University of Amsterdam

Amsterdam UMC
Universitair Medische Centra

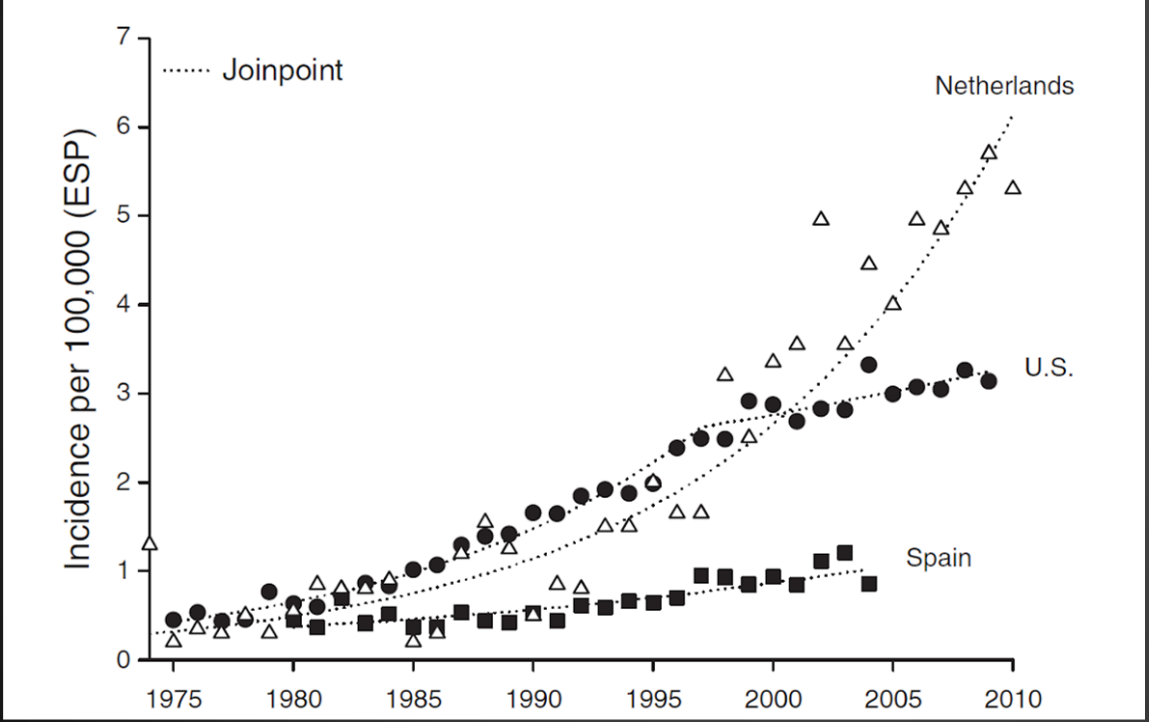
U-net Ensembles for Accurate Risk Stratification of Precursor Lesions of Esophageal Adenocarcinoma

Bryan Cardenas Guevara* & Vivian van Oijen*

*Graduate School of Informatics, University of Amsterdam

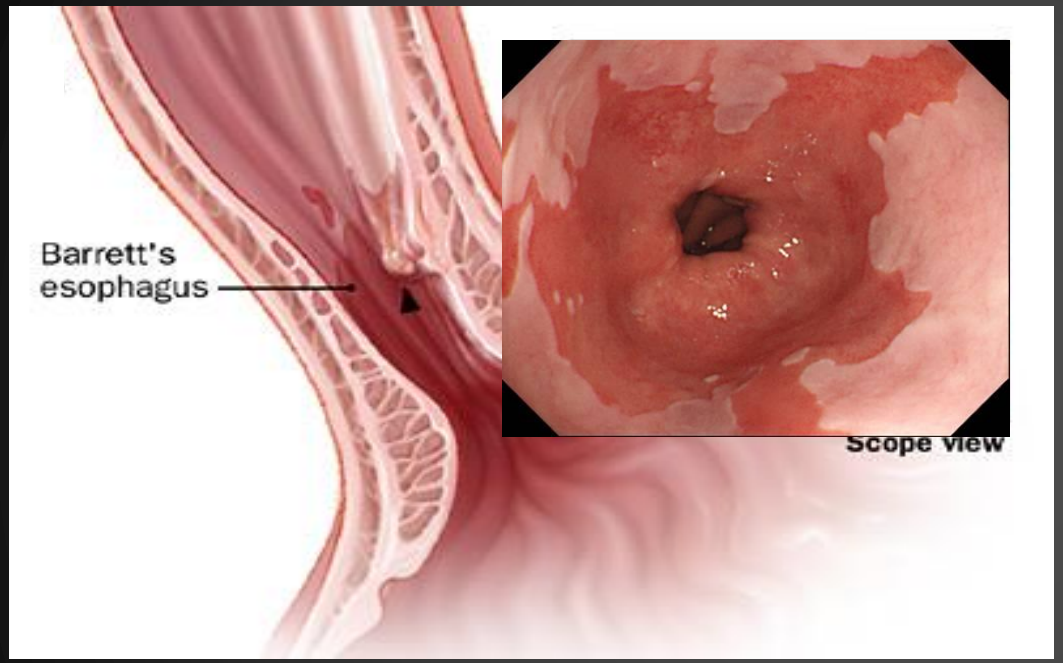
Incidence Rate of Esophageal Adenocarcinoma

- Sharp increase in the incidence rate



Am J Gastroenterol 2014; 109; 336-343

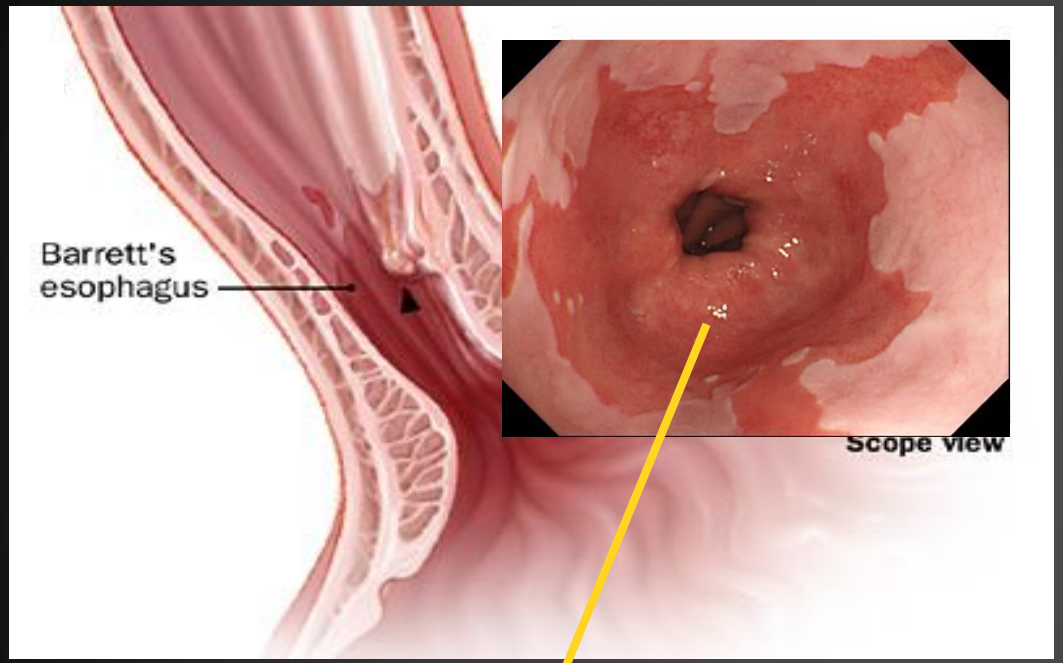
Barrett's Esophagus



Gastro Esophageal Reflux disease Barrett's Esophagus

At risk to develop Adenocarcinoma
Endoscopic surveillance
with biopsies for risk stratification

Barrett's Esophagus



Pink discoloration

Gastro Esophageal Reflux disease Barrett's Esophagus

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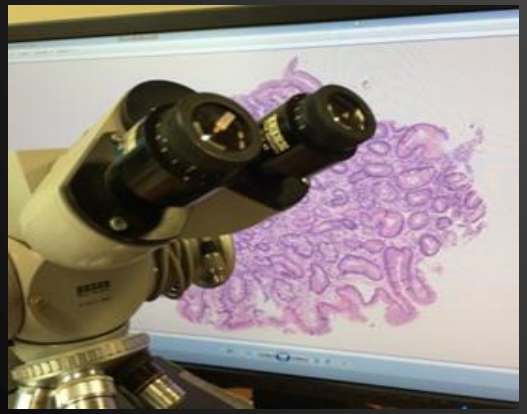
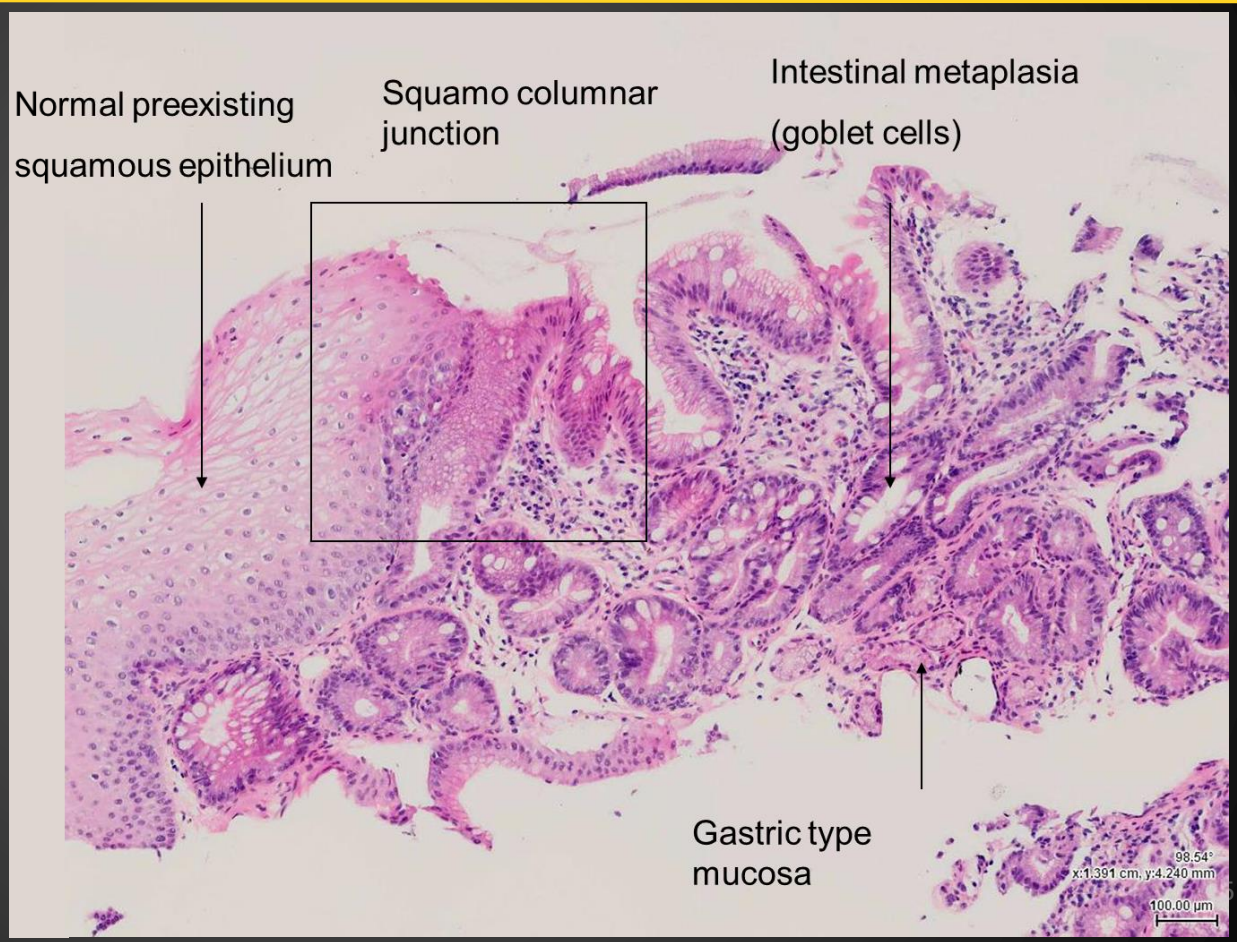
Barrett's on Biopsy





From Barrett's Esophagus to Adenocarcinoma

A proportion of patients with Barrett's Esophagus develop Adenocarcinoma

Risk of progression of Non-Dysplastic Barrett's Epitheleum to cancer is low:

- **~0.3 - 0.6 %** per year

Hvid-Jensen F. NEJM 2011, de Jonge P. Gut 2014; Dutch Barrett guideline

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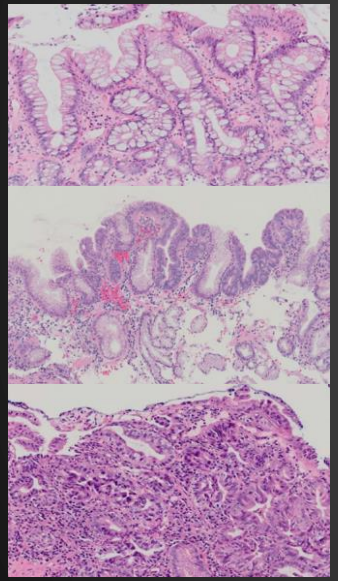

No Dysplasia (NDBE)	**Low interval of endscopic surveillance**
Low Grade Dysplasia	**High interval of endoscopic surveillance -- Endoscopic ablation therapy**
High Grade Dysplasia	**Endoscopic ablation therapy -- surgical therapy**

CANCER

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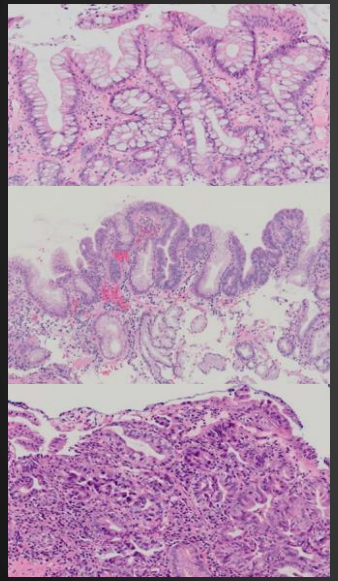

