Computational Pathology: Towards Precision Medicine

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CHUV

Swiss Consortium for Digital Pathology

Outline

1. Introduction to Computational Digital Pathology
2. Research Applications
3. HistoSuite Tools

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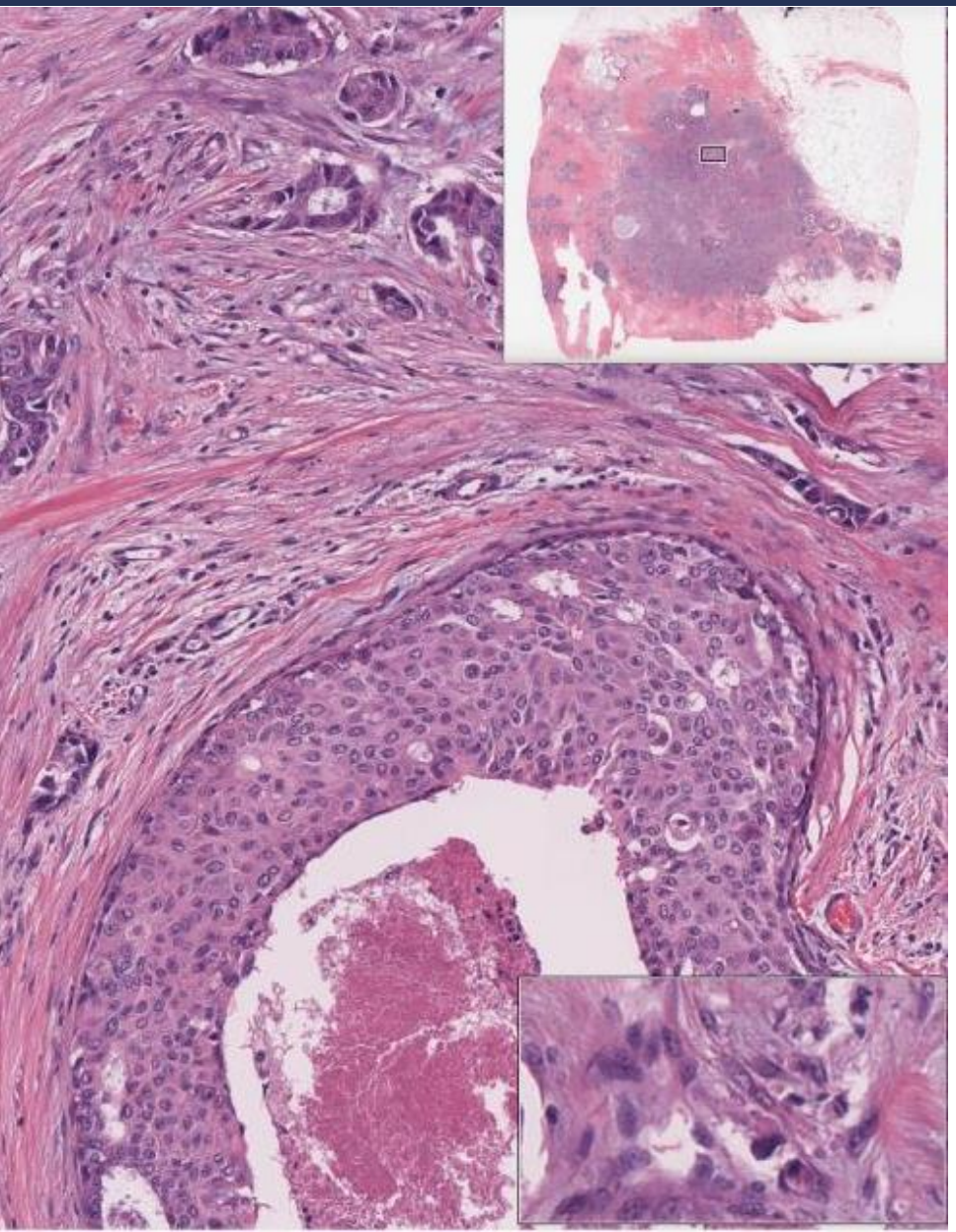
Brief Introduction



What is Computer Aided Diagnostics (CAD)?

- Using algorithms to help clinicians analyze data
- (f)MRI, **Histology**, Xray, CT, etc

Why is it useful?

- Improves efficiency & robustness of medical diagnoses
  - Fast, reproducible
- Leverage vast amounts of data already in existence
  - More being created daily at an increasing rate

How can we use this data?

- Can perform data mining to identify trends
- Identifying subtle image patterns that may not be visually discernible
- Build systems to *aid*, not replace, doctors through *decision support*
- Long term goal of leading to precision medicine

Research vs Clinical CAD Applications

- Clinical Applications
  - Recapitulate and automate existing processes
  - Cancer detection, grading, counting and area estimation tasks
  - Improvements through quantification, reproducibility, and definition refinement

>10 years

- Research Applications
  - Develop novel features and metrics
  - Sub-type discovery
  - Biology elucidation
  - Improvements through augmentation and new insights

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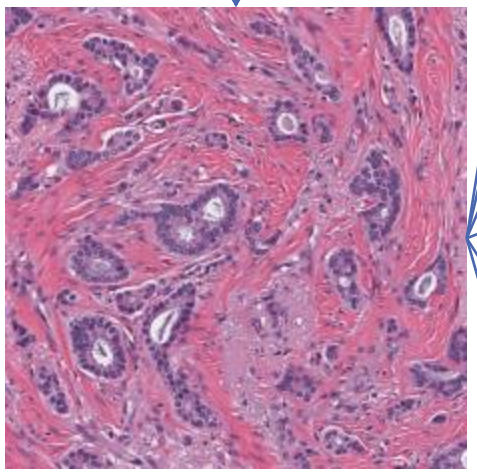

Nuclei Segmentation

Stroma Segmentation

Lymphocyte Segmentation

Mitosis Detection

Tubule Segmentation

ROI Identification

Morphology Density Texture

Structure Texture Orgainization

Infiltration Status

Number per ROI

Regularity

Area Heterogeneity

Classifier

Outcome / Sub-type / Clinical Variable

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Present – Deep Learning

Paradigm Shift

- Computation
- Storage
- Data

aws

Google Cloud

Network Attached Storage

NIH THE CANCER GENOME ATLAS
National Cancer Institute
National Human Genome Research Institute

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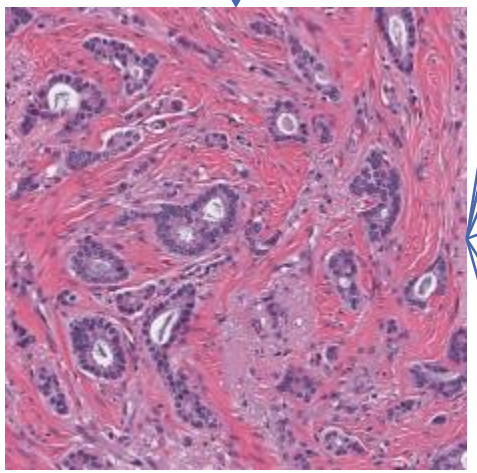

Deep Learning

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Stroma Segmentation

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Why use deep learning?

- Faster than creating hand-crafted features
  - Hand-crafted nuclei segmentation = 3 years
  - With deep learning = 3 hours
- Shows great robustness (both presentation and noise)
  - Able to examine more cases than developers

- At the end of the day:
  - Clinicians don't care *how the pieces were made*
  - Only care *what they can do with them*

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Our Proposed Framework

- "Deep learning for image analysis tasks in digital pathology: A comprehensive tutorial with selected applications in lymphoma, colorectal and breast cancer analysis", **Andrew Janowczyk** and Anant Madabhushi, JPI 2016 (Most viewed award, >51k downloads)

- Through 7 use cases, provide best practices, code + data + tutorial for:*
  1. nuclei segmentation (f-score of .83 across 12,000 nuclei)
  2. epithelium segmentation (f-score of .84 across 1,735 regions)
  3. tubule segmentation (f-score .83 from 795 tubules),
  4. lymphocyte detection (f-score .90 across 3,064 lymphocytes),
  5. mitosis detection (f-score .53 across 550 mitotic events),
  6. invasive ductal carcinoma detection (f-score .7648 on 50k testing patches)
  7. lymphoma sub-type classification (classification accuracy of .97 across 374 images)

