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Path R-CNN for Prostate Cancer Diagnosis and Gleason Grading of Histological Images

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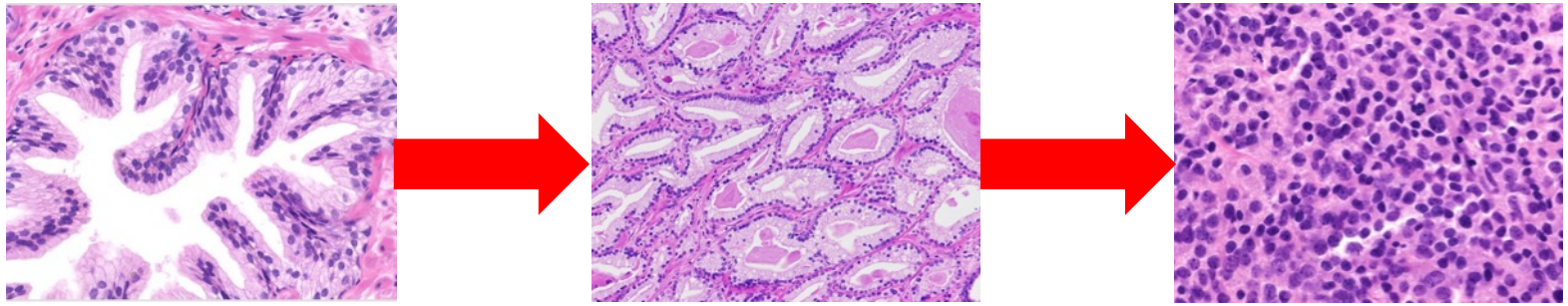
Histopathological Images for Prostate Cancer

- **Prostate cancer:** the most prevalent and second deadliest cancer in men in the U.S.
- **Histopathological images:** provide rich prognostic information

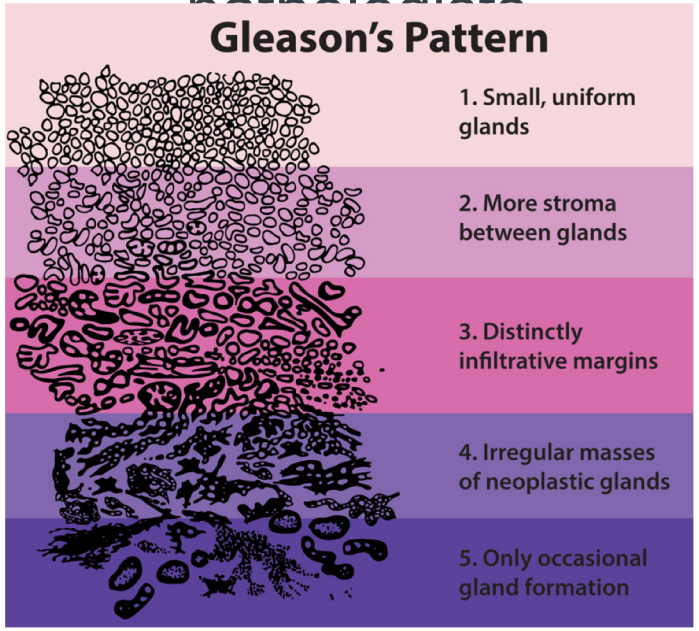


Benign | Low-grade | High-grade

Progression of prostate cancer

Slide Credit to Jiayun

Qualitative descriptions by pathologists



Traditional Diagnosis Process

- **Gleason grading system**

  Gleason 1(G1)→Gleason 5 (G5)

- **Time-consuming**

  80% prostate biopsies are benign

- **Inter- and intra-observer variability**

  57.9% concordance rates for Gleason score

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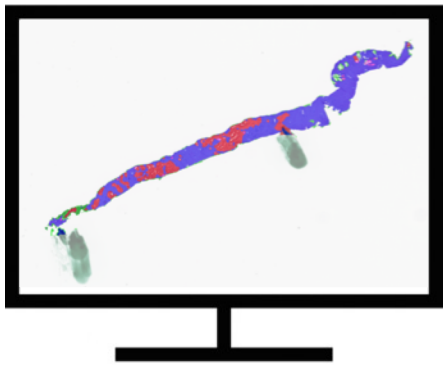
Benefit From Computer-aided Diagnosis



Computer-aided diagnosis tool (CAD)

- **Speed up diagnosis**
- **Quantitative assessment**

  Improve reproducibility of cancer grading

  Better model the underlying tumor characteristics
- **Pixel-wise segmentation**

  Pixel-wise grade prediction

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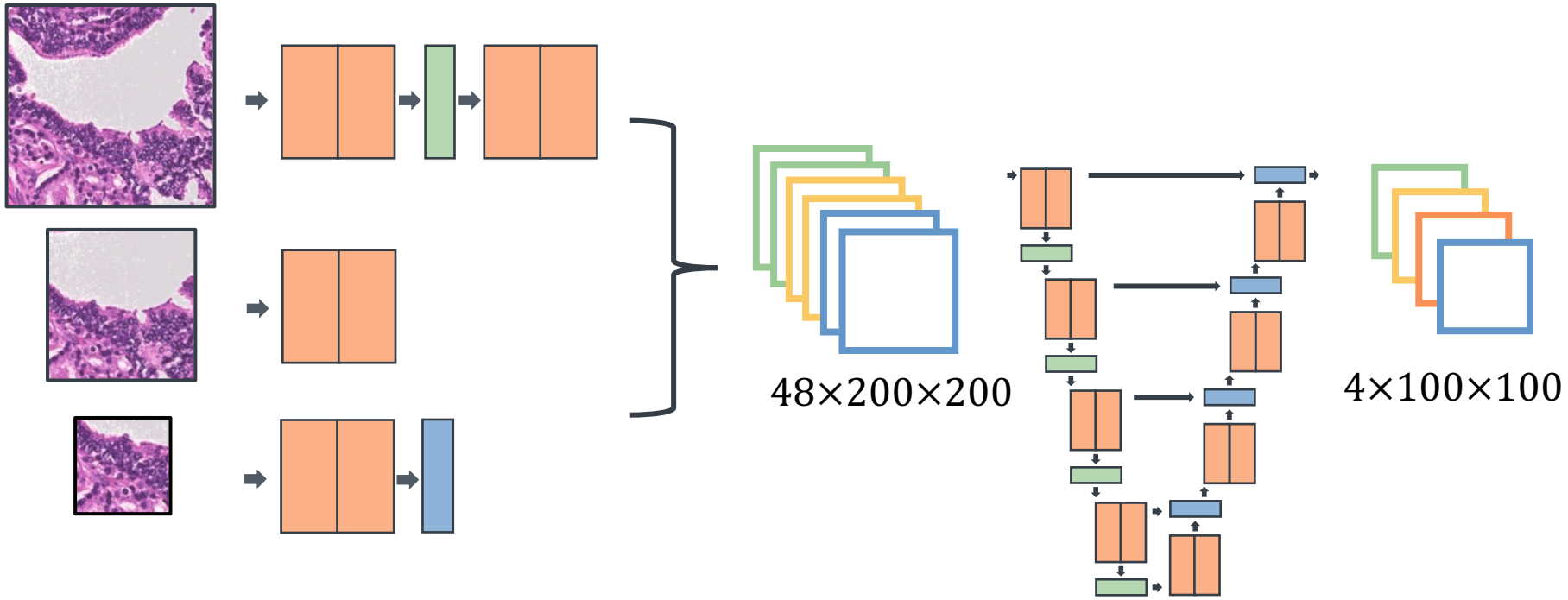
Previous Work

Multi-scale U-Net



3×3 Convolution
2×2 Max Pooling
2×2 Up Convolution

Achieves 72.91% mIOU and 87.30% overall pixel accuracy

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Motivation

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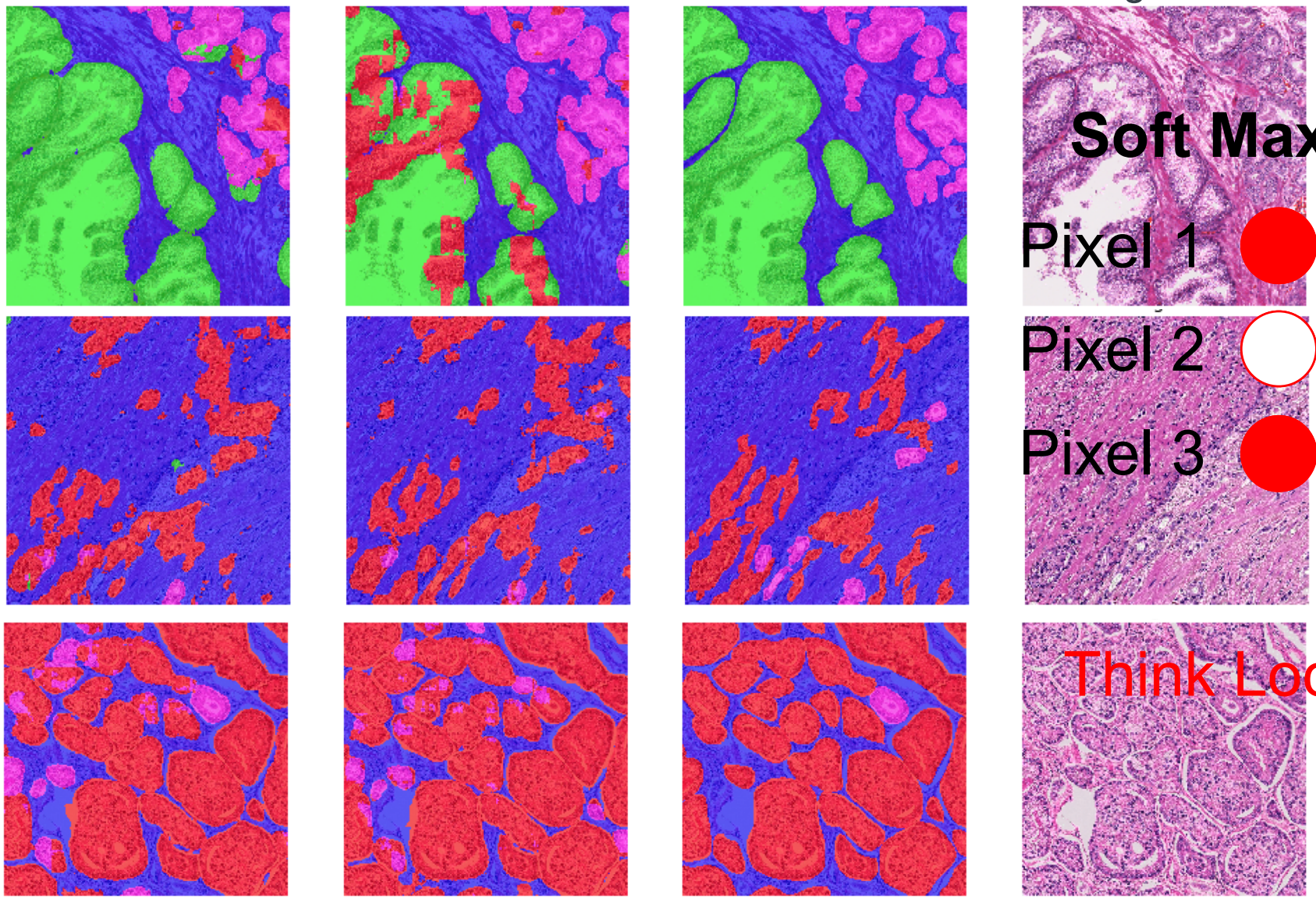
Multi-scale U-Net | U-Net | Ground Truth | Original Tile



Soft Max Layer

Pixel 1

Pixel 2

Pixel 3

Think Locally!

