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Pathomics Based Biomarkers, Tools and Methods

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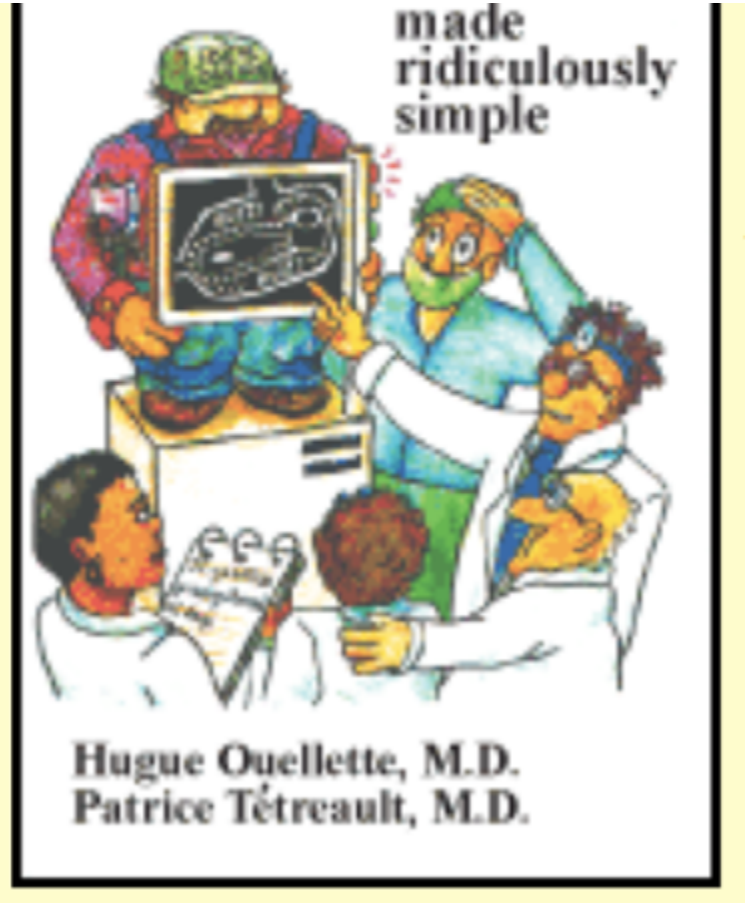
Imaging Community Call

October 24, 2016

Stony Brook University

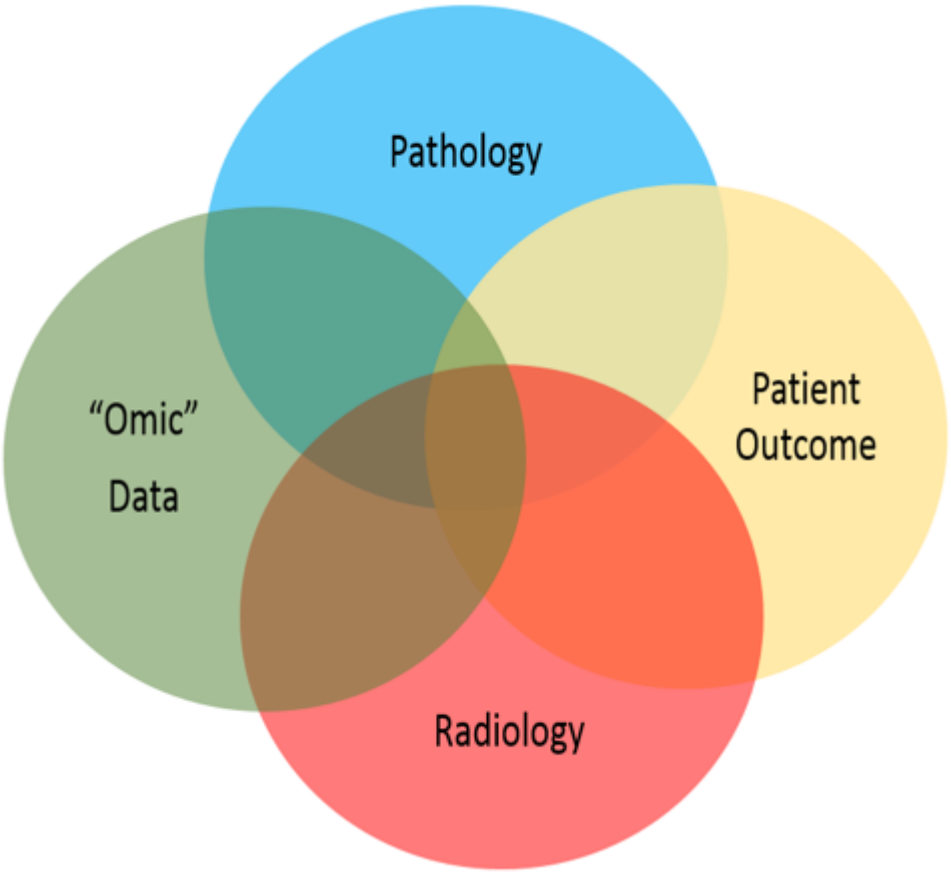
SUNY

Multi-Scale Precision Medicine



Multi-scale Integrative Analysis in Biomedical Informatics

- Predict treatment outcome, select, monitor treatments
- Reduce inter-observer variability in diagnosis
- Computer assisted exploration of new classification schemes
- Multi-scale cancer simulations



Pathomics, Radiomics

Identify and segment trillions of objects – nuclei, glands, ducts, nodules, tumor niches … from Pathology, Radiology imaging datasets

Extract features from objects and spatio-temporal regions

Support queries against ensembles of features extracted from multiple datasets

Statistical analyses and machine learning to link Radiology/Pathology features to “omics” and outcome biological phenomena

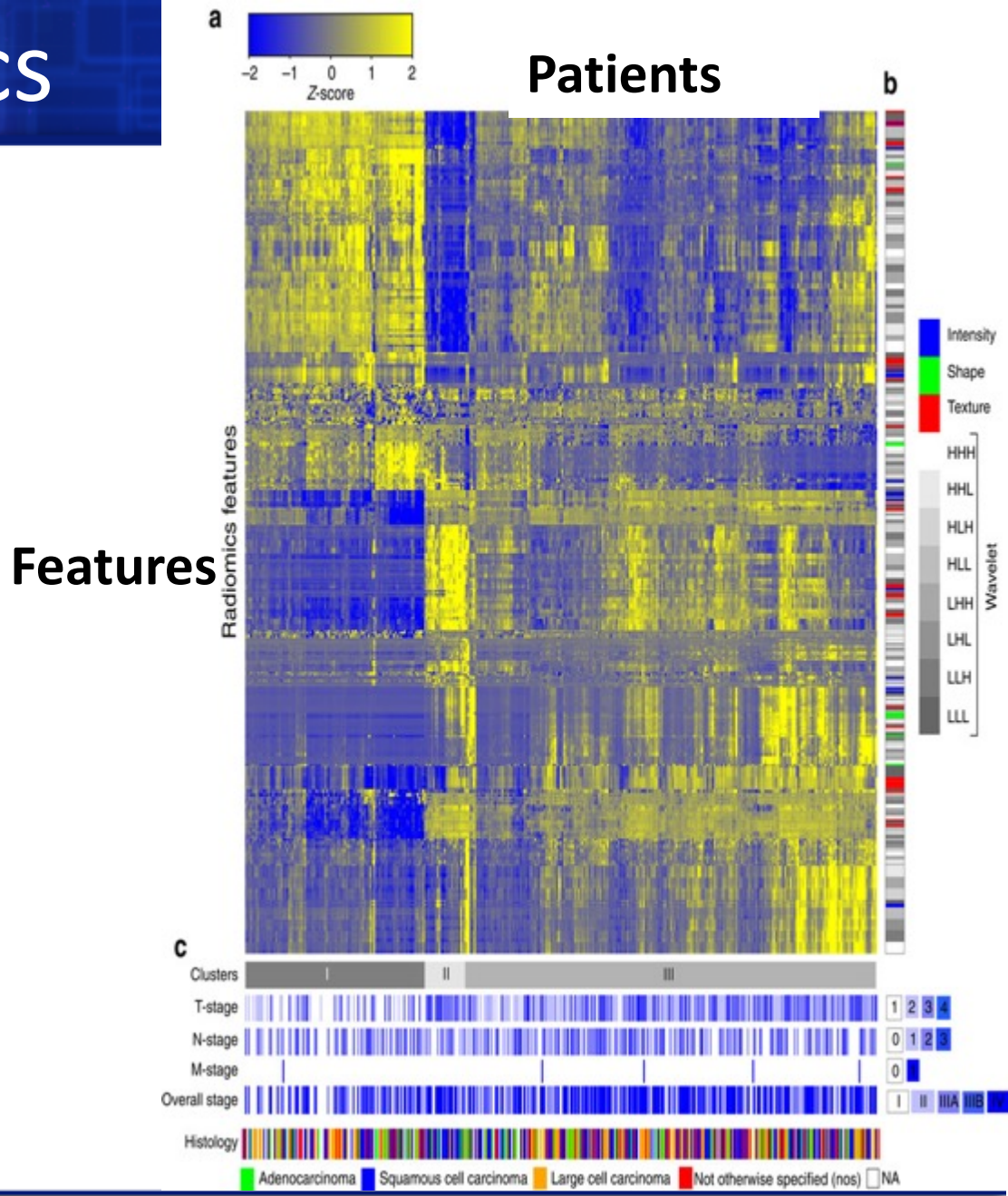
Principle based analyses to bridge spatio-temporal scales – linked Pathology, Radiology studies

Radiomics

[Decoding tumour phenotype by noninvasive imaging using a quantitative radiomics approach]

Hugo J. W. L. Aerts et. Al.

Nature Communications **5**, Article number: 4006
doi:10.1038/ncomms5006



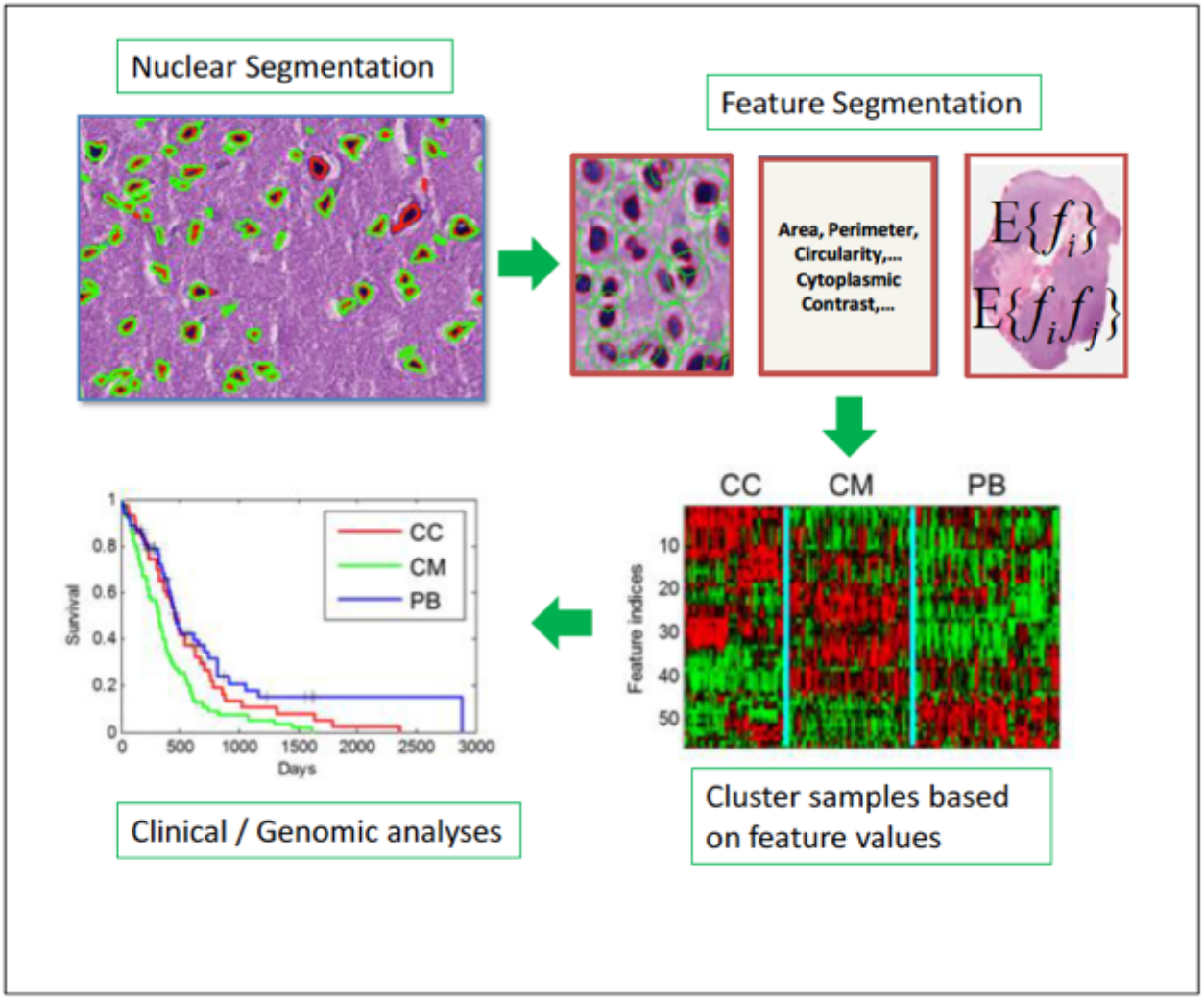
Pathomics

Integrative Morphology/"omics"

Quantitative Feature Analysis in Pathology: Emory In Silico Center for Brain Tumor Research (PI = Dan Brat, PD= Joel Saltz)

NLM/NCI: Integrative Analysis/Digital Pathology R01LM011119, R01LM009239 (Dual PIs Joel Saltz, David Foran)

J Am Med Inform Assoc. 2012 **Integrated morphologic analysis for the identification and characterization of disease subtypes**.



