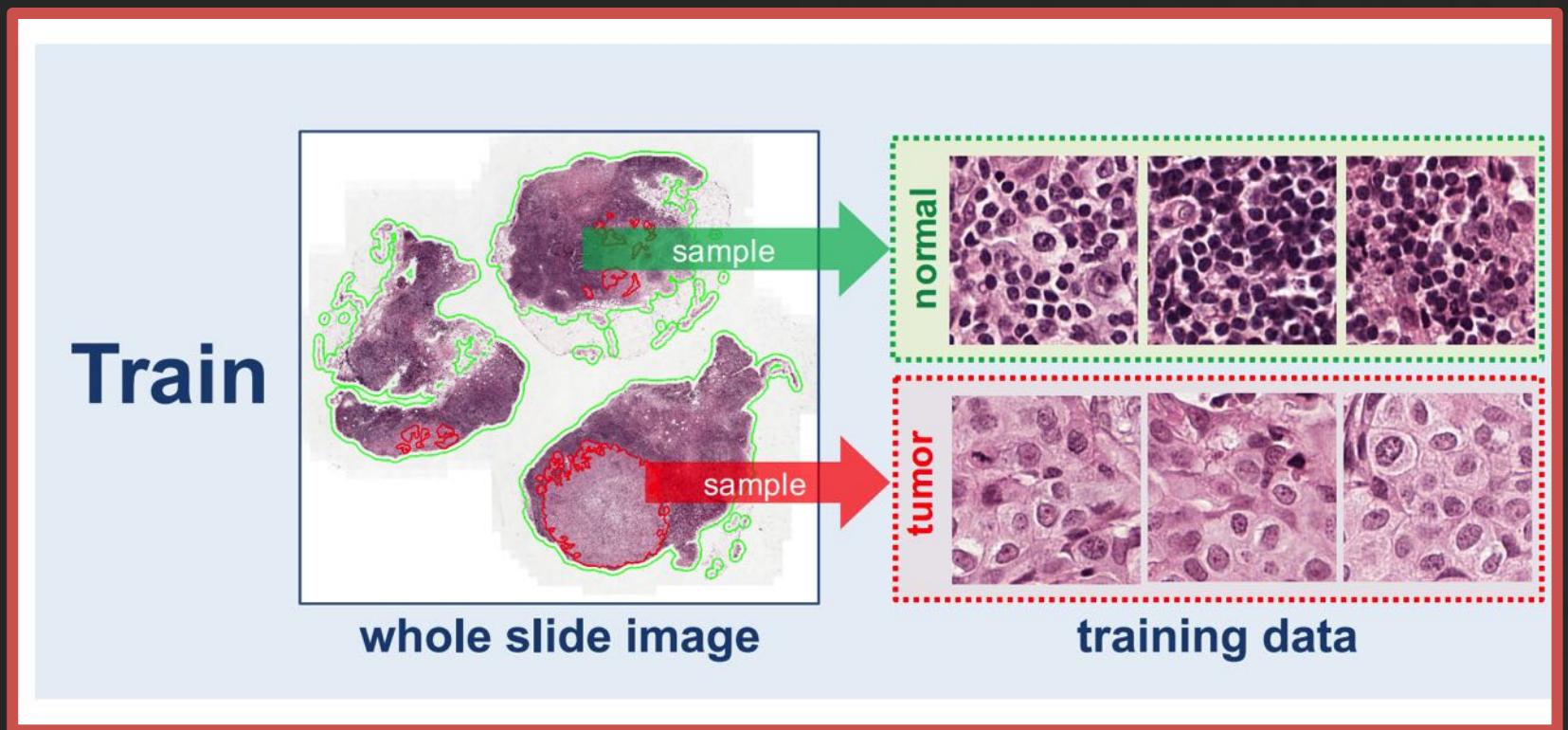
# The data – Whole-Slide Images

- WSIs are large ~20,000-200,000 pixels on a side (“gigapixel”)
  - mm-cm imaged at 20x/40x
- Demo - TCGA lung cancer



# Approach

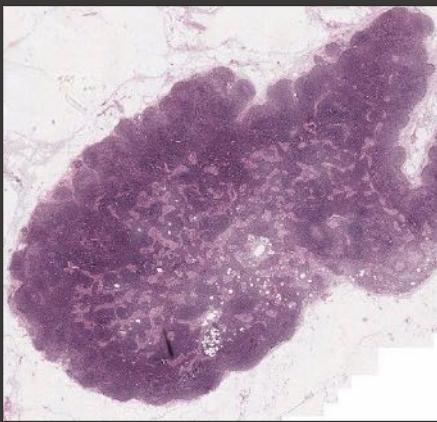
- Standard image classification approach needs a twist for WSIs: sampling



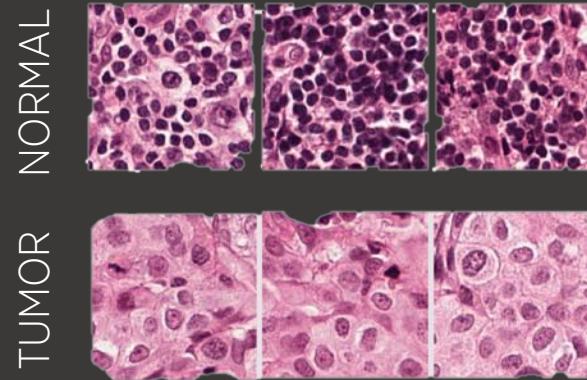
# Successfully applied deep learning approach to pathology

Our team won the Camelyon challenge in 2016, demonstrating outstanding initial performance in pathology

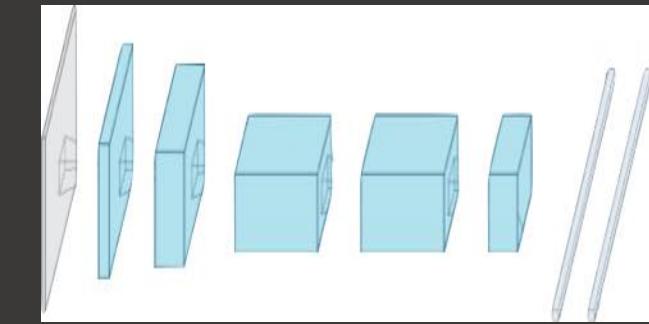
TRAIN



Whole Slide Image

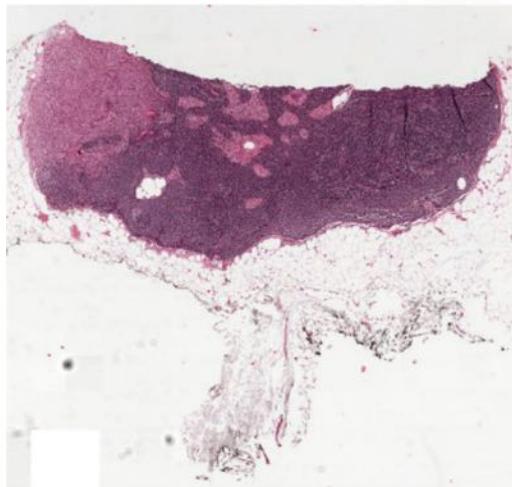


Training Data



Deep Model

TEST



Whole Slide Image

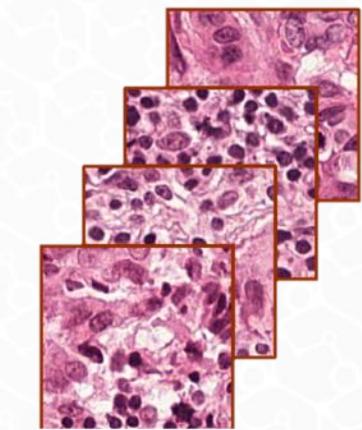
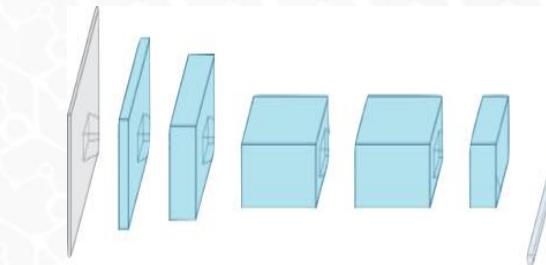
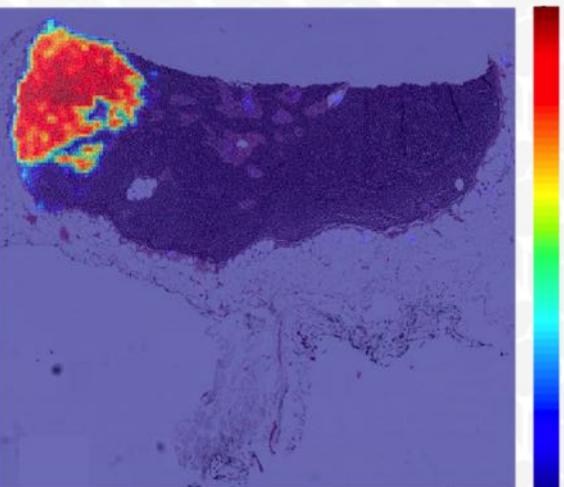


Image Patches



Deep Model from Training



Tumor Probability Map



# Deep learning model outperforms human pathologists in the diagnosis of metastatic cancer



<sup>1</sup>n=12

<sup>2</sup>Small tumors

References: Wang, Khosla, ... Beck (2016) <https://arxiv.org/abs/1606.05718> Camelyon16 (JAMA, 2017)

# Caveats and considerations

- Real world data vs. competition data

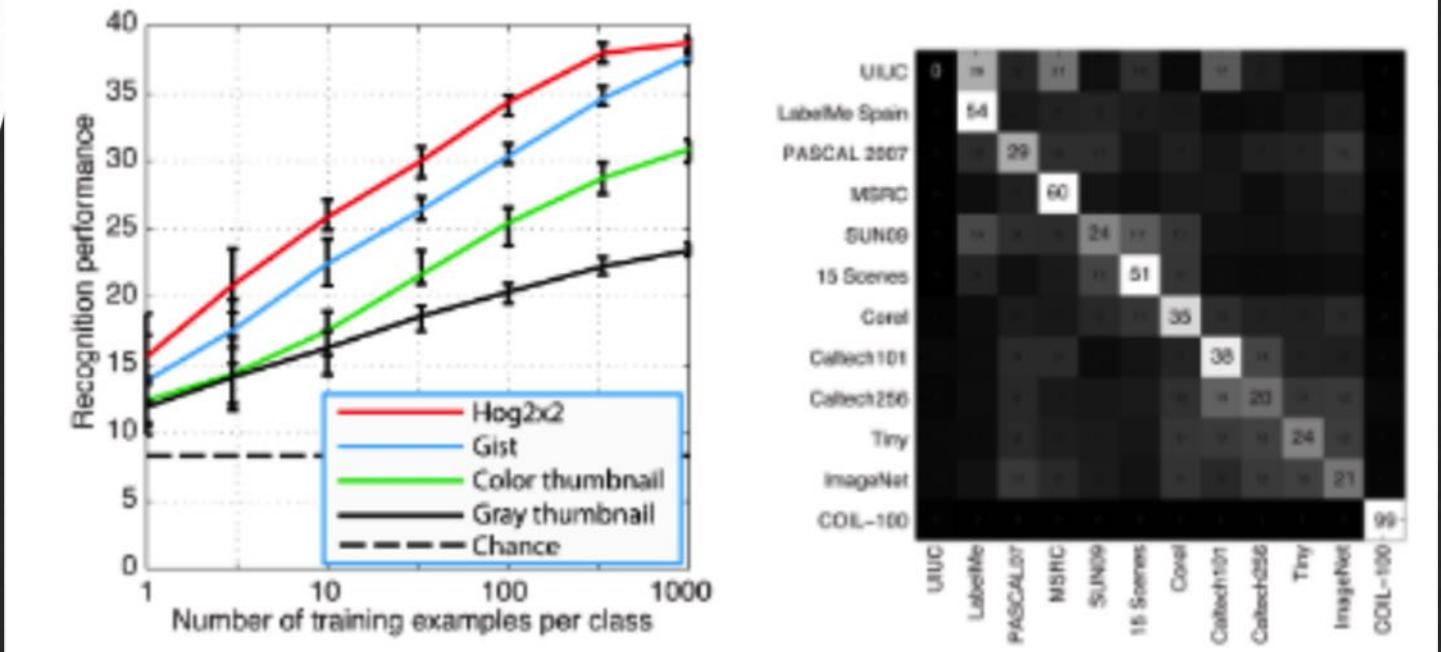
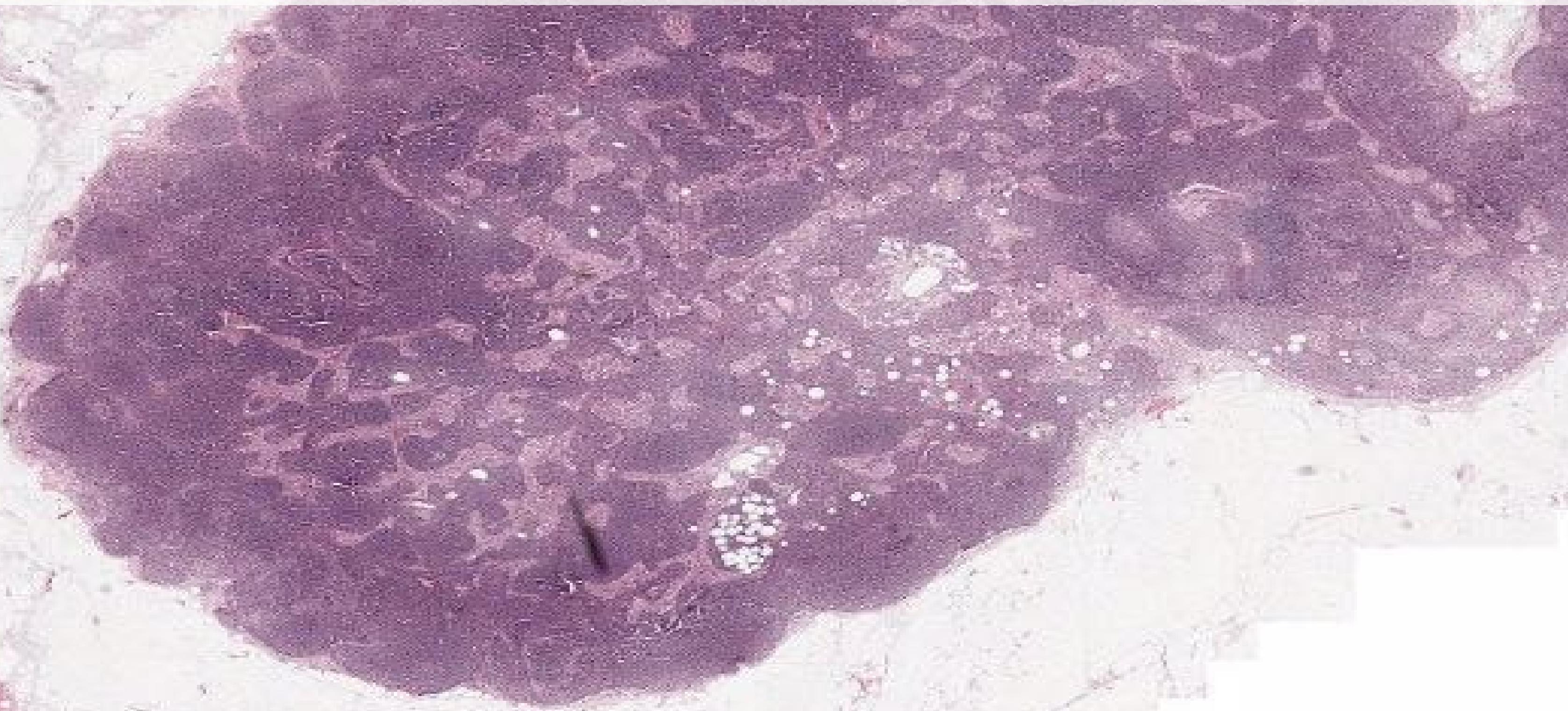


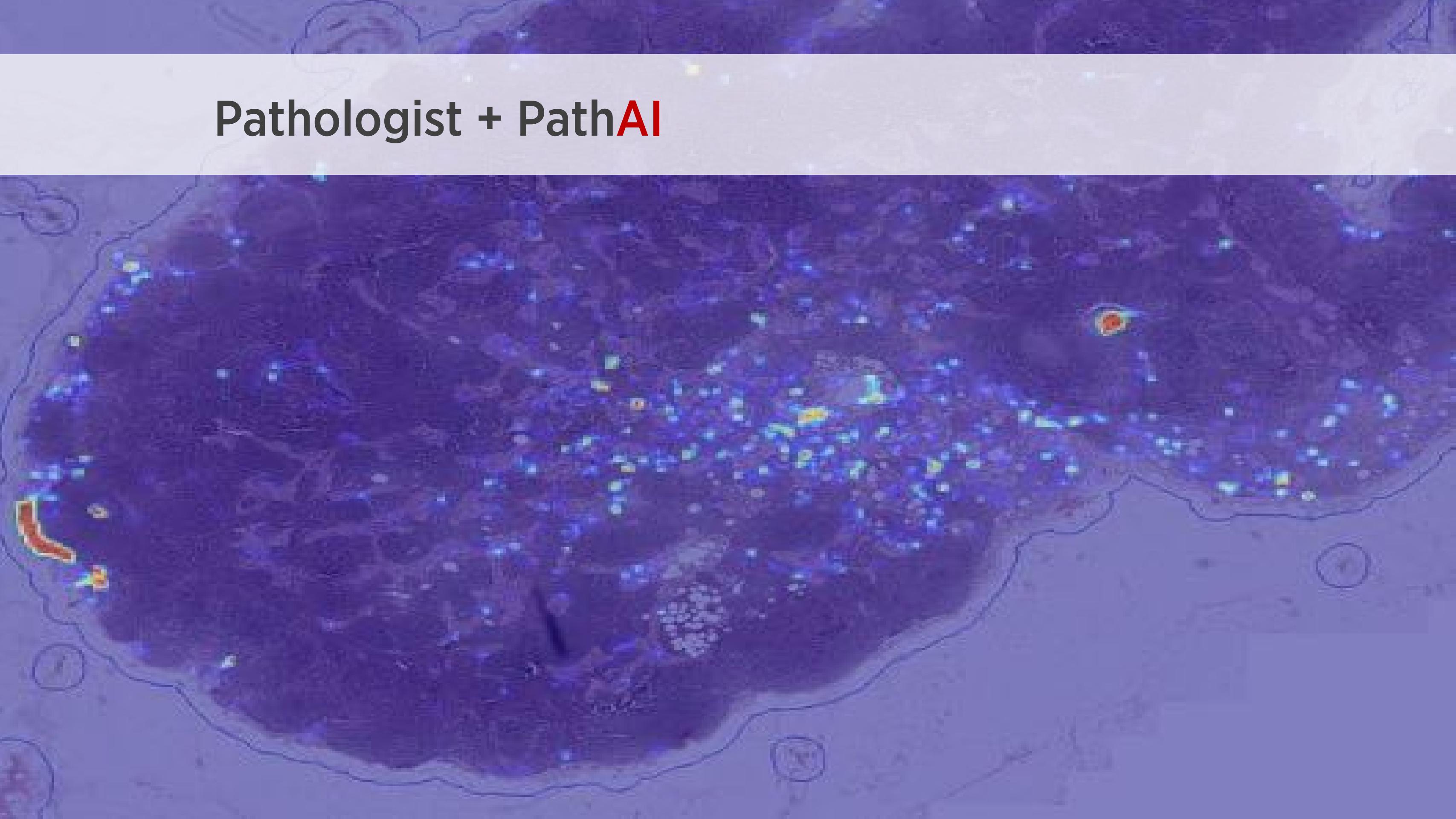
Figure 2. Computer plays *Name That Dataset*. Left: classification performance as a function of dataset size (log scale) for different descriptors (notice that performance does not appear to saturate). Right: confusion matrix.

