Stony Brook University

SUNY

Information Technology Powering Cancer Research for Discover and Novel Hypothesis Generation -- ***Pathomics***

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Stony Brook University

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BHI

- Pathology data is employed in care guidelines and clinical settings for virtually all cancer disease sites.
- Treatment decisions frequently hinge on subjective assessments -- poor inter-observer reproducibility.
- Widespread clinical adoption of Digital Pathology platforms in coming years
- Combination of Digital Pathology platforms and maturing of machine learning and artificial intelligence methodology will make possible adoption of image data driven decision support systems.
- Development and adoption of such systems will have tremendous impact on improving quality and consistency of clinical decision making.

Tools to Analyze Morphology and Spatially Mapped Molecular Data - U24 CA180924

- **Specific Aim 1** Analysis **pipelines** for multi- scale, integrative image analysis.
- **Specific Aim 2: Database** infrastructure to manage and query Pathomics features.
- **Specific Aim 3:** HPC software that targets **clusters, cloud computing, and leadership scale systems.**
- **Specific Aim 4:** Develop **visualization** middleware to relate Pathomics feature and image data and to integrate Pathomics image and “omic” data.

SEER Virtual Tissue Repository

Vision – Enable population/epidemiological cancer research that leverages rich cancer phenotype information available from Pathology tissue studies

NCIP/Leidos 14X138 and HHSN261200800001E - NCI

- Lynne Penberthy MD, MPH NCI SEER
- Ed Helton PhD NCI CBIIT Clinical Imaging Program
- Ulrike Wagner CBIIT Clinical Imaging Program
- Radim Moravec NCI PhD, NCI SEER
- Ashish Sharma PhD Biomedical Informatics Emory
- Joel Saltz MD, PhD Biomedical Informatics Stony Brook
- Tahsin Kurc PhD Biomedical Informatics Stony Brook
- Georgia Tourassi, Oak Ridge National Laboratory

SEER Virtual Tissue Repository

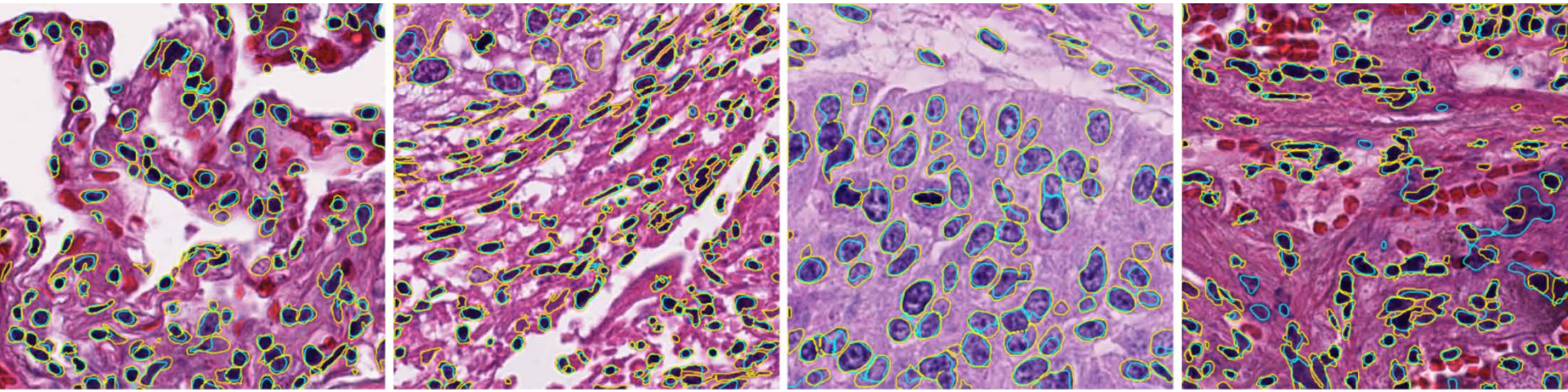
- SEER registries are a potential source of information about unusual outcomes and rare cancers
- Leverage Pathology labs which store FFPE tumors, slides and digital images
- Link to SEER data – track long term outcomes
- SEER: 500K Cancer patients ***per year***
- Accrue linked clinical data, Pathology slides from SEER sites

SEER VIRTUAL TISSUE REPOSITORY

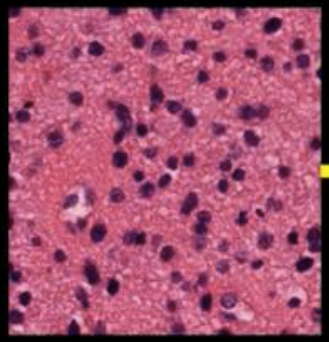
- Create linked collection of de-identified clinical data and whole slide images
- Extract features from a sample set of images (pancreas and breast cancer).
- Enable search, analysis, epidemiological characterization
- Pilot focus on extreme outcome Breast Cancer, Pancreatic Cancer cases
- Display images and analyzed features

Robust Nuclear Segmentation

- Robust ensemble algorithm to segment nuclei across tissue types
- Optimized algorithm tuning methods
- Parameter exploration to optimize quality
- Systematic Quality Control pipeline encompassing tissue image quality, human generated ground truth, convolutional neural network critique
- Yi Gao, Allen Tannenbaum, Dimitris Samaras, Le Hou, Tahsin Kurc



Whole Slide Images (WSI)



Segmentation Parameters

Compute Cluster

Process the images for subjects selected

Compute object-level (nucleus-level) image features

Compute aggregated patient-level image features from object-level features

FeatureDB

- Load object-level imaging features and segmentation results
- Load patient-level imaging features along with a selected subset of clinical and genomic data (e.g. gene mutations, days to death, vital status)

Feature Viz Suite

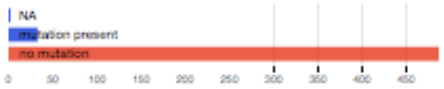
- Explore Relationship Between Imaging Features, Outcome, ”omics”
- Explore relationships between features and explore how features relate to images

Feature Explorer - Integrated Pathomics Features, Outcomes and "omics" – TCGA NSCLC Adeno Carcinoma Patients

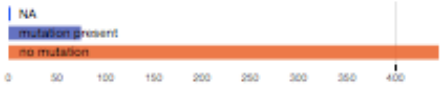
Gene Mutation

Click on bars to select molecular cohorts,
Xaxis: # patients; Yaxis: mutation status
[blue-red] color range indicates fraction of total.

EGFR

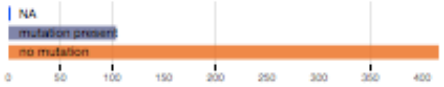


KRAS

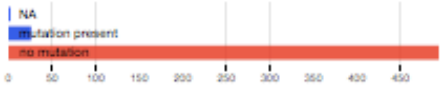


STK11_LKB1

TP53



NF1



BRAF

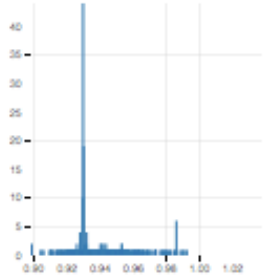
SETD2

Morphology, Epi, etc

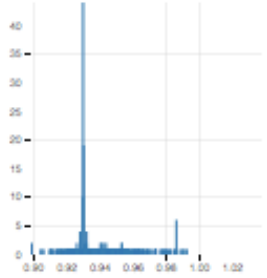
Var 1: Roundness_median
Var 2: StdR_median

Slide mouse click to select ranges
Xaxis: parameter value
Yaxis: #patients

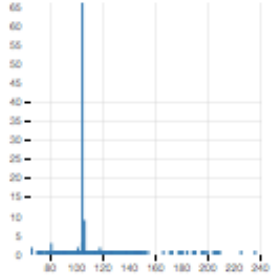
Var 1: Roundness_median



Var 1 Zoom: Roundness_median

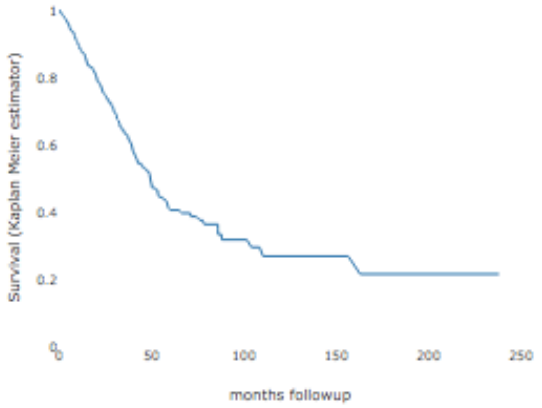


Var 2: StdR_median

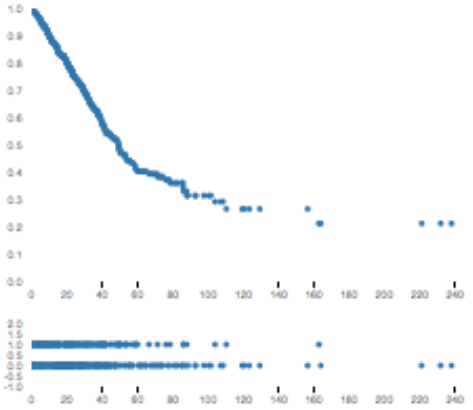


Survival

Blue - whole population; Orange - selected cohort



Zoomable KM estimator (i.e. select ranges, each dot is a patient)



