Frederick National Laboratory
for Cancer Research

sponsored by the National Cancer Institute

Accelerating Image Analysis Workflows using Deep Learning

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DEPARTMENT OF HEALTH AND HUMAN SERVICES • National Institutes of Health • National Cancer Institute

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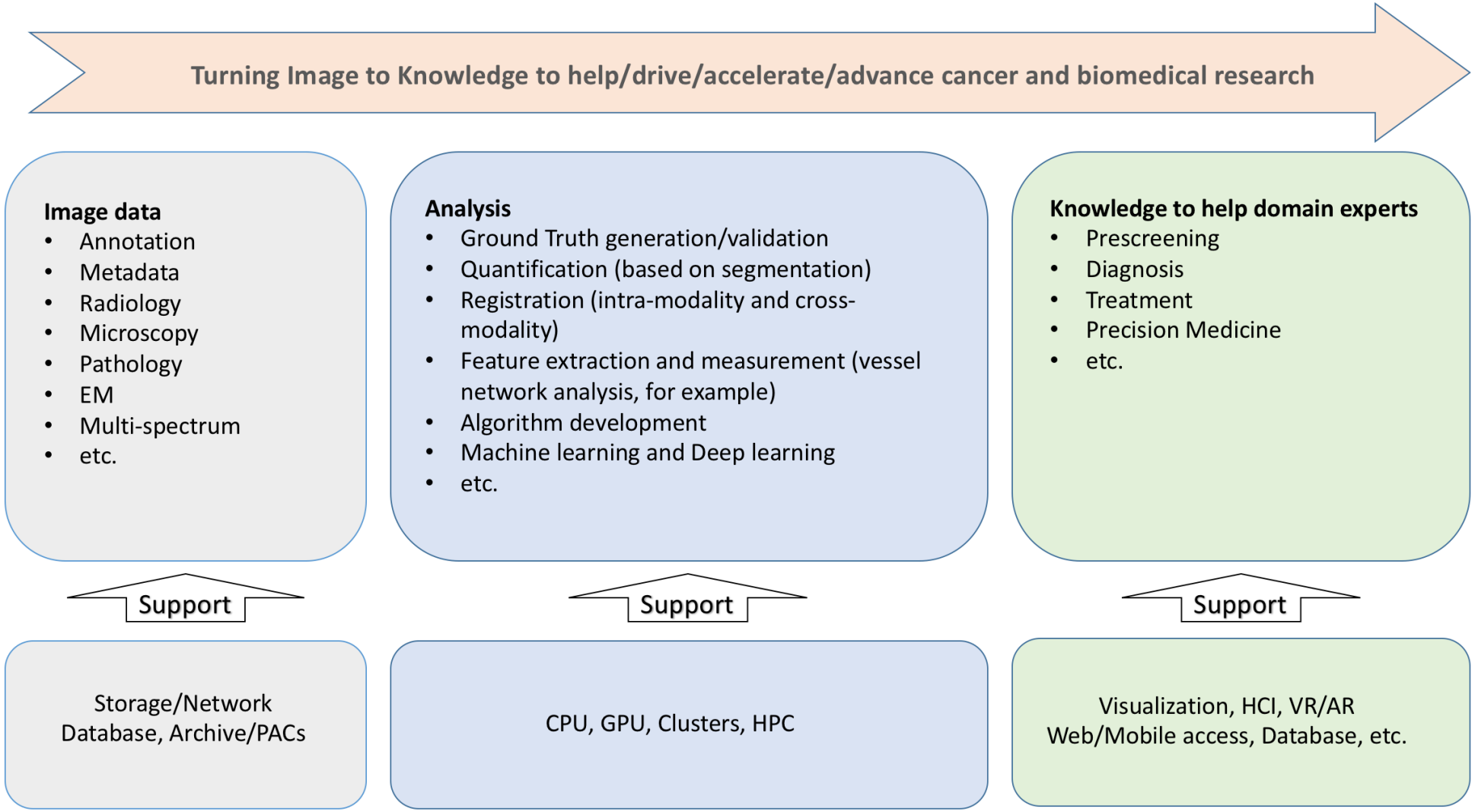
Overview of the Imaging Group

Focused on the **practice** of computational science as it applies to problems in cancer and biomedical research

Vision of Imaging and Visualization Group



Goals for Imaging and Visualization Group
Impact on cancer and biomedical research at FNLCR/NCI/NIH

- Reproducibility – Repeatable workflows
- Objective metrics – useful for diagnosis, characterization, therapy
  - Augment / Integrate with genomic, proteomic data
- Deterministic process as much as possible
  - Validate
- Easily deployable to most users and easy to maintain
- Scalable
- Human Computer Interface (Human is in the loop)
- Workflow optimization to optimize people time
  - Automate the tedious/boring stuff as much as possible

