AI-based assessment of cardiac allograft rejections

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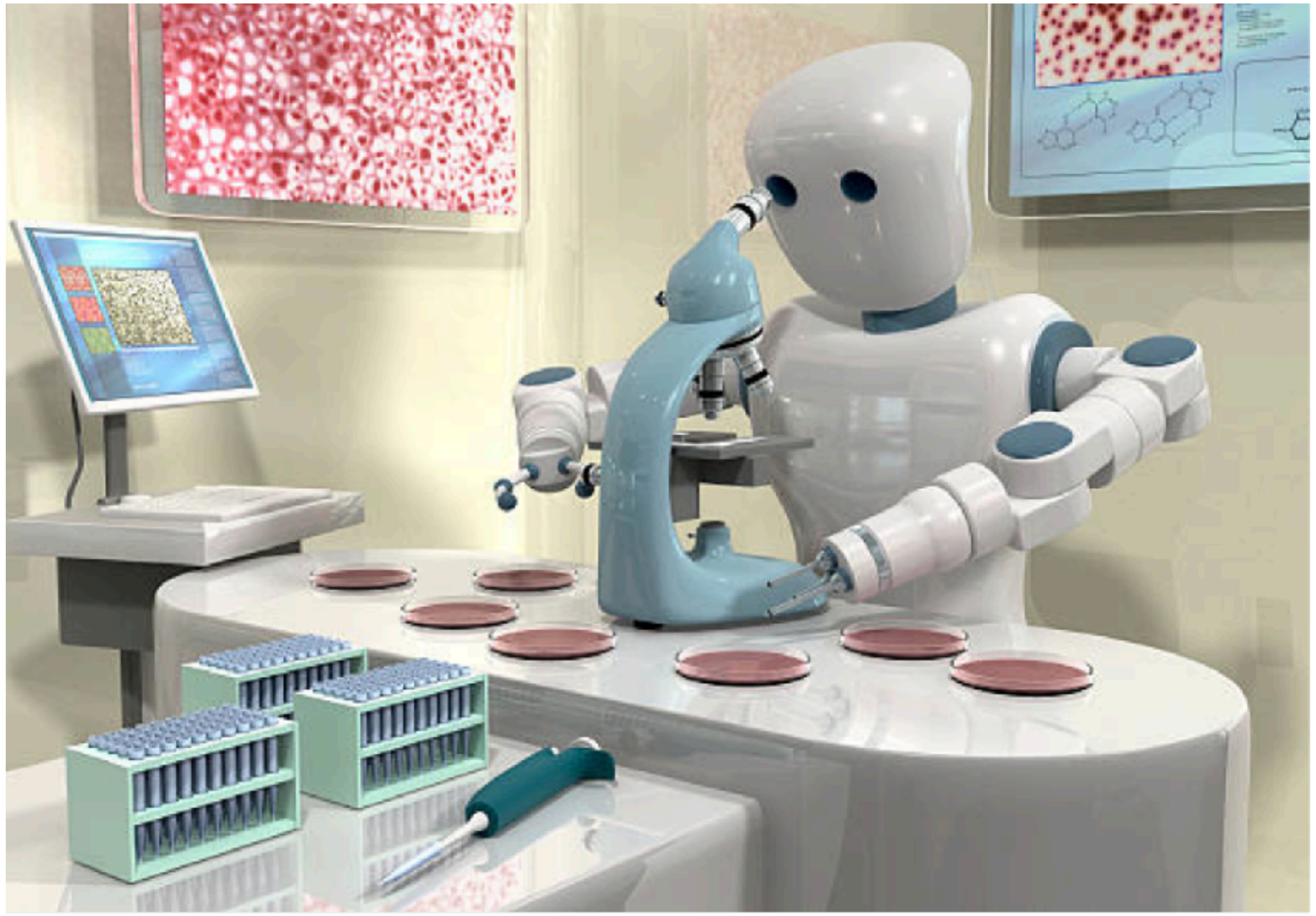
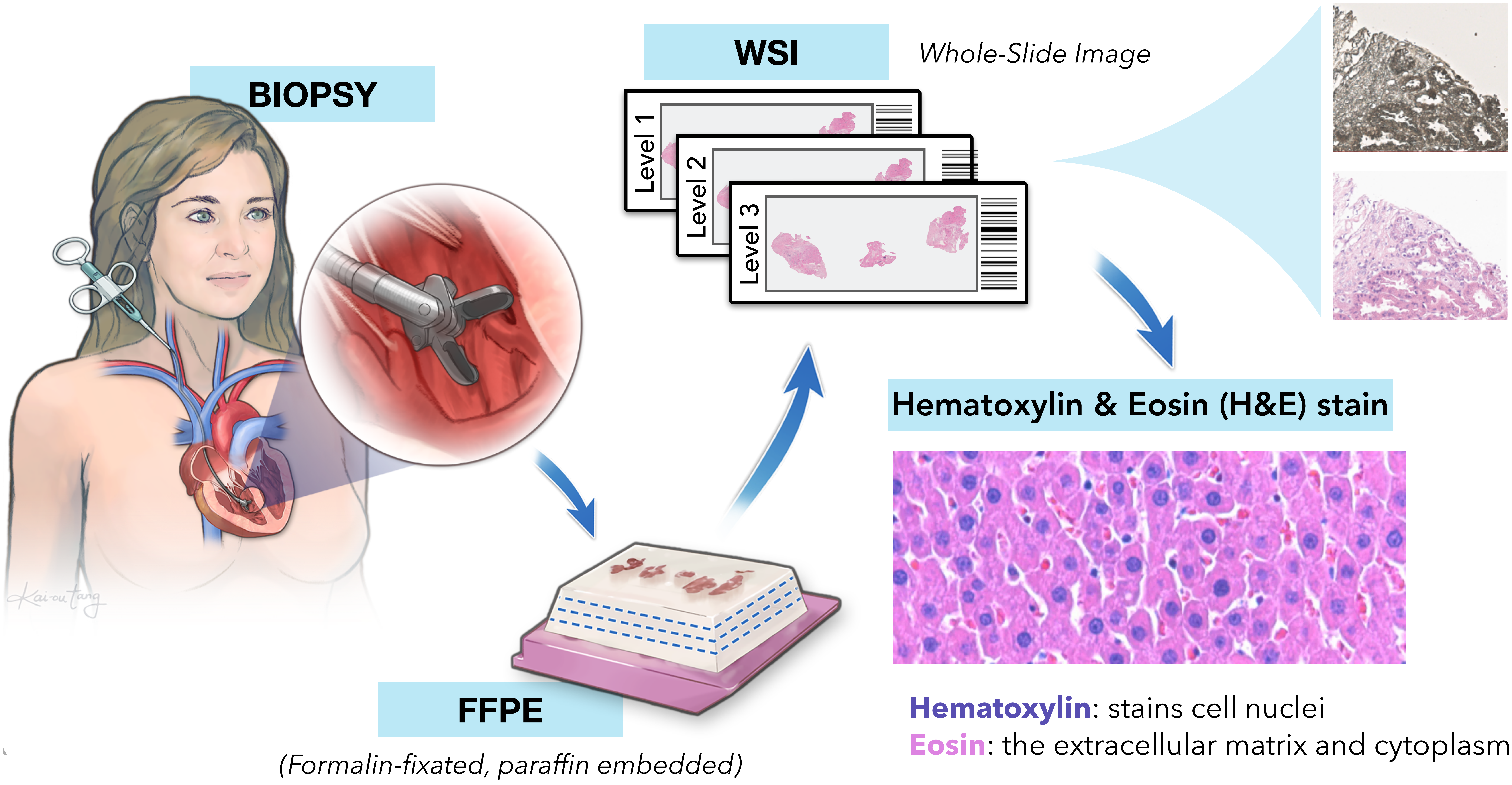
Overview

- **Background:**
  - Histopathology data
  - Cardiac Allograft Rejections
- **AI-based assessment of allograft rejections**



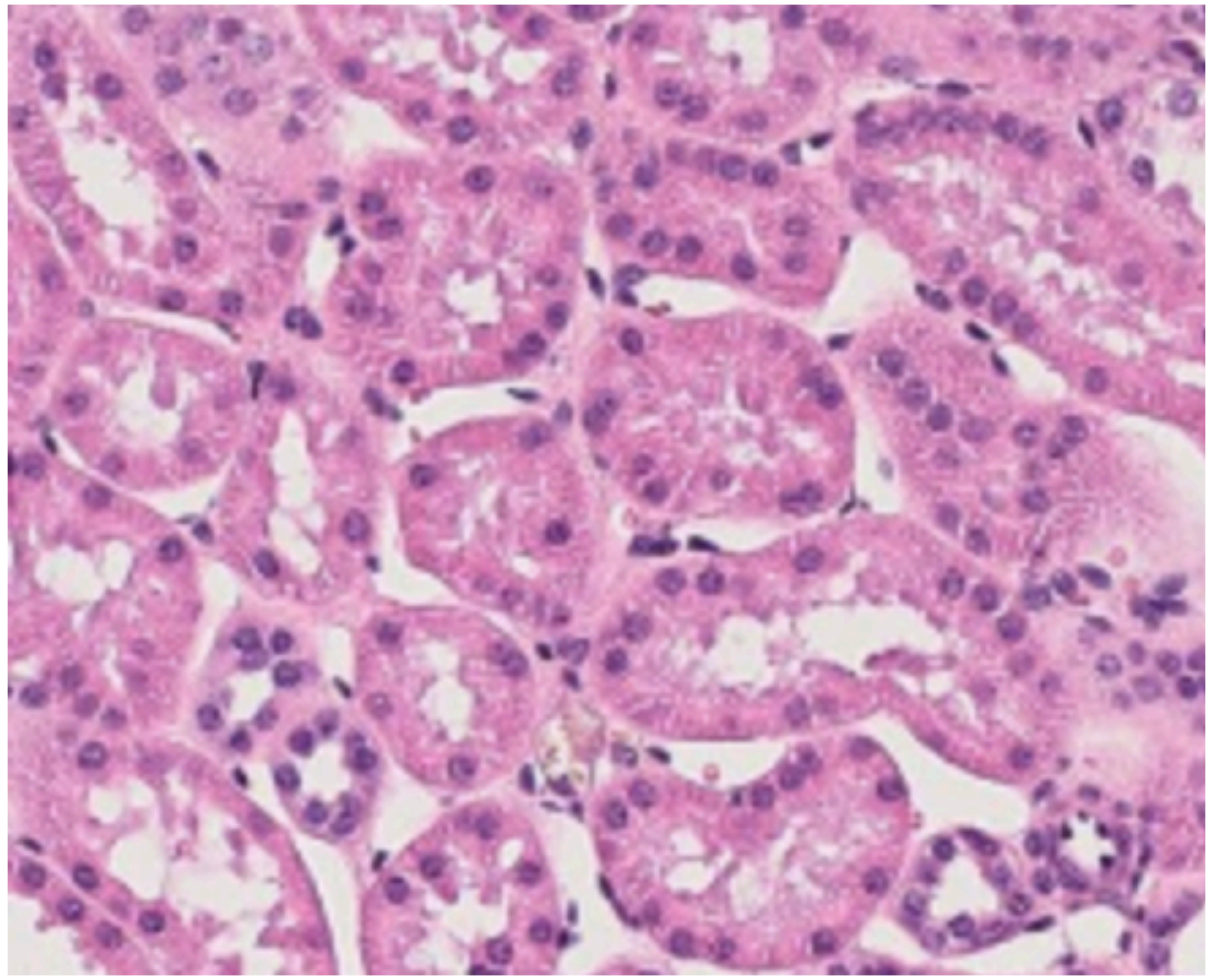
(source GettyImages)

Histology 101



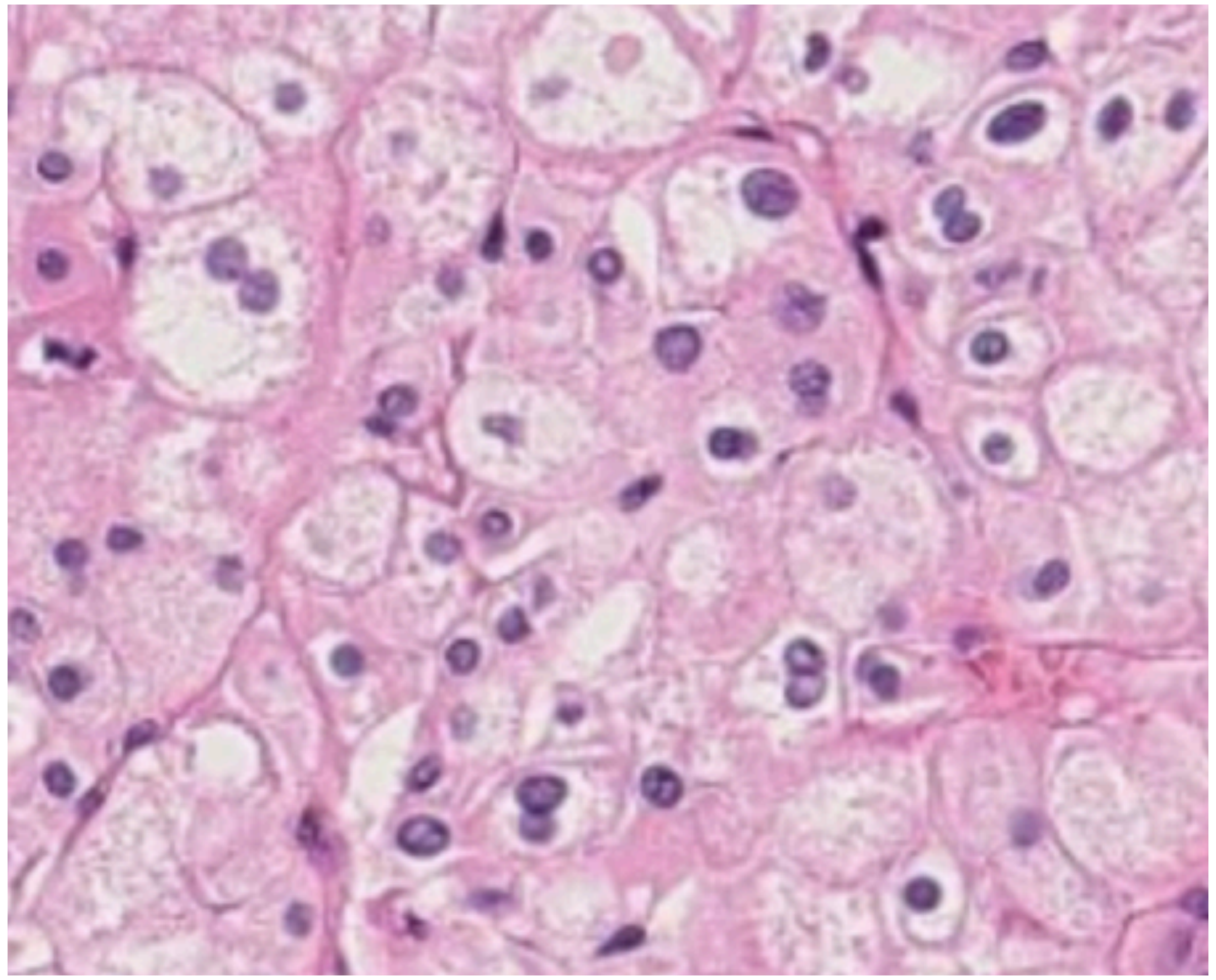
Cancer detection/classification 101

Normal tissue (kidney)



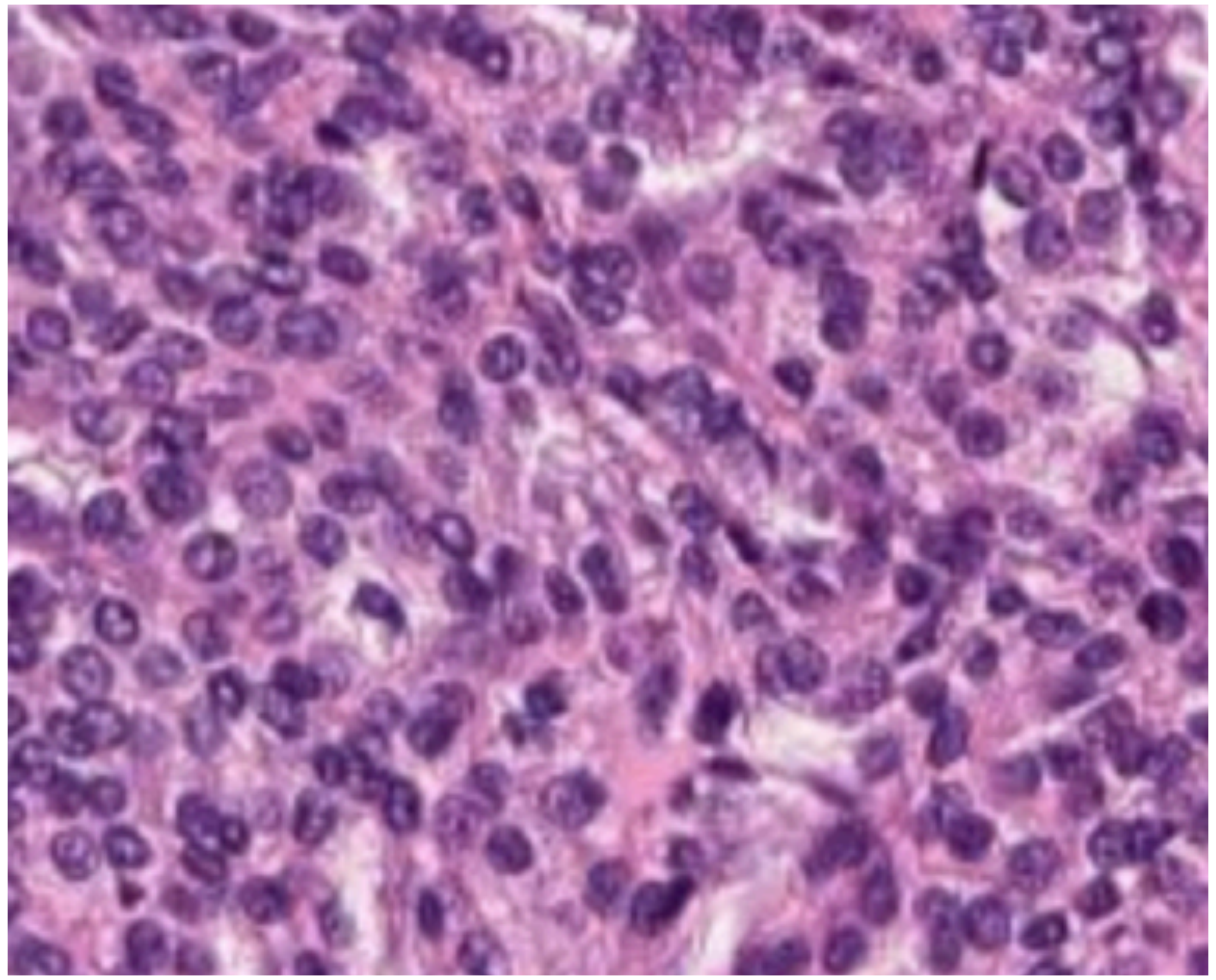
- Symmetric regular structure
- One nuclei per cell
- Cell/nuclei - regular shape