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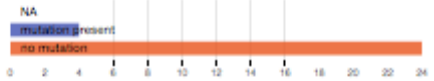

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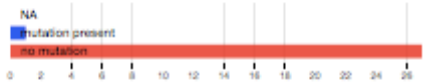

Morphology, Epi, etc

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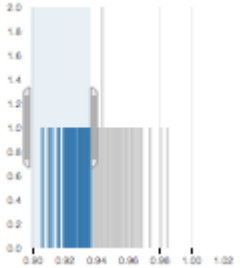
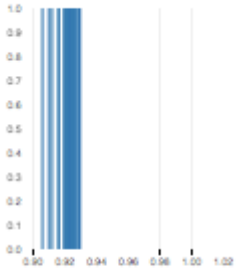
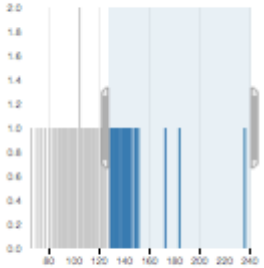


Var 1 Zoom: Roundness_median



Var 2: StdR_median



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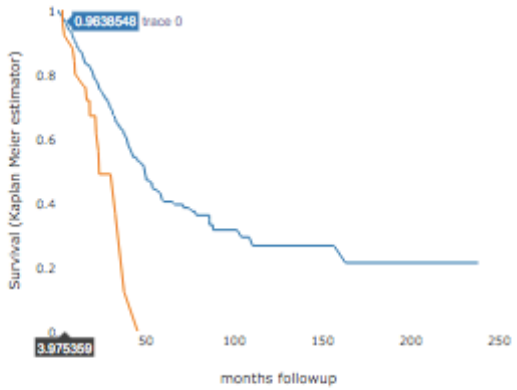

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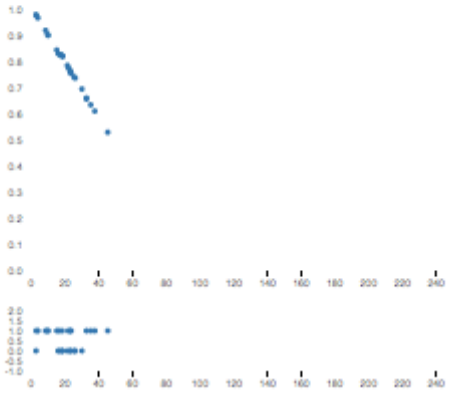
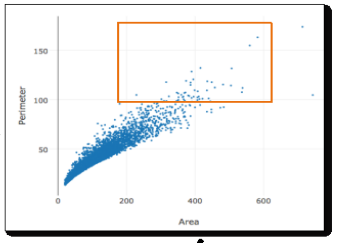


Pathomics

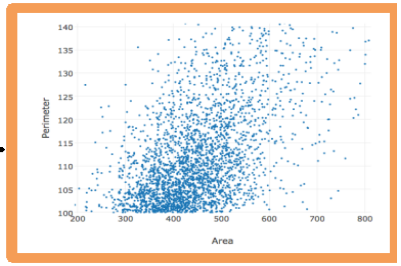
Relationship Between Image and Features

Step 1: Choose a case from the TCGA atlas (case #20)

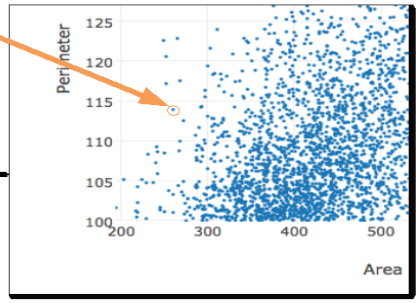
Step 2: Select two features of interest; X axis (*area*), Y axis (*perimeter*)



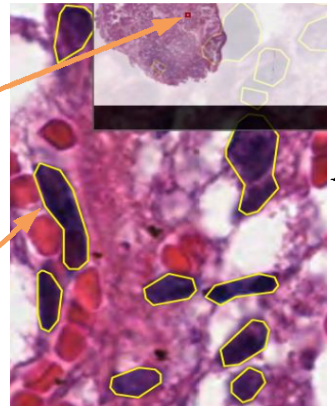
Step 3: Zoom in on region of interest



Step 4: Pick a specific nucleus of interest. Each dot represents a single nucleus



Step 5: Evaluate the features selected in the context of the specific nucleus and where this nucleus is located within the whole slide image



The tool provides visual context for feature evaluation. This technique maps both intuitive features (i.e. size, shape, color) and non-intuitive features (i.e. wavelets, texture) to the ground truth of source images through an interactive web-based user interface.

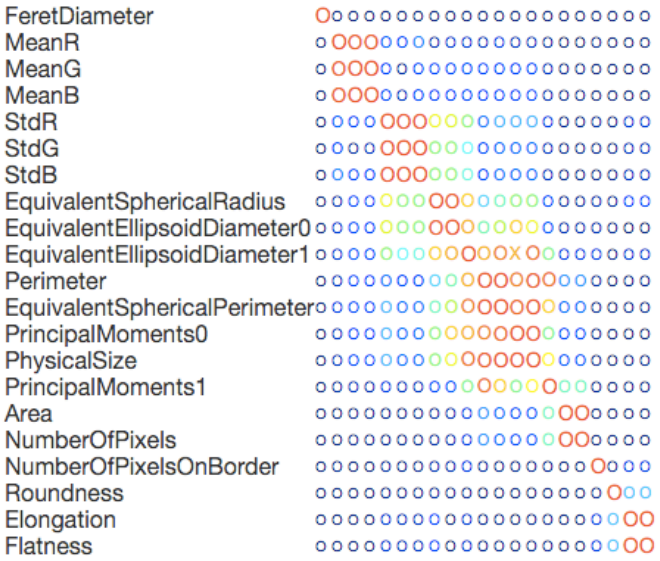
Select Feature Pair – dots correspond to nuclei

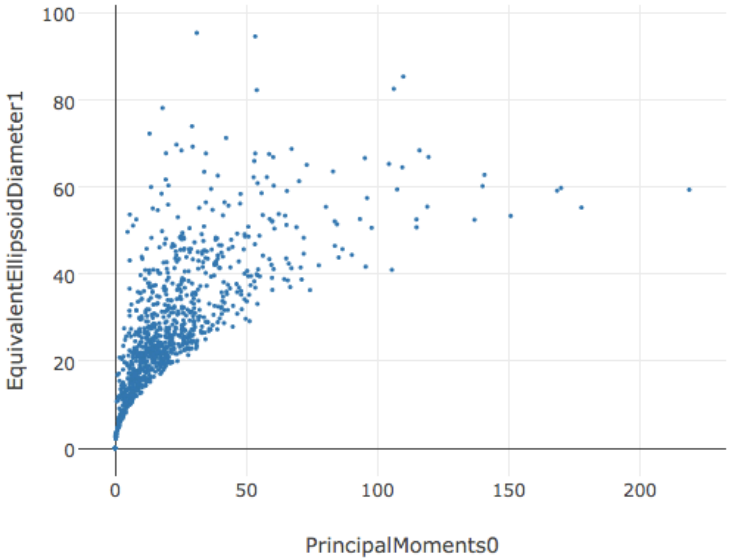
FeatureScape ← Preliminary demo of integrative use of multiple FeatureScape tools

1000 entries sampled from https://tahsin175.informatics.stonybrook.edu:4500/?limit=1000&find={%22randval%22:{%22$gte%22:0.149},%22provenance.analysis_execution_id%22:%22lung-features-v4%22,%22image.caseid%22:%22TCGA-38-4628-01Z-00-DX1%22}

+ Load Data

Cross-tabulated feature correlations





Pearson correlation between

- PrincipalMoments0
- EquivalentEllipsoidDiameter1

Resample from selected region (under development)

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Subregion selected – form of gating analogous to flow cytometry