•All results are either comparable or superior to current state of the art

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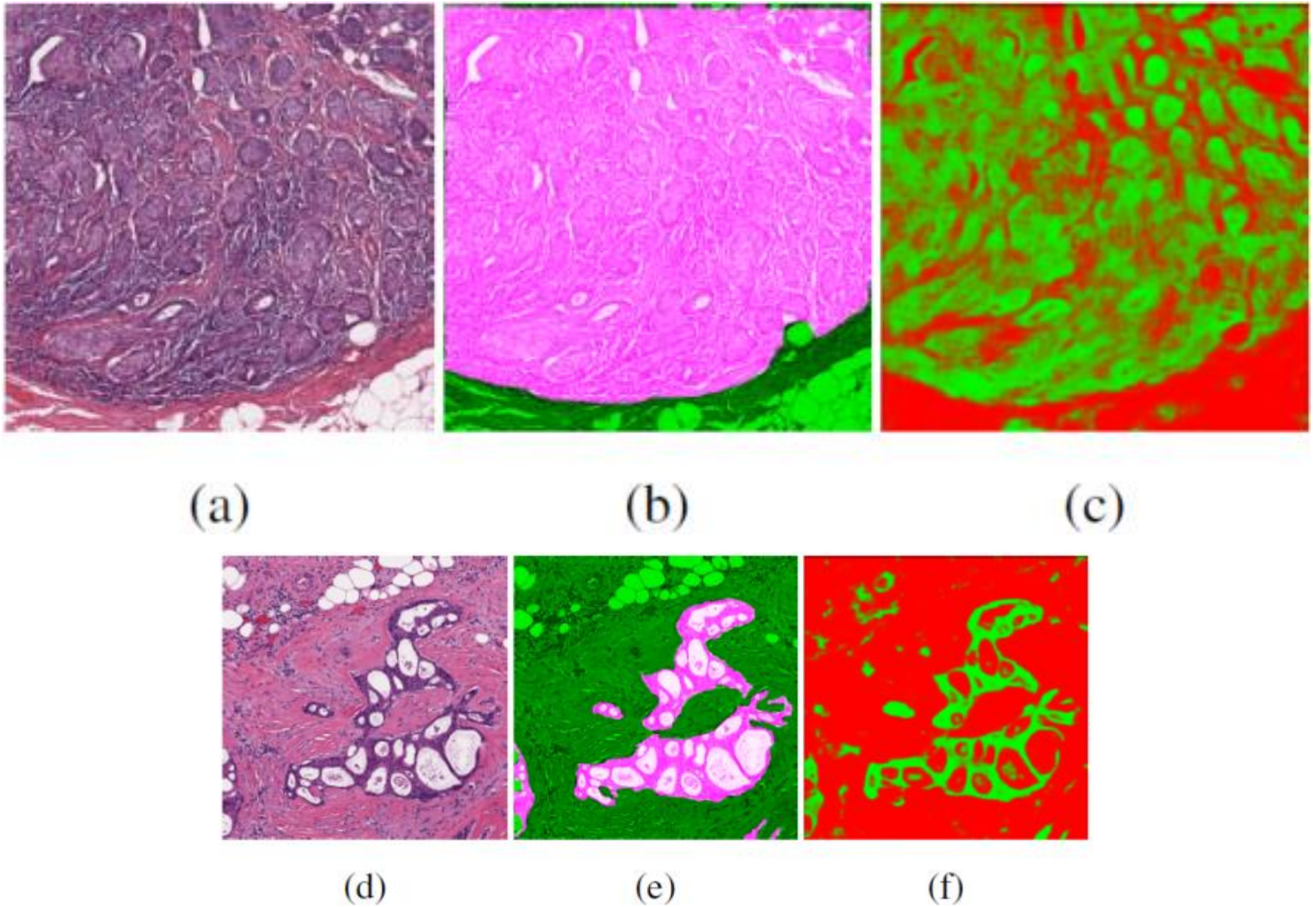
*Available: http://www.andrewjanowczyk.com

Segmenting Epithelium

Original images in (a) and (d) with their associated ground truth in (b) and (e) overlaid in fuchsia. We can see that the results from the deep learning, in (c) and (f), that a pixel level metric is perhaps not ultimately suited to quantify this task as DL is better able to provide a pixel level classification, intractable for a human expert to parallel.



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Development and evaluation of deep learning-based segmentation of histologic structures in the kidney cortex with multiple histologic stains

Study Aims:

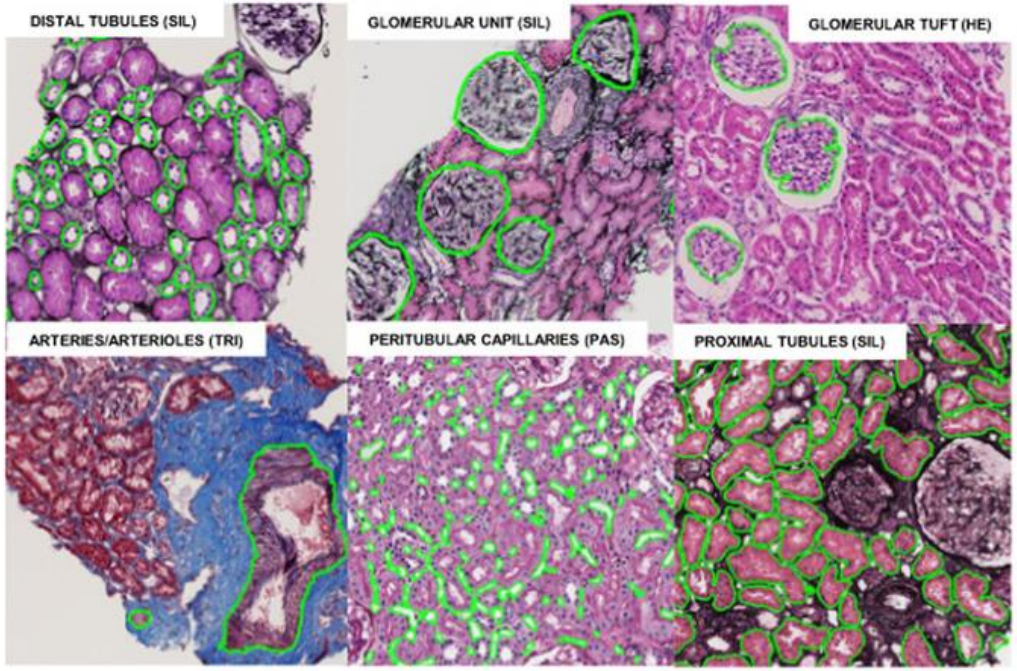
Novel protocols for renal biopsy assessment

Feasibility of deep learning-based (DL) convolutional neural networks (CNNs) for normal histology, to facilitate quantitation of prognostic histologic structures

Dataset:

- 125 NEPTUNE MCD biopsies
- H&E, PAS, TRI, SIL stains
- 459 WSIs of normal renal parenchyma (MCD)
- 38 pathology laboratories
- 30048 annotations generated across primitives

U-Net DL Segmentation using multistained WSIs



Results:

- Comparative DL performance across 4 stains (Best results on PAS stained WSIs)
- Multiple DL networks with suggested number of training exemplars across primitives
- Optimal digital magnification: 5X glomeruli, 10X tubules and arteries, 40X peritubular capillaries
- Validated on nephrectomies
- Online access to data and tutorials to setup DL networks

CONCLUSION:

DL-based CNNs permit **efficient** segmentation of kidney histologic structures on **multiple stains** with substantial **tissue heterogeneity** across centers. This work creates a technical foundation to support **pathology workflows** for better **disease characterization** and **risk assessment**.

ISN kidney INTERNATIONAL
OFFICIAL JOURNAL OF THE INTERNATIONAL SOCIETY OF NEPHROLOGY

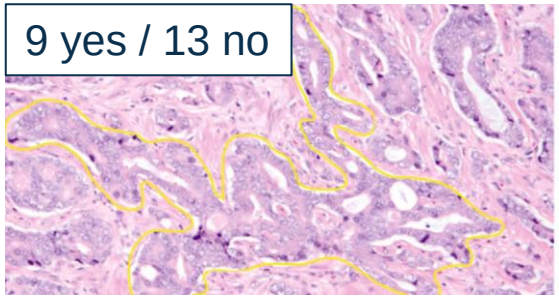
Jayapandian, Chen et al, 2020

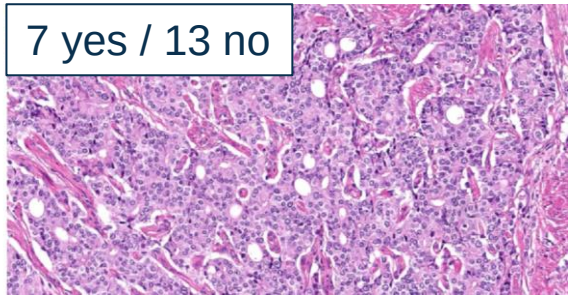
2. Research Applications

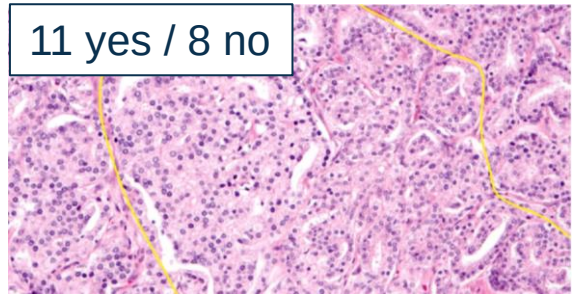
Automated cribriform quantification is prognostic of biochemical recurrence

- Cribriform increasingly recognized as high risk in prostate cancer
- Recent grading updates moved all cribriform patterns to Gleason 4
- ***Computers can take the subjectivity out of cribriform assessment***