Challenges of “Ground Truth” / “Gold Standard”

How these are derived/defined matters.
How accurate are the “gold standards”?
Usually derived from human segmentation.
The computer algorithms analyzes images differently from humans.
We may need to collect and process images differently to take advantage of machine analysis

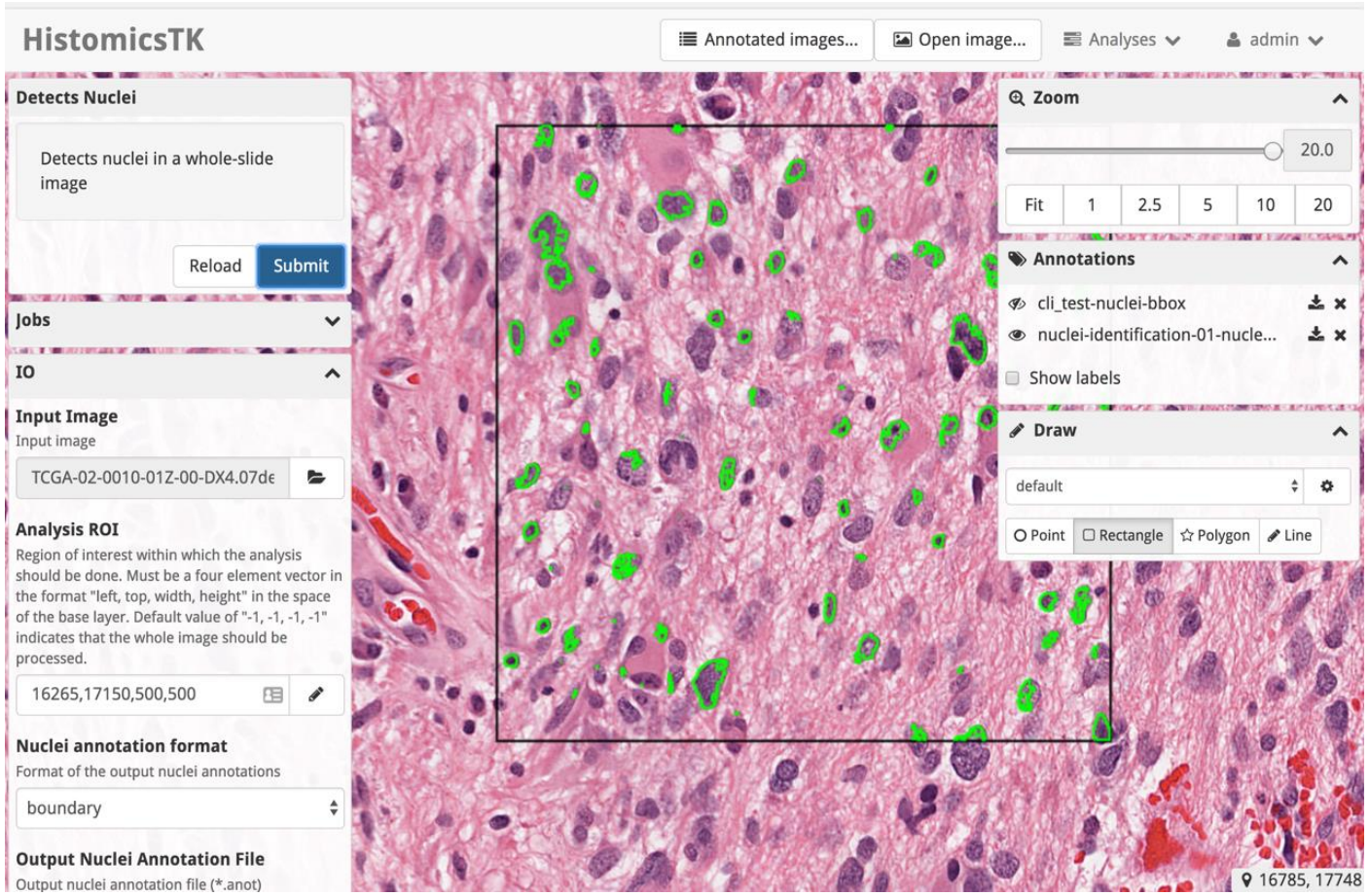
Collection of raw images specifically for machine learning/analysis will facilitate advancement

