A new auto-annotation method and machine learning strategy fordetection and annotation of cancer areas in prostate biopsies

- **L.Björk**[1,2], J.Gustafsson[3], F.HikmetNoraddin[3], K.Eurèn[2], C.Lindskog[3]

- [1]Karolinska Institutet, Sweden, [2]Contextvision, Sweden,[3]UppsalaUniversitet, Sweden

Prostate cancer

- The second most common cancer in men worldwide
- 1/7 men will be diagnosed with prostate cancer
- 1.3 million patients in Europe and 1 million in the US undergoing biopsies every year
- Inter-observer variability in Gleason scoring is high

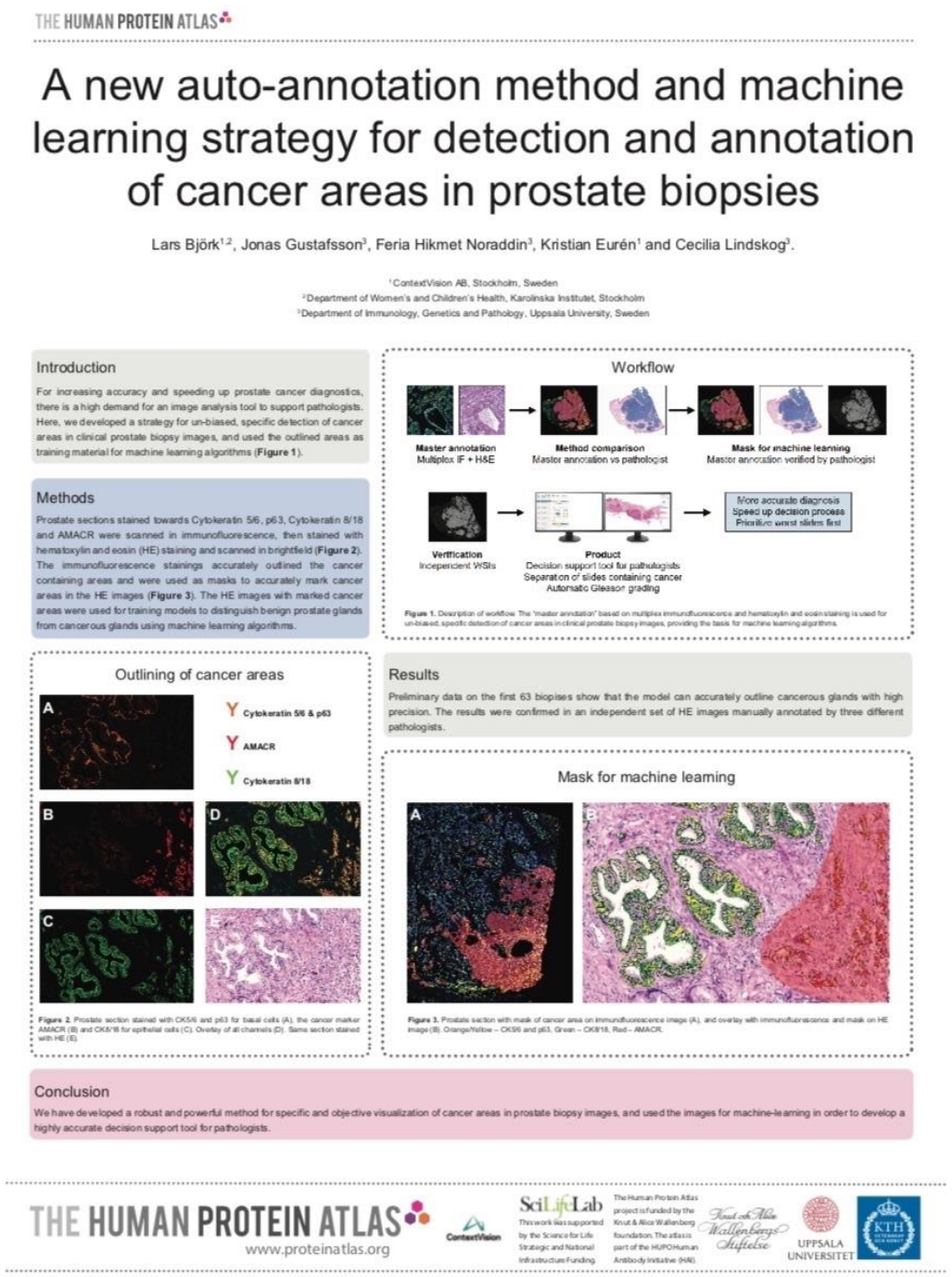
→ Major bottleneck in pathology workflow
→ Risk of therapeutic decision errors

Challenge

Implementation of an automated image analysis algorithm to serve as a decision support tool for pathologists.

Aim of study

Develop a strategy for highly specific detection and outlining of cancer areas in clinical biopsy whole slide images (WSI's), which will serve as training material for Machine-Learning algorithms.



THE HUMAN PROTEIN ATLAS

A new auto-annotation method and machine learning strategy for detection and annotation of cancer areas in prostate biopsies

Lars Björk[1,2], Jonas Gustafsson[3], Feria Hikmet Noraddin[3], Kristian Eurén[1] and Cecilia Lindskog[3].

[1]ContextVision AB, Stockholm, Sweden
[2]Department of Women's and Children's Health, Karolinska Institutet, Stockholm
[3]Department of Immunology, Genetics and Pathology, Uppsala University, Sweden

Introduction

For increasing accuracy and speeding up prostate cancer diagnostics, there is a high demand for an image analysis tool to support pathologists. Here, we developed a strategy for un-biased, specific detection of cancer areas in clinical prostate biopsy images, and used the outlined areas as training material for machine learning algorithms (**Figure 1**).

Methods

Prostate sections stained towards Cytokeratin 5/6, p63, Cytokeratin 8/18 and AMACR were scanned in immunofluorescence, then stained with hematoxylin and eosin (HE) staining and scanned in brightfield (**Figure 2**). The immunofluorescence stainings accurately outlined the cancer containing areas and were used as masks to accurately mark cancer areas in the HE images (**Figure 3**). The HE images with marked cancer areas were used for training models to distinguish benign prostate glands from cancerous glands using machine learning algorithms.

Workflow

Master annotation
Multiplex IF + H&E

Method comparison
Master annotation vs pathologist

Mask for machine learning
Master annotation verified by pathologist

Verification
Independent WSIs

Product
Decision support tool for pathologists
Separation of slides containing cancer
Automatic Gleason grading

More accurate diagnosis
Speed up decision process
Prioritize worst slides first

Figure 1. Description of workflow. The 'master annotation' based on multiplex immunofluorescence and hematoxylin and eosin staining is used for un-biased, specific detection of cancer areas in clinical prostate biopsy images, providing the basis for machine learning algorithms.

Outlining of cancer areas

A
B
C
D
E

Y Cytokeratin 5/6 & p63
Y AMACR
Y Cytokeratin 8/18

Figure 2. Prostate section stained with CK5/6 and p63 for basal cells (A), the cancer marker AMACR (B) and CK8/18 for epithelial cells (C). Overlay of all channels (D). Same section stained with HE (E).

Results

Preliminary data on the first 63 biopsies show that the model can accurately outline cancerous glands with high precision. The results were confirmed in an independent set of HE images manually annotated by three different pathologists.

Mask for machine learning

A
E

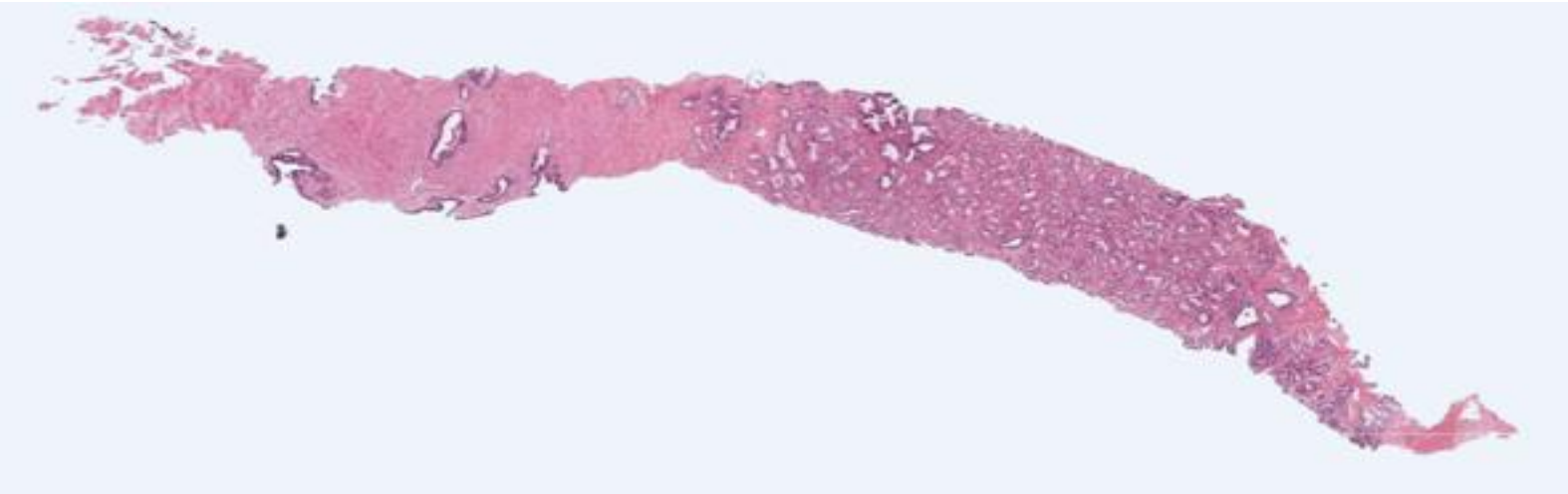
Figure 3. Prostate section with mask of cancer area on immunofluorescence image (A), and overlay with immunofluorescence and mask on HE image (B). Orange/Yellow – CK5/6 and p63, Green – CK8/18, Red – AMACR.