Lee Cooper, Jun Kong

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

- 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

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

NCIP/Leidos 14X138 and HHSN261200800001E - NCI

SEER Virtual Tissue Repository

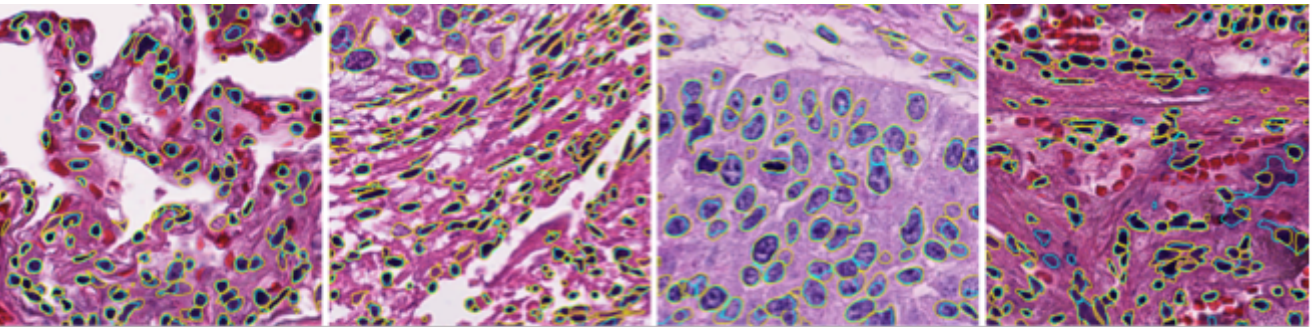
- SEER registries are a potential source of information about unusual outcomes and rare cancers
- Leverage Pathology labs which store FFPE tumors, slides and digital images
- Link to SEER data – track long term outcomes
- Accrue linked clinical data, Pathology slides from SEER sites

SEER VIRTUAL TISSUE REPOSITORY

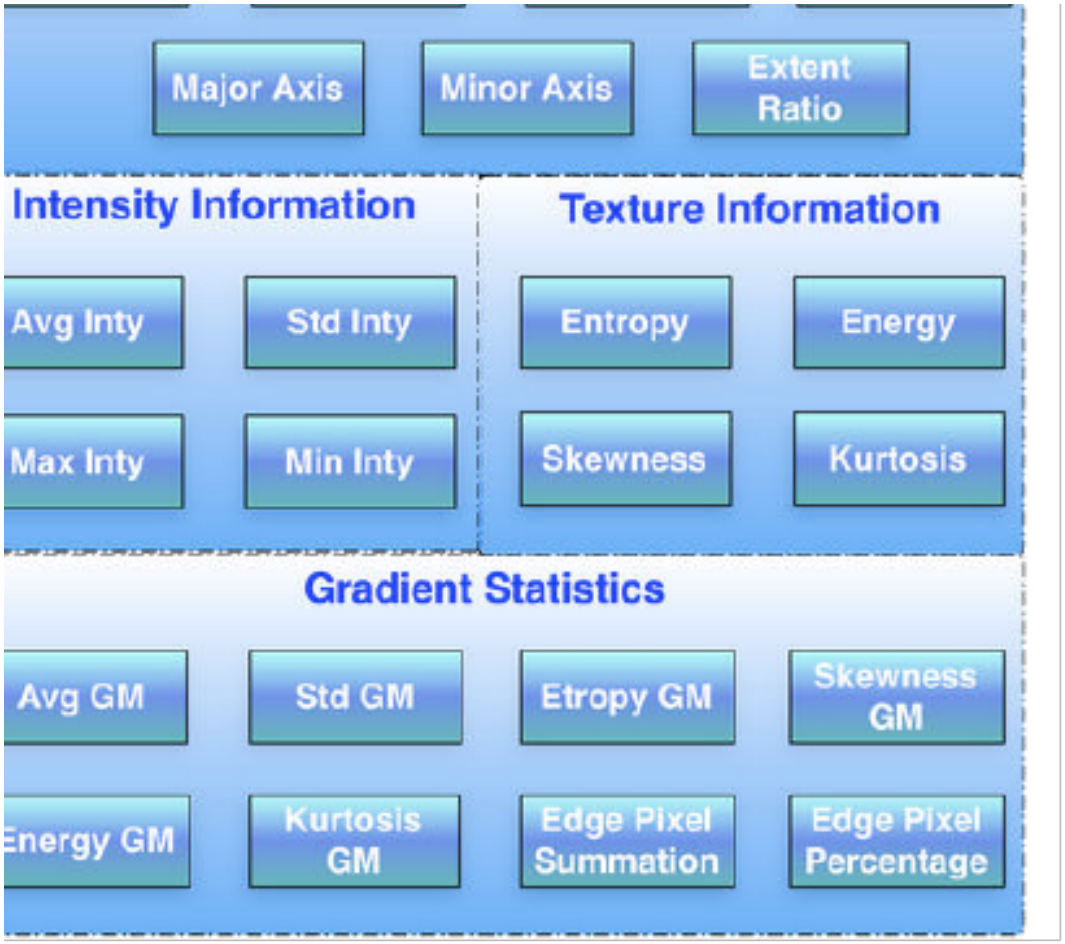
- Create linked collection of de-identified clinical data and whole slide images
- Extract features from a sample set of images (pancreas and breast cancer).
- Enable search, analysis, epidemiological characterization
- Pilot focus on extreme outcome Breast Cancer, Pancreatic Cancer cases
- Display images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

Robust Nuclear Segmentation

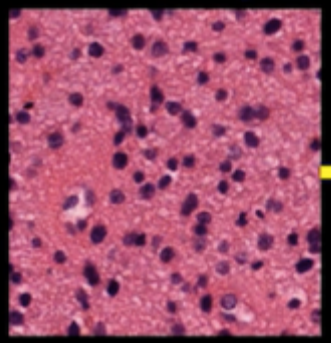
- Robust ensemble algorithm to segment nuclei across tissue types
- Optimized algorithm tuning methods
- Parameter exploration to optimize quality
- Systematic Quality Control pipeline encompassing tissue image quality, human generated ground truth, convolutional neural network critique
- Yi Gao, Allen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



Cell Morphometry Features



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

↓

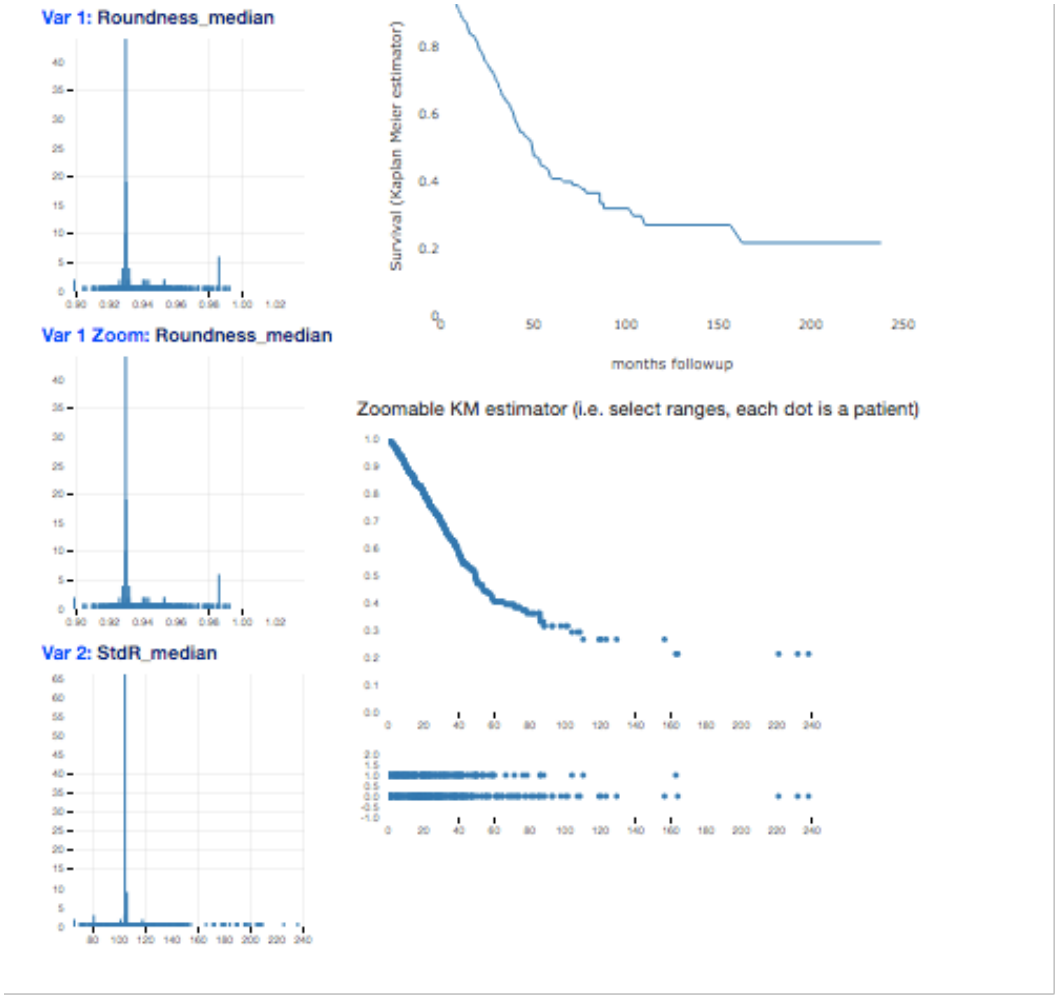
FeatureDB

- 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)

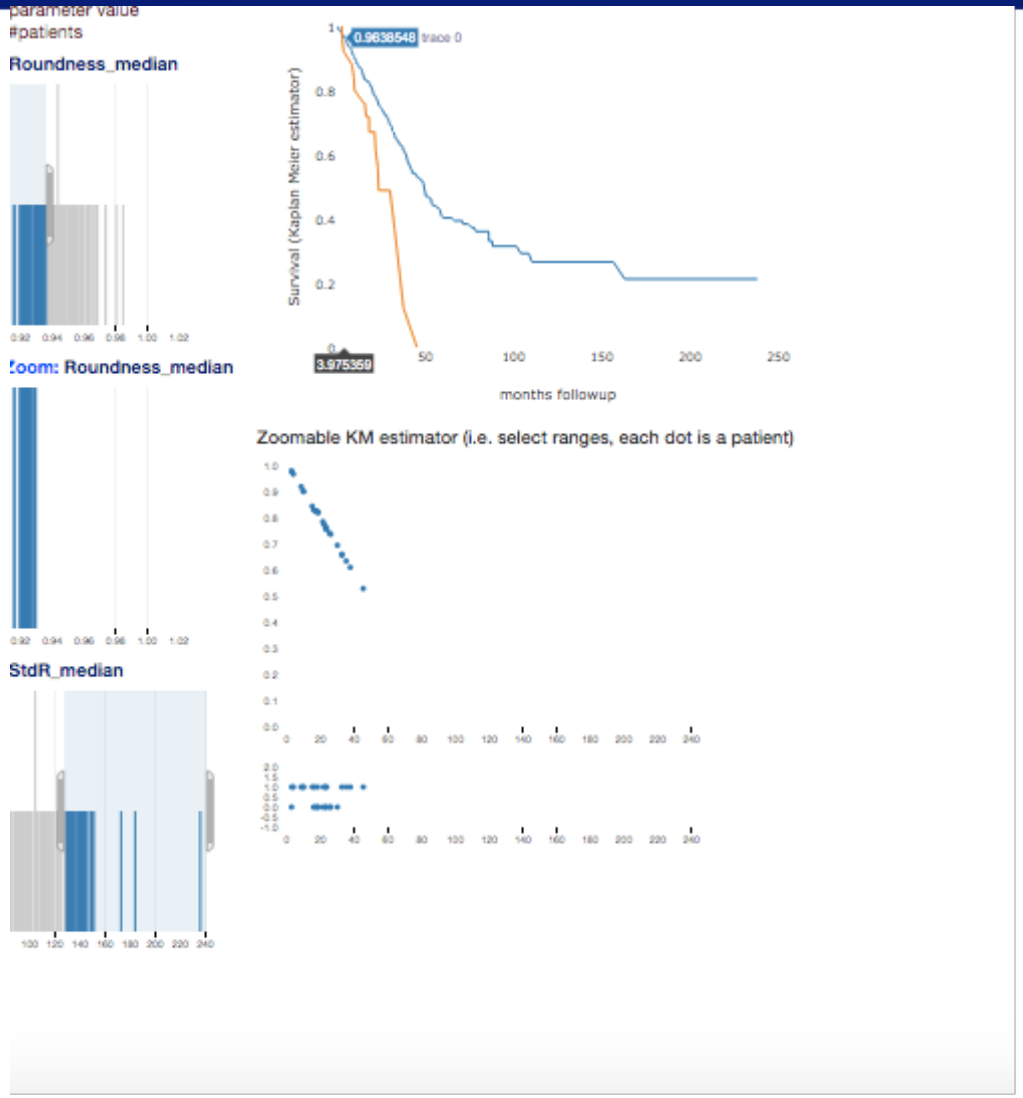
Feature Explorer Suite

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

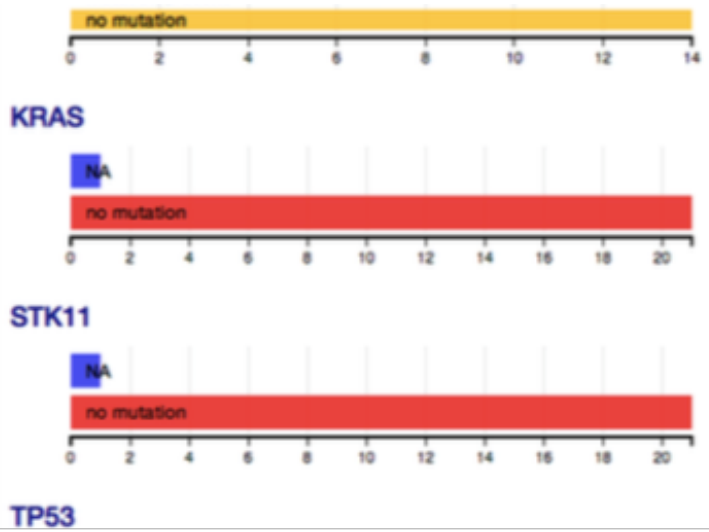
Feature Explorer - Integrated Pathomics Features, Outcomes and "omics" – TCGA NSCLC Adeno Carcinoma Patients

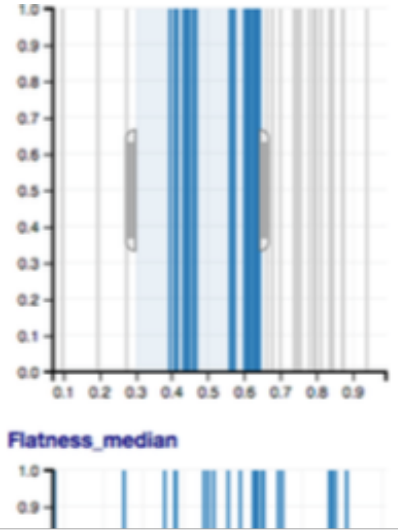


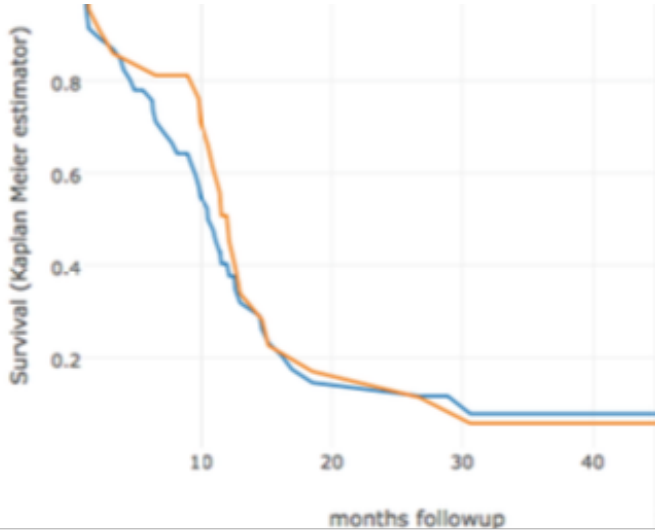
Feature Explorer - Integrated Pathomics Features, Outcomes and "omics" – TCGA NSCLC Adeno Carcinoma Patients