Torralba & Effros, 2011

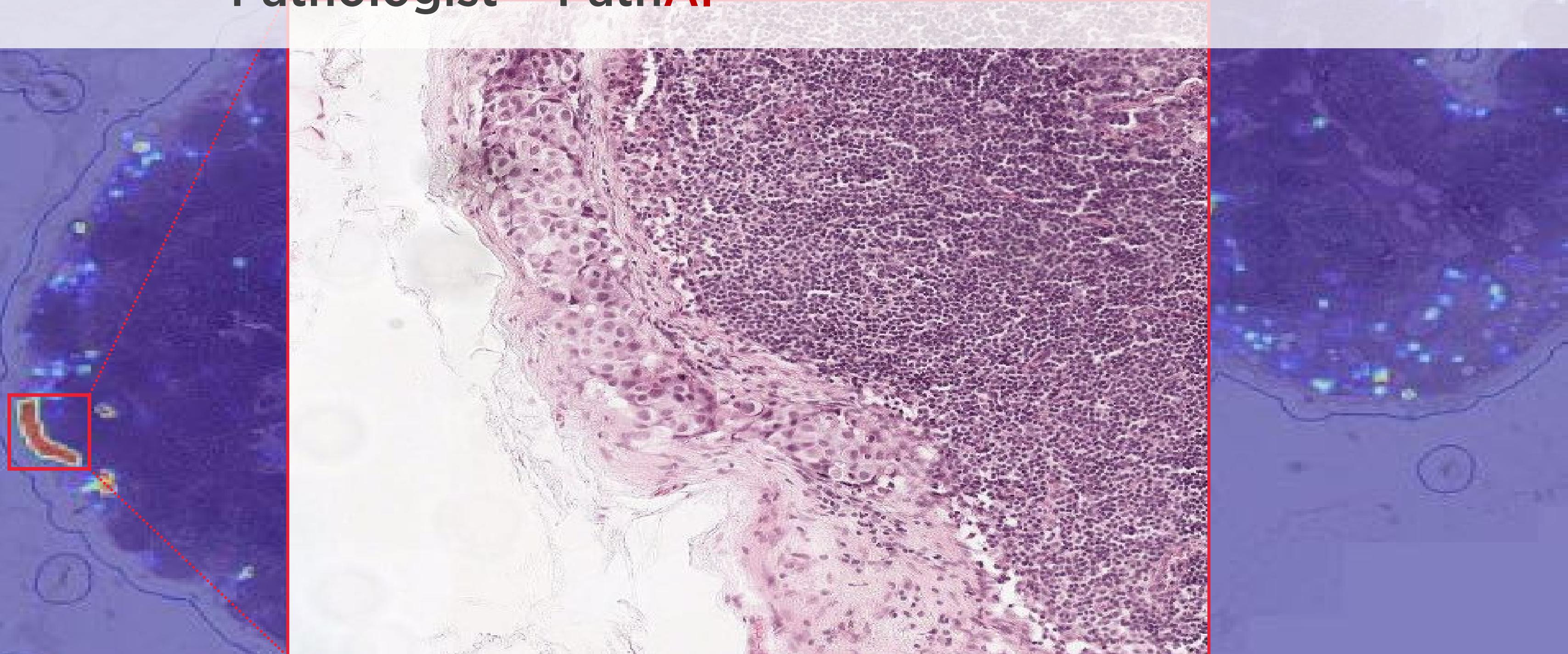
**Pathologist + PathAI**



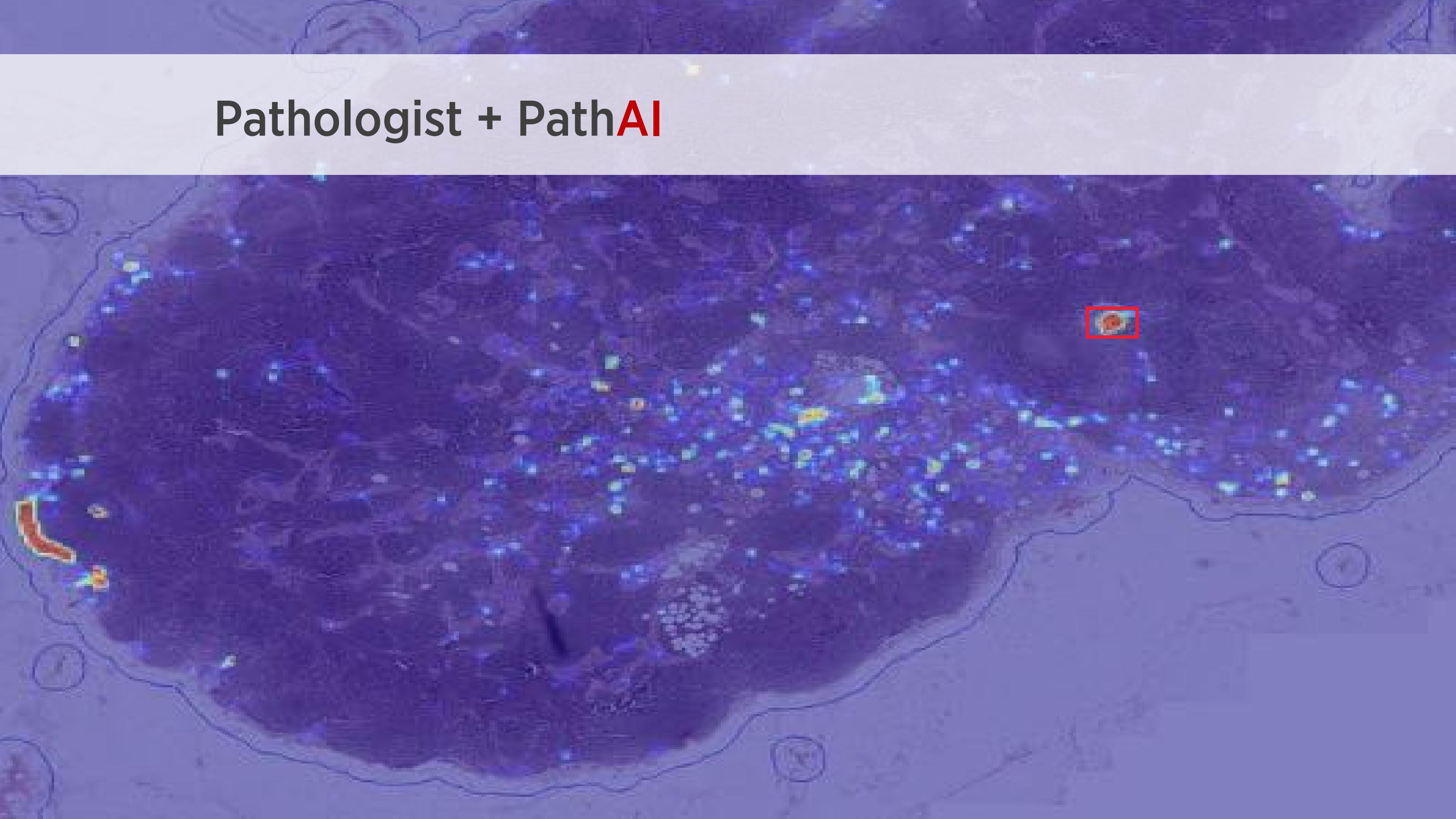
# Pathologist + PathAI



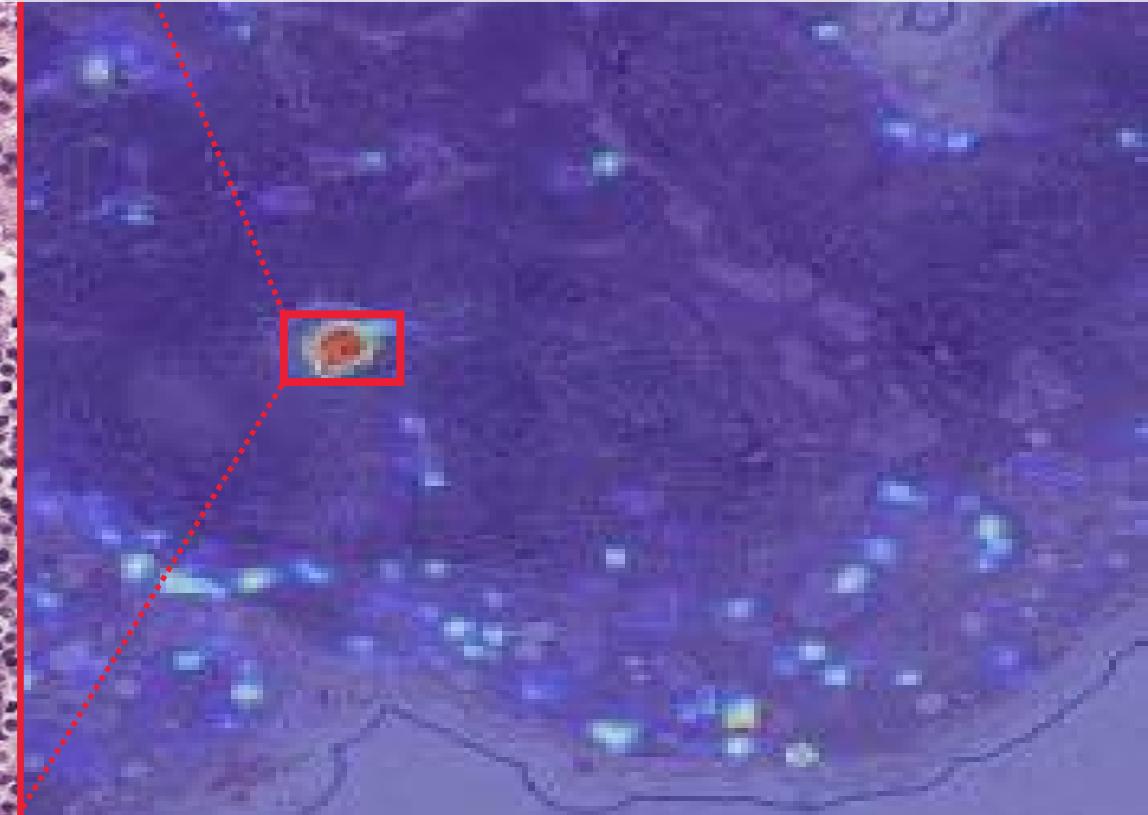
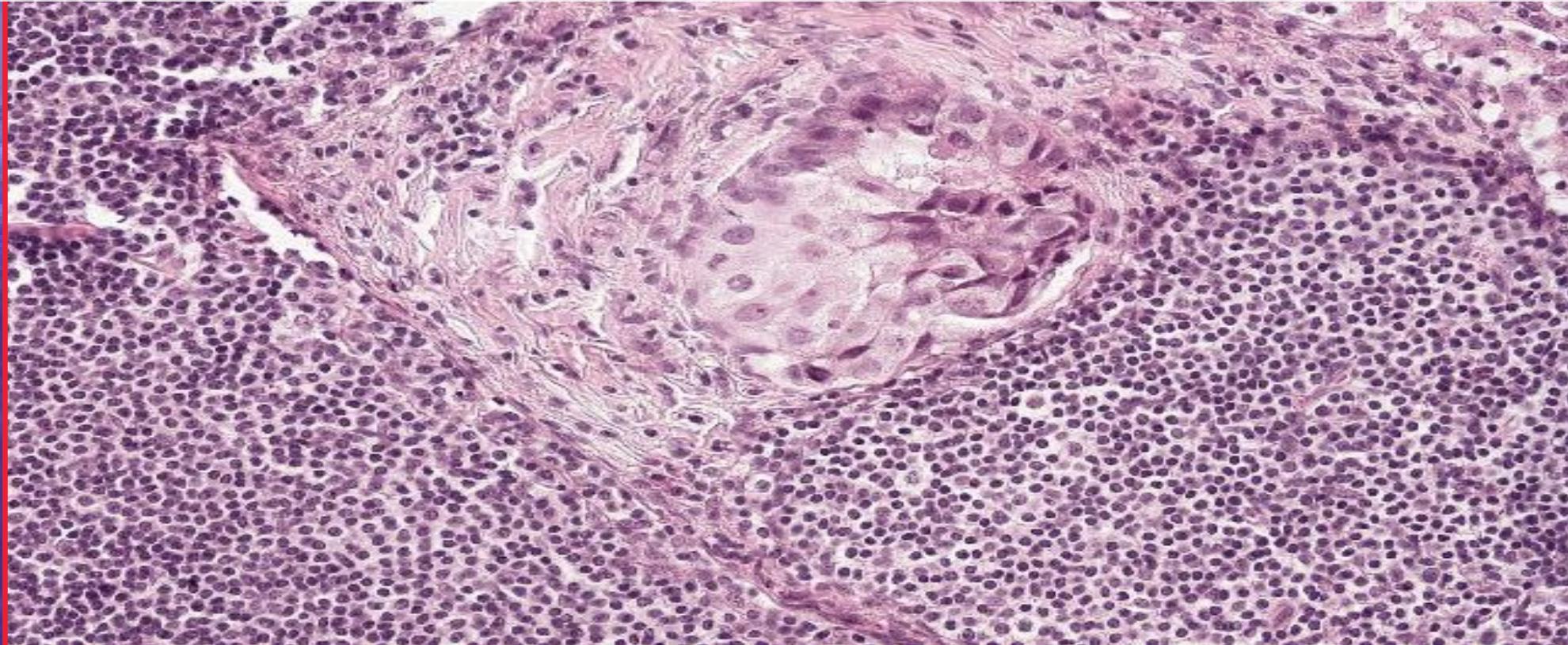
# Pathologist + PathAI

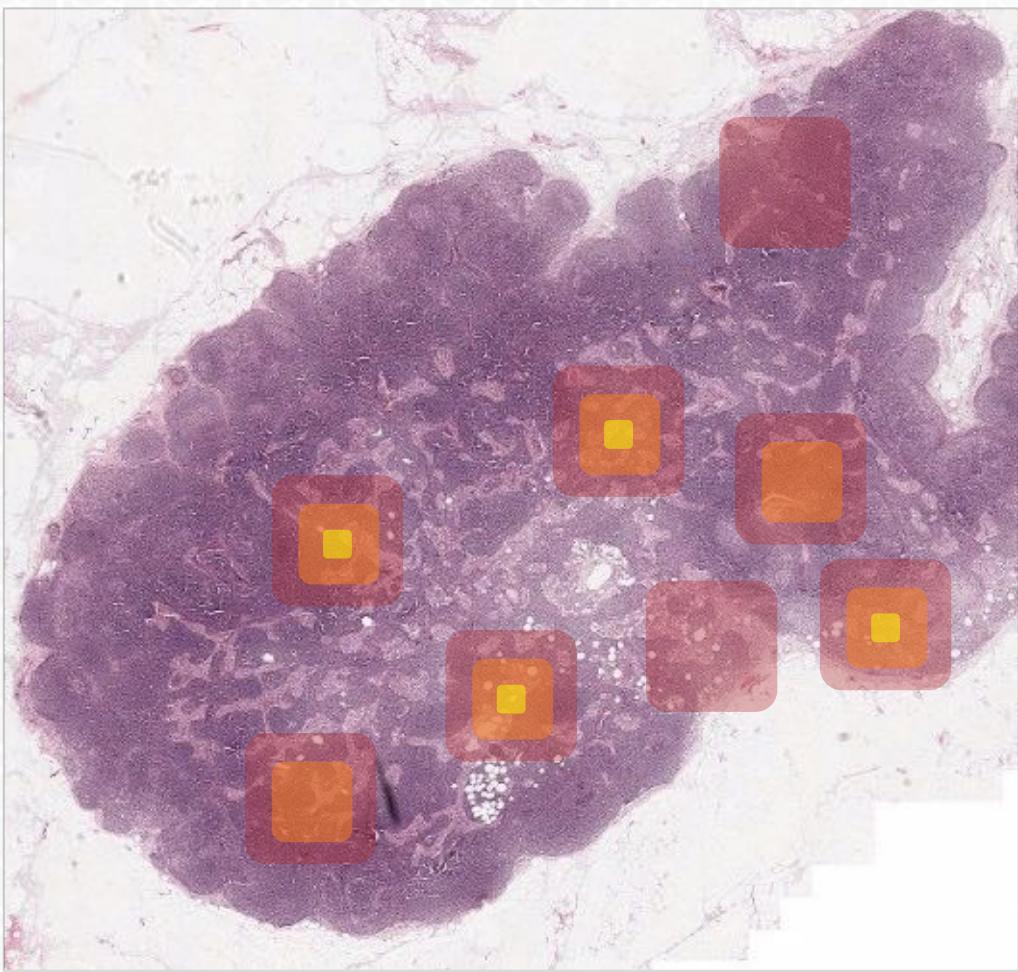


# Pathologist + PathAI



**Pathologist + PathAI**

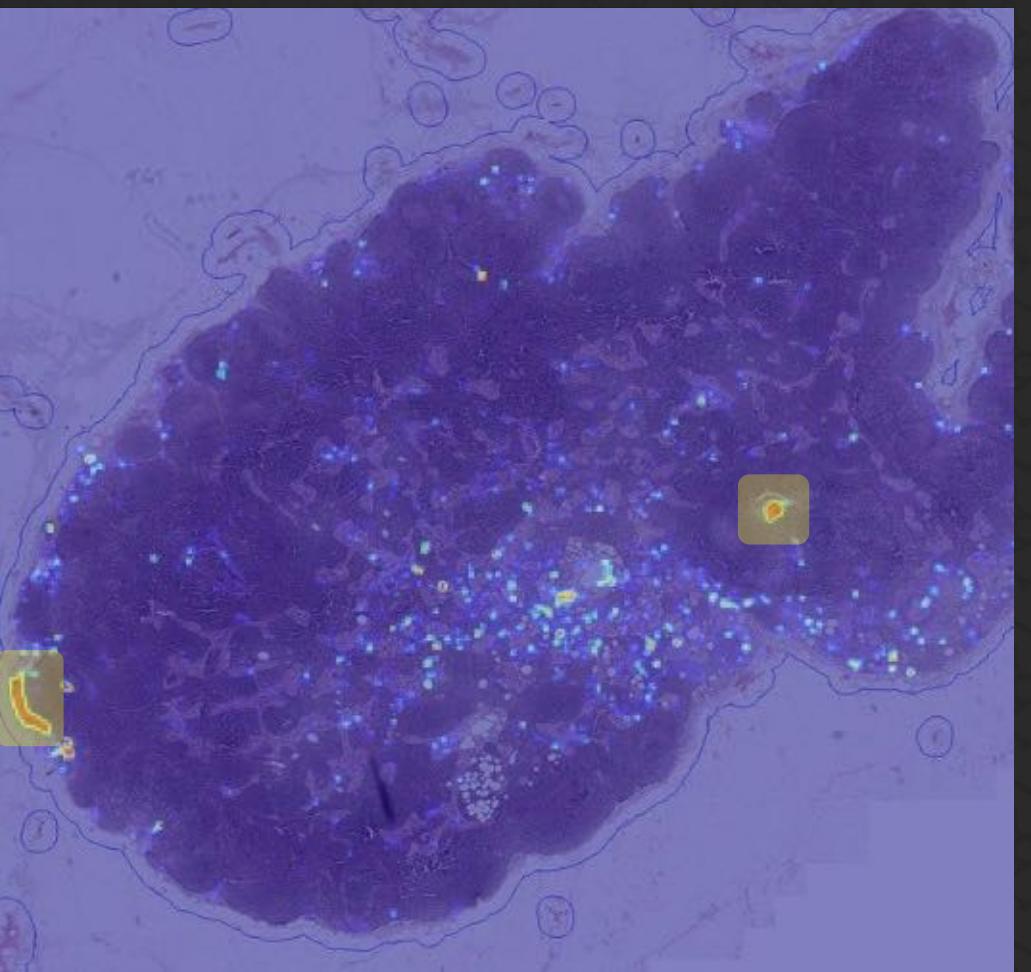




### Pathology Report

Patient: **John Doe** pTNM staging:  
Diagnosis: # of Pos LN:  
Size: # of Neg LN:

**Time per slide:** 1 - 10 minutes  
**Accuracy:** ~85%  
**Reproducibility:** Low



### Pathology Report

Patient: **John Doe** pTNM staging: pT2N1MX  
Diagnosis: Met. Cancer # of Pos LN: 1  
Size: 2.3mm # of Neg LN: 4

**Confirm**

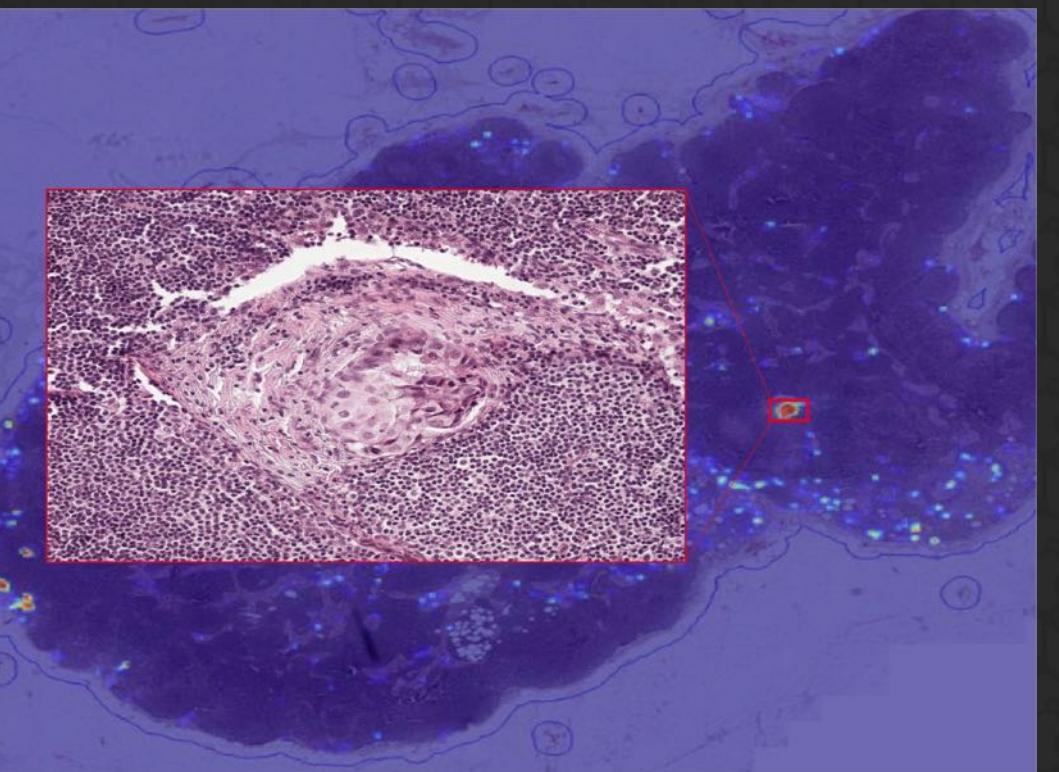
**Time per slide:** 10 - 60 seconds  
**Accuracy:** >99.5%  
**Reproducibility:** High



Proprietary & Confidential

# Why is this a good application for AI?

- Exhaustive analysis is beneficial
  - Large volume
- Local image data necessary and sufficient
- Interpretability: Heatmaps & simple models provide insight into how the *patient-level* prediction was made
- *Required accuracy is high*



# A predictive example: Precision immunotherapy

- Some cancers express immune-inhibitory ligands, activating immune “checkpoints”
- “checkpoint inhibitors” mask these signals, unleashing the immune system

**2018 Nobel Prize in Medicine Awarded to 2 Cancer Immunotherapy Researchers**



The Nobel Prize for Physiology and Medicine was awarded to James P. Allison, left, and Tasaku Honjo on Monday for their work on cancer research. Jonathan Nackstrand/Agence France-Presse — Getty Images

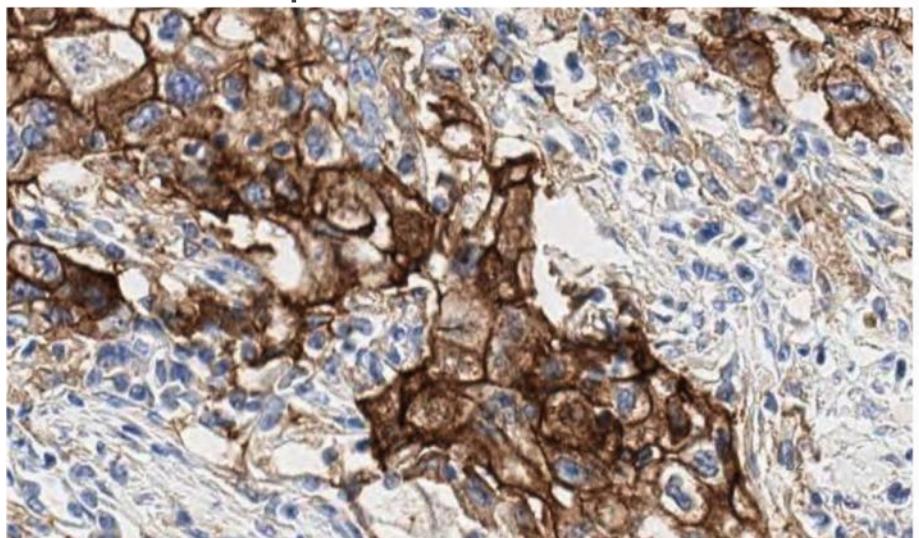
By The New York Times

Oct. 1, 2018



# A predictive example: Precision immunotherapy

- Response rate is low, but some fraction of patients are essentially “cured”
- PD-L1 expression is somewhat indicative of response



Suzanne L. Topalian, M.D., F. Stephen Hodi, M.D., Julie R. Brahmer, M.D., Scott N. Gettinger, M.D., David C. Smith, M.D., David F. McDermott, M.D., John D. Powderly, M.D., Richard D. Carvajal, M.D., Jeffrey A. Sosman, M.D., Michael B. Atkins, M.D., Philip D. Leming, M.D., David R. Spigel, M.D., Scott J. Antonia, M.D., Ph.D., Leora Horn, M.D., Charles G. Drake, M.D., Ph.D., Drew M. Pardoll, M.D., Ph.D., Lieping Chen, M.D., Ph.D., William H. Sharfman, M.D., Robert A. Anders, M.D., Ph.D., Janis M. Taube, M.D., Tracee L. McMiller, M.S., Haiying Xu, B.A., Alan J. Korman, Ph.D., Maria Jure-Kunkel, Ph.D., Shruti Agrawal, Ph.D., Daniel McDonald, M.B.A., Georgia D. Kollia, Ph.D., Ashok Gupta, M.D., Ph.D., Jon M. Wigginton, M.D., and Mario Sznol, M.D.

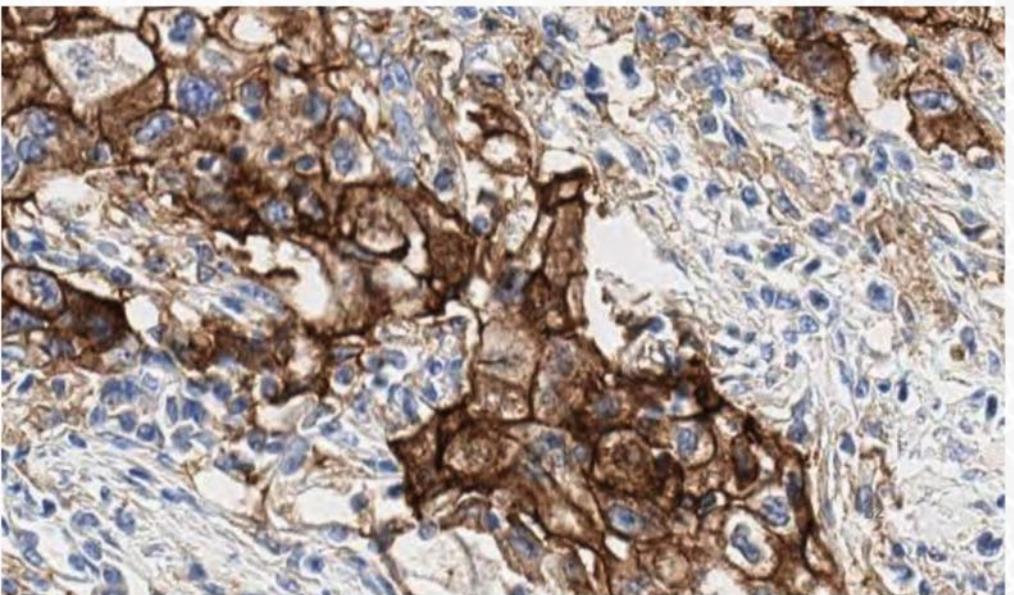
Patient with Melanoma



## CONCLUSIONS

Anti-PD-1 antibody produced objective responses in approximately one in four to one in five patients with non-small-cell lung cancer, melanoma, or renal-cell cancer; the adverse-event profile does not appear to preclude its use. Preliminary data suggest a relationship between PD-L1 expression on tumor cells and objective response. (Funded by Bristol-Myers Squibb and others; ClinicalTrials.gov number, NCT00730639.)

# Manual interpretation of PD-L1 IHC is highly variable



*PDL1 manual IHC scores on immune cells are unreliable*

Table 2. ICC for the Pathologist Scores and Concordance Statistics

Cells <sup>a</sup>	Antibody, ICC (95% CI)				Summary, Mean (SD)
	22c3	28-8	SP142	E1L3N	
Tumor cells	0.882 (0.873-0.891)	0.832 (0.820-0.844)	0.869 (0.859-0.879)	0.859 (0.849-0.869)	0.86 (0.02)
Immune cells	0.207 (0.190-0.226)	0.172 (0.156-0.189)	0.185 (0.169-0.203)	0.229 (0.211-0.248)	0.19 (0.03)

Abbreviation: ICC, intraclass correlation coefficient.

<sup>a</sup> N = 90.

# Manual scoring of PD-L1 is variable ...and not always predictive

## Nivolumab versus Docetaxel in Advanced Squamous-Cell Non-Small-Cell Lung Cancer

Julie Brahmer, M.D., Karen L. Reckamp, M.D., Paul Baas, M.D.,  
Lucio Crinò, M.D., Wilfried E.E. Eberhardt, M.D., Elena Poddubskaya, M.D.,  
Scott Antonia, M.D., Ph.D., Adam Pluzanski, M.D., Ph.D., Everett E. Vokes, M.D.,  
Esther Holgado, M.D., Ph.D., David Waterhouse, M.D., Neal Ready, M.D.,  
Justin Gainor, M.D., Osvaldo Arén Frontera, M.D., Libor Havel, M.D.,  
Martin Steins, M.D., Marina C. Garassino, M.D., Joachim G. Aerts, M.D.,  
Manuel Domine, M.D., Luis Paz-Ares, M.D., Martin Reck, M.D.,  
Christine Baudelet, Ph.D., Christopher T. Harbison, Ph.D.,  
Brian Lestini, M.D., Ph.D., and David R. Spigel, M.D.

### RESULTS

The median overall survival was 9.2 months (95% confidence interval [CI], 7.3 to 13.3) with nivolumab versus 6.0 months (95% CI, 5.1 to 7.3) with docetaxel. The risk of death was 41% lower with nivolumab than with docetaxel (hazard ratio, 0.59; 95% CI, 0.44 to 0.79;  $P<0.001$ ). At 1 year, the overall survival rate was 42% (95% CI, 34 to 50) with nivolumab versus 24% (95% CI, 17 to 31) with docetaxel. The response rate was 20% with nivolumab versus 9% with docetaxel ( $P=0.0081$ ).

0.47 to 0.81;  $P<0.001$ ). The expression of the PD-1 ligand (PD-L1) was neither prognostic nor predictive of benefit. Treatment-related adverse events of grade 3

prognostic nor predictive of benefit. Treatment-related adverse events of grade 3 or 4 were reported in 7% of the patients in the nivolumab group as compared with 55% of those in the docetaxel group.

# Can we do better?

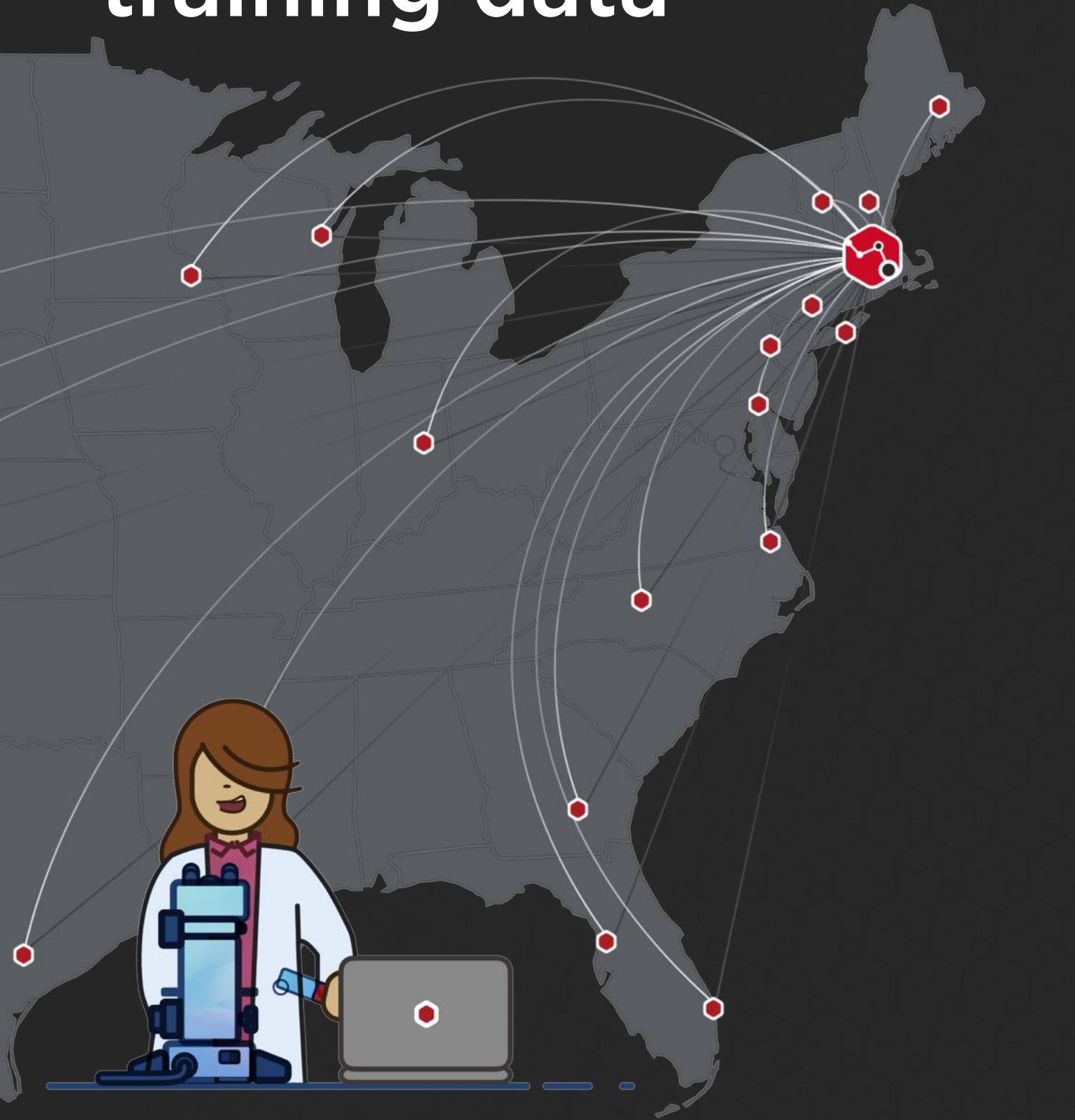
- Deep learning is data hungry
- Need 10s of thousands of precise cell annotations