Chromophobe renal carcinoma



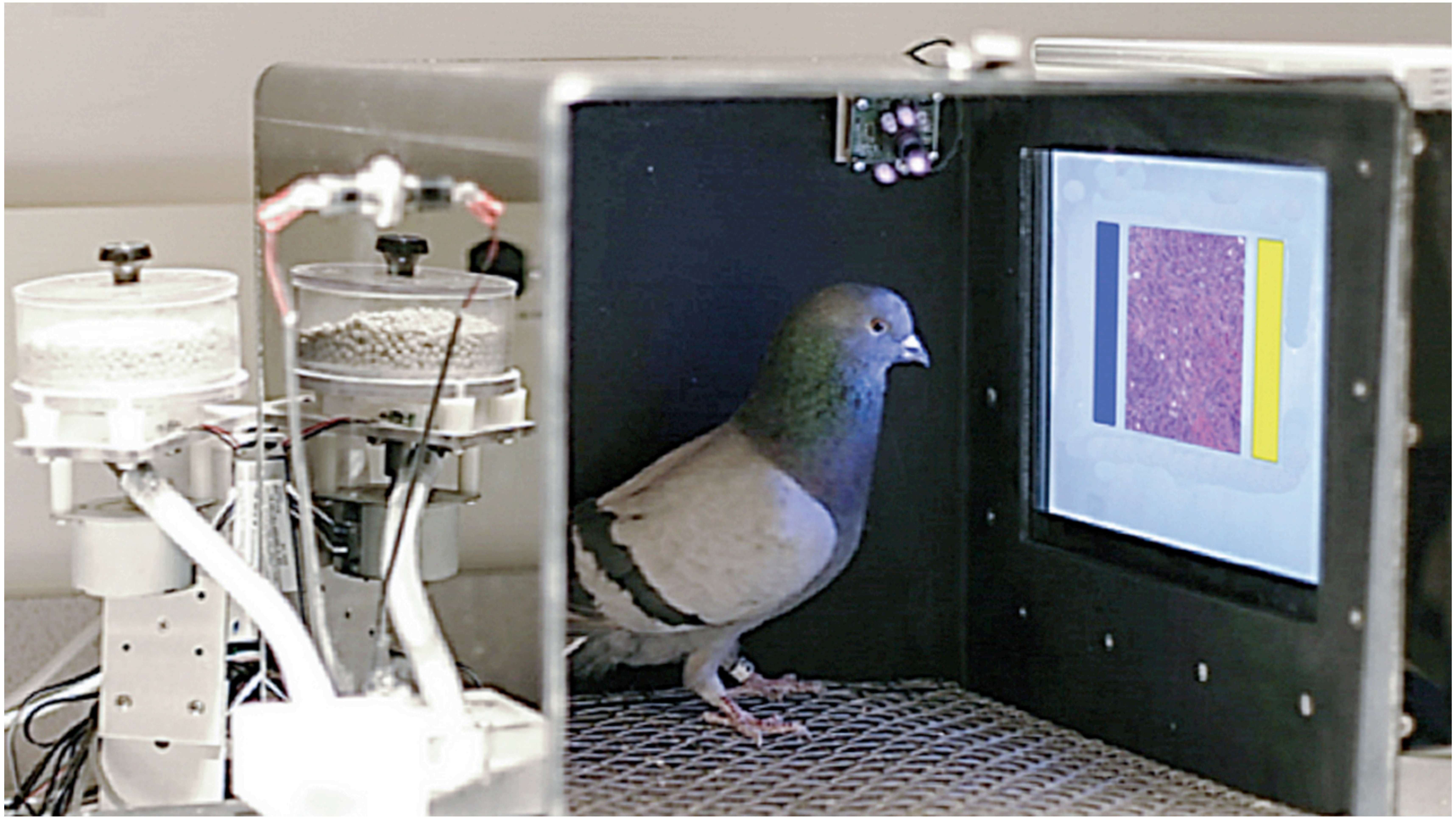
- Enlarged nuclei
- Double nuclei per cell
- Irregular shape

Papillary renal carcinoma



- Papillary cores lined by neoplsatic cells
- Tubulopapillary architecture

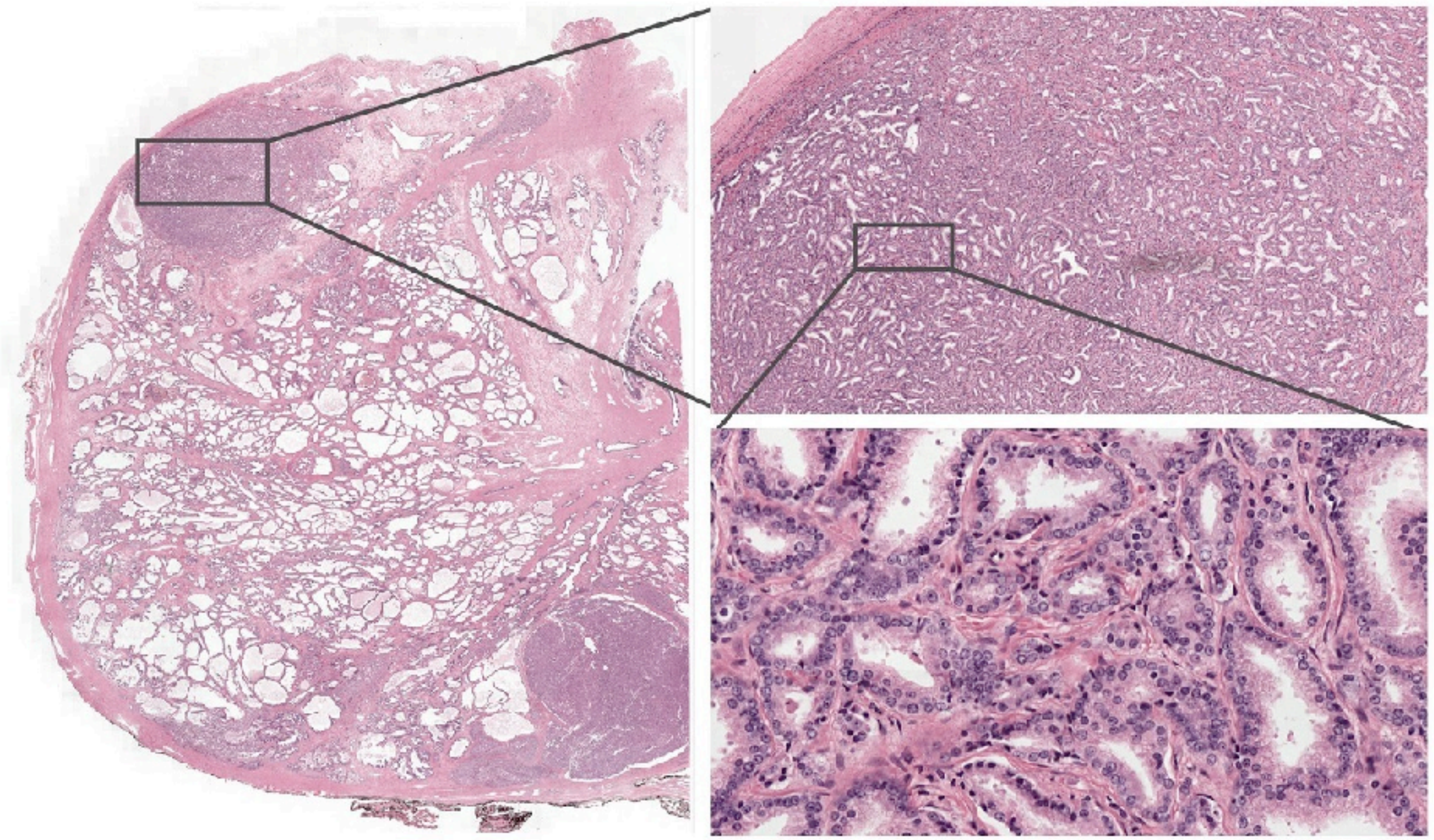
Fun fact: Also pigeons can detect cancer

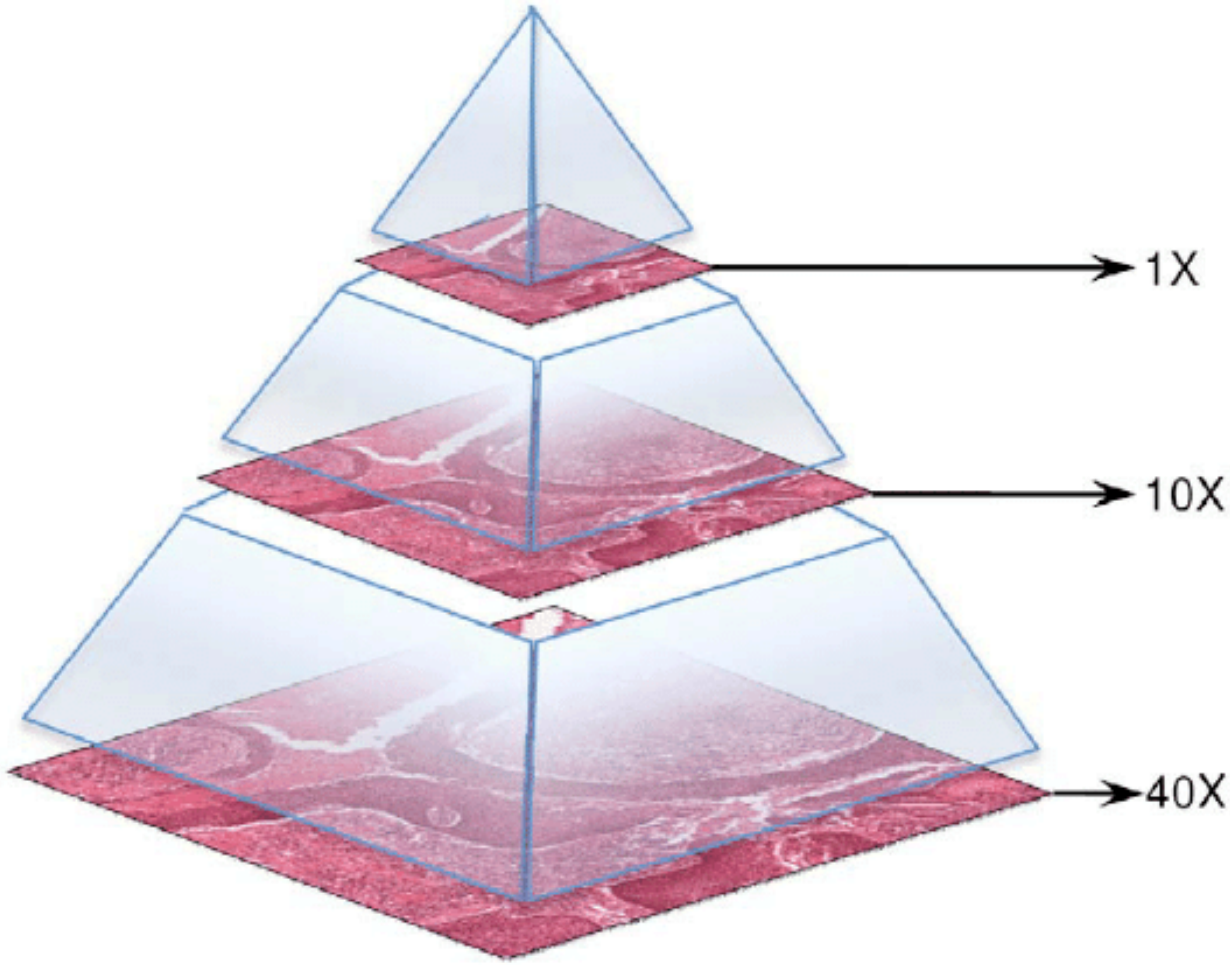


R. Levenson et al: Pigeons (Columba livia) as Trainable Observers of Pathology and Radiology Breast Cancer Images, PloS one, (2015)

Digital Pathology: Whole Slide Images (WSIs)

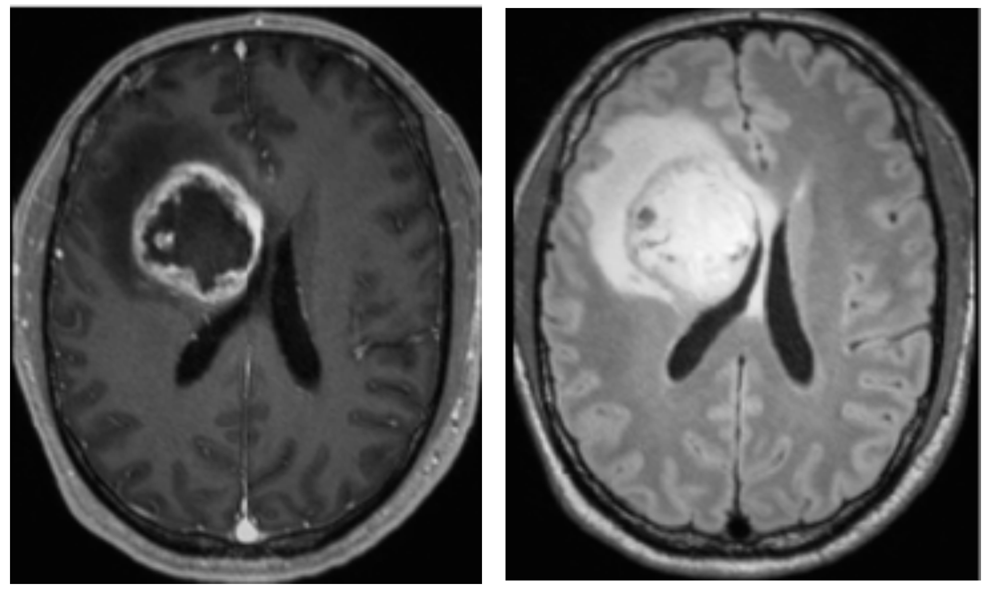
- High resolution scan of an entire tissue section (0.25 - 0.5 microns per pixel)
- Gigapixel image: 100,000 x 100,000 pixels
- **100 WSI have cca same amount of pixels as whole ImageNet**
- Different Stains: H&E, IHC





Medical Data

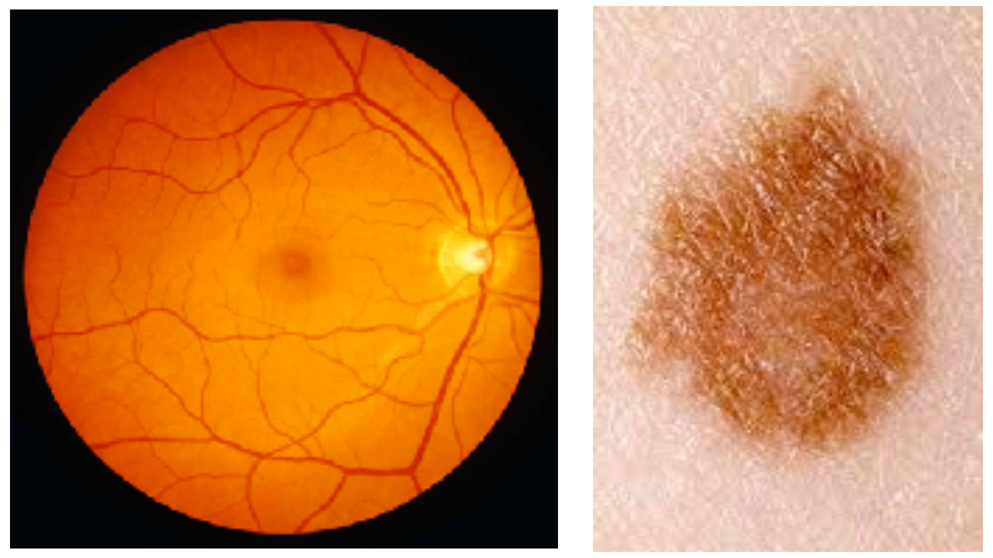
Radiology



(MRI head scan)

- 3D images
- gray-scale images
- resolution: ~1 mm
- size: 256x256x256 voxels

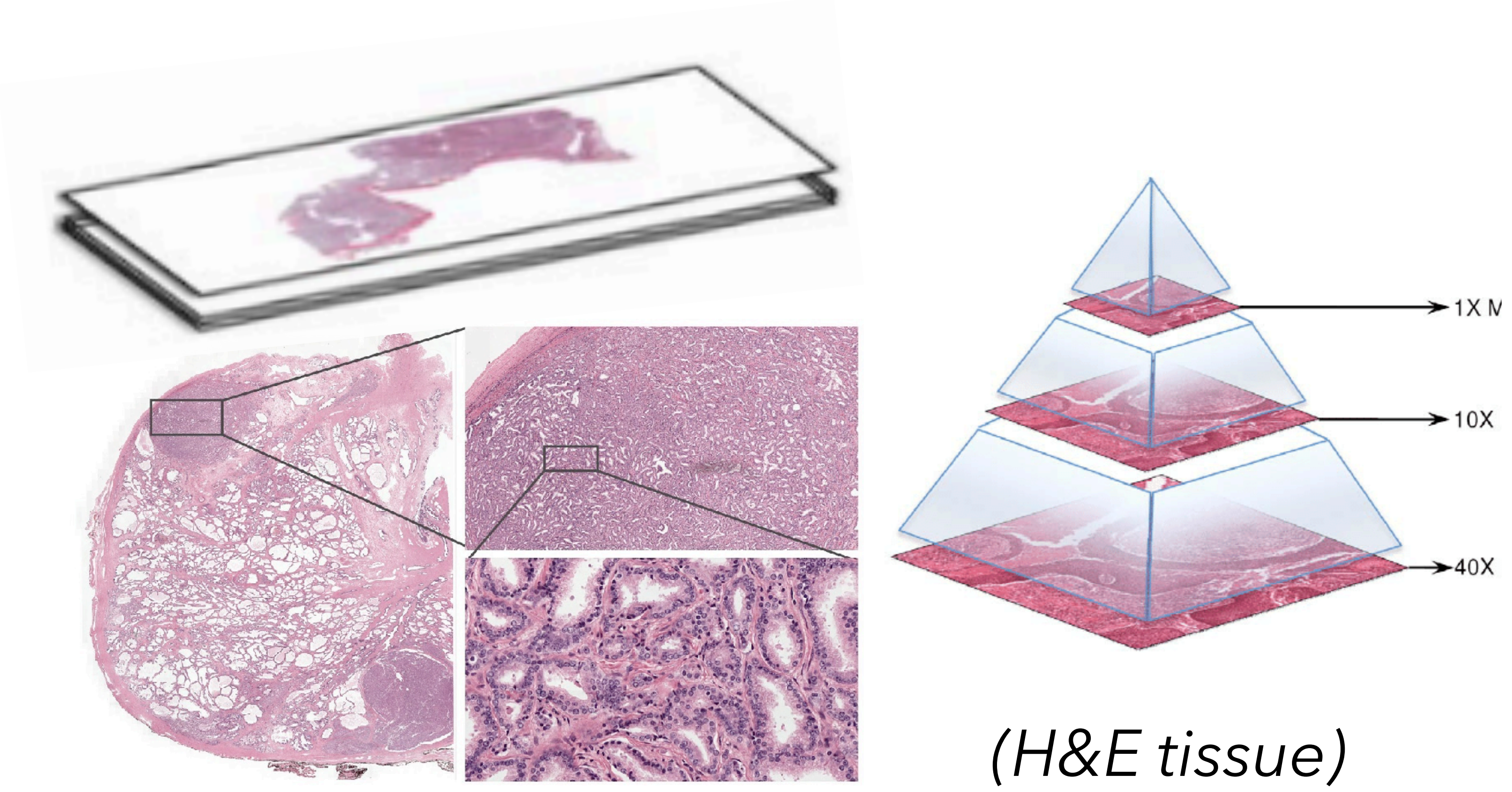
Photography



(Fundus / skin photography)