Conclusion

We have developed a robust and powerful method for specific and objective visualization of cancer areas in prostate biopsy images, and used the images for machine-learning in order to develop a highly accurate decision support tool for pathologists.

THE HUMAN PROTEIN ATLAS
www.proteinatlas.org
ContextVision
SciLifeLab
This work was supported by the Science for Life Strategic and National Infrastructure Funding.
The Human Protein Atlas project is funded by the Knut & Alice Wallenberg foundation. The atlas is part of the HUPO Human Antibody Initiative (HAI).
Knut och Alice Wallenbergs Stiftelse
UPPSALA UNIVERSITET
KTH

INIFY™ - Prostate



PROSTATE BIOPSY

→ Benign
vs
Malignant

NOTE; INIFY™ Prostate is an investigational device, not yet CE-marked for clinical use

Why use a decision support tool?

Potential:

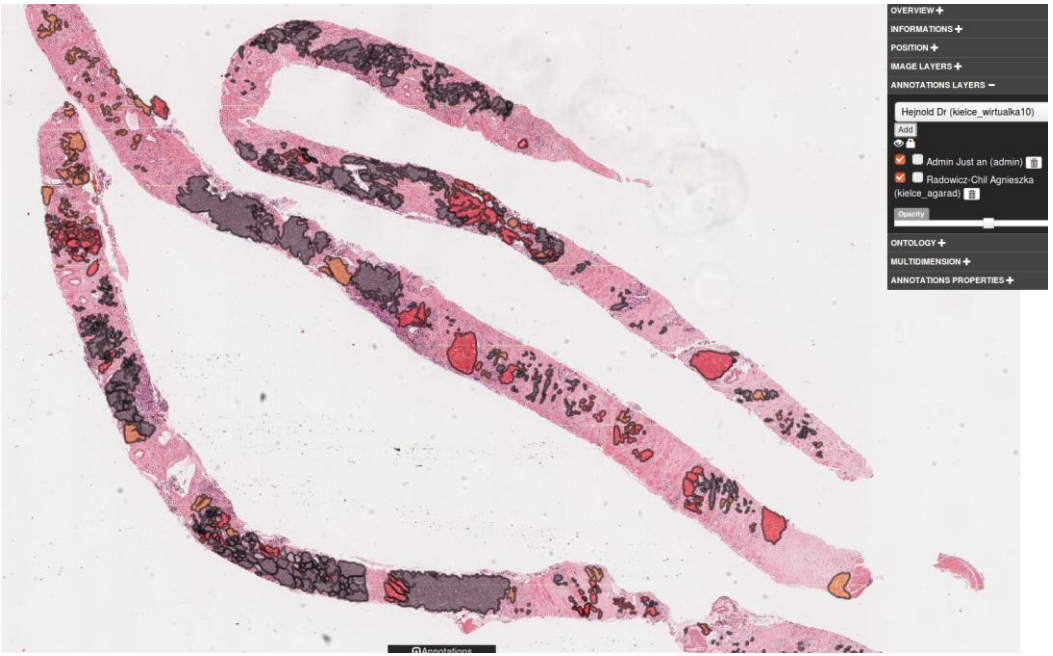
1. Reduce time for diagnosis
2. Minimize intra- and inter-individual variation
3. Increase accuracy and precision
4. Reduce Overall Work load for the Pathologist

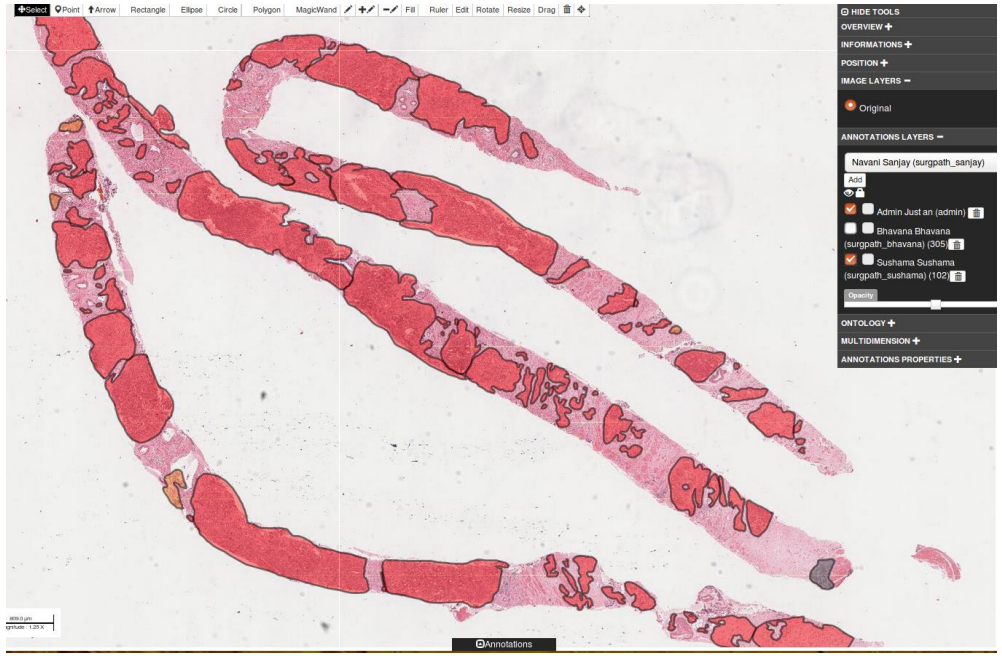
Ground truth for training of algorithm?

When the intra- and inter-individual variation is high

In machine learning, the term "ground truth" refers to the accuracy of the training set's classification for supervised learning techniques.

Inter-individual variations in annotation





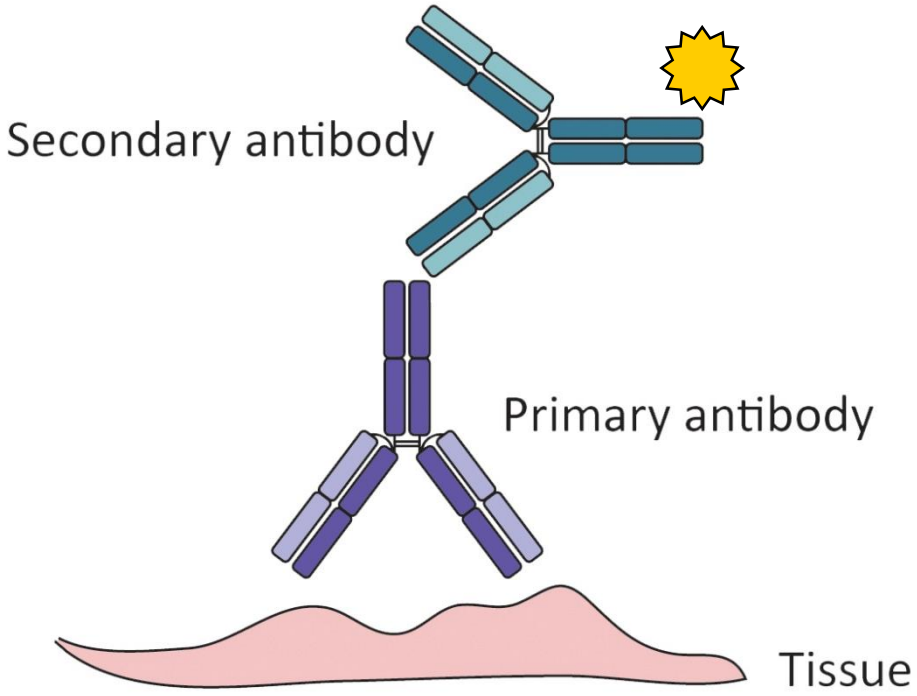
Goodman et al

Frequency of disagreement and error in Gleason scores, the kappa values reflecting agreement between the pathology reports and the “gold standard,” were 0.61 for biopsies (0 = pure chance 1= complete agreement 0.80 =very good agreement)