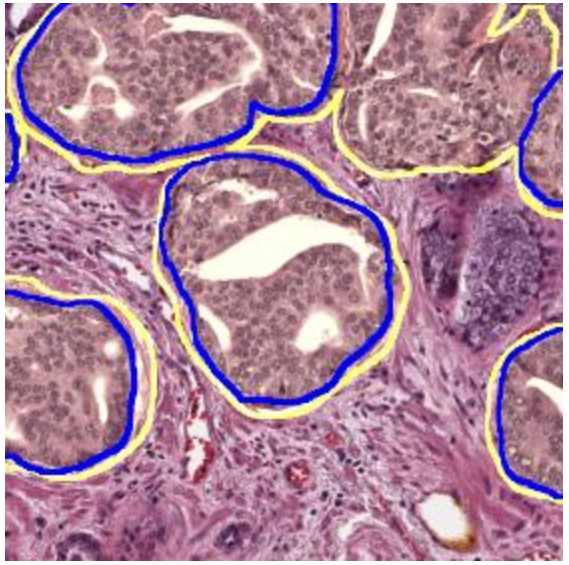
Kweldam et al. (2016) asked pathologists: Is this cribriform? Found just 23% agreement



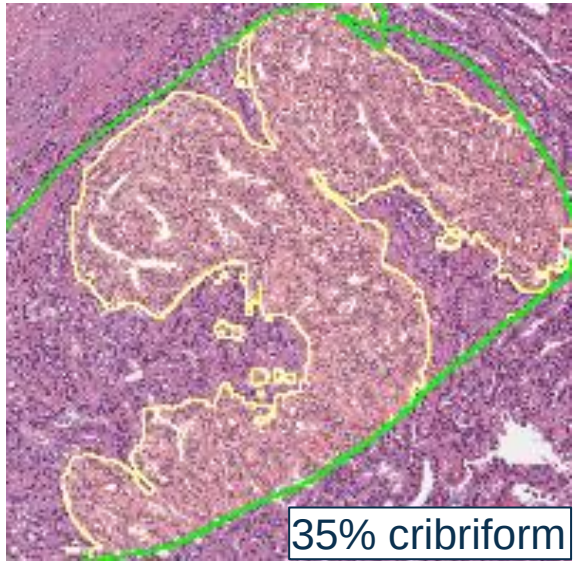




Pathologist annotations train deep learning model

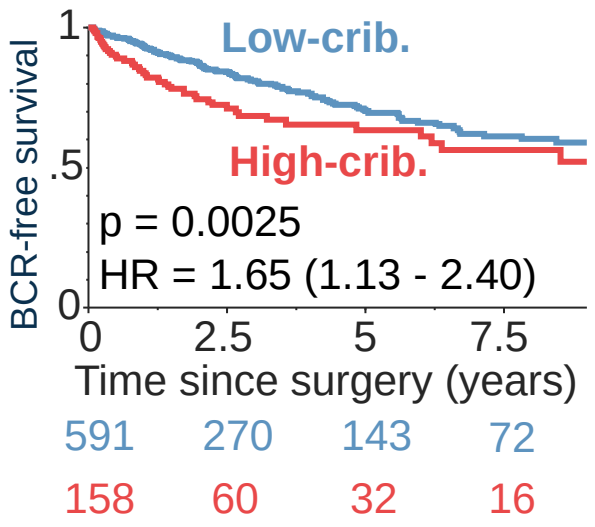


Model measures tumor cribriform fraction

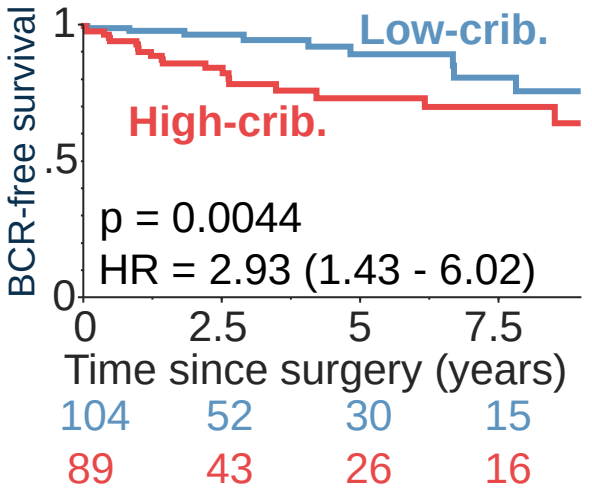


Automated cribriform assessment was prognostic in:

n=745 patient validation set



Especially grade group 2



- Doubling of cribriform had HR of 1.19 when controlling grade, stage, pre-operative PSA, age
- Model was similarly prognostic across four institutions
- C-index of 0.66 in grade group 2 patients with cribriform, potential role in active surveillance

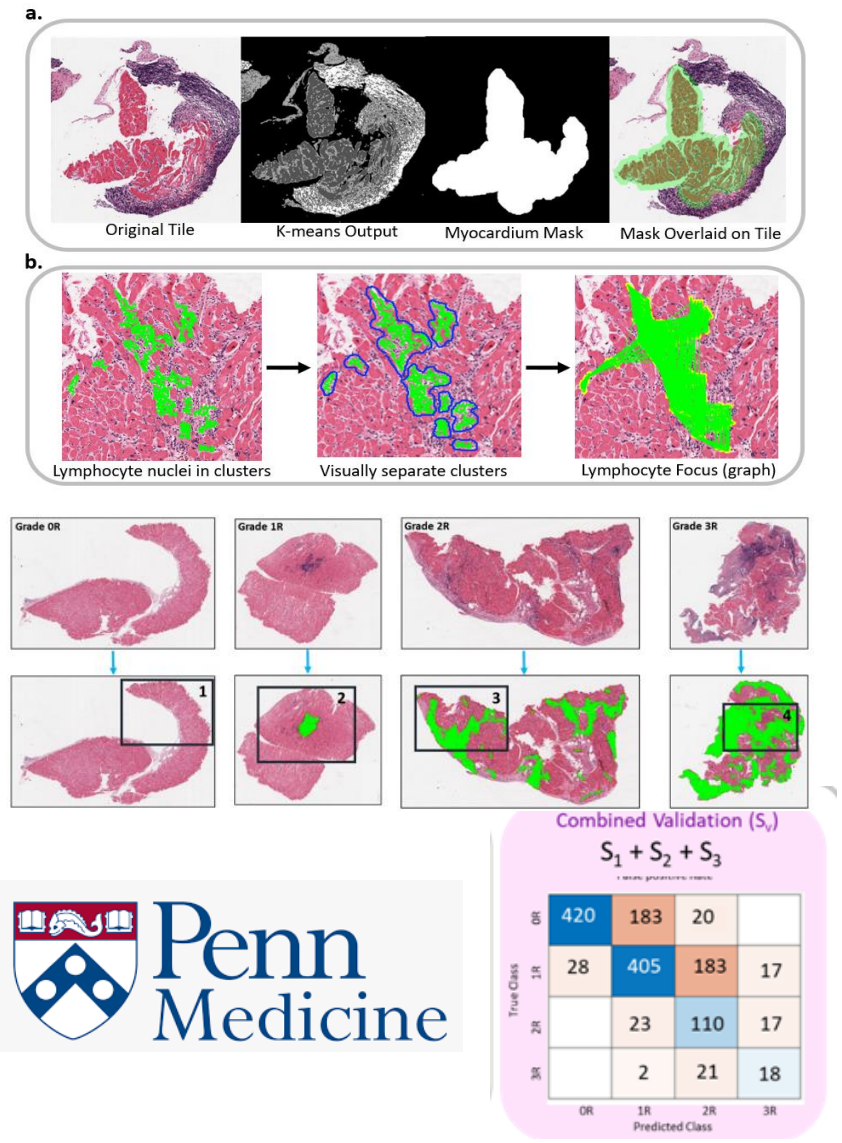
Leo et al, European Urology Focus 2021

An Automated Computational Image Analysis Platform for Accurate and Reliable Histologic Grading of Cardiac Allograft Rejection

- Studies demonstrate the poor reliability of ISHLT grading (kappa = 0.39)
- Overall Inter-pathologist agreement of 65-70%
- Inter-pathologist agreement of 28.4% at the higher grades of rejection (2R and 3R)
- Potentially affect immunosuppressive therapy decisions

- Computer-assisted cardiac histology evaluation (CACHE)-Grader
- N=2472 endomyocardial biopsy slides, 3 sites
- Features associated with interactions between myocytes, lymphocytes (counts, areas, spatial relationships)