First, we need the data



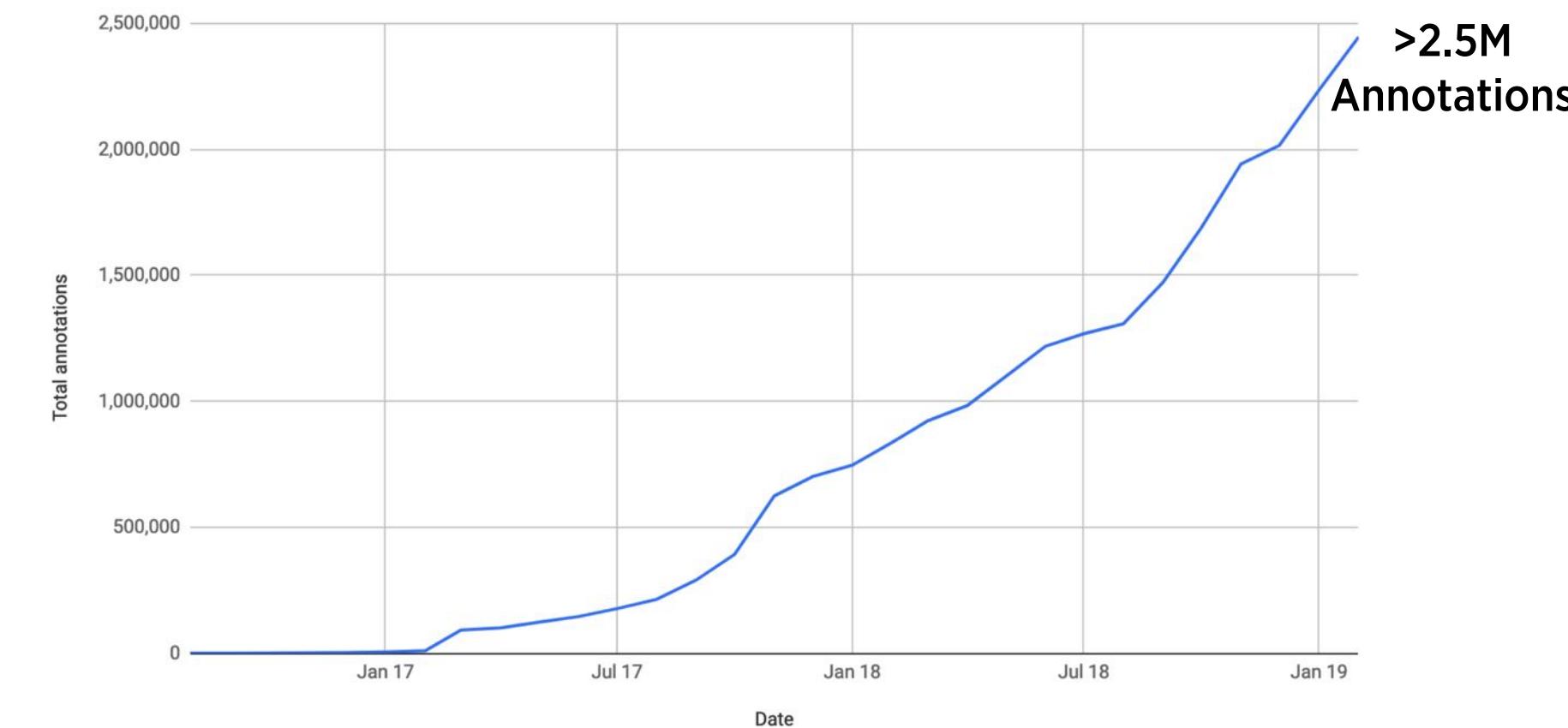
Proprietary & Confidential

# Board-certified training data



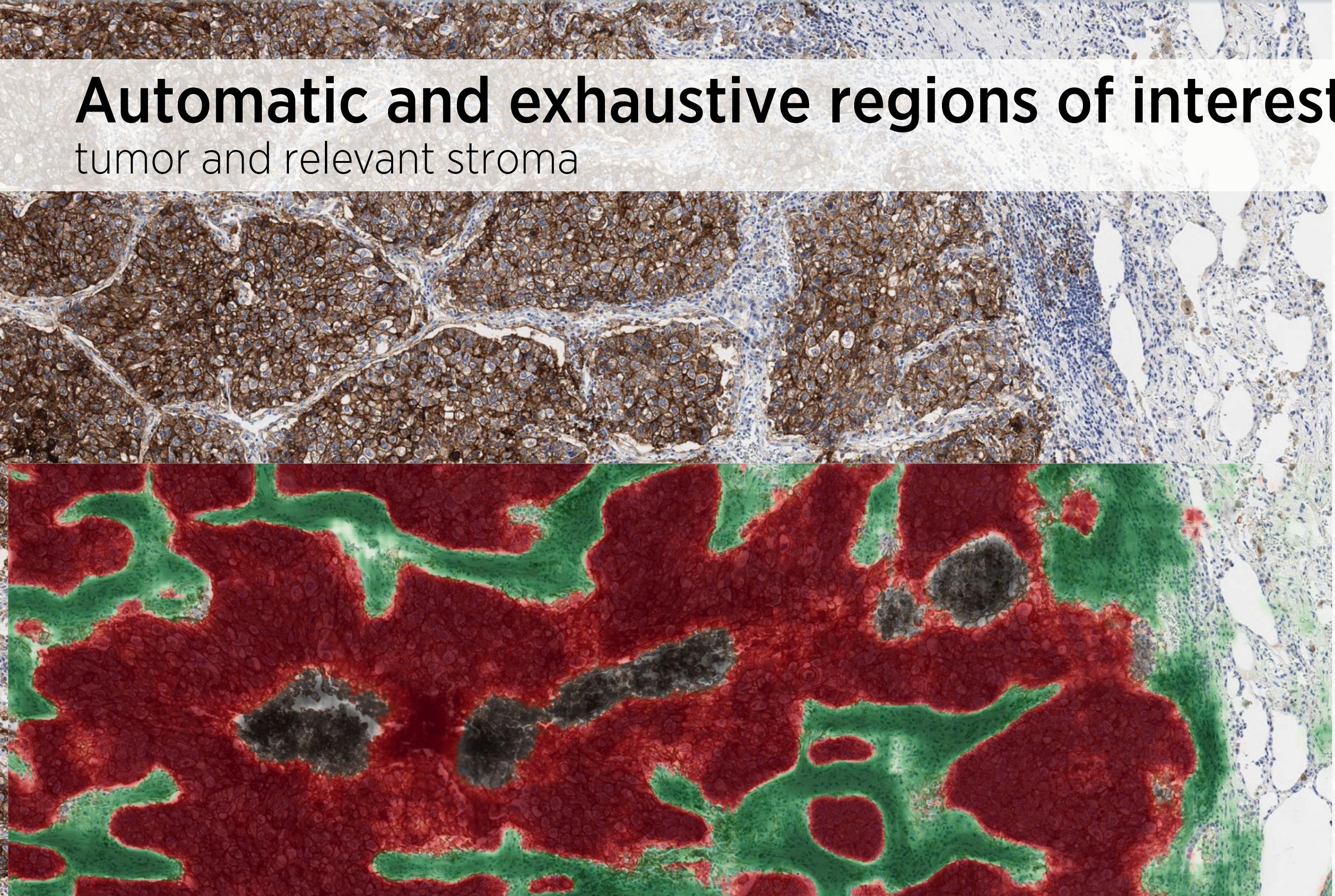
Working with pathologists around  
the country to generate high-quality  
annotations

Total annotations, 2017 - 2019



# Automatic and exhaustive regions of interest

tumor and relevant stroma



# IHC expression difficult to detect

on immune and tumor cells



DEMO PROJECT

Case Case 3

Slide 3021 - PD-L1 ▾

▼ Features

PathAI PDL1 Immune Cell % 2.33

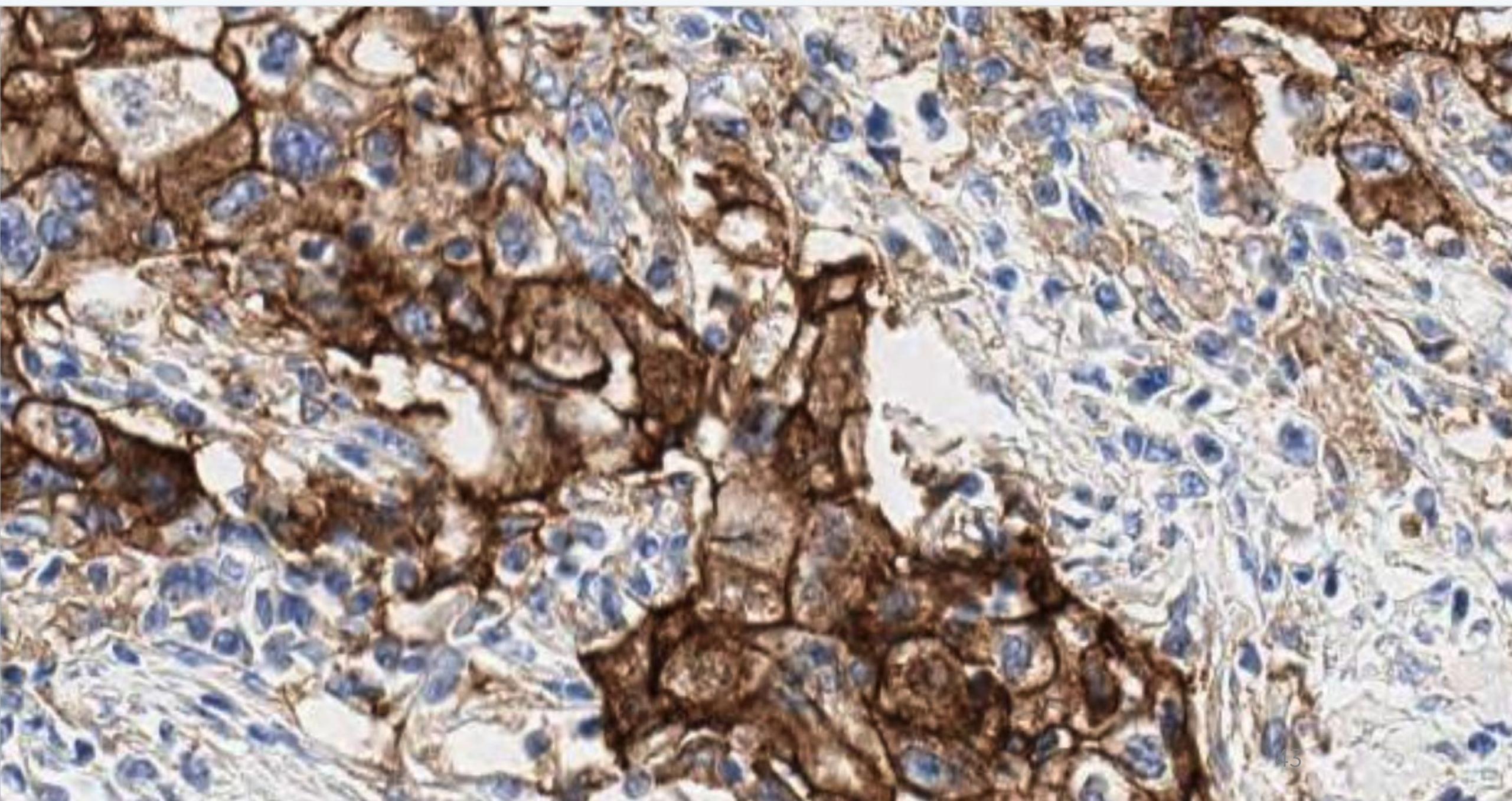
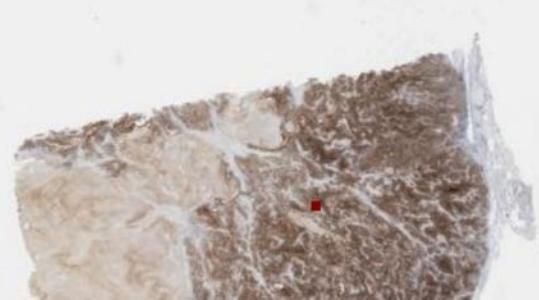
PathAI PDL1 Tumor % 96.31

▼ Overlays

#1162 Cell Detection (yellow border: IHC positive) (Green: Lymphocyte, Orange: Macrophage, Blue: Fibroblast, Red: Cancer epithelial cell)

#1160 Tissue map (Green: Stroma, Red: Cancer epithelium, Black: Necrosis)

▼ Navigation



# Exhaustive automated classification

Cell type and cellular IHC positivity classification

PathAI

DEMO PROJECT

Case Case 3

Slide 3021 - PD-L1 ▾

Features

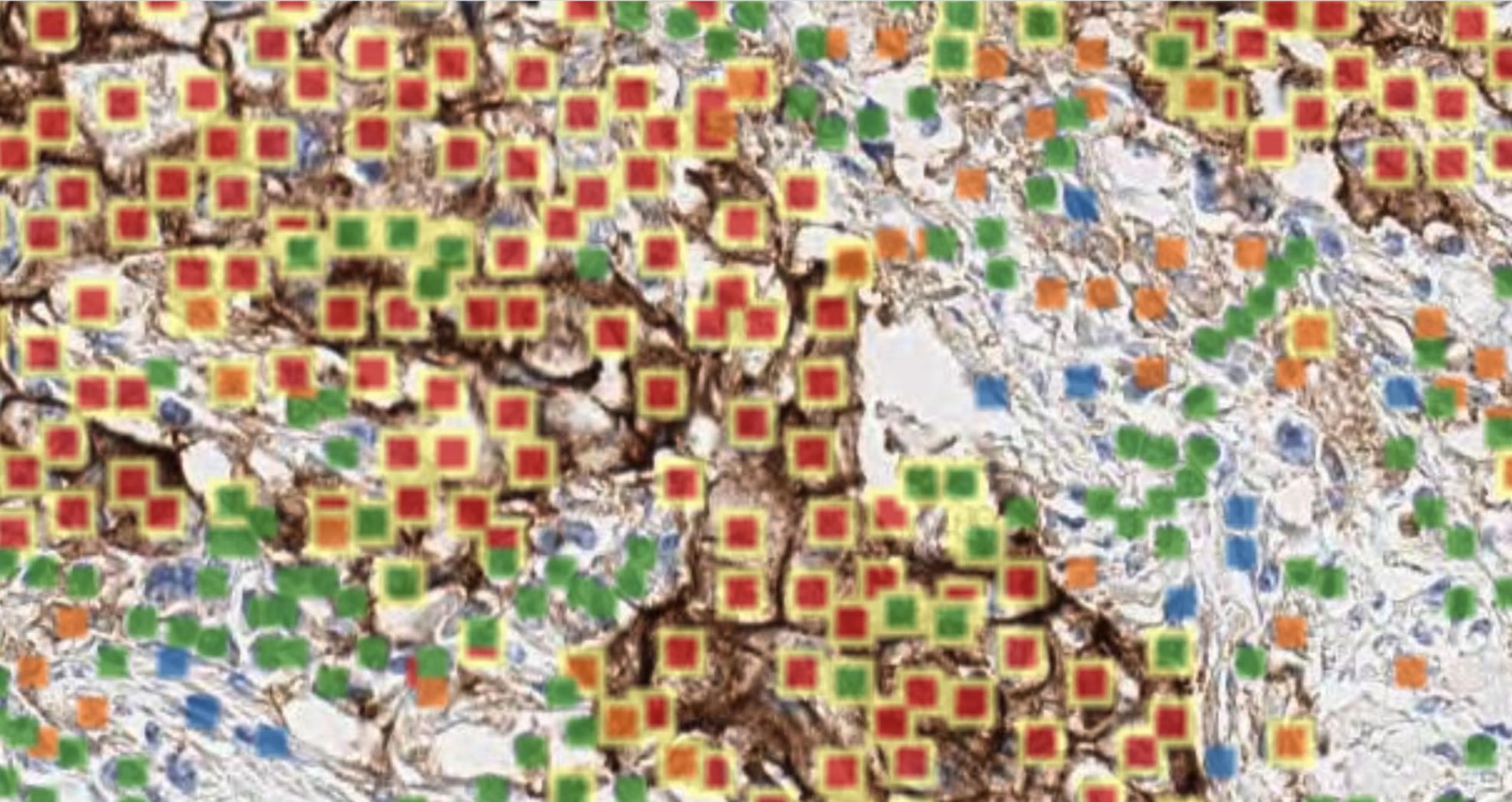
PathAI PDL1 Immune Cell %	2.33
PathAI PDL1 Tumor %	96.31

Overlays

#1162 Cell Detection (yellow border: IHC positive) (Green: Lymphocyte, Orange: Macrophage, Blue: Fibroblast, Red: Cancer epithelial cell)

#1160 Tissue map (Green: Stroma, Red: Cancer)

Navigation



# Quantitative and reproducible PD-L1 scoring

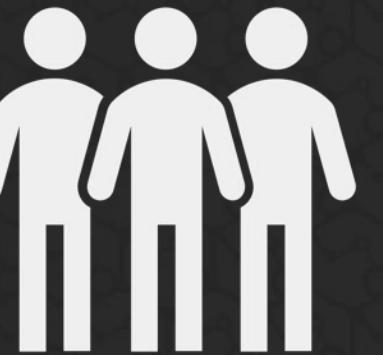
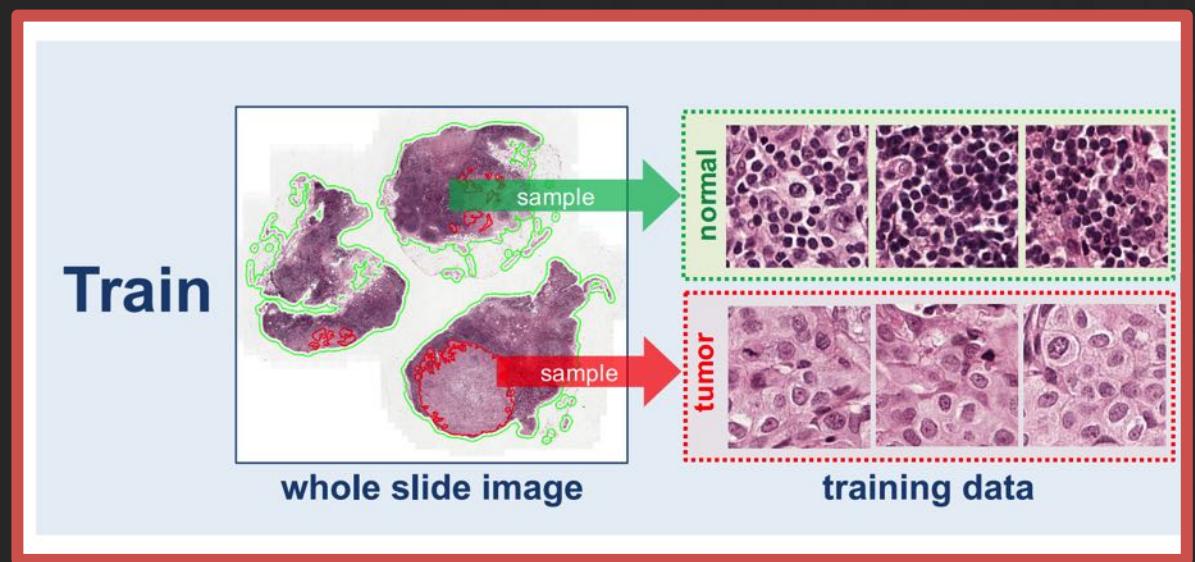
- Manual review: few hundred cells over a few arbitrary high-power fields of view
- Automated analysis: exhaustive classification of 10k-1million cells



# Taking it further

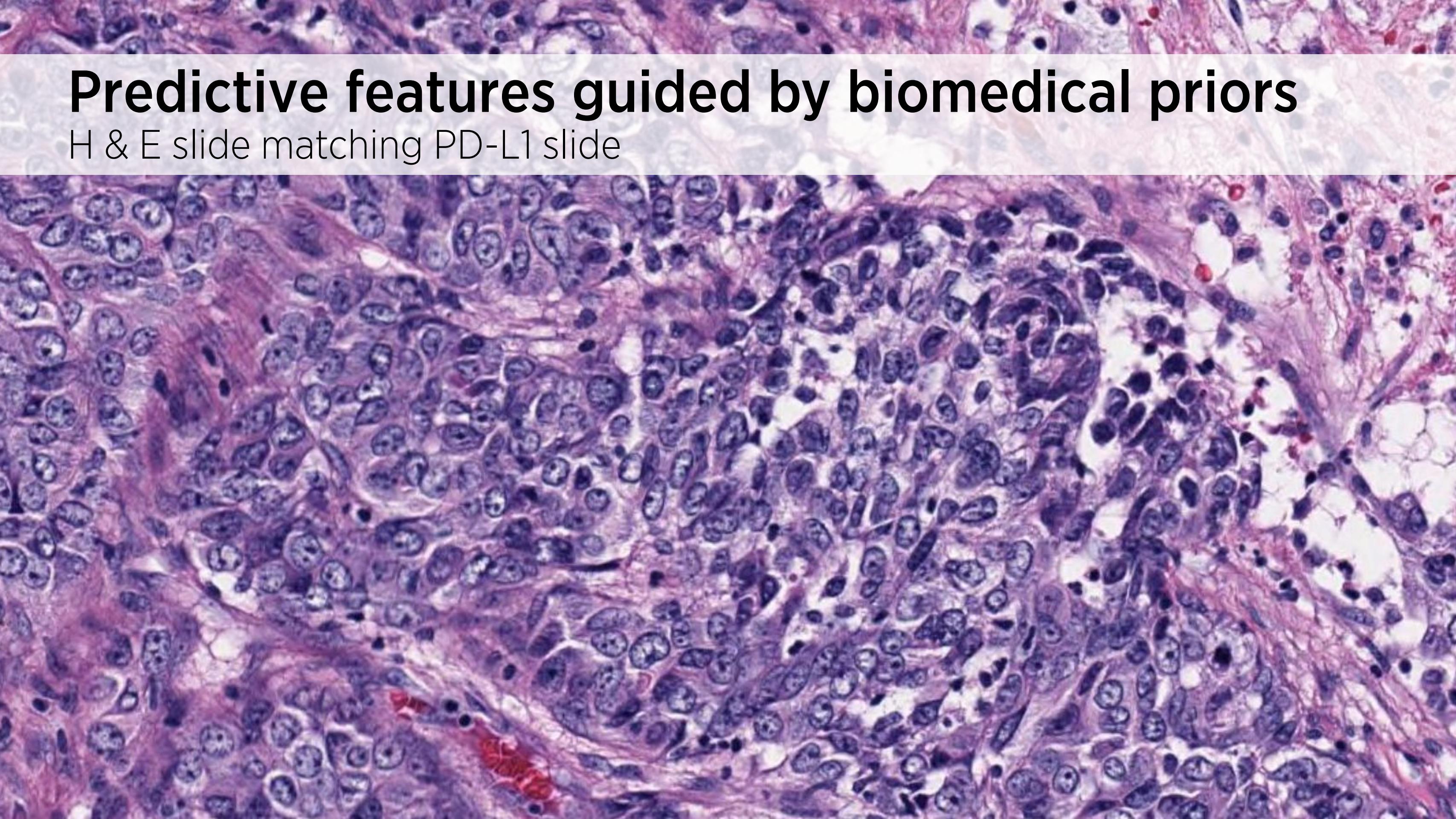
## From quantitative assay to patient prediction