Ground Truth Challenges
Our experience at FNLCR

- Often no “Ground Truth” for the problem at hand
  - Tissue Doppler imaging for Chemotherapy induced Cardio Toxicity
  - Locating and quantifying metastases in mouse models (usually genetically modified)
  - Vessel segmentation for angiography
  - Lymphangiography of HIV/SIV infection
  - Particle picking in Cryo-EM
  - Feature segmentation on digital pathology images
  - Apoptosis quantification via Ultrasound imaging
- Can synthetic data and simulations help address the issue as a refinement step
  - Cryo-EM is a real possibility (Computationally intensive)
  - Generative Adversarial Networks (GAN)

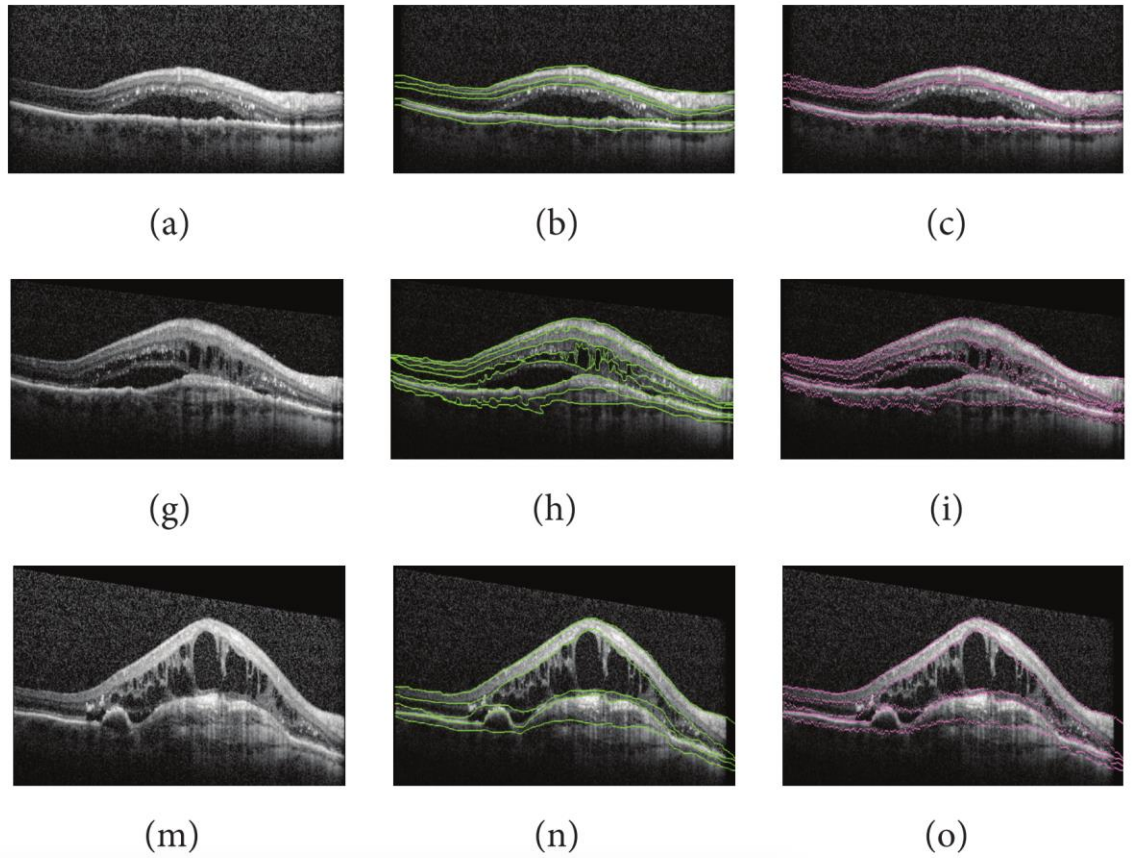
Ground Truth Challenges
Facilitating more complete pathology annotation

- There is need for more gold standard annotations
- Currently looking at tools needed for pathologists to label imagery
  - Emory/Kitware HistomicsTK
  - Cytomine
- What about crowdsourcing annotation?



Nuclei classification algorithms (from 3D Slicer) run on uploaded pathology imagery

Ground Truth Challenges
Example of Crowdsourcing Annotations



Research Article

Use of Mechanical Turk as a MapReduce Framework for Macular OCT Segmentation

Aaron Y. Lee,[1,2] Cecilia S. Lee,[1,2] Pearse A. Keane,[2,3,4] and Adnan Tufail[2,3,4]

completing an average of 5.5 HITs. Each HIT was completed in an average of 4.43 minutes. *Conclusions.* Amazon Mechanical Turk provides a cost-effective, scalable, high-availability infrastructure for manual segmentation of OCT images.