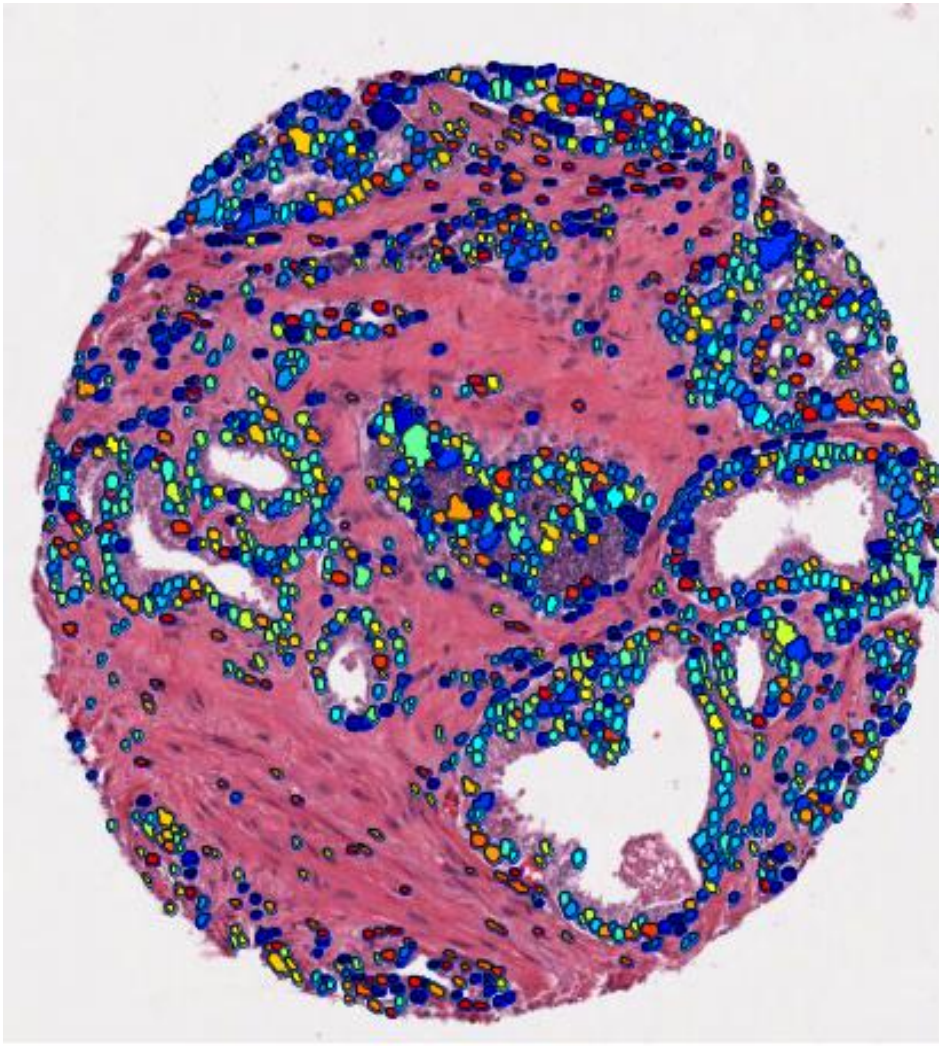
- CACHE - 65.9%
- Inter-Pathologist agreement – 60%

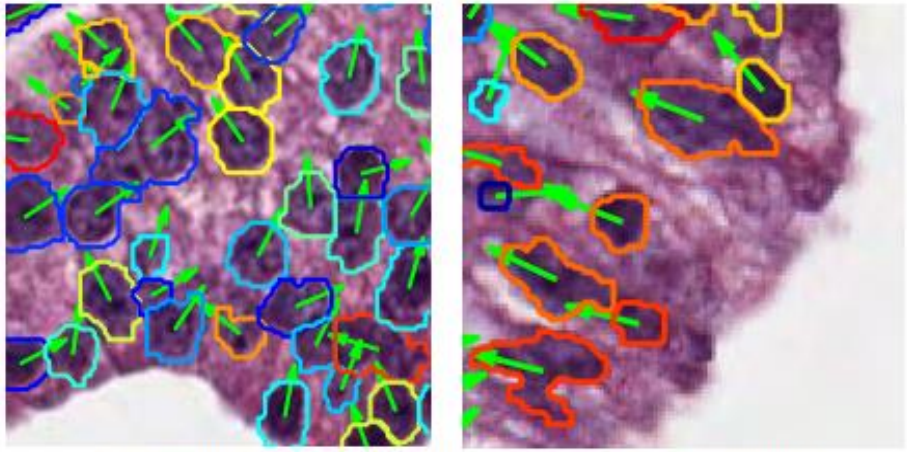


Penn Medicine

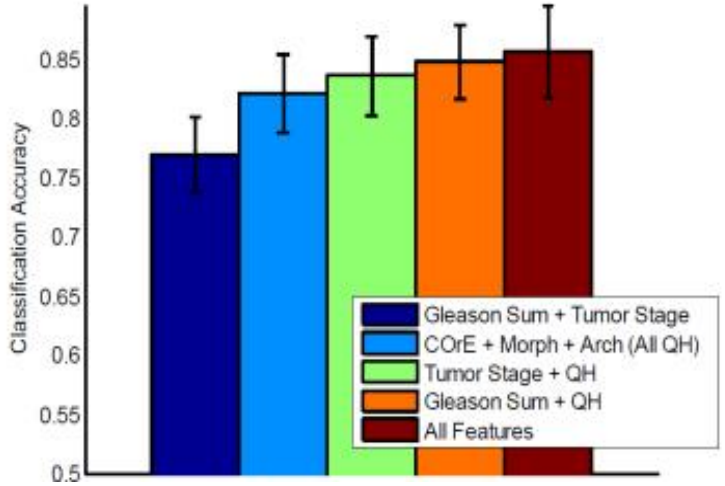
Peyster E., Arabyarmohammadi S., Janowczyk A., Azarianpour-Esfahani S., Sekulic M., Cassol C., Blower L., Parwani A., Lal P., Feldman M., Margulies K., Madabhushi A., "An Automated Computational Image Analysis Pipeline for Histologic Grading of Cardiac Allograft Rejection", European Heart Journal, 2021

Cell orientation entropy (COrE) features stratify more and less aggressive prostate cancer on tissue microarrays



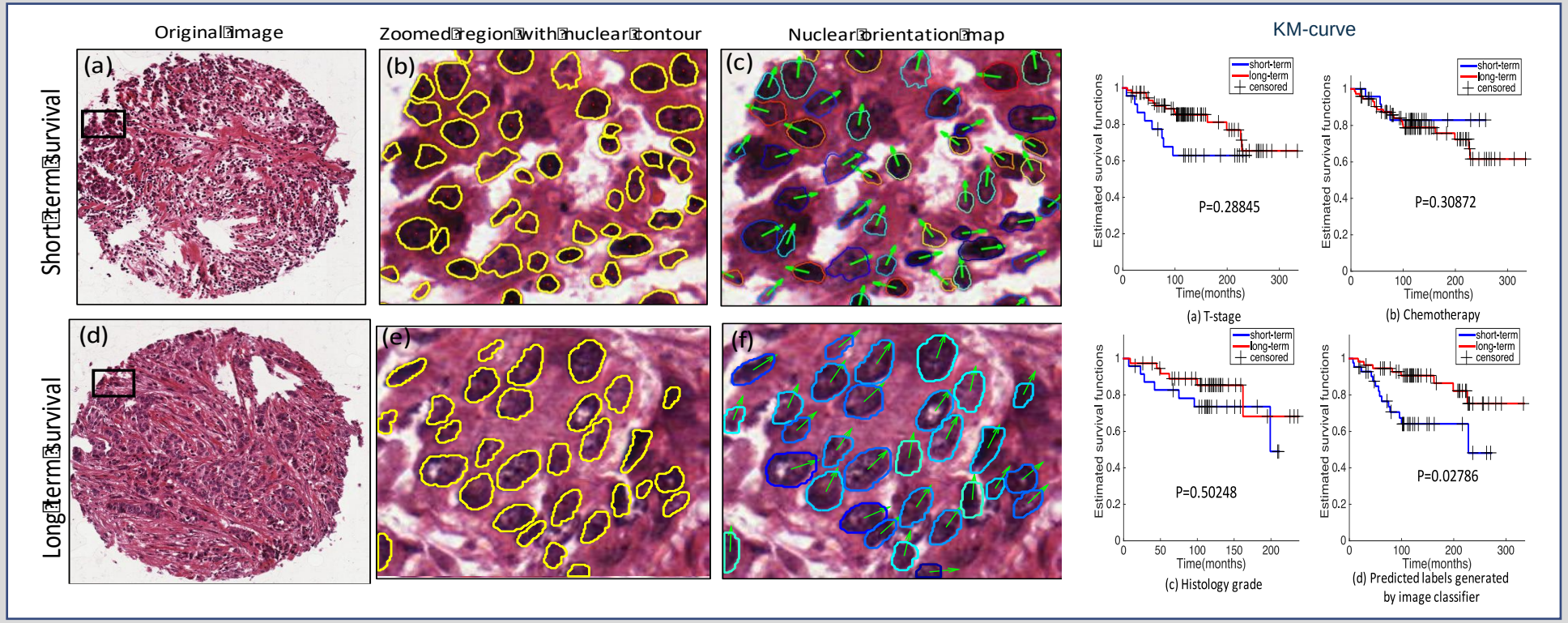


Aggressive cancer (left) shows more disorder in orientation of the nuclei compared to less aggressive cancer (right)



Lee, G, Ali, S, et al., “Cell Orientation Entropy (Core): Predicting Biochemical Recurrence from Prostate Cancer Tissue Microarrays”, In Proc of Medical Image Computing and Computer Assisted Interventions (MICCAI), vol. 3, pp. 396-403, 2013.