FeatureScape

← Preliminary demo of integrative use of multiple FeatureScape tools

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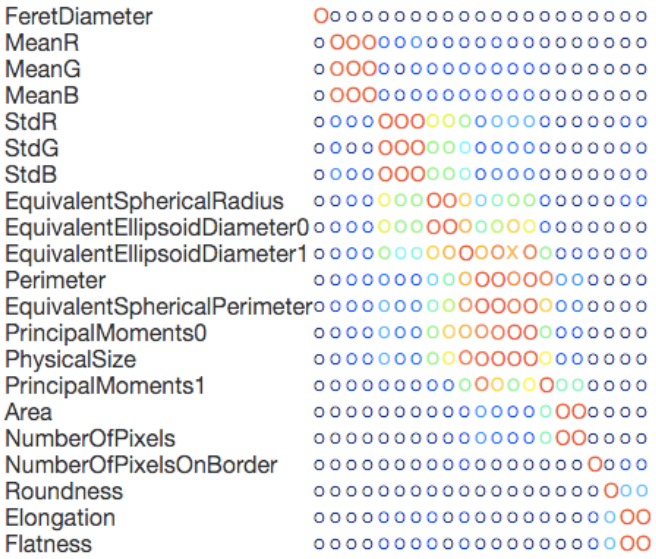

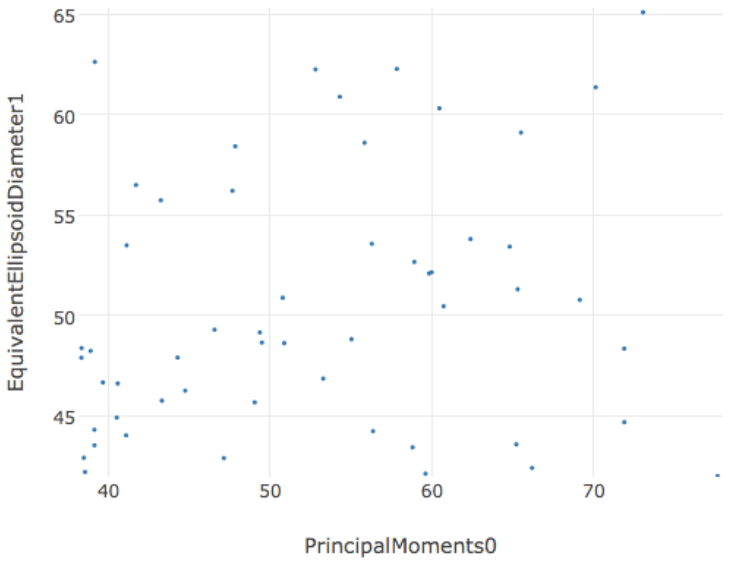

Pearson correlation between

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Resample from selected region (under development)

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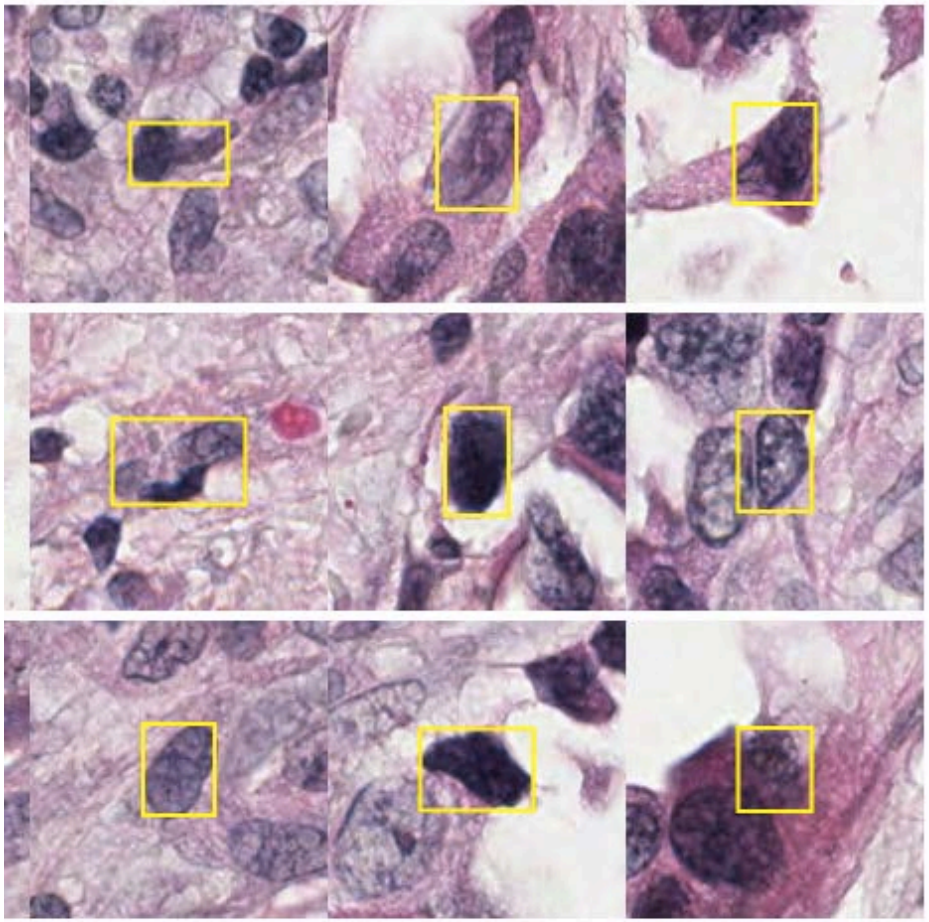
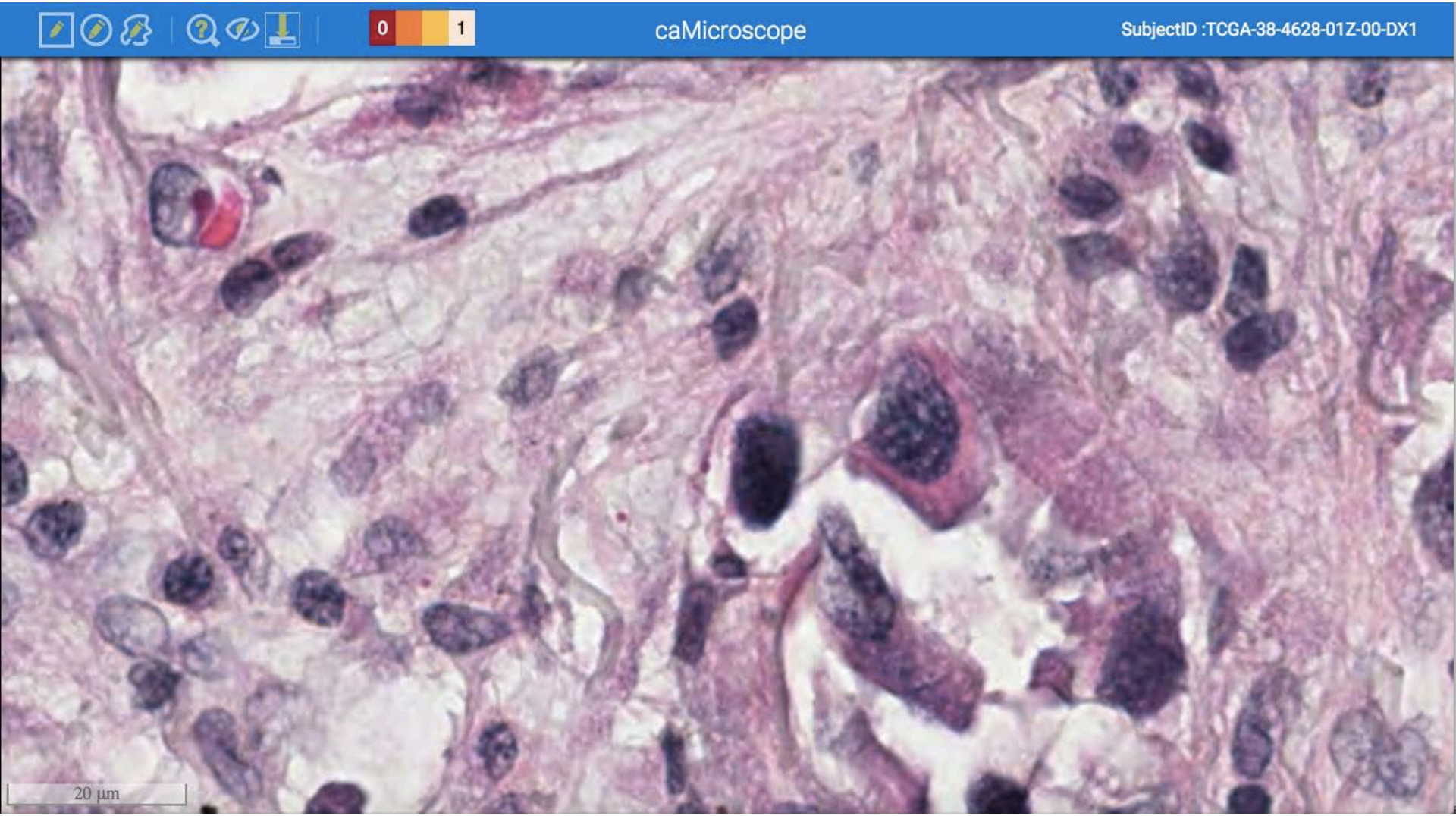
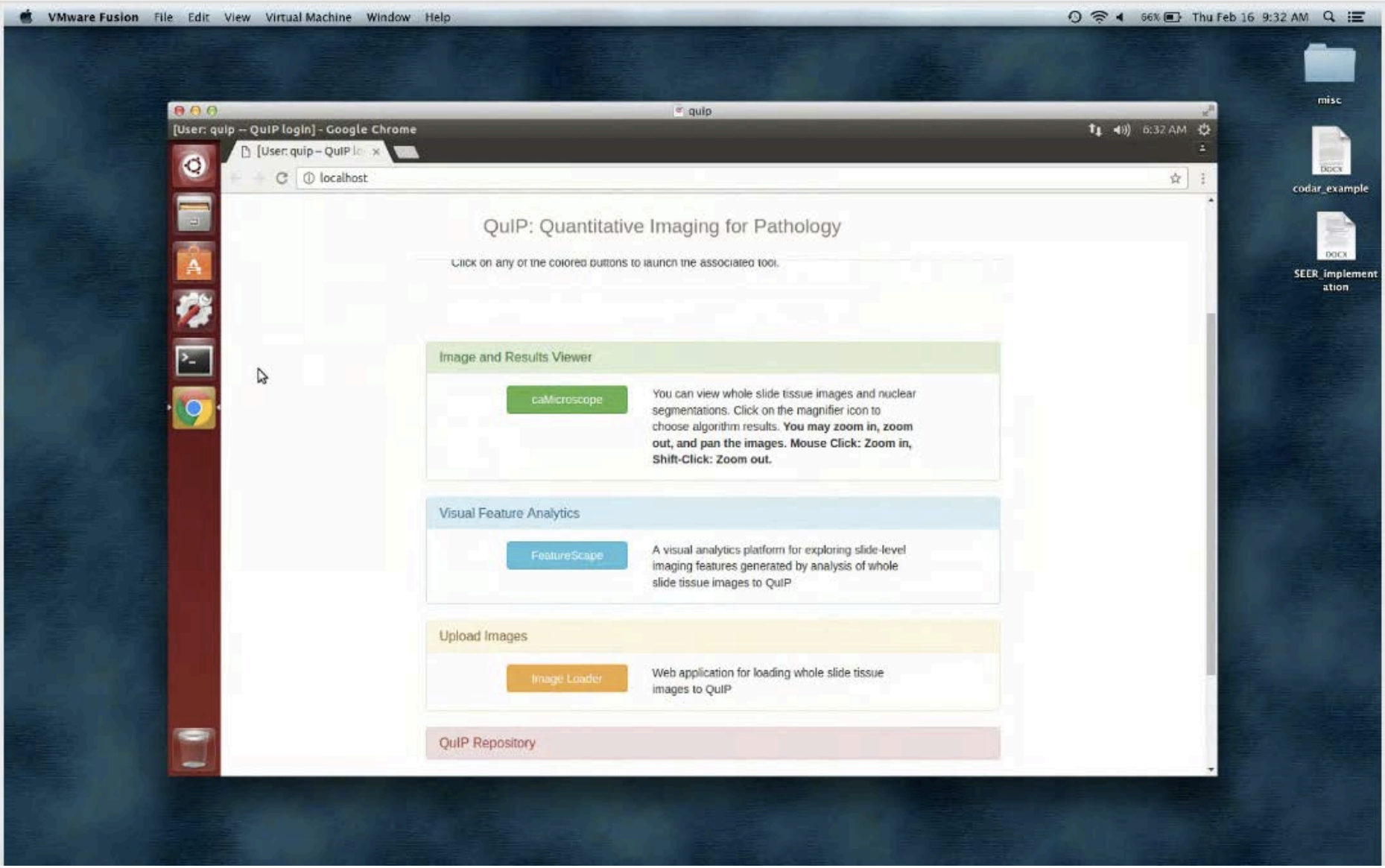
Sample Nuclei from Gated Region