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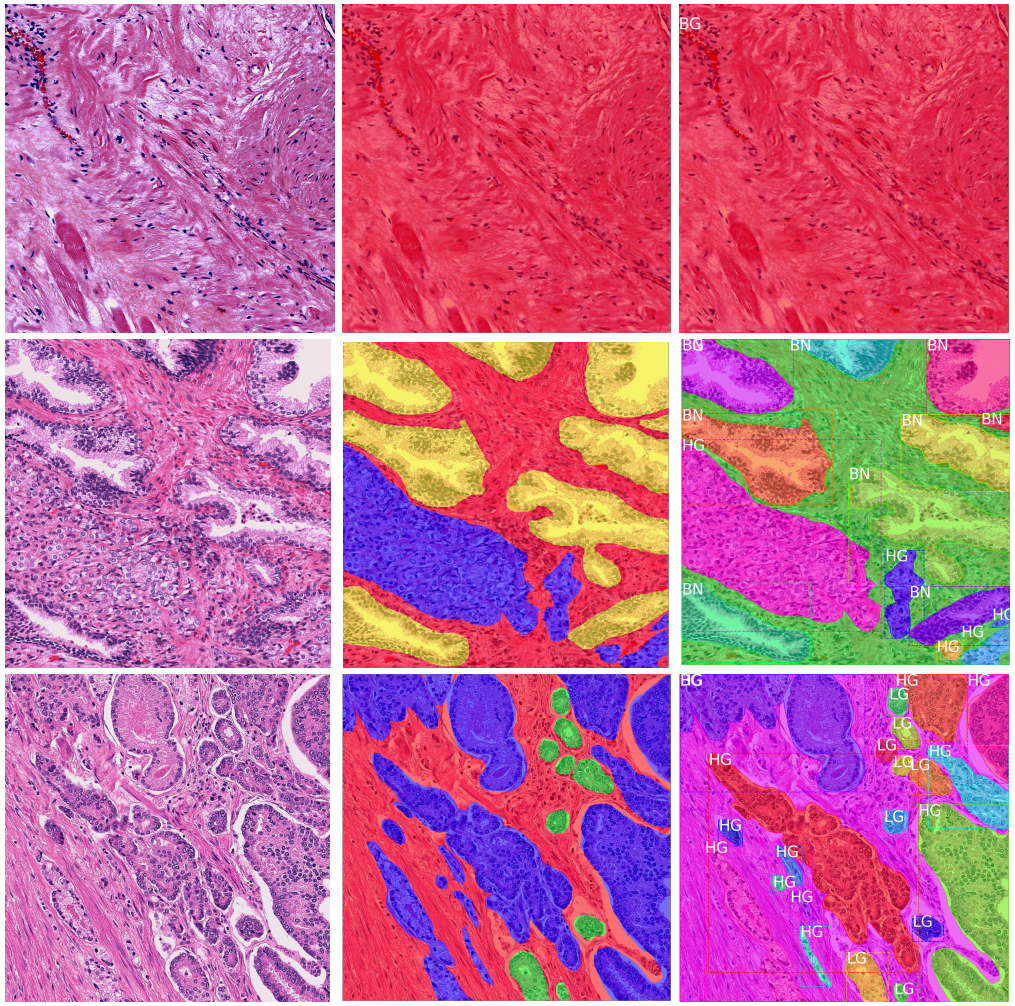
Problem Formulation: Think Regionally



Original Image | Ground Truth | Problem Setting

Detection

Find the epithelial cells' areas.

"Region of Interest (ROI)"

Segmentation

Draw a segmentation mask for each epithelial area.

"Binary Classification"

Classification

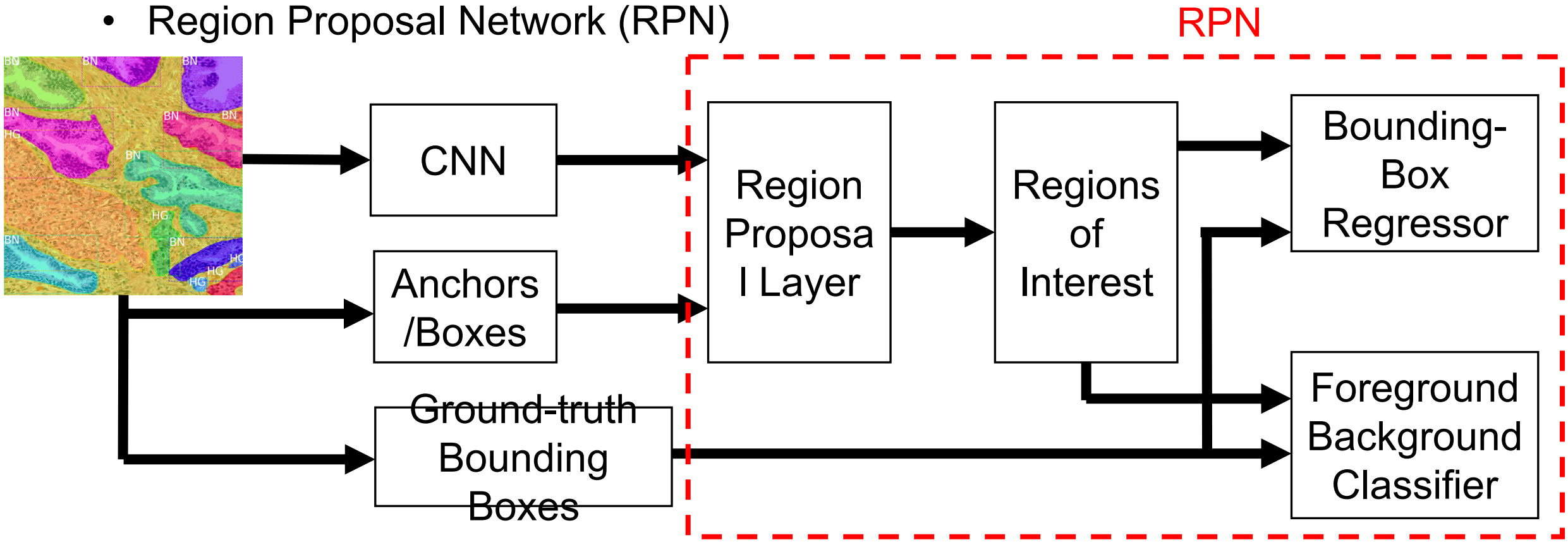
Grade the severity of the epithelial cells.

"Benign, Low-grade, High-grade"

An Instance Segmentation Problem.

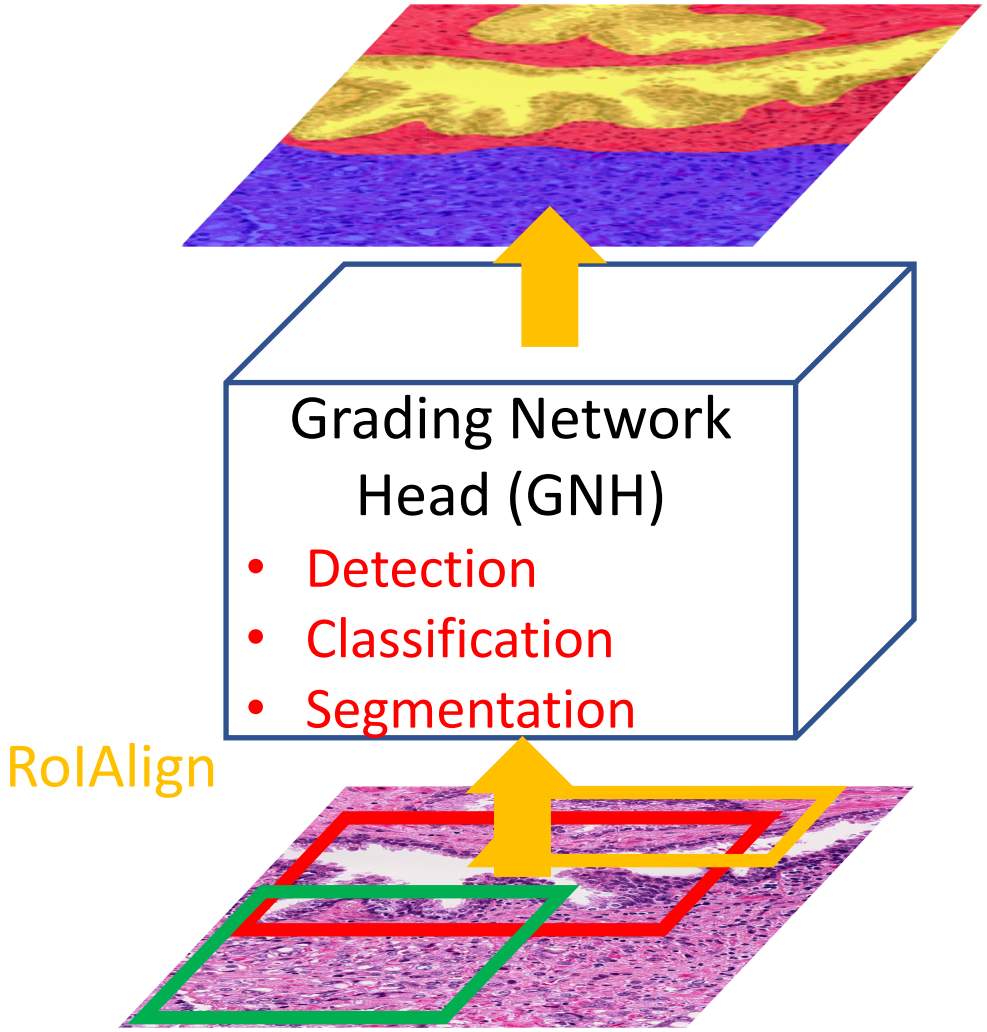
Two Stage Approach: R-CNN

- **First Stage: Find the ROI and tell the network where to look. (Attention Mechanism)**
  - Region Proposal Network (RPN)