Nuclear Shape and Orientation Features from H&E Images Predict Survival in Early Stage Estrogen Receptor Positive (ER+) Breast Cancers



Unmet Clinical Need

- Early stage ER+ breast cancer (BCa) is the most common type of breast cancer in the United States
- Identifying which patients will receive added benefit from adjuvant chemotherapy is important

Data

- TMA of 276 ER+ LN- patients
- Training cohort (n=177)
- Validation cohort (n=99)

Lu C., Romo D., Janowczyk A., Ganesan S., Gilmore H., Rimm D., Madabhushi A., "Nuclear Shape and Orientation Features from H&E Images Predict Survival in Early Stage Estrogen Receptor Positive (ER+) Breast Cancers", Nature Laboratory Investigation 2018

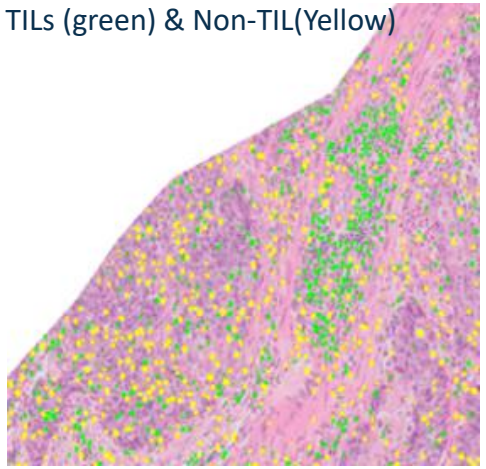
Spatial arrangement of tumor infiltrating lymphocytes (TILs) predict response to Nivolumab in non-small cell lung cancer (NSCLC)

Hypothesis: Spatial arrangement of TILs and local density variance are highly correlated to the patient response.

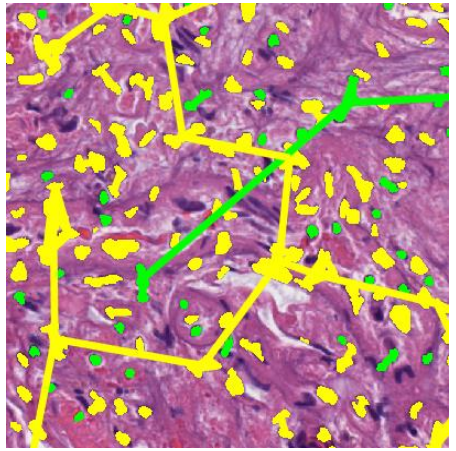
Data sets:
Two independent data (whole slide image) acquired from UPenn (32) and CCF (24)

TIL detection and image feature extraction

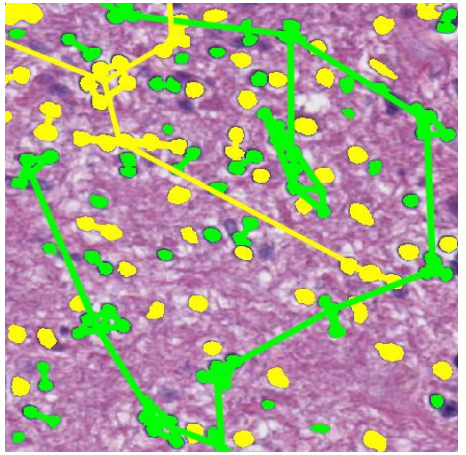
TILs (green) & Non-TIL(Yellow)



Non-Responder

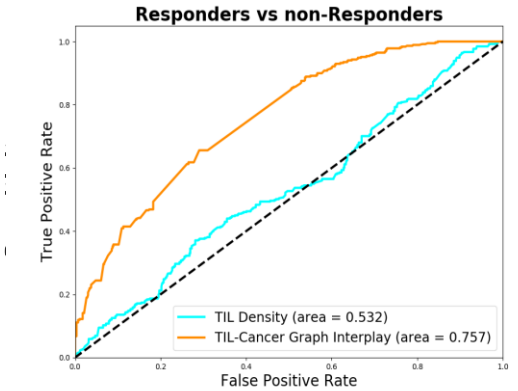


Responder



Top 5 most significant features obtained by feature selection

1. Median of TILs formed areas
2. Ratio of Cancer cells to TILs cells
3. Cancer cell averaged Density
4. Density of TILs
5. Median of Cancer cell formed areas



A QDA classifier was trained using a Training set (n=32) and a independently validation set from a different institution (n=24).

Wang, X, Barrera, C, Velu, P, Bera, K, Prasanna, P, Khunger, M, Khunger, A, Velcheti, V, Madabhushi, A, "Computer extracted features of cancer nuclei from H&E stained tissues of tumor predicts response to Nivolumab in non-small cell lung cancer", American Society for Clinical Oncology (ASCO) Annual Meeting (Poster), Chicago, IL, 2018

3. HistoSuite Tool Development U01 NIH-NCI-ITCR

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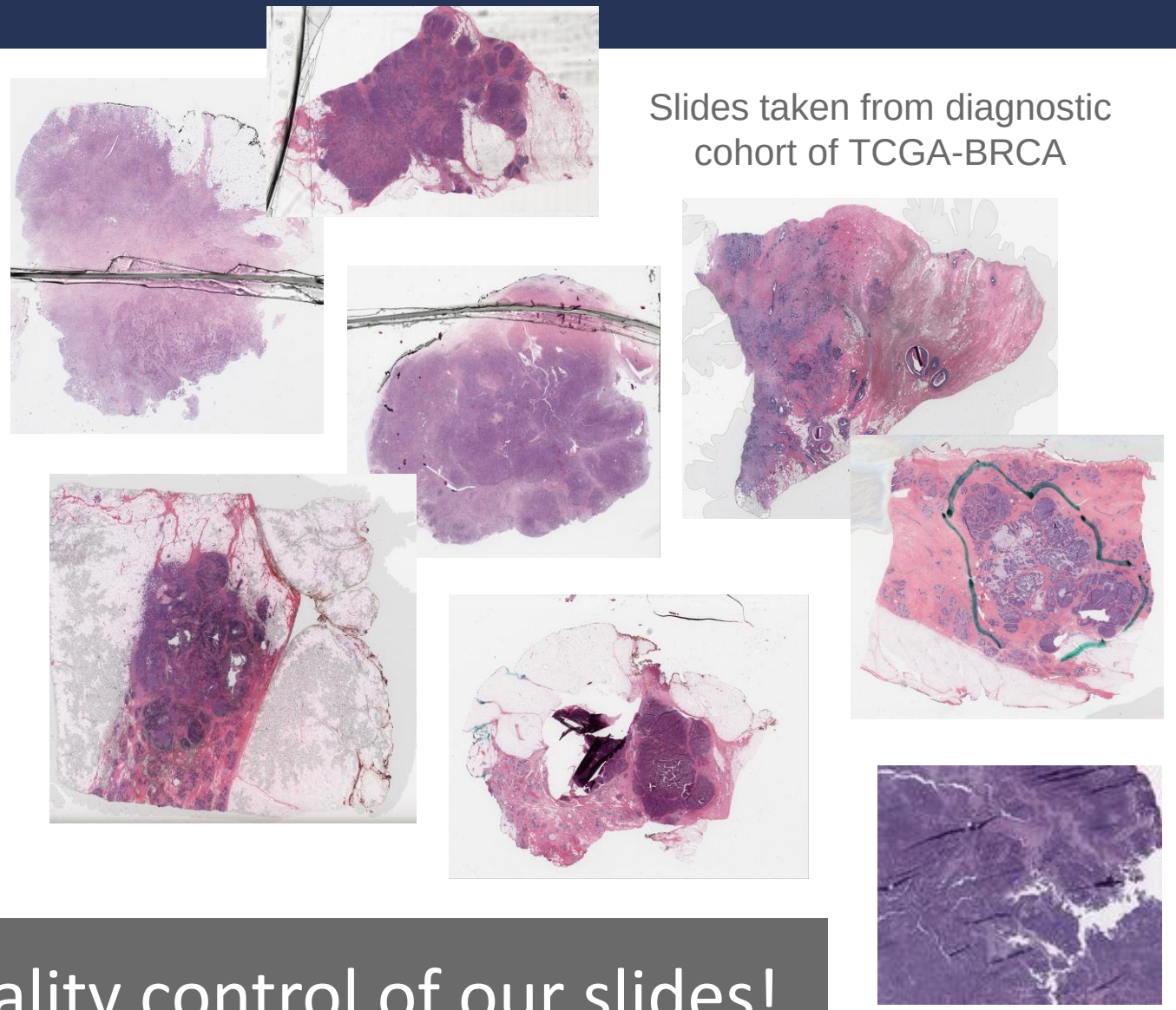
Unmet Need For Quality Control

- Transition to digital pathology workflows
  - Digital Quality Control is paramount
  - Recut and rescan slides immediately before getting into a workflow to a pathologist
  - Cost and efficiency savings
- Previously not insurmountable
  - Increasingly too time consuming to do manually
  - Non-reproducible



Slides taken from diagnostic cohort of TCGA-BRCA

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We need better quality control of our slides!

Surprising lack of reproducibility in manual QC

- For n=330 slides we simply provided a protocol and asked 3 readers:
- “Is this a good enough quality slide to computationally analyze?”
- We looked at the concordance between 3 readers

- This implies that each of these 3 readers would have started with a different datase before even beginning their experiment

- Irreproducible QC = Irreproducible Experiments!