- PD-L1 scoring alone reduces billions of pixels to 1-2 numbers.
- Can we identify additional relevant information?
  - Using data from randomized controlled clinical trials
- However: Millions of patches, *hundreds* of patients



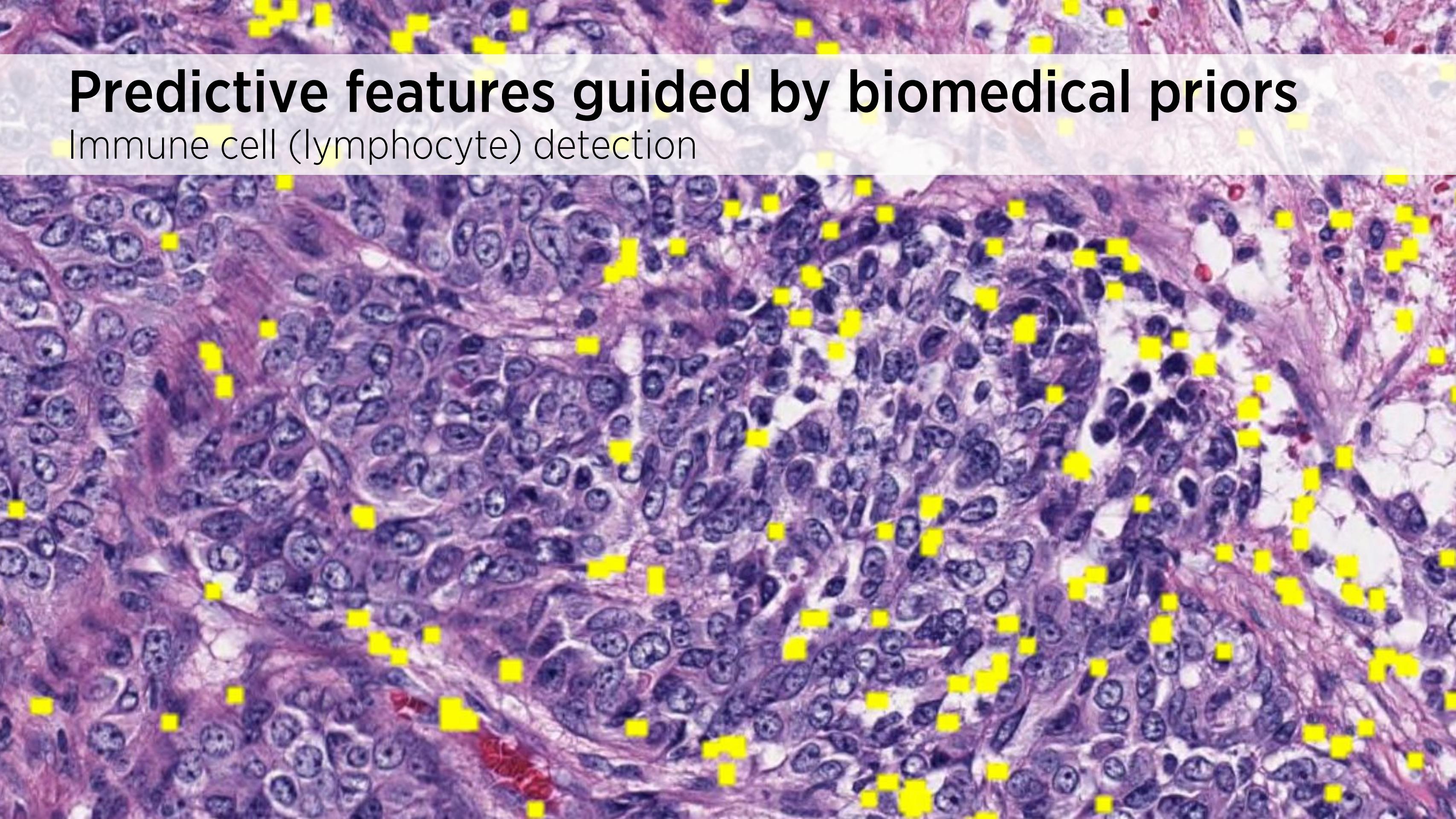
# Predictive features guided by biomedical priors

H & E slide matching PD-L1 slide



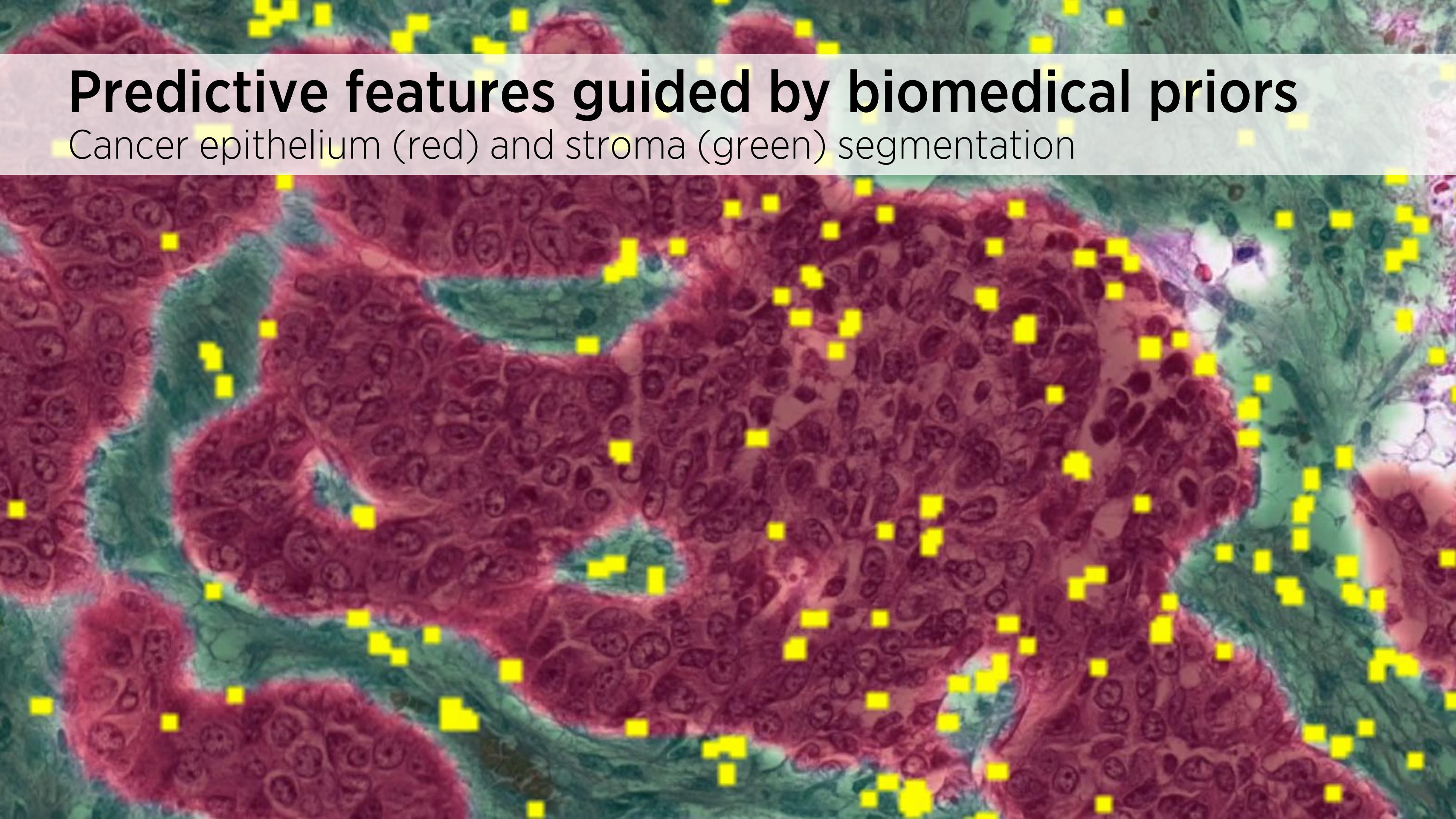
# Predictive features guided by biomedical priors

- Immune cell (lymphocyte) detection



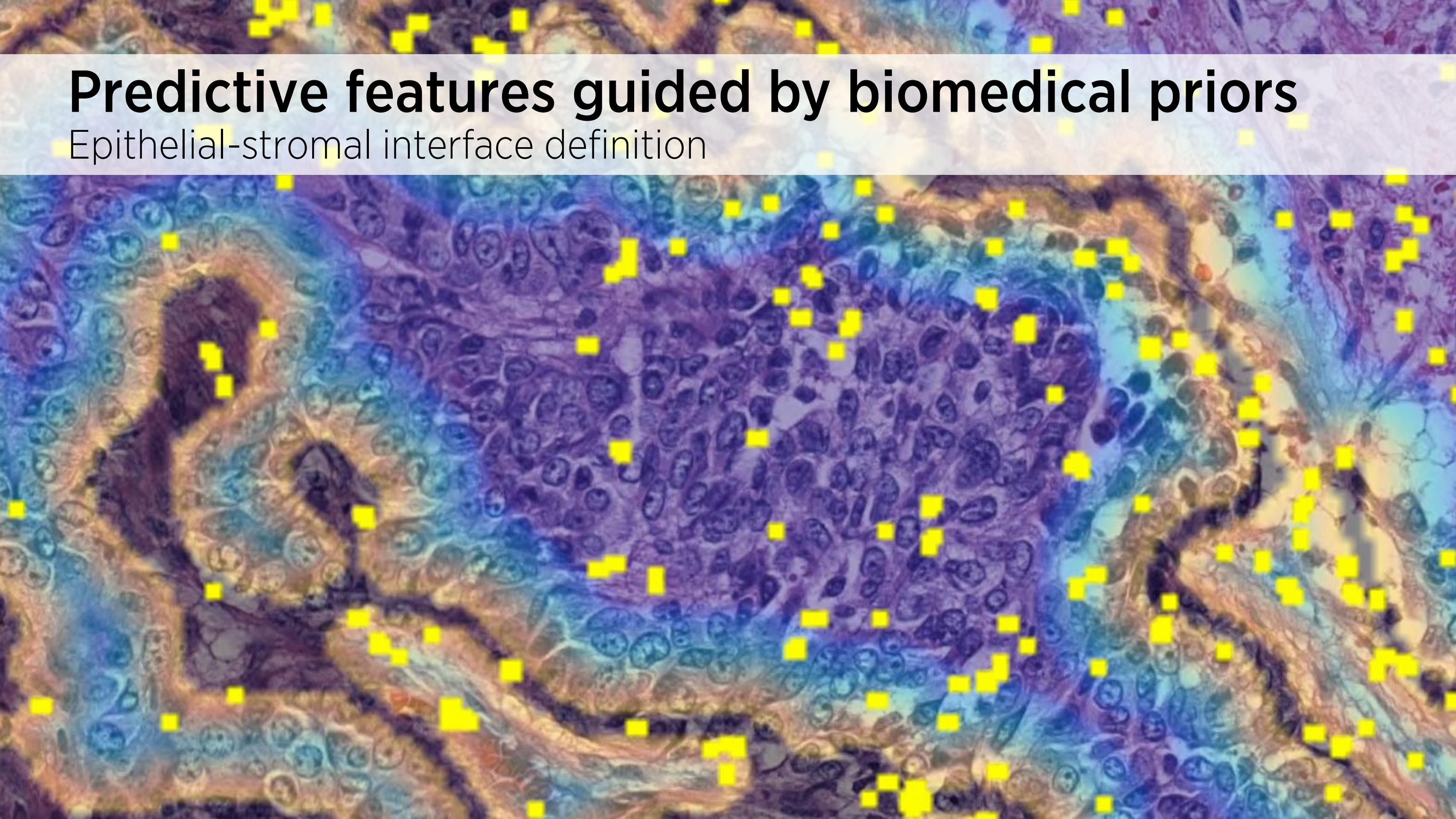
# Predictive features guided by biomedical priors

Cancer epithelium (red) and stroma (green) segmentation

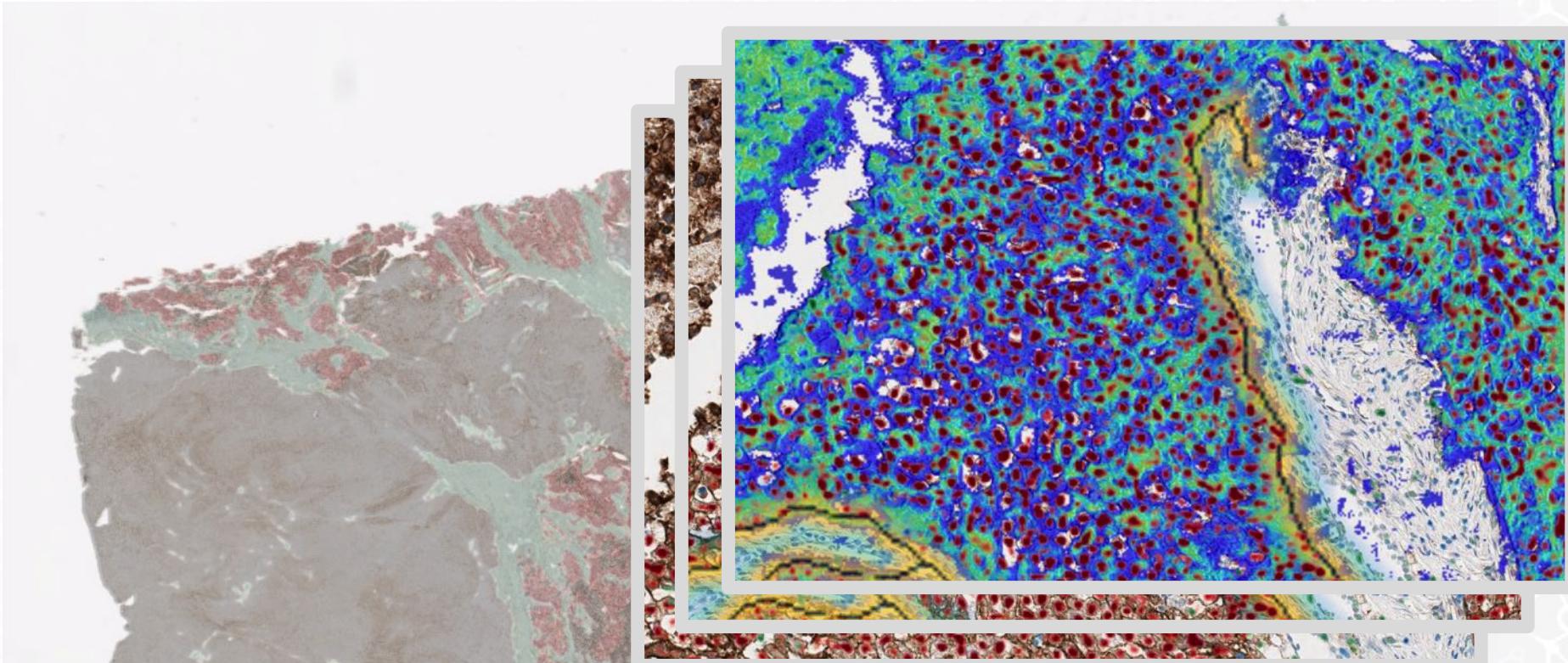


# Predictive features guided by biomedical priors

Epithelial-stromal interface definition



# Cell-type specific, tissue context-aware IHC-quantification



Lymphocyte  
Macrophage  
Cancer epithelial  
cell

# Data-driven identification of pathological phenotypes associated with drug response

Total number of macrophages in epithelial/stroma interface (80um)

Total number of macrophages in epithelial/stroma interface (120um)

Total number of macrophages in invasive margin (250um)

Total number of lymphocytes in epithelial/stromal interface on H&E stain

Total number of plasma cells in epithelium on H&E stain

Total number of plasma cells in stroma on H&E stain

Tumor (epithelium + stroma) area on H&E stain

Total number of plasma cells in epithelial/stroma interface (40um)

Total number of plasma cells in epithelial/stroma interface (80um)

Area (mm<sup>2</sup>) of epithelial/stroma interface (80um) target positive cancer cells on target stain

Area (mm<sup>2</sup>) of epithelial PDL-1 positive macrophages on target stain

Necrosis area on target stain

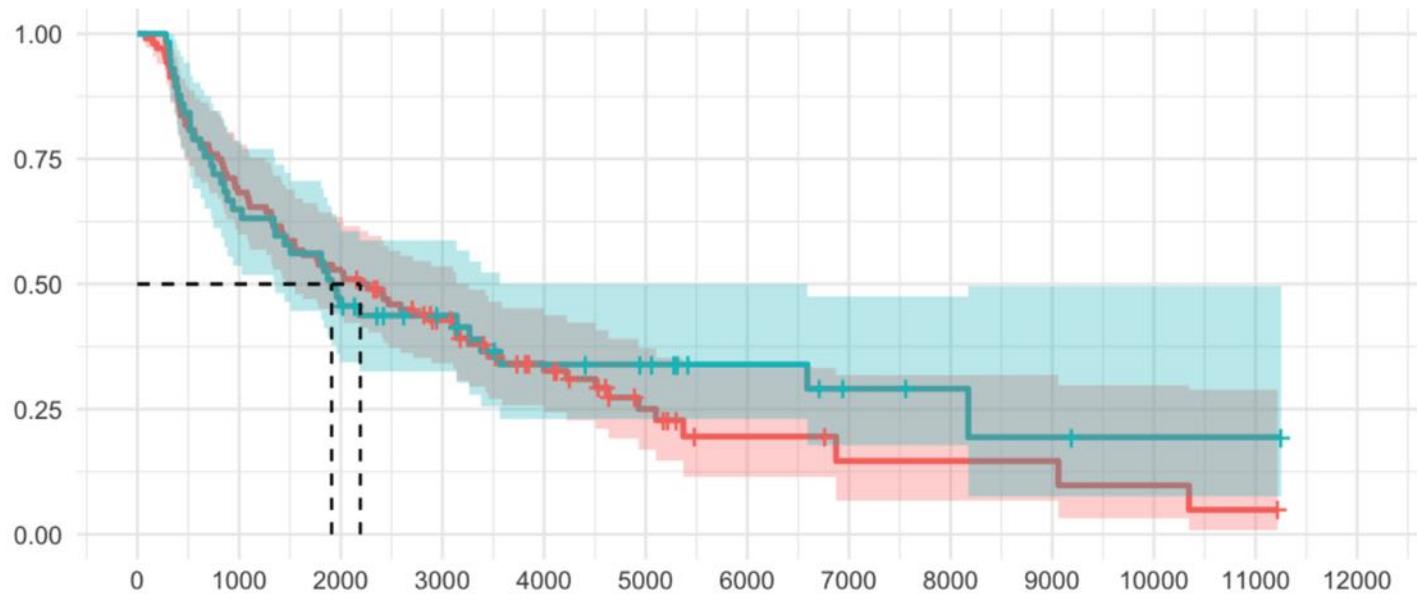
Proportion of tumor infiltrating lymphocytes engaged by target positive macrophages