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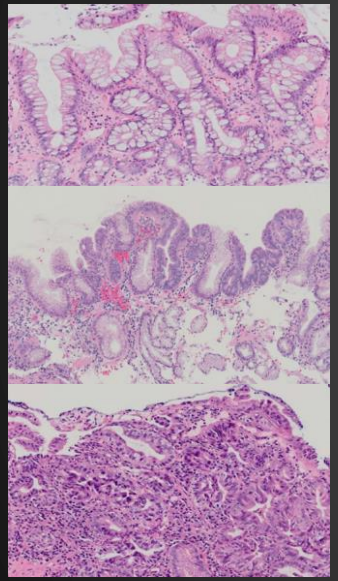

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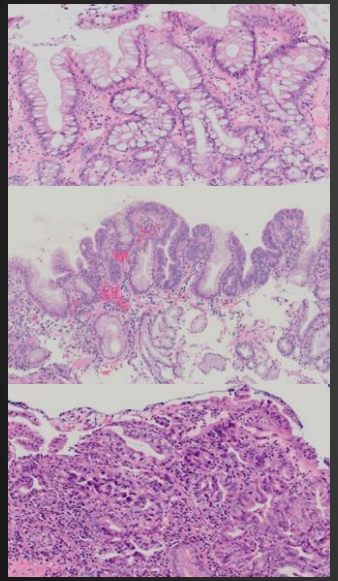

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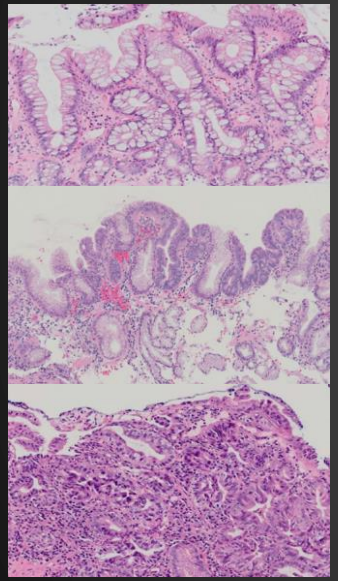

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Interobserver Variation in Low Grade Dysplasia

Gastroenterology 2017;152:564–570

Discordance Among Pathologists in the United States and Europe in Diagnosis of Low-Grade Dysplasia for Patients With Barrett's Esophagus

Prashanth Vennalaganti,[1,2] Vijay Kanakadandi,[1,2] John R. Goldblum,[3] Sharad C. Mathur,[4] Deepa T. Patil,[3] G. Johan Offerhaus,[5] Sybren L. Meijer,[6] Michael Vieth,[7] Robert D. Odze,[8] Saligram Shreyas,[1,2] Sravanthi Parasa,[1,2] Neil Gupta,[9] Alessandro Repici,[10] Ajay Bansal,[1,2] Titi Mohammad,[1,2] and Prateek Sharma[1,2]

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ORIGINAL CONTRIBUTIONS CME

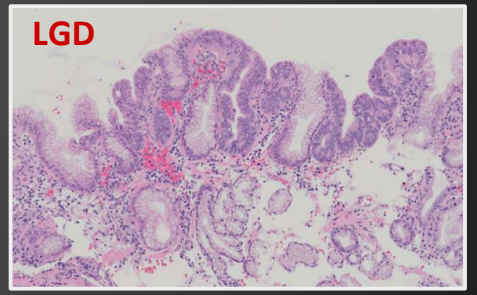
Pathology

Poor Interobserver Agreement in the Distinction of High-Grade Dysplasia and Adenocarcinoma in Pretreatment Barrett's Esophagus Biopsies

Erinn Downs-Kelly, D.O.,[1] Joel E. Mendelin, M.D.,[1] Ana E. Bennett, M.D.,[1] Elias Castilla, M.D.,[1] Walter H. Henricks,[1] Lynn Schoenfield, M.D.,[1] Marek Skacel, M.D.,[1] Lisa Yerian, M.D.,[1] Thomas W. Rice, M.D.,[2] Lisa A. Rybicki, M.S.,[3] Mary P. Bronner, M.D.,[1] and John R. Goldblum, M.D.[1]
[1]*Cleveland Clinic Departments of Anatomic Pathology,* [2]*Thoracic Surgery, and* [3]*Quantitative Health Sciences, Cleveland, Ohio*

Observer variability has led to need for expert review

All cases of Barrett's dysplasia should be confirmed by a second **EXPERT** gastro-intestinal pathologist



Curvers W. Am J Gastroenterol 2010

Aim of Study

Reliable and Reproducible diagnosis of dysplasia in patients with Barrett's Esophagus

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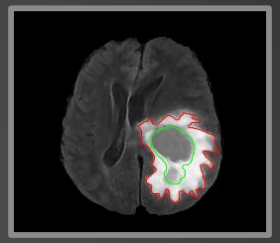
Deep Learning Methods with promising results in

- Brain Tumor Detection



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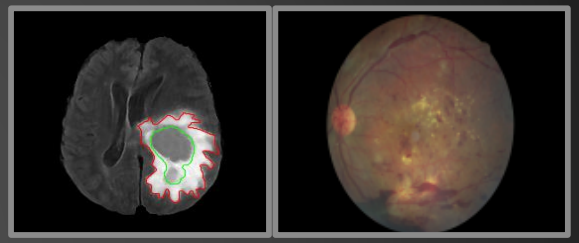

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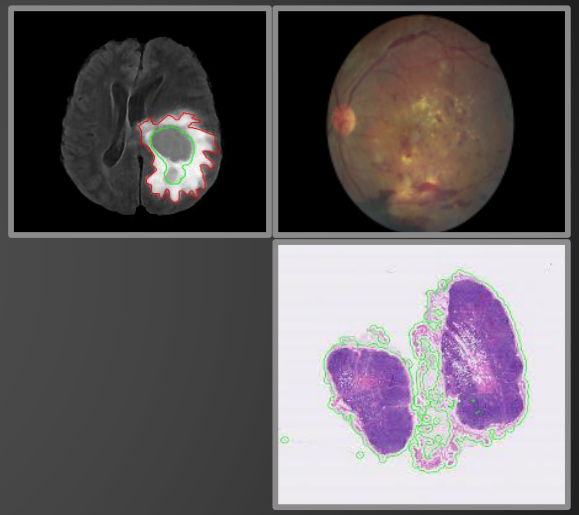

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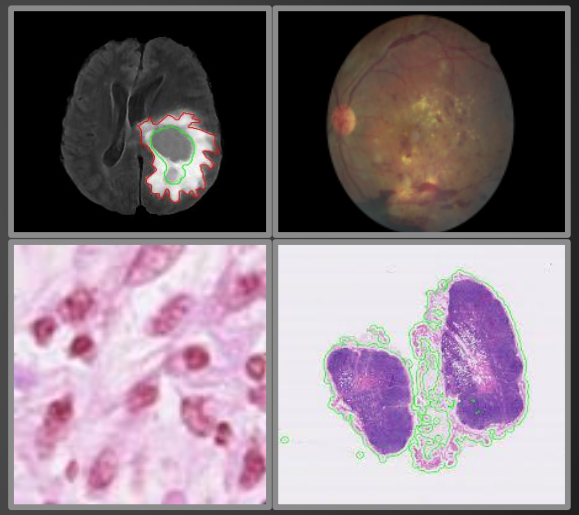

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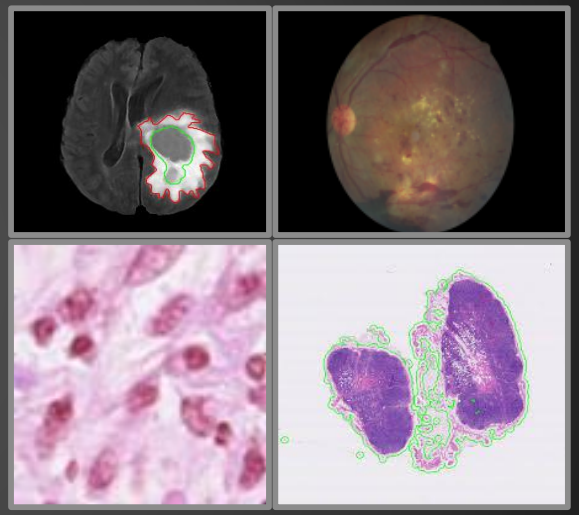
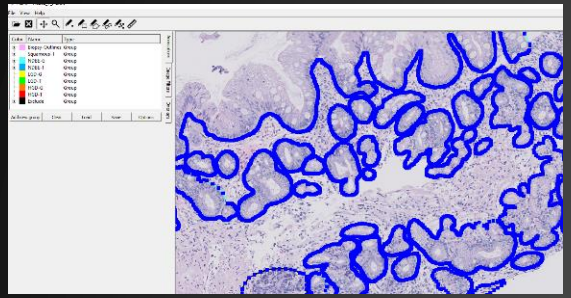


Lack of research in the segmentation of dysplasia - carcinoma sequence in Barrett's Esophagus

The Work Flow



1. Annotate slides in high detail for:
    - Squamous epithelium (Sq)
    - Non dysplastic epithelium (NDBE)
    - Low grade dysplasia (LGD)
    - High Grade dysplasia (HGD)

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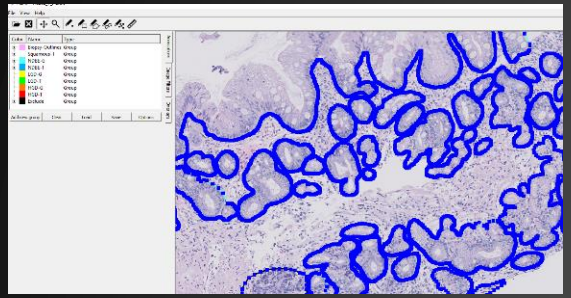
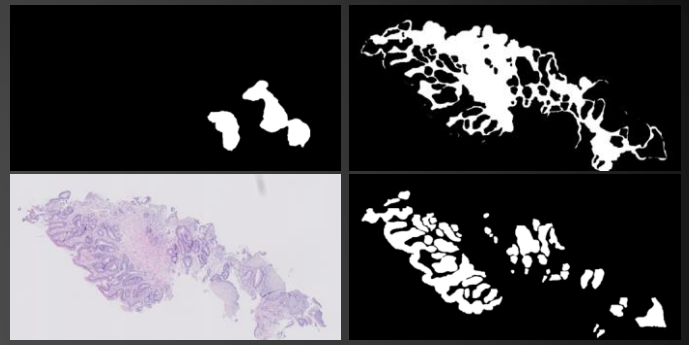


2. Create the masks



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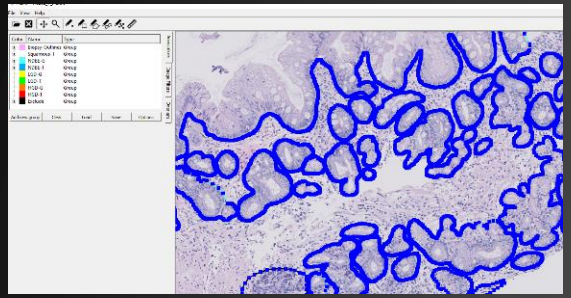

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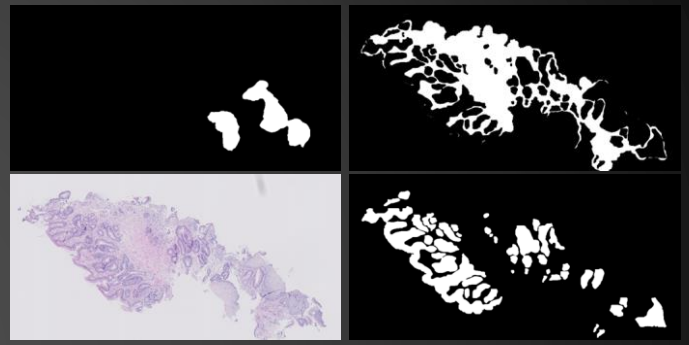
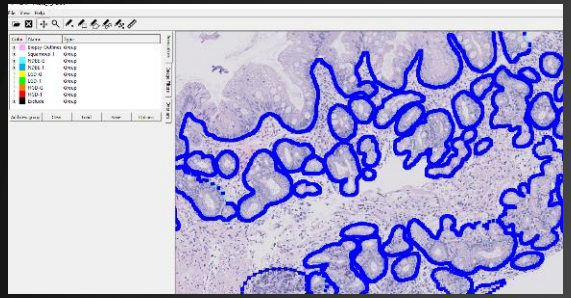


3. Extract Patches (512 x 512)

The Work Flow



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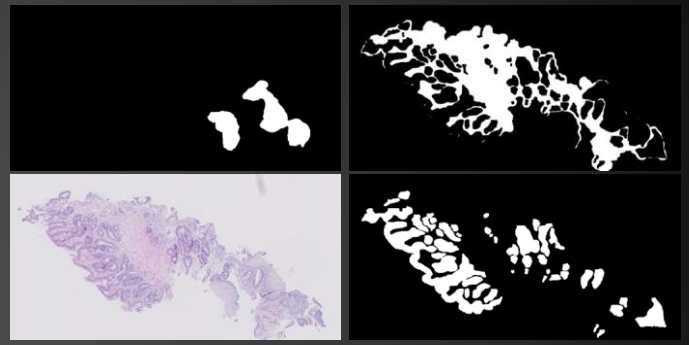
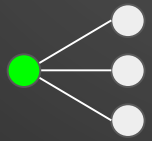
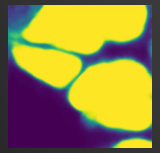