Stain	Agreement	Kappa	Gwet's AC1
Without HistoQC			
H&E	0.73	0.26	0.59
PAS	0.73	0.31	0.56
SIL	0.75	0.50	0.52
TRI	0.69	0.36	0.43
With HistoQC			
H&E	0.96	0.91	0.92
PAS	0.89	0.75	0.79
SIL	0.96	0.93	0.93
TRI	0.90	0.77	0.81

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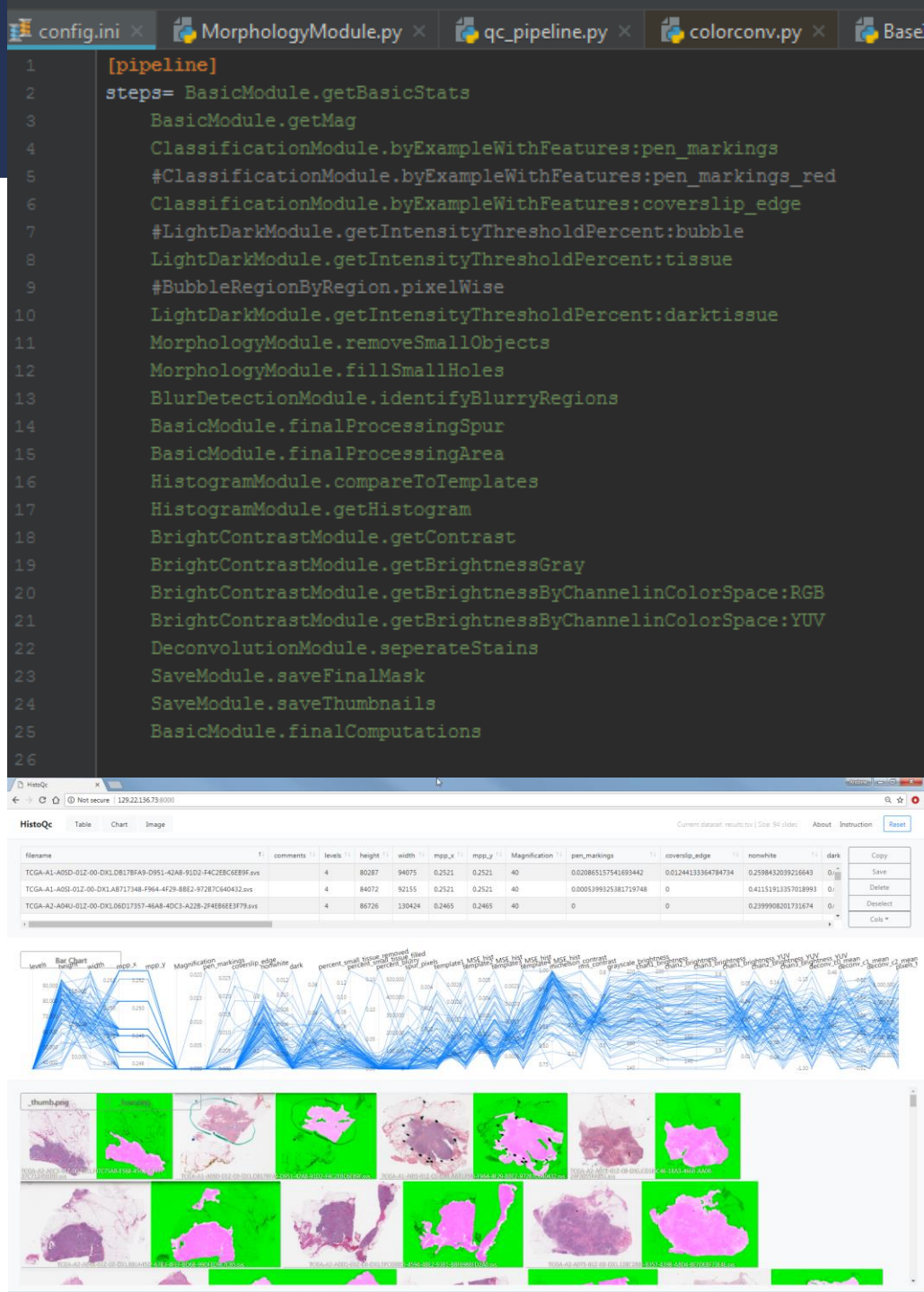
Chen, Zee, Smith et al, Assessment of a Computerized Quantitative Quality Control Tool for Kidney Whole Slide Image Biopsies, Journal of Pathology, 2021

What is HistoQC?

- Open source reproducible slide quality metrics with artifact localization
- Python backend
  - identify artifacts and produce binary masks of “good” tissue
  - compute actionable quality scores and metrics
- HTML5 front end for visualizing and investigating results
- Able to aid in detection of Batch Effects!

- Available: http://HistoQC.com



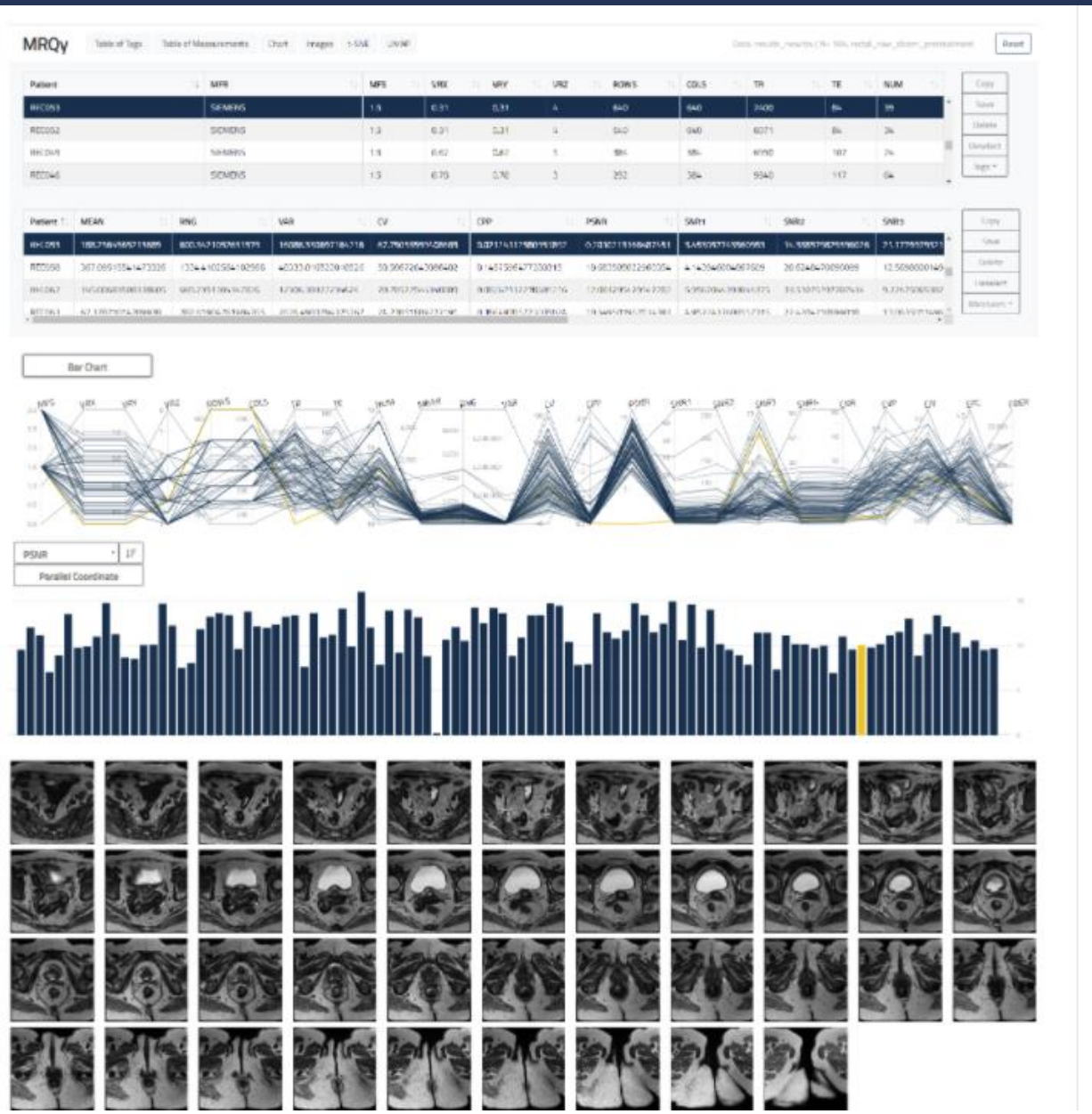
1. Janowczyk A., Zuo R., Gilmore H., Feldman M., Madabhushi A., “HistoQC: An open-source quality control tool for digital pathology slides", JCO Clinical Cancer Informatics, 2019
2. Chen, Zee, Smith et al, Assessment of a Computerized Quantitative Quality Control Tool for Kidney Whole Slide Image Biopsies, Journal of Pathology, 2021

Extended HistoQC to imaging space with MRQy

Sadri A., Janowczyk A., Zhou R., Verma R., Beig N., Antunes J., Madabhushi A., Tiwari P. and Viswanath S., "Technical Note: MRQy -- An Open-Source Tool for Quality Control of MR Imaging Data", Medical Physics, 2020 (In press)