Brimo et.al

A major discrepancy in Gleason score was present in 14.7%, defined as a change to a different risk category

High-throughput immunostaining

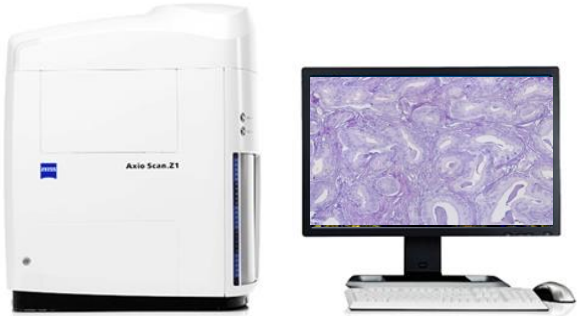


Alexa 488
Alexa 555
Alexa 633

KRT5/6 (basal cells)
KRT8/18 (epithelial cells)
AMACR (cancer marker)

Human prostate cancer sections

Workflow

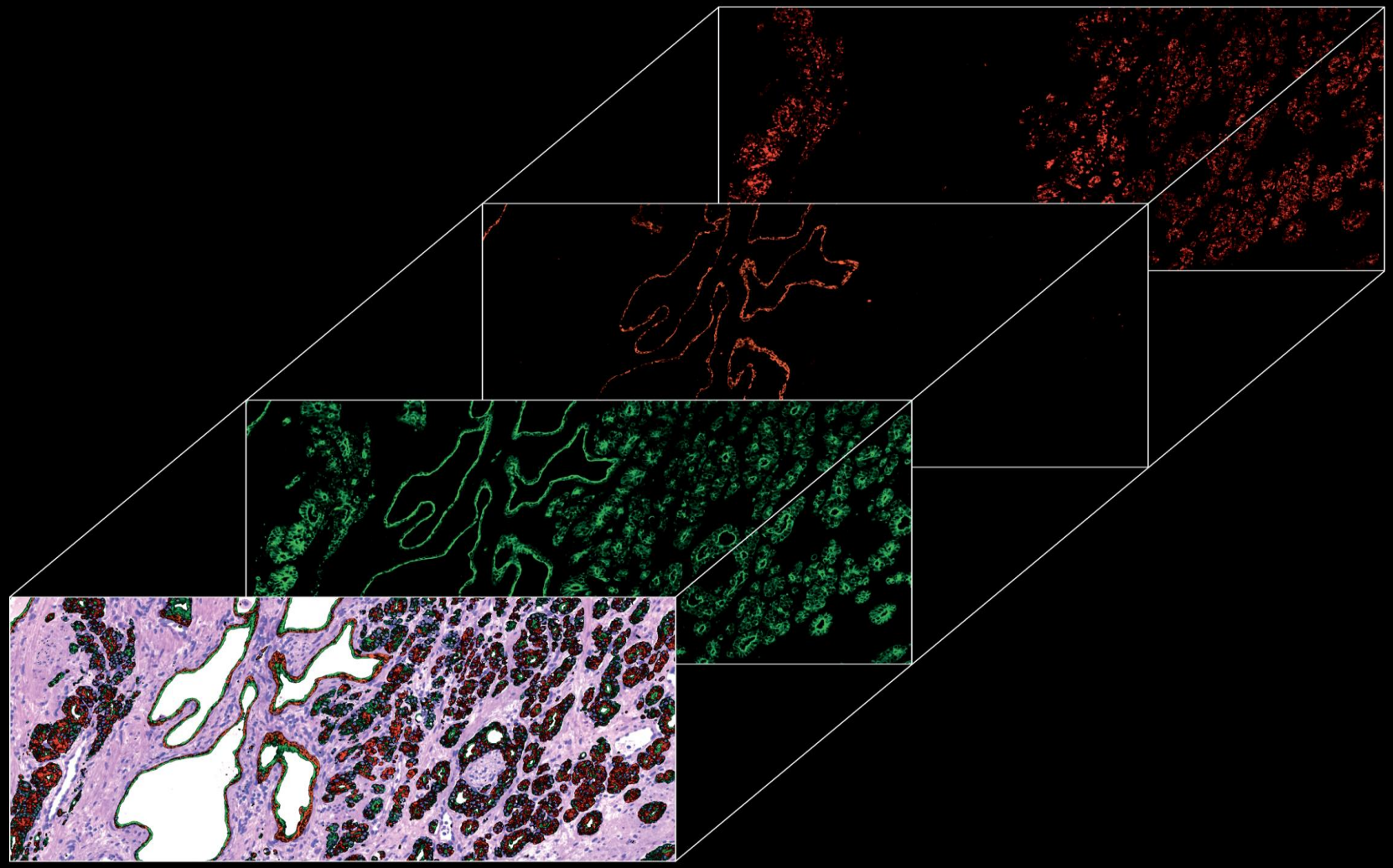


High-throughput immunostaining of prostate cancer sections

Immunofluorsescence scanning

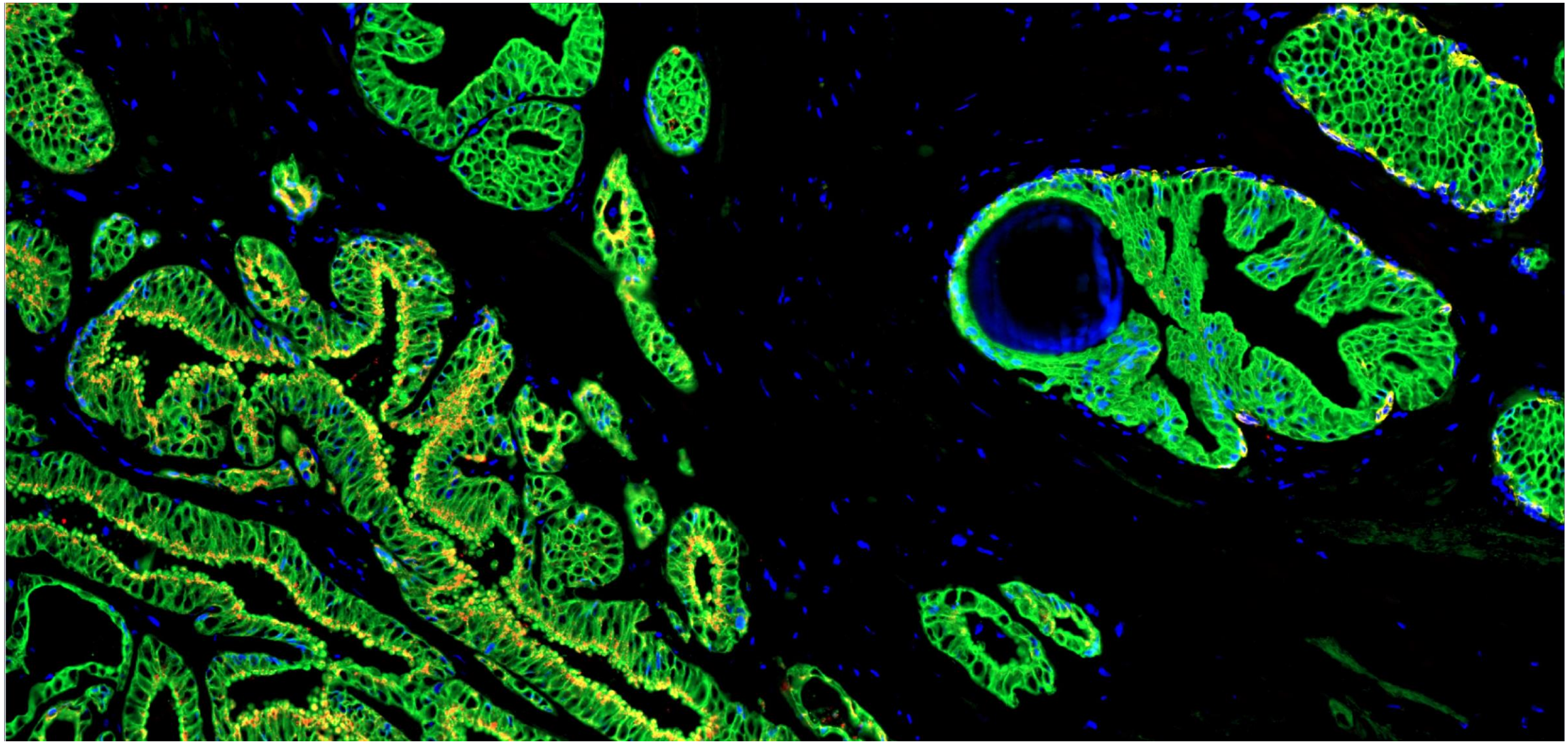
Detachment of coverslip
High-throughput H&E staining