3. Extract Patches (512 x 512)

4. Artificial Neural Network



Predictions



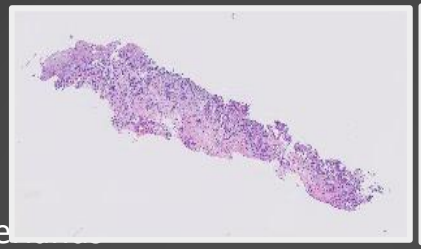
The Data: Whole Slide Image

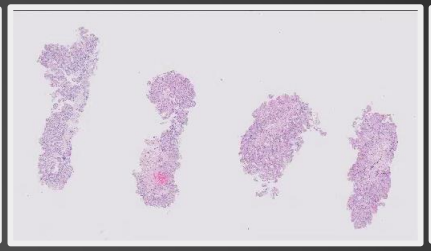
114 H&E stained whole slide images

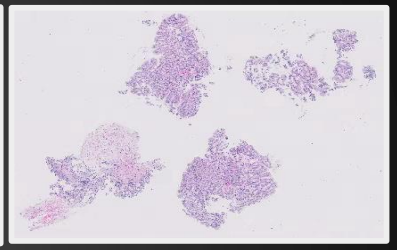
- At 20x magnification:
  - 2 pixels = 1μ
- 94 different patients
- Four Different Labs

  From the Nethe

- ~3 Biopsies per slide







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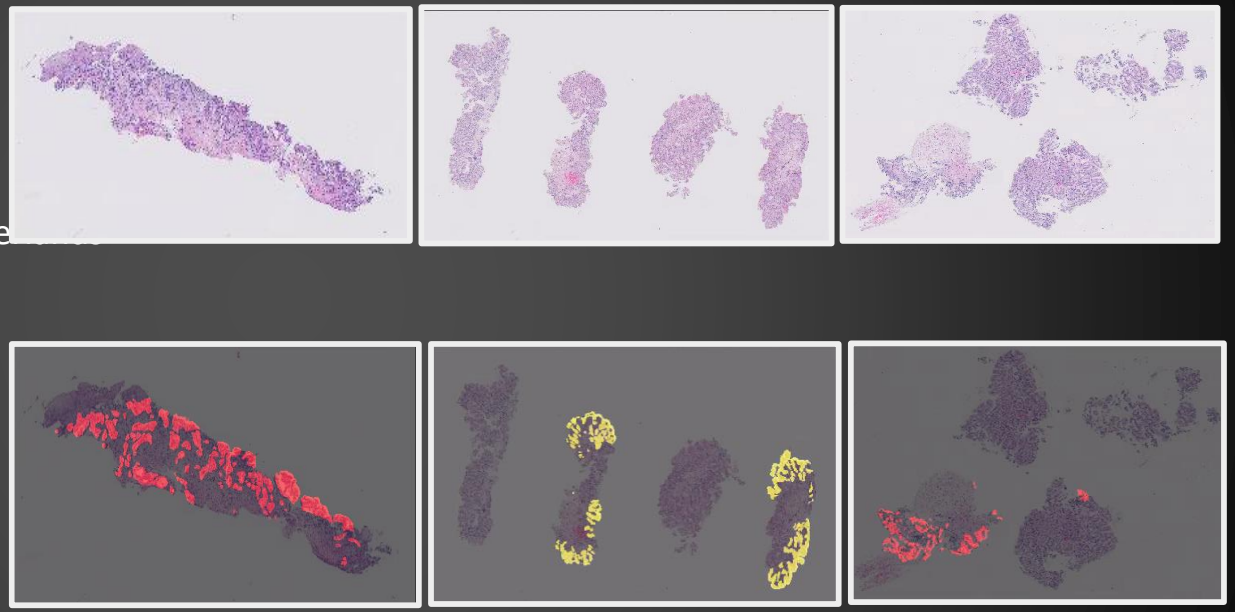

High Grade Dysplasia (HGD)

Low Grade Dysplasia (LGD)

Background (B)

The Data: Partitioning

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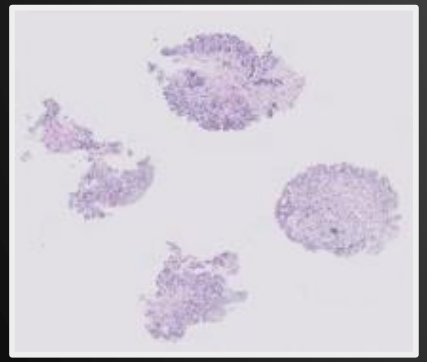
- 21 for testing



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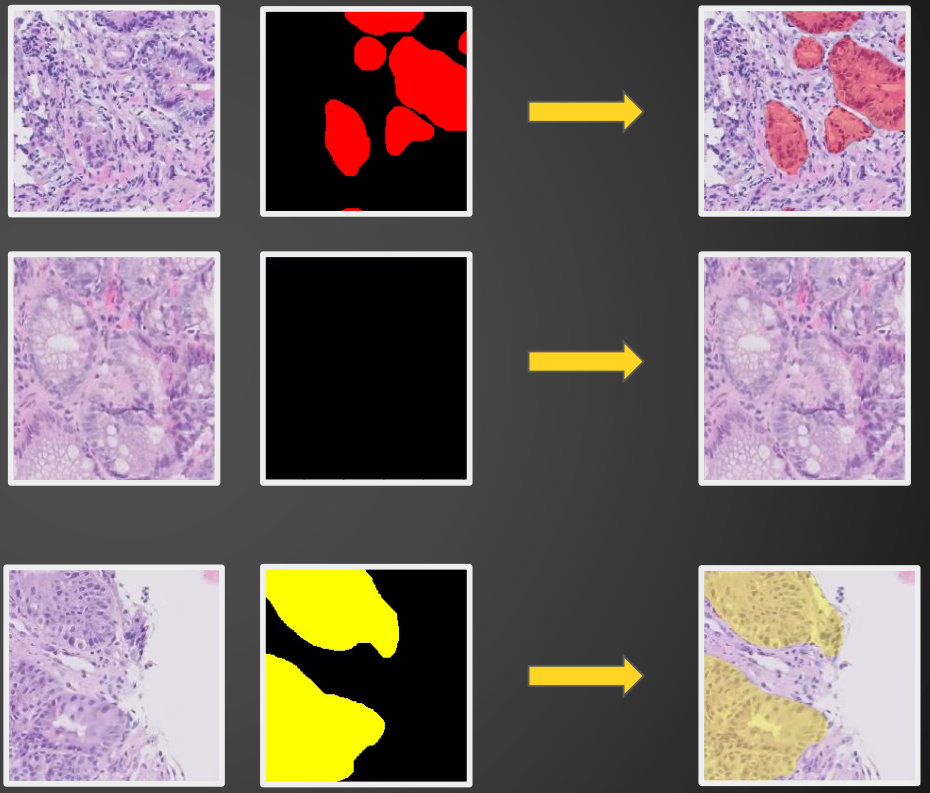

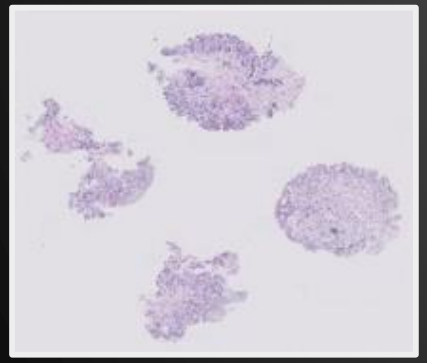

The Data: Partitioning

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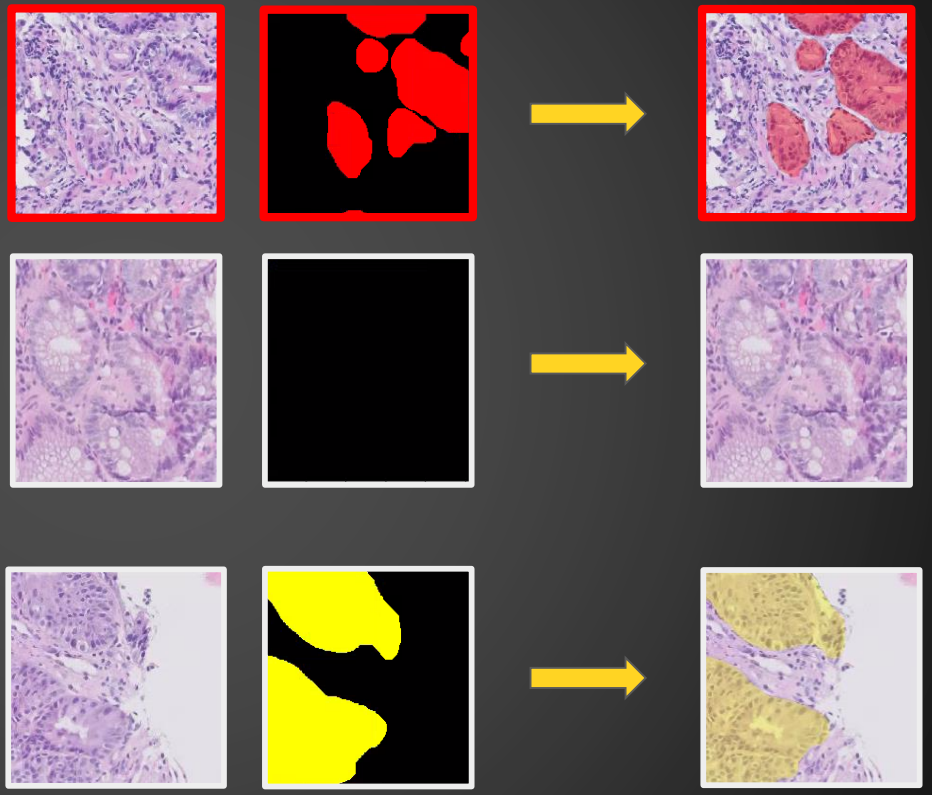
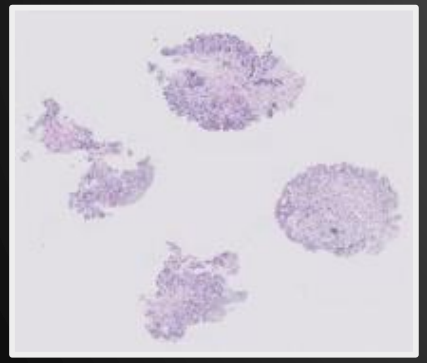
Slicing resulted in ~5000 patches
For training and ~2000 for testing

- 512 x 512 x 3
- One half contains Dysplastic regions





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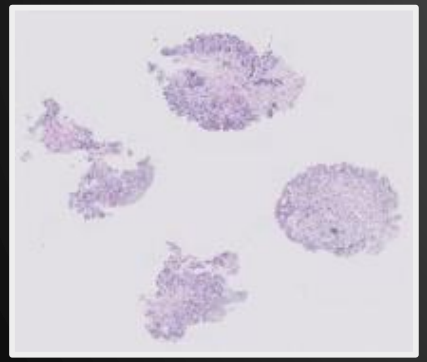
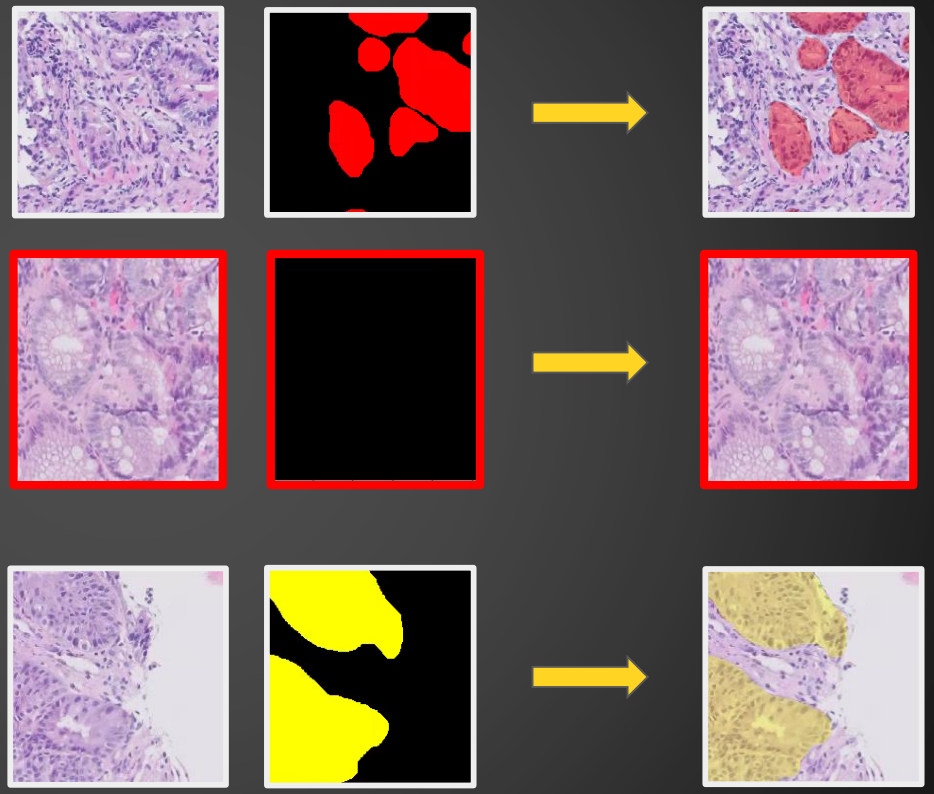
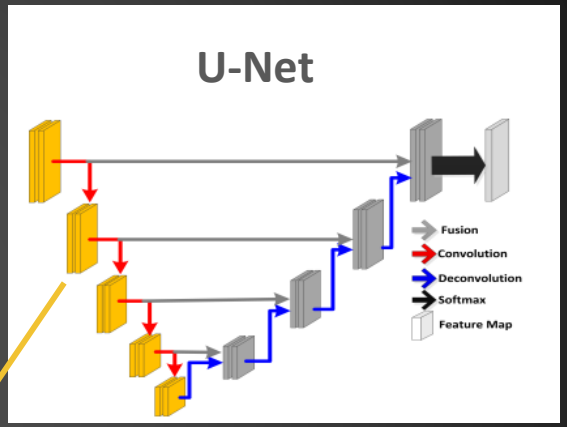