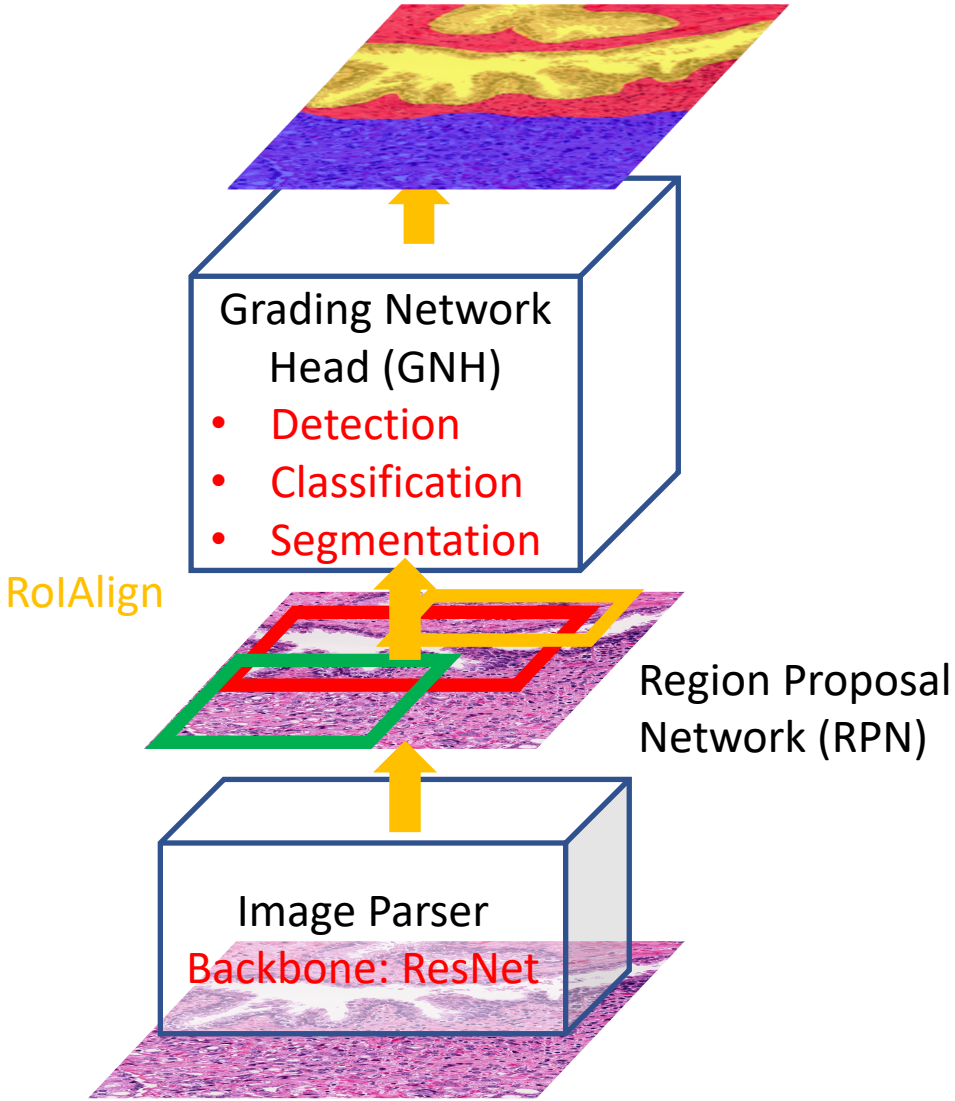


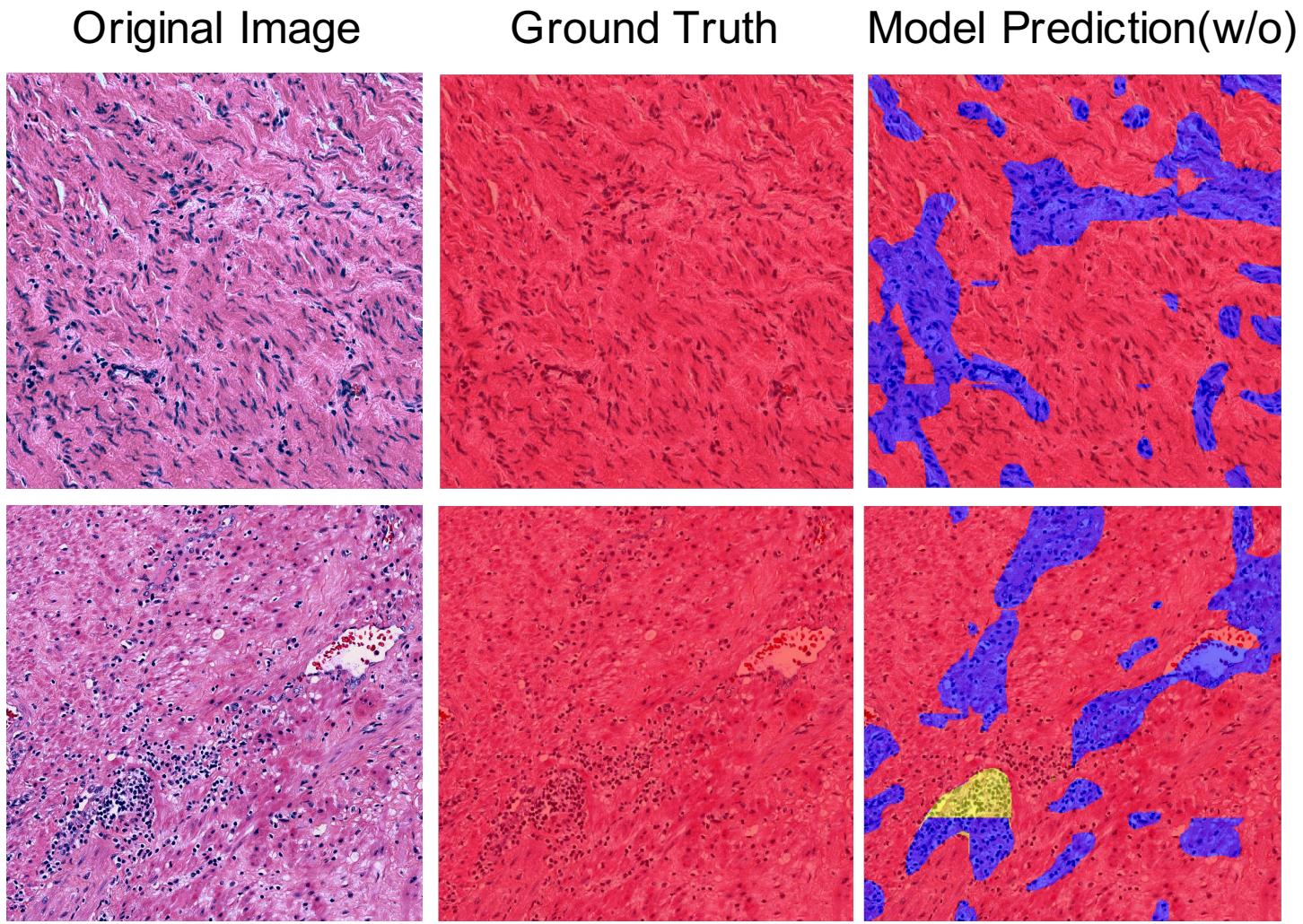
Two Stage Approach: R-CNN

- **Second Stage: RoIs classification, detection, and segmentation.**
  - RoIAlign Layer
  - Grading Network Head (GNH)
    - Detection
    - Classification
    - Segmentation

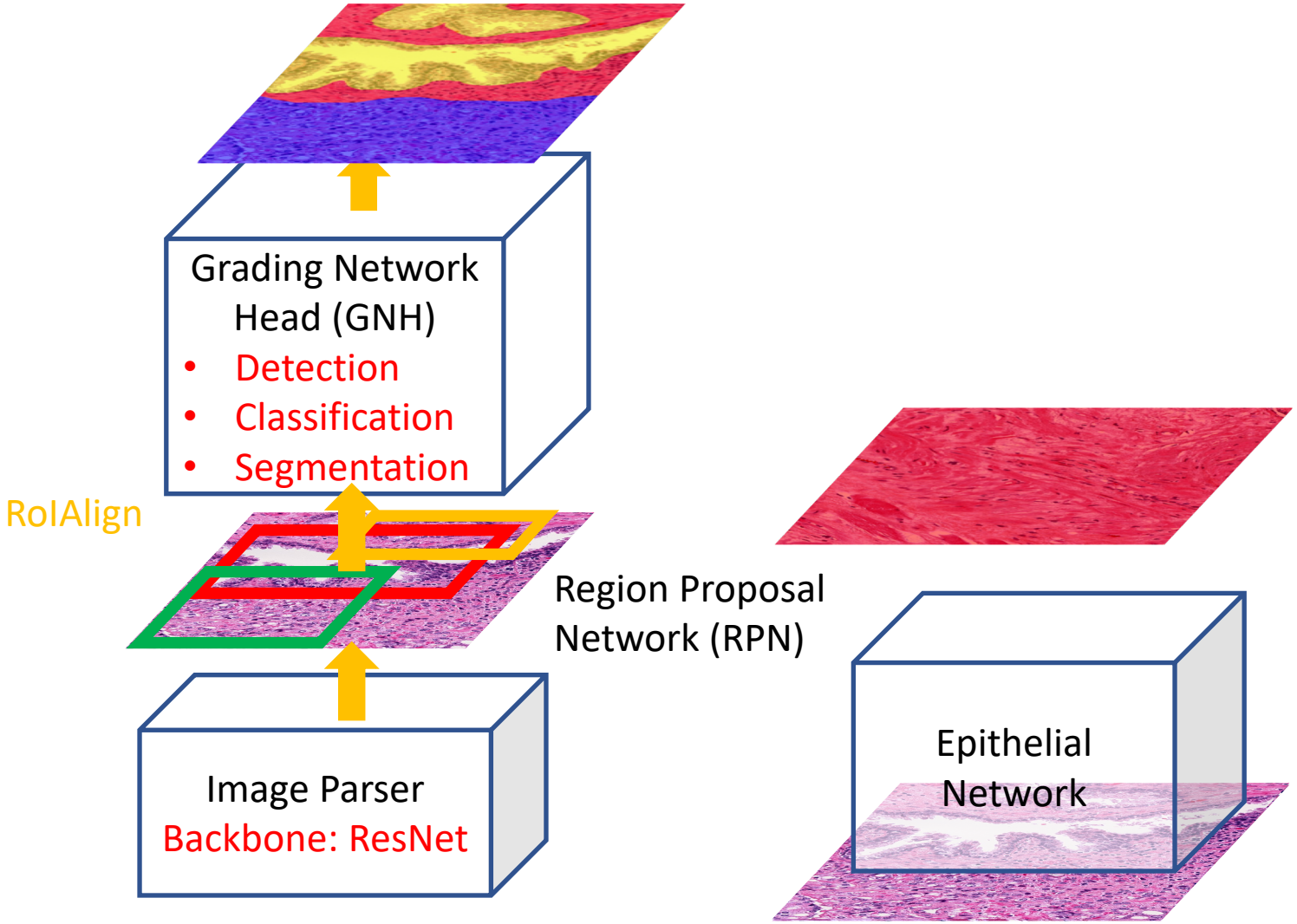


Two Stage Approach: R-CNN





Epithelial Network Head Play a Role!