Stroma area on target stain

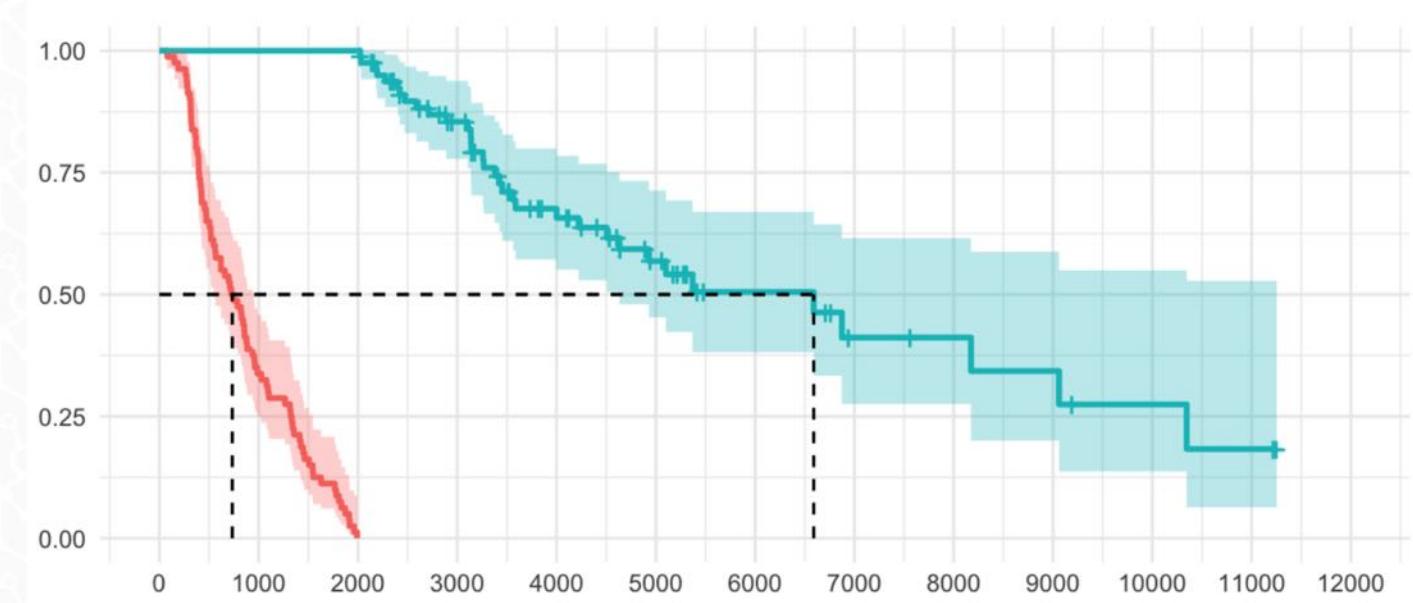
Tissue area on target stain

# Multivariate models predictive of IO response

- Low  $n$ , interpretability and measures of uncertainty valuable:
  - No deep learning (gasp!)
- Feature importance/selection in these models can provide disease insight
  - *Now we're doing things pathologists can't rather than automating / improving what they already can*

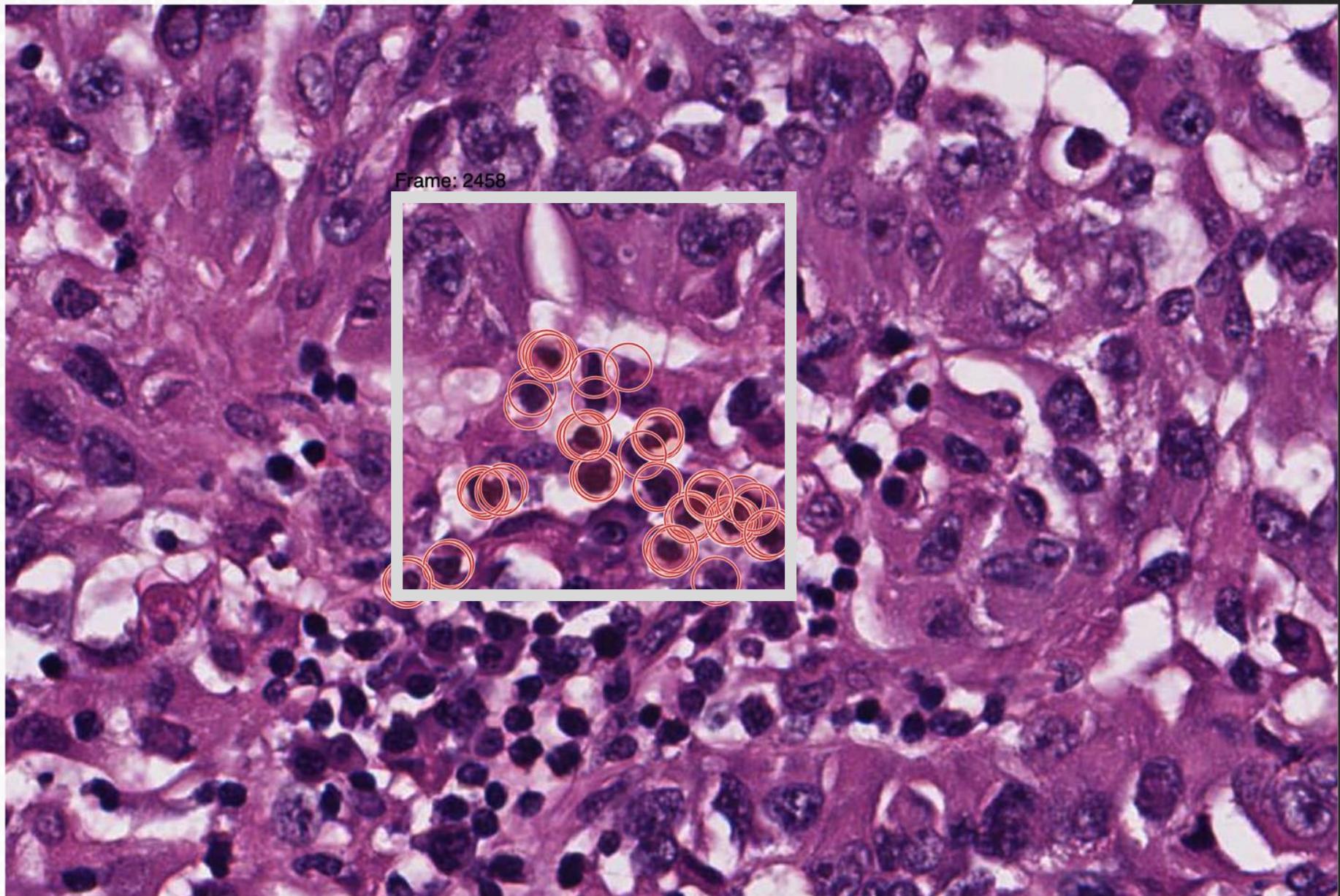


Variable	N	Hazard ratio	p
target	161	0.89 (0.60, 1.32)	0.6



Note: KM curves for illustration only

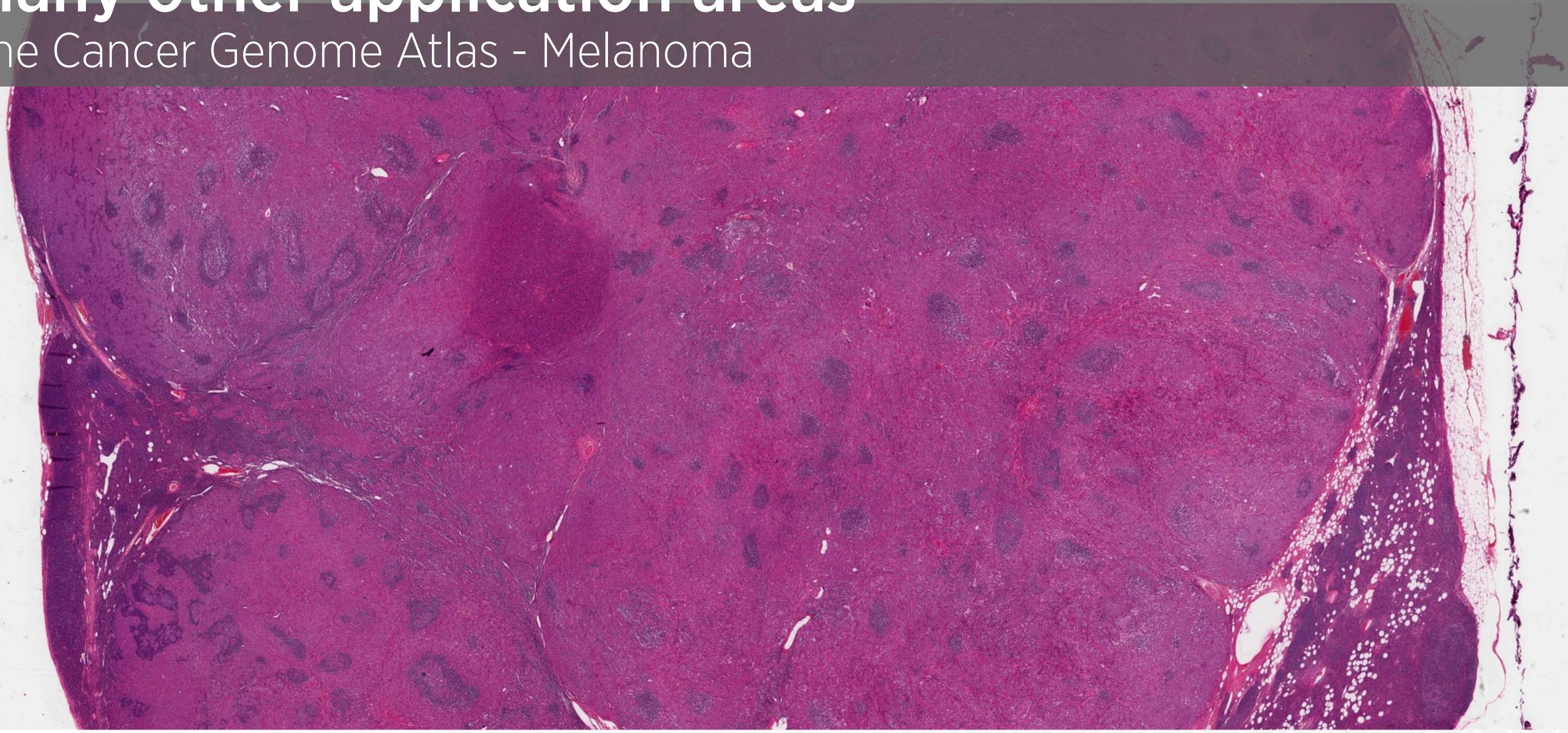
# How do we know these features are *correct*?