Brightfield scanning

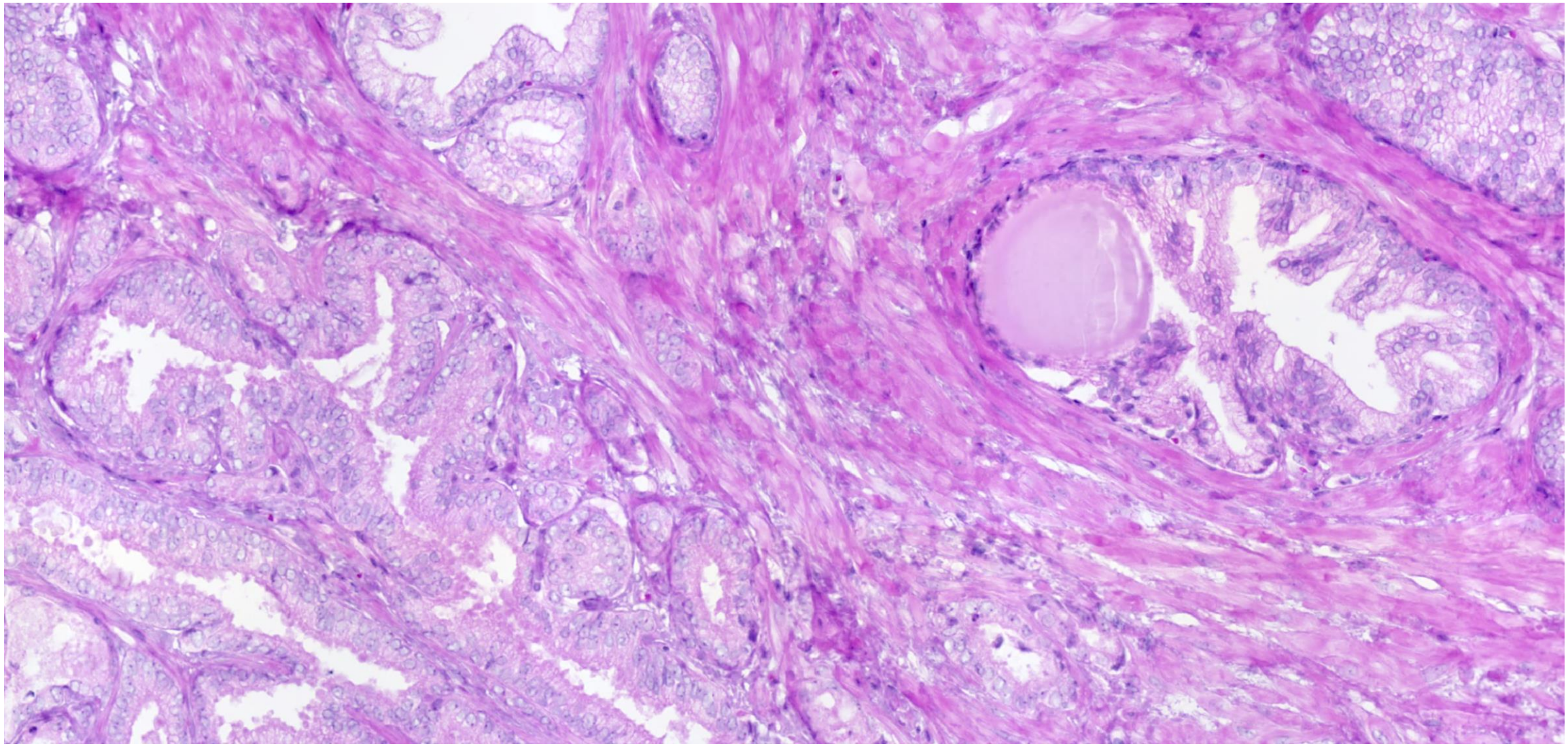


Fluourescence image

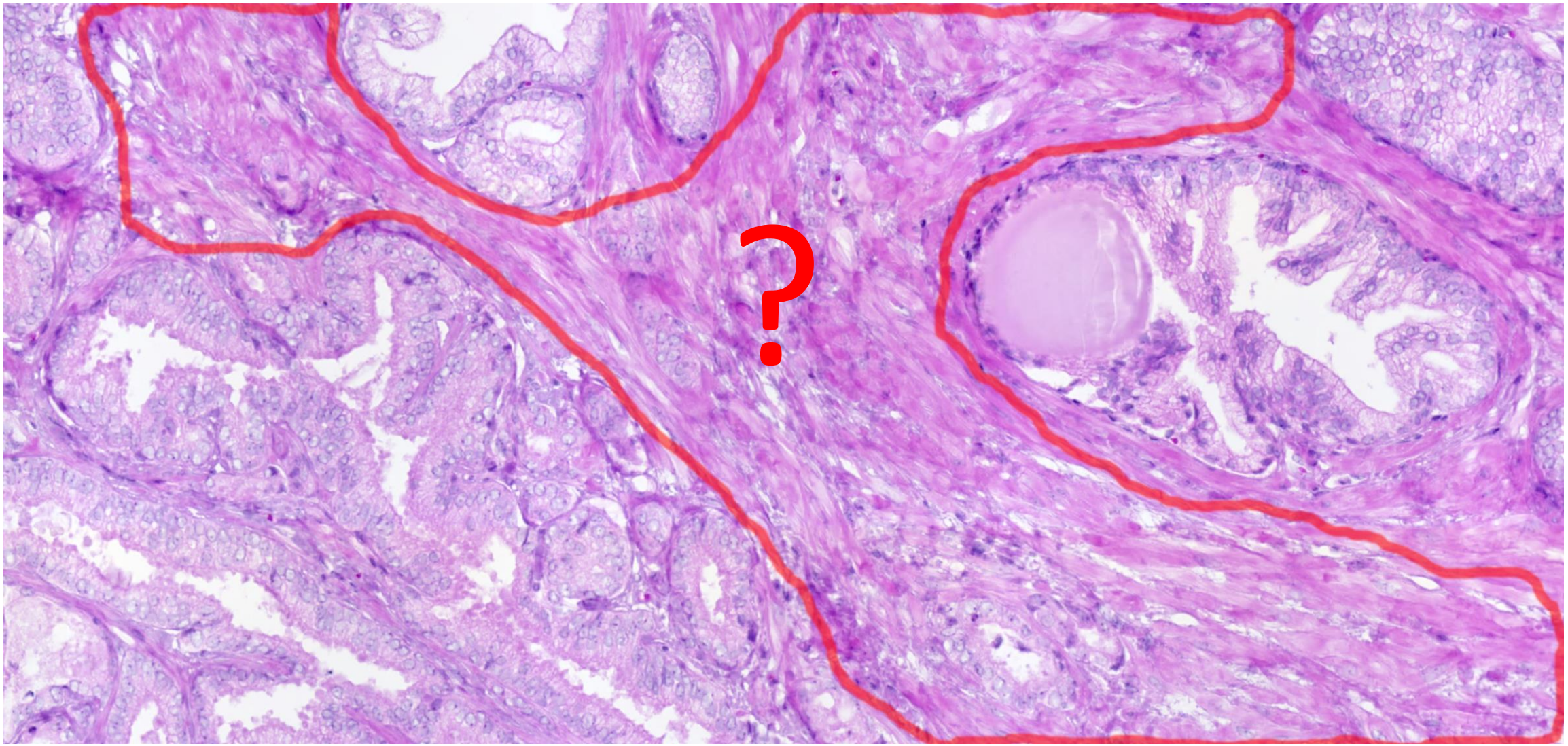
DAPI (blue), KRT8/18 (green), KRT5/6 (orange) and AMACR (red)