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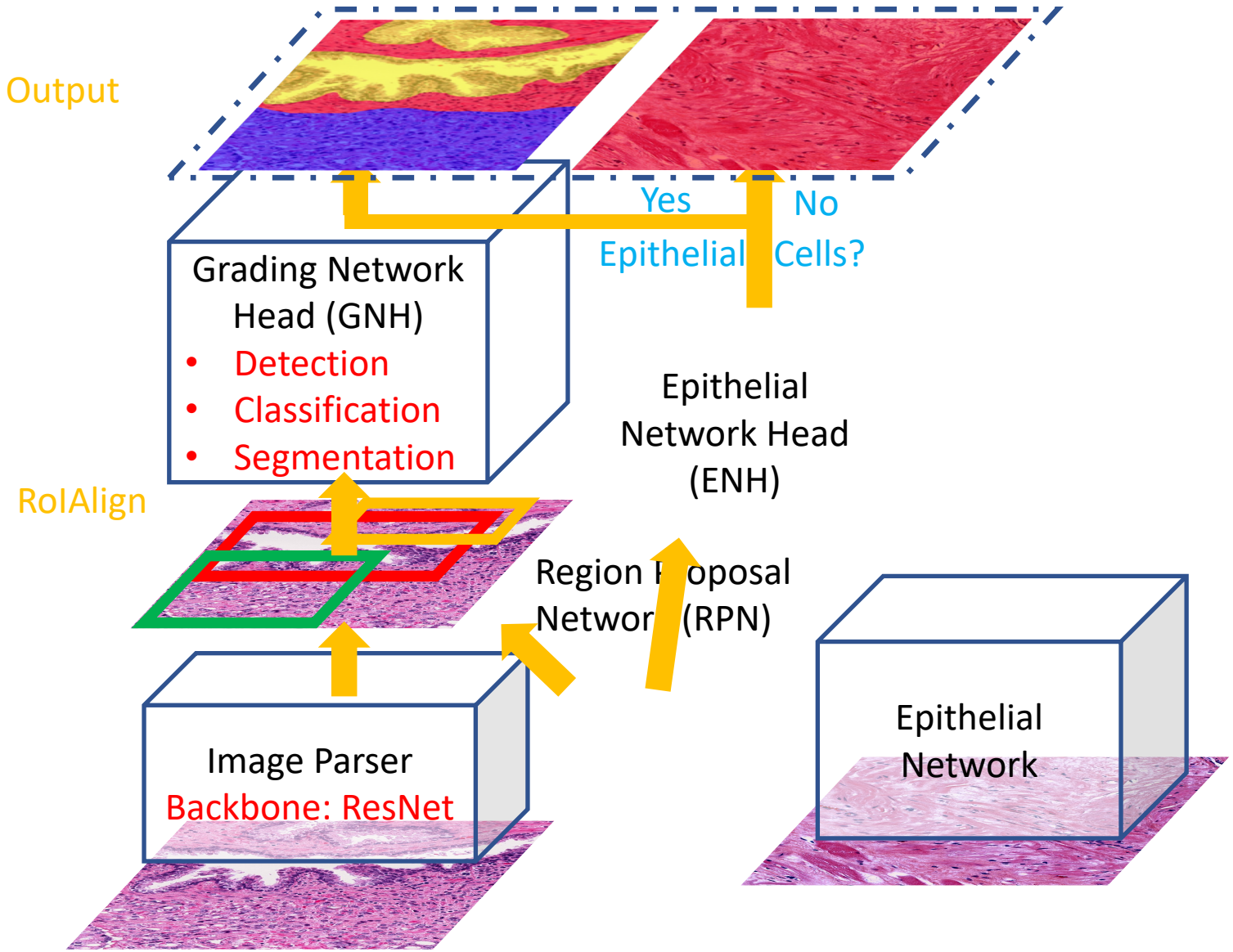
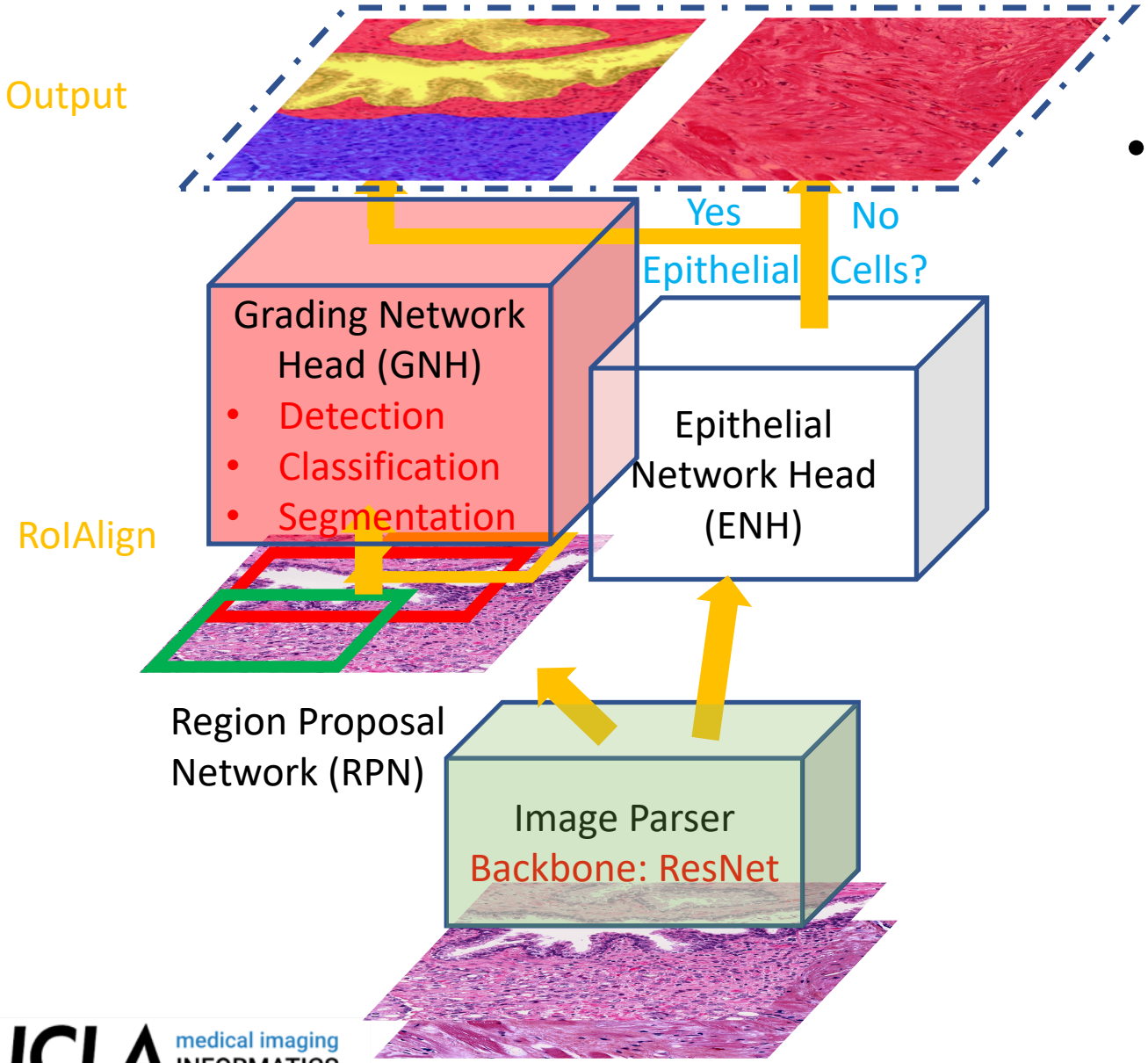
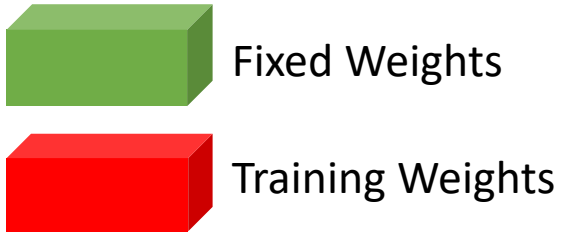