Frames  
Validation by  
exhaustive  
consensus

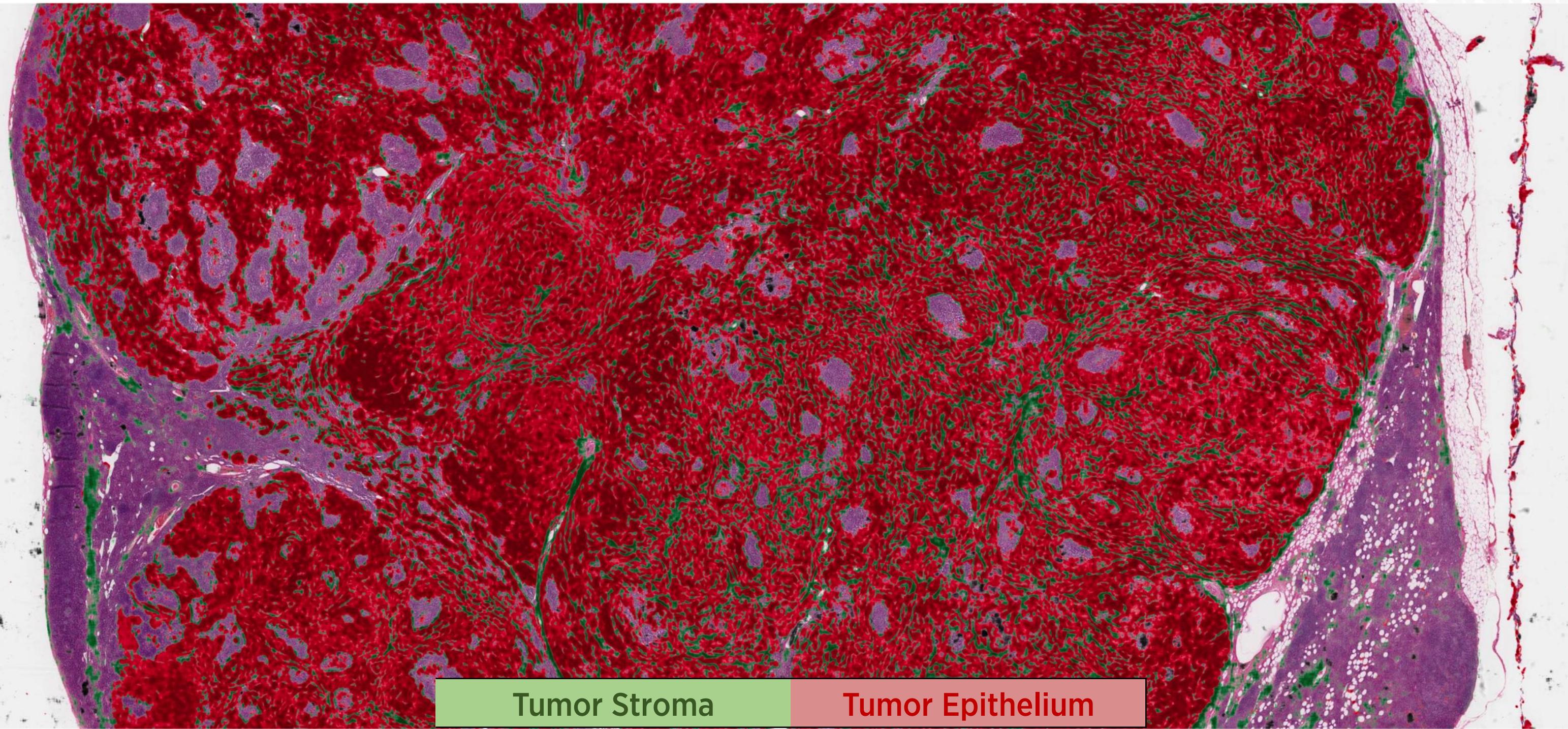
# Many other application areas

The Cancer Genome Atlas - Melanoma



**TCGA-EE-A2GL, Malignant Melanoma**

# Melanoma Tissue Map

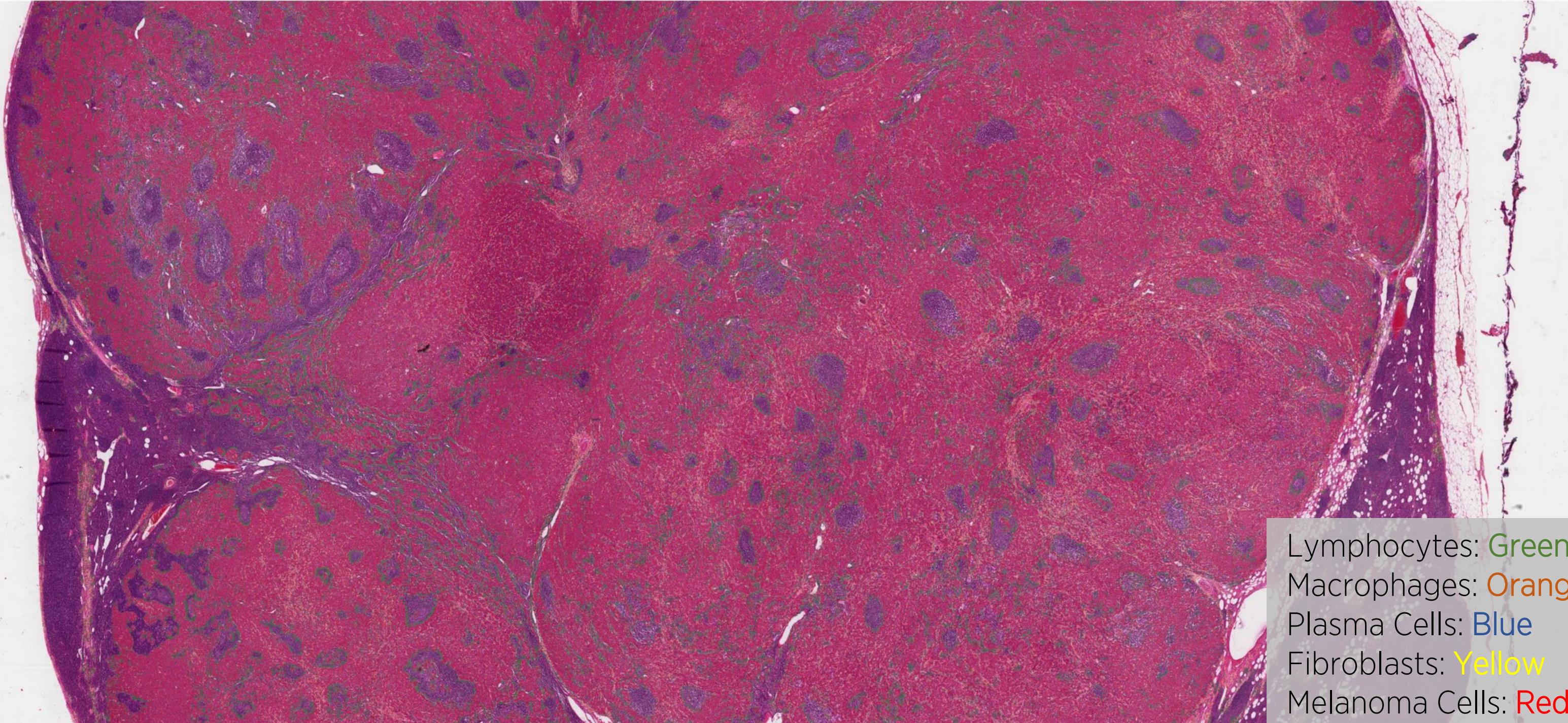


Tumor Stroma

Tumor Epithelium

TCGA-EE-A2GL, Malignant Melanoma

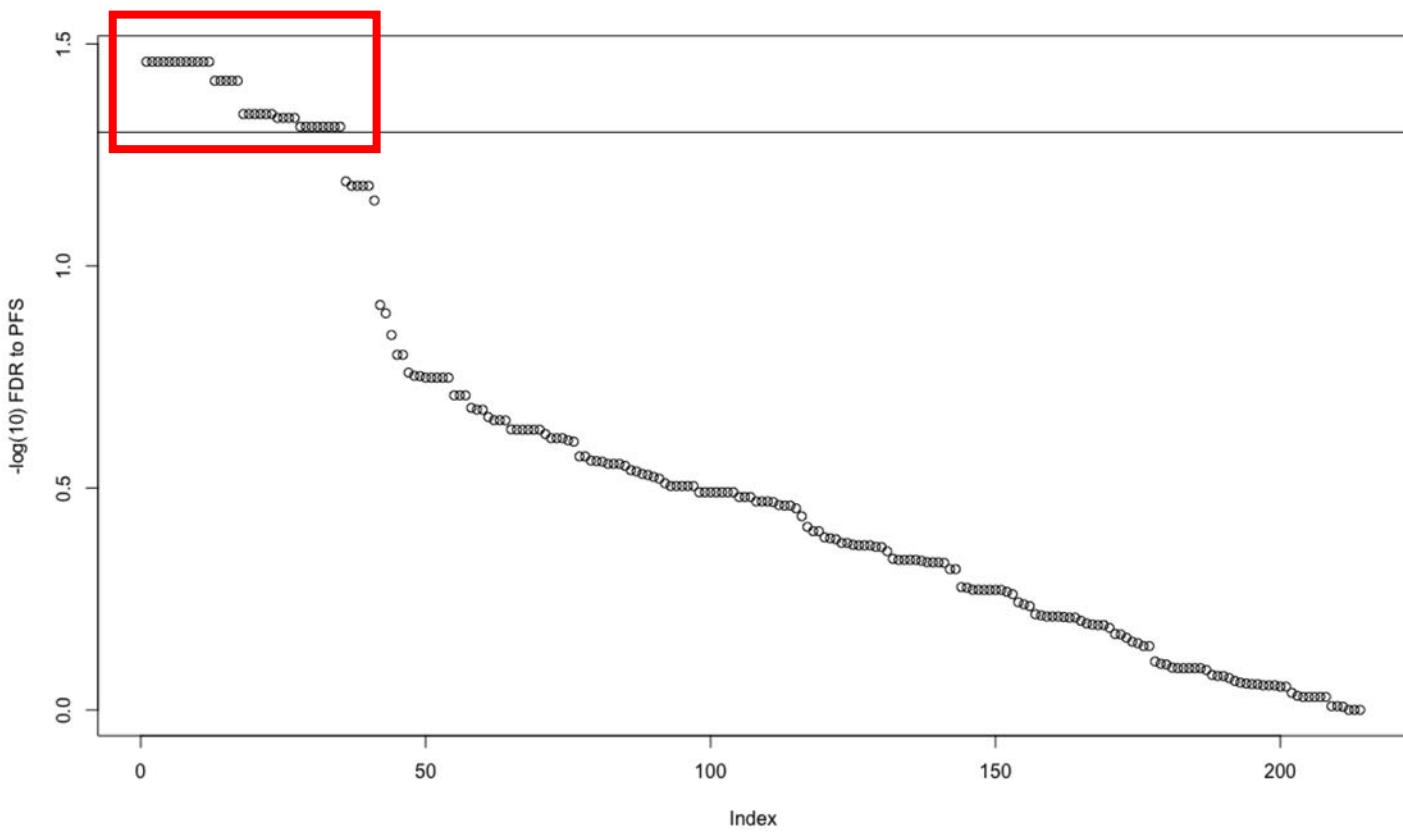
# Melanoma Cell Map



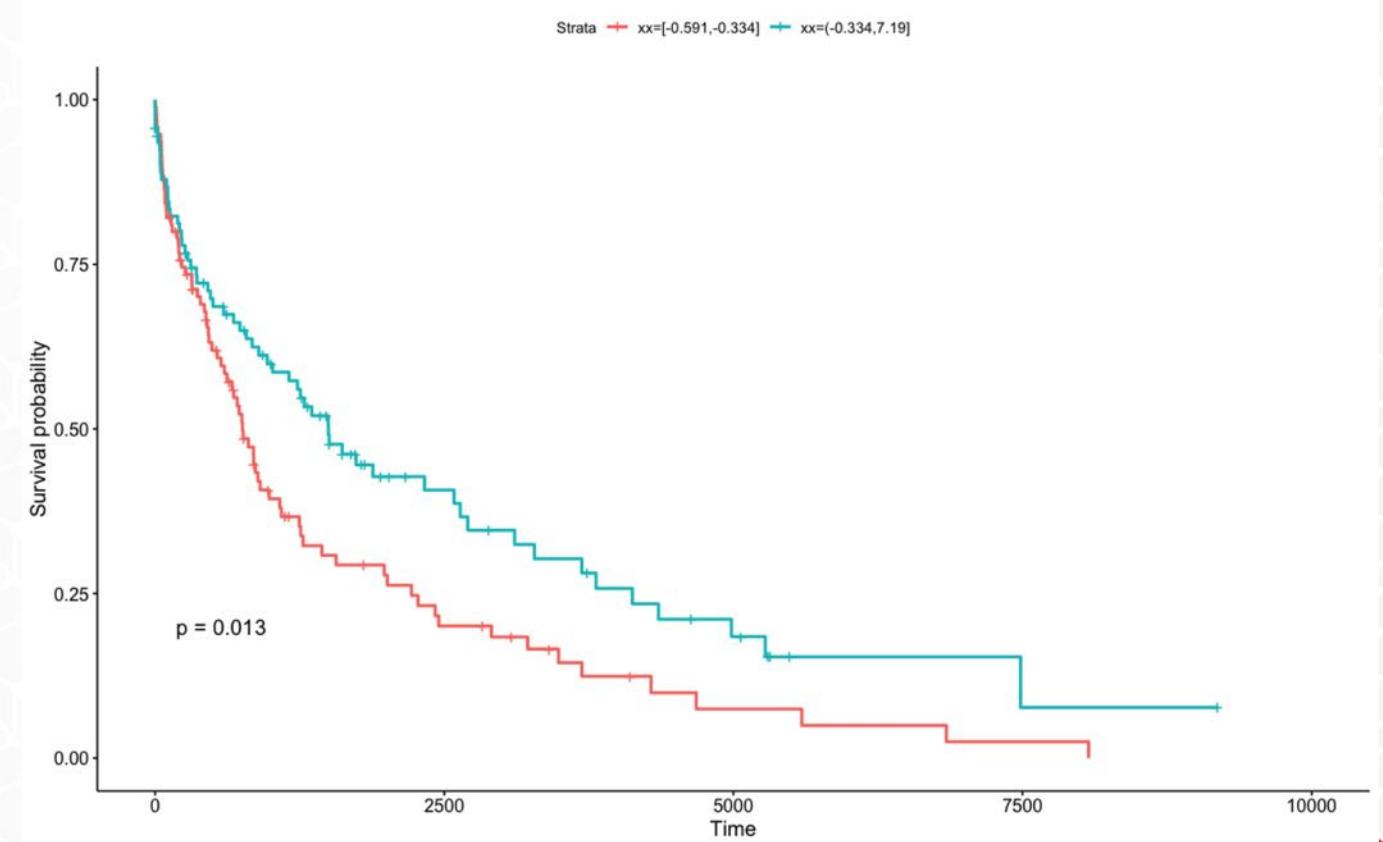
TCGA-EE-A2GL, Malignant Melanoma

# Exhaustive analysis of cellular features in TCGA to enable data-driven identification of pathological predictors of survival in malignant melanoma

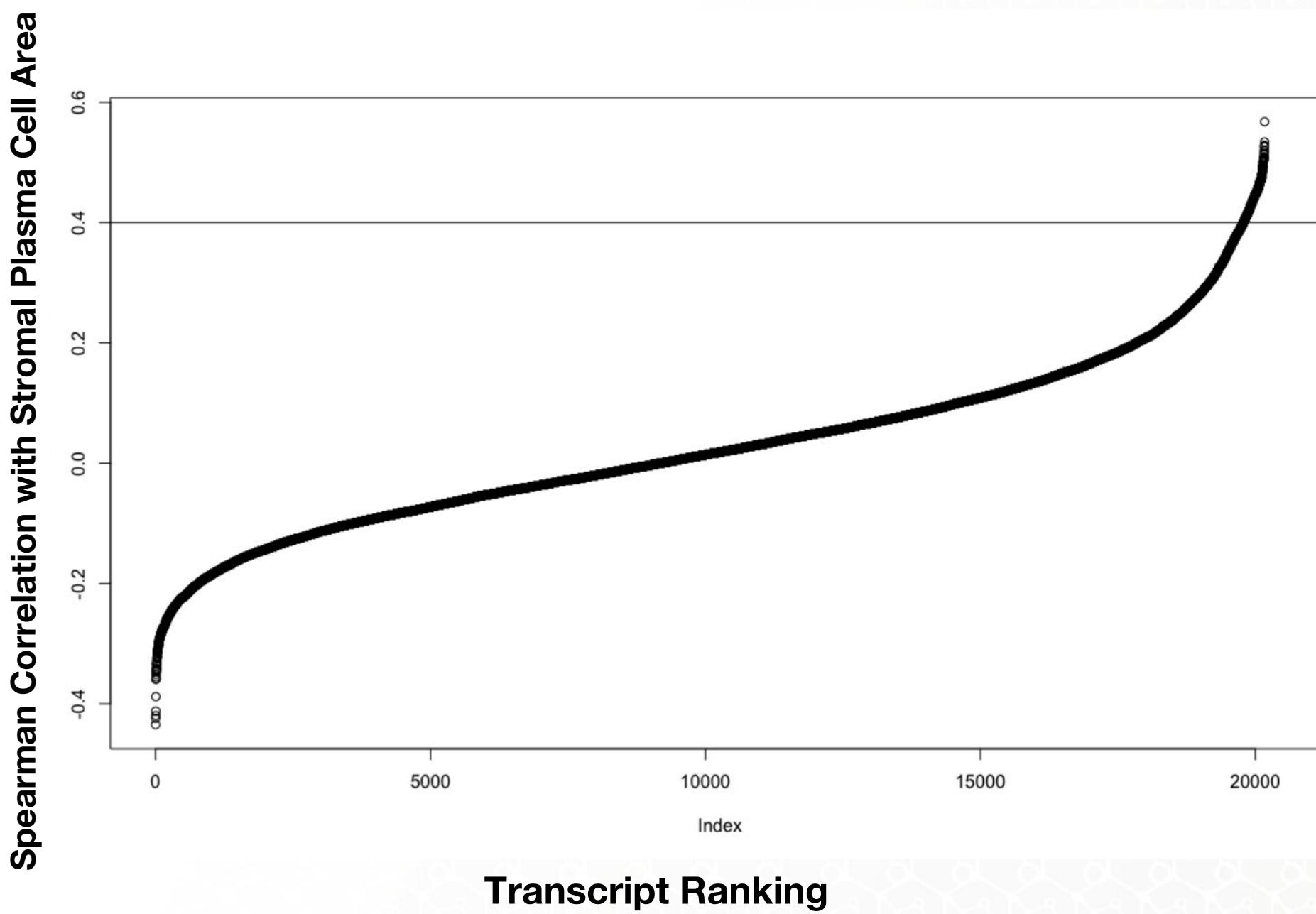
Pathological phenotypes with FDR < 5% for association with  
Progression Free Survival



Increased area of stromal plasma cells associated with  
improved survival in melanoma



# Data-driven identification of transcriptional signature underlying stromal area of plasma cells in melanoma



**Top-ranking transcripts associated with stromal area of plasma cells**

Gene	Correlation
REC8	0.57
GPR174	0.53
CD38	0.53
LAX1	0.53
TOX	0.53
AKAP5	0.53
C8orf80	0.52
JSRP1	0.52
IGJ	0.52
TNFRSF17	0.51
EAF2	0.51

# Stromal plasma cell area RNA signature strongly enriched for immune genes

Gene Set Name	Description	FDR q-value
REACTOME_IMMUNE_SYSTEM	Genes involved in Immune System	7.62E-57
REACTOME_ADAPTIVE_IMMUNE_SYSTEM	Genes involved in Adaptive Immune System	6.02E-42
PID_TCR_PATHWAY	TCR signaling in naive CD4+ T cells	4.24E-30
REACTOME_IMMUNOREGULATORY_INTERACTIONS_BETWEEN_A_LYMPHOID_AND_A_NON_LYMPHOID_CELL	Genes involved in Immunoregulatory interactions between a Lymphoid and a non-Lymphoid cell	6.07E-26
KEGG_PRIMARY_IMMUNODEFICIENCY	Primary immunodeficiency	7.98E-24
PID_IL12_2PATHWAY	IL12-mediated signaling events	9.27E-24
PID_CD8_TCR_PATHWAY	TCR signaling in naive CD8+ T cells	9.27E-24
KEGG_CELL_ADHESION_MOLECULES_CAMS	Cell adhesion molecules (CAMs)	3.00E-22
KEGG_CYTOKINE_CYTOKINE_RECECTOR_INTERACTION	Cytokine-cytokine receptor interaction	6.38E-22
KEGG_INTESTINAL_IMMUNE_NETWORK_FOR_IGA_PRODUCTION	Intestinal immune network for IgA production	3.37E-21
REACTOME_TCR_SIGNALING	Genes involved in TCR signaling	3.24E-20
REACTOME_PD1_SIGNALING	Genes involved in PD-1 signaling	3.44E-19
REACTOME_COSTIMULATION_BY_THE_CD28_FAMILY	Genes involved in Costimulation by the CD28 family	5.48E-19

# Another AI plus: scalability

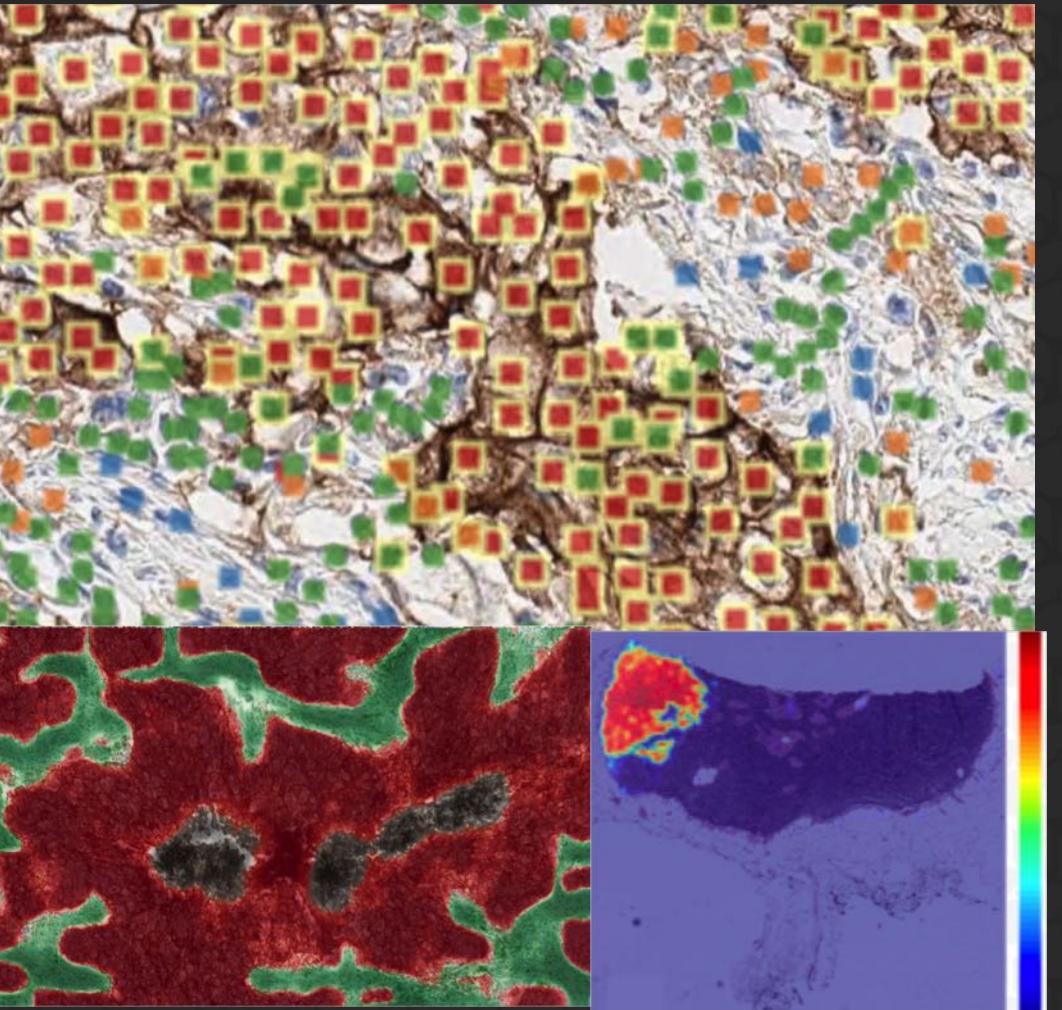
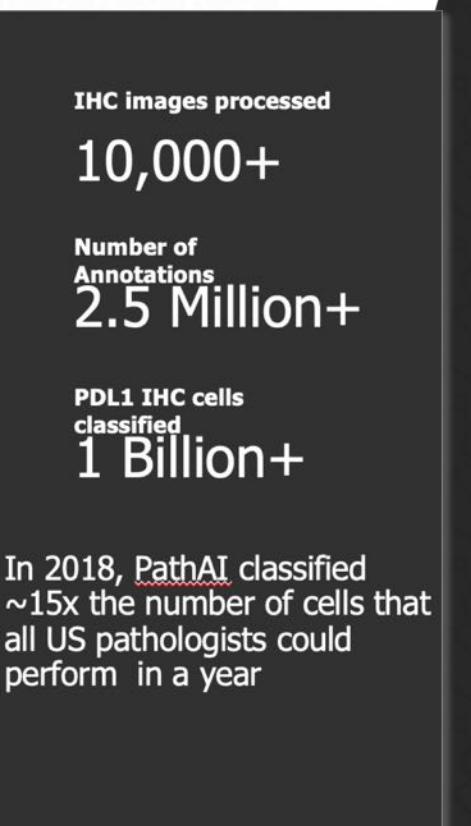
- Same pipeline for any solid tumor type
  - Contrast to traditional approach: hand-crafted algorithms.