Use Cases and Observations

Experience using Deep Learning (Segmentation)

Assessing/Understanding Deep Learning Models

Understanding HIV/SIV Infection
DLNN analysis/quantification for RNAscope

- Quantification goals
  - Isolated particles
  - Aggregation
  - Productive Infections

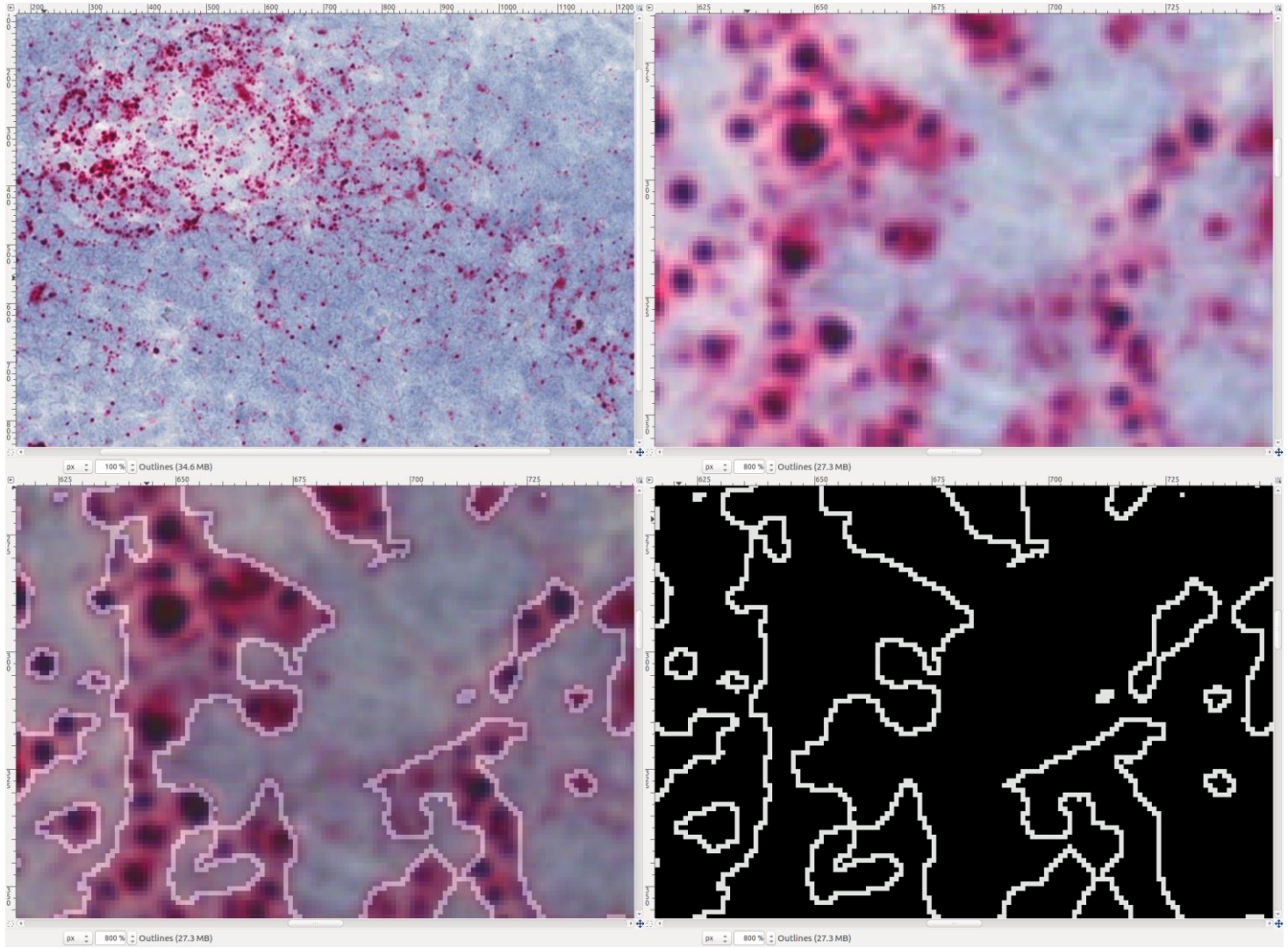
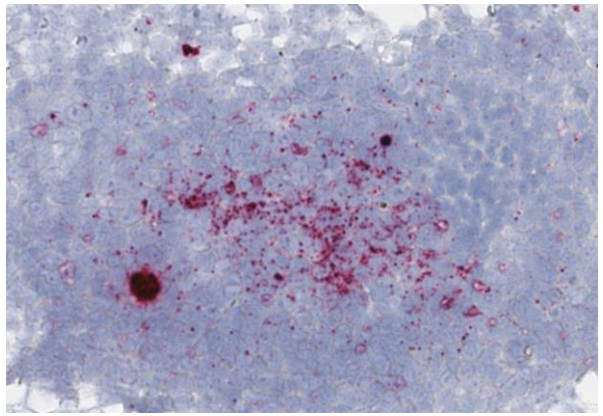