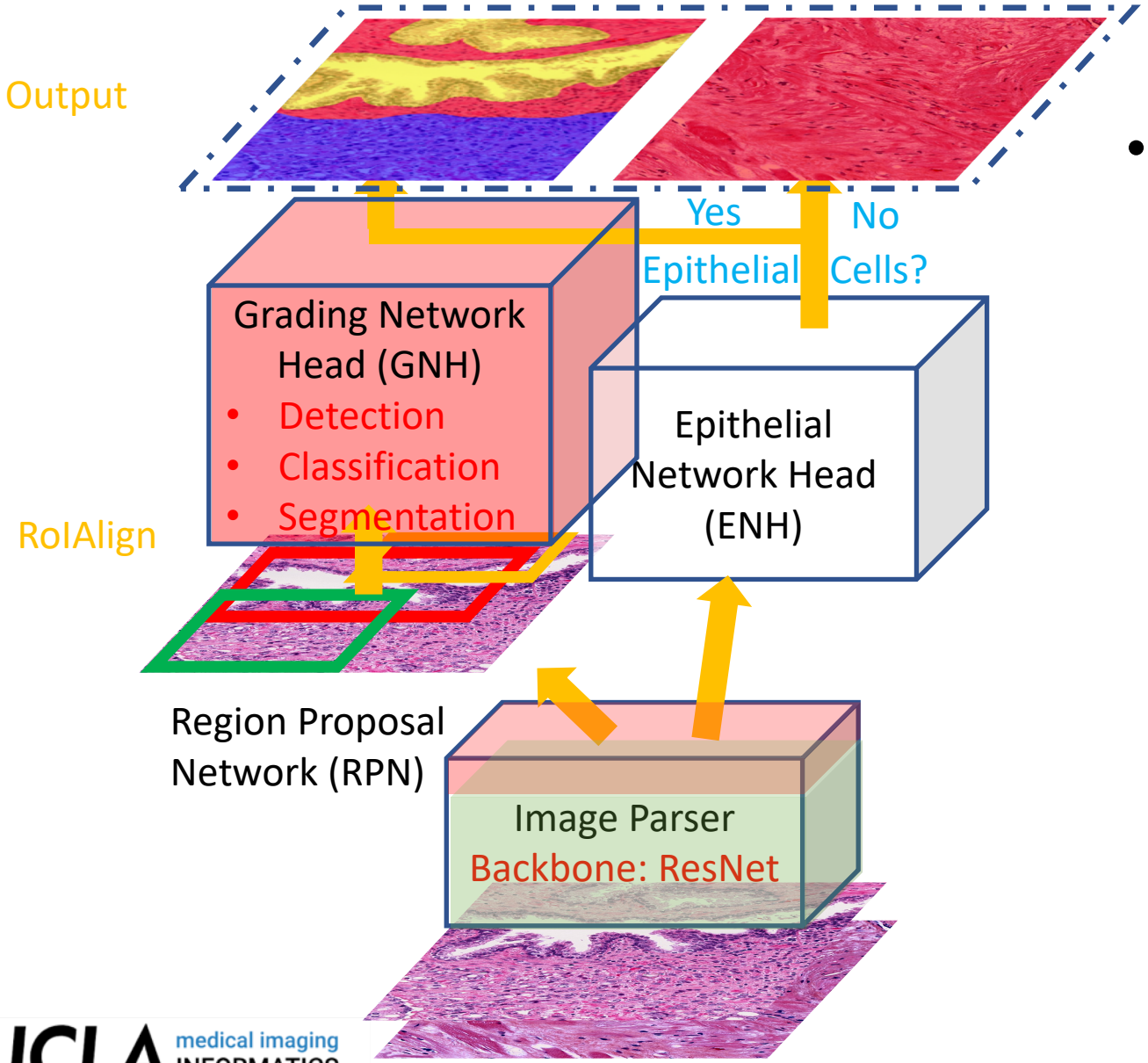
Two-Stage Training



- First Stage: trained the GNH along with the higher layers of the ResNet backbone.



Two-Stage Training



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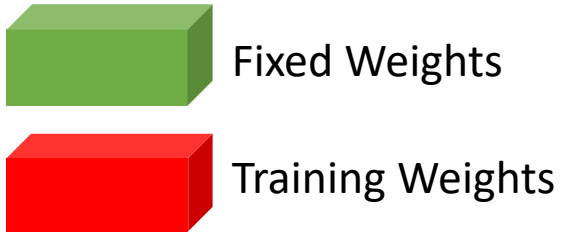

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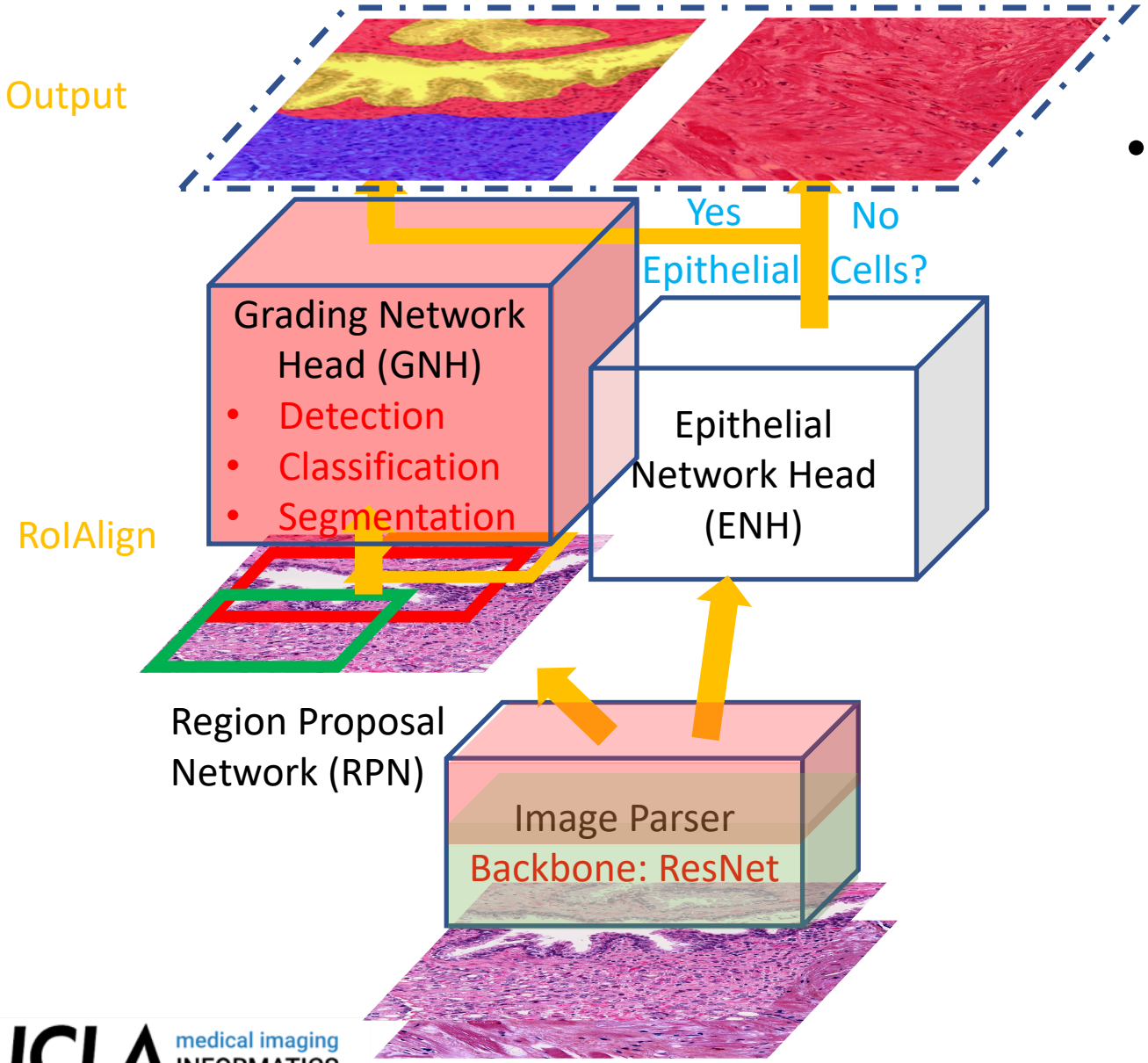

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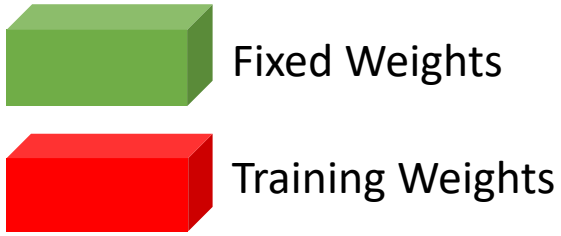
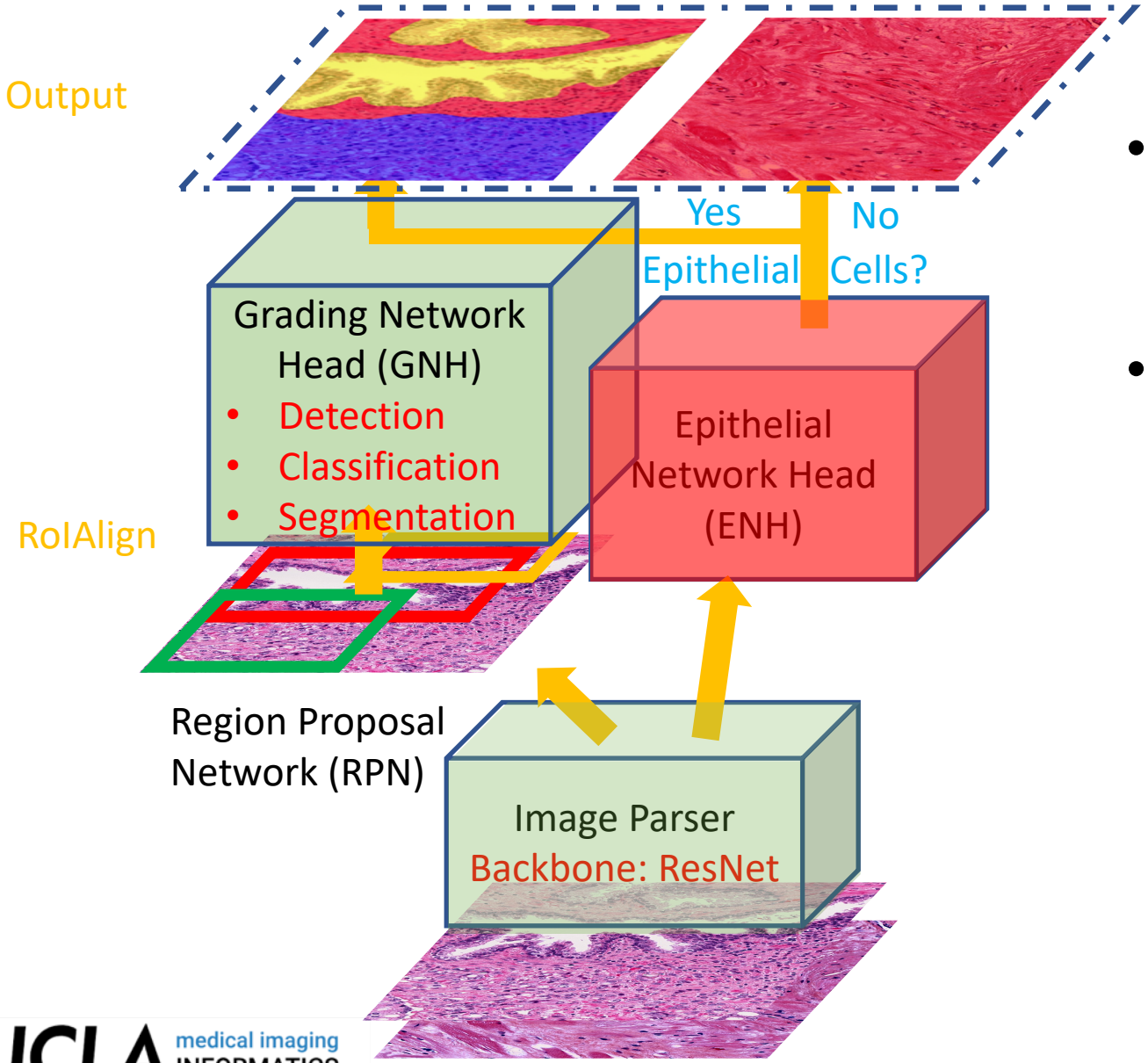
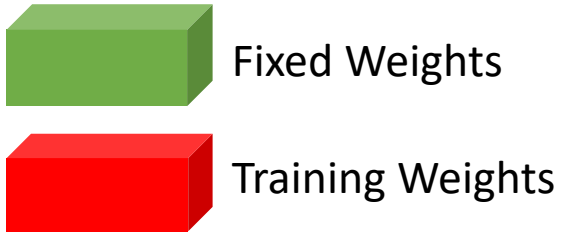