The Neural Network

U-Net Architecture

- Encoding done by DenseNet-161 and ResNet-50



Encoding

The Neural Network

U-Net Architecture

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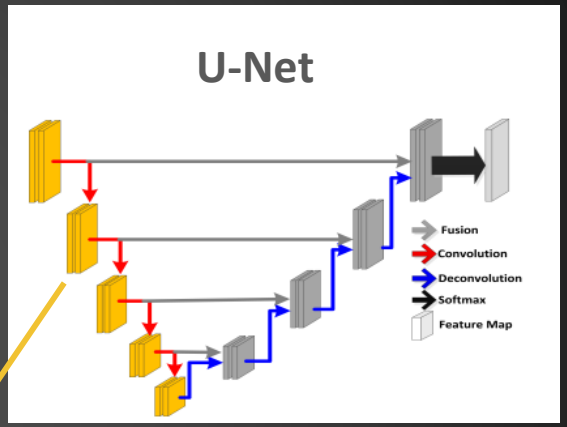
Ensemble of 10 Imagenet pre-trained U-nets

- 5 networks based on DenseNet-161
- 5 networks based on ResNet-50



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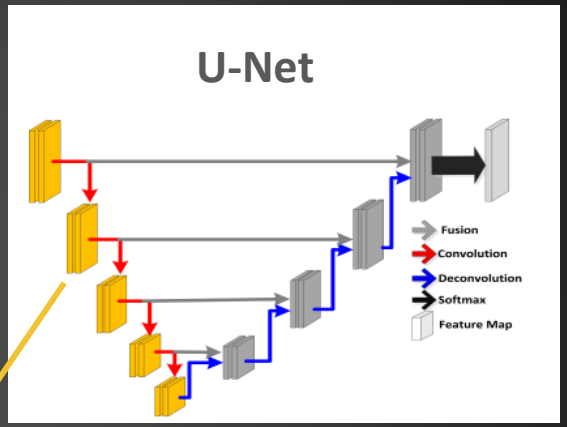

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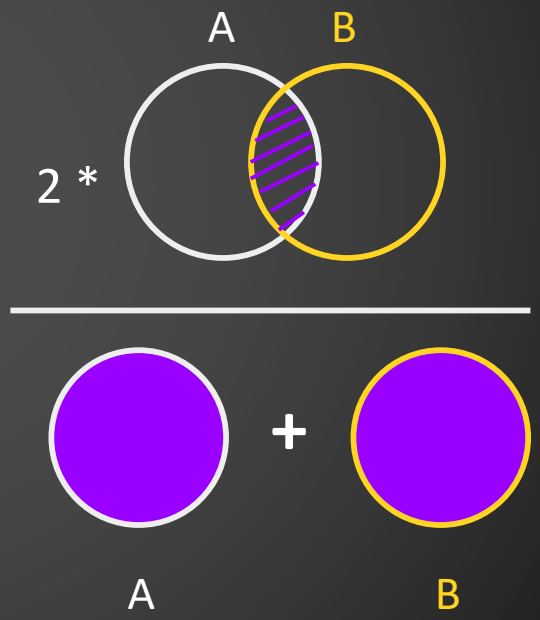
Evaluation Metric and Annotations Considered

Main evaluation metric:

$$\text{Dice-Score} = F_1\text{-Score} = \frac{2|A \cap B|}{|A| + |B|}$$



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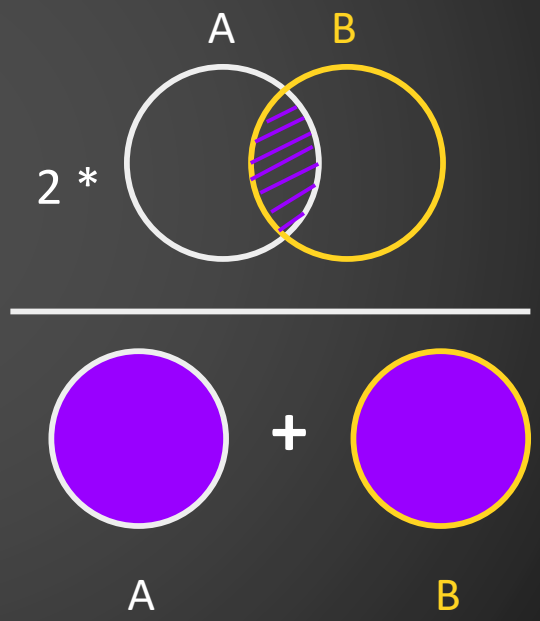

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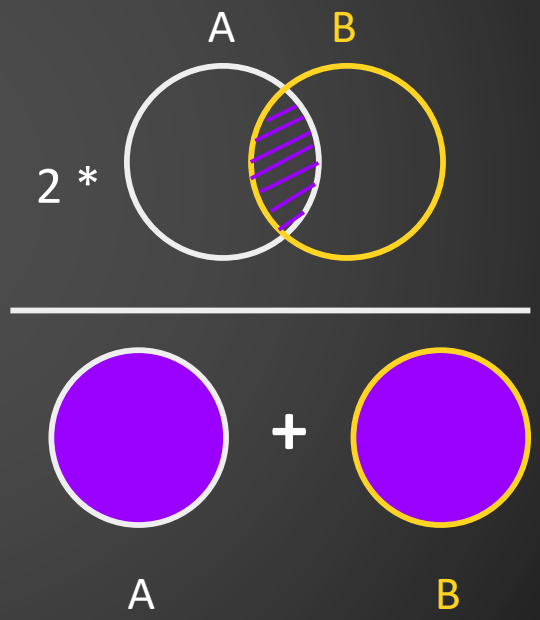
$$\text{Dice-Score} = F_1\text{-Score} = \frac{2|A \cap B|}{|A| + |B|}$$

Weighted average Dice score

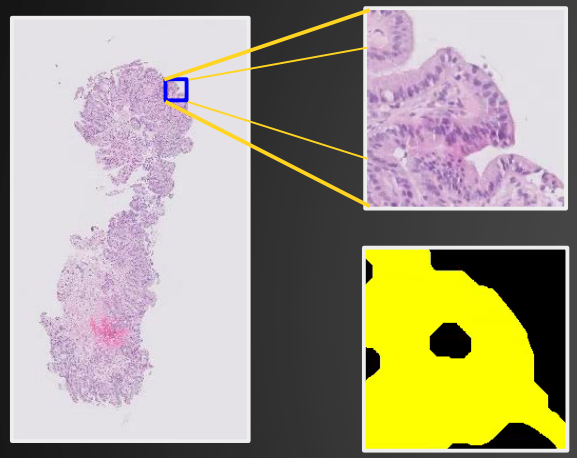
Low Grade Dysplasia vs Background

High Grade Dysplasia vs Background

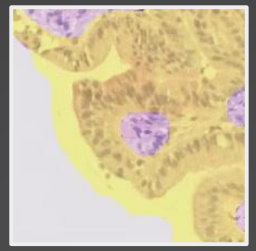


Patch Feeding the Neural Network

Extracted Patch



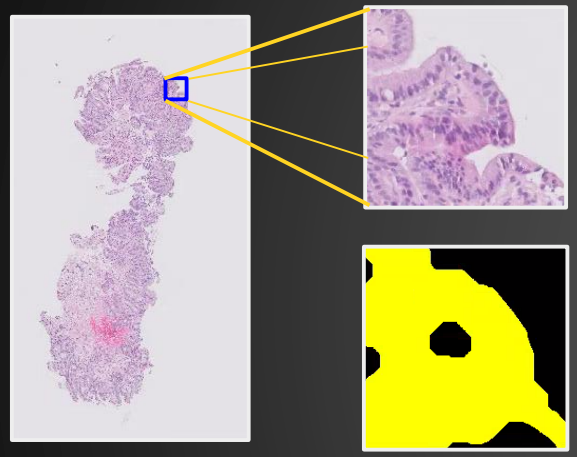
Data Augmentation



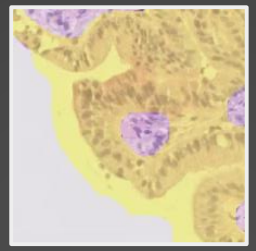
- Rotations
- Flips
- Random Noise
- Random Crops

Patch Feeding the Neural Network

Extracted Patch

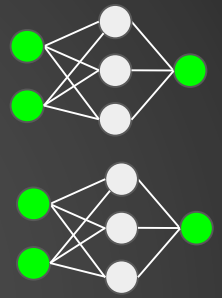


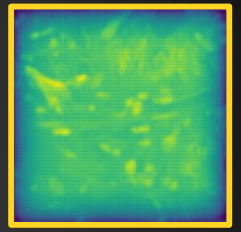
Data Augmentation



- Rotations
- Flips
- Random Noise
- Random Crops

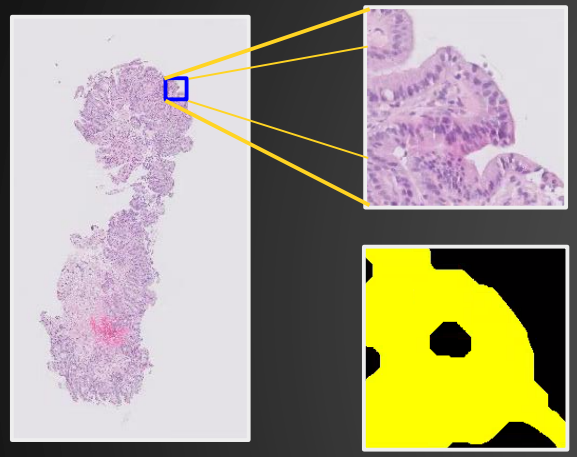
Neural Networks



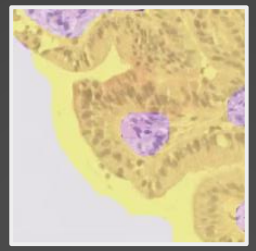


Patch Feeding the Neural Network

Extracted Patch



Data Augmentation



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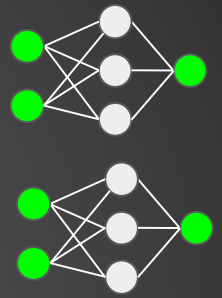
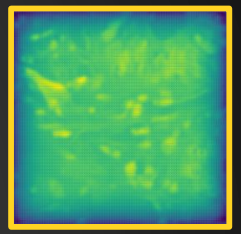
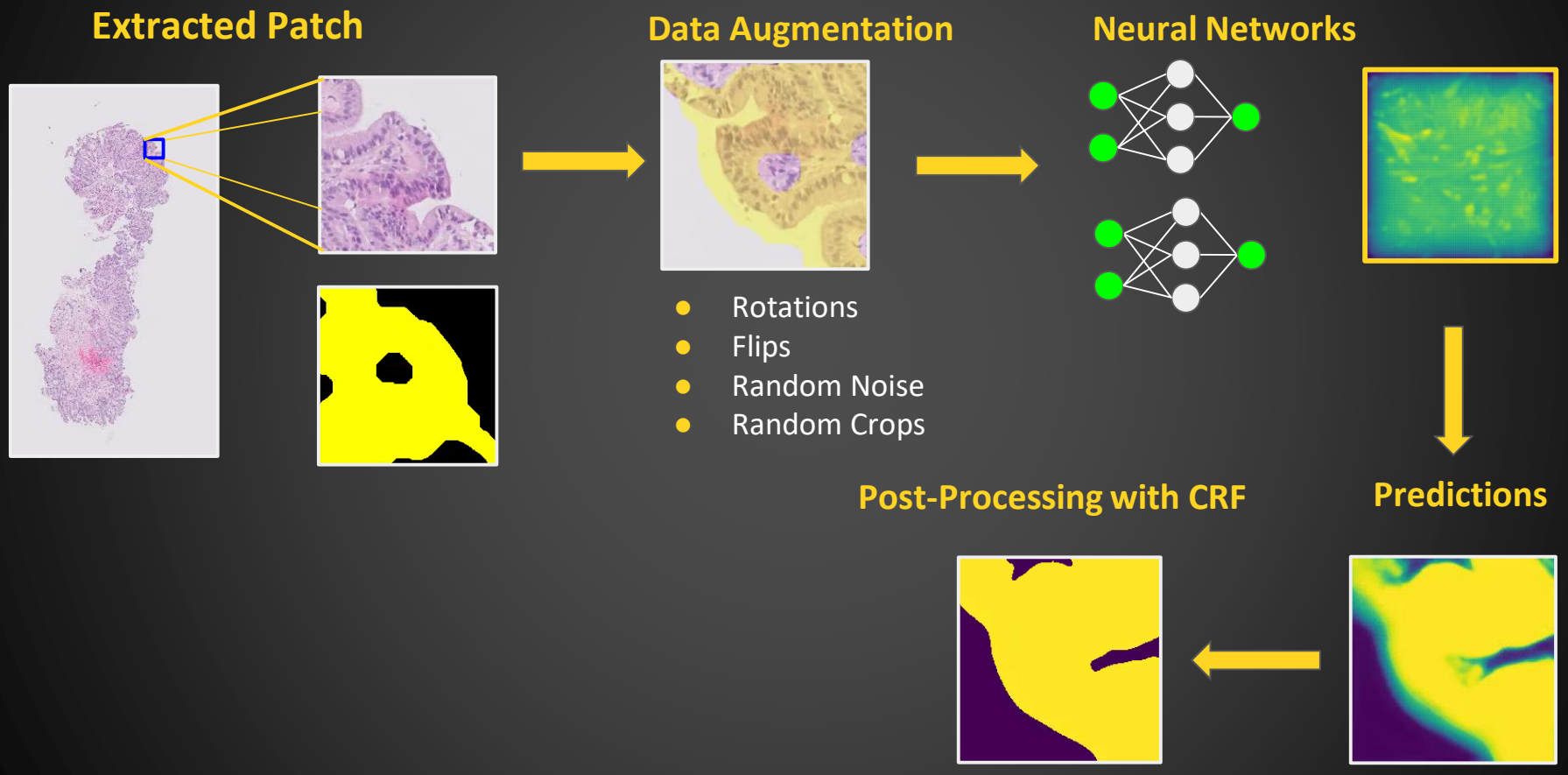