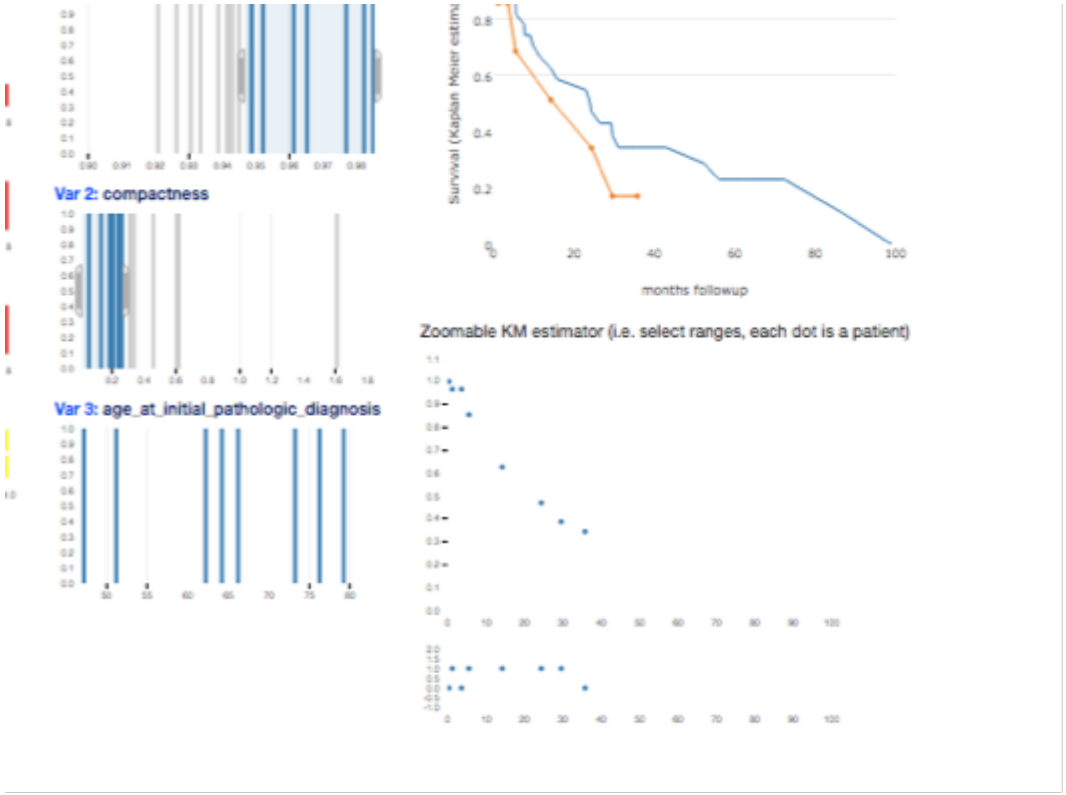
Collaboration with MGH – Feature Explorer – Radiology Brain MR/Pathology Features







Collaboration with SBU Radiology – TCGA NSCLC Adeno Carcinoma
Integrative Radiology, Pathology, “omics”, outcome

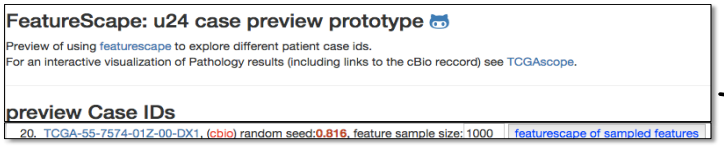


Mary Saltz, Mark Schweitzer SBU Radiology

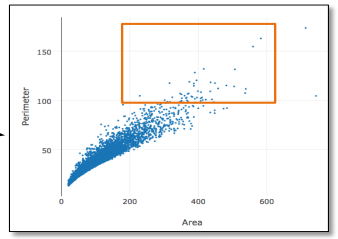
Pathomics

Relationship Between Image and Features

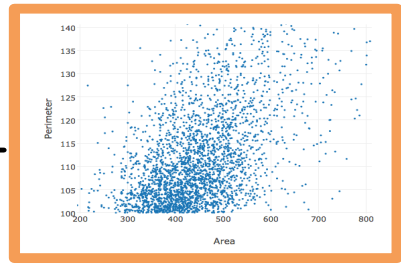
Step 1: Choose a case from the TCGA atlas (case #20)



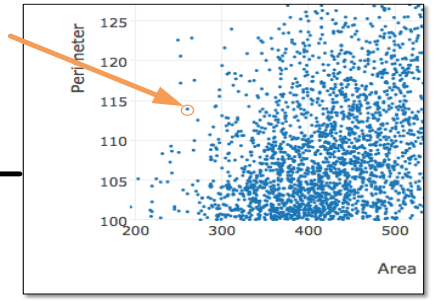
Step 2: Select two features of interest; X axis (*area*), Y axis (*perimeter*)



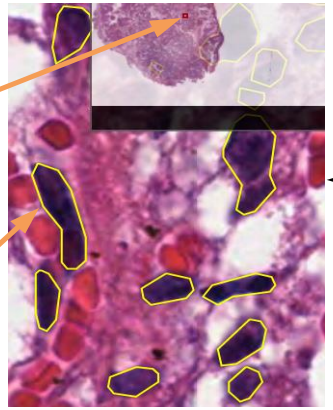
Step 3: Zoom in on region of interest



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.

FeatureScape: u24 case preview prototype

Preview of using featurescape to explore different patient case ids.
For an interactive visualization of Pathology results (including links to the cBio reccord) see TCGAscope.

preview Case IDs

1. TCGA-34-2605-01Z-00-DX1, (cbio) random seed:**0.559**, feature sample size: 1000 featurescape of sampled features
2. TCGA-38-4625-01Z-00-DX1, (cbio) random seed:**0.628**, feature sample size: 1000 featurescape of sampled features
3. TCGA-38-4626-01Z-00-DX1, (cbio) random seed:**0.700**, feature sample size: 1000 featurescape of sampled features
4. TCGA-38-4628-01Z-00-DX1, (cbio) random seed:**0.016**, feature sample size: 1000 featurescape of sampled features
5. TCGA-38-4629-01Z-00-DX1, (cbio) random seed:**0.185**, feature sample size: 1000 featurescape of sampled features
6. TCGA-38-6178-01Z-00-DX1, (cbio) random seed:**0.317**, feature sample size: 1000 featurescape of sampled features
7. TCGA-38-A44F-01Z-00-DX1, (cbio) random seed:**0.906**, feature sample size: 1000 featurescape of sampled features
8. TCGA-50-5044-01Z-00-DX1, (cbio) random seed:**0.055**, feature sample size: 1000 featurescape of sampled features
9. TCGA-50-5045-01Z-00-DX1, (cbio) random seed:**0.946**, feature sample size: 1000 featurescape of sampled features
10. TCGA-50-5045-01Z-00-DX2, (cbio) random seed:**0.551**, feature sample size: 1000 featurescape of sampled features
11. TCGA-50-5055-01Z-00-DX1, (cbio) random seed:**0.127**, feature sample size: 1000 featurescape of sampled features
12. TCGA-34-5232-01Z-00-DX1, (cbio) random seed:**0.208**, feature sample size: 1000 featurescape of sampled features
13. TCGA-50-5055-01Z-00-DX2, (cbio) random seed:**0.321**, feature sample size: 1000 featurescape of sampled features
14. TCGA-50-5066-01Z-00-DX1, (cbio) random seed:**0.711**, feature sample size: 1000 featurescape of sampled features
15. TCGA-50-5066-02Z-00-DX1, (cbio) random seed:**0.008**, feature sample size: 1000 featurescape of sampled features
16. TCGA-50-5942-01Z-00-DX1, (cbio) random seed:**0.031**, feature sample size: 1000 featurescape of sampled features
17. TCGA-50-5946-01Z-00-DX1, (cbio) random seed:**0.768**, feature sample size: 1000 featurescape of sampled features
18. TCGA-50-6590-01Z-00-DX1, (cbio) random seed:**0.668**, feature sample size: 1000 featurescape of sampled features
19. TCGA-50-6591-01Z-00-DX1, (cbio) random seed:**0.498**, feature sample size: 1000 featurescape of sampled features

Select Feature Pair – dots correspond to nuclei

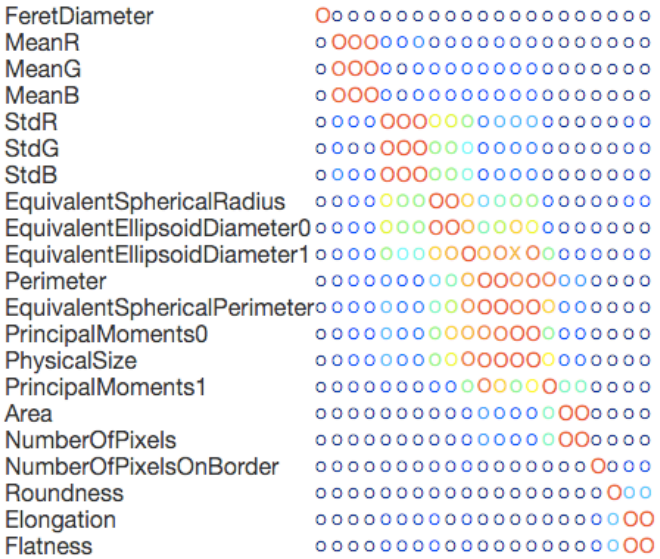
FeatureScape

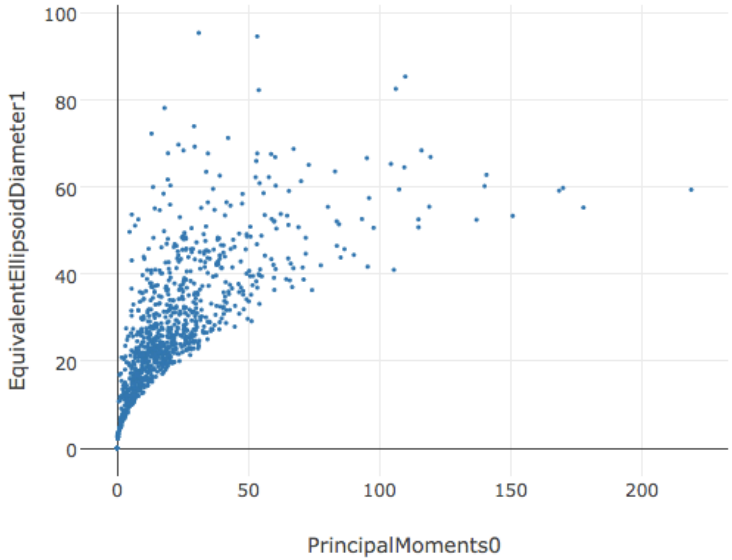
← Preliminary demo of integrative use of multiple FeatureScape tools

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)

Subregion selected – form of gating analogous to flow cytometry

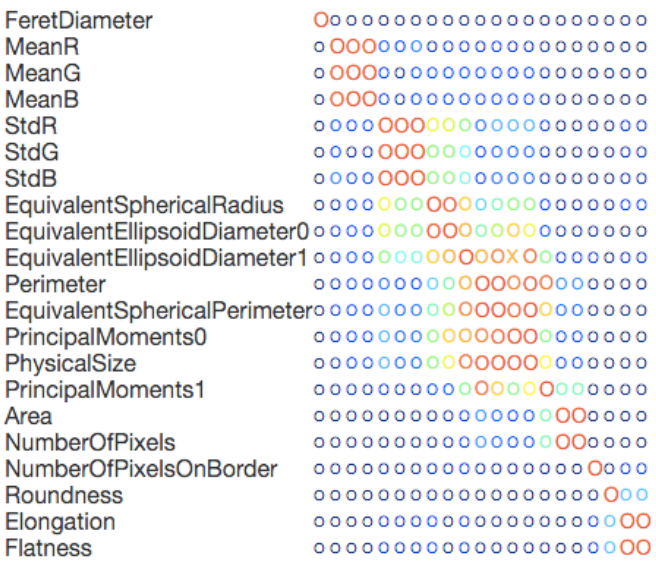
FeatureScape

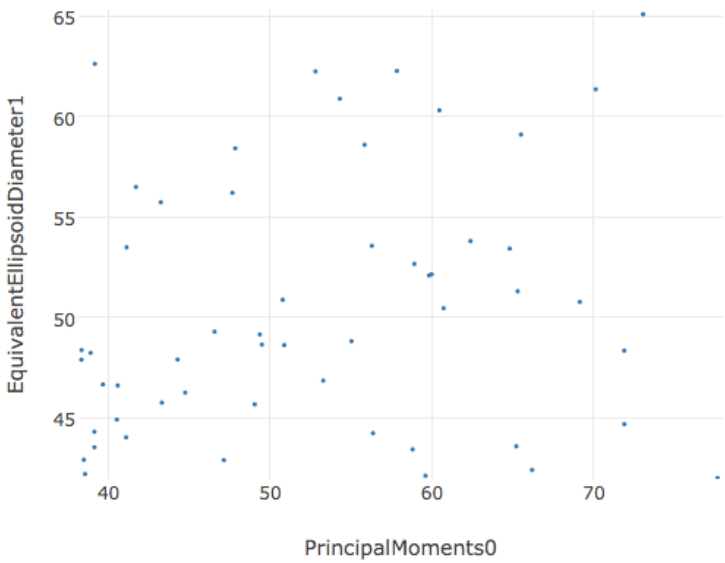
← Preliminary demo of integrative use of multiple FeatureScape tools