- 2D images
- RGB
- 10 µm - 1 mm
- size: ~1,700x1,700 pixels

Histology

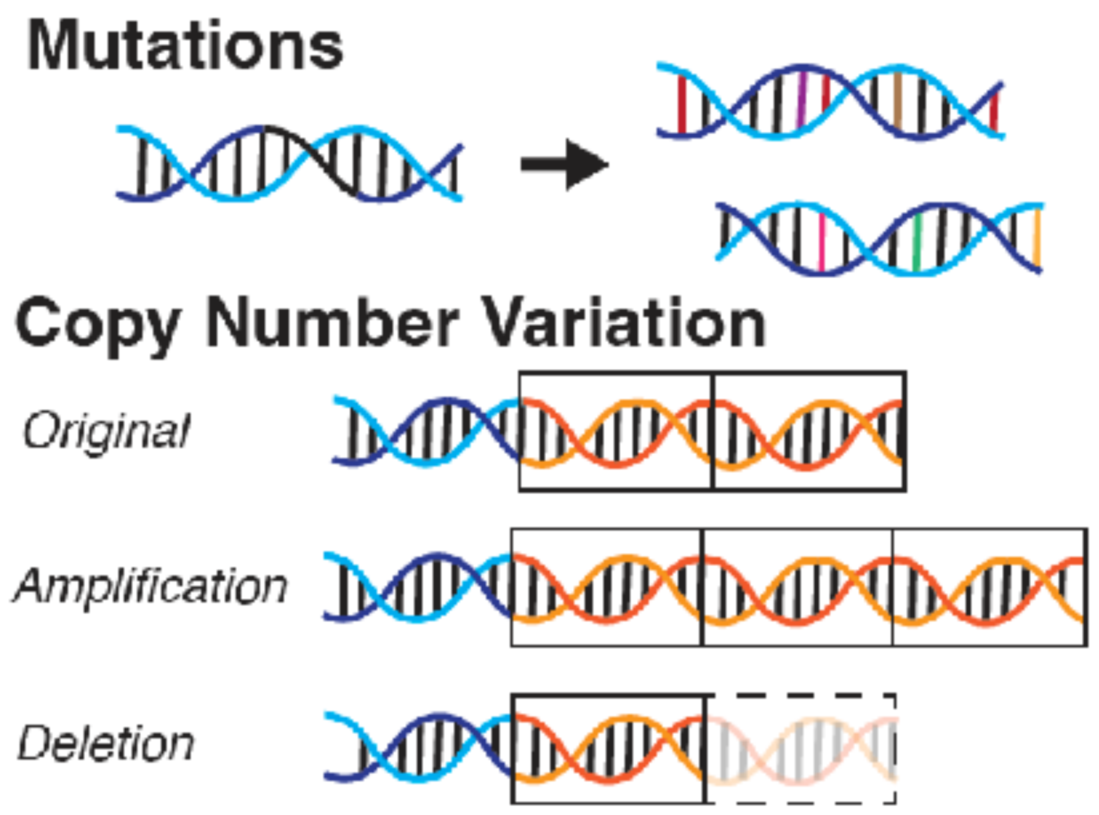


(H&E tissue)

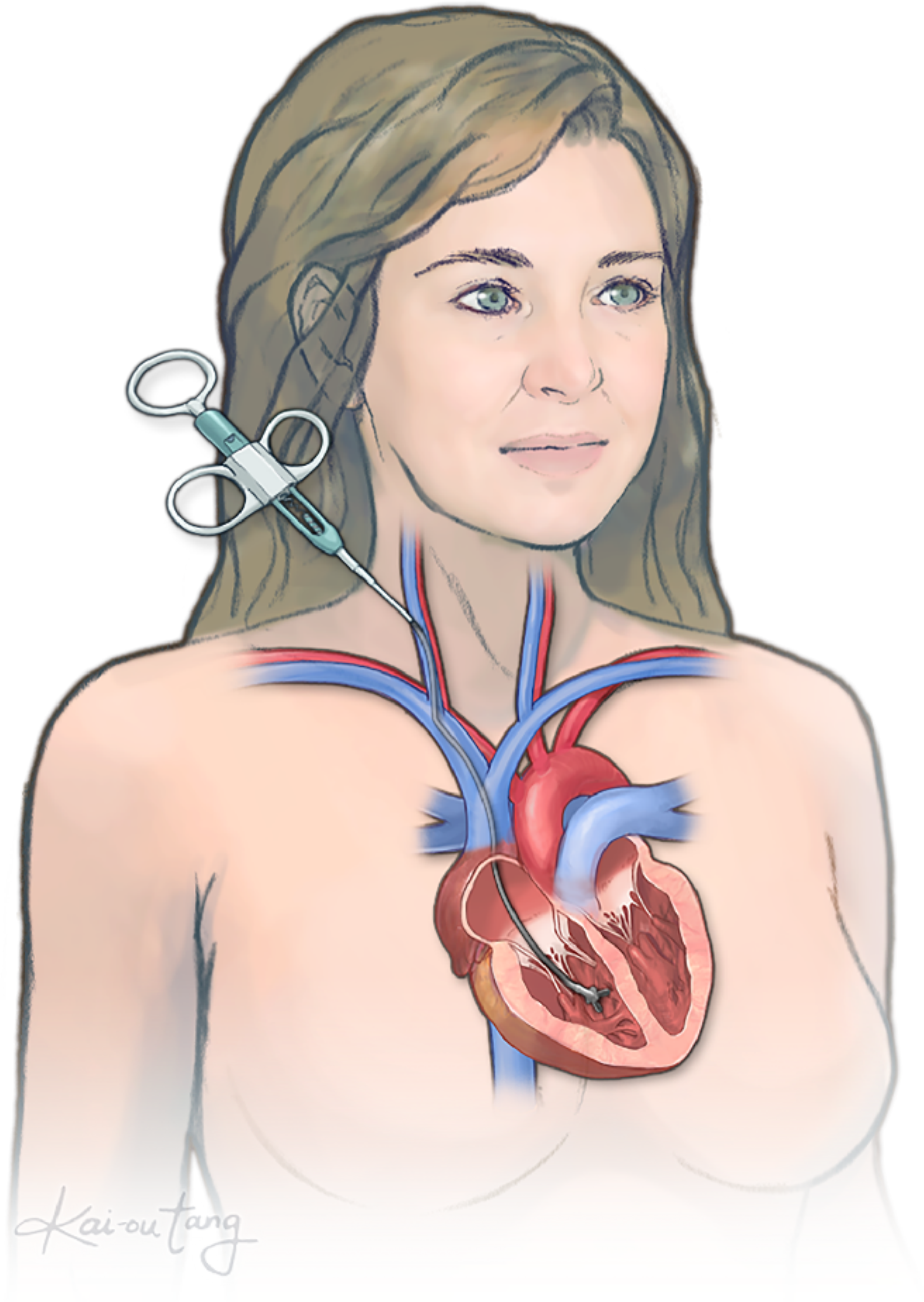
- 2D images
- RGB
- scale: ~0.1µm
- 100,000x100,000 pixels

(varies with magnification, tissue size etc)

Genomics



- 1D array
- float (e.g. '0' wild type, '1' mutation)
- scale: 1µm - 1nm
- ~20,000 protein-coding genes



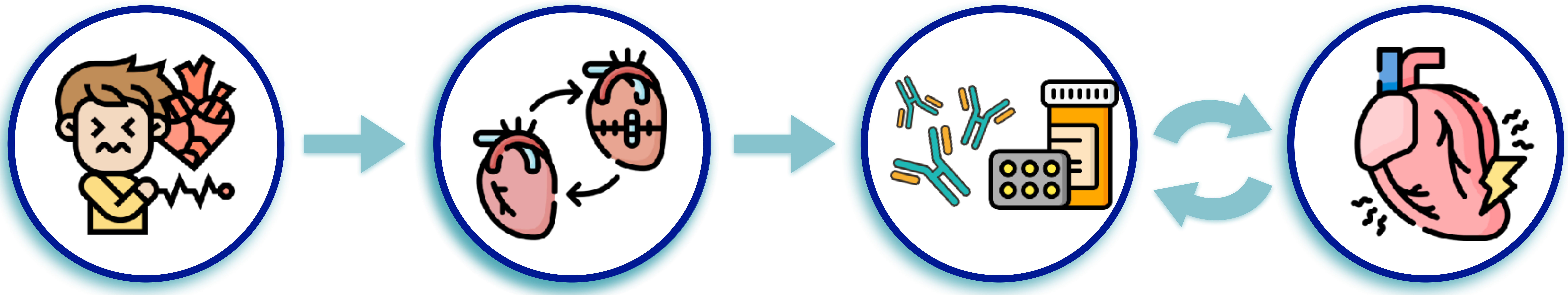
AI-Assessment of Cardiac Allograft Rejections

Jana Lipkova, Tiffany Y Chen, Ming Y Lu, Jingwen Wang, Maha Shady, Mane Williams, Richard Mitchell, Mehmet Turan, Gulfize Coskun, Derya Demir, Deniz Nart, Funda Y Barbet, Katja E Odening, Yara Banz, Faisal Mahmood

Lipkova et al. Nature Medicine (2022)

BACKGROUND

Heart Failure | **Heart Transplant** | **Immune Response** | **Allograft Rejection**



Heart Failure
- Leading cause of hospitalization in USA/EU
- 26 million cases / year

Heart Transplant
- Patients with end-stage failure
- 5000 transplants / year

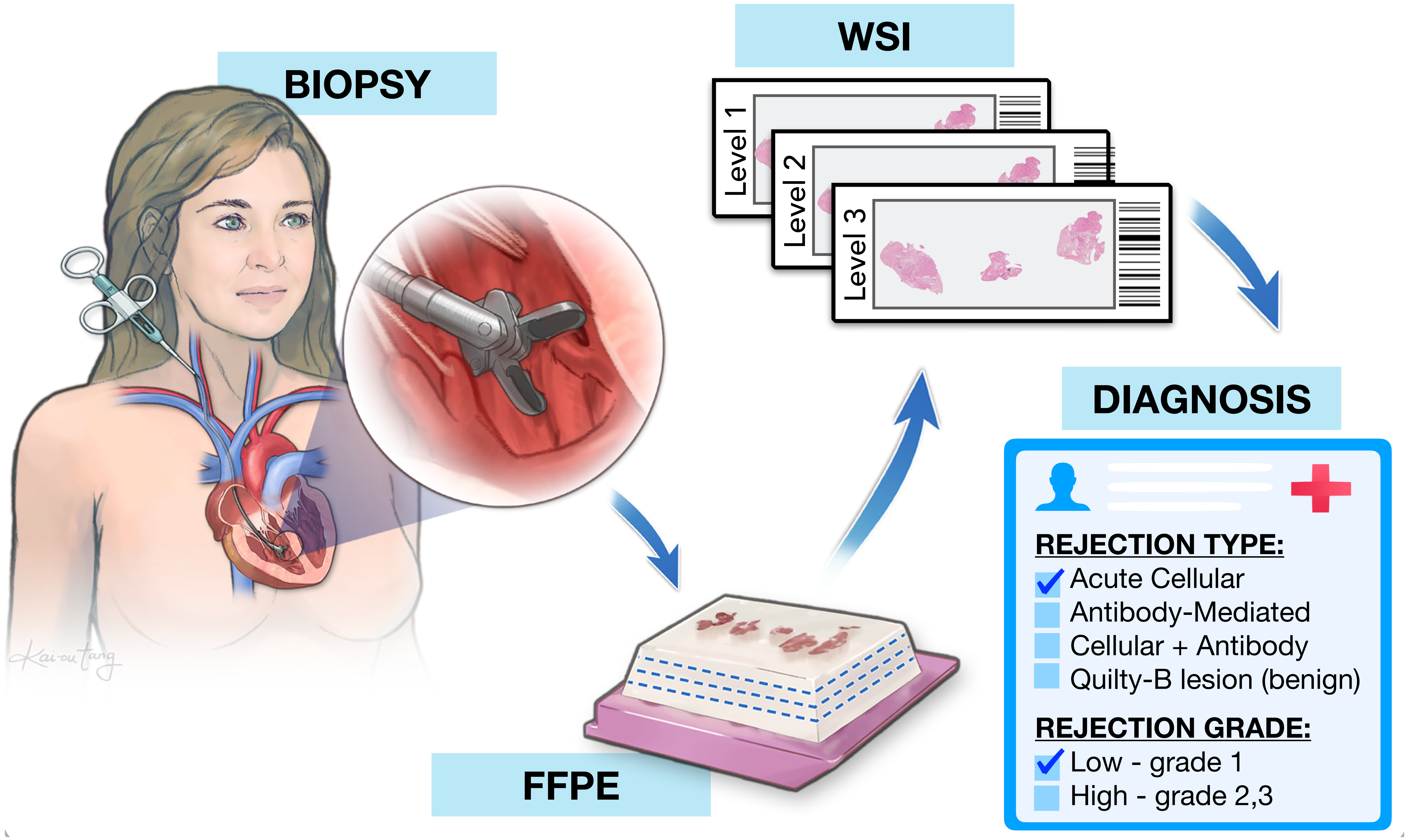
Immune Response
- Immunosuppressives
- Patient-specific set-up

Allograft Rejection
- Main complication & main cause of death
- 40% recipients

MOTIVATION

APPLICATION:

- Early stages of rejections are **asymptomatic** → surveillance **Endomyocardial biopsy** (EMB)
- Gold-standard: manual assessment H&E-stained biopsies:
  - **detection** and **subtyping** of rejections (***acute cellular***, ***antibody-mediate***, ***benign mimickers***) and **grading** (I-III)
- Rejection type & grade **determines the immunosuppressive treatment regime**

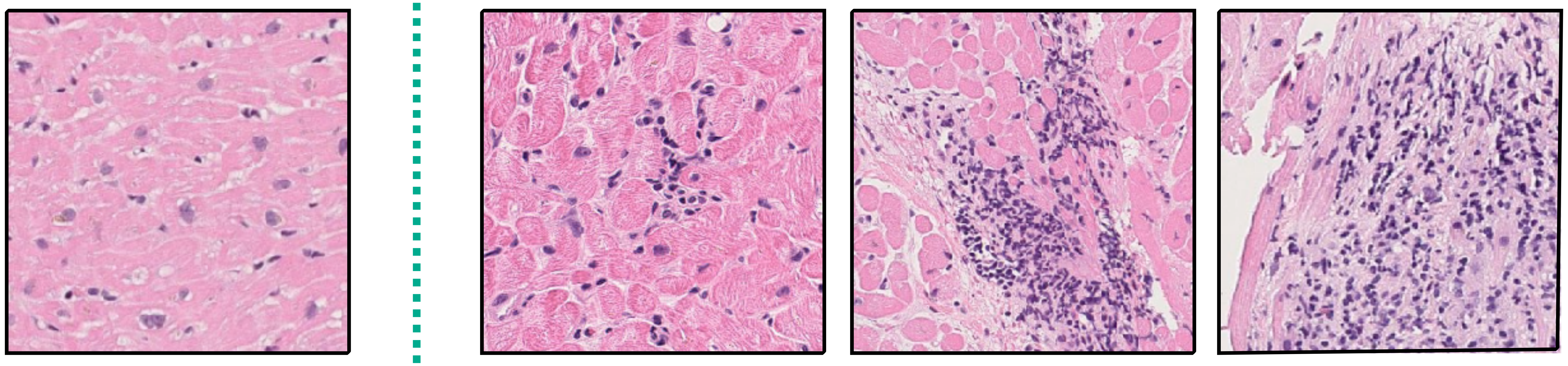


- [1] Concordance among pathologists in the second cardiac allograft rejection gene expression observational study (CARGO II) In: *Transplantation* 94.11 (2012), pp. 1172–1177

Lipkova et al. Nature Medicine (2022)

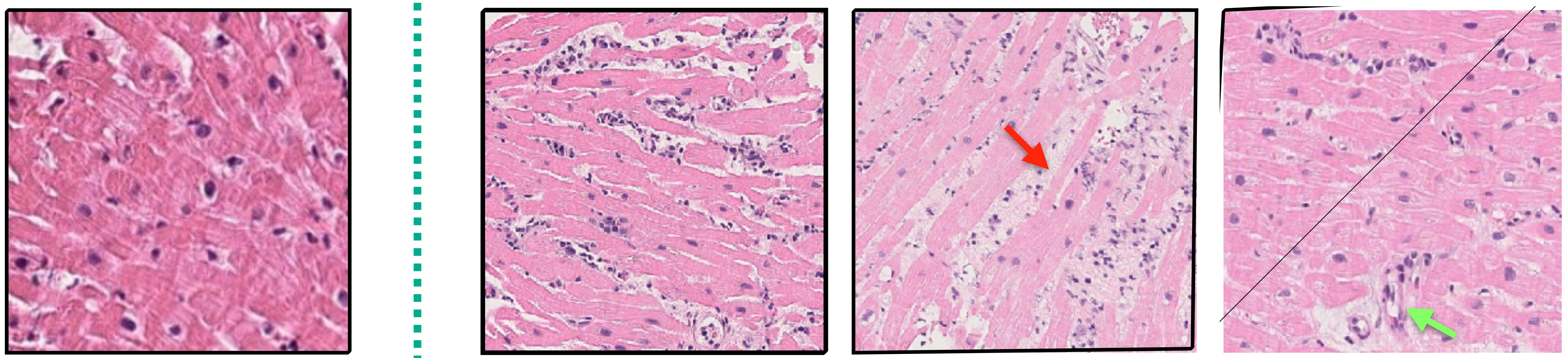
101: Rejection Types

Normal tissue | **Abnormal tissue**



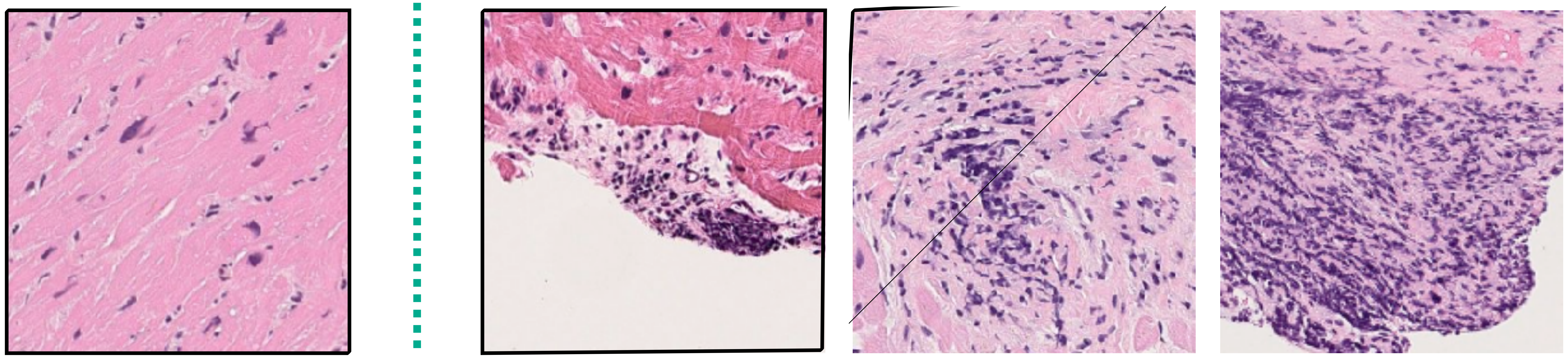
Acute Cellular

- Lymphocyte infiltrates in muscle tissue
- Homogenous structure
- Comprised of T-cells



Antibody Mediated

- Increased extracellular space + **edema**
- **Capillary** endothelial **changes**
- Increase cell damage
- More macrophages and necrosis



Quilty B Lesions

- Benign lesions
- Mixed B and T-cells, macrophages and plasma cells
- commonly mistaken for cellular rejections