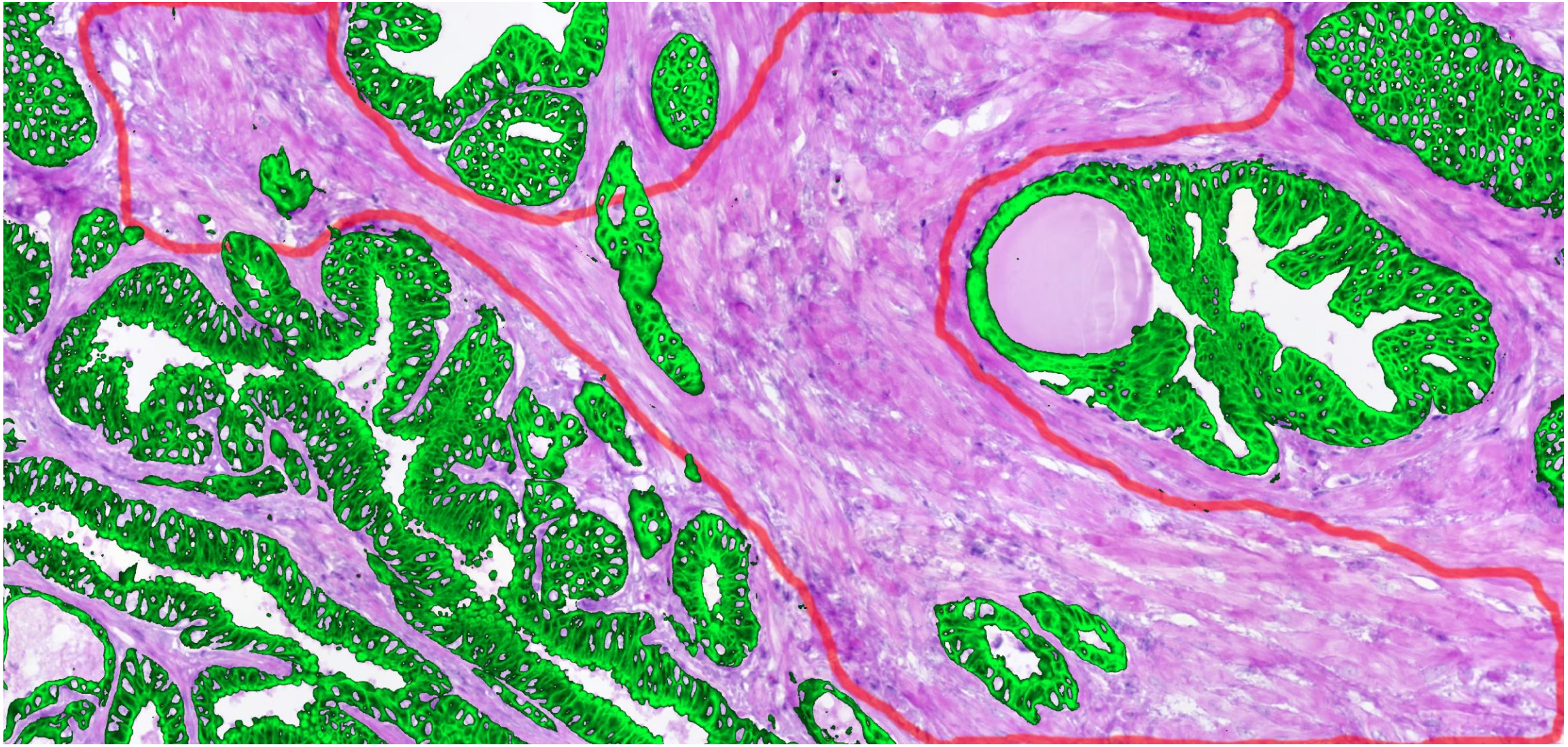
Brightfield image



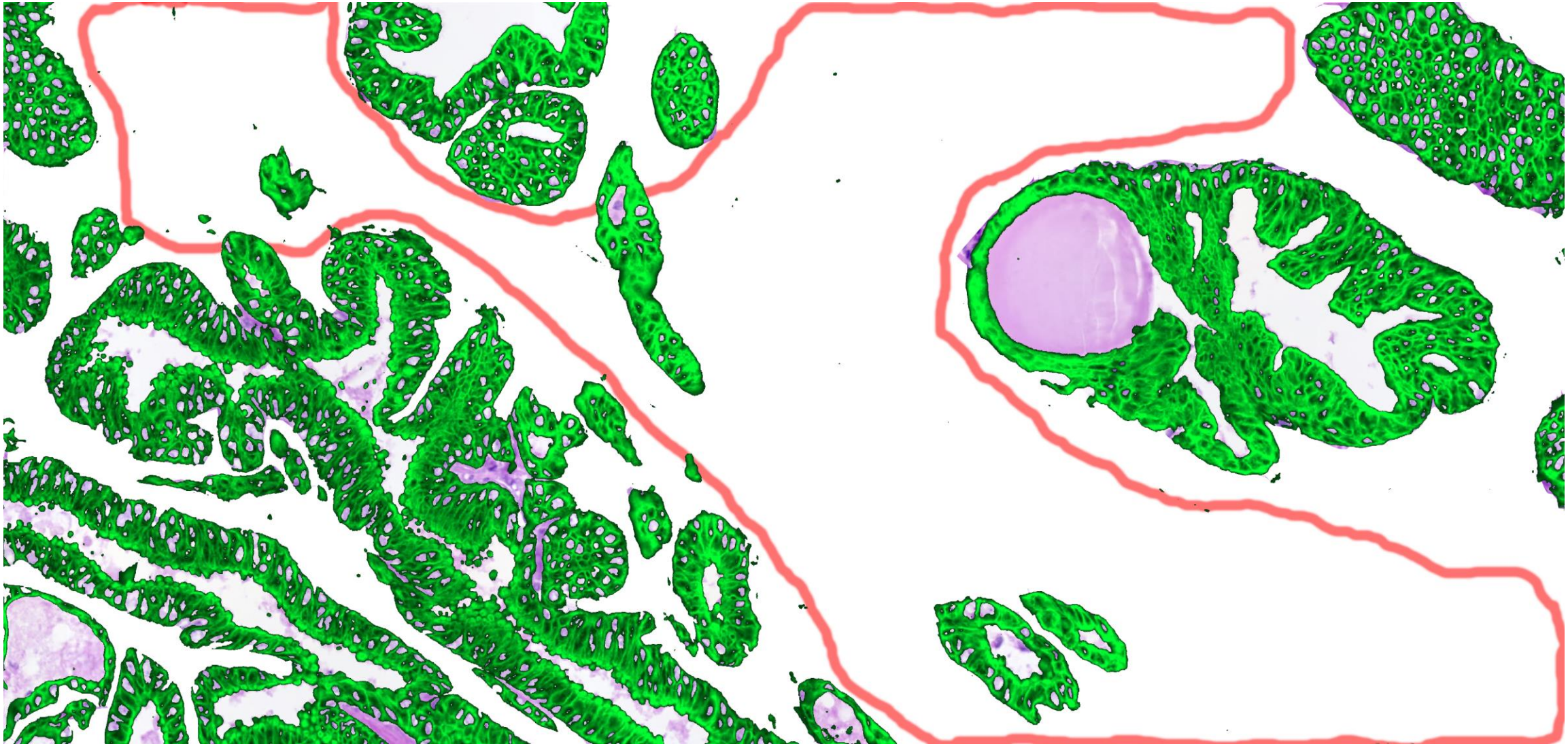
Difficult area for marking epithelial cells