Image provided by TAC/ACVP, FNLCR

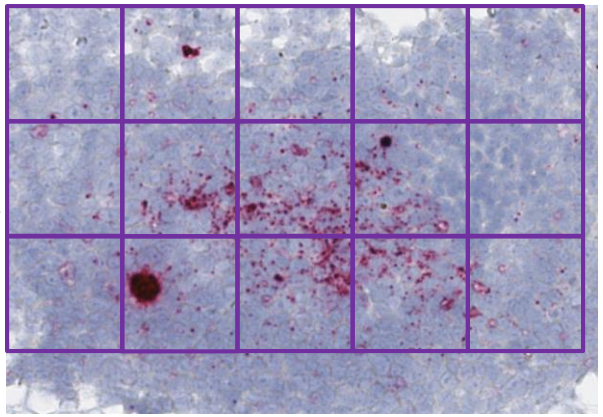
Understanding HIV/SIV Infection
DLNN analysis/quantification for RNAscope

Training Summary:
- Avg. validation score (Dice coef.): ~0.93
- Avg. testing score (Dice coef.): ~0.96

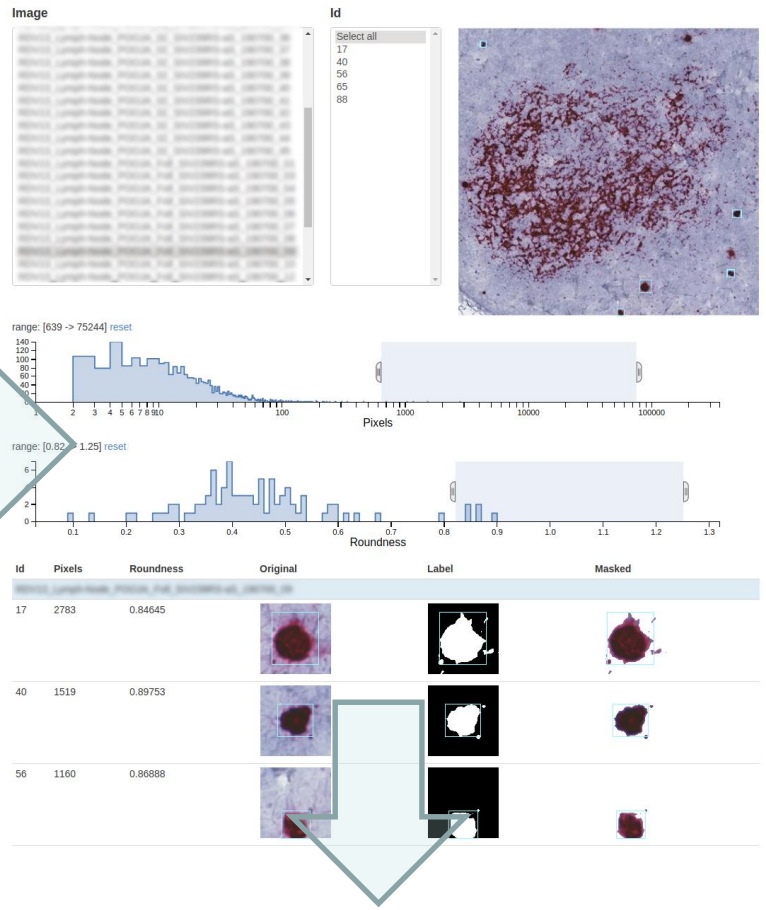
Patch generation for DLNN training, 3184 patches (256x256) in total, un-augmented