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



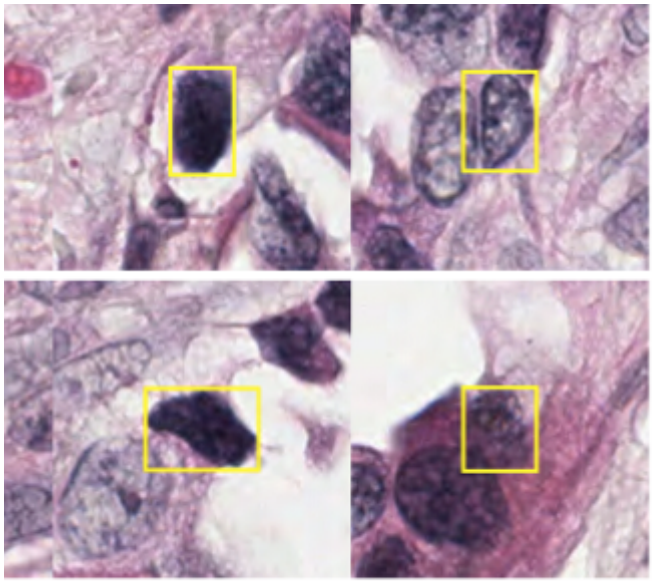


Pearson correlation between

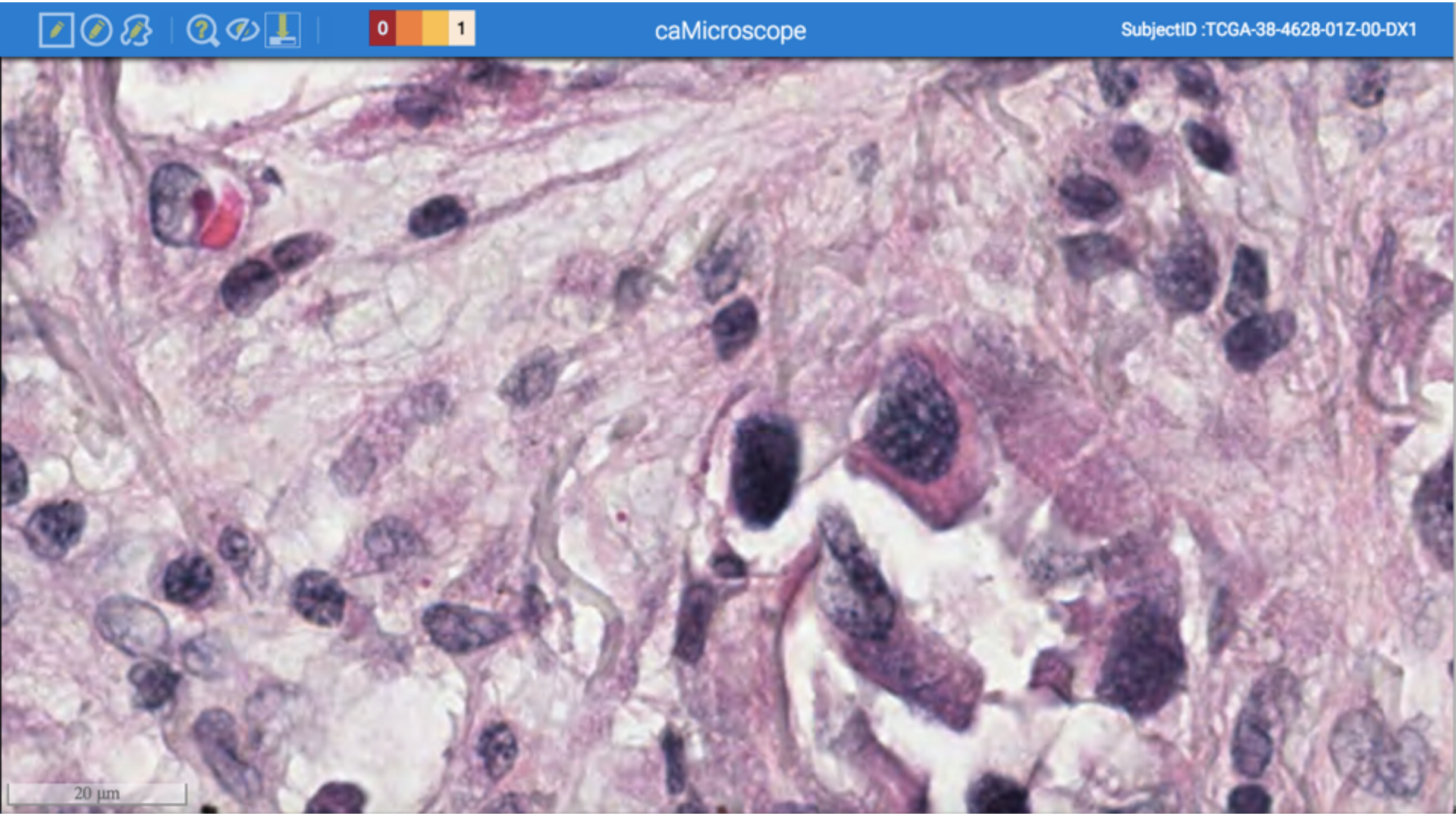
- PrincipalMoments0
- EquivalentEllipsoidDiameter1

Resample from selected region (under development)

Sample Nuclei from Gated Region



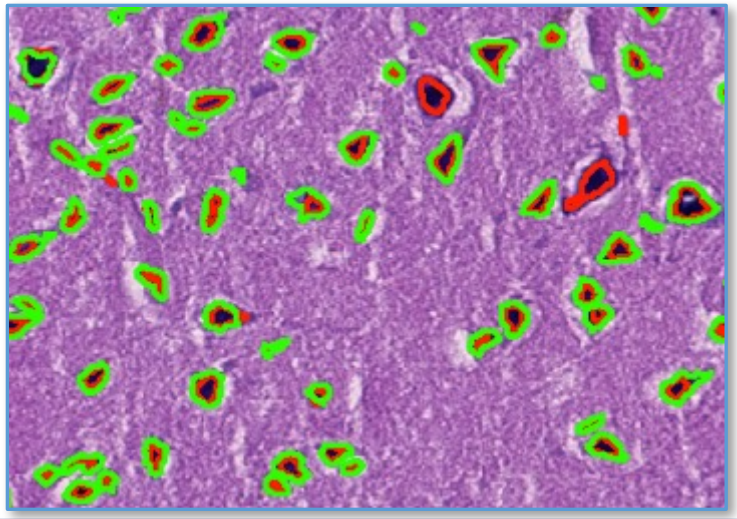
Gated Nuclei in Context



Algorithm Comparison, Validation, Uncertainty Quantification

- High quality image analysis algorithms are essential to support biomedical research and diagnosis
  - Validate algorithms with human annotations
  - Compare and consolidate different algorithm results

e.g.: what are the distances and overlap ratios between markup boundaries from two algorithms?



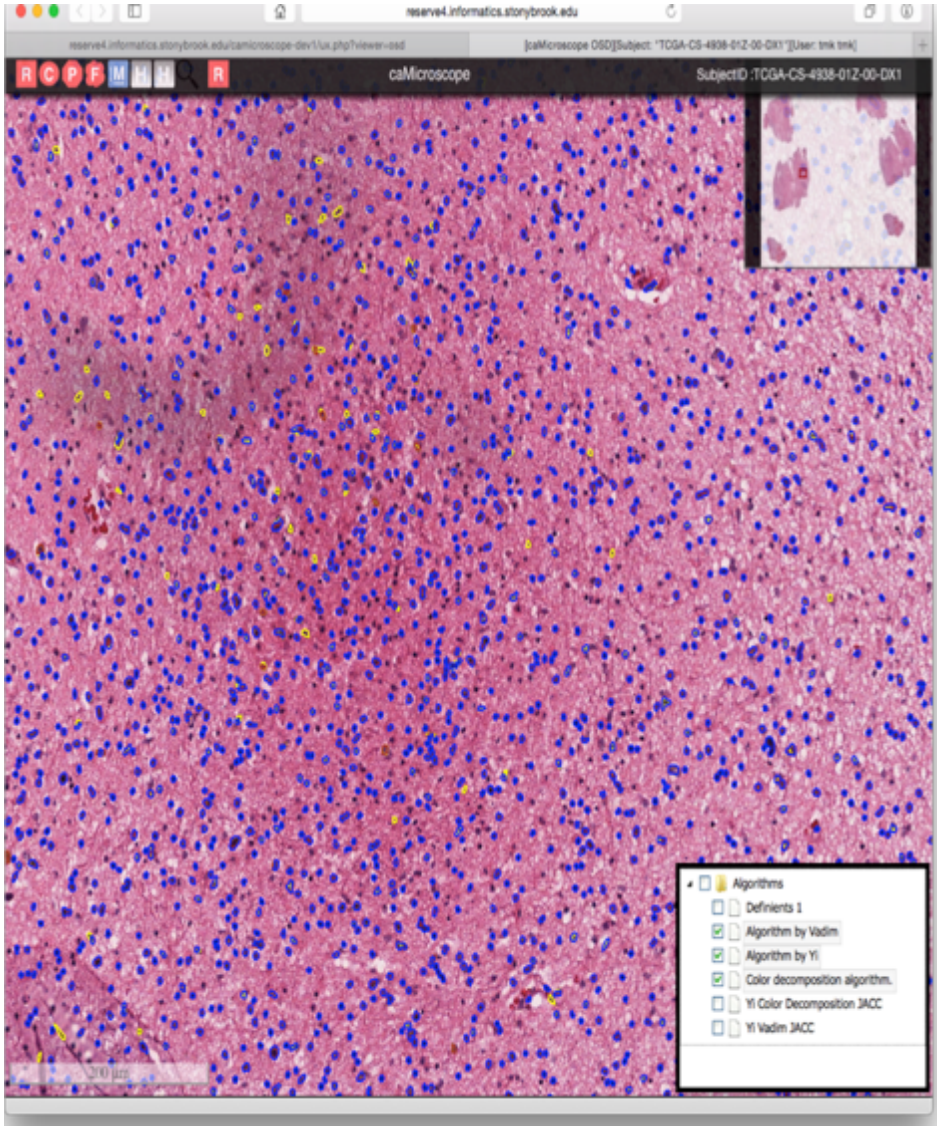
Cross matching of two spatial data sets

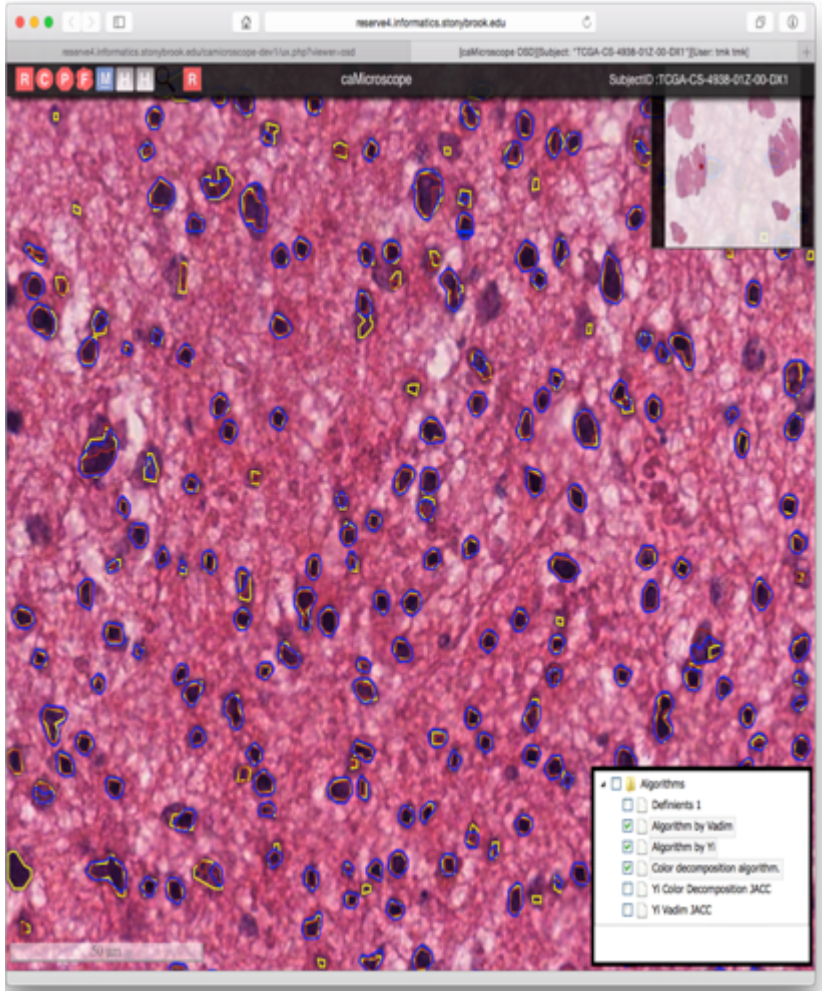
Green: algorithm 1

Red: algorithm 2

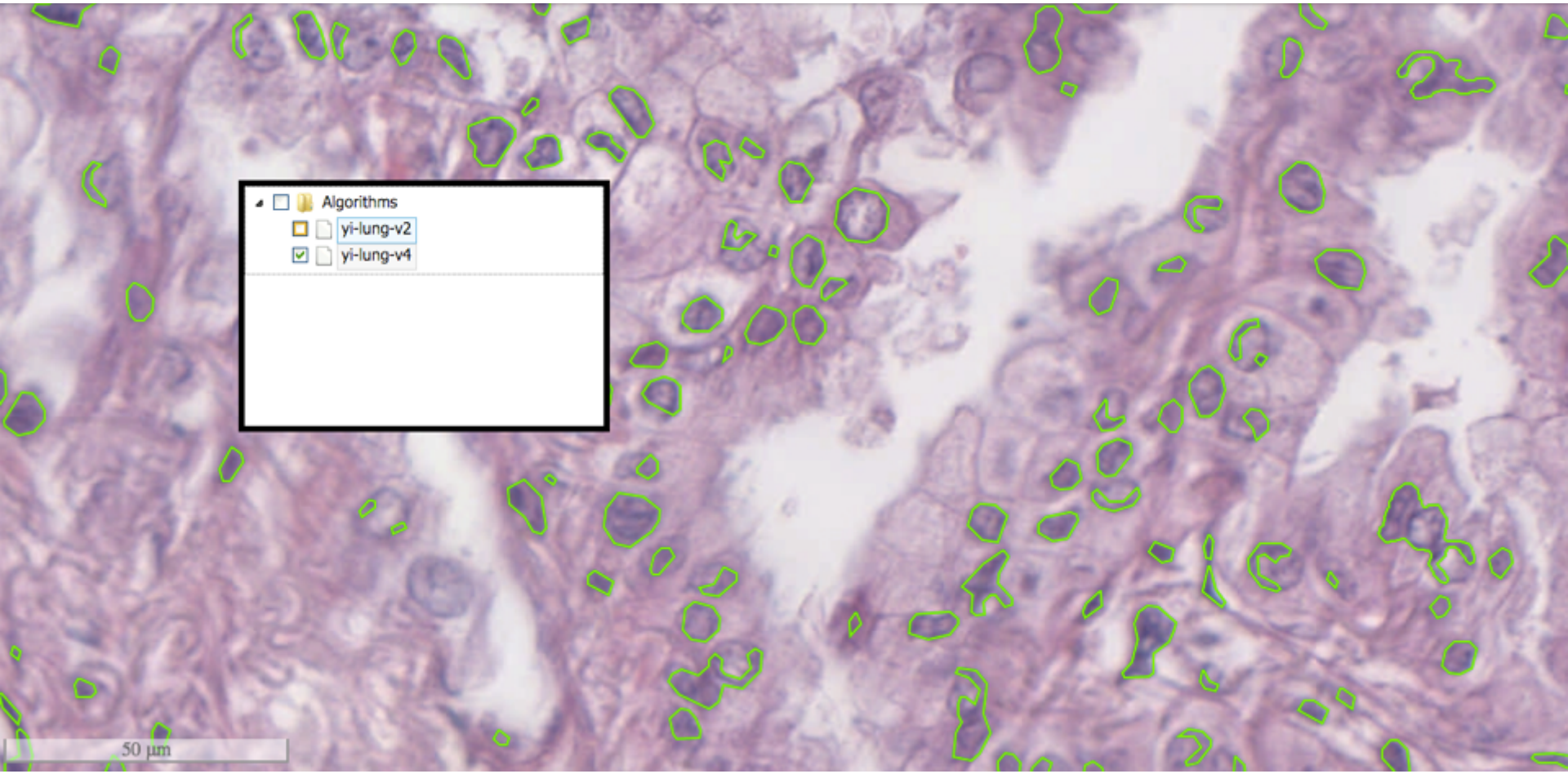
MICCAI 2014
Brain Tumor

caMicroscope/MongoDB - Multiple Algorithm Comparison; Generate and Curate Pathomics Feature set