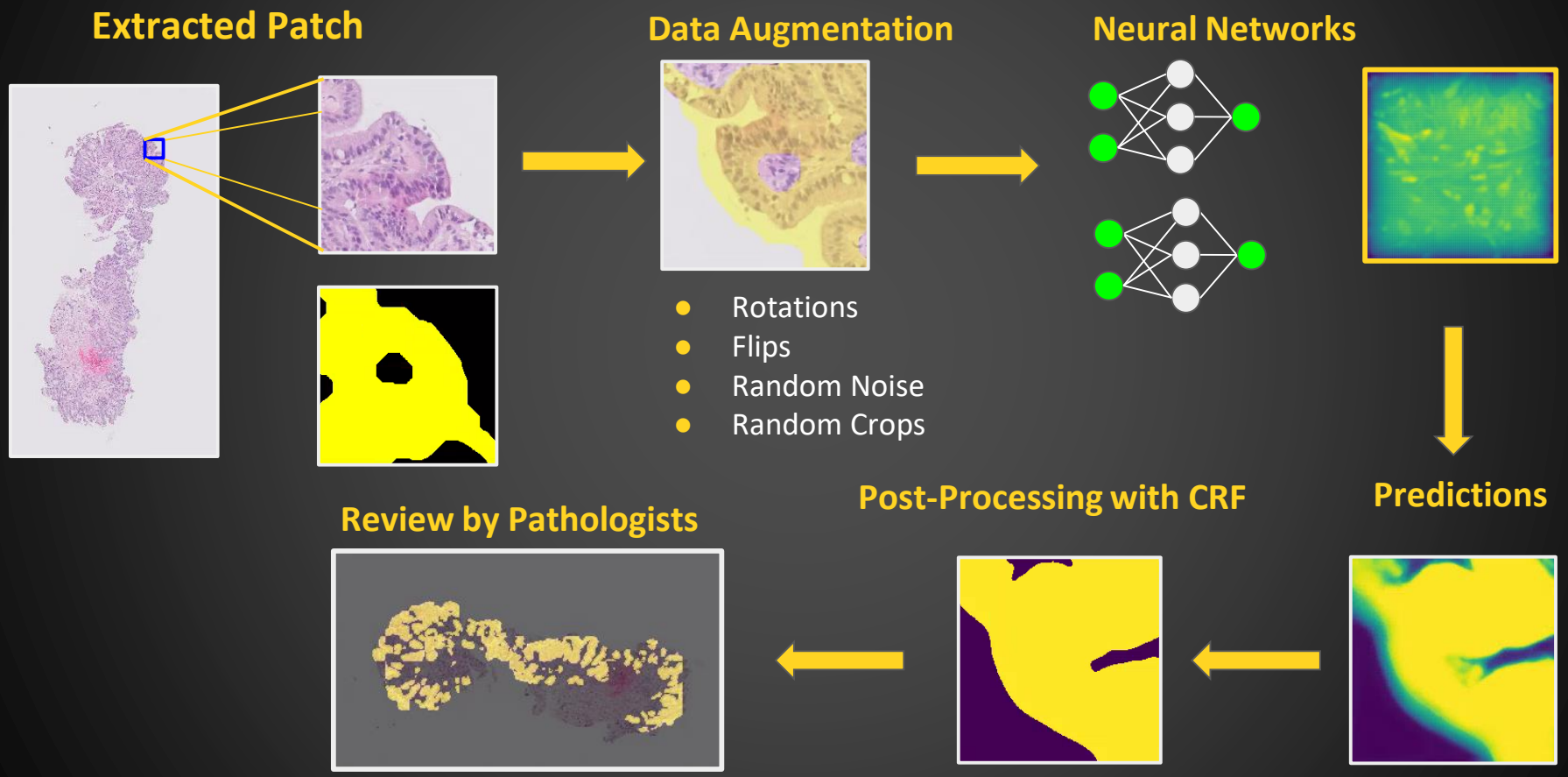


Predictions

Patch Feeding the Neural Network



Patch Feeding the Neural Network

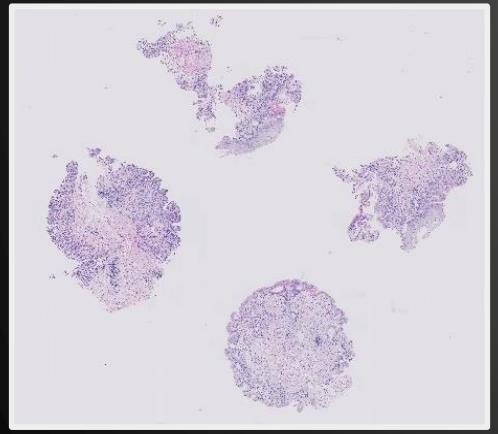


Results: High Grade Dysplasia

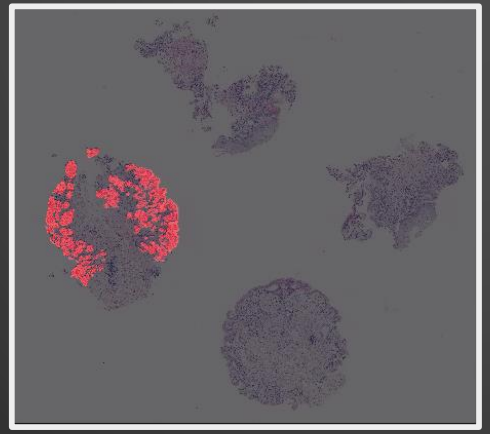
Weighted Dice-Score of **0.83** on the held out set

	F1-Score	Precision	Recall	Pixel-wise accuracy
Background	0.96	0.97	0.95	-
High Grade Dysplasia	0.80	0.76	0.85	-
Weighted Score	0.83	0.8	0.87	0.94

WSI



Mask



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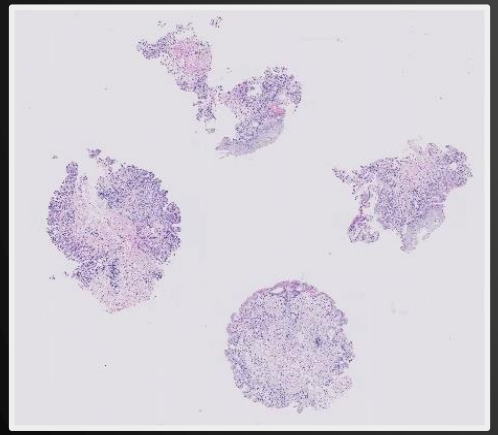

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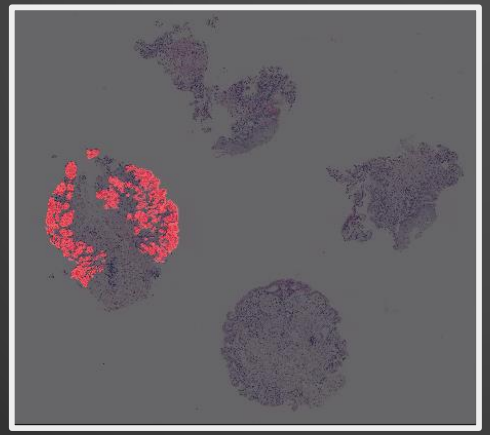
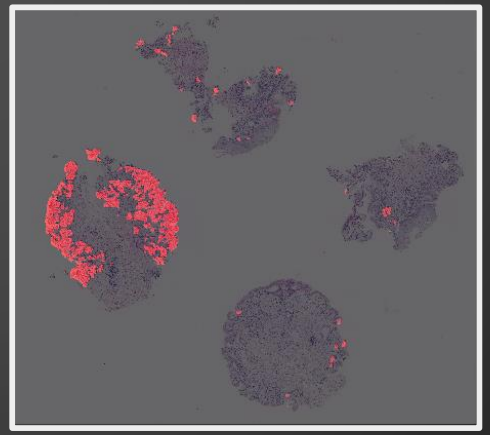


Prediction



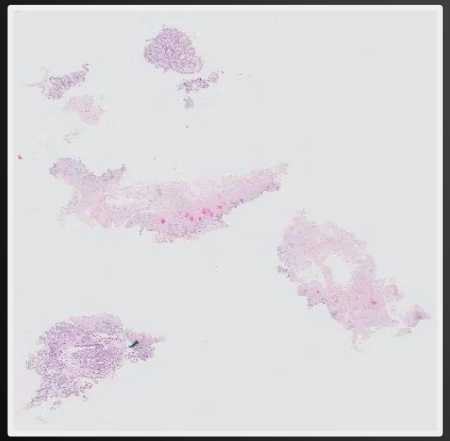
WSI
Weighted Dice-Score:
0.865

Results: Low Grade Dysplasia

Weighted Dice-Score of **0.74** on the held out set

	F1-Score	Precision	Recall	Pixel-wise accuracy
Background	0.91	0.92	0.90	-
Low Grade Dysplasia	0.67	0.64	0.70	-
Weighted Score	0.74	0.72	0.76	0.86

WSI



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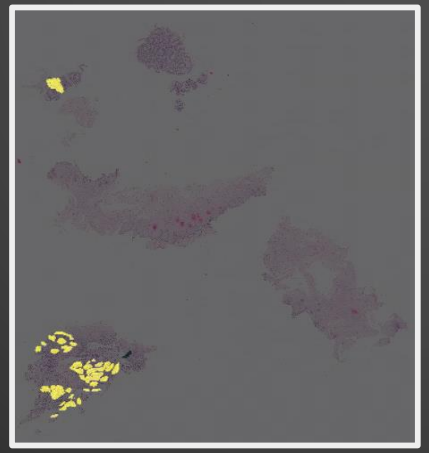

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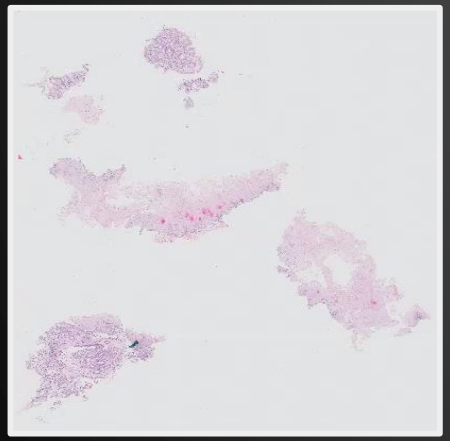

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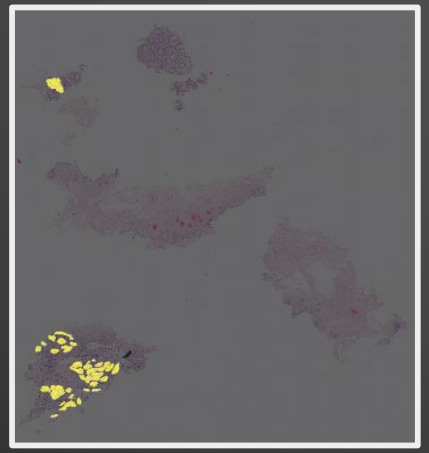
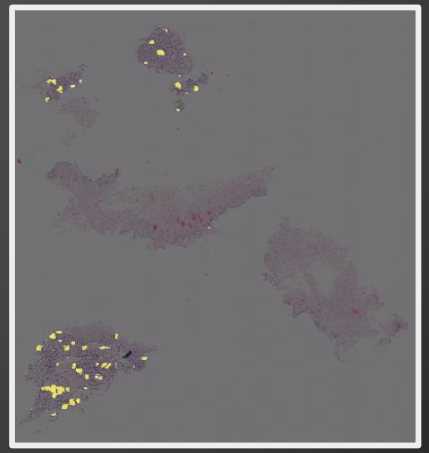


Prediction



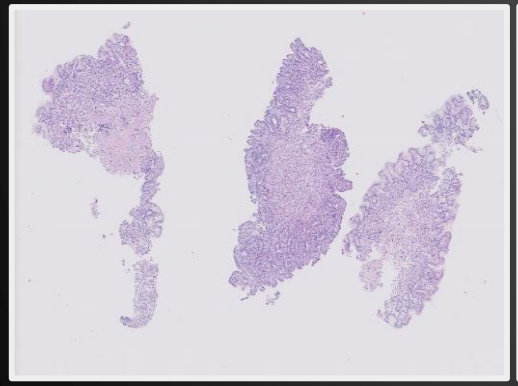
WSI
Weighted Dice-Score:
0.451

Results: Low Grade Dysplasia

Weighted Dice-Score of **0.74** on the held out set

	F1-Score	Precision	Recall	Pixel-wise accuracy
Background	0.91	0.92	0.90	-
Low Grade Dysplasia	0.67	0.64	0.70	-
Weighted Score	0.74	0.72	0.76	0.86

WSI



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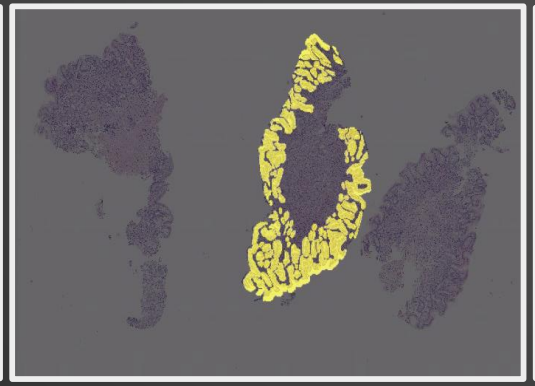
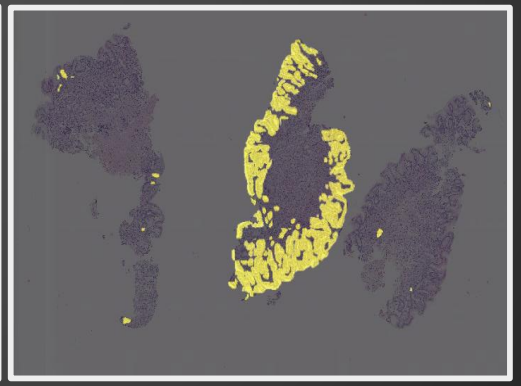