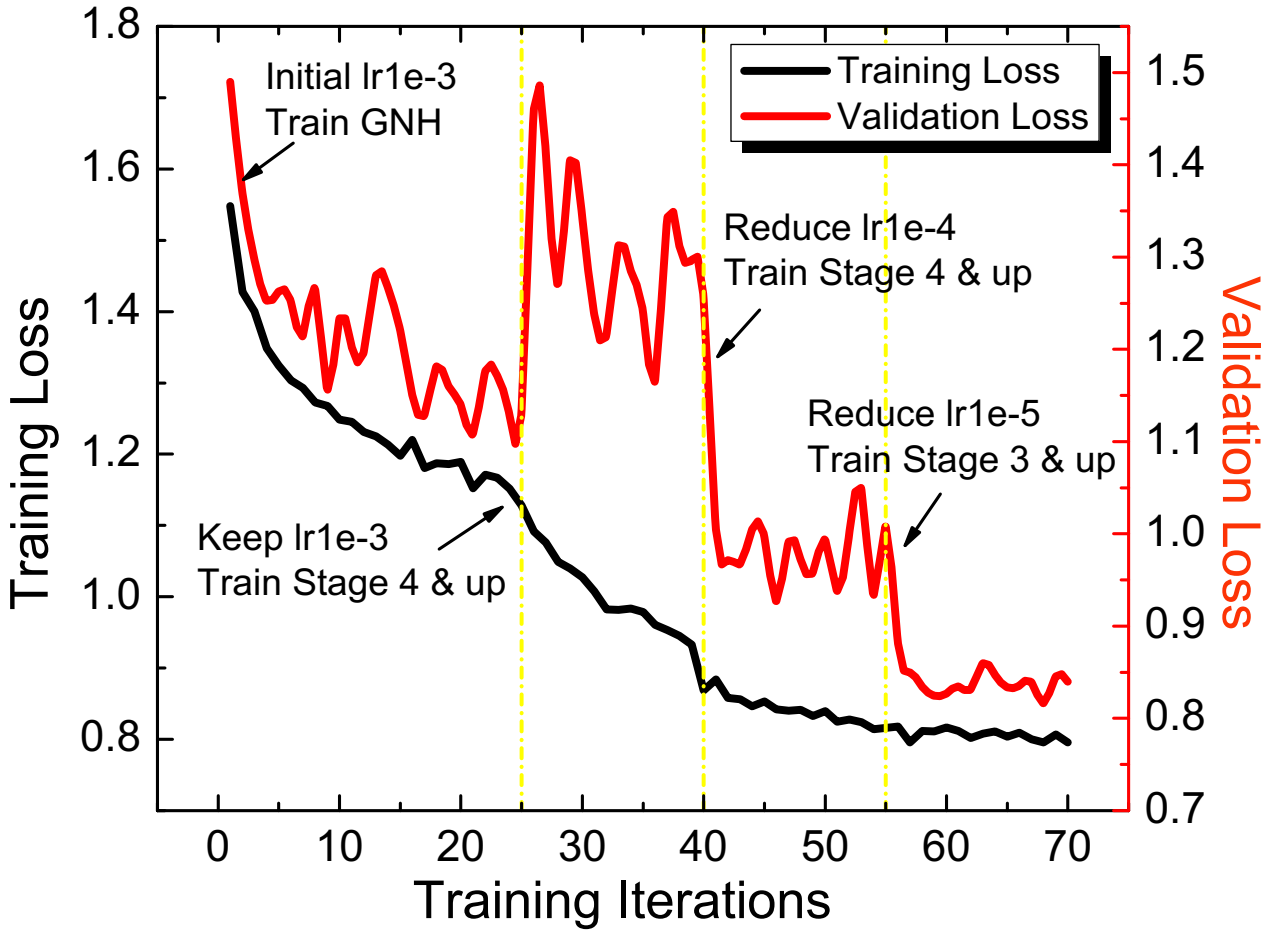
Two-Stage Training



- First Stage: trained the GNH along with the higher layers of the ResNet backbone.
- Second Stage: took the fixed weights trained in Stage 1 and only trains the ENH.



Two-Stage Training



- First Stage: trained the GNH along with the higher layers of the ResNet backbone.
- Second Stage: took the fixed weights trained in Stage 1 and only trains the ENH.

The training process to train our proposed model in Stage 1. The model was initialized with the pre-trained weights on MS COCO dataset.

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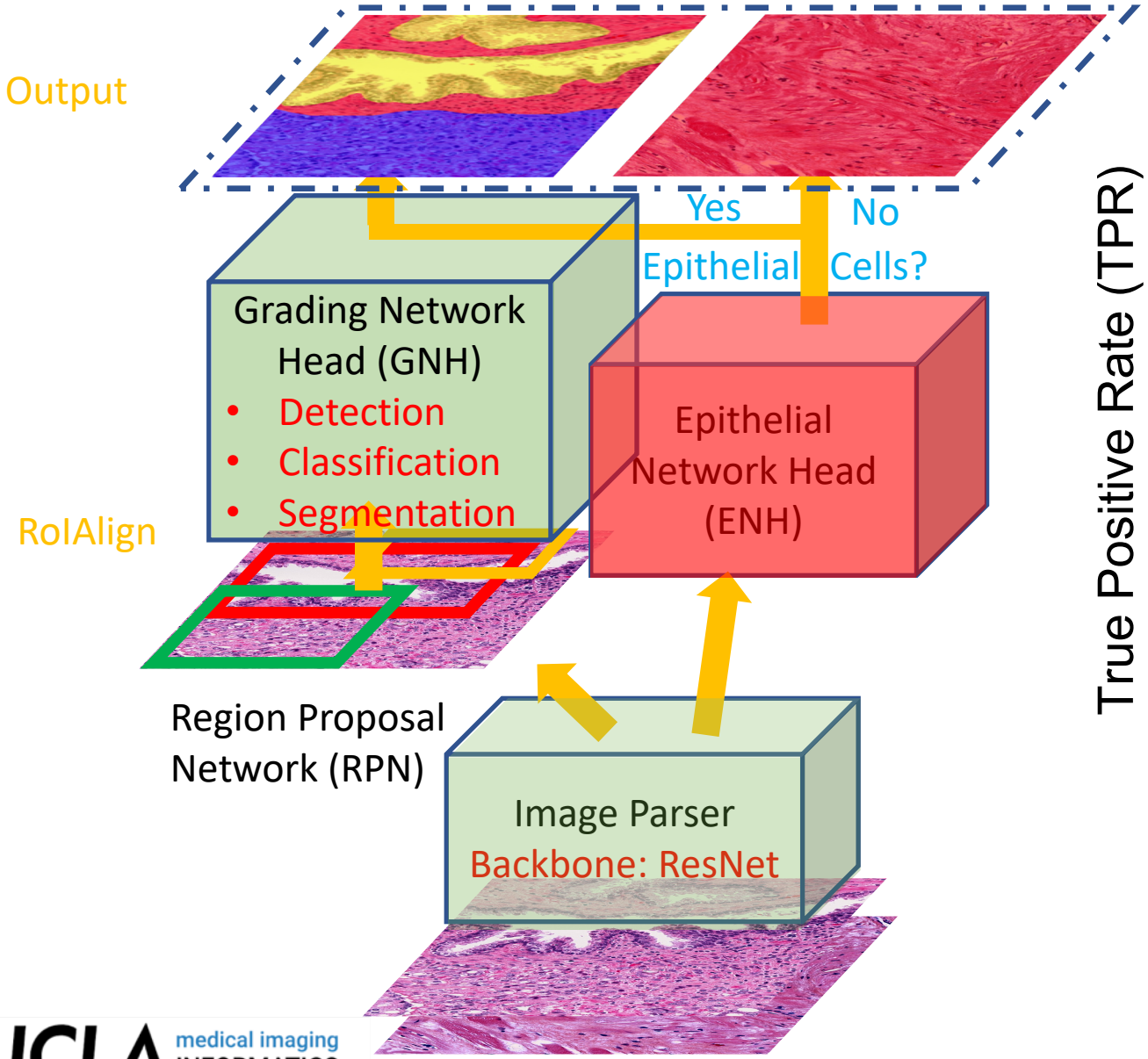
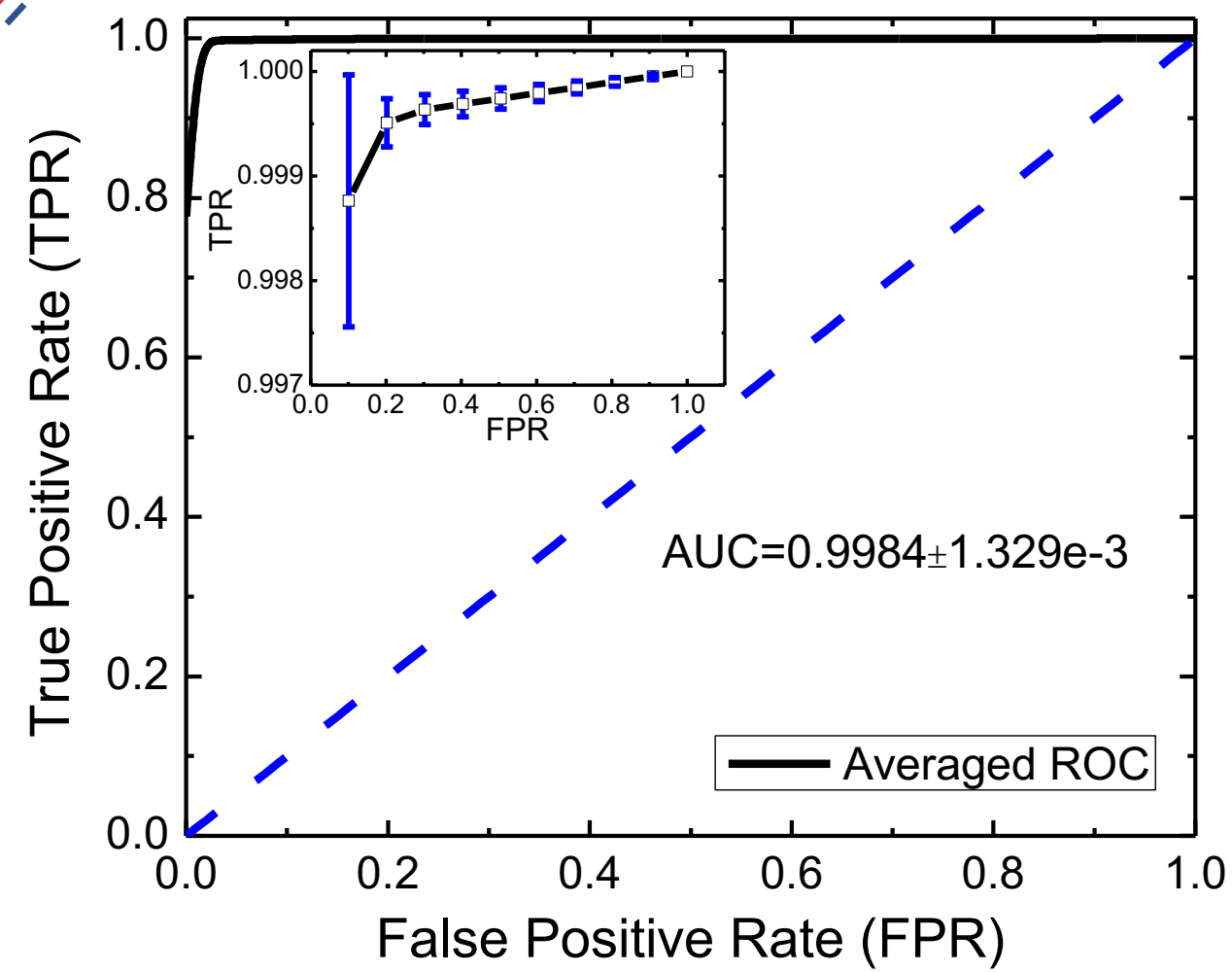
Why Two-Stage Training Works?