Gated Nuclei in Context

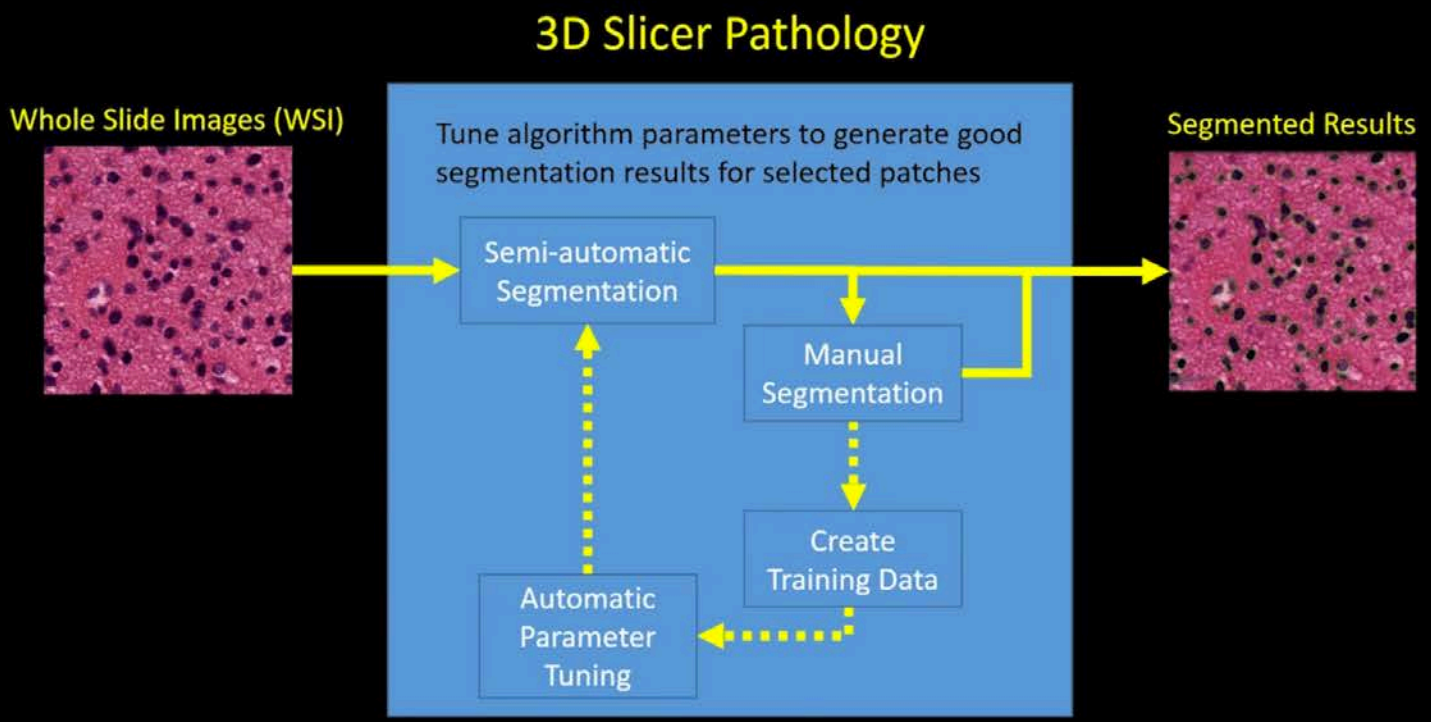


Docker and Virtual Machine Distributions



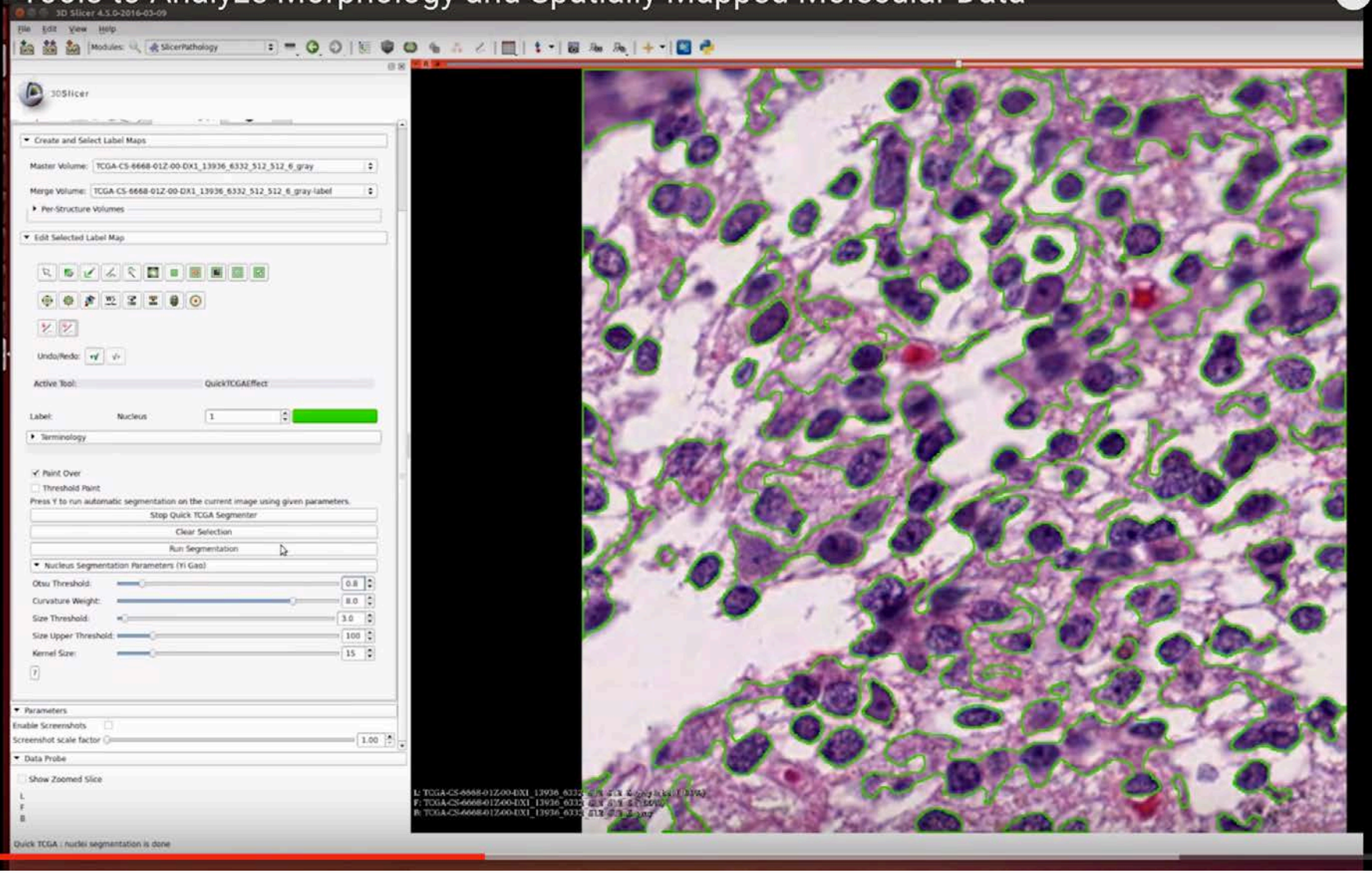
3D Slicer Pathology – Generate High Quality Ground Truth

ITCR - Tools to Analyze Morphology and Spatially Mapped Molecular Data

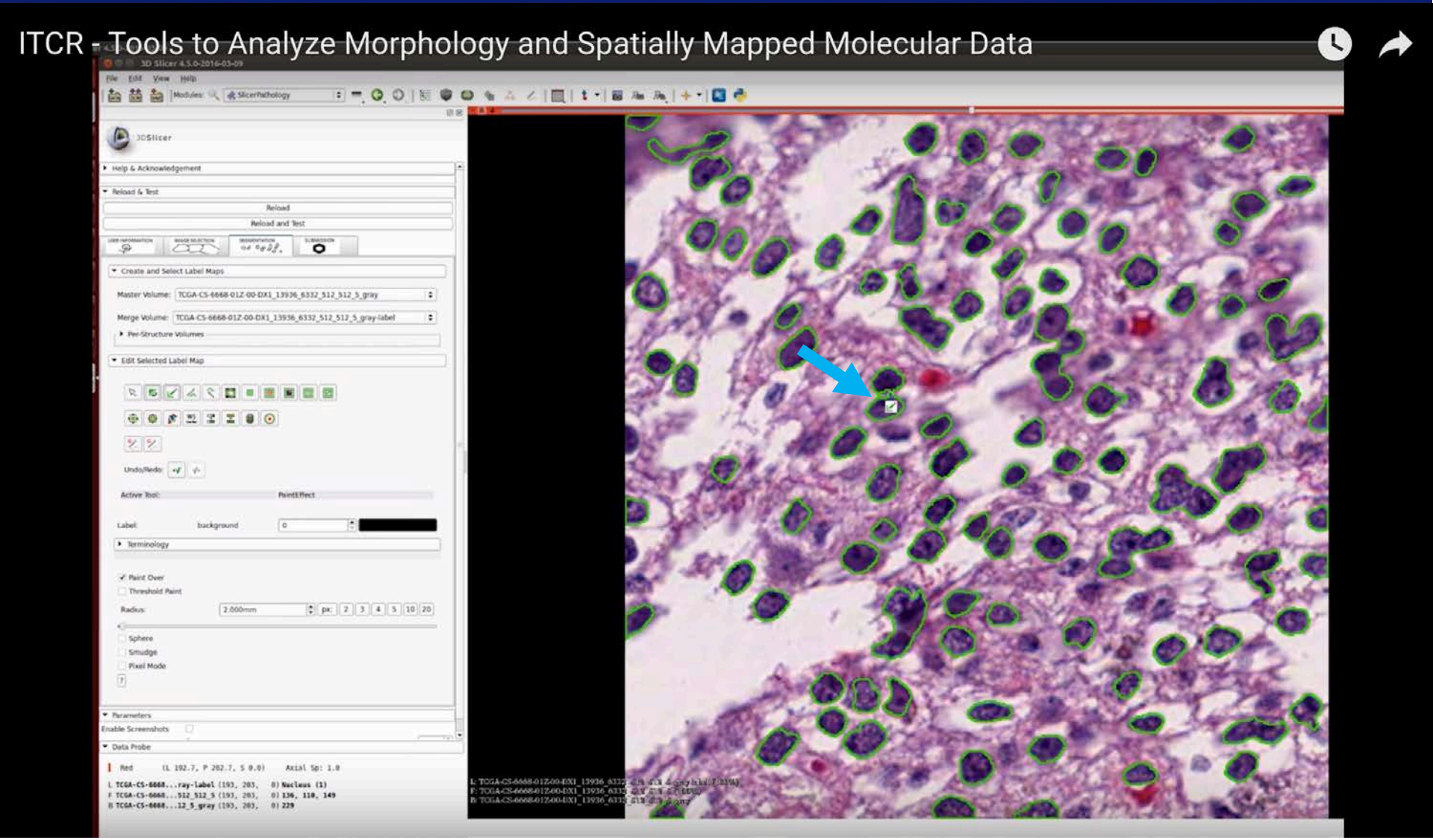


Apply Segmentation Algorithm

ITCR - Tools to Analyze Morphology and Spatially Mapped Molecular Data



Adjust algorithm parameters, manual fine tuning



Classification

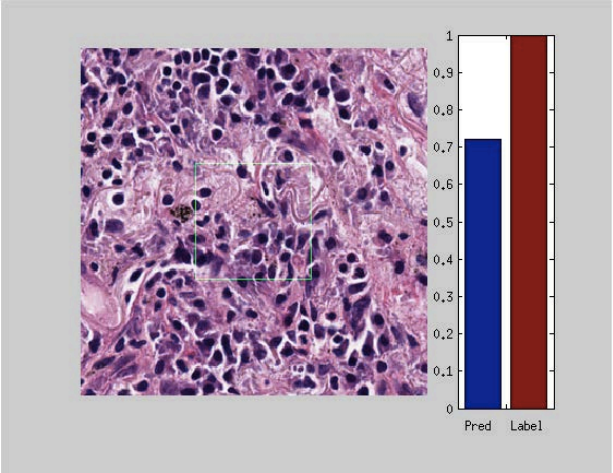
- Automated or semi-automated identification of tissue or cell type
- Variety of machine learning and deep learning methods