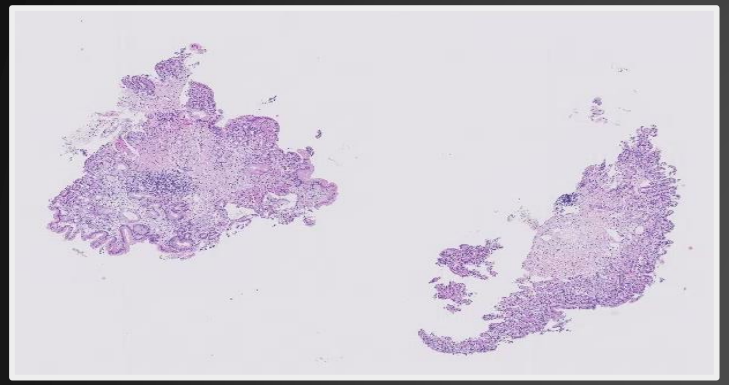
Prediction



WSI
Weighted Dice-Score:
0.94

Variability in the Predictions

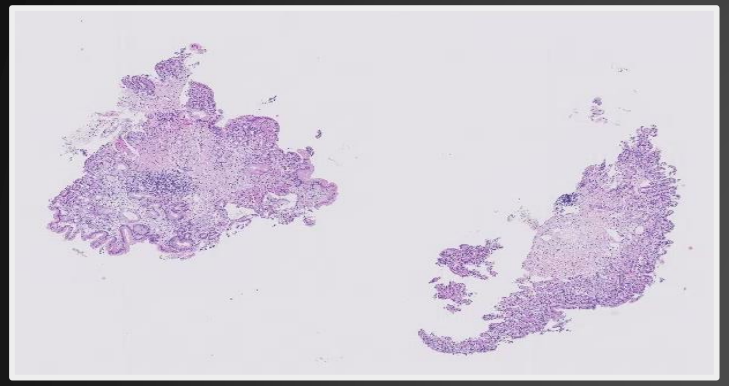
WSI



Mask for High Grade Dysplasia

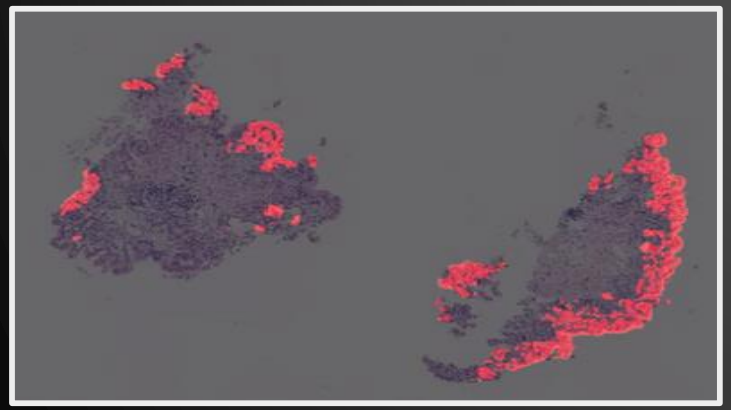
Variability in the Predictions

WSI



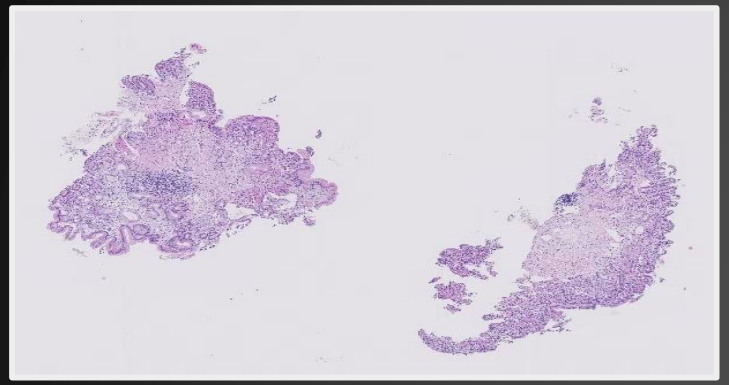
Mask for High Grade Dysplasia

Model Prediction for HGD



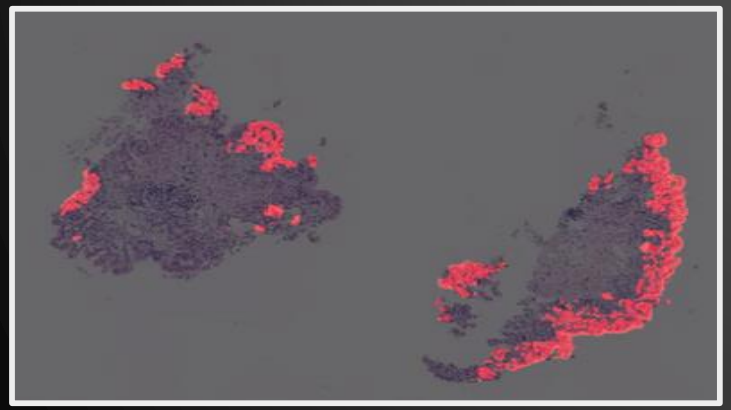
Variability in the Predictions

WSI

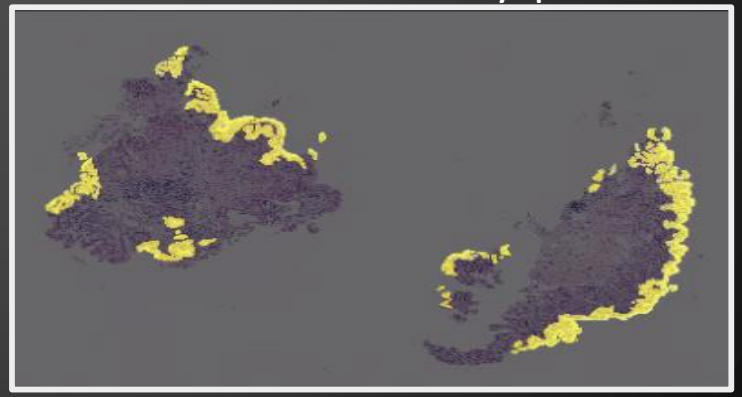


Mask for High Grade Dysplasia

Model Prediction for HGD

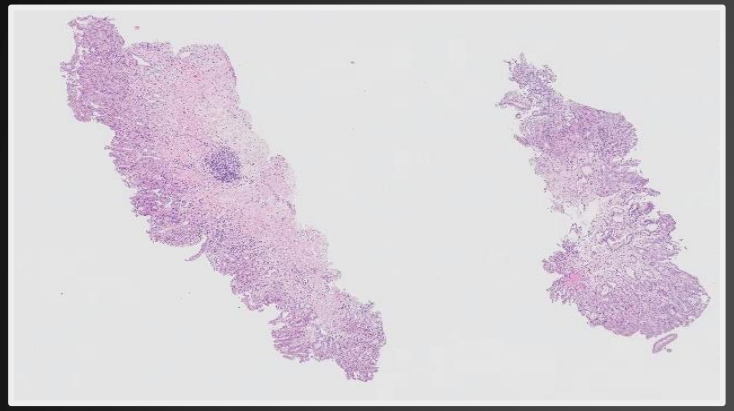


Mask for Low Grade Dysplasia

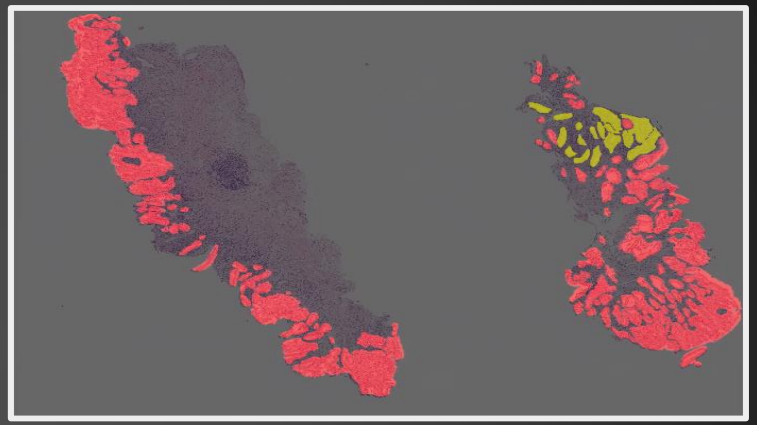


Variability in the Predictions

WSI

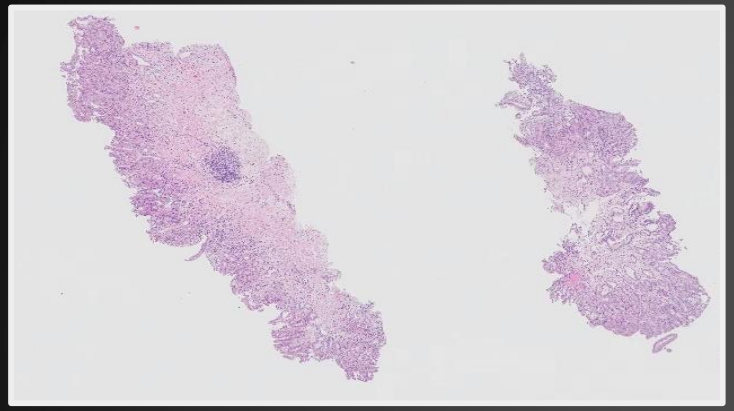


Mask for HGD and LGD



Variability in the Predictions

WSI



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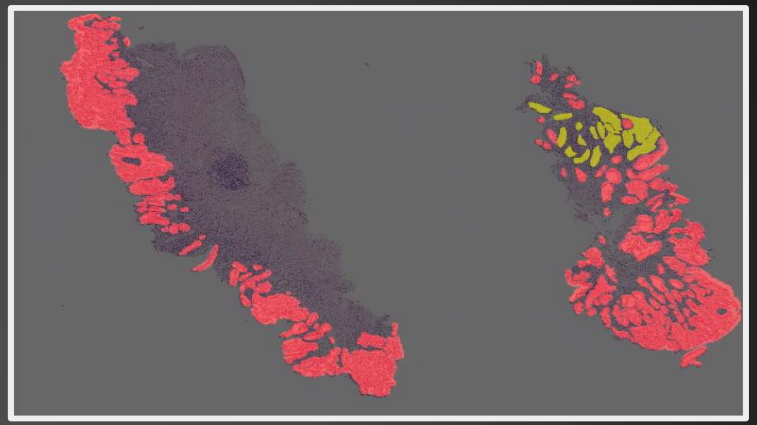
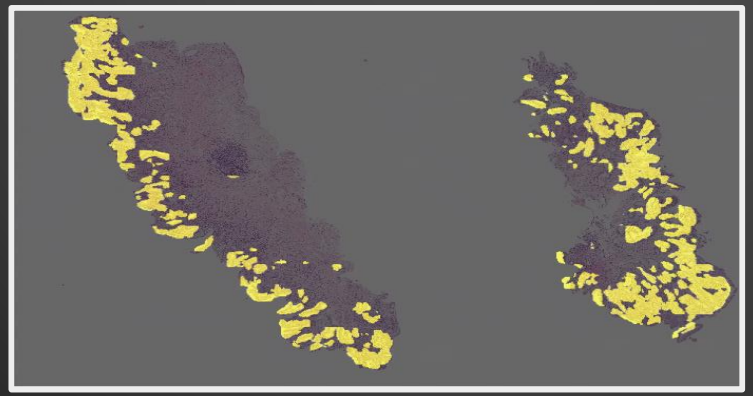


Model Prediction for LGD



Summarization

Good results with the models trained on HGD

Both models make a lot of false positives

The models have more uncertainty regarding LGD

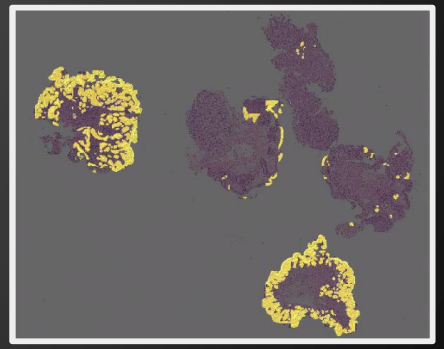
Summarization

Good results with the models trained on HGD

Both models make a lot of false positives

The models have more uncertainty regarding LGD

Visually Useful Predictions



Improvements

Annotations could be coarse

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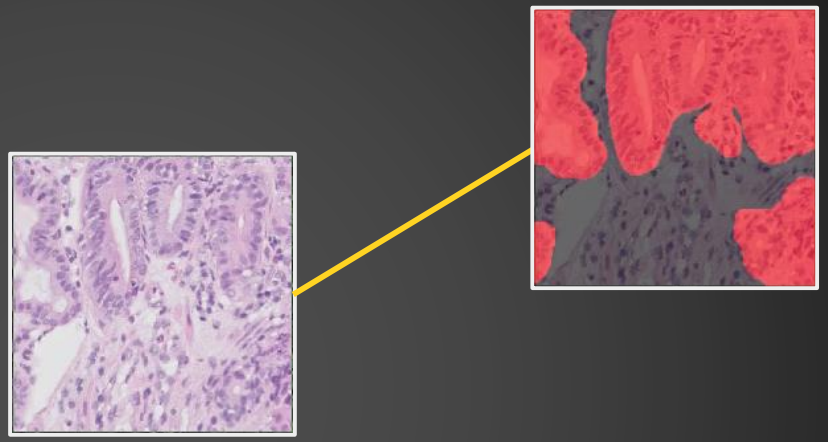