MOTIVATION

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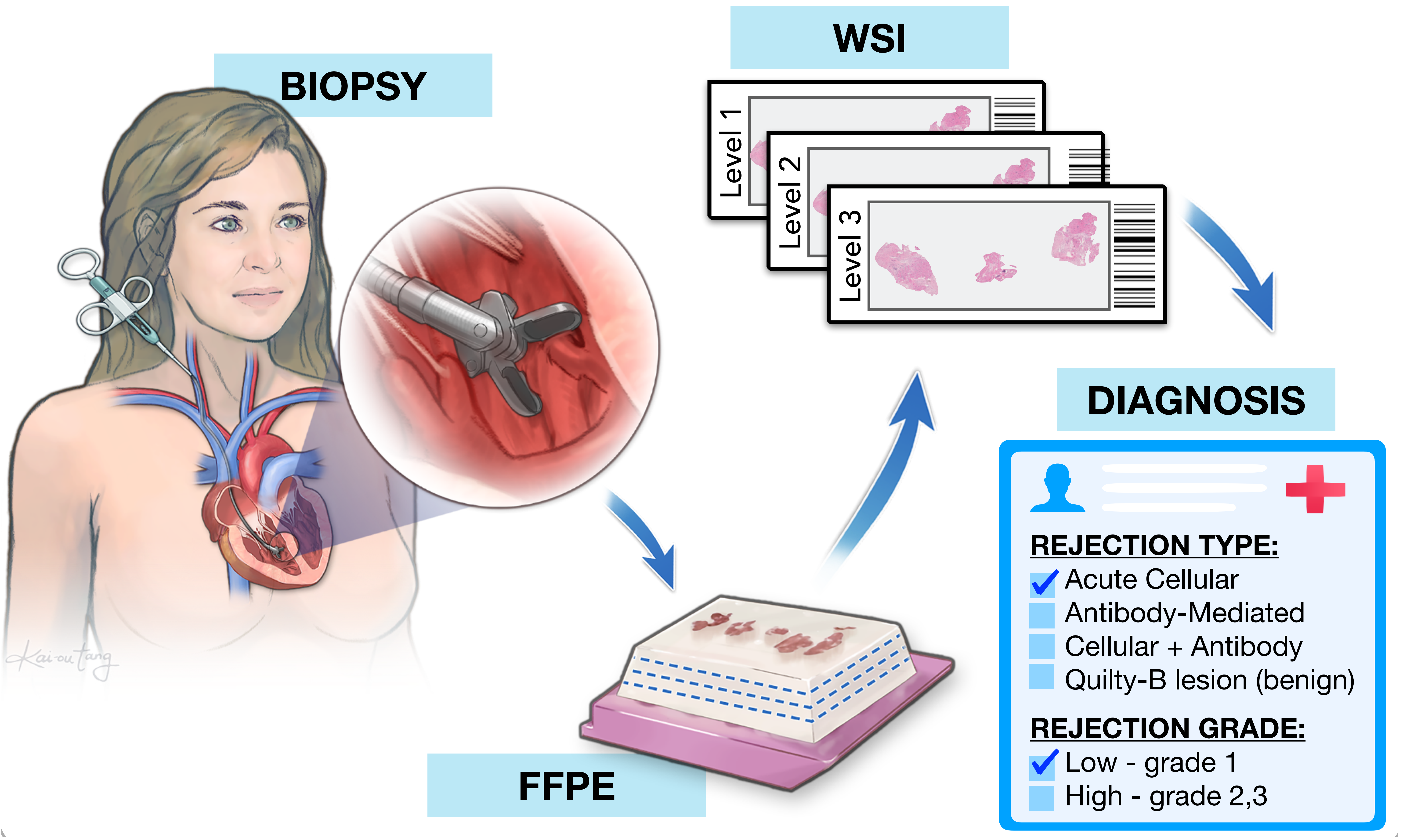
- Rejection type & grade determines the immunosuppressive treatment regime



CHALLENGES:

- **Substantial inter-rater variability** [1]:
  - <71 % agree if recipient is rejecting the heart
  - <28 % agree on the grade of advance rejections
  - 19 % unable to reach majority agreement
- **Misinterpretation**:
  - under/over treatment with immunosuppressives
  - unnecessary follow-up biopsies
  - worse outcomes

AIM:

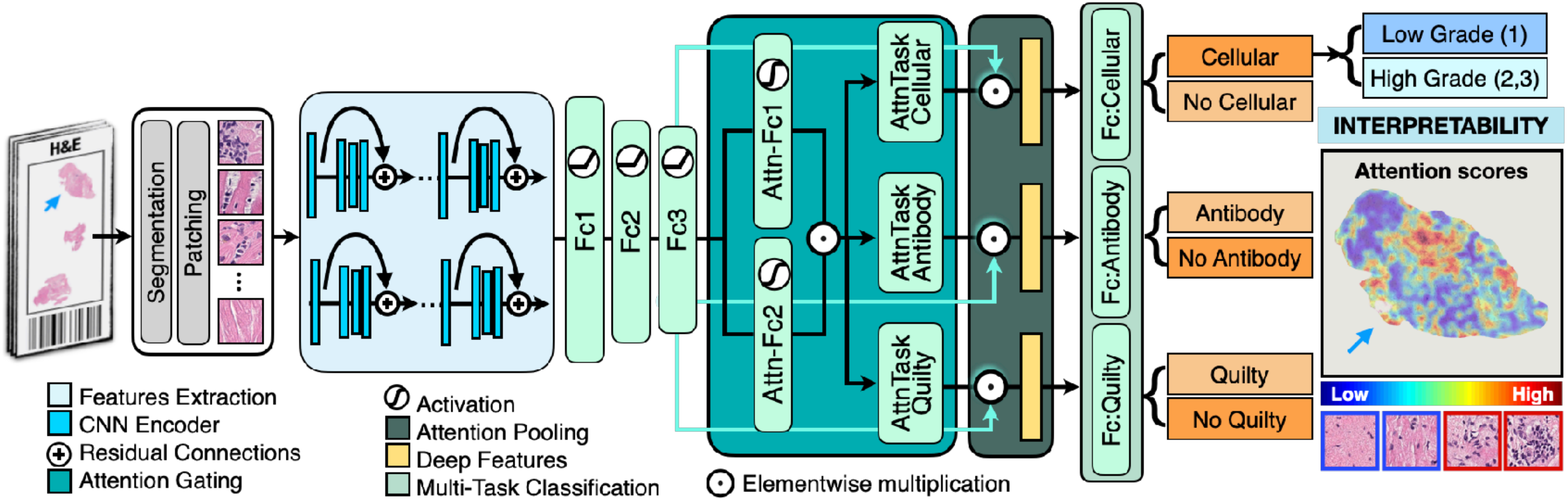
- **Objective and automated EMBs assessment**

[1] Concordance among pathologists in the second cardiac allograft rejection gene expression observational study (CARGO II) In: *Transplantation* 94.11 (2012), pp. 1172–1177

Cardiac Rejection Assessment Neural Estimator

CRANE

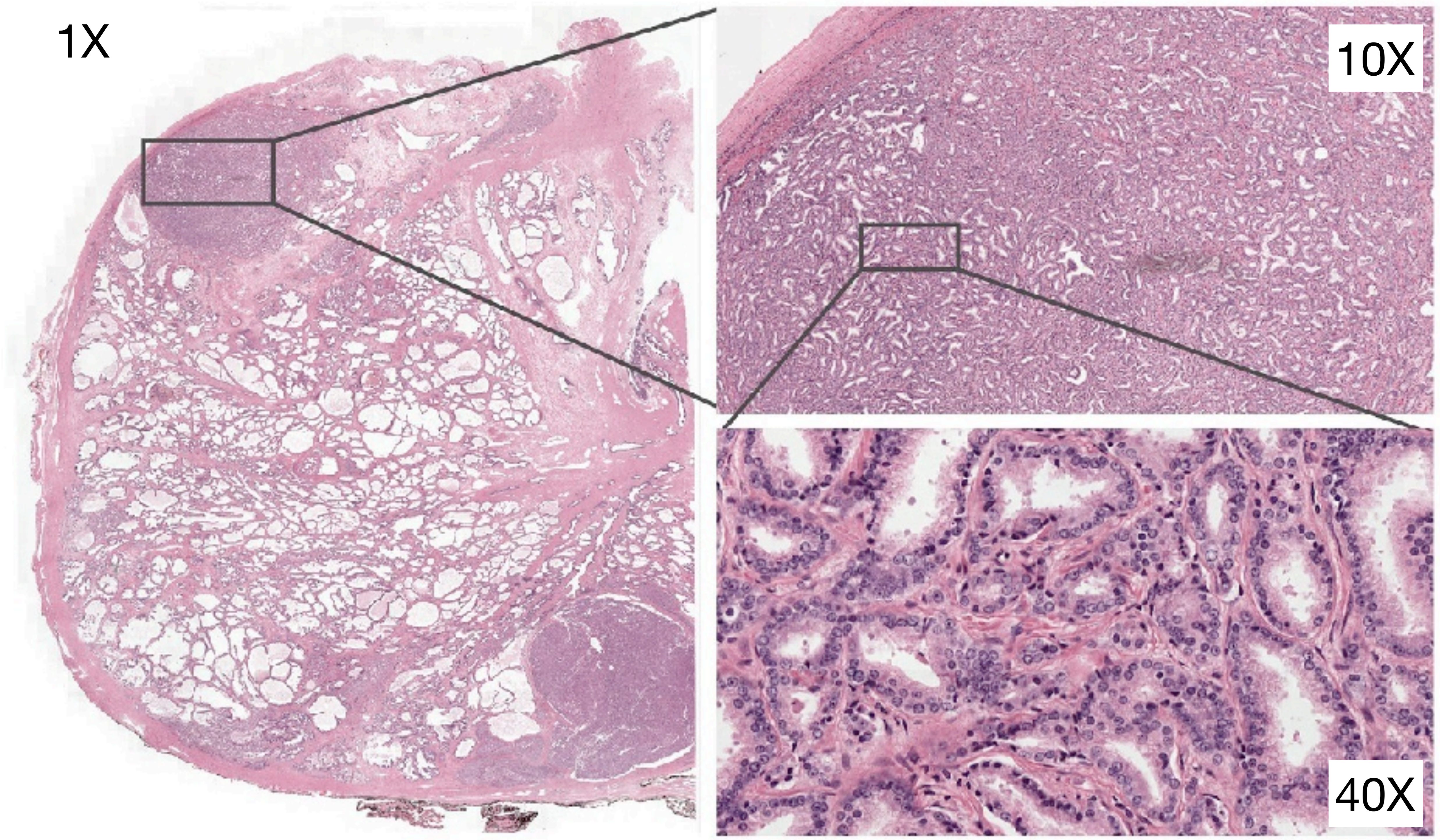
- **Input:** H&E-stained EMBs whole-slide-images (WSIs)
- **Multi-task, multi-label model:** simultaneously identifies **presence** and **type of the rejection** (cellular, antibody, and/or quilty lesions). Separate classifier estimate **rejection grade**
- **Multiple-instance learning:** use **patient diagnosis** as only **label**
  - (avoid pixel-level annotations, supports large-scale deployment)
- **Attention scores,** reflecting relevance of each biopsy region, enable **visual interpretation** of the model's predictions

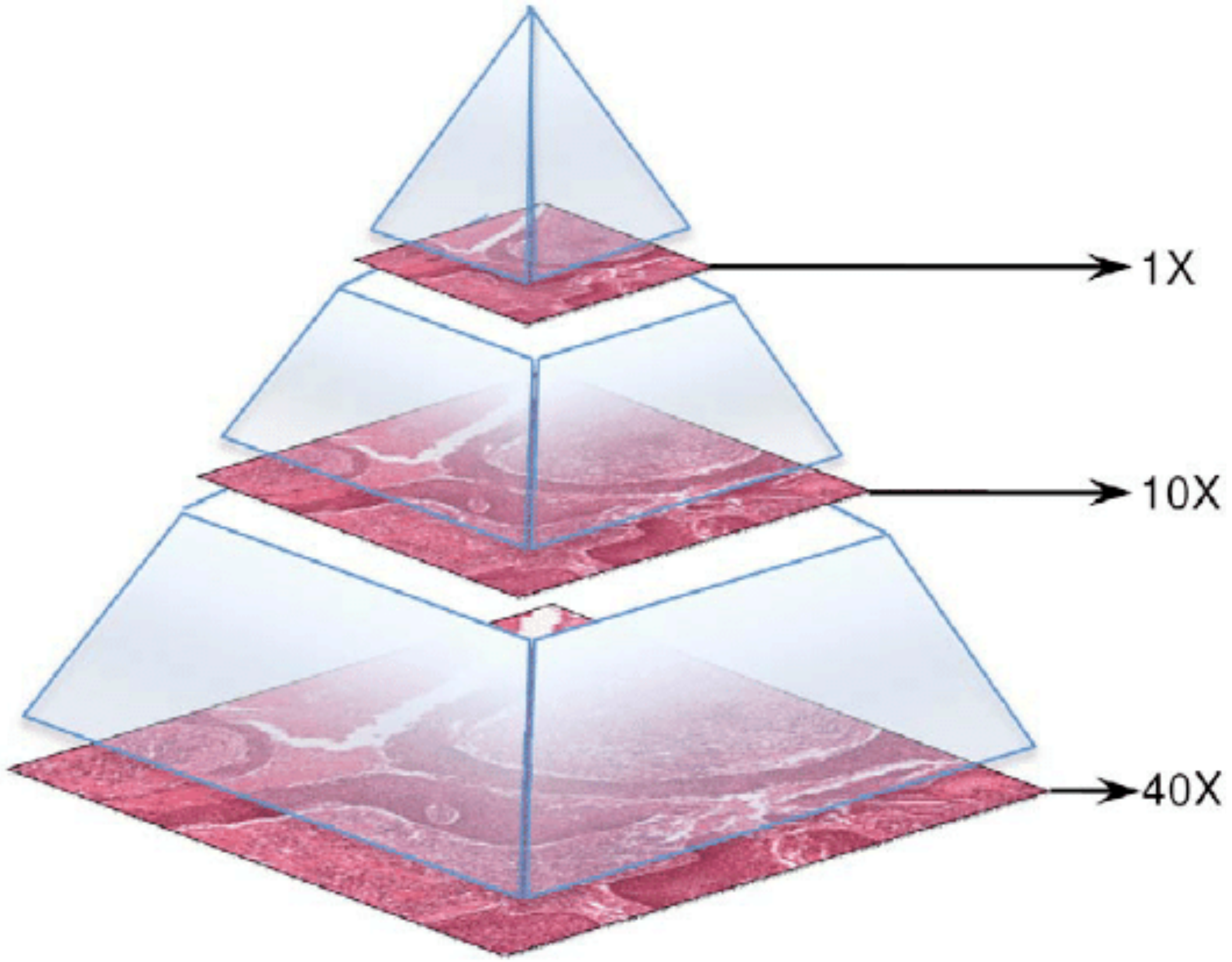


Lipkova et al. Nature Medicine (2022)

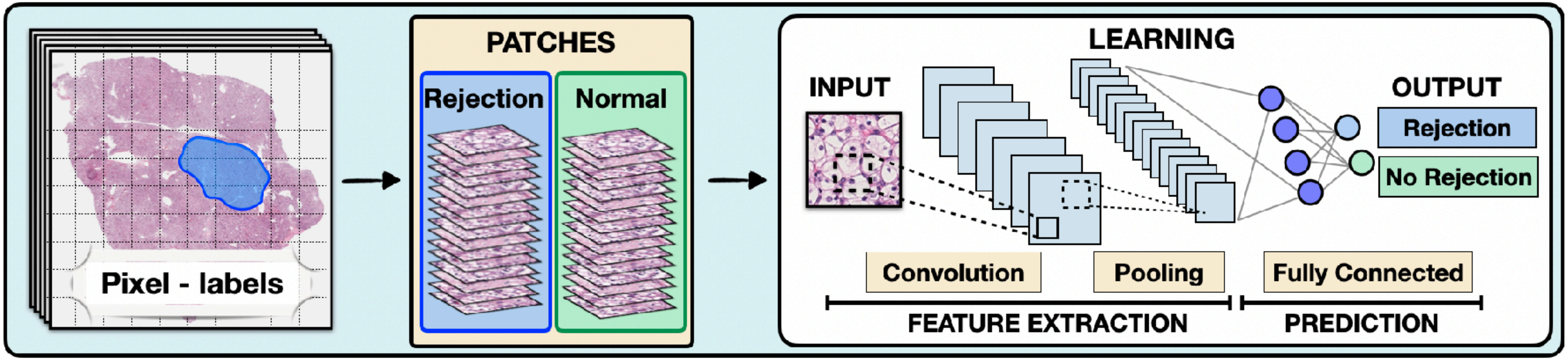
Digital Pathology: Whole Slide Images (WSIs)

- High resolution scan of an entire tissue section (0.25 - 0.5 microns per pixel)
- 1 WSI ~ 1 billion pixels !!!
- **100 WSI has more pixels than <u>whole</u> ImageNet**
- Difficult to train AI directly on WSI





Typical Deep Learning for Pathology

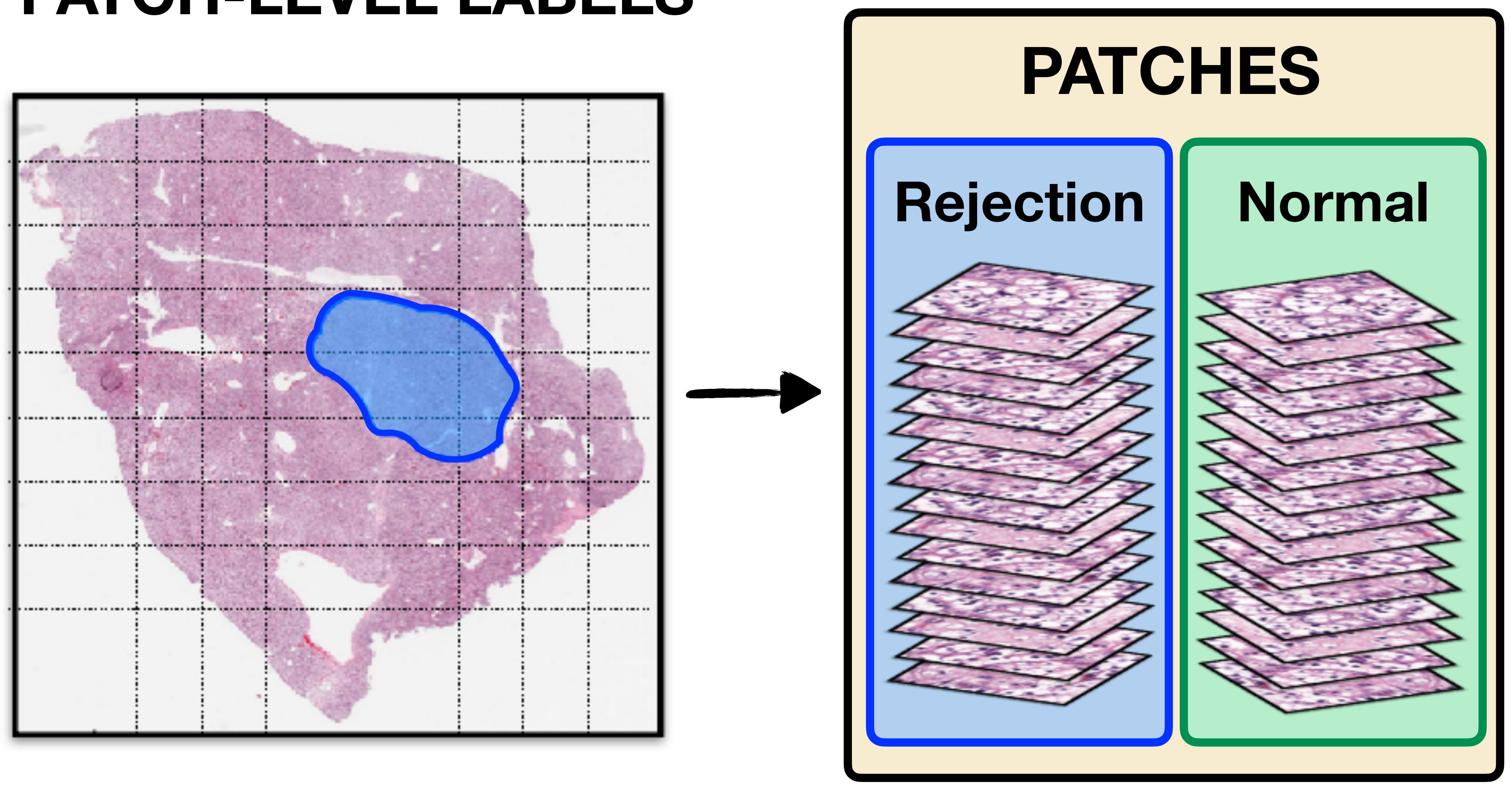


- **Laborious** and **time consuming** to annotate gigapixels large histology images
- Disease borders not always well defined → **inter-rater variability** → **bias**
- **Predictive regions** for some tasks (e.g. treatment response) **might be unknown**
- **Possible data imbalance:** small proportion of image contain the disease (needle-in-haystack problem)
- **Image annotation is not part of standard clinical practice**