- **Quantification of lymphocyte infiltration**
  - **Collaboration with TCGA Pan Can Atlas Immune Group**
- Classification of Neuroblastoma
- Classification of Gliomas

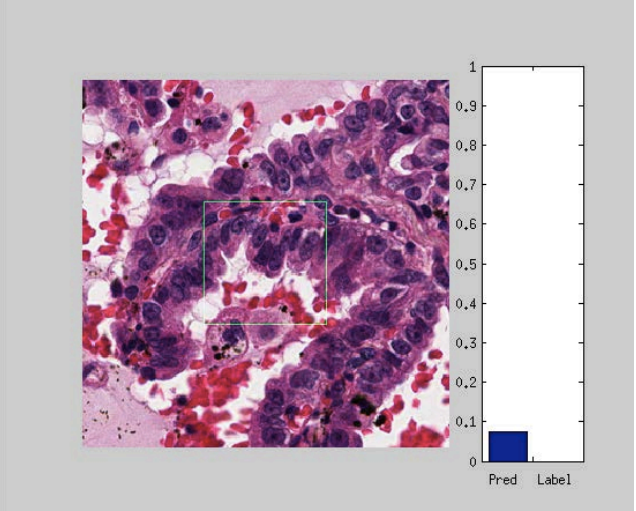
Team

- TCGA Pan Can Immune:
  - Vesteinn Thorsson
  - Iya Shmulevich
- TIL Project Leads
  - Joel Saltz
  - Dimitris Samaras
  - Tahsin Kurc
  - Alex Lazar
- caMicroscope Lead
  - Ashish Sharma
- Deep Learning Graduate Students
  - Le Hou
  - Vu Nyugen
- Pathology Fellows/ Faculty
  - Anne Zhao
  - John Van Arnam
  - Rebecca Batiste
- Biostatistics
  - Arvind Rao
- Active Learning Collaborator
  - Lee Cooper