cropping



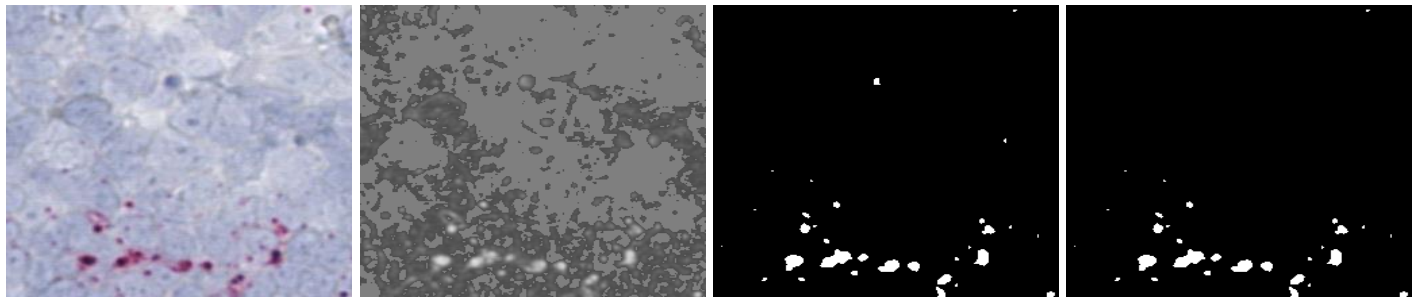
Customized Data Analysis Workflow



DLNN training and prediction

Original

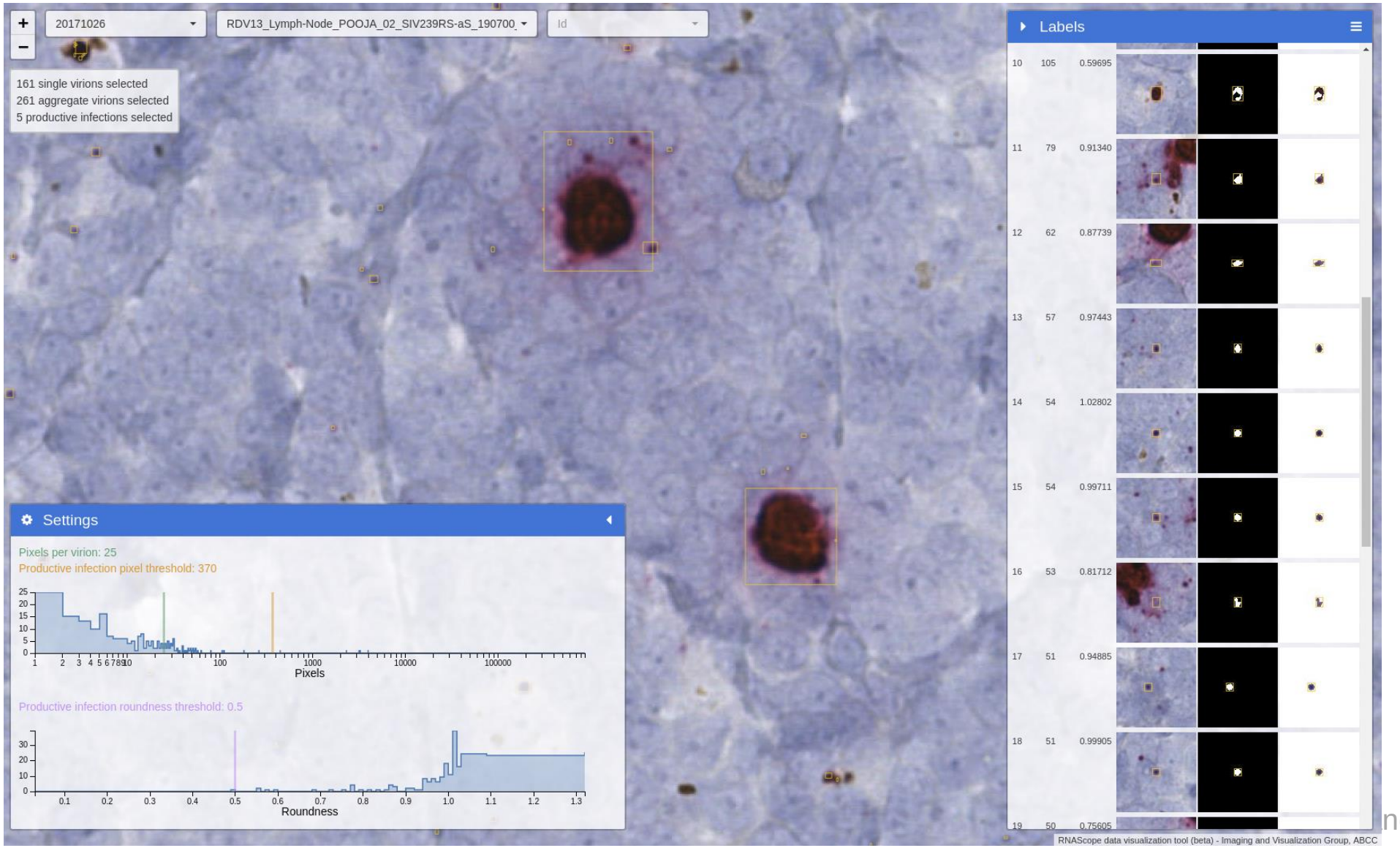
Final Label



Multi-step label generation for DLNN training

Counts, statistics, etc.