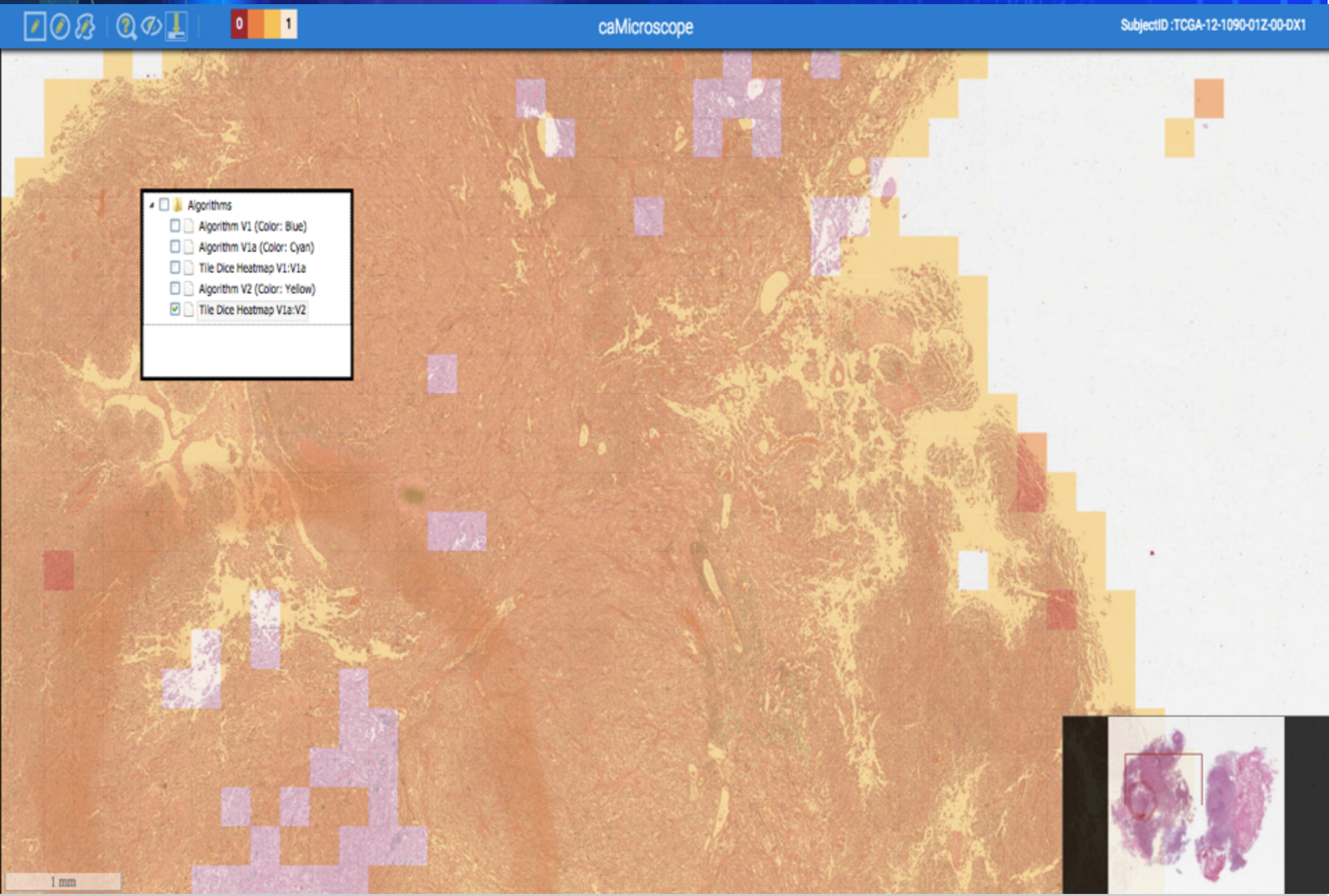




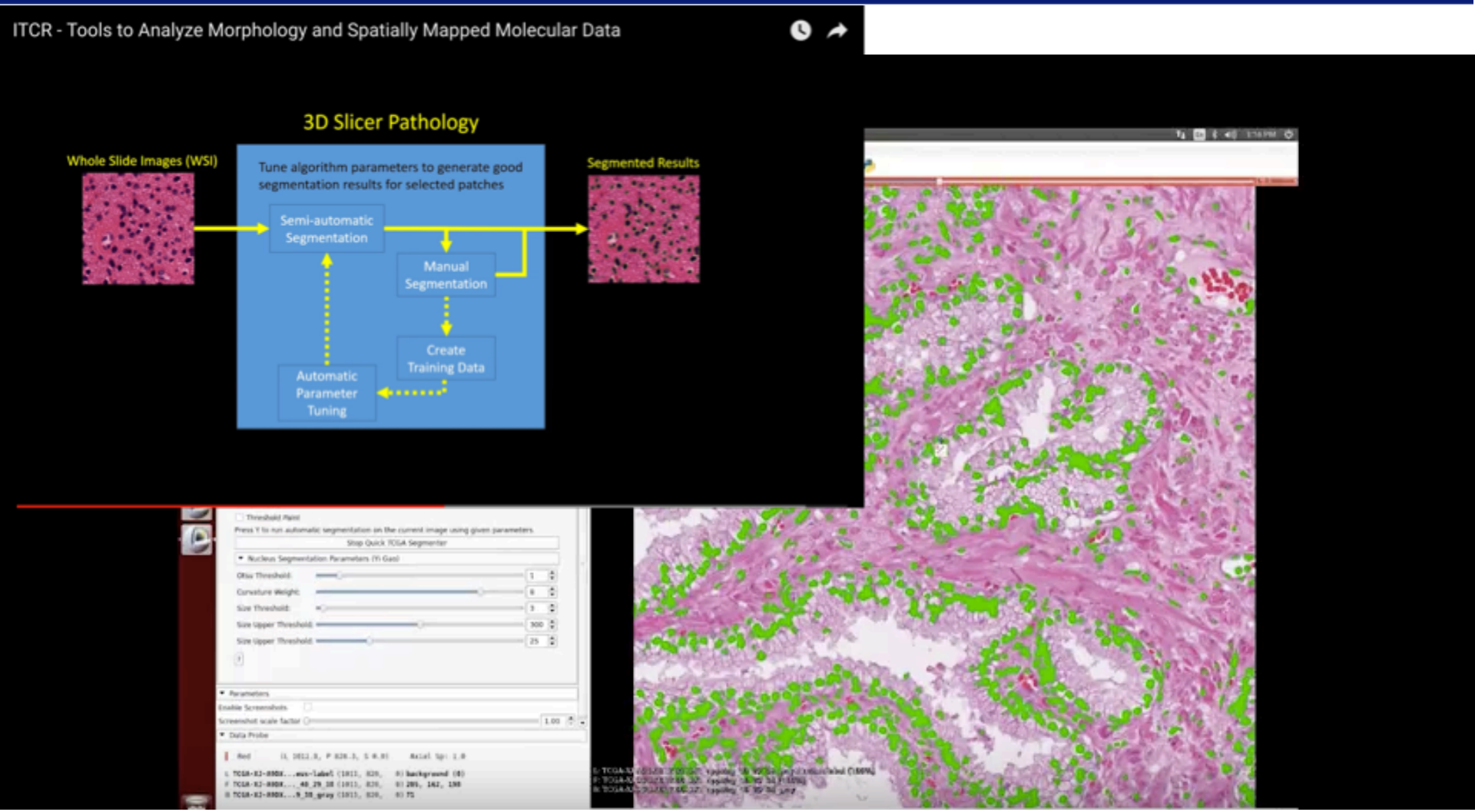
Compare Algorithm Results



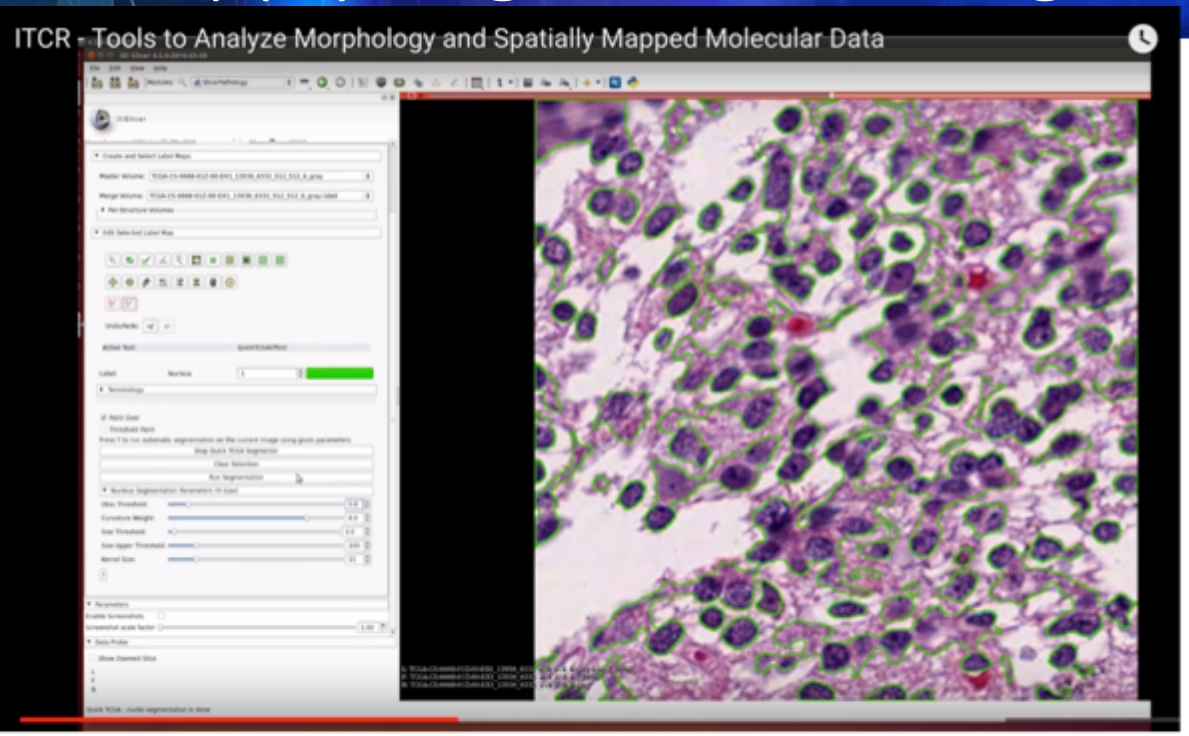
Heatmap – Depicts Agreement Between Algorithms



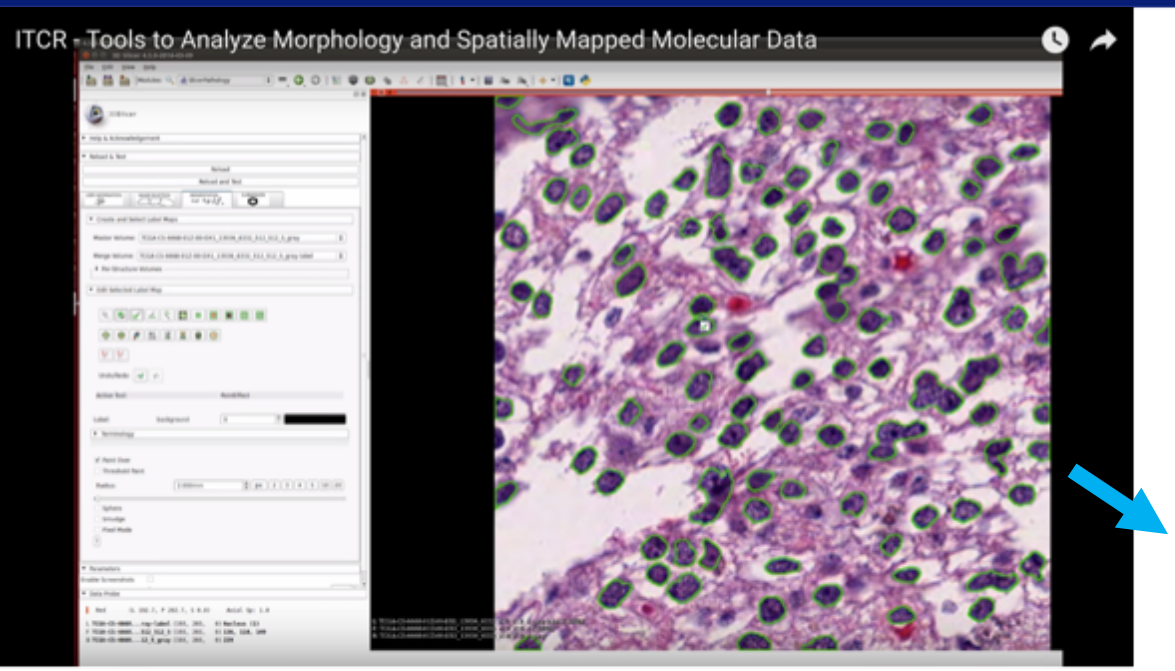
3D Slicer Pathology – Generate High Quality Ground Truth