NIH ITCR U01 CA248226
RadxTools for assessing tumor treatment response on imaging

- https://github.com/ccipd/MRQy



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Quick Annotator

An open source digital pathology tool for rapidly annotating objects

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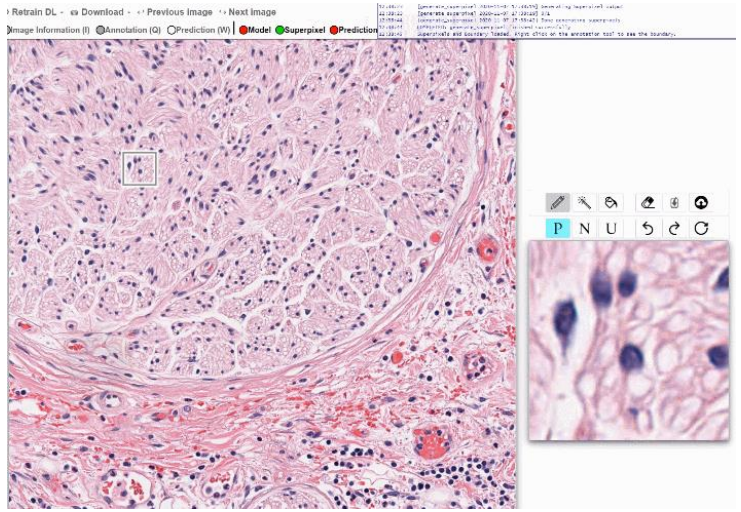
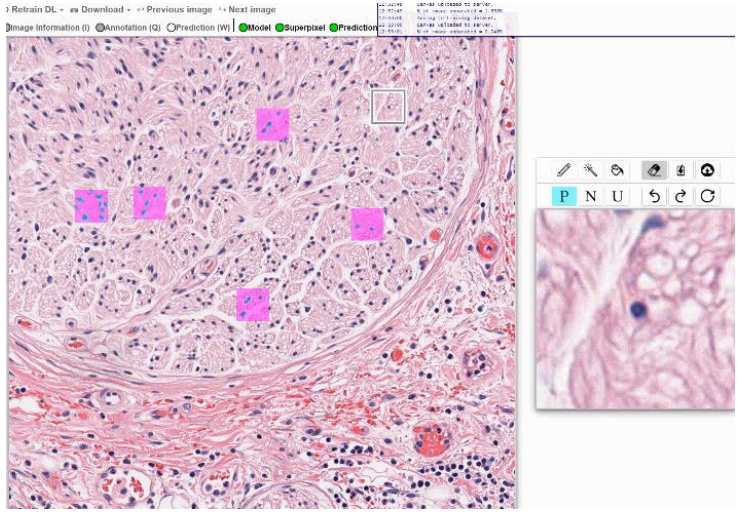
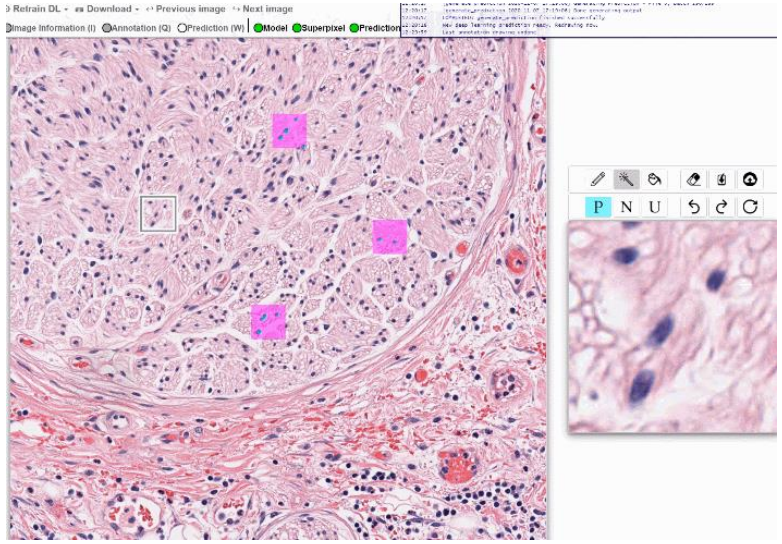
Quick Annotator Approach



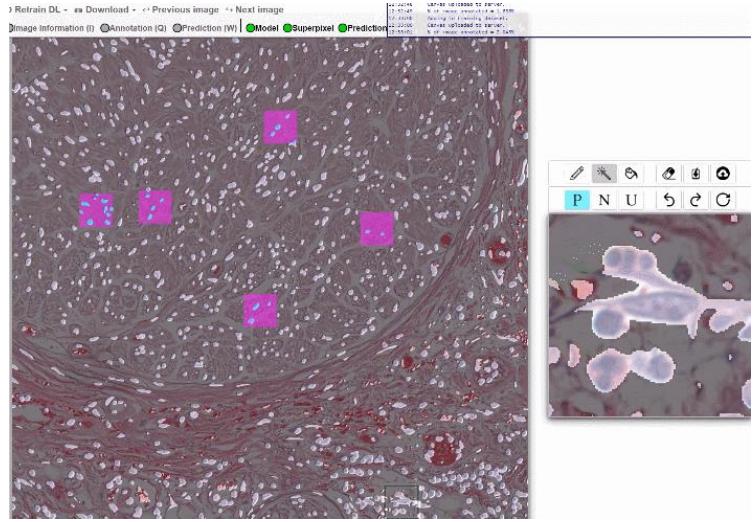
Annotating images



Deep learning prediction



Accept



Revision

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Quick Annotator – Results

- Quick annotator significant improves efficiency of annotation gathering
- Deep learning results in stain and domain agnostic tool
- Potential to improve upon human capabilities
- Tool Open Source for community usage and feedback
- Future work: support whole slide images

Tissue scale	Histologic structure	Number of slides	Number of ROIs	Number of histologic structures	QA total time	QA human time	Manual Time	Speed up	F-score
Small	Cell Nuclei	5	400	337,386	473	391	40,165	102X	0.97
Medium	Tubules	10	100	5,692	121	101	923	9X	0.95
Large	Epithelium	10	100	14,187	167	113	4,433	39X	0.89

https://www.youtube.com/watch?v=J34_lSZn-CM

http://quickannotator.com

Miao R., Toth R., Zhou Y., Madabhushi A., Janowczyk A. “Quick Annotator: an open-source digital pathology based rapid image annotation tool”, The Journal of Pathology: Clinical Research, 2021

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PatchSorter

A High Throughput Digital Pathology Tool for Cell Labeling

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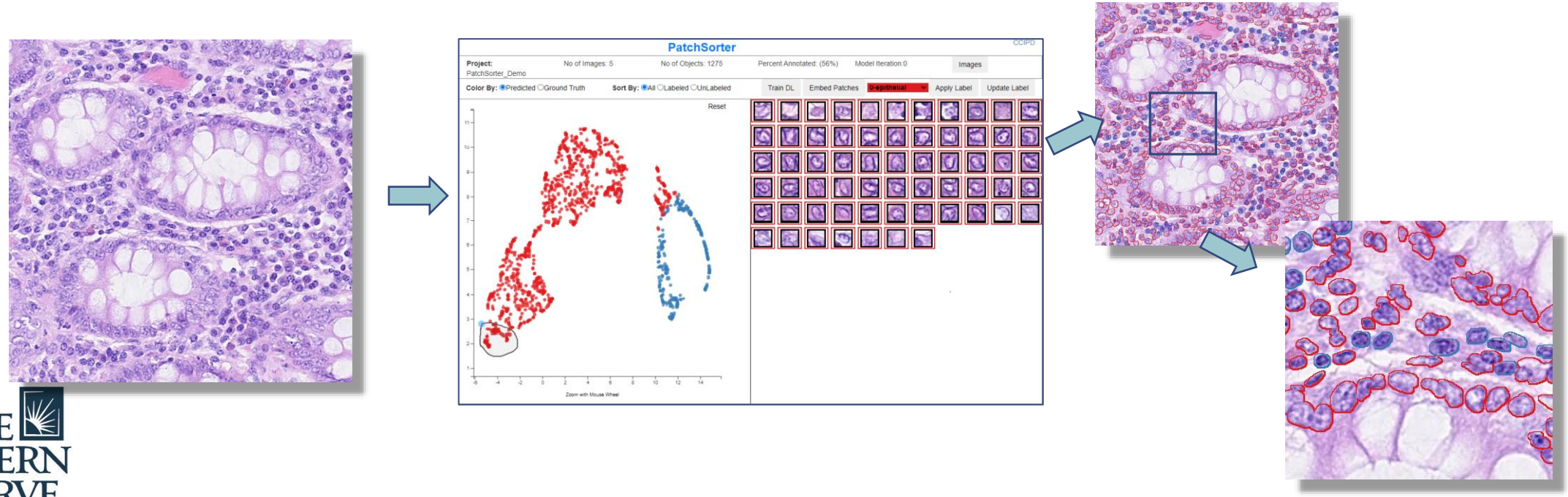
Motivation and Experimental Design

Motivation

- Computational pathology often requires assigning class-types, or labels, to segmented cells.
- Manually labeling the millions of cells present in digital pathology images is intractable at scale.