Strong vs Weak Supervision

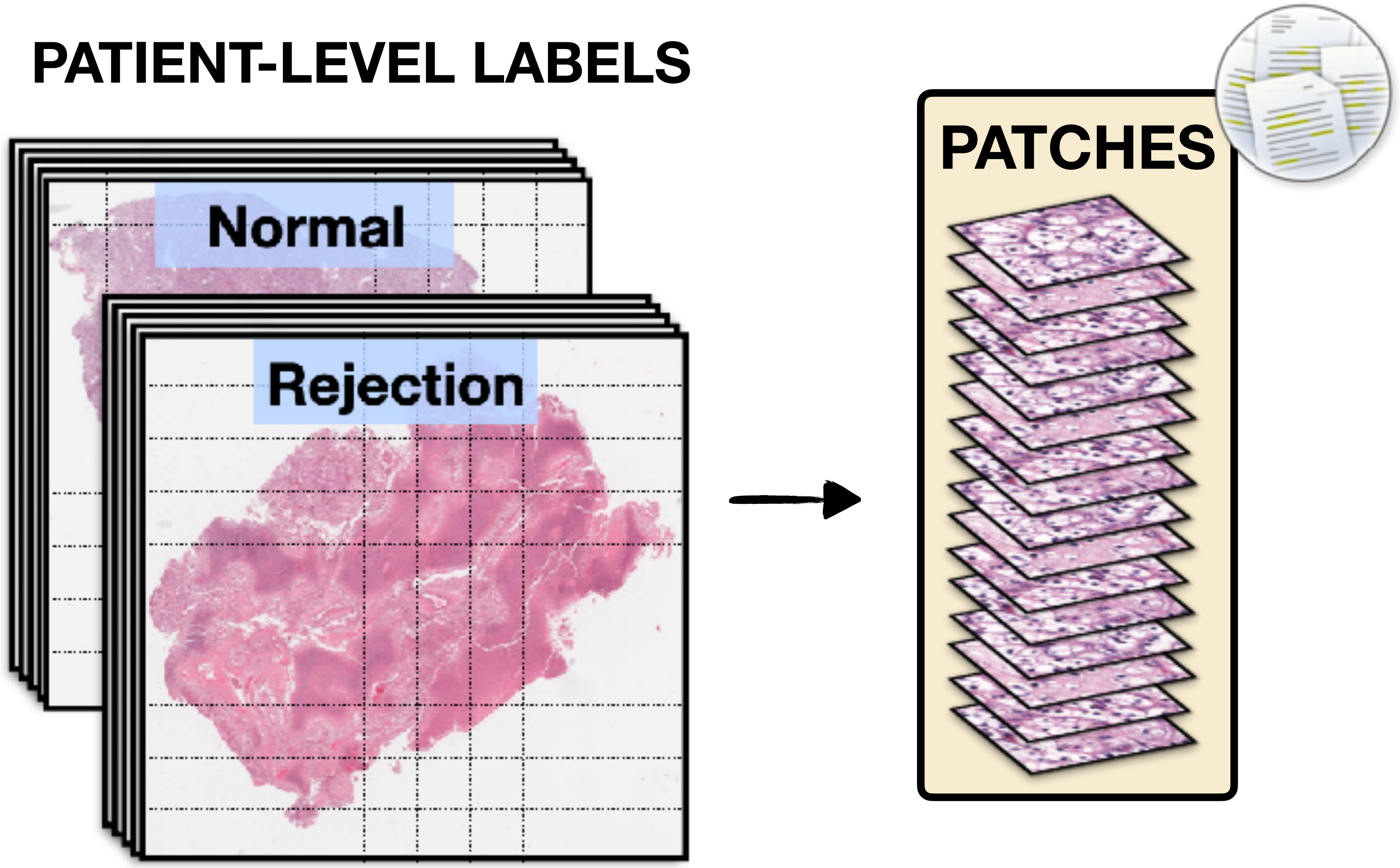
STRONG LABELS

PATCH-LEVEL LABELS



WEAK LABELS

PATIENT-LEVEL LABELS



➡ Model alone must discover which tissue regions and which features are predictive for rejections.

Analogy with Natural Images

STRONG LABELS

- Label for each input

Muffin

Chihuahua

WEAK LABELS

- Label for bag of inputs

Contains Chihuahua

No Chihuahua

➡ The model alone has to discover which image items and features correspond to chihuahua

Cardiac Rejection Assessment Neural Estimator

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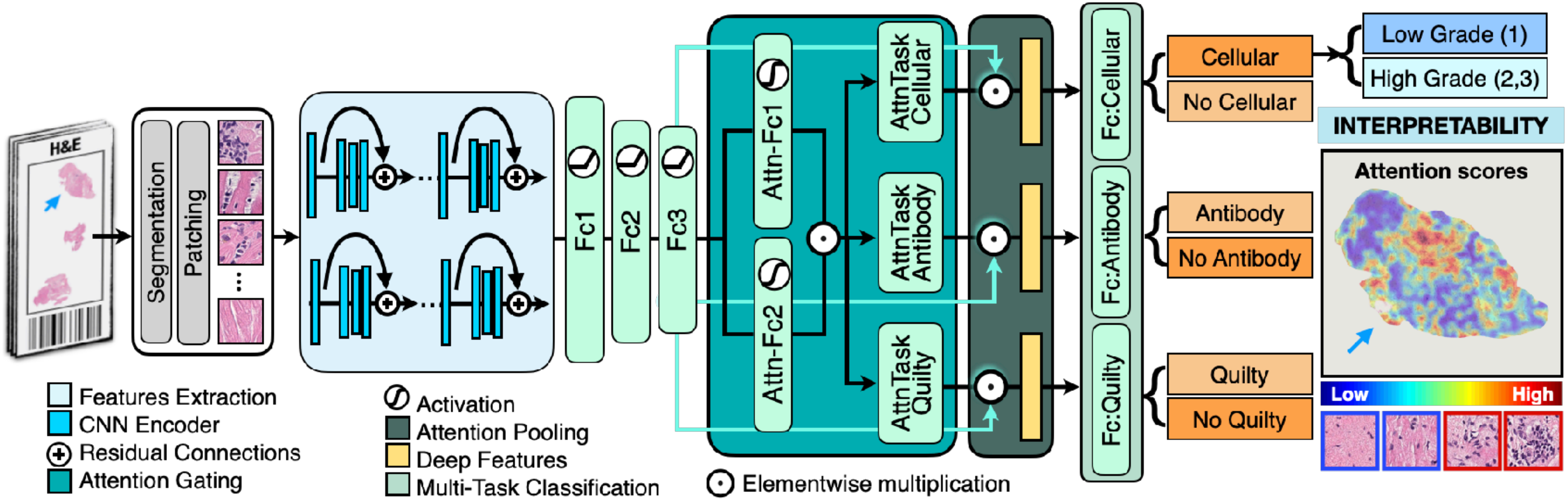
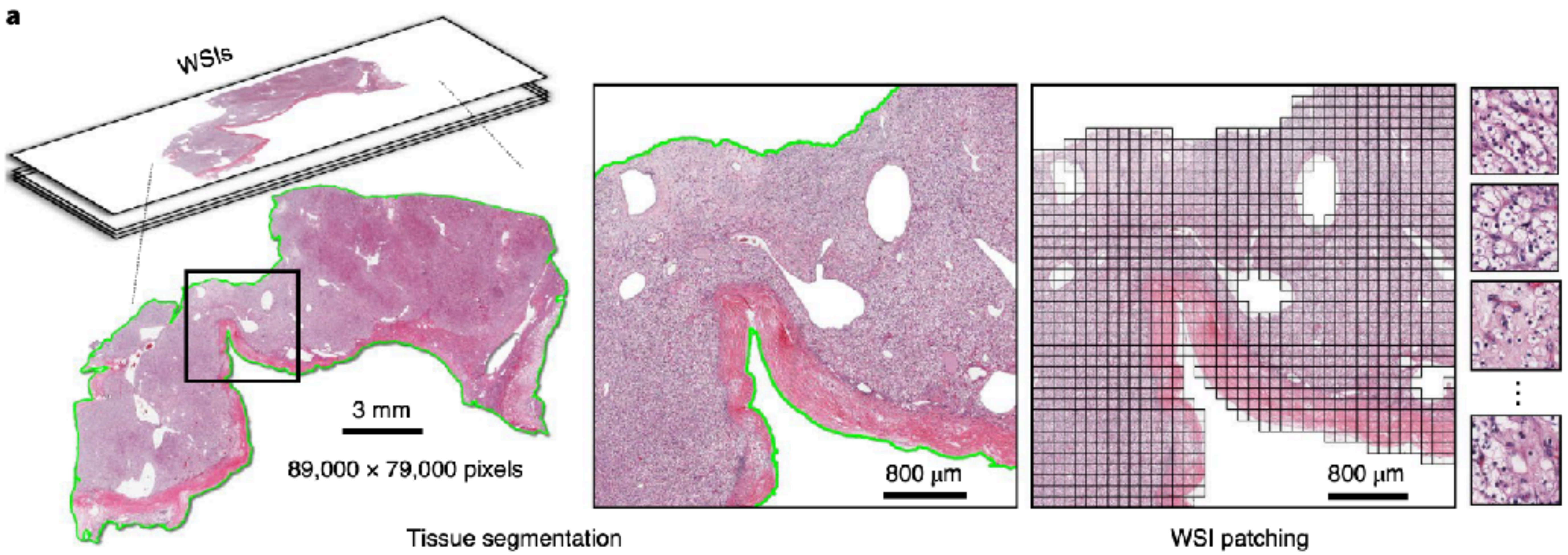
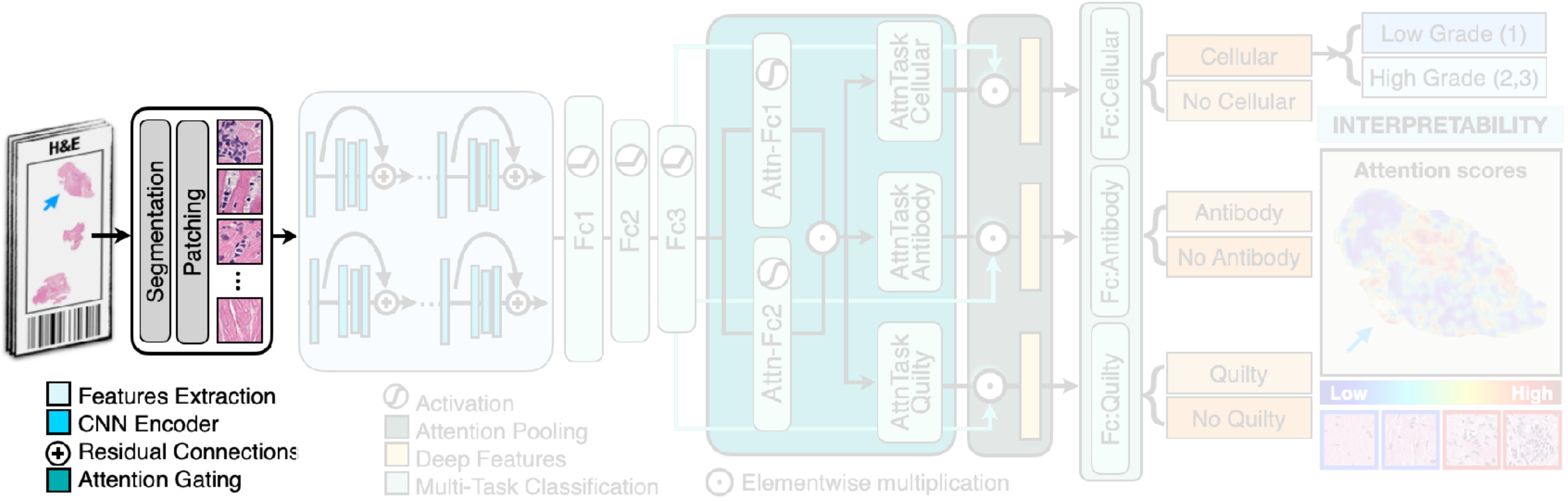


Lipkova et al. Nature Medicine (2022)

PREPROCESSING



≈ 1 Billion Pixels!

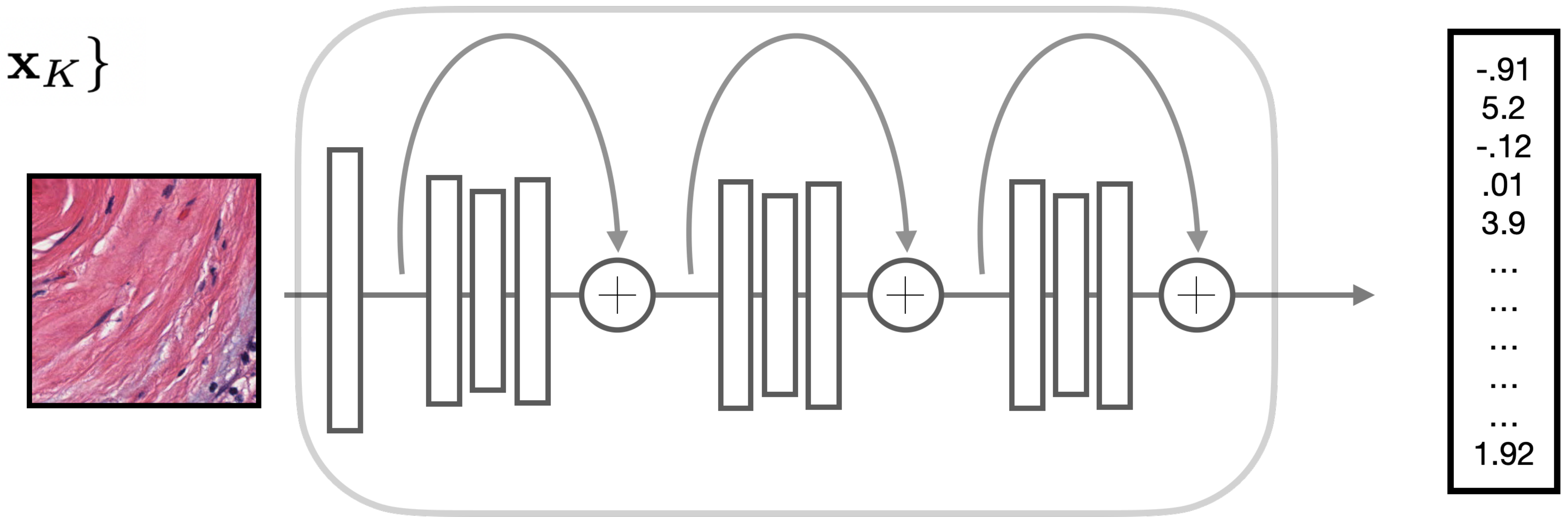


EMBEDDINGS

- Patch-level representation of patch k from {1,...,K}

$X = \{\mathbf{x}_1, \mathbf{x}_2, \ldots, \mathbf{x}_K\}$

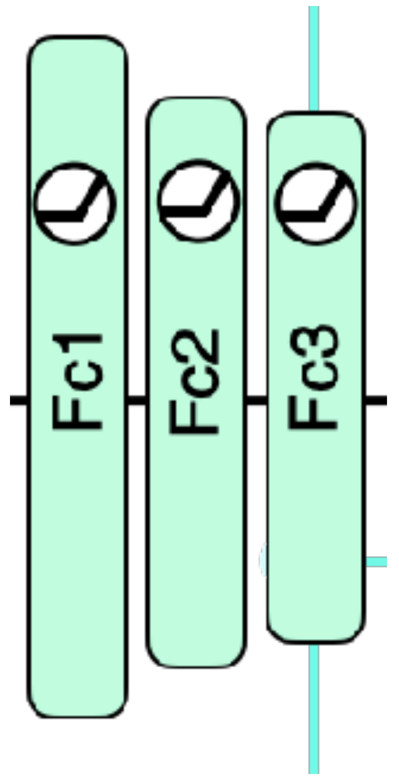
Input x_k :
$256 \times 256 \times 3$



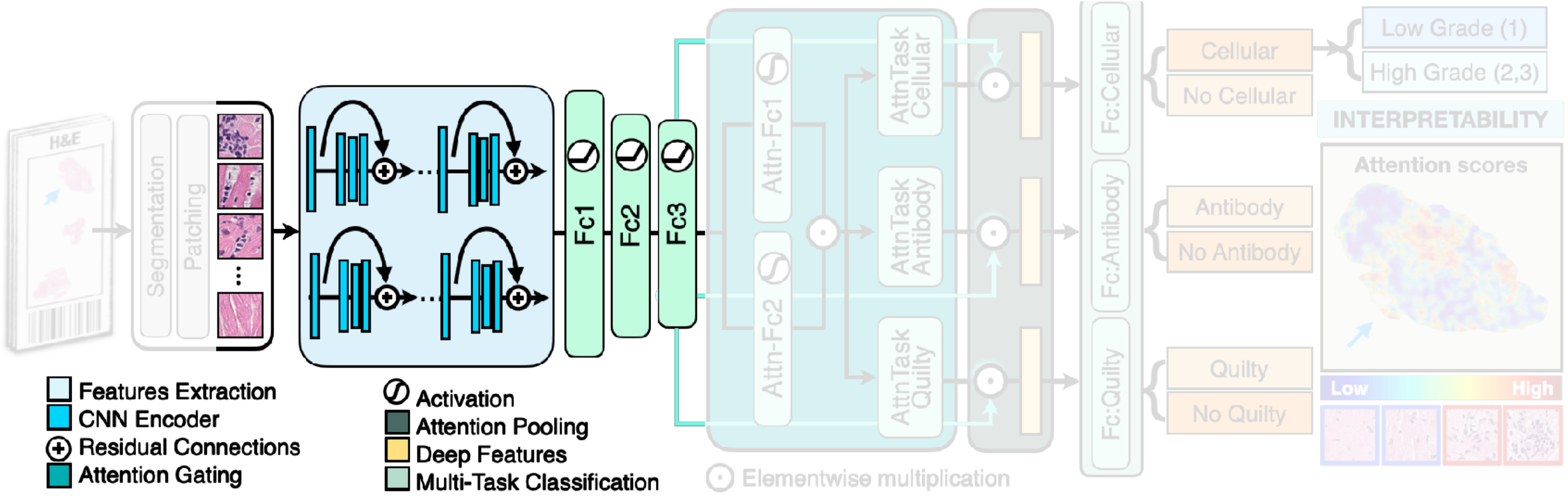
Pretrained Encoder

$f(\cdot;\theta) : \mathbb{R}^{C \times H \times W} \rightarrow \mathbb{R}^{1024}$