Apply Segmentation Algorithm

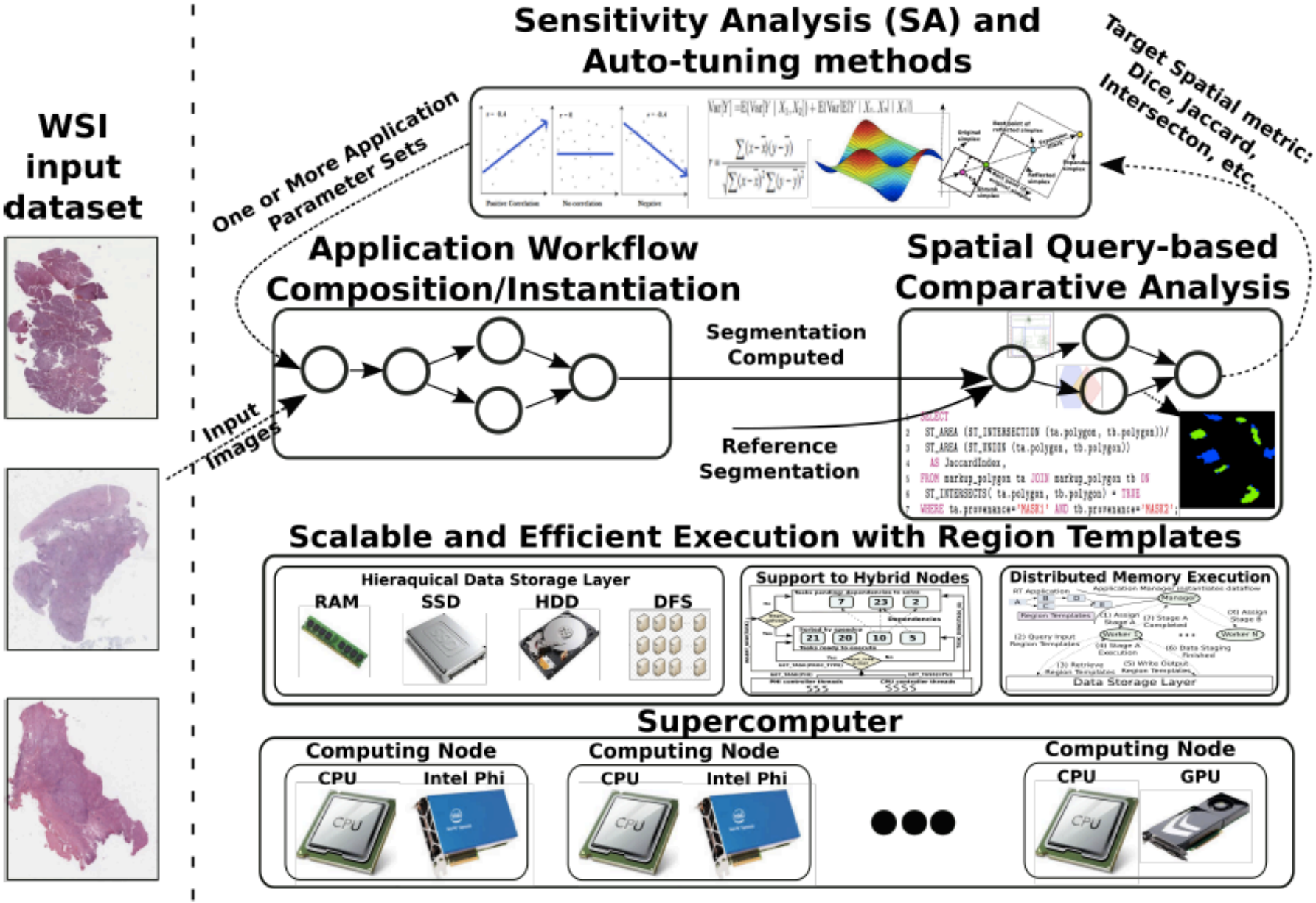


Adjust algorithm parameters, manual fine tuning

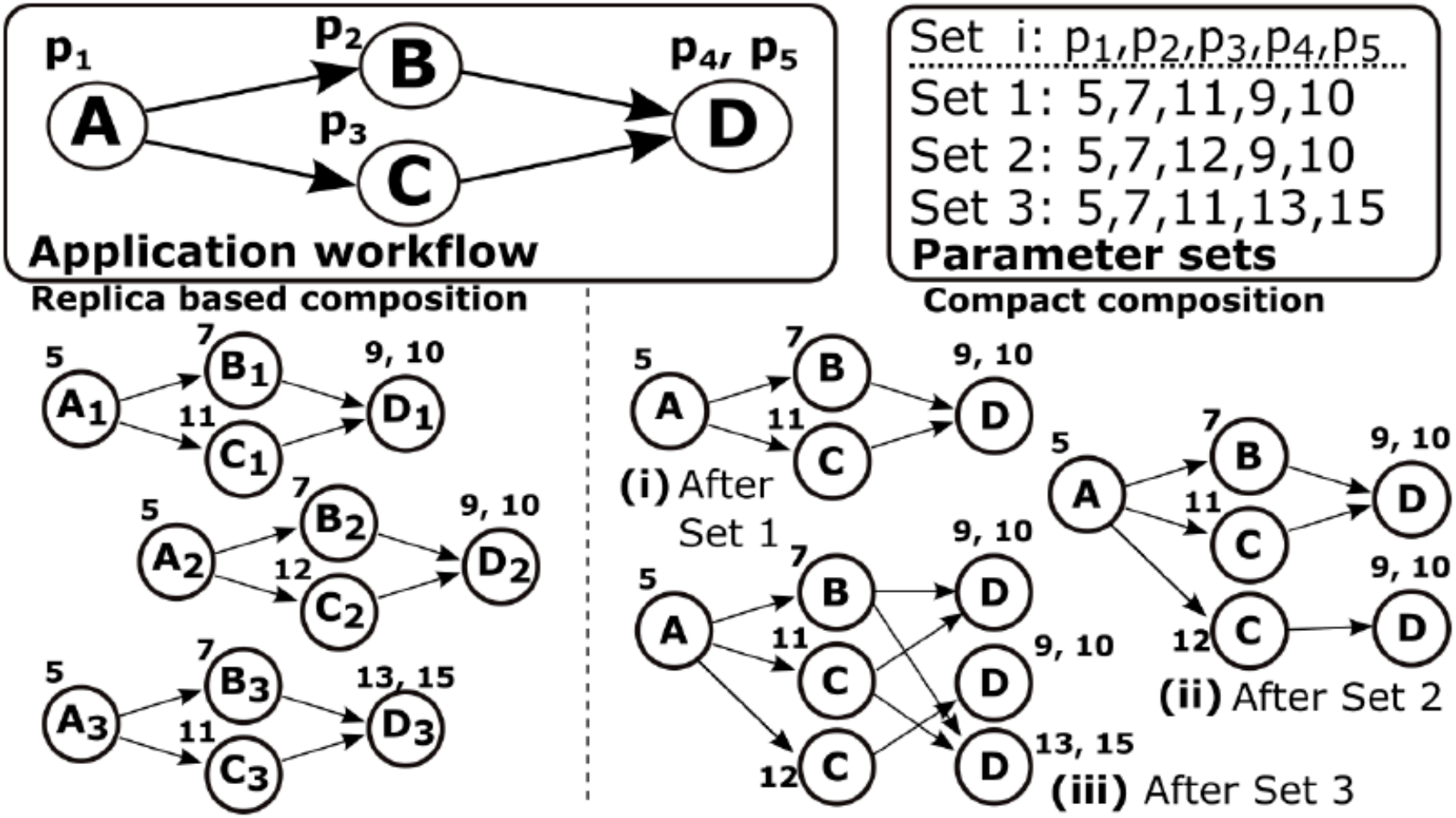


Auto-tuning and feature extraction

- Goal – correctly segment trillions of objects (nuclei)
- Adjust algorithm parameters
- Autotuning – finds parameters that best match ground truth in an image patch
- Region template runtime support to optimize generation and management of multi-parameter algorithm results
- Eliminates redundant computation, manages locality
- Active Harmony – Jeff Hollingsworth!!
- Collaboration – George Teodoro, Tahsin Kurc

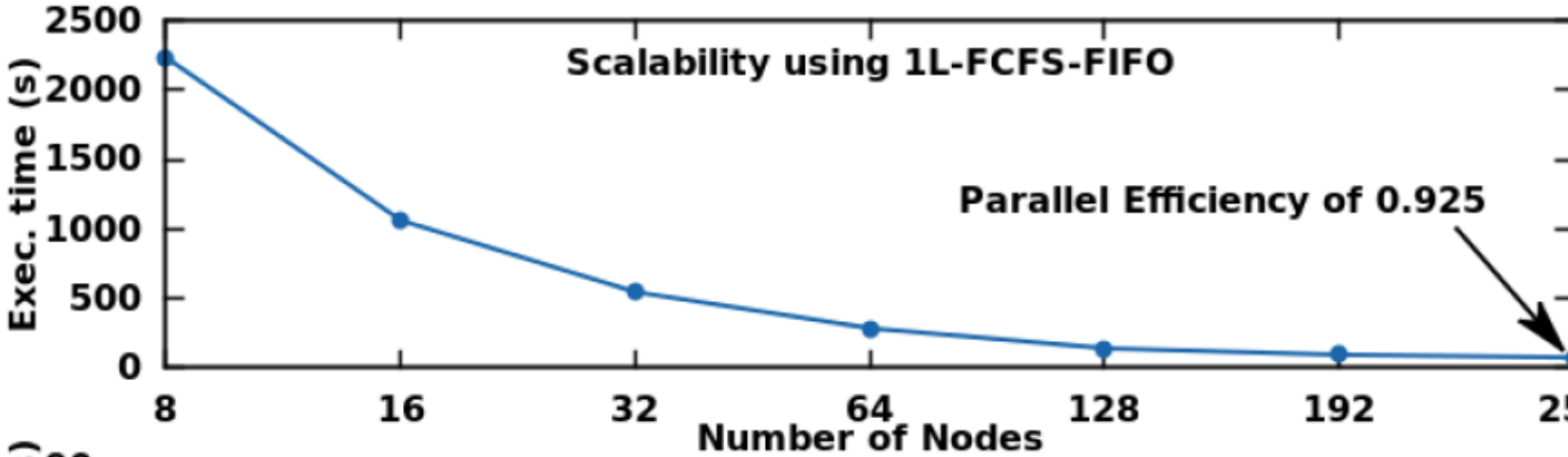

WSI input dataset
Sensitivity Analysis (SA) and Auto-tuning methods
Target Spatial metric: Dice, Jaccard, Intersecton, etc.
One or More Application Parameter Sets
Application Workflow Composition/Instantiation
Spatial Query-based Comparative Analysis
Segmentation Computed
Reference Segmentation
Input Images
Scalable and Efficient Execution with Region Templates
Hieraquical Data Storage Layer
RAM
SSD
HDD
DFS
Support to Hybrid Nodes
Distributed Memory Execution
Data Storage Layer
Supercomputer
Computing Node
CPU
Intel Phi
Computing Node
CPU
Intel Phi
Computing Node
CPU
GPU

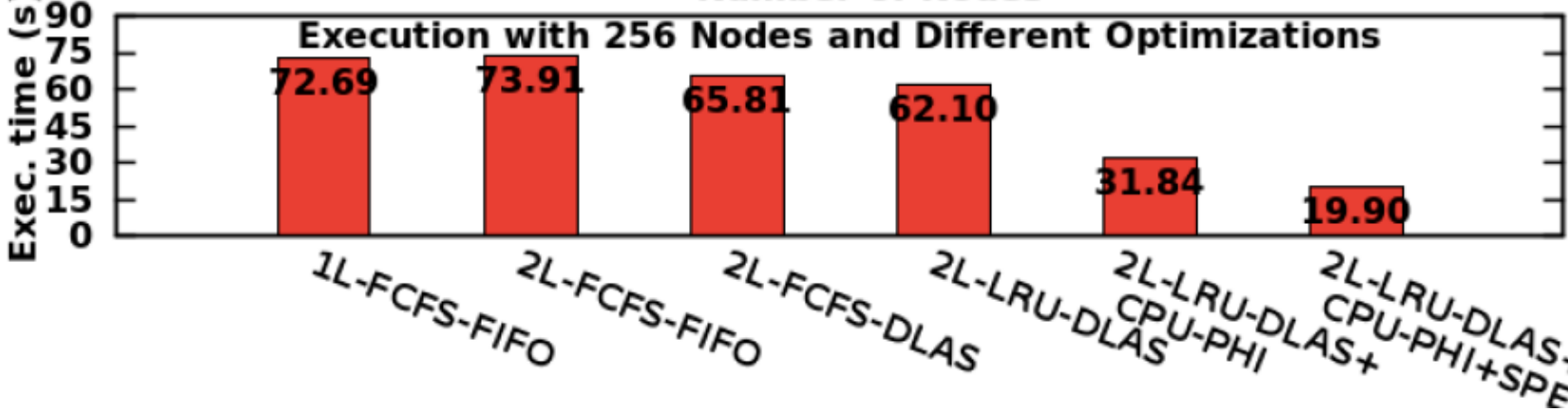
E=Eliminate Duplicate Compuations



Performance Optimization

256 nodes of Stampede. Each node of the cluster has a dual socket Intel Xeon E5-2680 processors, an Intel Xeon Phi SE10P co-processor and 32GB RAM.The nodes are inter-connected via Mellanox FDR Infiniband switches.





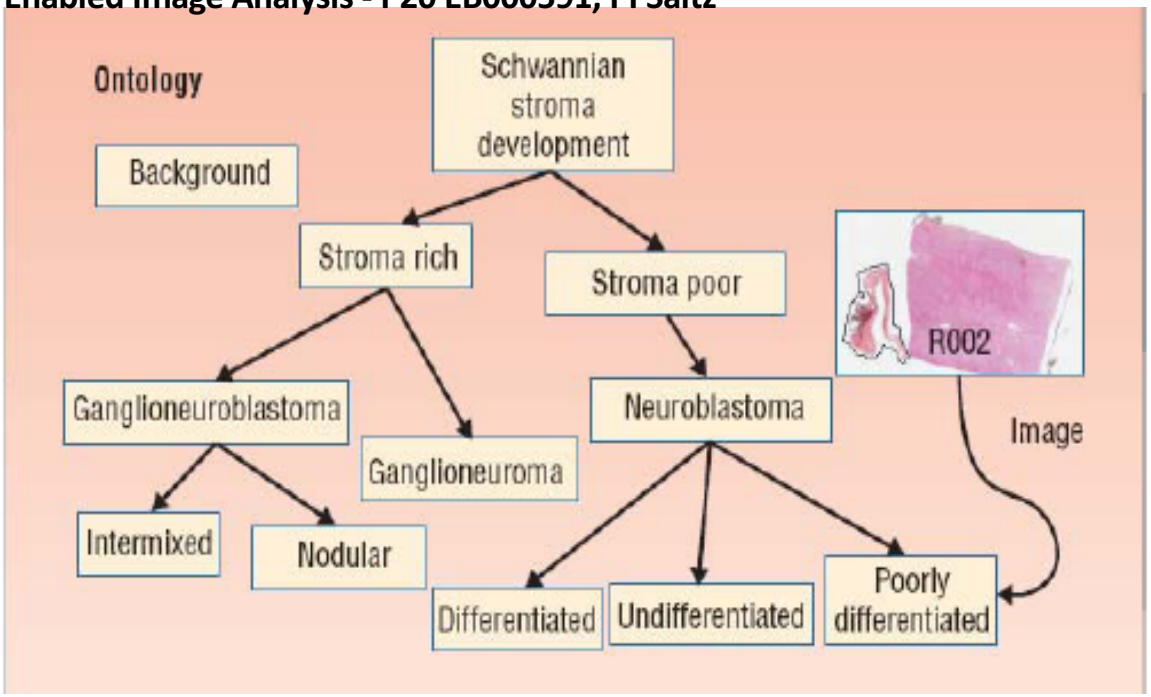
Classification

- Automated or semi-automated identification of tissue or cell type
- Variety of machine learning and deep learning methods
- Classification of Neuroblastoma
- Classification of Gliomas
- Quantification of lymphocyte infiltration