## PathAI for Immuno-oncology

PathAI platform has been applied to:

- Non-small cell lung cancer (Adenocarcinoma)
- Non-small cell lung cancer (Squamous Cell Carcinoma)
- Small cell carcinoma of the lung
- Urothelial carcinoma of the bladder
- Head and neck squamous cell carcinoma
- Melanoma
- Breast cancer
- Prostate cancer
- Colon cancer

>30 IO-IHC biomarkers studied



PathAI

Proprietary & Confidential

# Extensive Slide Search & Data Standardization

## Slides Search

 Filter Images  
Choose criteria

TCGA

TCGA

Any case

Any stain

Any group

Original file name

Overlays:

Yes  No  Either

Annotations:

Yes  No  Either

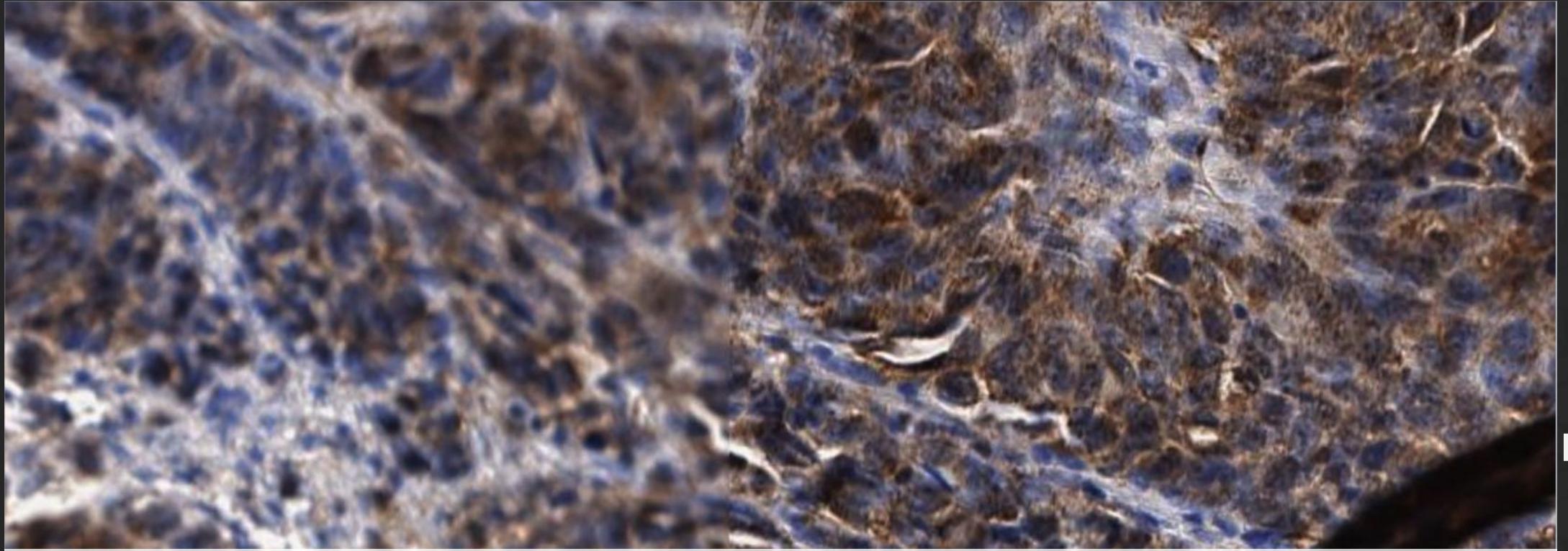
30872 matching images

Clear filters

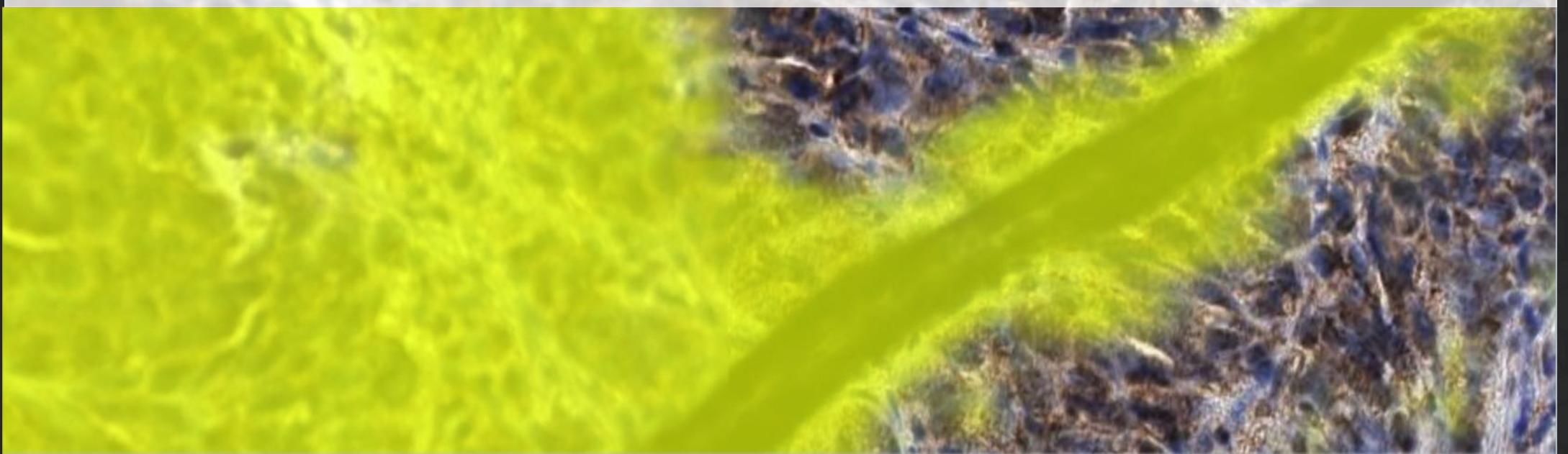


# Automated quality control

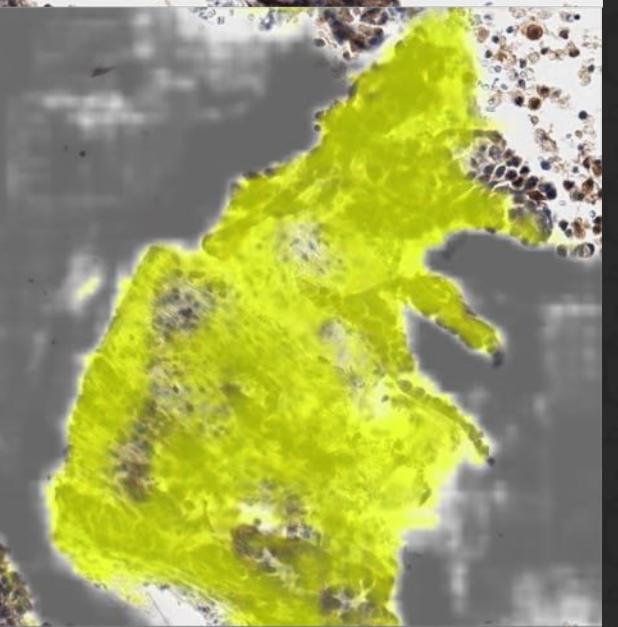
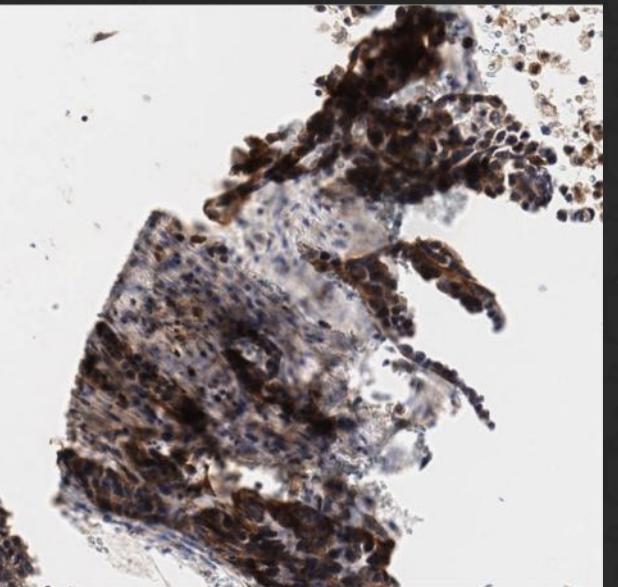
Blurred areas



Debris

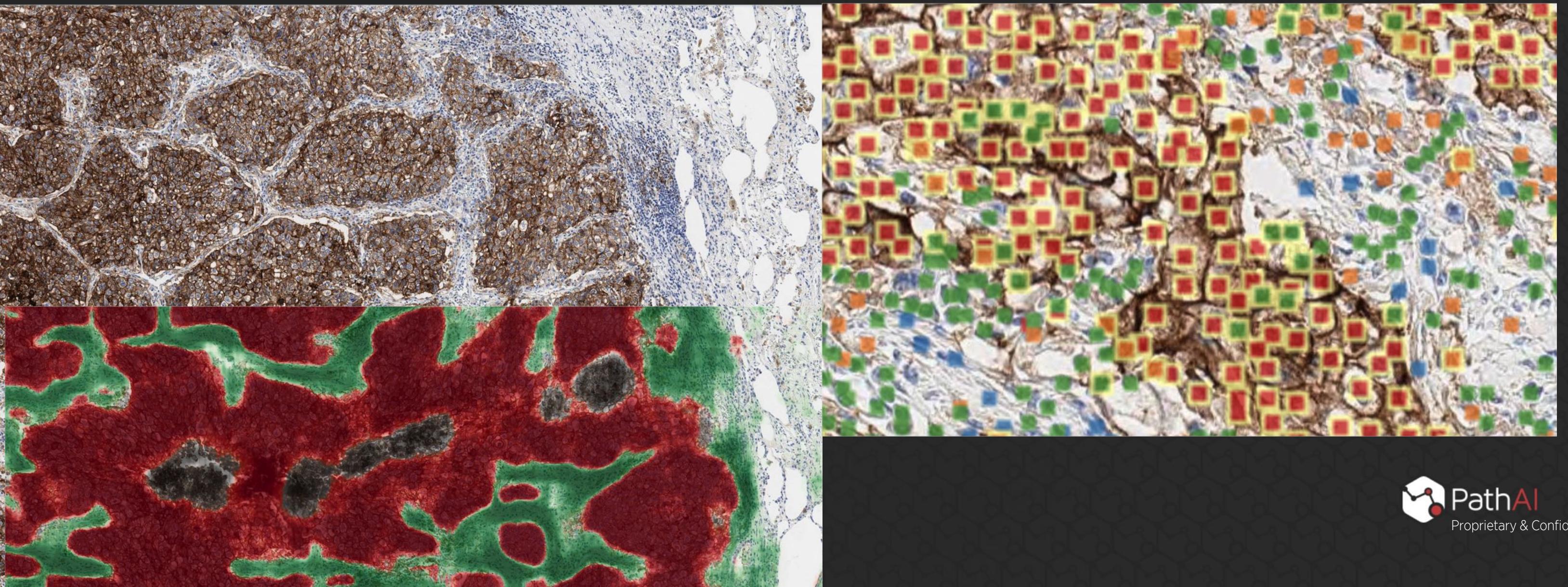


Folded /  
damaged  
tissue



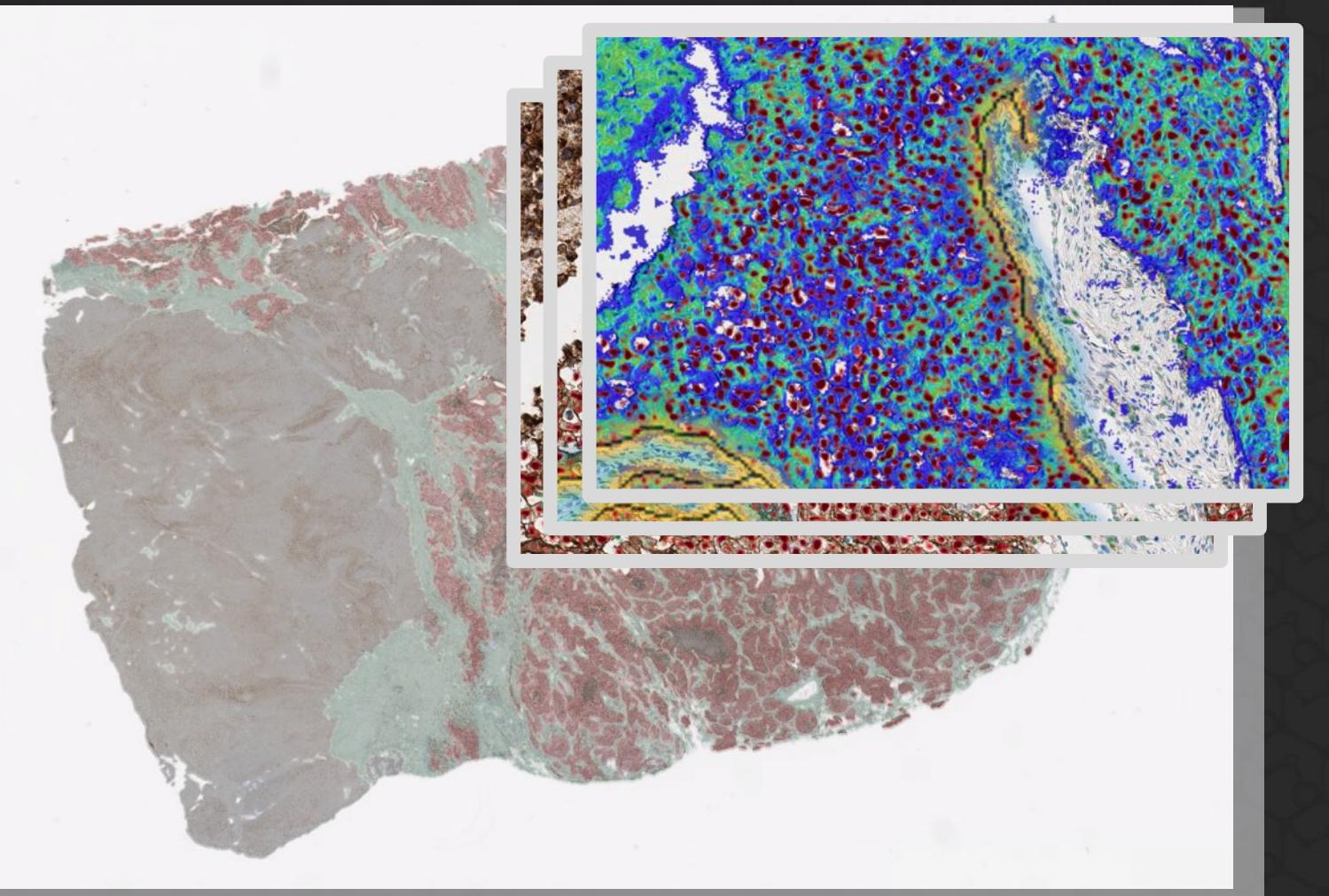
# Annotate, train and deploy task-specific models

- Determined by partner needs



# Interpretable feature extraction

- Hypothesis & data driven



# Interactive Reports & Live Project Progress

The screenshot displays a project management interface for PharmaCorp. At the top, there's a navigation bar with icons for Projects, Slides, Help, and User JA. Below the navigation bar, the main area shows a 'Projects' section with two items: 'IN PROGRESS (2)' and 'COMPLETED (2)'. The 'IN PROGRESS' section contains a card for the 'Melanoma Study Project'. This card includes a summary of the project's goal, which is to leverage the PathAI platform to quantitate cellular and morphologic phenotypes from IHC (PD-L1) stained images in melanoma clinical trial data sets. It also mentions that the algorithms developed will be validated using exhaustive annotations on selected window frames, and algorithm improvements will be implemented to include new features and rule-based region-of-interest (ROI) selection. Once validated, extracted image features will be used to find associations with patient clinical outcomes (Best OR, PFS, OS). The project status is listed as 'Predictive analysis'. The 'OVERVIEW' tab is currently active. The 'REPORT' and 'CASES' tabs are also visible. The 'COMPLETED' section contains a card for the 'Bladder Research' project, which has a similar structure and summary. A large central panel shows the detailed 'Melanoma Study Project' page. This page features an 'Overview' section with the same detailed project description, a 'KEY RESULTS' section containing a statement about a multivariate model separating patients into responders and non-responders, and a 'Progress' section on the right listing recent activity items.

PharmaCorp

Projects

IN PROGRESS (2)

Melanoma Study Project

The goal of this project is to leverage the PathAI platform to quantitate cellular and morphologic phenotypes from IHC (PD-L1) stained images in melanoma clinical trial data sets. The algorithms developed will be validated using exhaustive annotations on selected window frames, and algorithm improvements will be implemented to include new features and rule-based region-of-interest (ROI) selection. Once validated, extracted image features will be used to find associations with patient clinical outcomes (Best OR, PFS, OS).

Predictive analysis

OVERVIEW

REPORT

CASES

COMPLETED (2)

Bladder Research

The goal of this project is to leverage the PathAI platform to quantitate cellular and morphologic phenotypes from IHC (PD-L1) stained images in melanoma clinical trial data sets. The algorithms developed will be validated using exhaustive annotations on selected window frames, and algorithm improvements will be implemented to include new features and rule-based region-of-interest (ROI) selection. Once validated, extracted image features will be used to find associations with patient clinical outcomes (Best OR, PFS, OS).

Completed May 15, 2018

PharmaCorp

Melanoma Study Project

Overview

The goal of this project is to leverage the PathAI platform to quantitate cellular and morphologic phenotypes from IHC (PD-L1) stained images in melanoma clinical trial data sets. The algorithms developed will be validated using exhaustive annotations on selected window frames, and algorithm improvements will be implemented to include new features and rule-based region-of-interest (ROI) selection. Once validated, extracted image features will be used to find associations with patient clinical outcomes (Best OR, PFS, OS).

KEY RESULTS

Our multivariate model separates patients into XX responders and non-responders

Progress

Predictive analysis

PathAI added a key result.  
2d ago

Project status changed to Predictive analysis.  
3d ago

PathAI uploaded a report.  
3d ago

PathAI released slide overlays Cell Detection v1, Tissue map V1  
21d ago

Project status changed to Extracting features  
21d ago

# The PathAI Deep Learning Process



## Whole-Slide Images + Data

Transmit training data securely to the PathAI cloud



## Annotations

Network of board-certified pathologists to provide ground truth consensus



## Deep Learning Analysis

Cell detection, tissue & region classification



## Deep Learning Feature Analysis

Over 200 relevant features extracted, measured and analyzed



## Assay Validated

Identified features of significance reduced to practice



## Assay Deployed

Analyze samples, quantified & visual results delivered

We can execute process in 4 – 8 weeks for new assays

# AI in medicine

## Some closing thoughts

- ML in the real world:
  - Building the right dataset is 75% of the challenge
- Modern ML: engineering and empirical science
  - Rigorous validation is key
- Ideas and algorithms vs. teams and infrastructure

# Core challenges and road ahead

Technology

Regulatory

Financial

Workflow  
transformation

# Key Takeaways

- Researchers have been working on AI for pathology for ~30 years
- In the past 5 years, advances in:
  - Availability of digital data
  - Access to large-scale computing resources
  - Major algorithmic advances (e.g., Deep CNNs)
- AI works extremely well when these 3 factors are all available and fails when they are not

# Key Takeaways

- AI-powered pathology is broadly applicable across all image-based tasks in pathology and enables integration with other structured data types (e.g., ‘Omics)
- As AI and digital pathology are incorporated into clinical workflow, they will offer significant operational and efficiency advantages
- AI will drive improvements in the accuracy and predictiveness of pathology leading to research advances and improved care for patients

# “In the Future...” (1987)

- “Integrated information systems, patient care management by exception, decision support tools, and, in the future, "artificial intelligence" assists can all be expected to become staples of pathology practice, especially impacting those pathologists who choose to be responsive to the new practice milieu of medical information science.”

**“Using the computer to optimize human performance in health care delivery. The pathologist as medical information specialist.”**  
**(Arch Pathol Lab Med. 1987)**



# Thank you!

Hunter Elliott



Director, Machine Learning Research

**pathai.com**  
Opportunities for ML  
engineers/scientists, software  
engineers, pathologists,...

The PathAI team