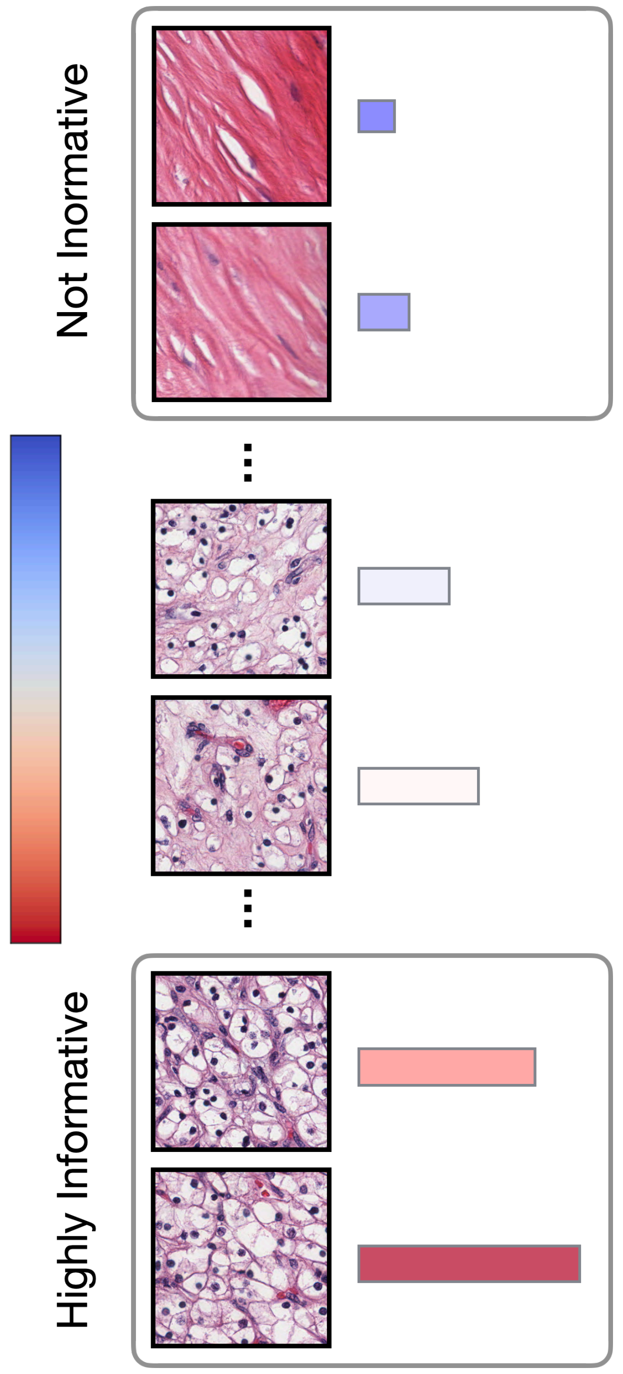
Embedding z_k:
1024



- ResNET50 features $\mathbf{z}_k \in \mathbb{R}^{1024}$
- Three FC layers:
  - FC1: $\mathbf{W}_1 \in \mathbb{R}^{768 \times 1024}$
  - FC2: $\mathbf{W}_2 \in \mathbb{R}^{512 \times 768}$
  - FC3: $\mathbf{W}_3 \in \mathbb{R}^{512 \times 512}$



ATTENTION LEARNING

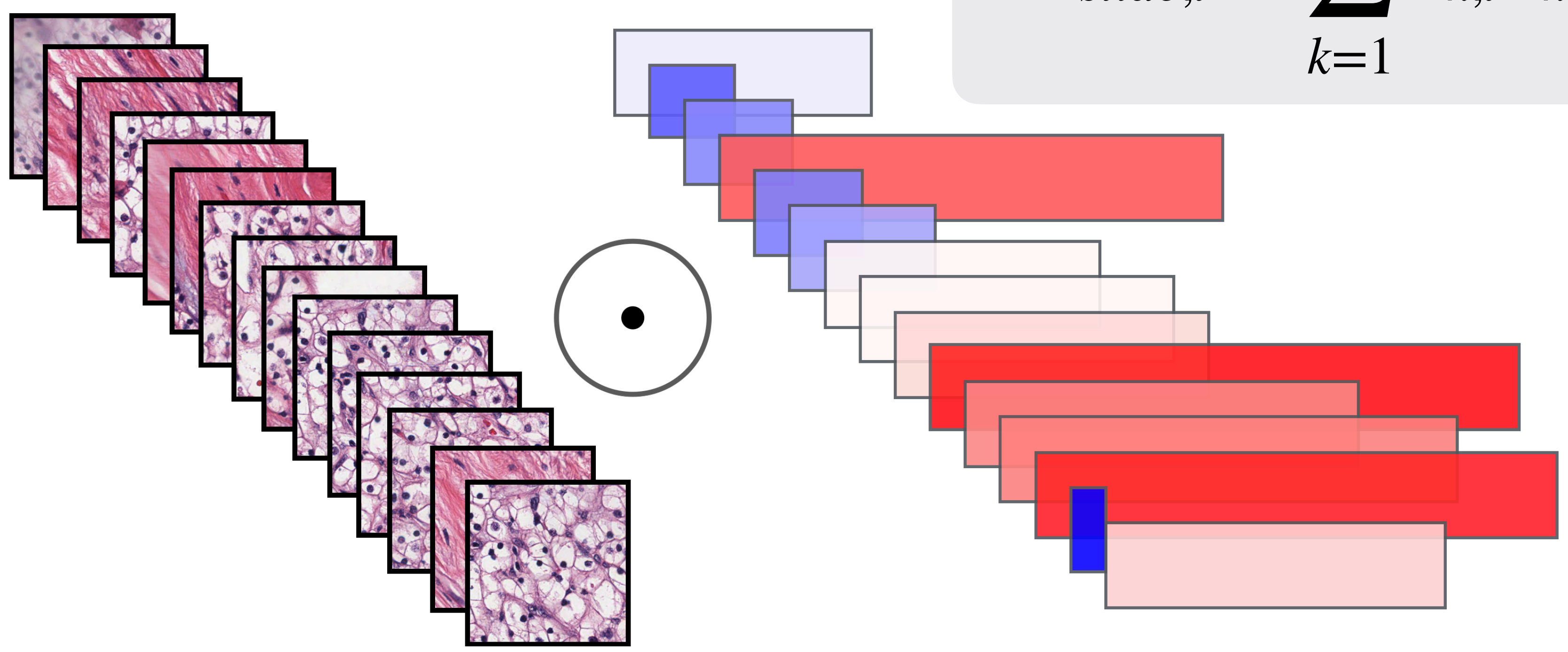


Attention score *(for patch k and task t):*

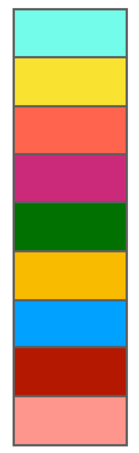
$$a_{k,t} = \frac{\exp\left\{\mathbf{W}_{a,t}\left(\tanh\left(\mathbf{V}_a\mathbf{h}_k\right)\odot \mathrm{sigm}\left(\mathbf{U}_a\mathbf{h}_k\right)\right)\right\}}{\sum_{j=1}^{N}\exp\left\{\mathbf{W}_{a,t}\left(\tanh\left(\mathbf{V}_a\mathbf{h}_j\right)\odot \mathrm{sigm}\left(\mathbf{U}_a\mathbf{h}_j\right)\right)\right\}}$$

Attention-based pooling

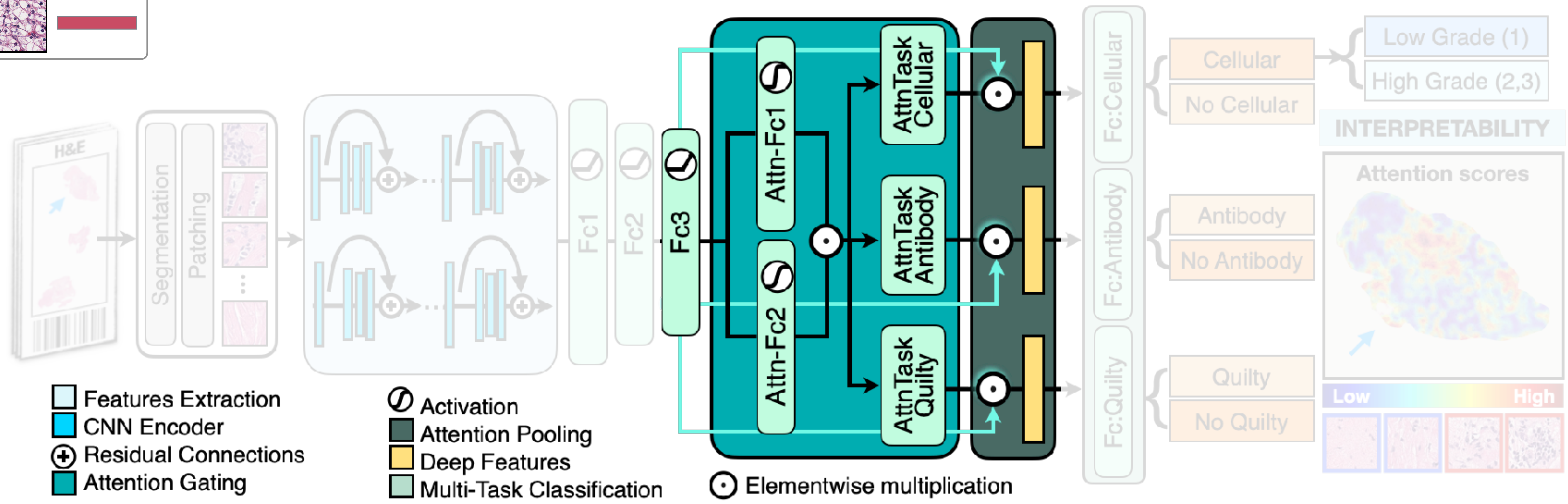
$$\mathbf{h}_{slide,t} = \sum_{k=1}^{K} a_{k,t}\mathbf{h}_k$$



Learned WSI Embedding

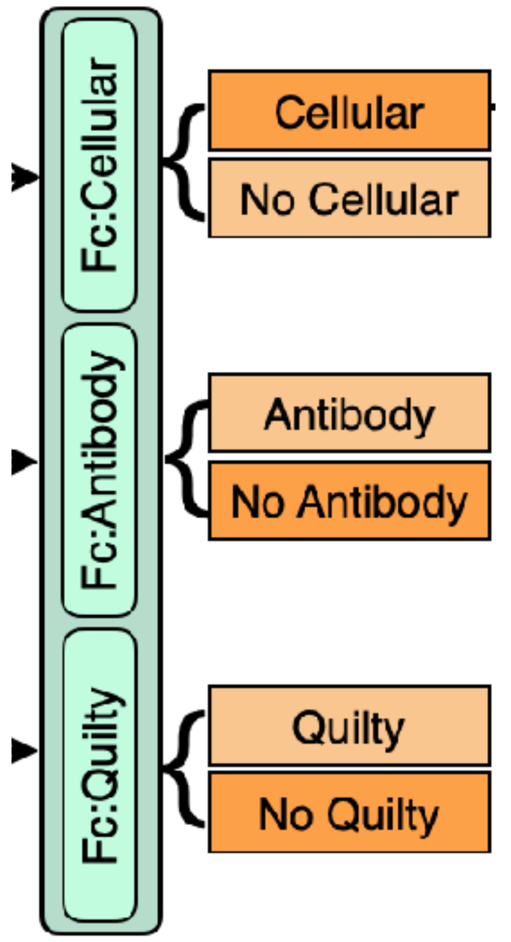


(Ilse et al. ICML 2018)



MULTI-TASK CLASSIFIER

Learned WSI Embedding



- Slide-level representations for task *t*:

$$\mathbf{h}_{slide,t} = \sum_{k=1}^{K} a_{k,t}\mathbf{h}_k$$

- Slide-level predictions for task t:

$$\mathbf{p}_t = \text{Softmax}(\mathbf{W}_{cls,t}\,\mathbf{h}_{slide,t} + \mathbf{b}_{cls,t})$$

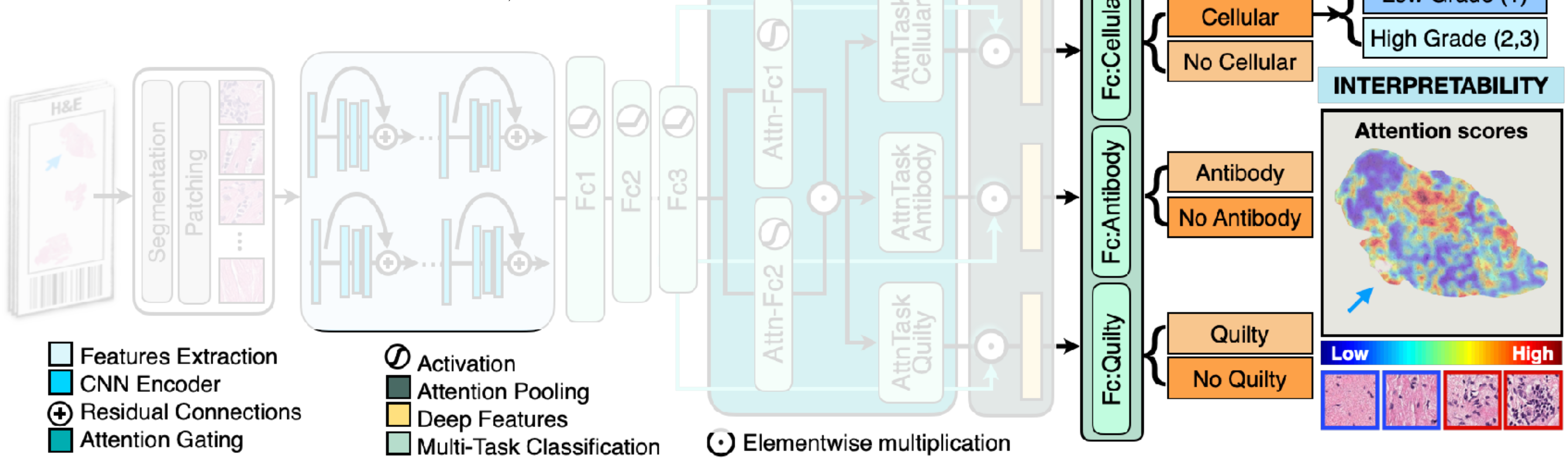
$$\mathbf{W}_{cls,t} \in \mathbb{R}^{2\times512}$$

REJECTION GRADE

- Same MIL model, just single-task

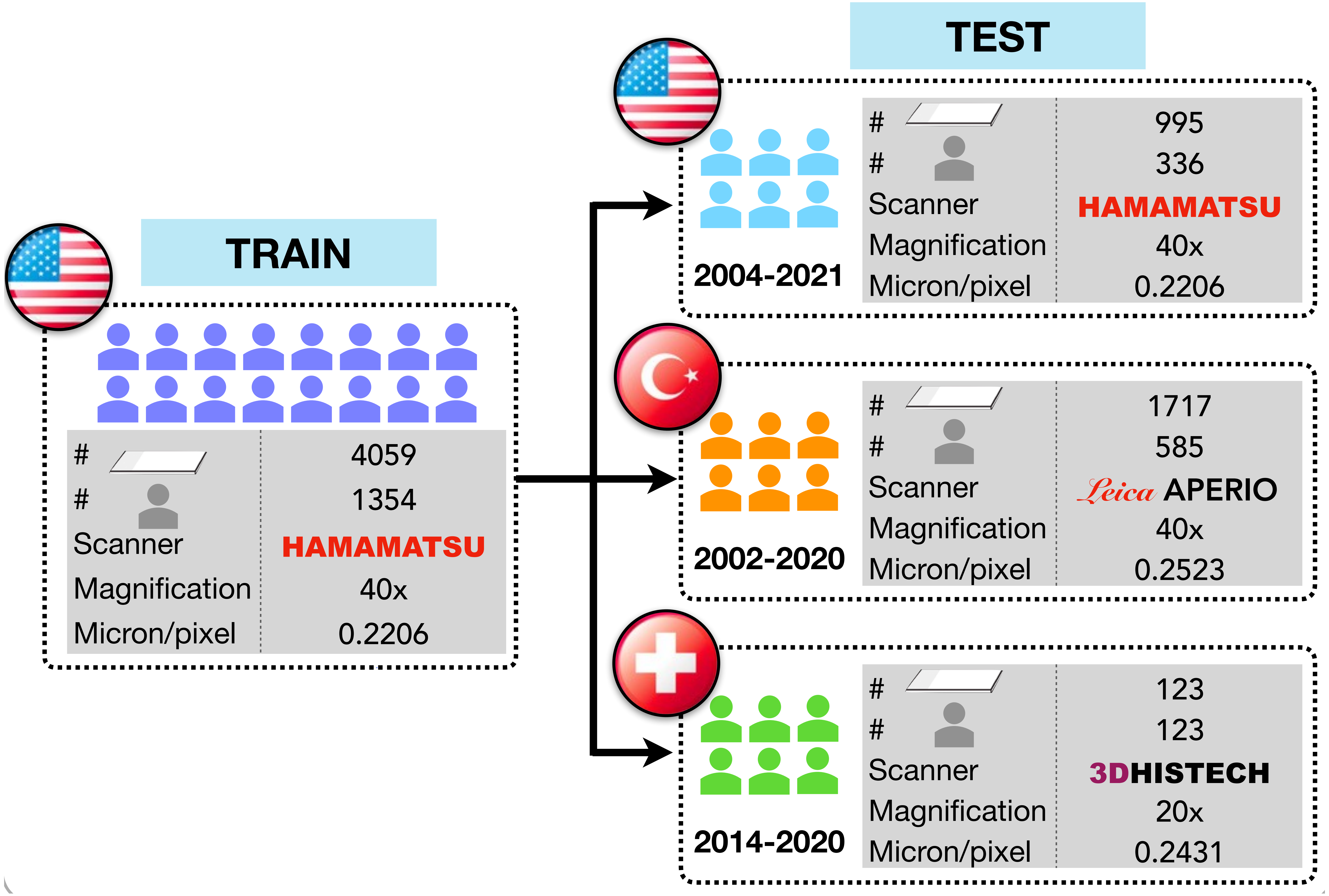
INTERPRETABILITY

- WSI attention heatmaps



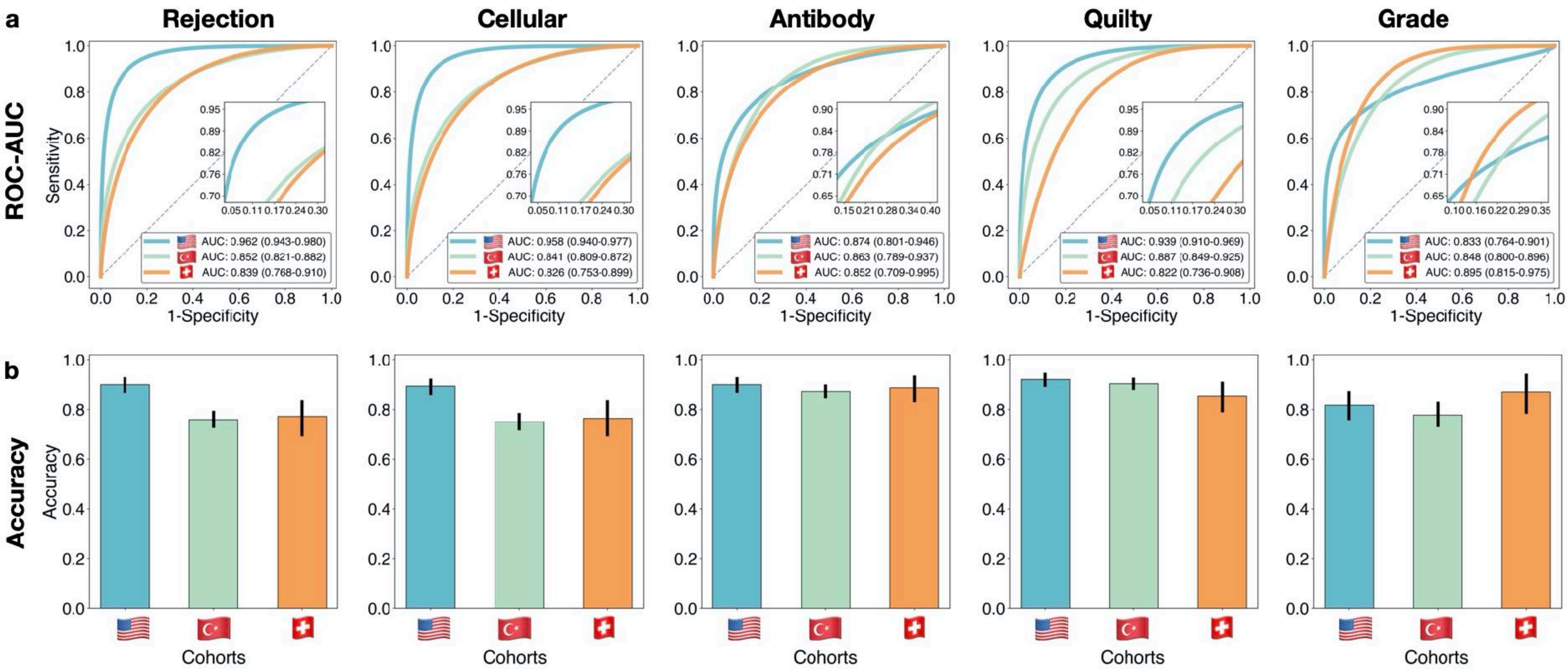
Study Design

- Over 7000 WSI from 3 **independent centers**
- **Large diversity:**
  - *population (geo., pediatric vs adult),*
  - *scanners,*
  - *biopsy protocols,*
  - *staining (manual vs automated),*
  - *noise,*
  - *micron/pixel,*
  - *etc*
- The model is trained on subset of data collected in USA
  - 70/10/20% split (balance diagnosis)
- **Generalization** to external cohorts **without domain-specific adaptations**