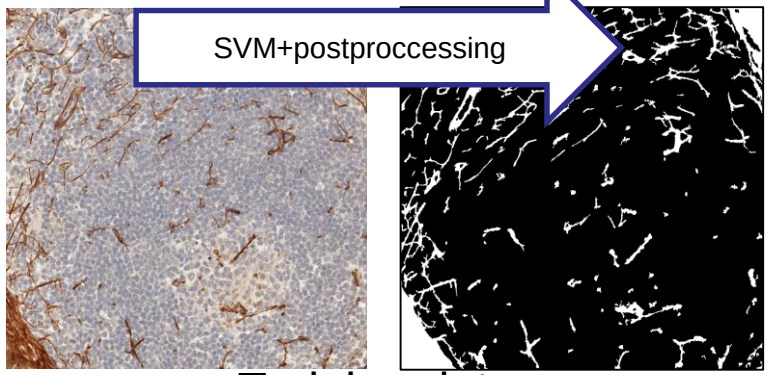
DLNN as a component of biomedical research workflows



Understanding HIV/SIV Infection
Deep Learning in Digital Pathology (collagen segmentation)

- Object detection/classification is popular and easier to implement
- Segmentation, on the other hand, is more challenging, demands more accuracy

Image provided by TAC, ACVP, FNLCR

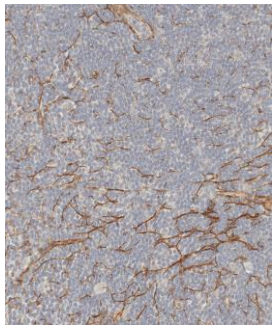


Training data

DLNN training

Trained Network
U-Net
LCNN (in house)
etc.