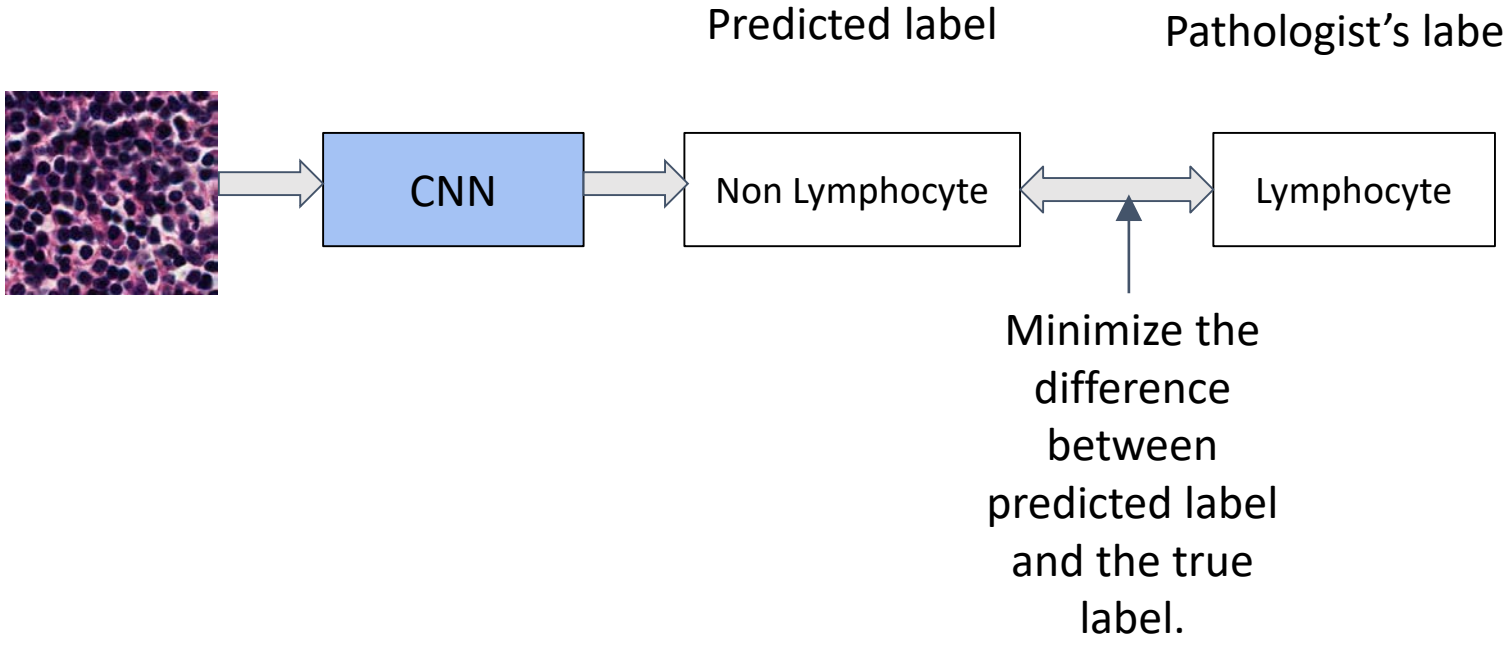
TCGA PanCan TILS Collaborative Effort

- Deep learning algorithm trained on 20K+ patches
- Pathologist correction is essential to reduce false positives as there are many patches.
- ***GUI developed to accomplish this – rolled out to TCGA Pathologists***
- ***TCGA TIL rich tumors including – NSCLC adenocarcinoma, breast, pancreatic, colorectal, skin and uveal melanoma***
- ***Working group of TCGA Pathologists - leverage tool to generate TCGA TIL data and TIL maps (Alex Lazar)***
- ***CNN Algorithm presented at USCAP 2017 – Zhao et al***

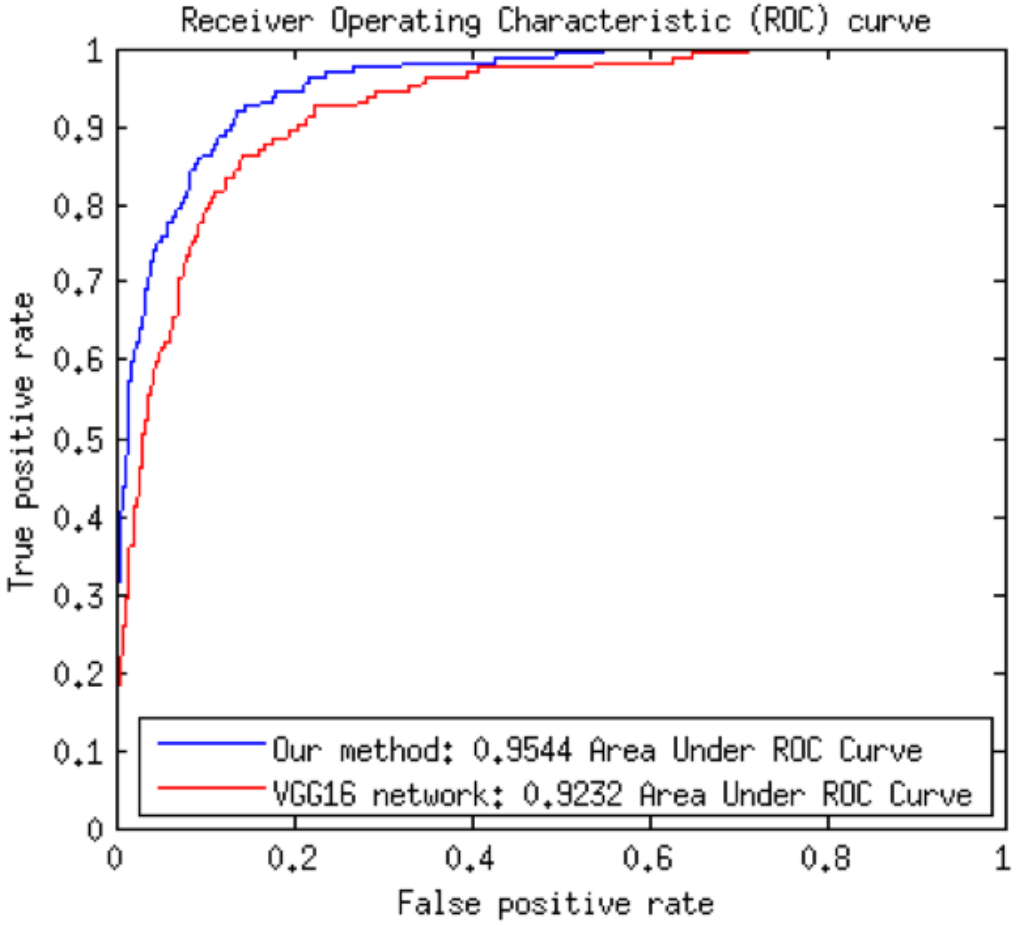




Training a CNN



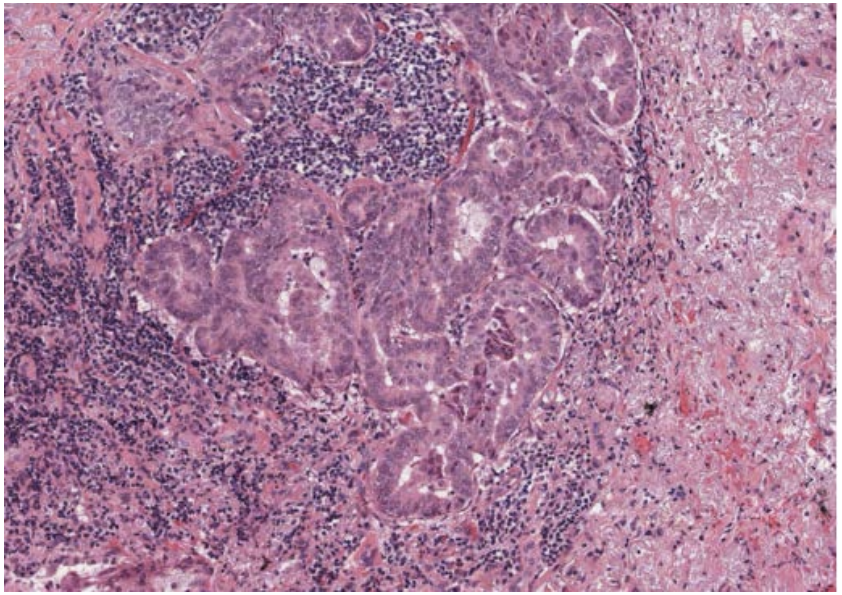
Patch Based Performance Evaluation of CNN Classification – TCGA Non Small Cell Lung Cancer