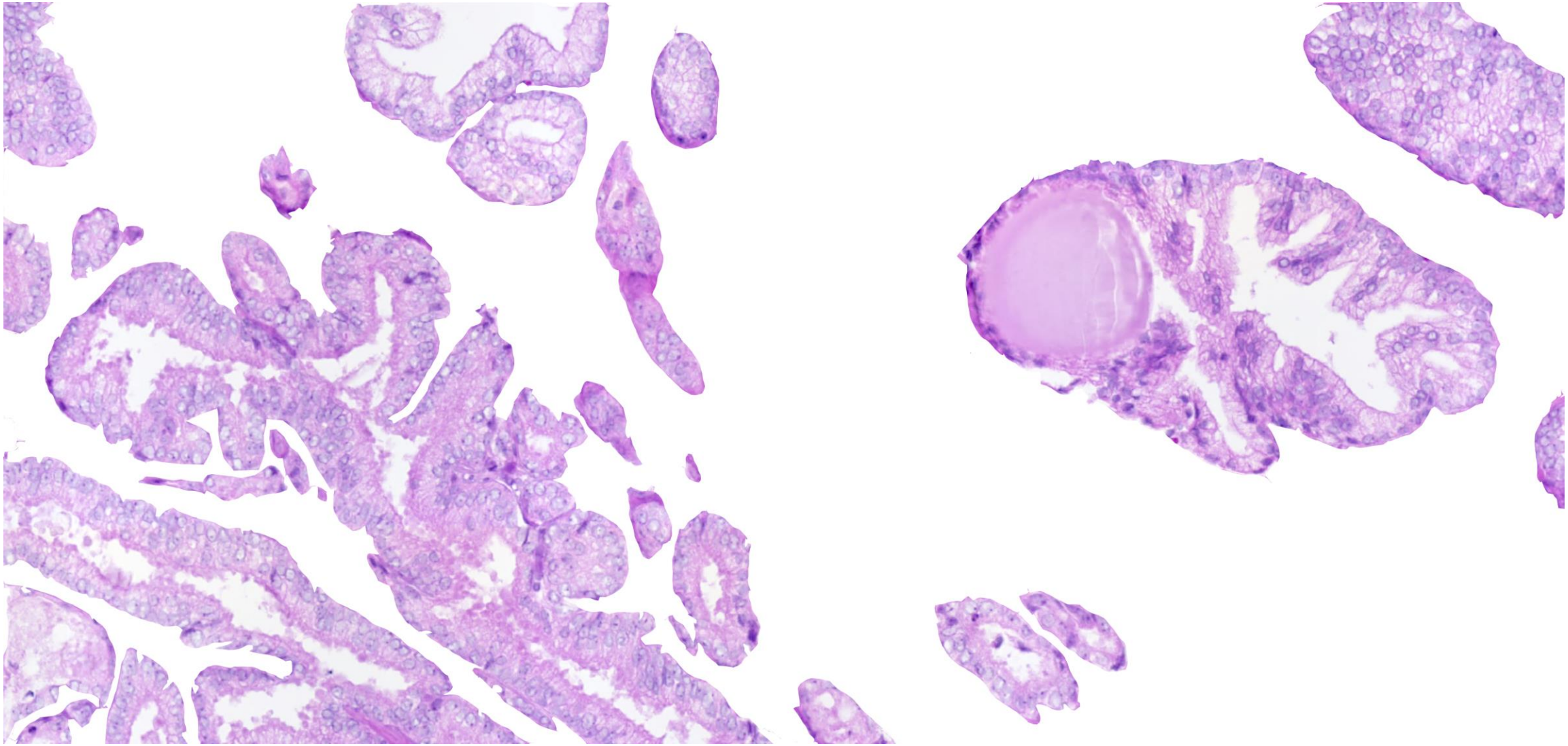
Immunofluorescence with KRT8/18



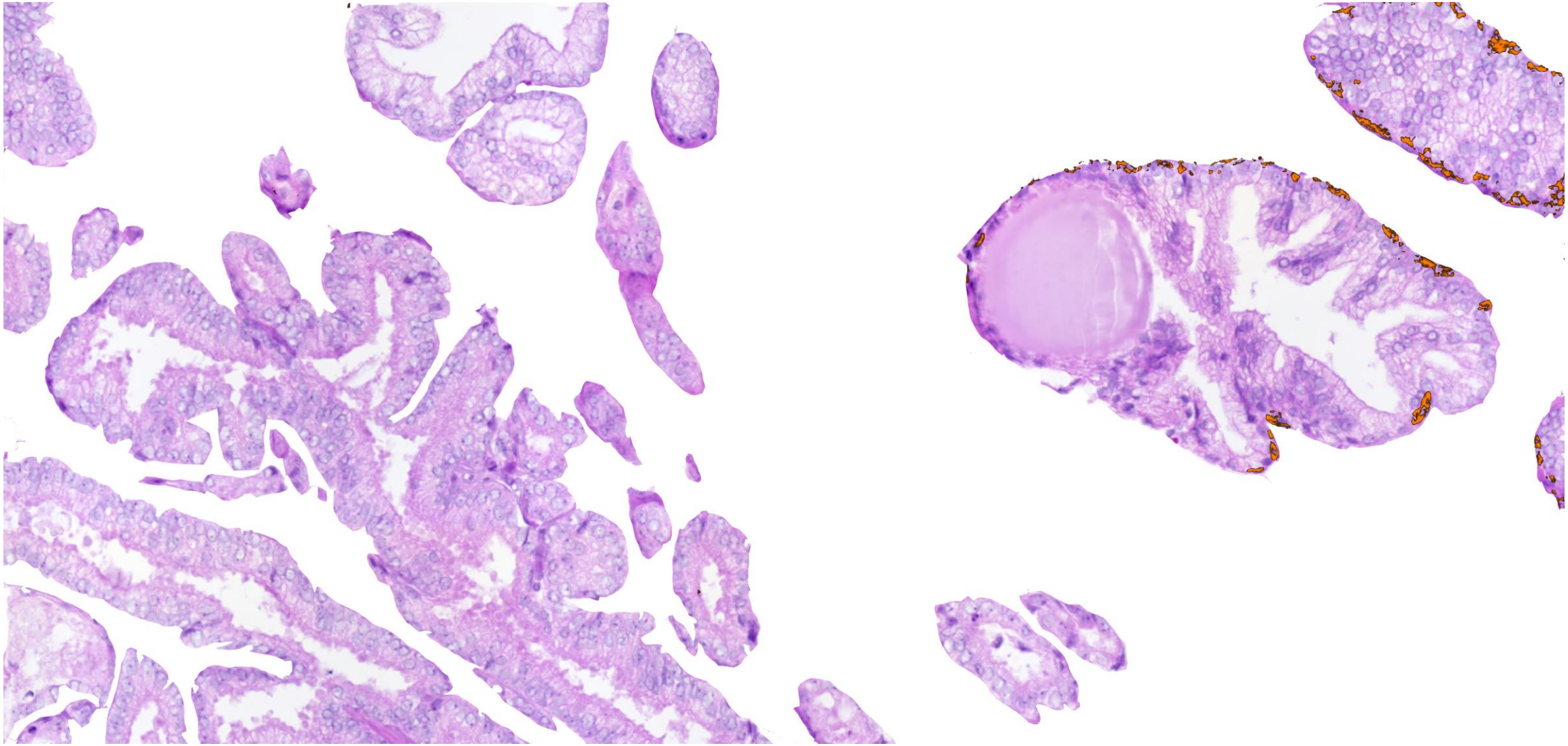
Use immunostaining as a mask



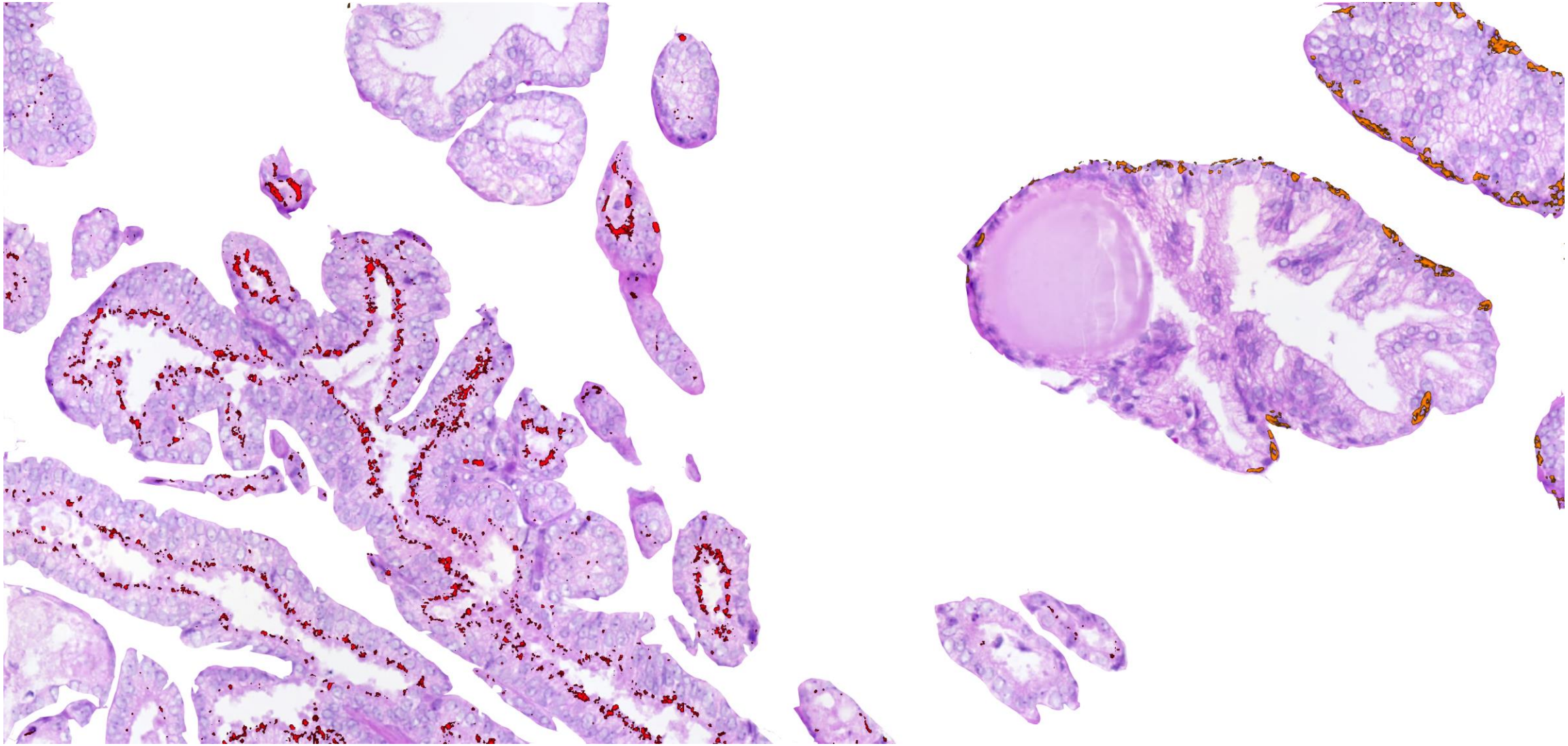
Cut out only epithelial cells



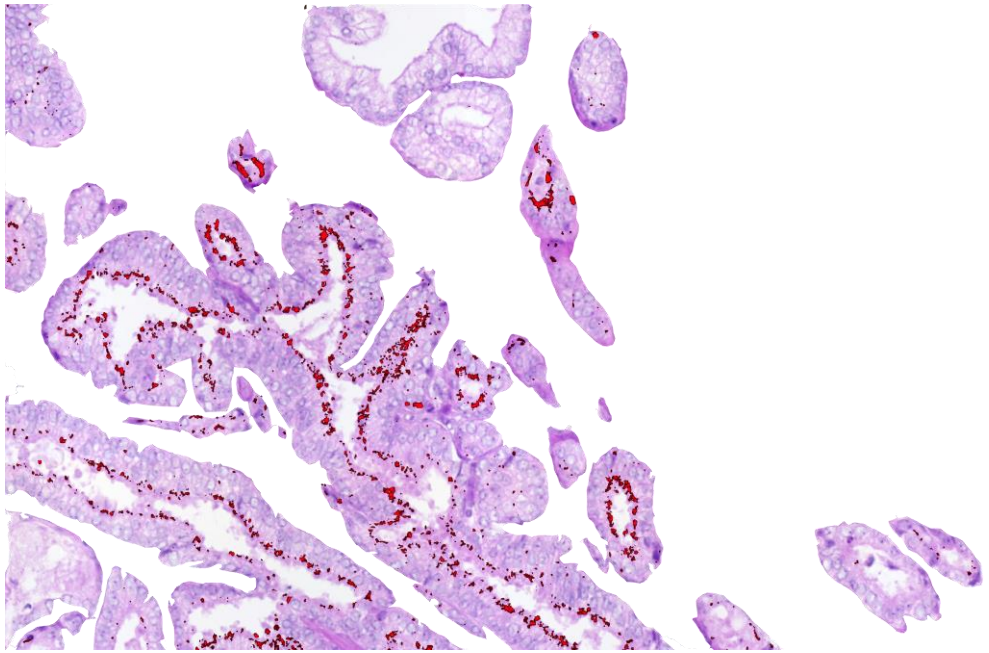
Basal cells detected with KRT5/6



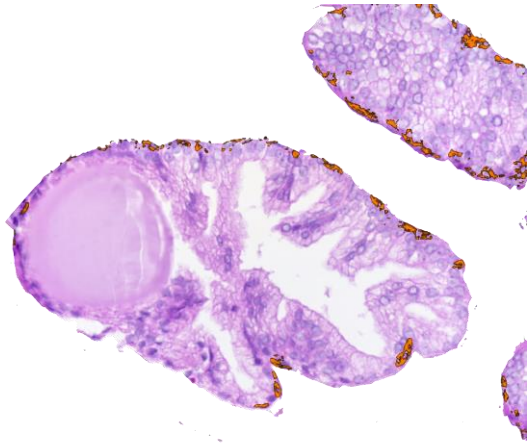
Neoplastic cells detected with AMACR



Train neural network on cancer vs. benign

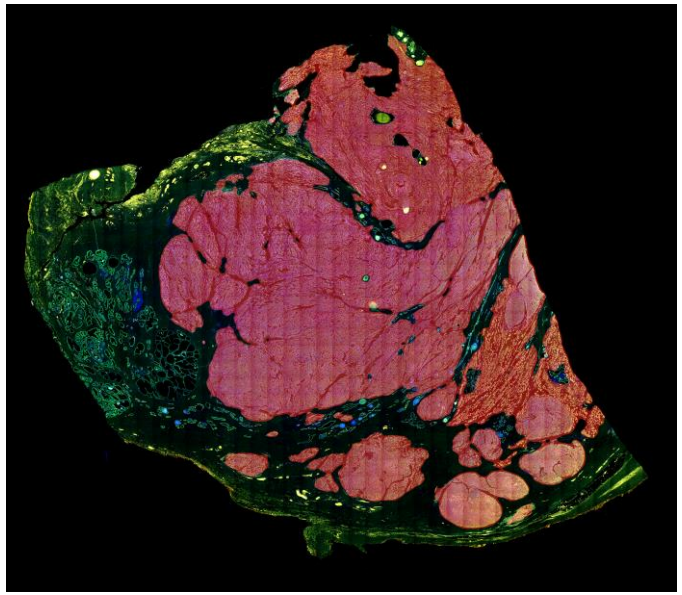


Cancer

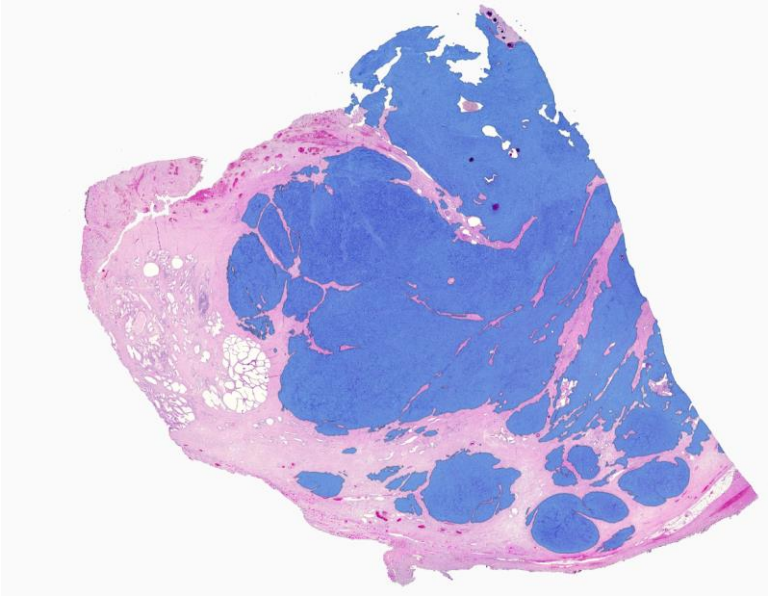


Benign

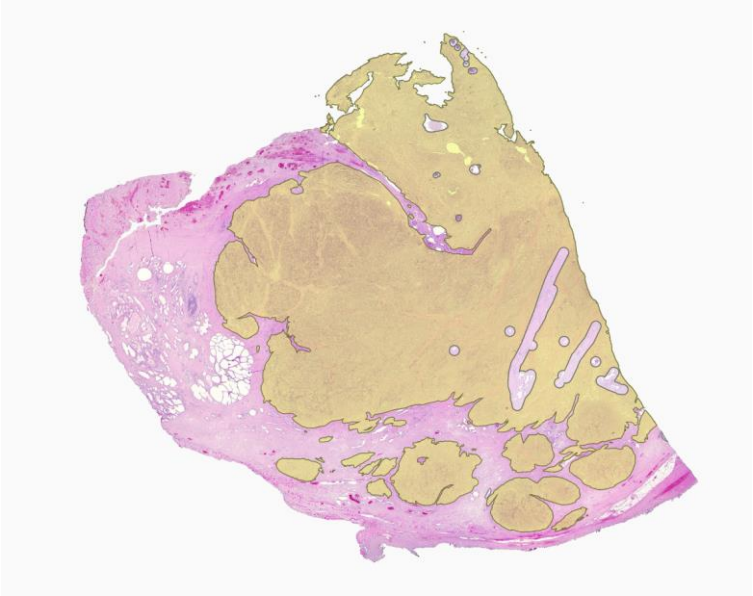
Verification by pathologists



Automated generated MasterAnnotation

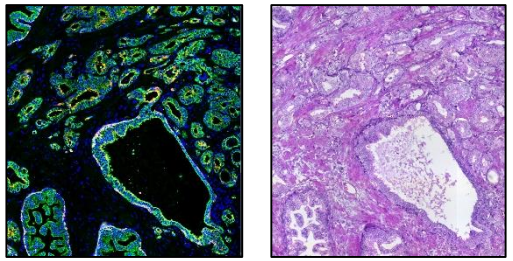


Pathologist 1

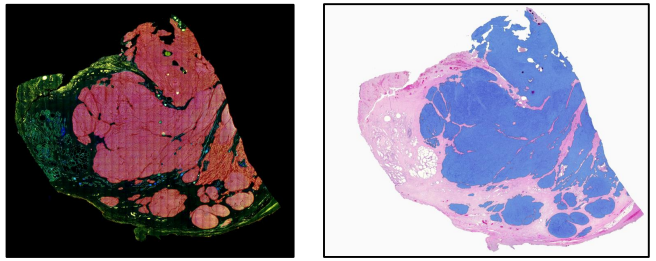


Pathologist 2

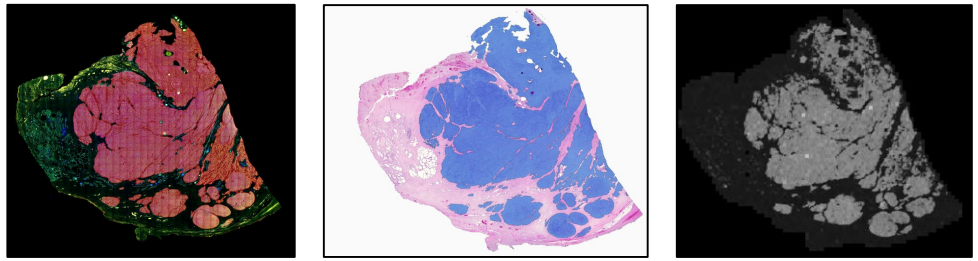
Development of a decision support tool



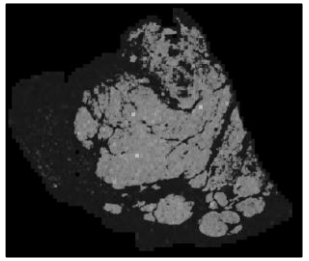
Master annotation
Multiplex IF + H&E



Method comparison
Master annotation vs pathologist



Mask for machine learning
Master annotation verified by pathologist



Verification
Independent WSIs

Product
Decision support tool for pathologists
Separation of slides containing cancer
Automatic Gleason grading

More accurate diagnosis
Speed up decision process