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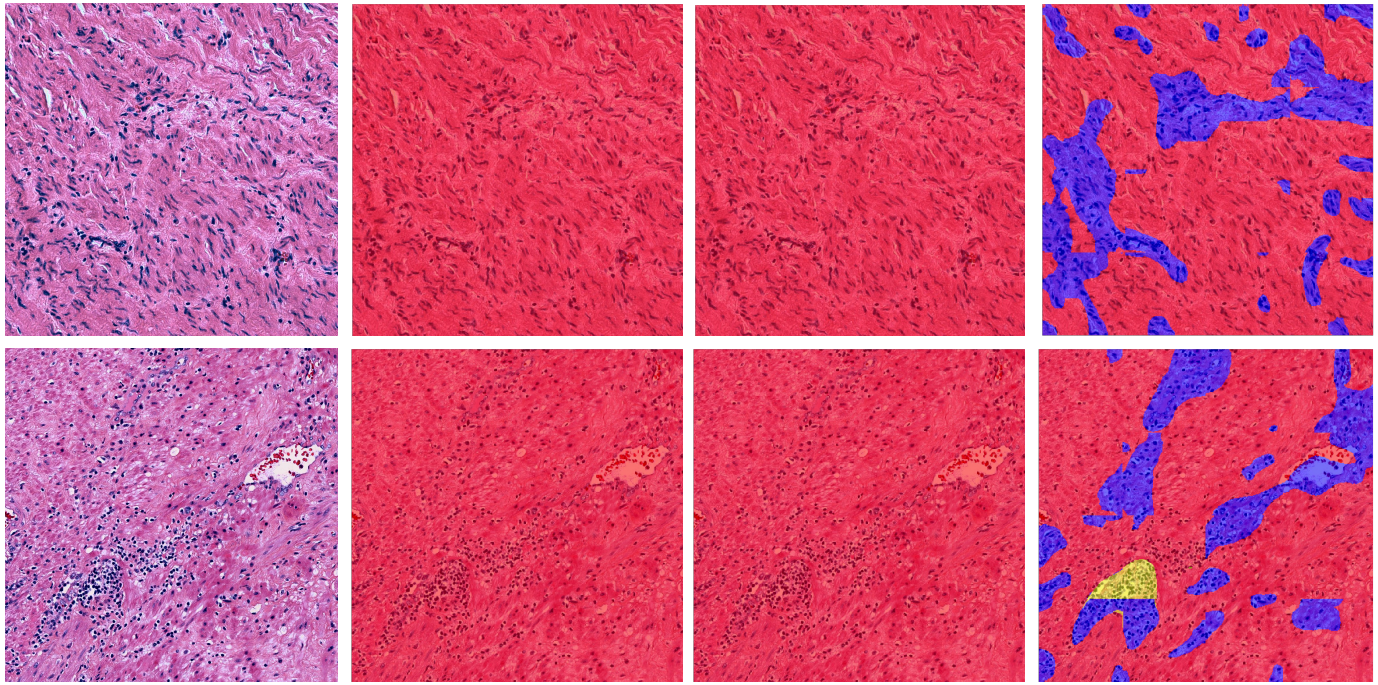
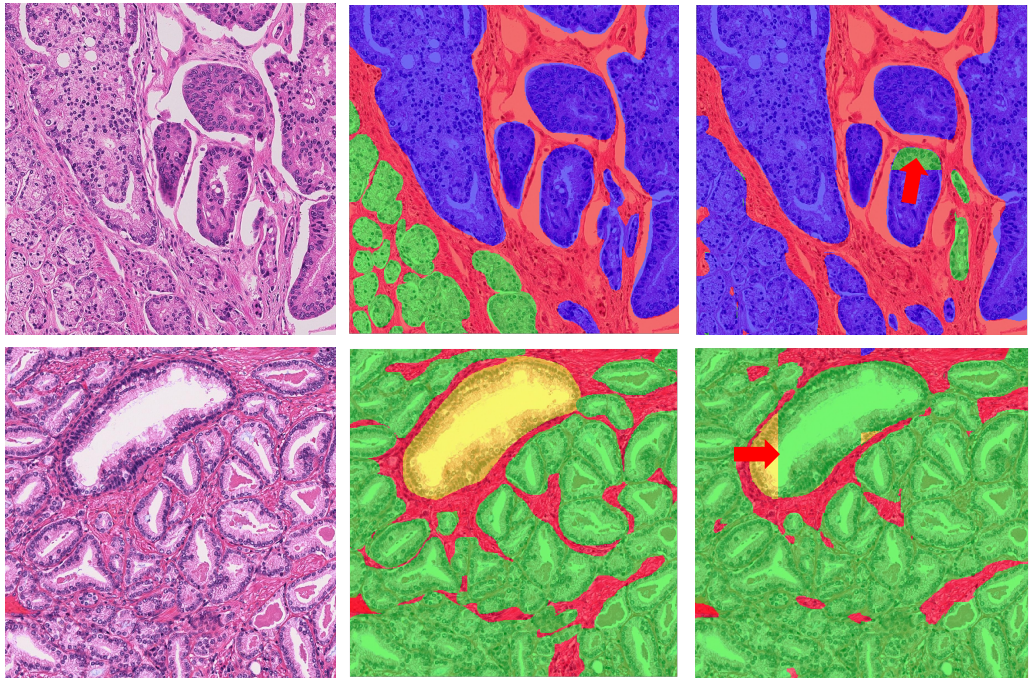
Results with ENH

Original Image | Ground Truth | Model Prediction(w) | Model Prediction(w/o)

Epithelial Network Head (ENH)