Mask

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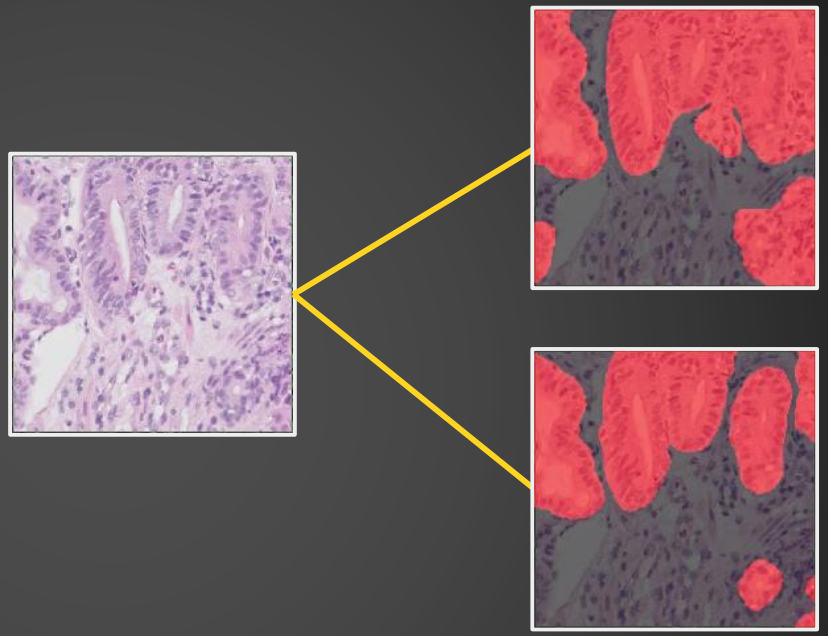


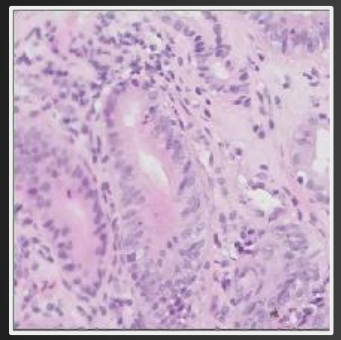
Mask

Prediction

Improvements

Annotations could be coarse

Patch



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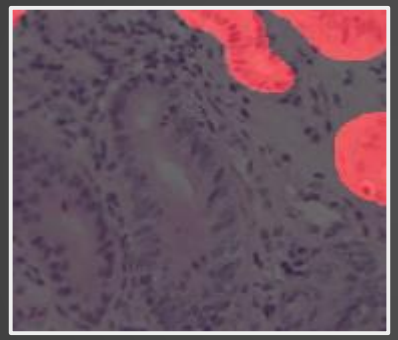

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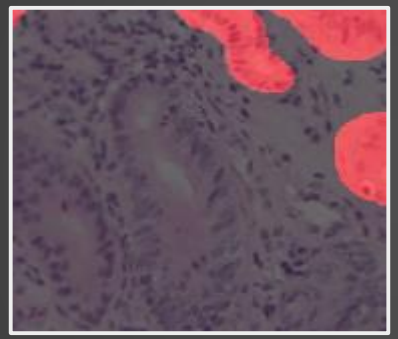

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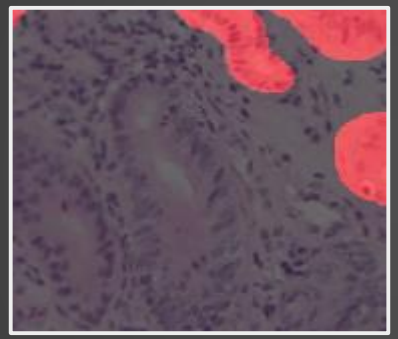
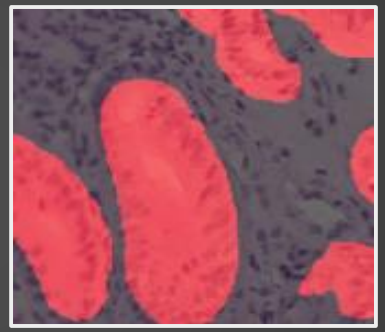


Prediction



Improvements

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Patch

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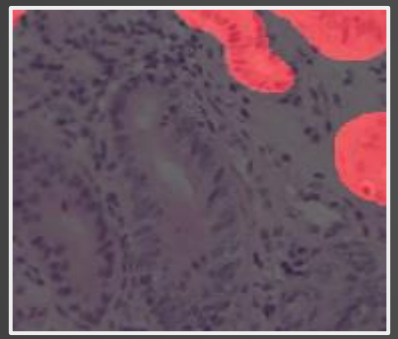
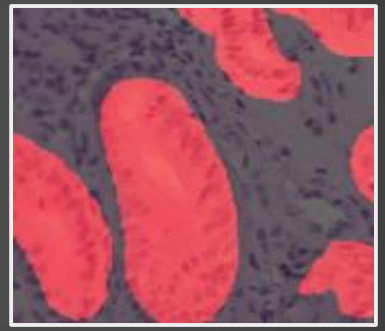


Prediction



More data!

Multiple annotators to isolate regions of interest: Inject Expert Knowledge

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Acknowledgments

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Amsterdam University Medical Center

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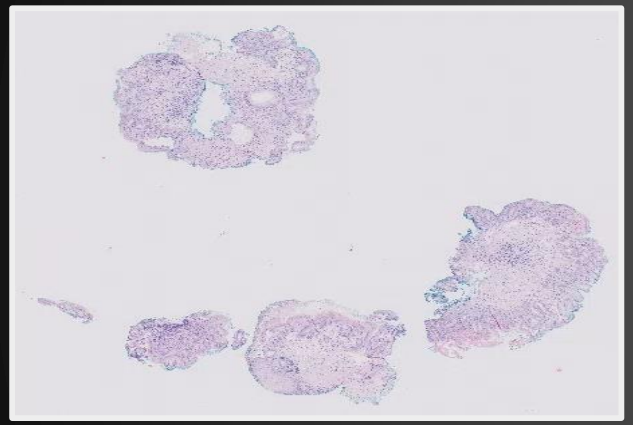
Myrtle van der Wel
Onno de Boer
Sybren Meijer

THE END

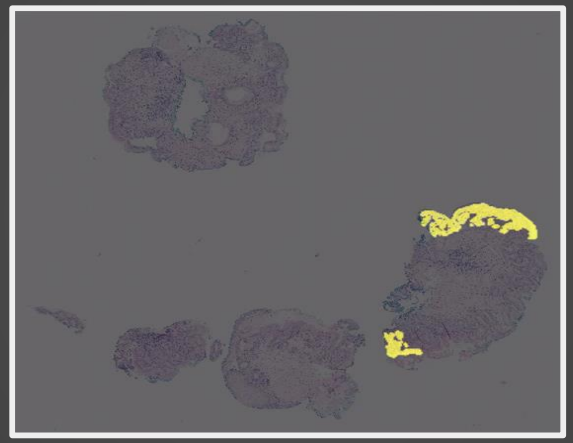
UNUSED SLIDES

Variability in the Predictions

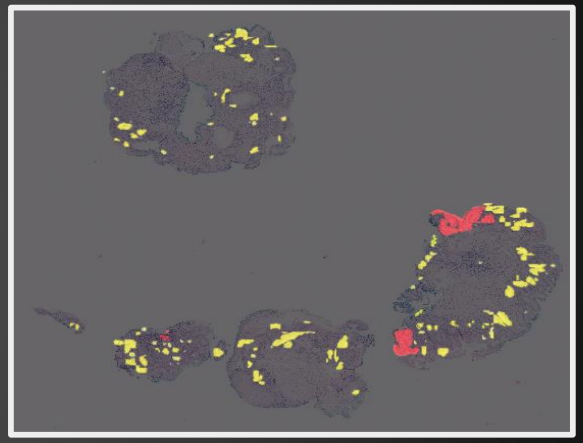
WSI



Mask for HGD and LGD

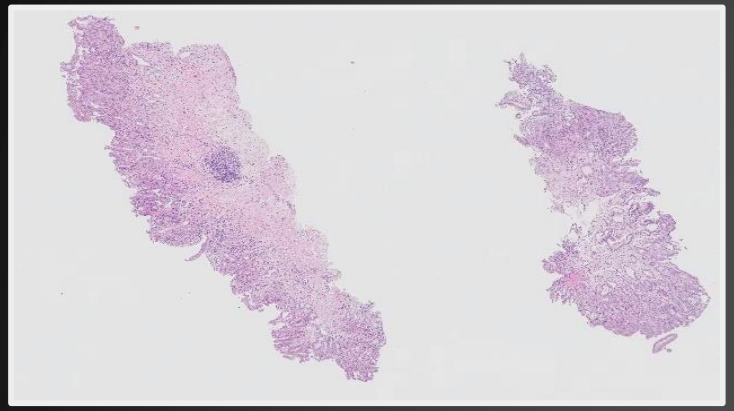


Prediction

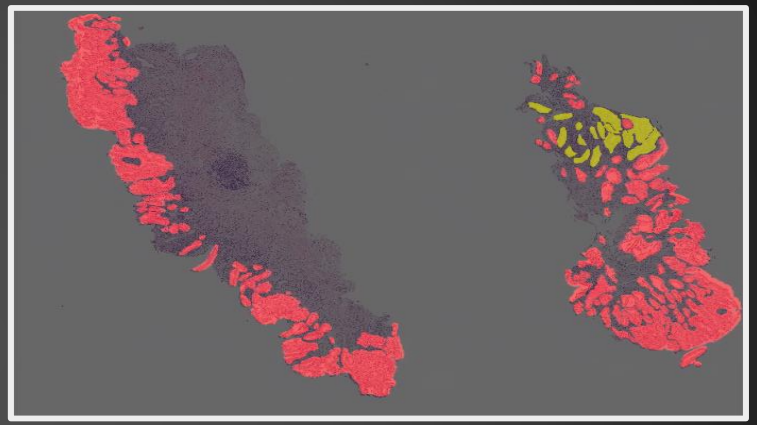


Variability in the Predictions

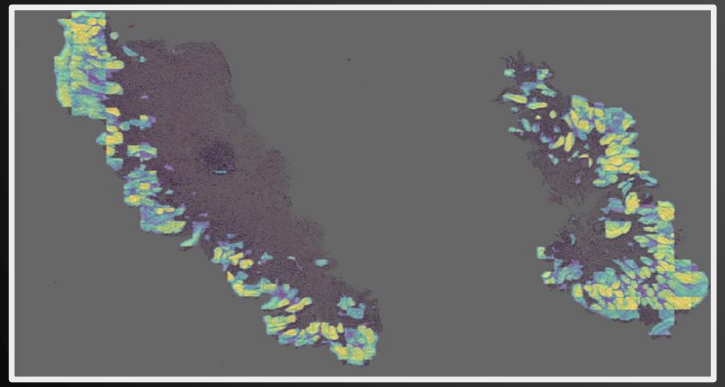
WSI



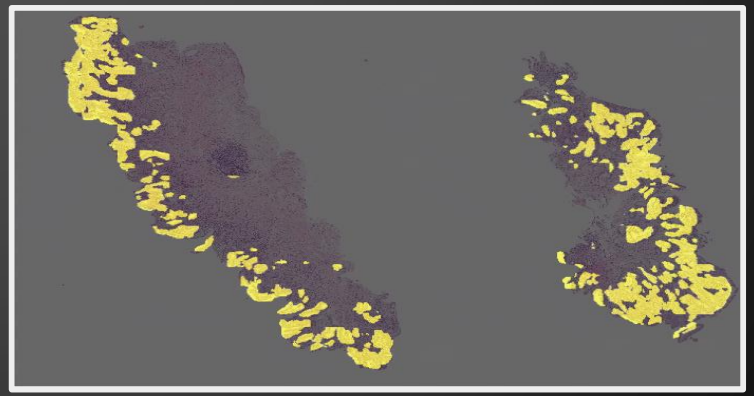
Mask for HGD and LGD



Probabilities for LGD



Thresholded Prediction for LGD

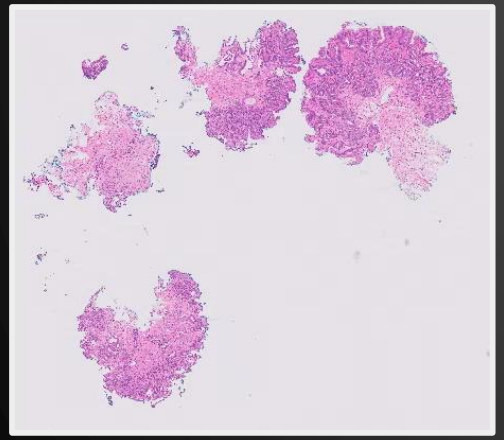


Results: High Grade Dysplasia

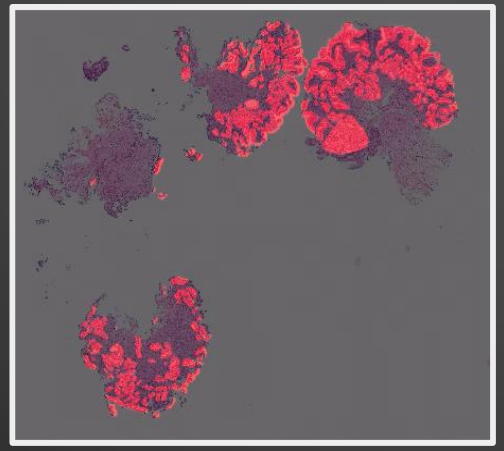
Weighted Dice-Score of **0.83** on the held out set

	F1-Score	Precision	Recall	Pixel-wise accuracy
Background	0.96	0.97	0.95	-
High Grade Dysplasia	0.80	0.76	0.85	-
Weighted Score	0.83	0.8	0.87	0.94