Lymphocyte Classification Heat Map

Trained with 22.2K image patches

Pathologist corrects and edits



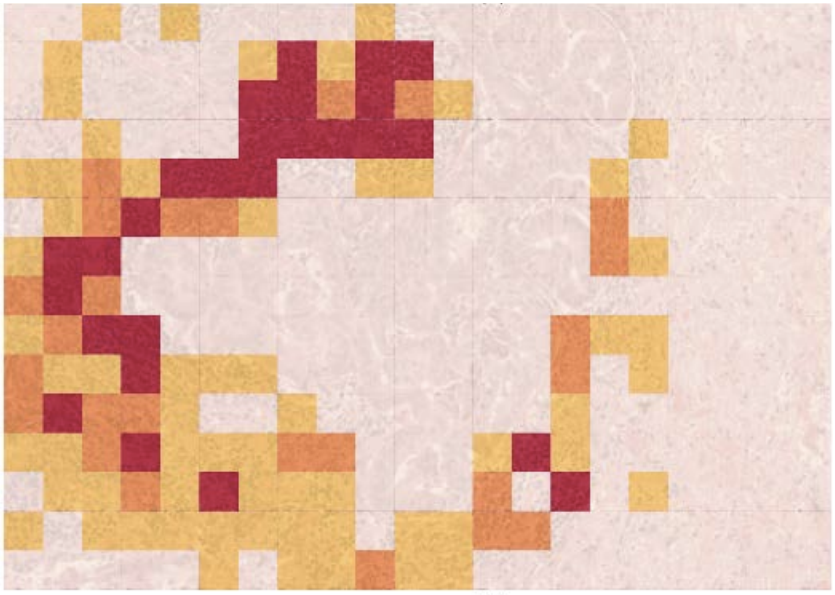
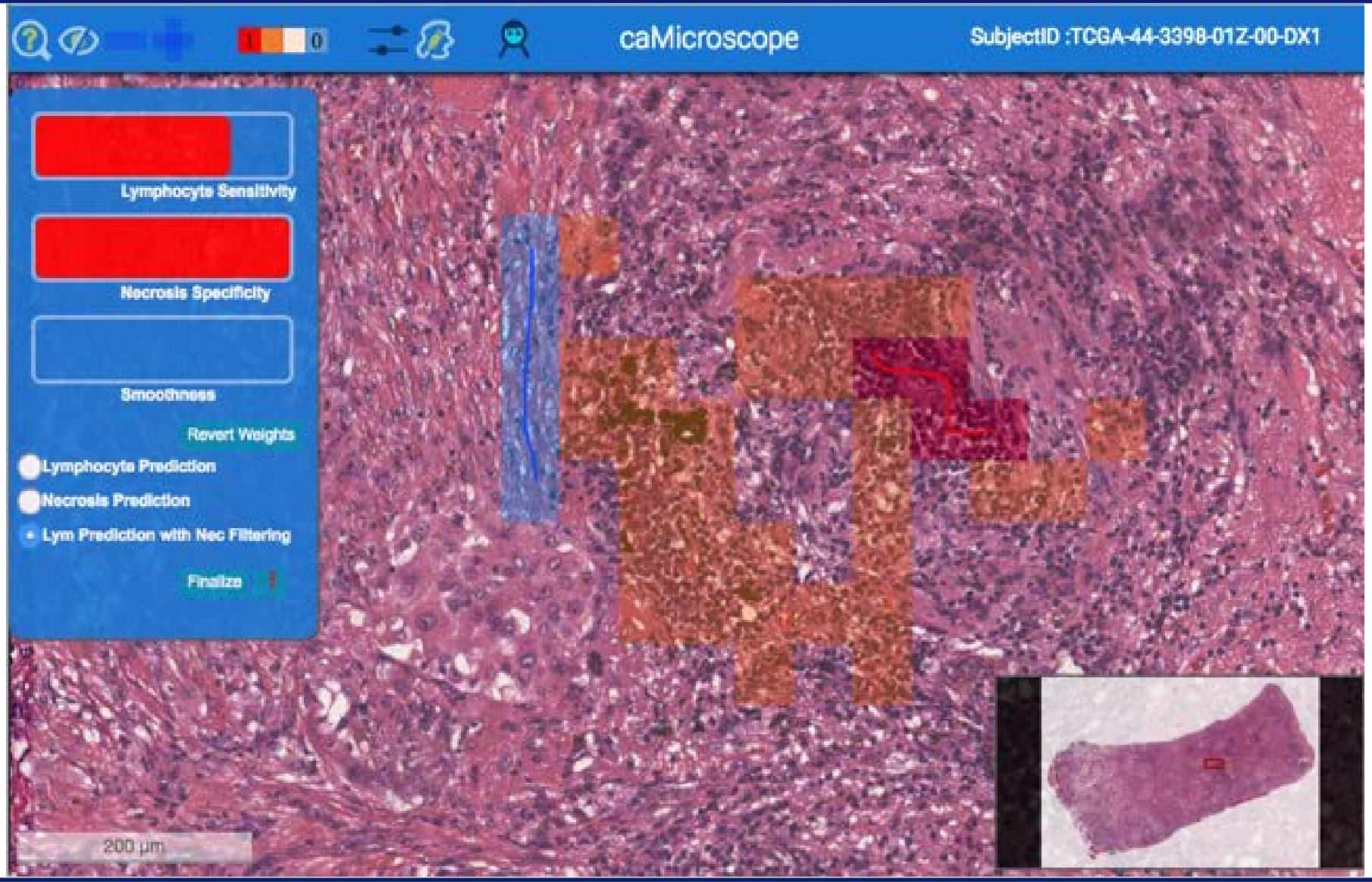


Image based TIL prediction

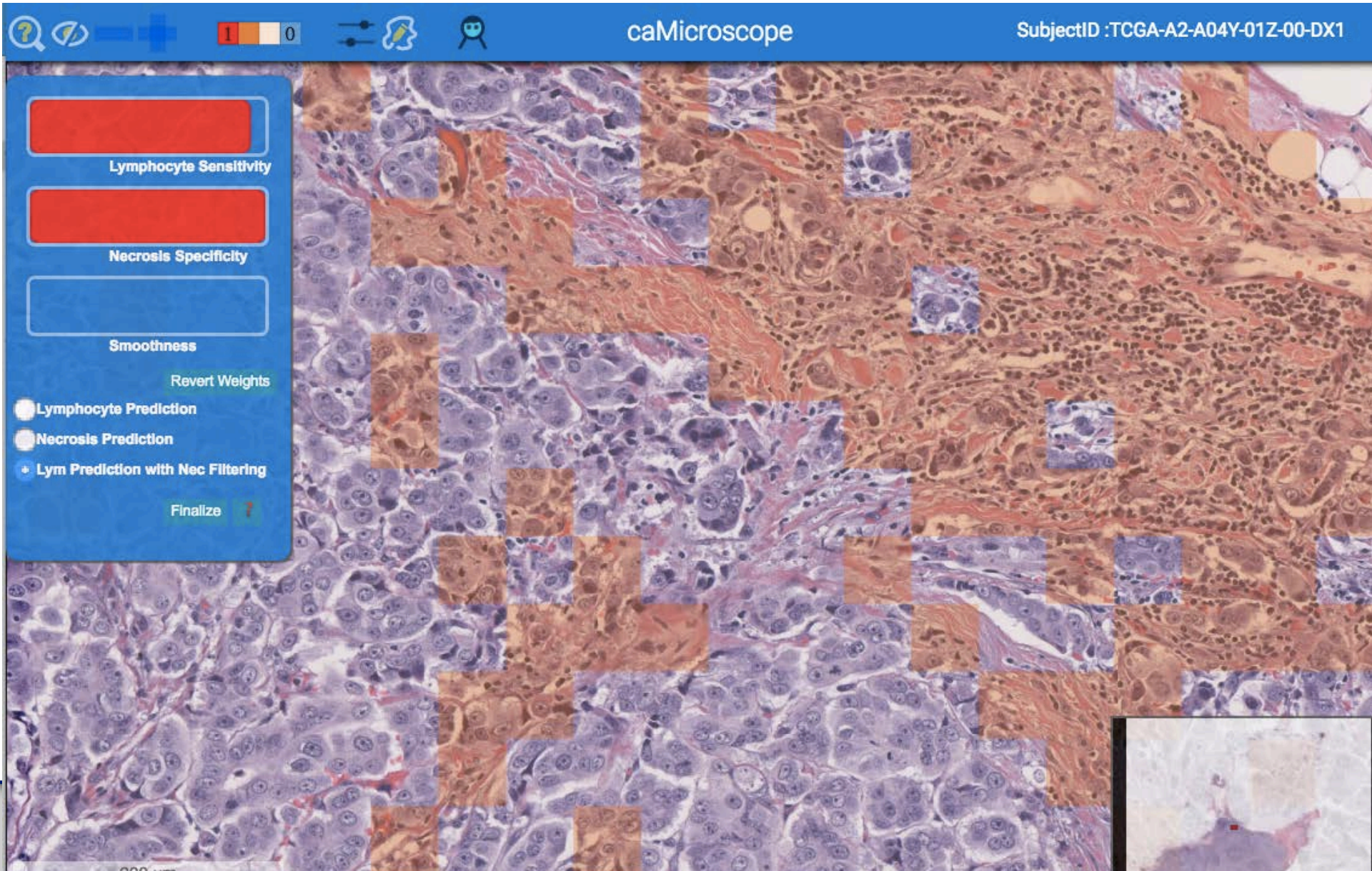
- Initial unsupervised training step (autoencoder) - initialize CNN
- Train CNN on initial supervised dataset
- Apply CNN to obtain predicted lymphcyte heatmaps
- Pathologists edit heatmaps using caMicroscope
- Extract new training data from edited heatmaps
- Sampling algorithm to adjust thresholds