Classification and Characterization of Heterogeneity

BISTI/NIBIB Center for Grid Enabled Image Analysis - P20 EB000591, PI Saltz

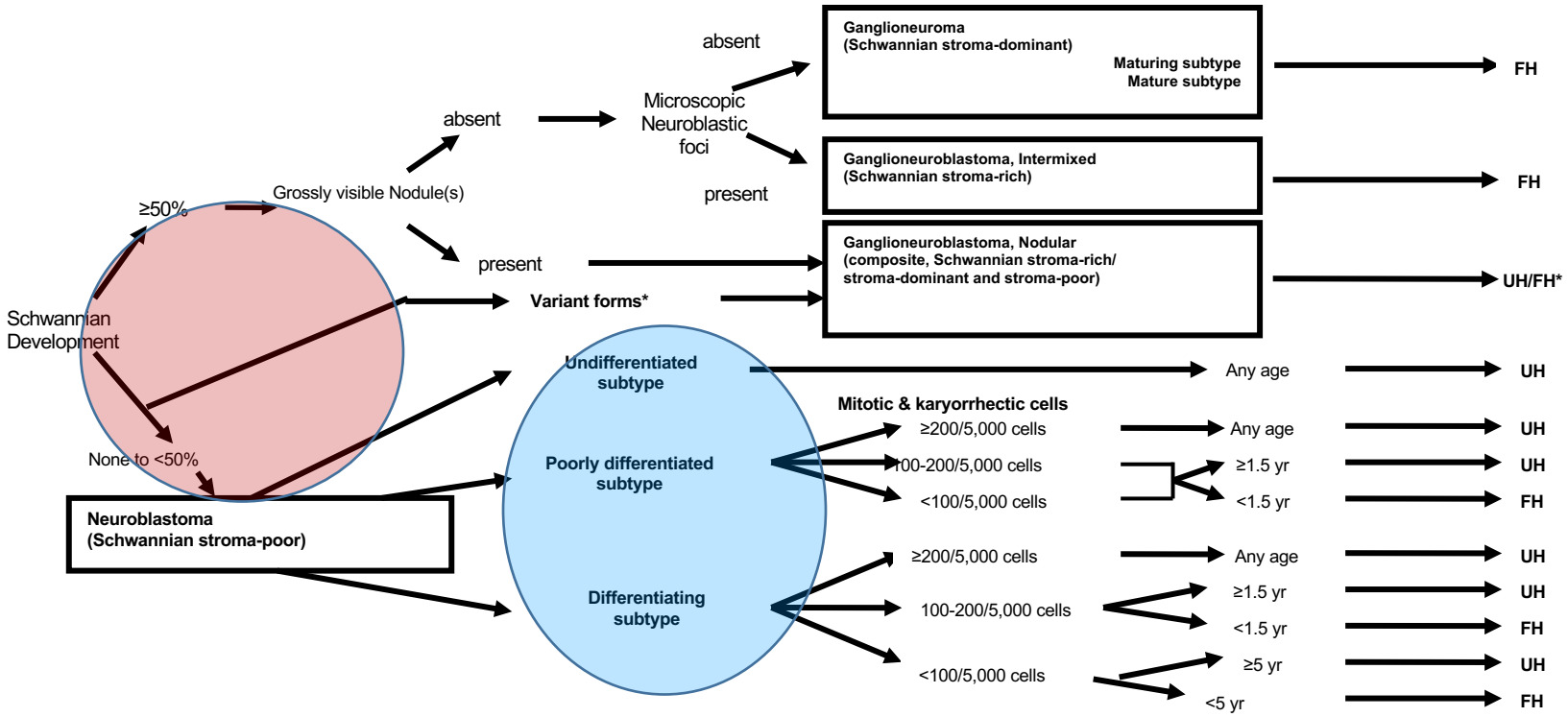
- Analyze images by computer
- Analyze the whole tissue, several slides
- Provide quantitative information to the pathologist
- Reduce inter- and intra-reader



Hiro Shimada, Metin Gurcan, Jun Kong, Lee Cooper Joel Saltz

Gurcan, Shamada, Kong, Saltz

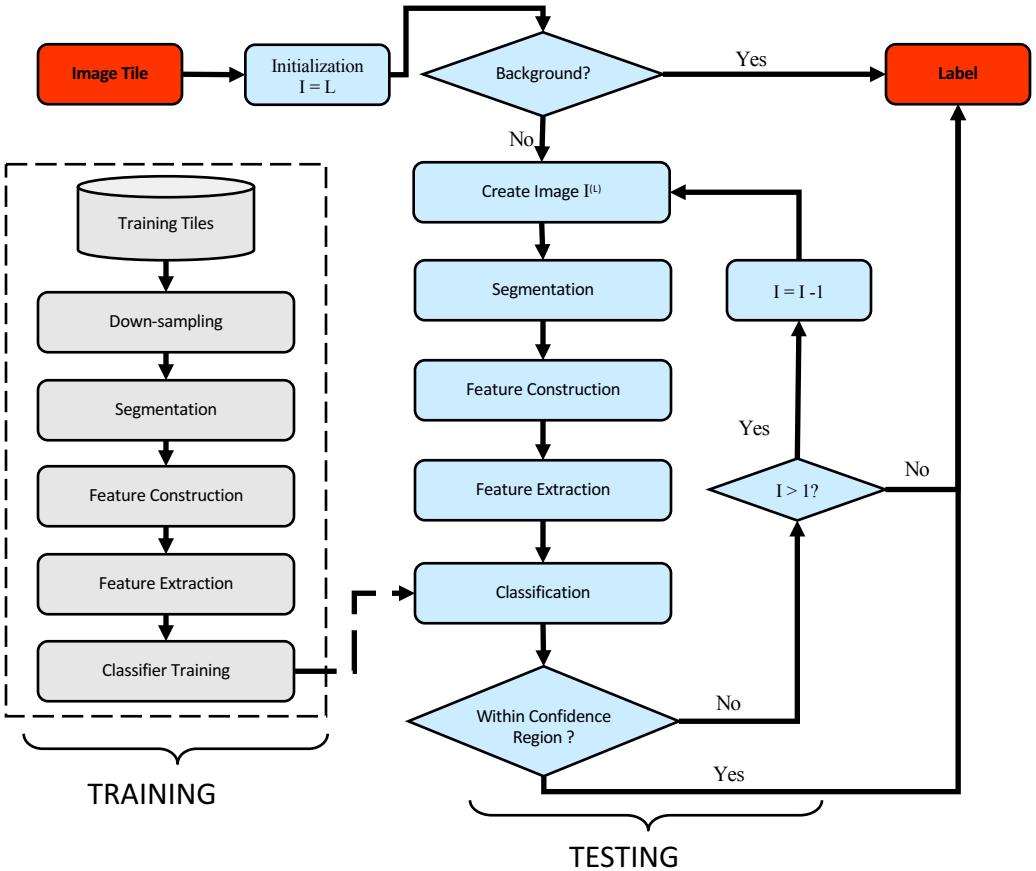
Neuroblastoma Classification



FH: favorable histology **UH:** unfavorable histology

CANCER 2003; 98:2274-81

Multi-Scale Machine Learning Based Shimada Classification System



- Background Identification
- Image Decomposition (Multi-resolution levels)
- Image Segmentation (EMLDA)
- Feature Construction (2nd order statistics, Tonal Features)
- Feature Extraction (LDA) + Classification (Bayesian)
- Multi-resolution Layer Controller (Confidence Region)

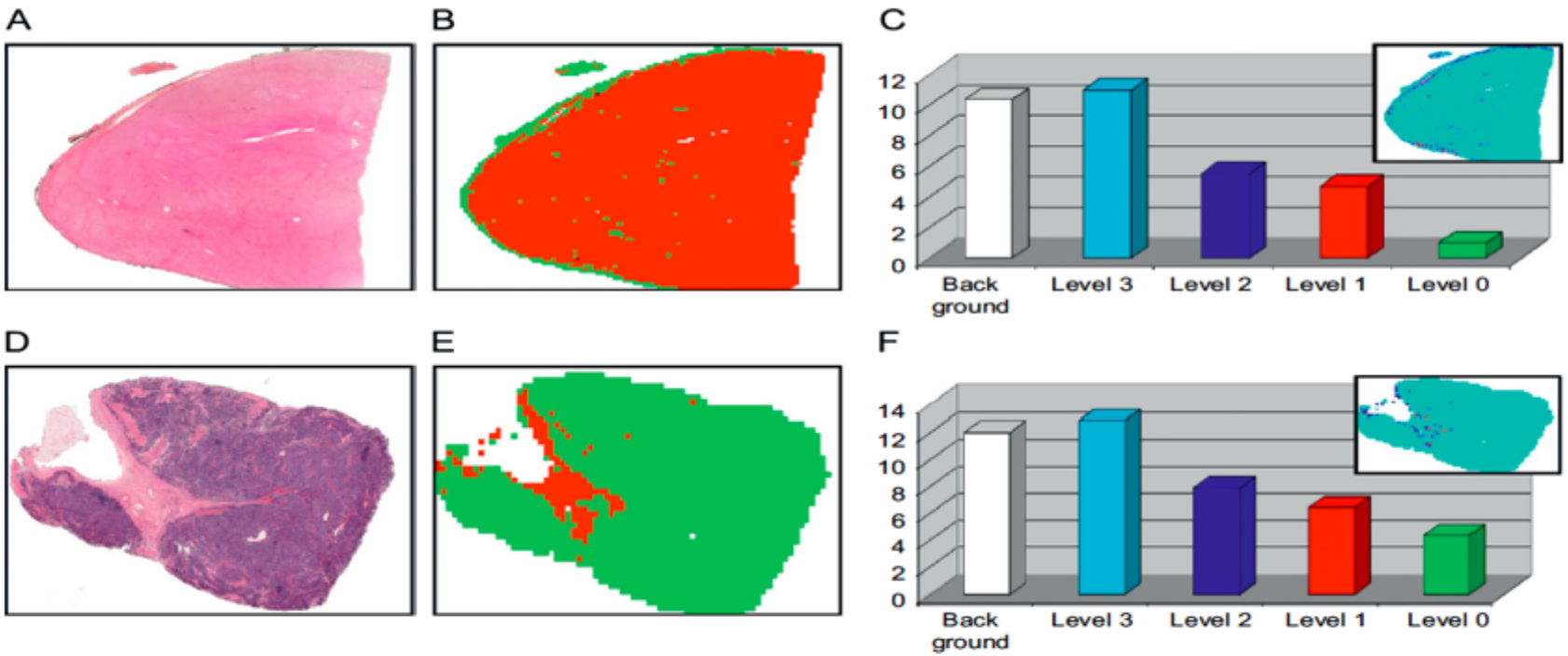


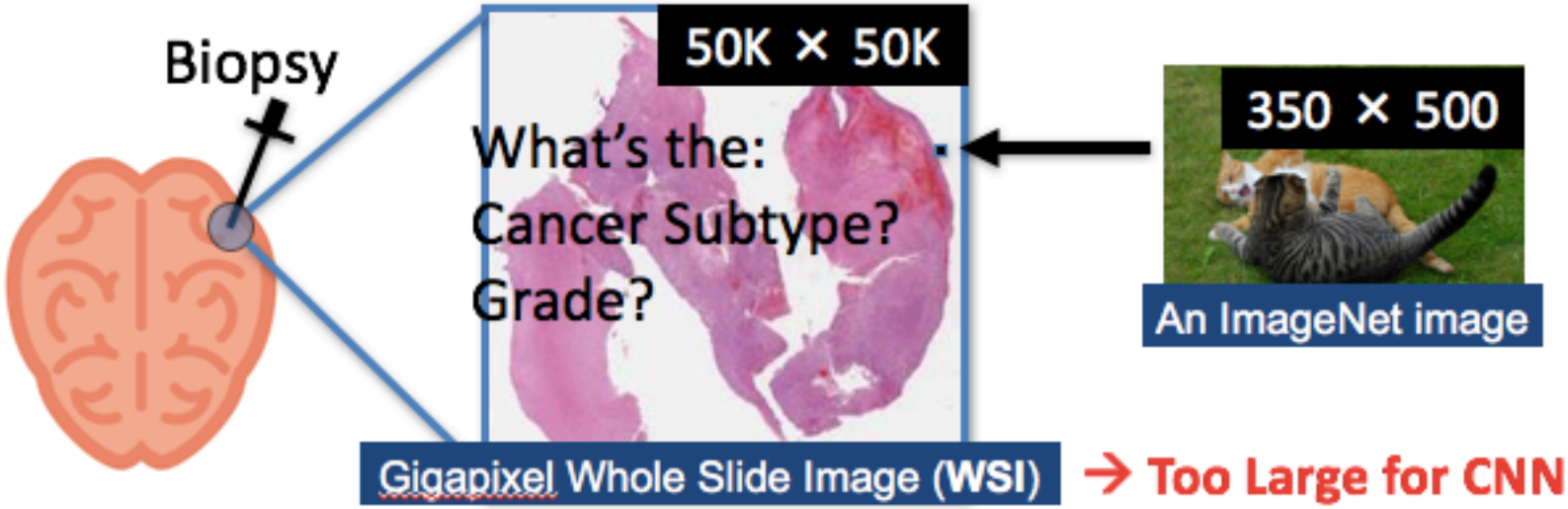
Fig. 8. Sample classification results after processing a whole-slide NB image. (a) and (d) are the H&E stained NB slides associated with stroma-rich and stroma-poor by an expert pathologist. (b) and (e) are the classification maps identified by the computerized system where the red color corresponds to stroma-rich regions and the green color corresponds to stroma-poor regions. (c) and (f) are the corresponding decision level statistics that show in log-scale the number of image tiles classified at a certain resolution level. In the resolution level map on the upper right, cyan color represents the lowest resolution and green color represents the highest resolution, respectively.

Brain Tumor Classification – CVPR 2016

Contributions

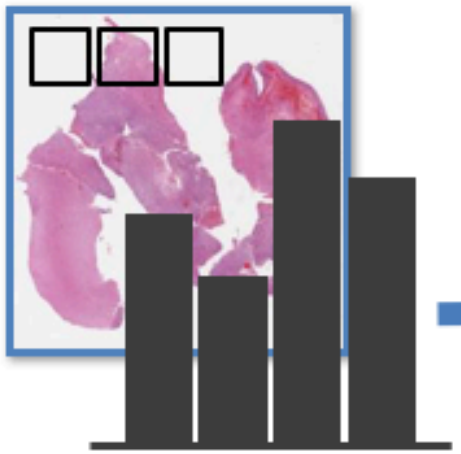
- Automatic discriminative patch identification for patch-CNN training
- A robust, general method to combine patch-level predictions

An important application: cancer classification



→ Too Large for CNN!