Lipkova et al. Nature Medicine (2022)

Evaluation & Results



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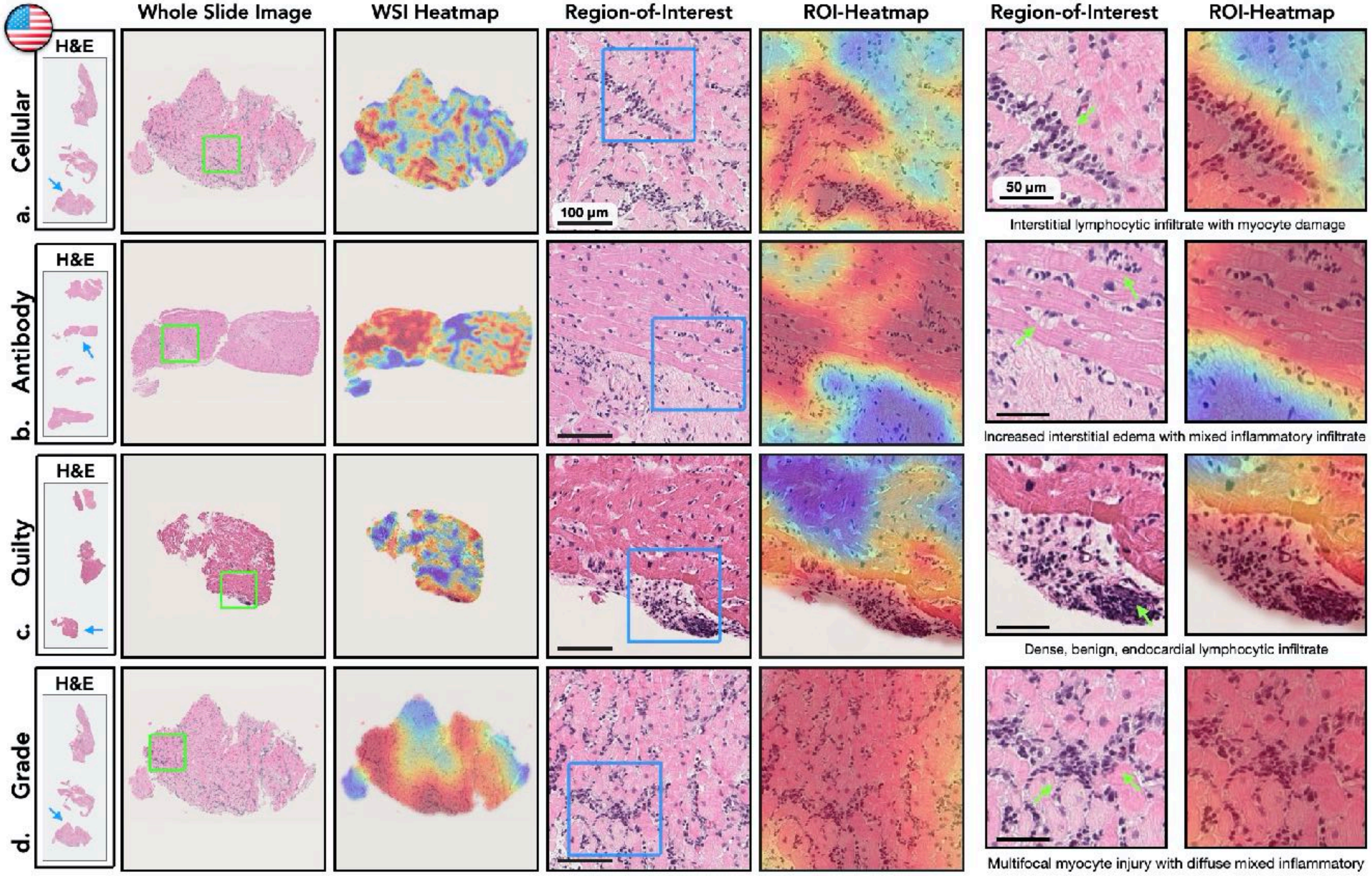
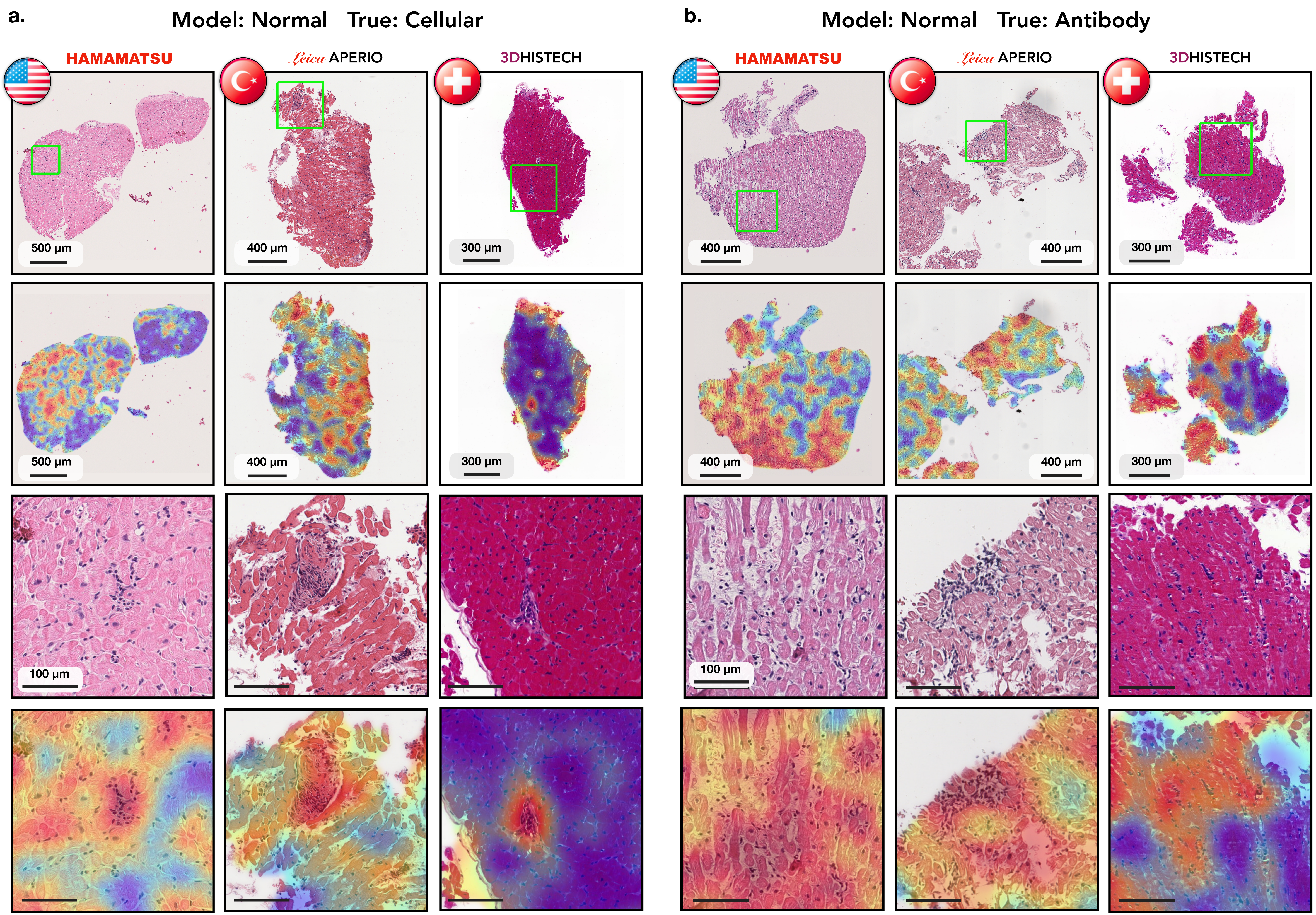
Interpretability



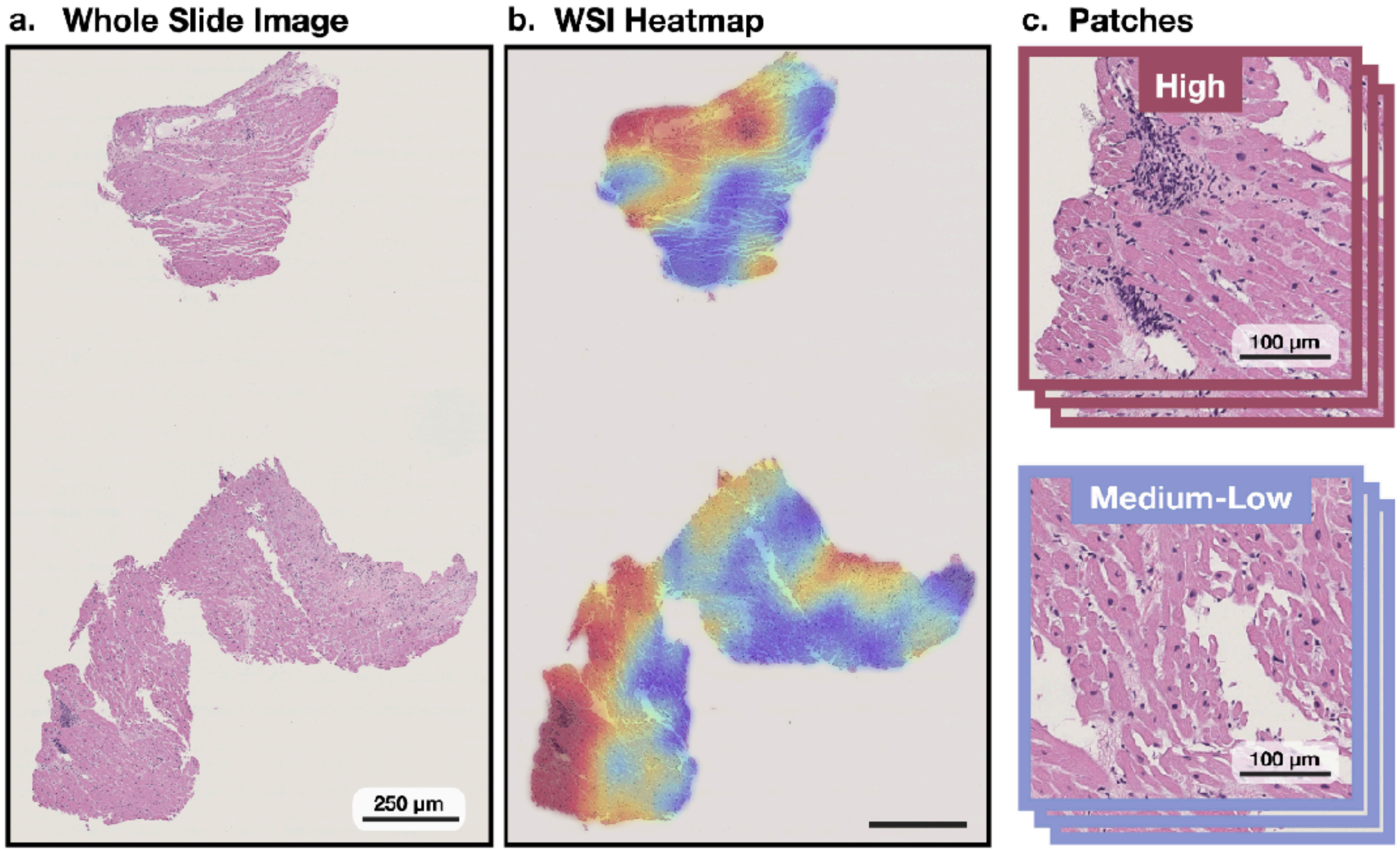
- **High-attention (red)** regions **correspond to rejection morphology used by** pathologist for diagnosis
- **Low-attention (blue)** scores are assigned mostly to **benign tissue**

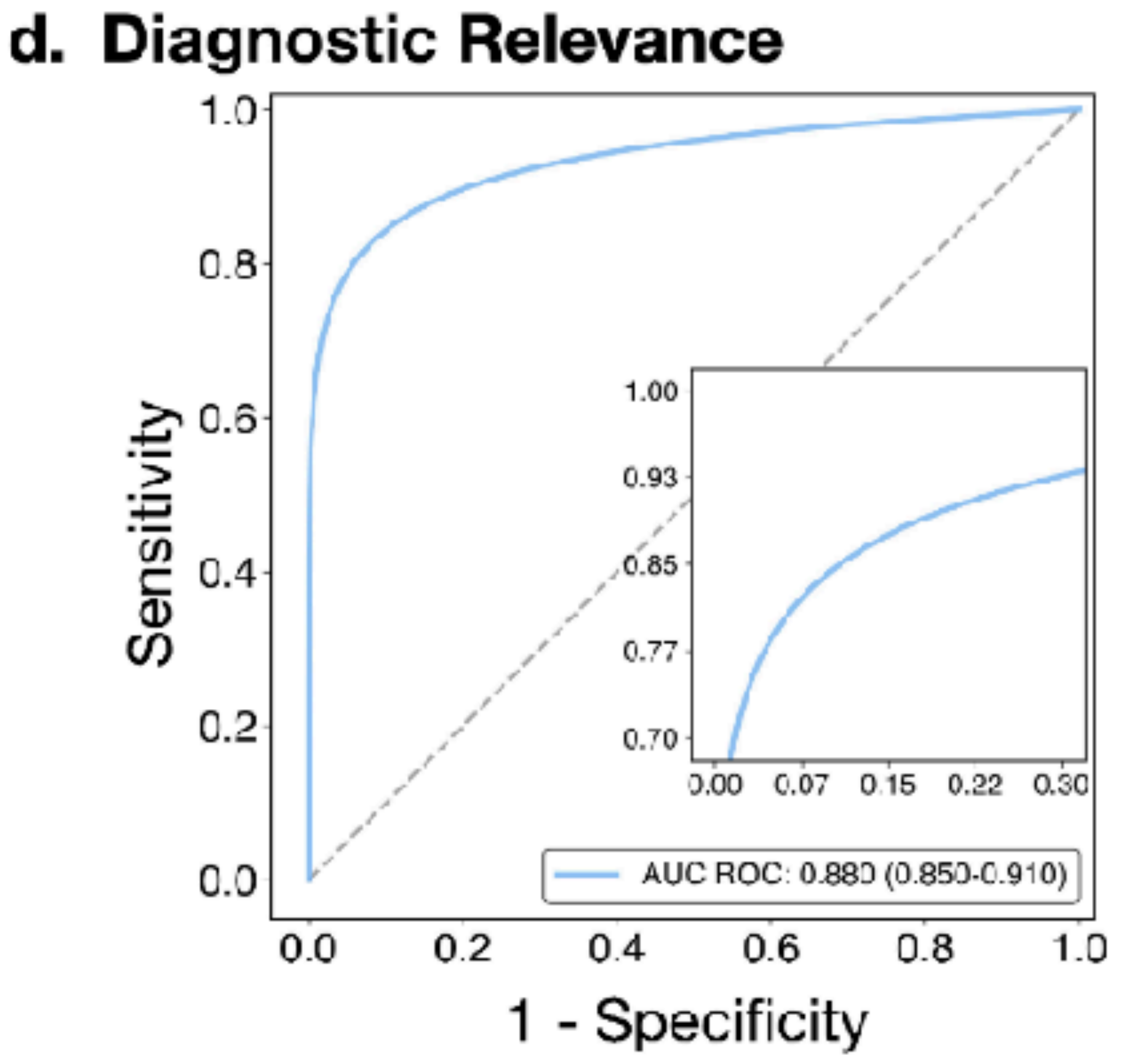
Lipkova et al. Nature Medicine (2022)

Assessment of Failure Cases



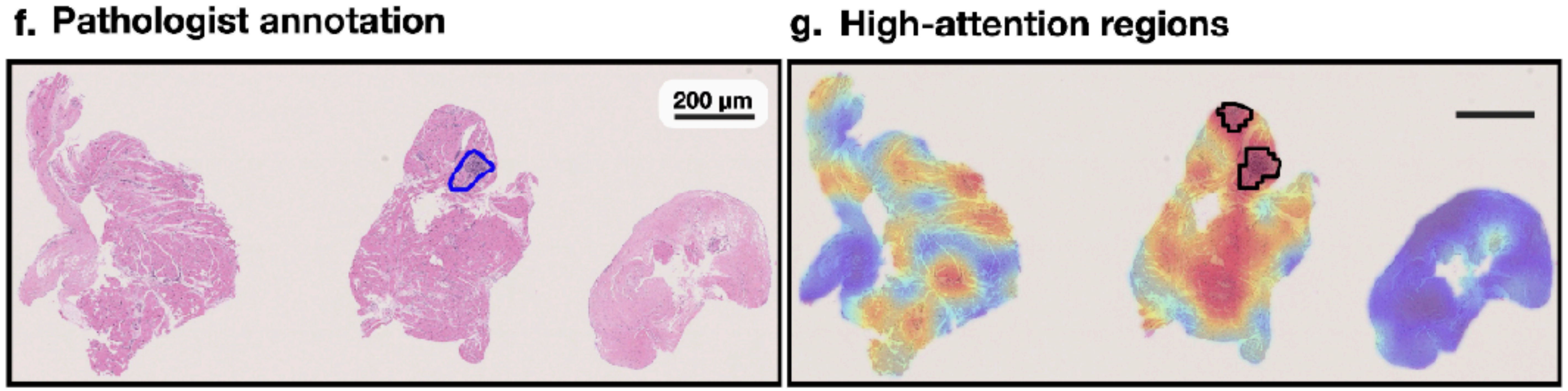
Quantitative Assessment of Interpretability





e. Patch-Level Scores

Tasks:	Accuracy	F1	κ
All	0.873	0.855	0.744
Cellular	0.925	0.914	0.848
Antibody	0.902	0.911	0.802
Quilty	0.809	0.729	0.596



h. Slide-Level Scores

Tasks:	Detection rate
All	0.922
Cellular	0.942
Antibody	0.901
Quilty	0.924

CRANE - Website

crane.mahmoodlab.org

MAIN METADATA

SELECT PATIENT:

Patient1

Select Attention map:

Cellular Antibody

Quilty Grade

Modes

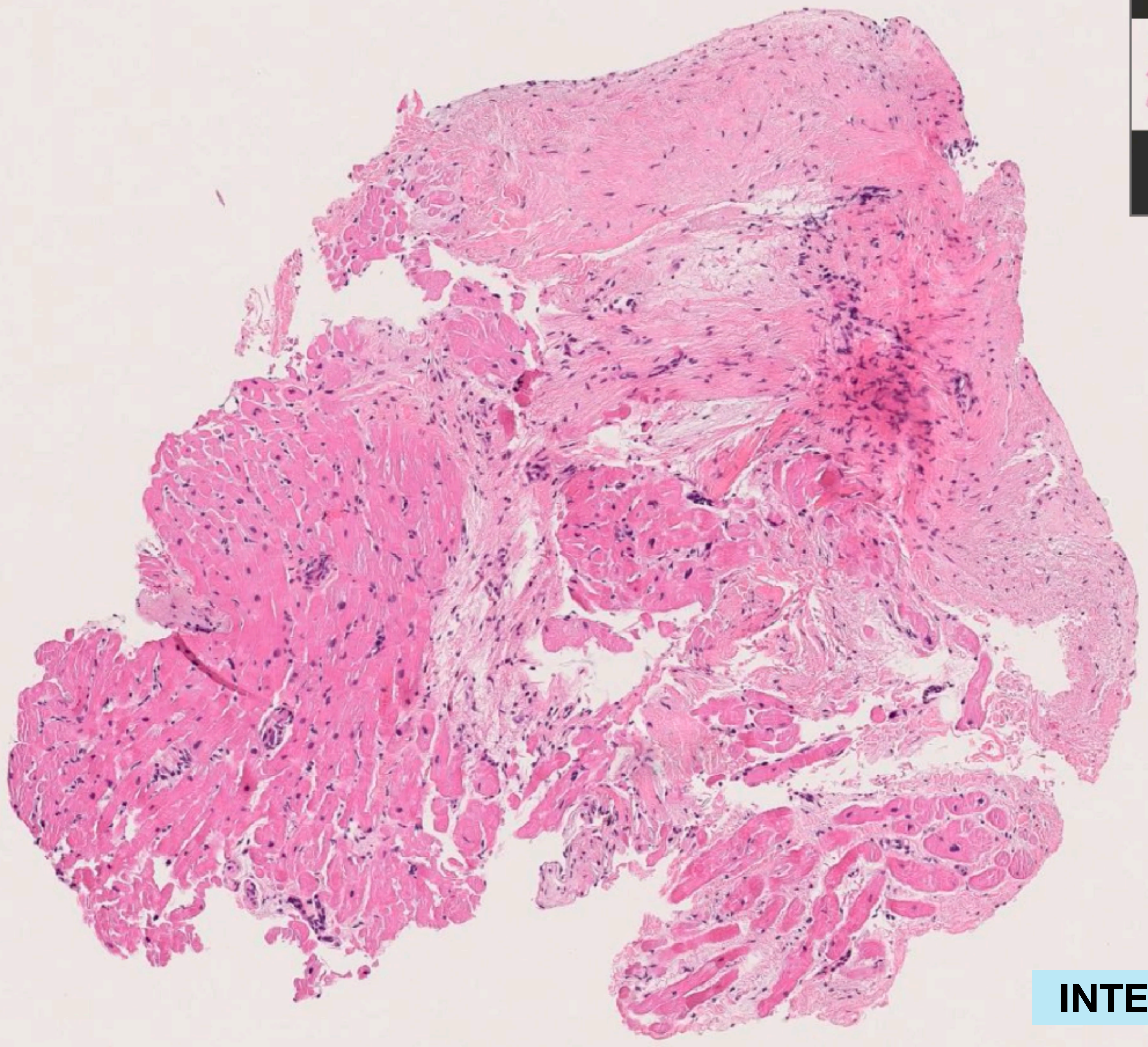
Curtain Side By Side

Overlay

Diagnosis	Confidence
Cellular:	0.9840
Antibody	0.0040
Quilty	0.0141
Grade	0.9186

CRANE

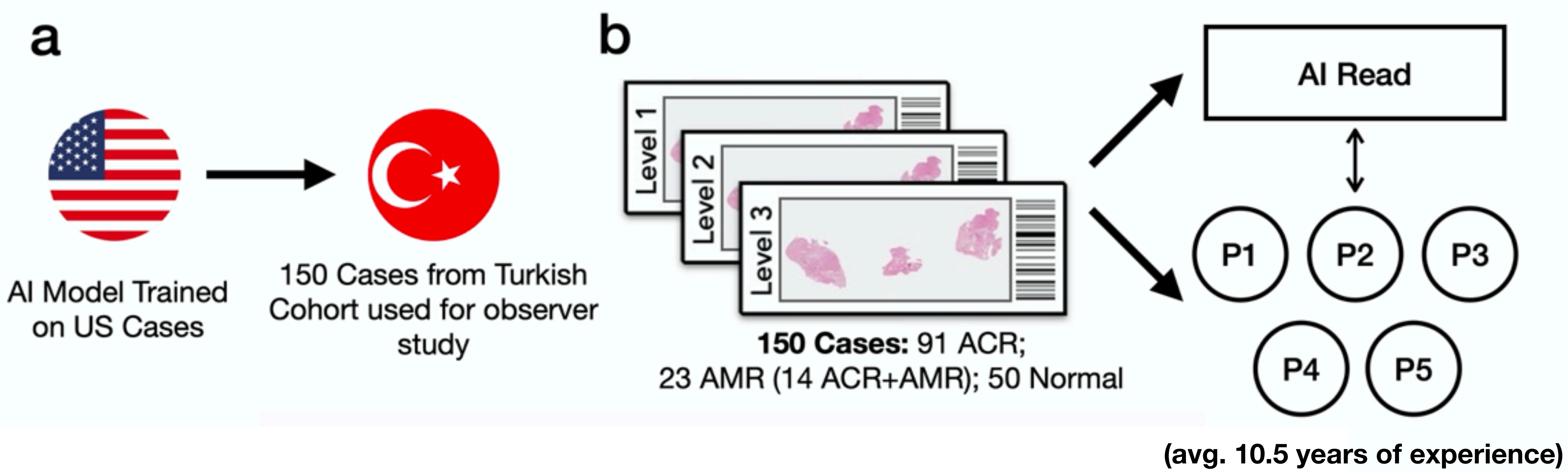
www.mahmoodlab.org
fmahmood@broadinstitute.org

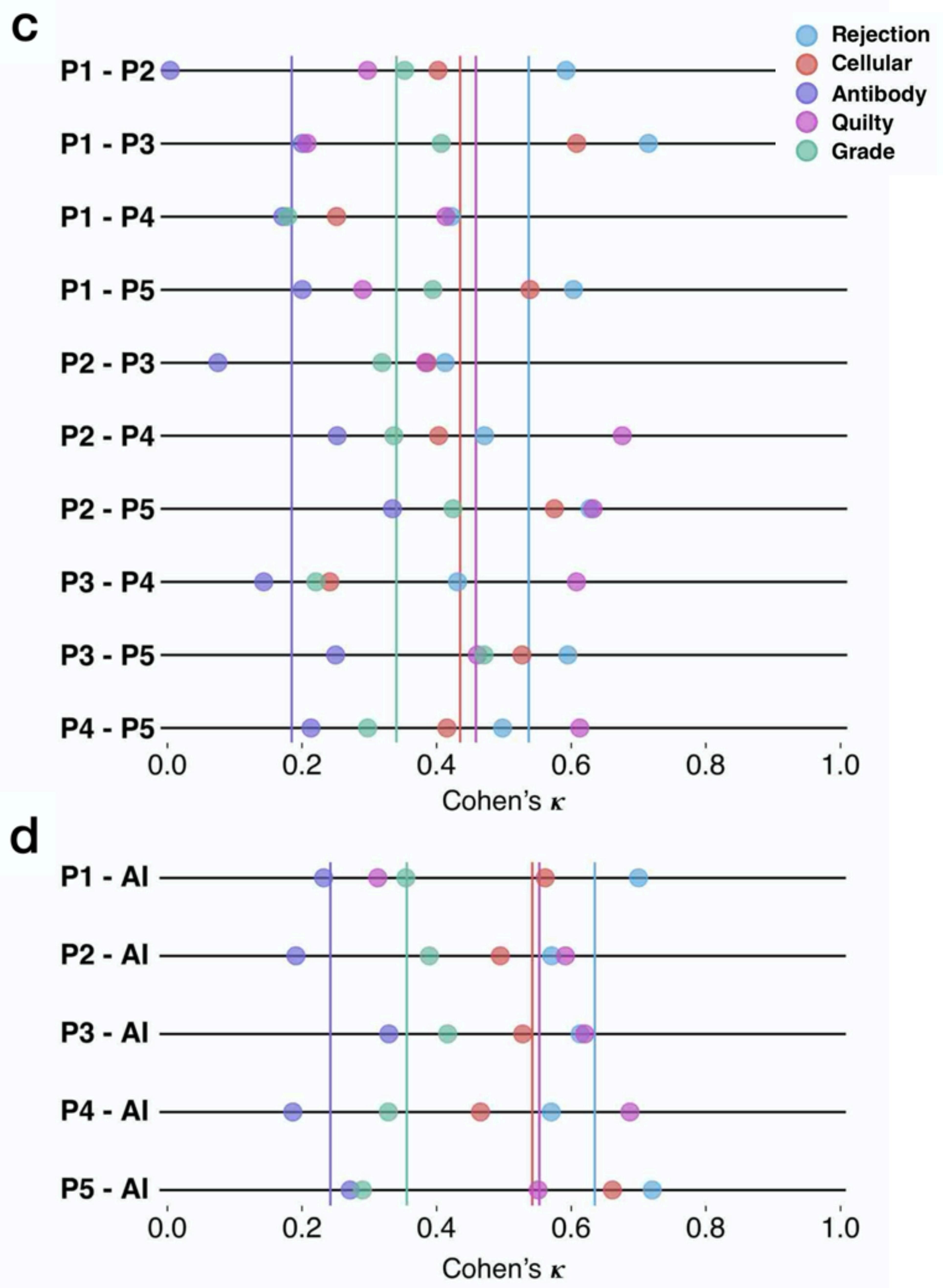


INTERACTIVE DEMO

crane.mahmoodlab.org

Comparison with human readers





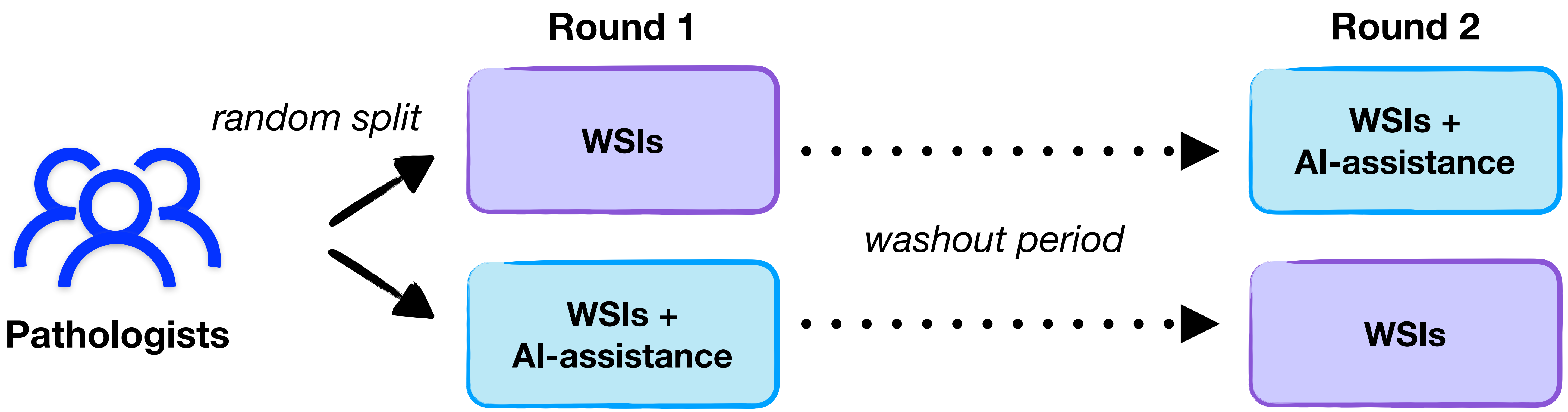
- **Cohens' κ** (-1 to 1): inter-observer agreement:
- Agreement between expert is comparable to previous studies

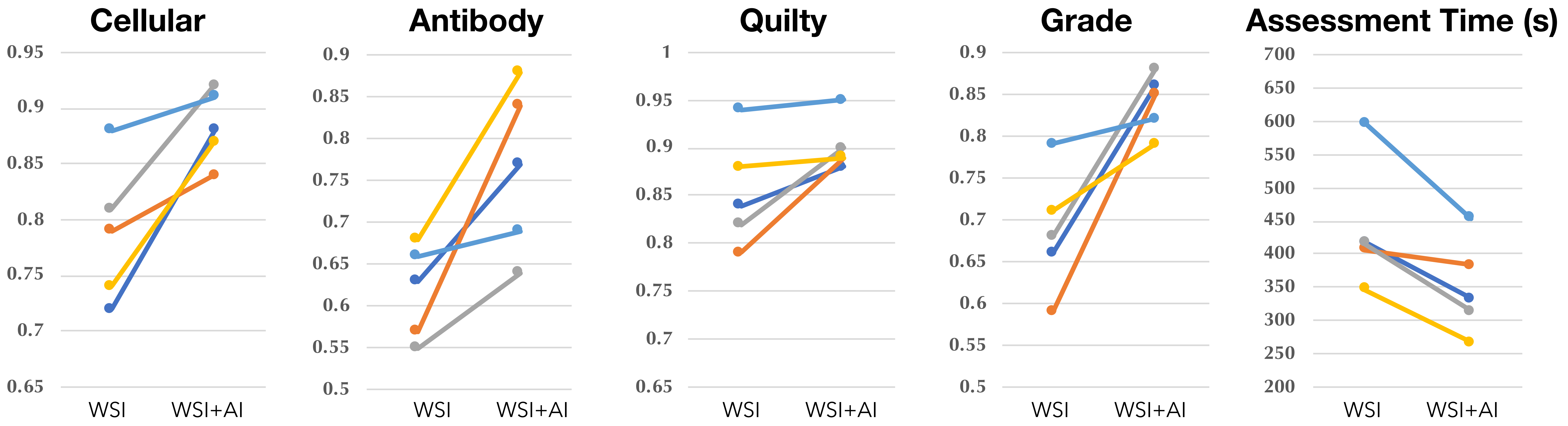
- For all tasks **AI-predictions are <u>not inferior</u> to human experts:**
  - avg. agreement on **rejection** between **pathologists** κ = 0.537 (moderate agreement)
  - avg. agreement between **pathologists and model** κ = 0.639 (substantial agreement)

Clinical Potential

- **Ground-truth labels**: consensus of readers from the first study
- **AI-assistance**: attention heatmaps as semi-transparent layer at the top of H&E slide

- **For all readers:**
  - **Increase accuracy**
  - (i.e. reduce inter-rater variability)
  - **Decrease assessment time**





Lipkova et al. Nature Medicine (2022)

Study Design Flow Chart

The Mahmood Lab

HARVARD MEDICAL SCHOOL

BROAD INSTITUTE

BWH BRIGHAM AND WOMEN'S HOSPITAL

Dana-Farber Cancer Institute

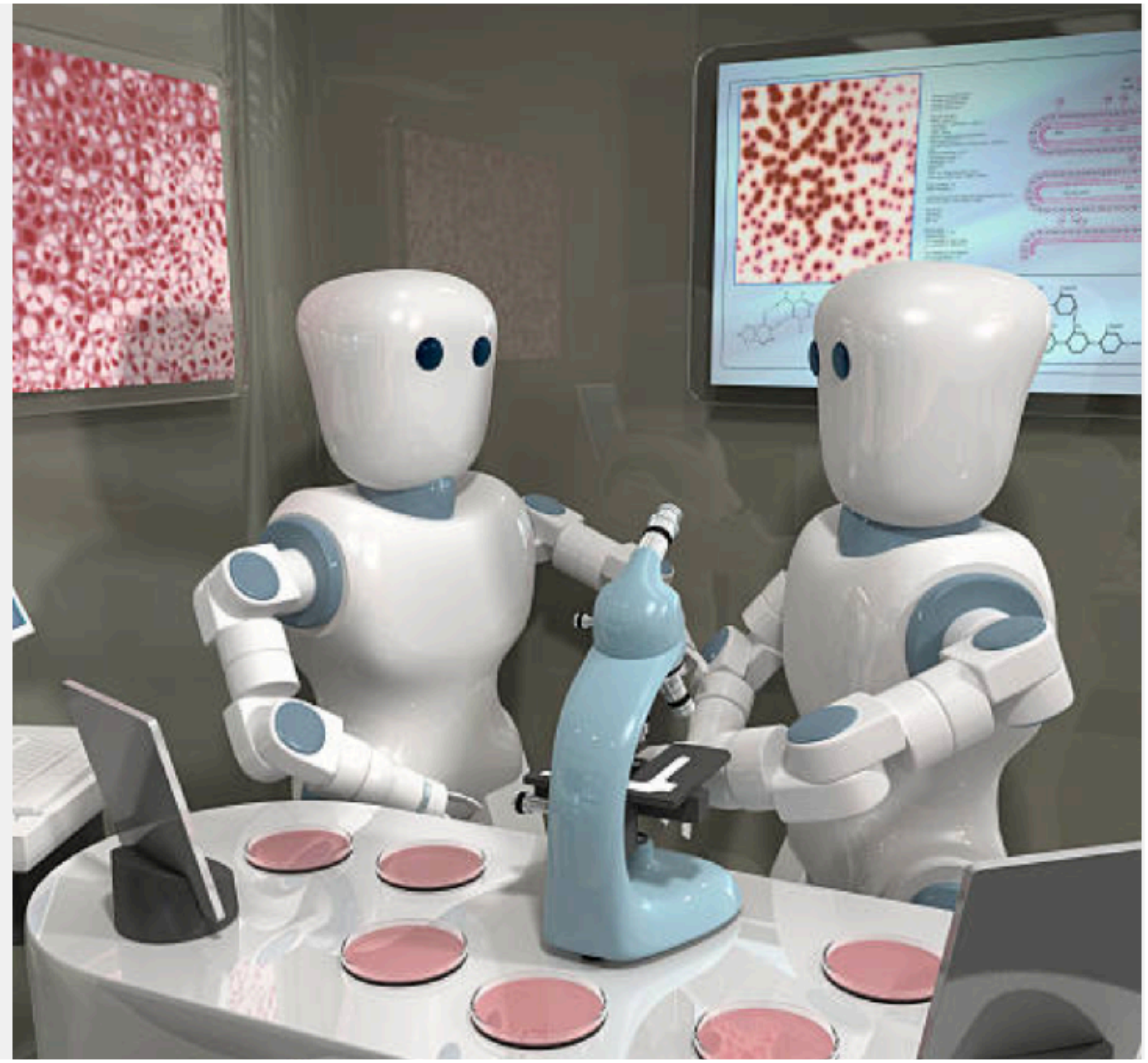
Mahmood Lab
AI for Pathology

OCTOPATH

AI for Pathology

Jana's Lab

SCAN ME



UC Irvine Health

School of Medicine