  - USCAP 2017 Zhao et al, submitted publication to International Conference on Computer Vision

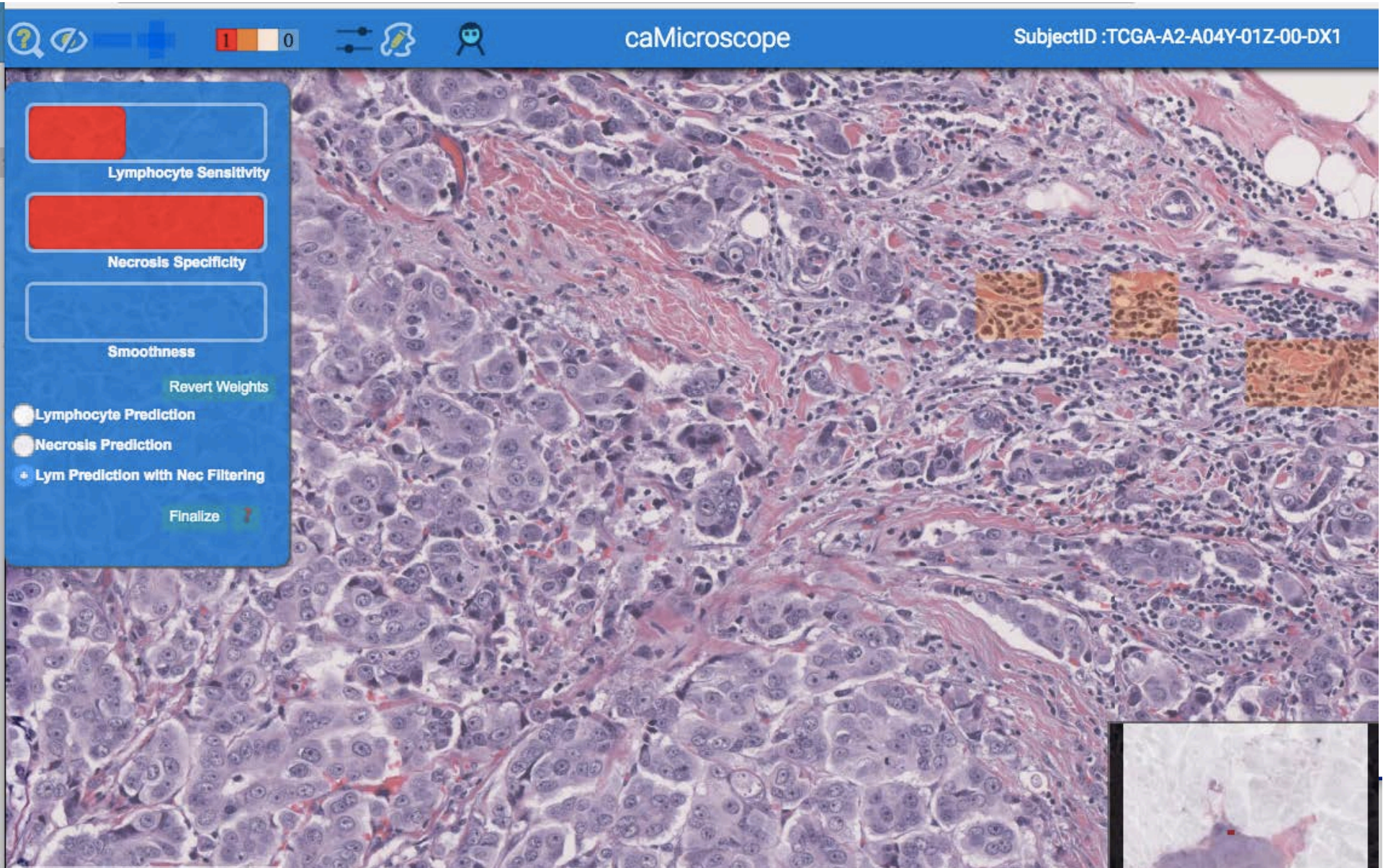
caMicroscope with TIL heatmap



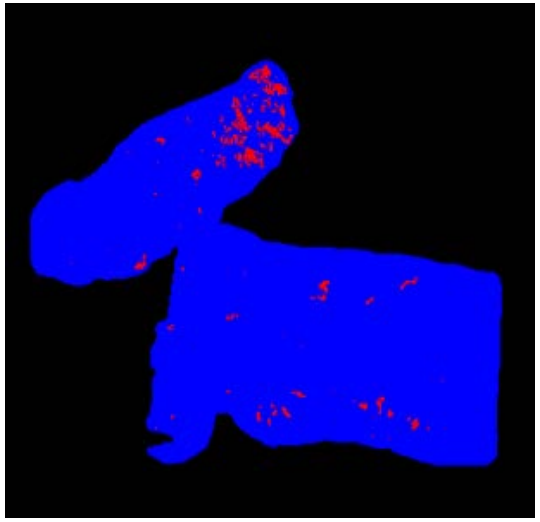
Adjust sensitivity - High



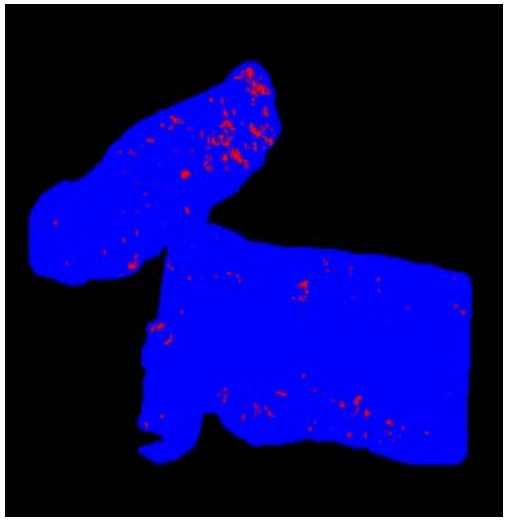
Adjust sensitivity - Low



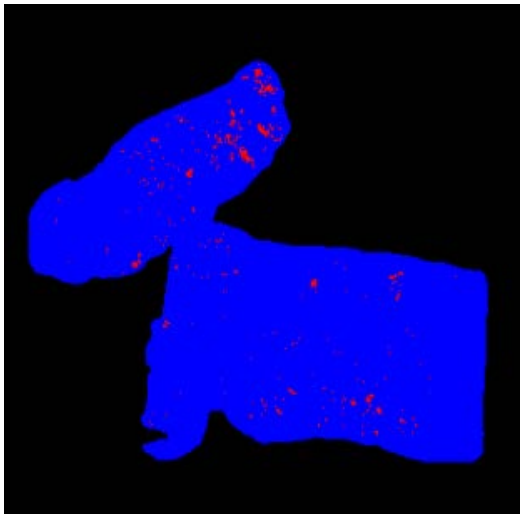
TIL Distribution Maps



Prediction edited by Pathologist 1



Prediction without editing



Prediction edited by Pathologist 2

Tissue Specimen

TCGA Pan Can Immune

- Roughly 3.5K TIL maps generated to date with pipeline on track to complete roughly 10K by mid-April
- Comparison with TIL molecular epigenetic and RNA seq data
- Initial draft manuscript completed March 24th
- Deeper dive into TCGA “omics” analytics

Dissemination

- *Containers*
  - *Containerized segmentation algorithm/FeatureDB Employed to support TIES, MICCAI, and competitions supported through Kalpathy-Kramer ITCR*
  - *Full containerized implementation of caMicroscope/FeatureDB/Segmentation algorithm/Feature Scape - Feb 1 2017*
- Cloud Pilots
- TCIA
- HPC via NSF and DOE
- TCGA – PanCanAtlas – Lymphocyte characterization
- Integrated Features/NLP joint with TIES

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Thanks!