Prioritize worst slides first

MIDL Paper 2019

Segmenting Potentially Cancerous Areas in Prostate Biopsies using Semi-Automatically Annotated Data

Nikolay Burlutskiy* NIKOLAY.BURLUTSKY@CONTEXTVISION.SE
Nicolas Pinchaud* NICOLAS.PINCHAUD@CONTEXTVISION.SE
Feng Gu FENG.GU@CONTEXTVISION.SE
Daniel Hägg DANIEL.HAGG@CONTEXTVISION.SE
Mats Andersson MATS.ANDERSSON@CONTEXTVISION.SE
Lars Björk LARS.BJORK@CONTEXTVISION.SE
Kristian Eurén KRISTIAN.EUREN@CONTEXTVISION.SE
Cristina Svensson CRISTINA.SVENSSON@CONTEXTVISION.SE
Lena Kajland Wilén LENA.KW@CONTEXTVISION.SE
Martin Hedlund MARTIN.HEDLUND@CONTEXTVISION.SE
ContextVision AB, Linkoping, Sweden

MIDL Paper, results

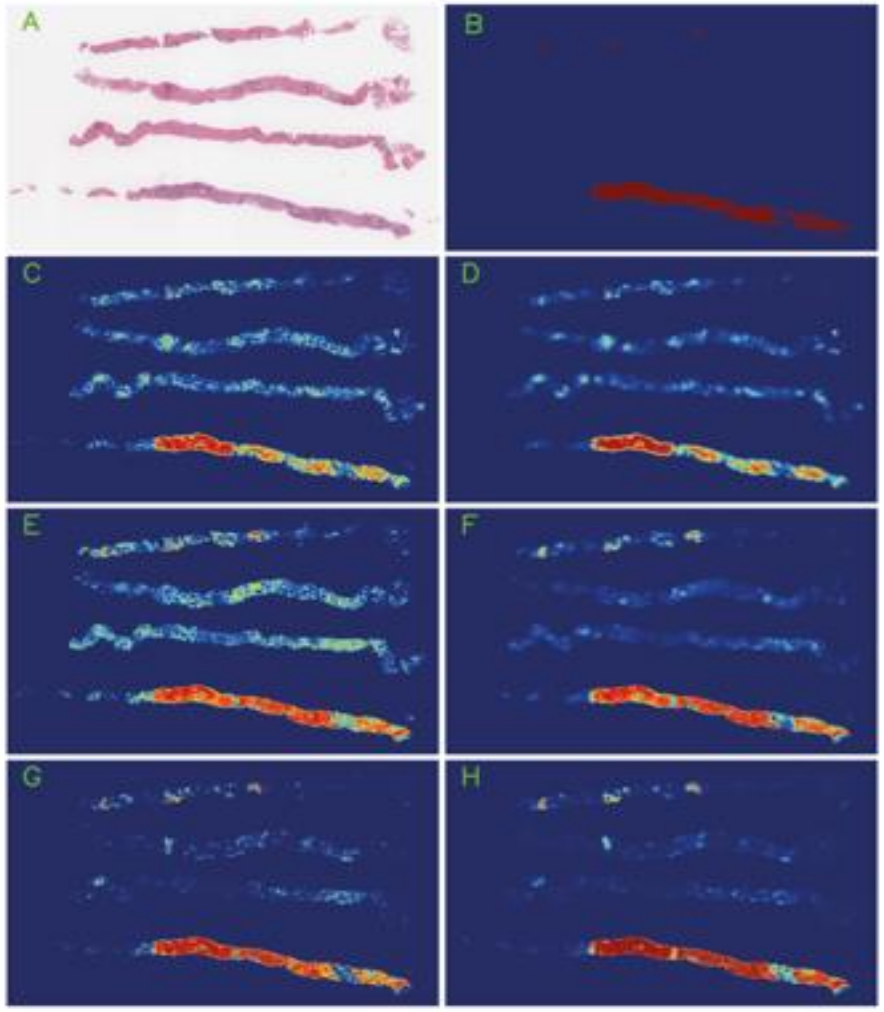
- The model produced promising predictions for the test biopsies
- The model performed on par with three pathologists
- The model even found missed, by the pathologists, areas in a few biopsies

Examples of heatmap predictions and the annotated ground thruth

- HE slide
- Annotated by pathologist

Predictions

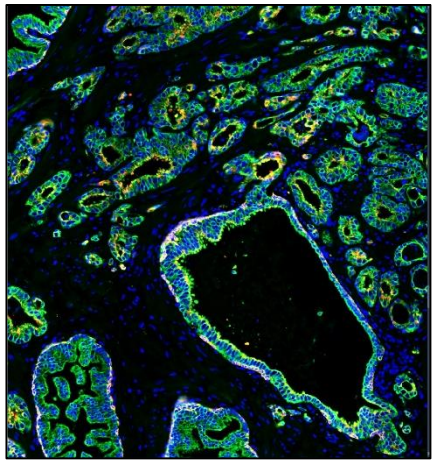
- M1pr
- M1,2pr
- M1bi
- M1,2bi on both 1 mpp and 2 mpp
- M1pr,bi and M1,2pr,bi were trained on prostatectomies first and then tuned on biopsies at 1 mpp and then both 1 and 2 mpp.