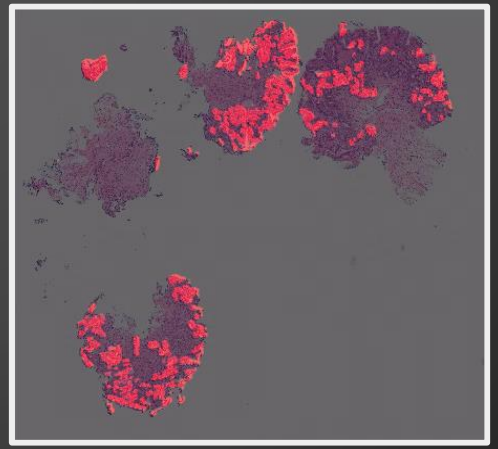
WSI



Mask

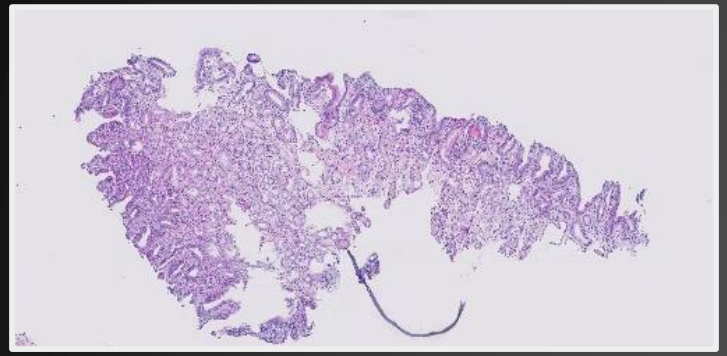


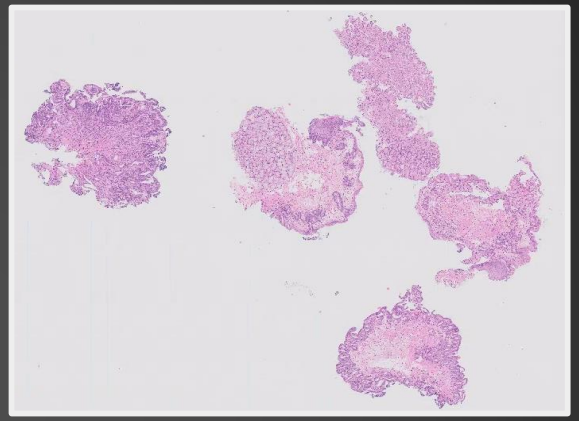
Prediction

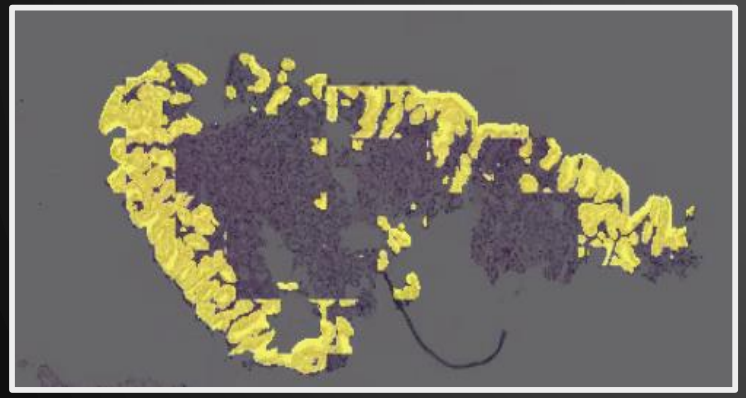


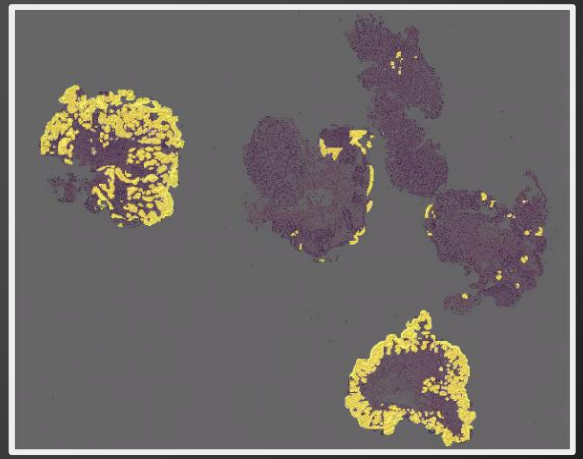
WSI
Weighted Dice-score:
0.754

Remarks



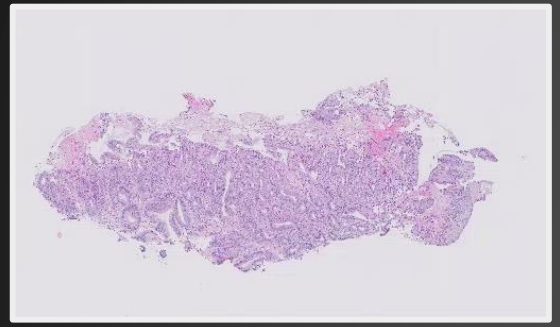




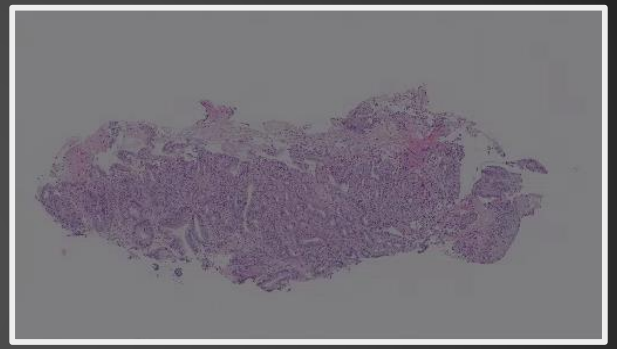


Variability in the Predictions

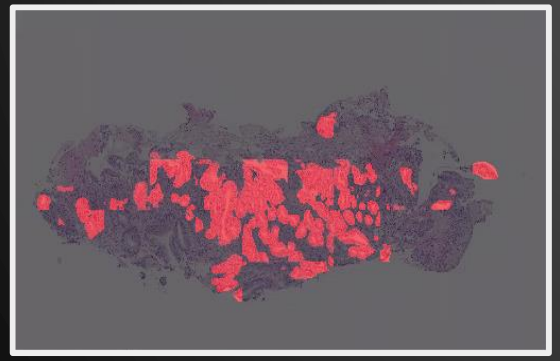
WSI



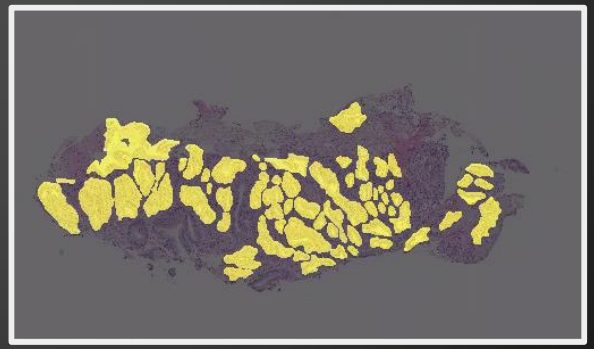
Mask for High Grade Dysplasia



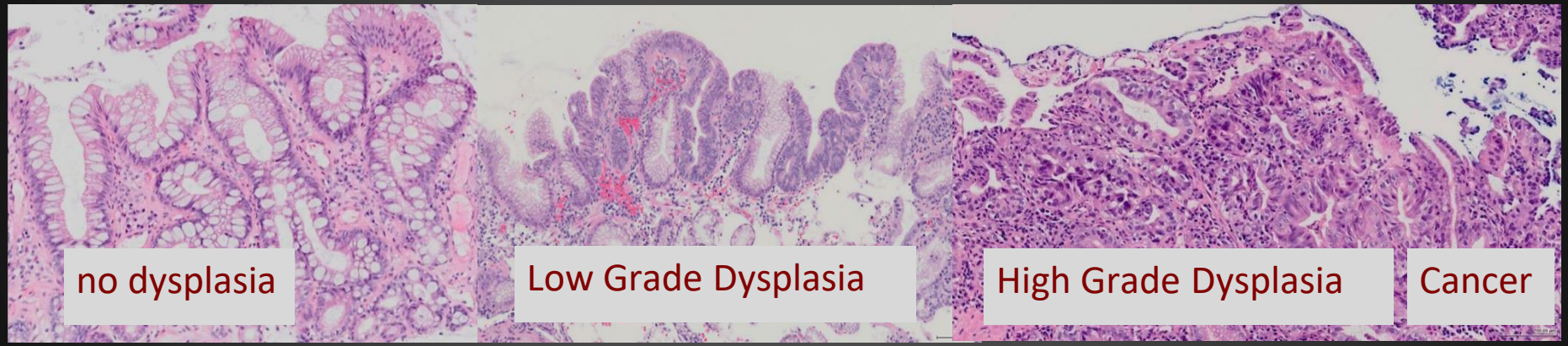
Model Prediction



Mask for Low Grade Dysplasia



Metasplasia - Dysplasia to Adenocarcinoma Sequence



Hvid-Jensen F. NEJM 2011, de Jonge P. Gut 2014; Dutch Barrett guideline

Aim of Study

Reliable and Reproducible diagnosis of dysplasia in patients with Barrett's Esophagus

Deep Learning Methods with promising results in

- Brain Tumor Detection

Hao Dong et al, automatic Brain Tumor Detection and Segmentation Using U-net Based Fully Convolutional Networks, CoRR 2018

- Diabetic Retinopathy classification

S.M.S Islam et al, Deep Learning based Early Detection and grading of Diabetic Retinopathy Using Retinal Fundus Images, MIND, 2019

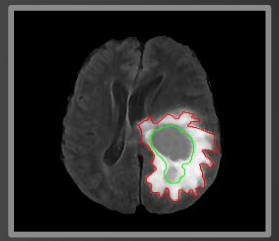
- Detecting breast cancer metastasis (Camelyon16/17)

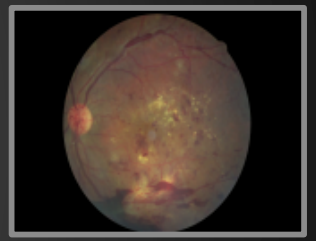
Yun Liu et al, Artificial intellignece-Based Brast cancer Nodal metastasis Detection, APLM, 2018

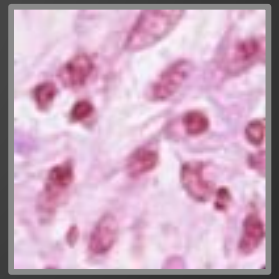
Ehsteshami Bejnordi et al., Diagnostic Assessment of Deep Learning Algorithms for Detection of Lymph Node Metastases in Women with Breast Cancer, JAMA, 318(22), 2199-2210, 2017

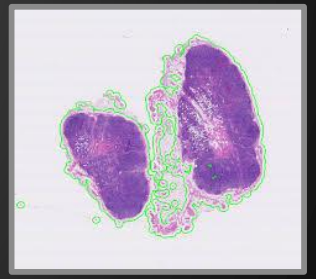
- Microscopic nuclei classification

Md. Z. Alom et al., Microscopic Nuclei Classification, Segmenation and Detection with improved Deep Convolutional Neural Network Approaches, 2018









Lack of research in the segmentation of dysplasia - carcinoma sequence in Barrett's Esophagus

The Neural Network

U-Net Architecture

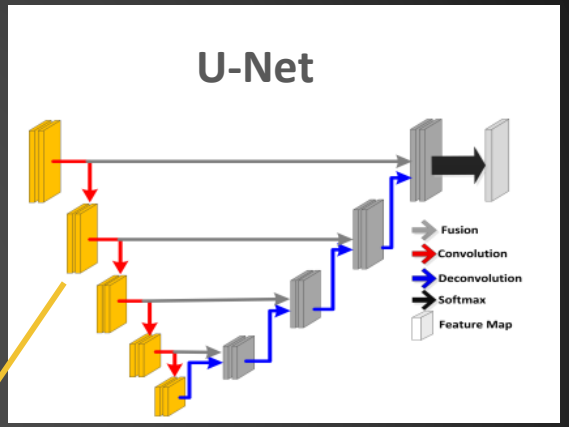
- Encoding done by DenseNet-161 and ResNet-50

Gao Huang et al., Densely Connected Convolutional Networks, CoRR, 2016

Kaiming He et al., Deep Residual Learning for Image Recognition, CoRR, 2015

Ensemble of 10 Imagenet pre-trained U-nets

- 5 networks based on DenseNet-161
- 5 networks based on ResNet-50



Encoding

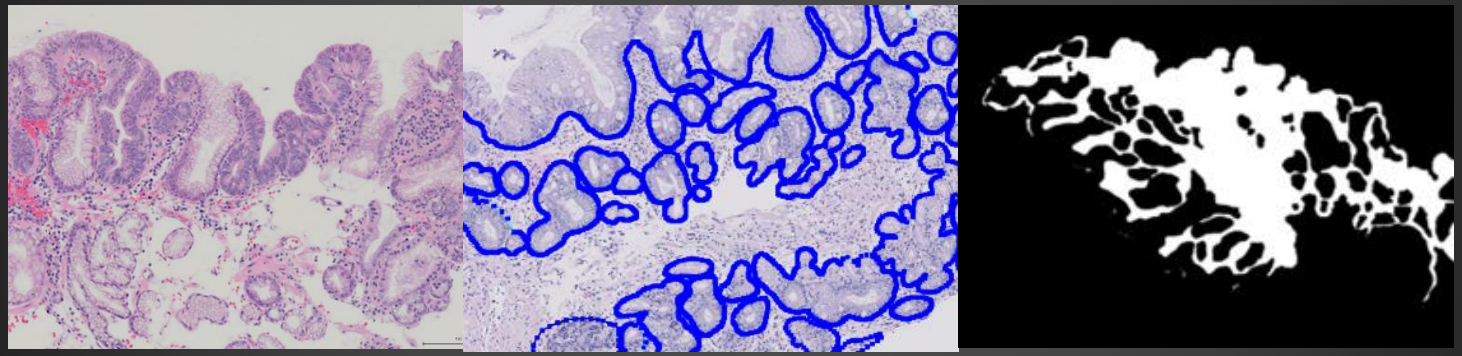
Qikui Zhu et al., Deeply-Supervised CNN for Prostate Segmentation, CoRR, 2018

Olaf Ronneberger et al., U-Net Convolutional Networks for Biomedical Image Segmentation, CoRR, 2015

Cross Entropy Loss and Focal Loss

Tsung Yi Lin et al., Focal Loss for Dense Object Detection, CoRR, 2017

Annealed Learning rate between 2e-5 and 8e-5



Results: Full Dysplasia

Weighted Dice-Score of **0.77** on the held out set

	F1-Score	Precision	Recall	Pixel-wise accuracy
Background	0.95	0.99	0.91	-
Dysplasia	0.69	0.56	0.90	-
Weighted Score	0.77	0.69	0.90	0.91