Combining Information from Patches



Histogram of Patch-level Classes

Advantage:

- The prediction of every patch counts
  → robustness & generalization

SVM or
Logistic Regression

Engineering details

- CNN architecture: AlexNet and VGG16
- Patch size: 500x500, Multiple scale
- Dataset: TCGA [gdc-portal.nci.nih.gov]
- Number of Patches: 1000 per WSI

Brain Tumor Classification Results

Glioma is
- The most common brain cancer
- The leading cause of cancer-related deaths in people under age 20

Methods	Accuracy
VGG16 features + BoW + SVM	0.667
Patch-CNN + Voting	0.710
Patch-CNN + Max-pooling	0.710
Our method	**0.771**
Pathologists' Agreement [M. Gupta 2015] (on a similar dataset)	0.7-0.8

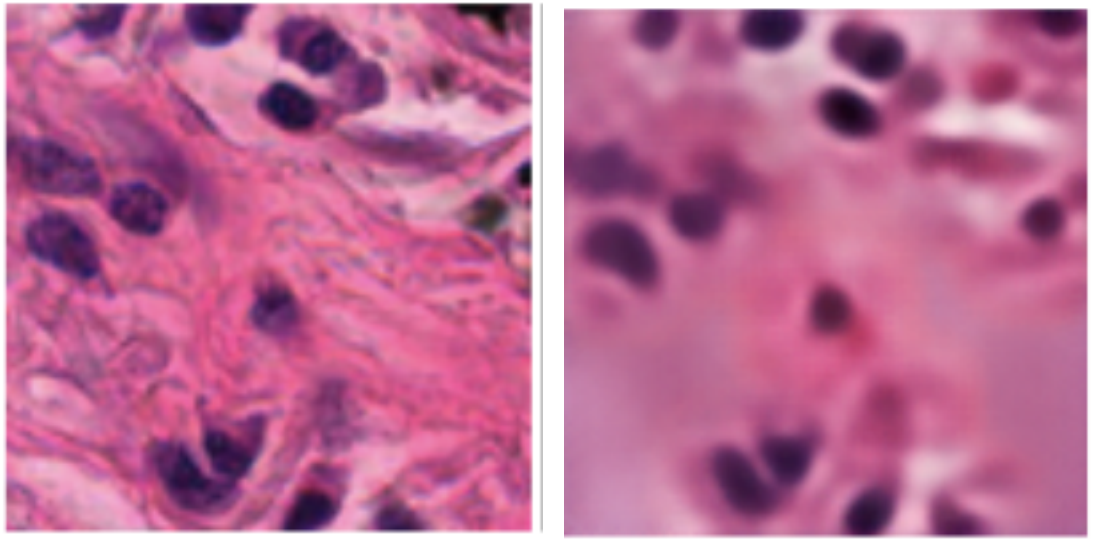
Confusion Matrix: OA is very hard even for pathologists	GBM	OD	OA	DA	AA	AO
Glioblastoma, Grade IV (GBM)	214		2		1	
Oligodendroglioma, Grade II (OD)	1	47	22	2		1
Oligoastrocytoma, Grade II & III (OA)	1	18	40	8	3	1
Diffuse Astrocytoma, Grade II (DA)	3	9	6	20		1
Anaplastic Astrocytoma, Grade III (AA)	3	2	3	3	4	
Anaplastic Oligodendroglioma, Grade III (AO)	2	2	3			1

Le Hou, Dimitris Samaras, Tahsin Kurc, Yi Gao, Liz Vanner, James Davis, Joel Saltz

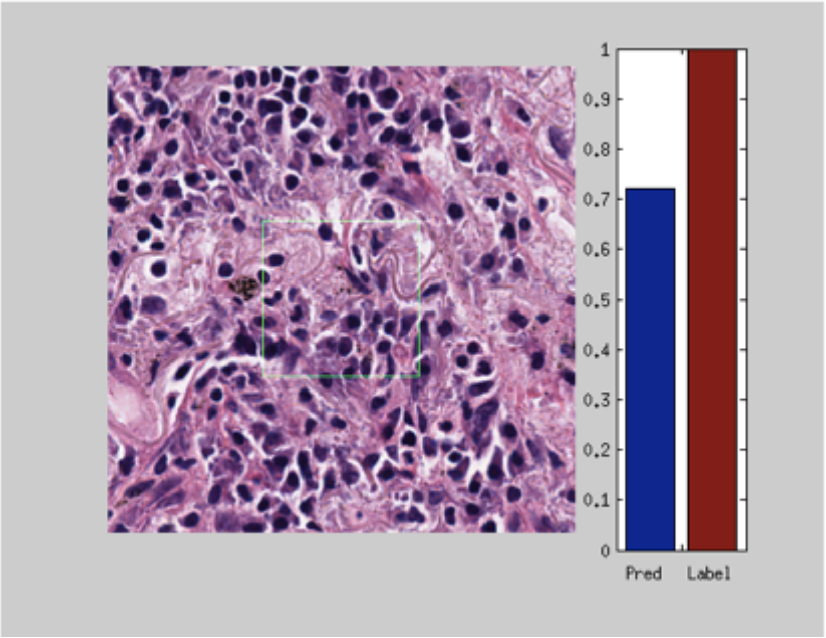
Tumor Infiltrating Lymphocyte quantification

- Convolutional neural network to classify lymphocyte infiltration in tissue patches
- Convolutional neural network and random forest to classify individual segmented nuclei
- Extensive collection of ground truth
- Joint work with Emory and TCGA PanCanAtlas Immune group

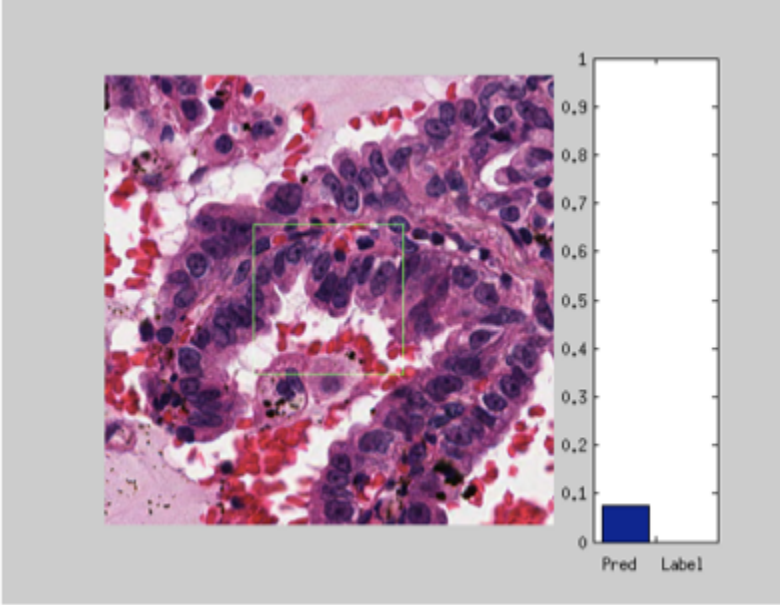
Unsupervised Autoencoder – 100 feature dimensions



Lymphocyte identification



Lymphocytes Infiltration



No Lymphocyte Infiltration

Receiver Operating Characteristic – Area Under Curve – 95%

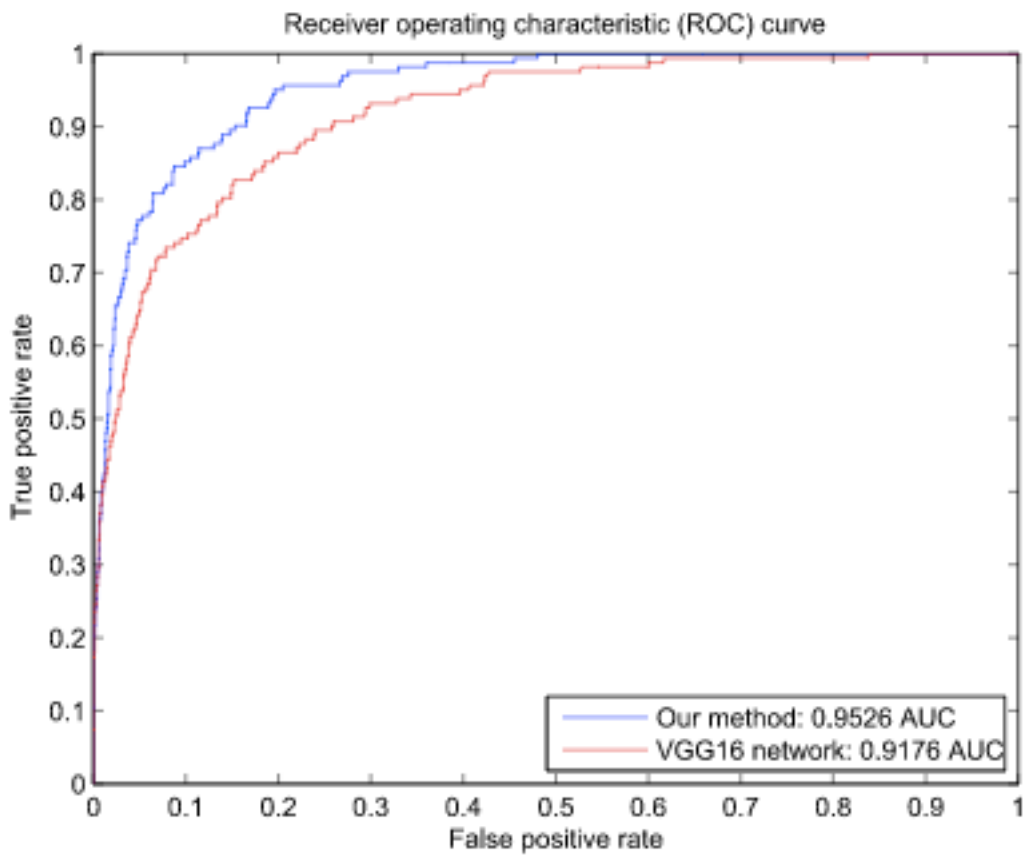
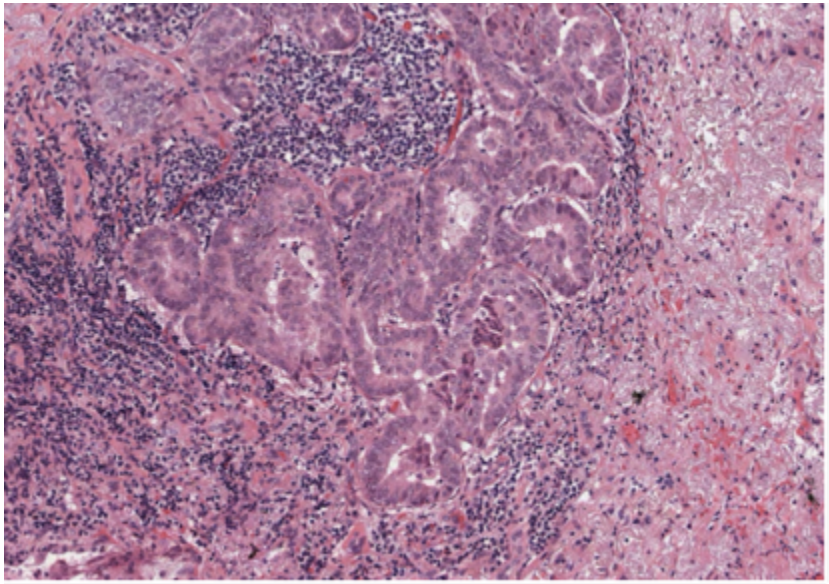
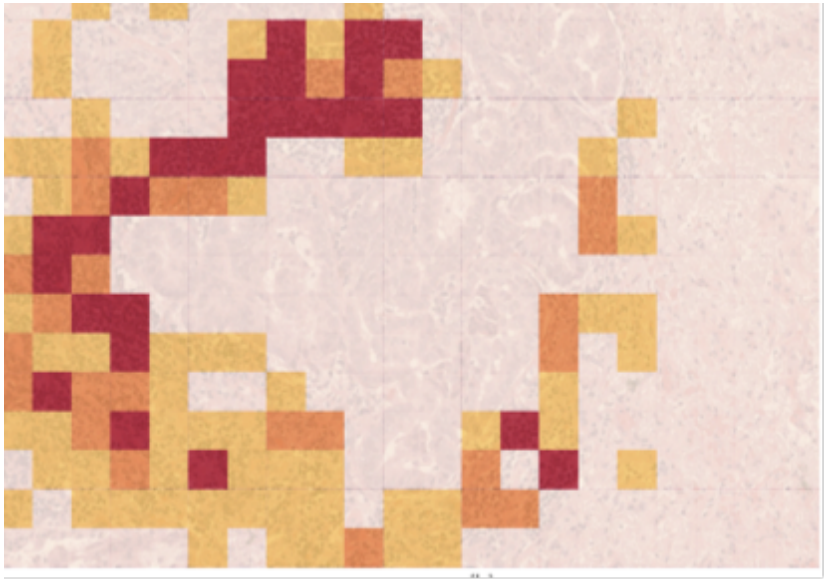


Figure 3 ROC curve

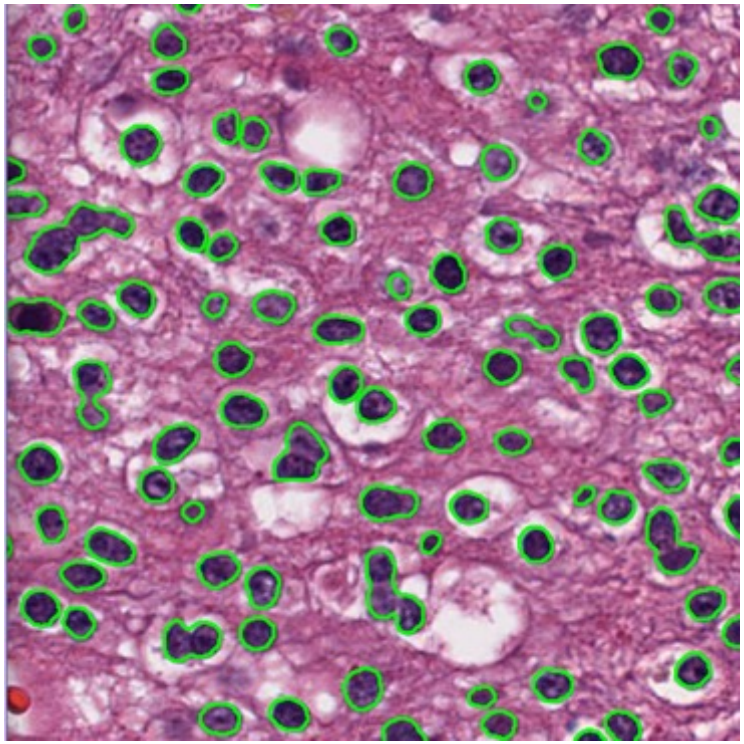
Lymphocyte Classification Heat Map

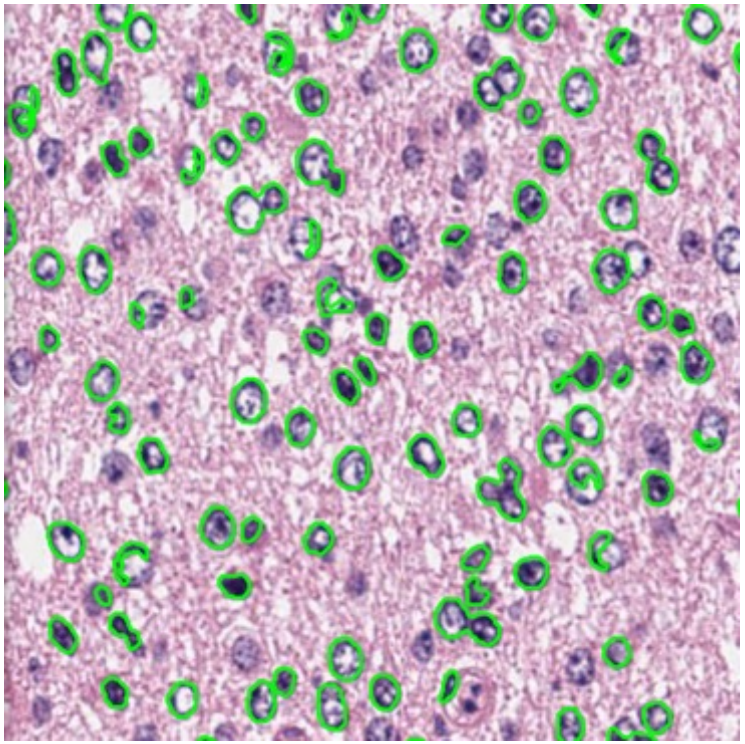
Trained with 22.2K image patches
Pathologist corrects and edits





Machine Learning and Quality Critiquing





	Good	Bad
Test as Good	2916	33
Test as Bad	28	2094

Dissemination

- Containers
- Cloud
- TCIA
- HPC via NSF and DOE
- TCGA – PanCanAtlas – Lymphocyte characterization
- Integrated Features/NLP joint with TIES

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Funding – Thanks!

- This work was supported in part by U24CA180924-01, NCIP/Leidos 14X138 and HHSN261200800001E from the NCI; R01LM011119-01 and R01LM009239 from the NLM
- This research used resources provided by the National Science Foundation XSEDE Science Gateways program under grant TG-ASC130023 and the Keeneland Computing Facility at the Georgia Institute of Technology, which is supported by the NSF under Contract OCI-0910735.

Thanks!