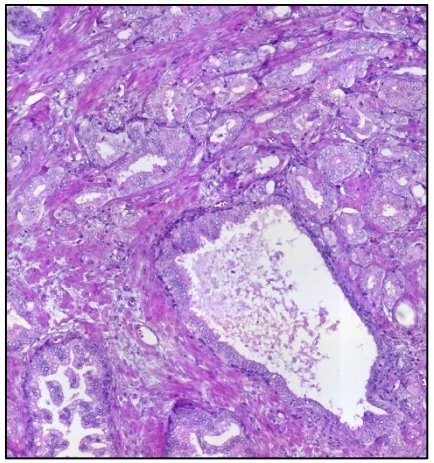


NOTE; This is a concept description, the product is not yet CE-marked for clinical use

Conclusion

- We have developed a robust and powerful method (master annotation) for specific and objective visualization of cancer areas in prostate biopsy whole slide images
- This forms the basis for machine learning to generate a highly accurate decision support tool for pathologists.





Project team

ContextVision

Medical technology software company specialized in image analysis and artificial intelligence

www.contextvision.com

Lars Björk

Kristian Eurén

Exhibit booth #36

THE HUMAN PROTEIN ATLAS

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Cecilia Lindskog B

Jonas Gustafsson

Feria Hikmet N

Dr Filippo Fraggetta, Ospedale Cannizarro, Catania, Italy

▸ One-Day Computational Pathology Symposium

ContextVision installation

JUNE 18 2018

007 18:45–19:00

Implementation of the ContextVision INIFY™ tool for the automatic detection of prostatic cancer in a fully digital routine workflow

Filippo Fraggetta, *Italy*

S. Lionti, G. Giuffrida, C. Emmanuele, P. Pepe

OSPEDALE CANNIZZARO CATANIA

NOTE This prototype was installed for *research use only*


Wilier
TRIESTINA
CYCLOLOGY