- PatchSorter enables users to assign labels at a group, as opposed to individual cell level, greatly improving labeling efficiency by over 60%.
- As the backend deep learning model is trained, clusters become more distinct further improving efficiency.



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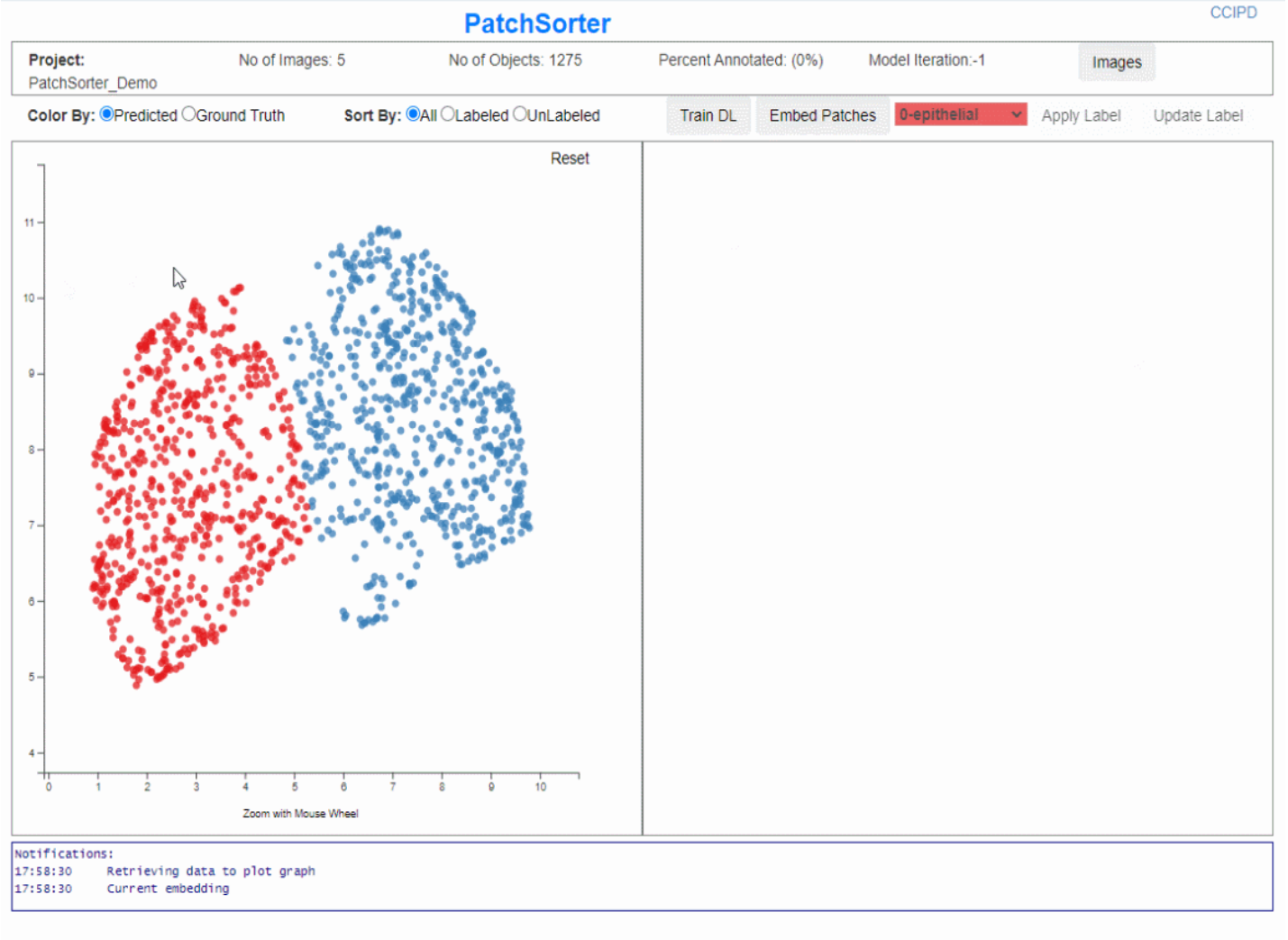
1. S. Graham, Q. D. Vu, S. E. A. Raza, A. Azam, Y-W. Tsang, J. T. Kwak and N. Rajpoot. "HoVer-Net: Simultaneous Segmentation and Classification of Nuclei in Multi-Tissue Histology Images." Medical Image Analysis, Sept. 2019.

Collecting First Set of Labels

- A deep learning model is iteratively trained using provided labels to improve class separation.
- In the left plot, increased separation further facilitates rapid group selection and labeling.
- Options to view labeled or remaining unlabeled cells helps focus effort where needed.



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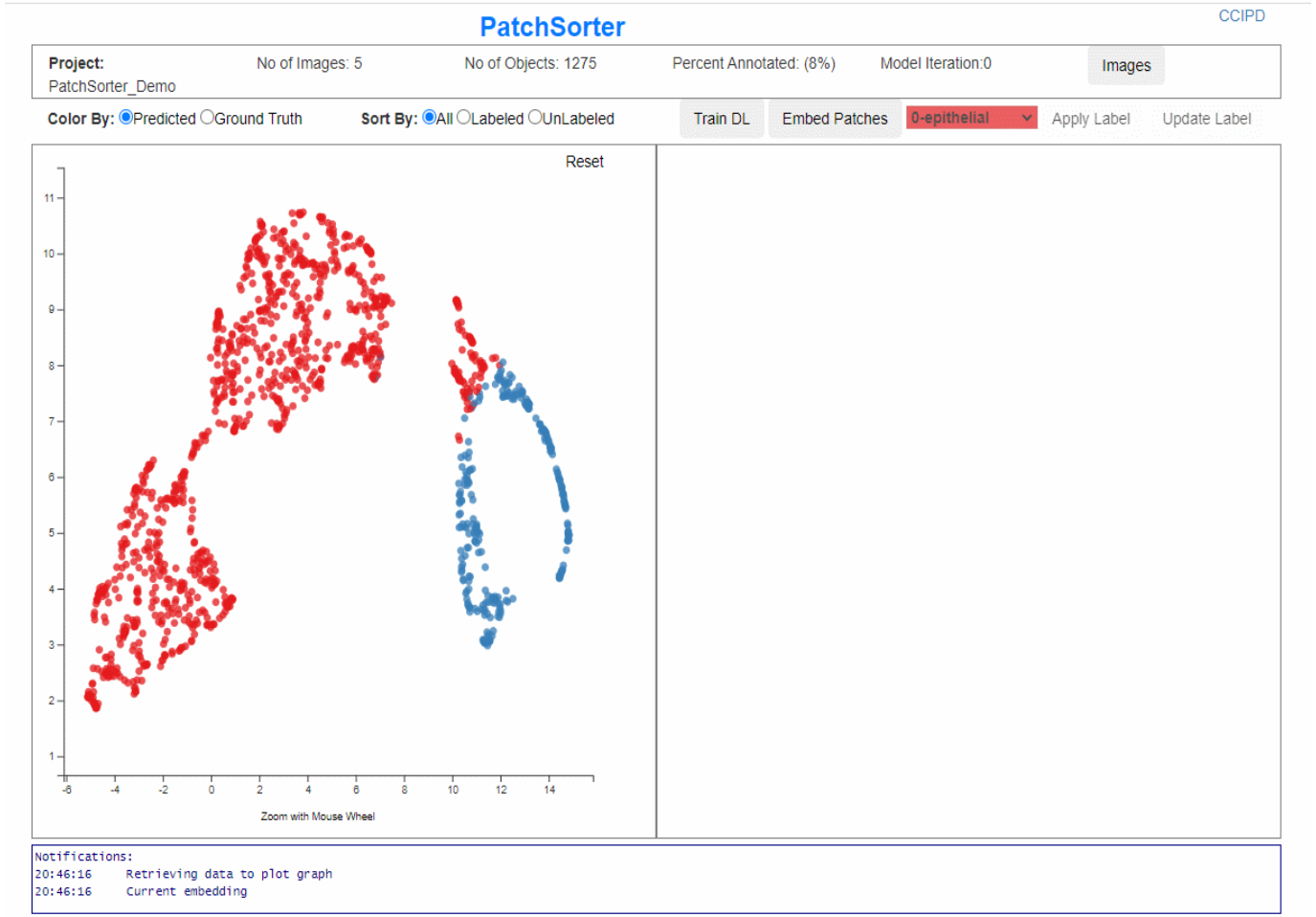
After Deep Learning Model Training

- After importing images, an unsupervised embedding of cells into 2 predicted classes is visible in the plot (left).
- The user lassos points of interest in the plot and subsequently applies a definitive epithelial label (right, red-boxes).
- Importantly, similar cells appear near each other, enabling bulk selection, review, and labeling.



371% efficiency improvement for assigning labels to appropriate objects

Thank you!

Interested in Collaborating? Email me!

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Digital pathology blog: andrewjanowczyk.com

HistoQC: http://histoqc.com

Quick Annotator: http://quickannotator.com

MRQy: https://github.com/ccipd/MRQy

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