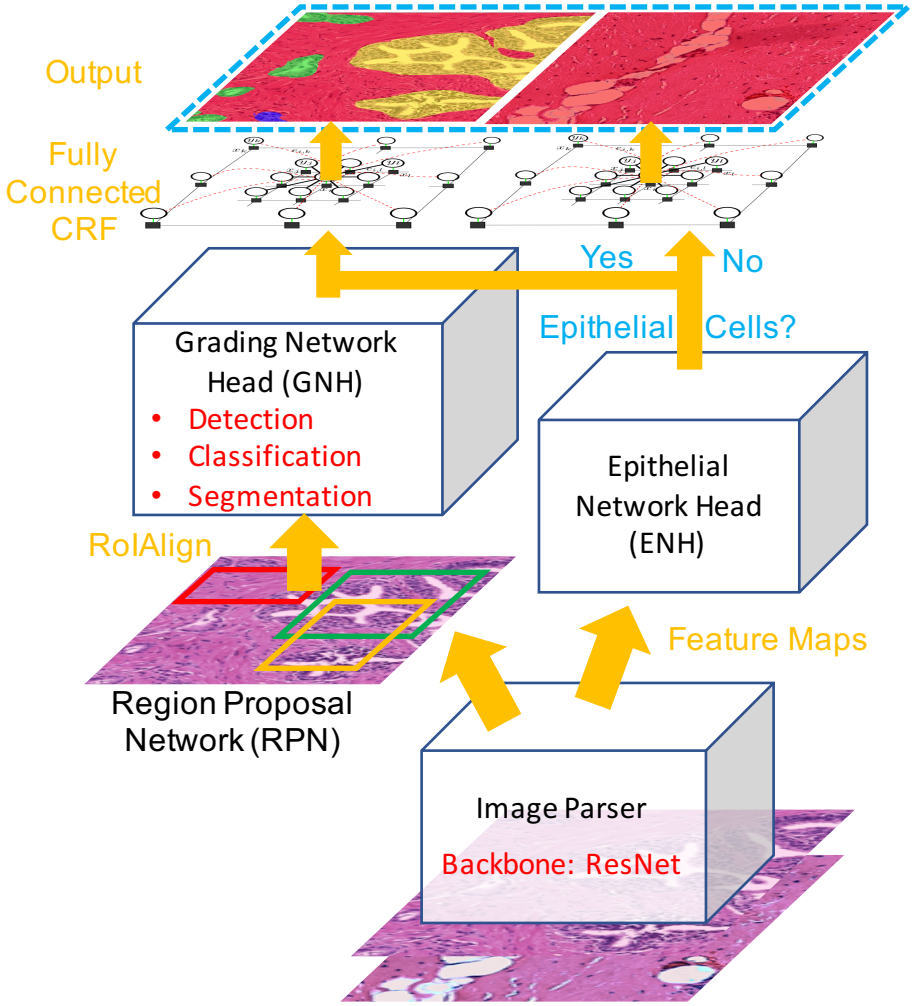
Stroma
Low-grade
High-grade
Benign



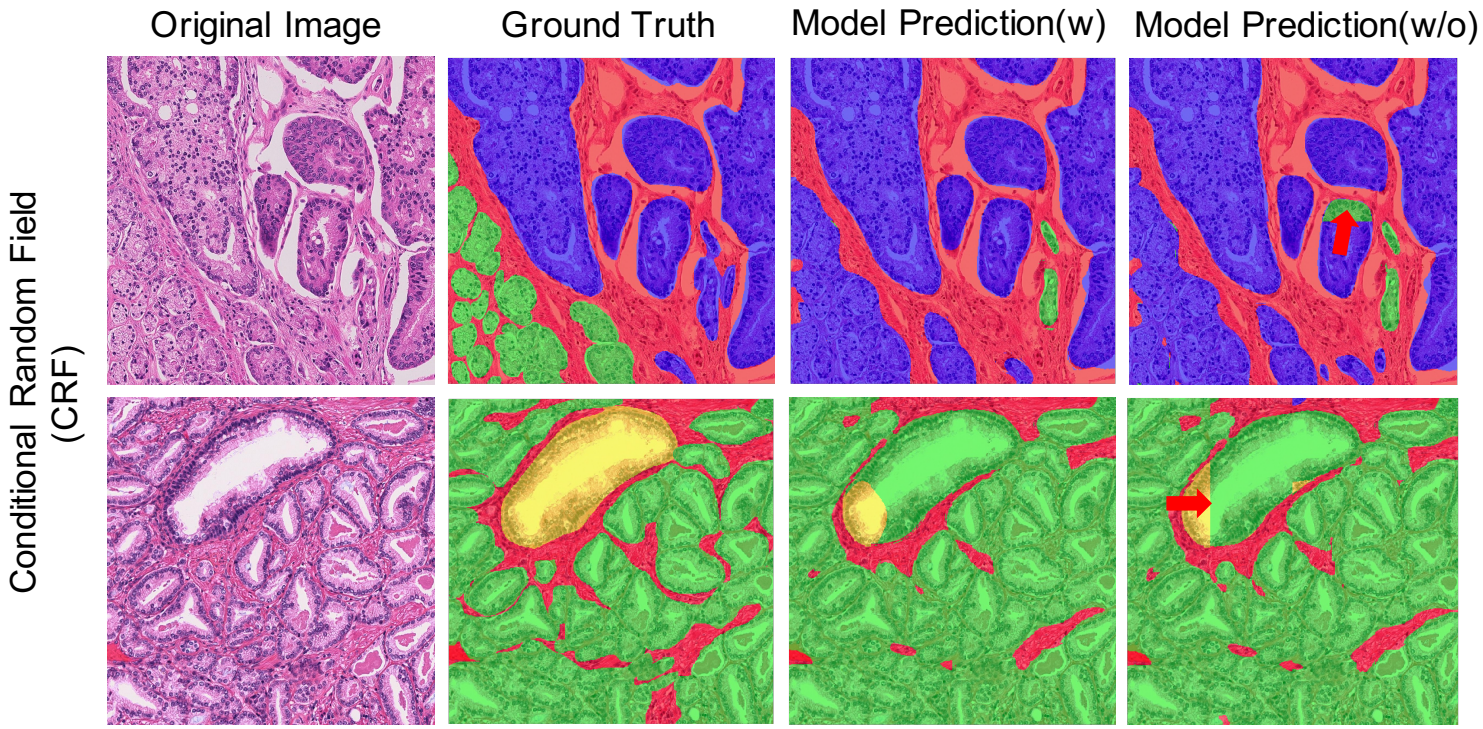
Without the ENH, our model is prone to predict RoIs even if the figure is full of “stroma”.

Stitching tiles together might cause unnatural boundary.

Results with CRF



Path R-CNN



The CRF can help refine unnatural boundaries in the model prediction. The two red arrows show artifacts created while stitching together prediction patches; as can be seen, the CRF removes these artifacts.

- Stroma
- Low-grade
- High-grade
- Benign

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More Results of Path R-CNN

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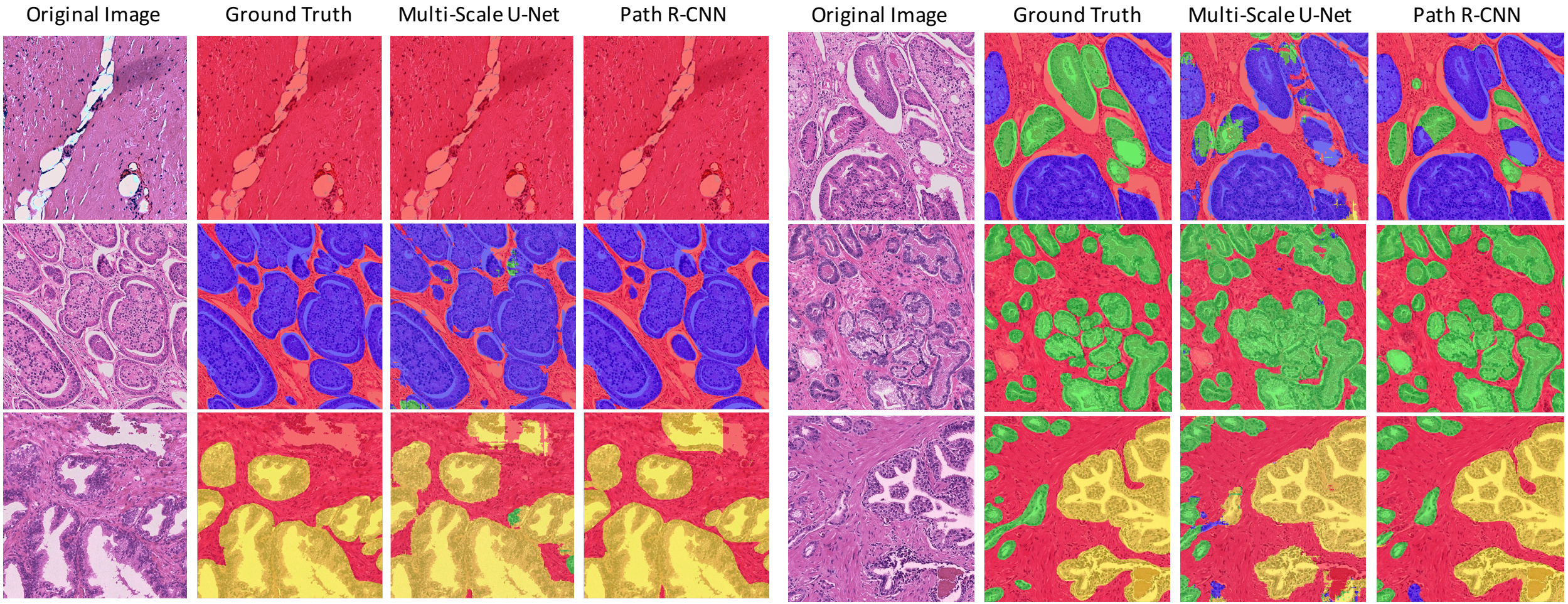

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Evaluation of Path R-CNN

- 5-fold cross validation
  - mIOU: mean intersection over union
  - OPA: overall pixel accuracy

	J_{BG}	J_{BN}	J_{LG}	J_{HG}	mIOU	OPA
Handcrafted Feature Approach	59.5%	35.2%	49.5%	NA	48.1%	N/A
Multi-Scale U-Net	82.42%	72.13%	58.70%	78.38%	72.91%	87.30%
Path R-CNN	**83.14%**	**83.78%**	**71.54%**	**79.69%**	**79.56%**	**89.40%**
Path R-CNN w/o ENH	73.26%	75.71%	71.13%	71.57%	72.91%	84.13%
Path R-CNN w/o CRF	82.94%	83.63%	71.32%	79.48%	79.34%	89.26%

Limitations and Future work

- The training method consist of two stage.
  - An end-to-end training method may be provided if we carefully tune the different loss to the same scale.
- RoIAlign lose the scale information of each RoI.
  - Incorporating scale information in the GNH might be helpful to improve the system's performance.

Conclusions

- Address the challenge of automatically do Gleason grading for prostate cancer.
- Our model achieved an epithelial cells detection accuracy of 99.07%, a mIOU of 79.56% for Gleason grading.
- Our method would help the pathologist to make the diagnosis more efficiently in the near future.

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Acknowledgement

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Data

Cedars-Sinai Pathology Department

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Thank You

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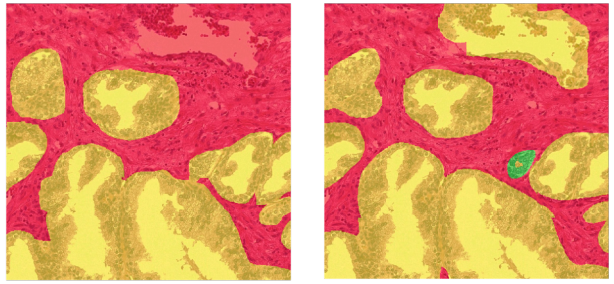
Intrinsic problem with ground truth.

Even pathologist may not agree with each other given a histological image.

Our Network do generalize!



Fully Connected Conditional Random Field (CRF)

A conditional random filed $(\boldsymbol{I}, \boldsymbol{X})$ is characterized by:

$$P(\boldsymbol{X}|\boldsymbol{I}) = \frac{1}{Z(\boldsymbol{I})}\exp(-E(\boldsymbol{X}|\boldsymbol{I}))$$

where $\boldsymbol{X}$ defined over the whole image set $\{x_1, x_2, \dots, x_N\}$. x_i denotes the label of the ith pixel, N is the total number of pixels.

$$E(\boldsymbol{X}|\boldsymbol{I}) = \sum_i \theta_i(x_i) + \sum_{i,j} \theta_{ij}(x_i, x_j)$$

- Unary Potential $\theta_i(x_i) = -\log P(x_i)$, where $P(x_i)$ is the label assignment probability at pixel i.
  - The unary potential used in this case is computed by Mask-RCNN which incorporates shape, texture, location and color information.
- Pairwise Potential $\theta_{ij}(x_i, x_j) = \mu(x_i, x_j)\sum_{m=1}^{K}\omega_m \cdot k^m(\boldsymbol{f}_i, \boldsymbol{f}_j)$.
  - $\mu(x_i, x_j) = 1$ if $x_i \neq x_j$ and 0 otherwise $(i.e.,$ Potts Model$)$.
  - Fully connected: one pair of pixels i and j in the image no matter how far from each other they lie.
  - It introduces a penalty for nearby similar pixels that are assigned different labels.
  - Each k^m is the Gaussian kernel and is weighted by parameter ω_m. Specifically the kernels are

$$\omega_1\exp\left(-\frac{\|p_i-p_j\|^2}{2\sigma_\alpha^2} - \frac{\|I_i-I_j\|^2}{2\sigma_\beta^2}\right) + \omega_2\exp\left(-\frac{\|p_i-p_j\|^2}{2\sigma_\gamma^2}\right)$$

  - The first kernel assumes that nearby pixels with similar color are likely to be in the same class.
  - The second kernel removes small isolated regions.