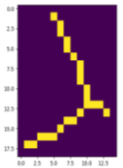
Quantification based on DLNN prediction



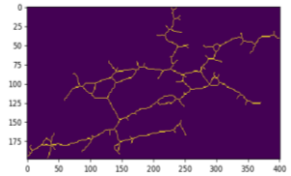
Original image

Generated label

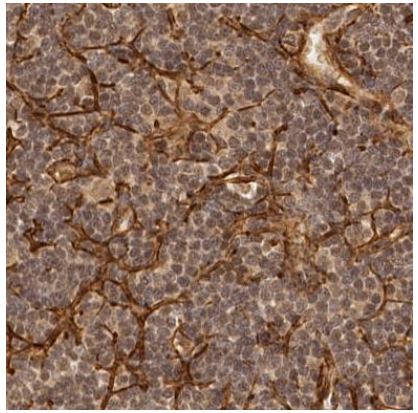
Quantification

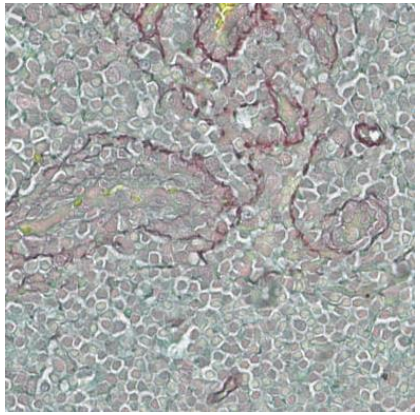


Collagen index: 253
Number of branches: 3
Length: 24.14
Curvature: 1.12



Collagen index: 192
Number of branches: 131
Length: 528.22
Curvature: 0.60





New images with different stains

Color transfer

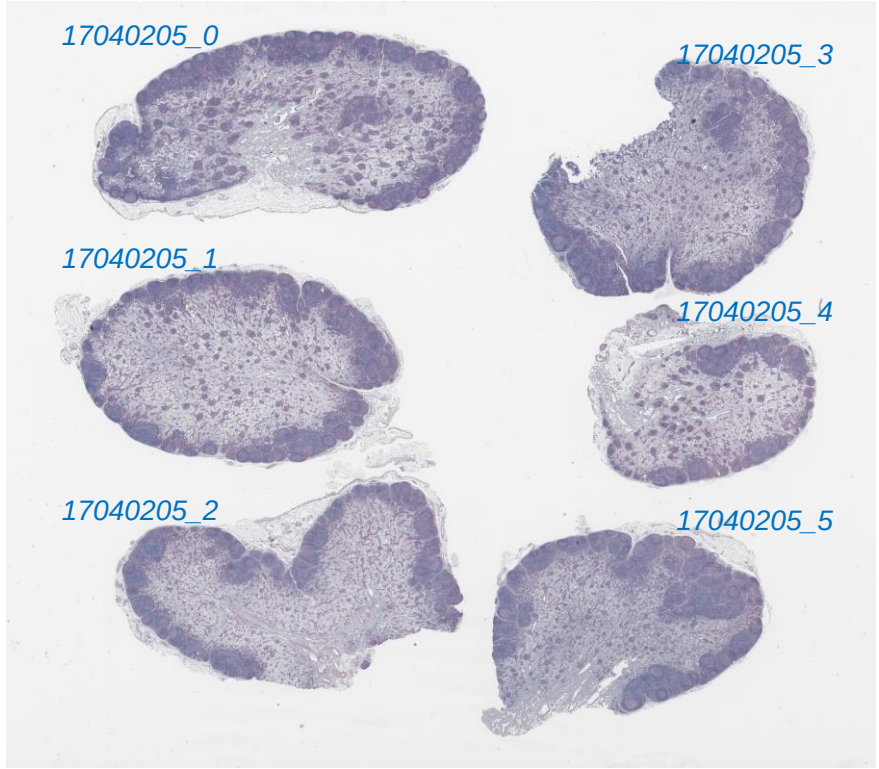
Color matched images

Training Statistics

- Original images utilized for training
  - Before augmentation: 800 x 800 in size, 275 images
  - After augmentation: 400 x 400 in size, 37,400 images
- Images utilized for Validation
  - 91 images, 800 x 800 in size, divided into four, no augmentation
  - 400 x 400 in size, 364 images
- Images utilized for Testing
  - 91 images, 800 x 800 in size, divided into four, no augmentation
  - 400 x 400 in size, 364 images
- Latest results (single training: 14 hours, 40 epochs, 4x1080 Ti, U-Net variation)
  - Training Accuracy: 96.69% (Dice coefficient)
  - Validation Accuracy: 95.17% (Dice coefficient)
  - Testing Accuracy: 94.65% (Dice coefficient)

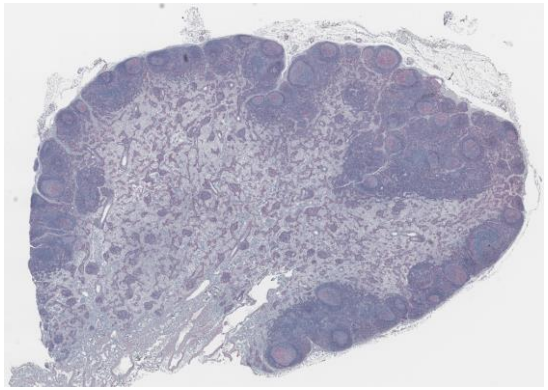
DLNN as a component of biomedical research workflows (WSI Tissue Section Collagen Quantification)

Input Tissue Section Images (Lymph Nodes)
Image provided by PHL, LASP, FNLCR

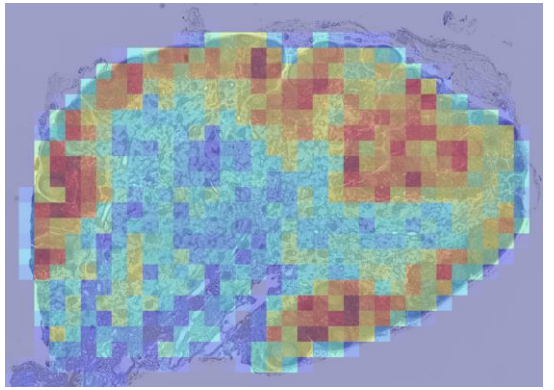


Whole slide image
(17040205.svs, 51,791 x 45,864, ~2.3 billion pixels)

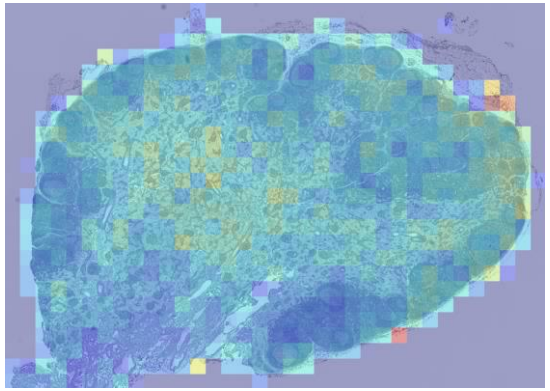
Preliminary quantification results based on DLNN segmentation correlating to anatomical structures



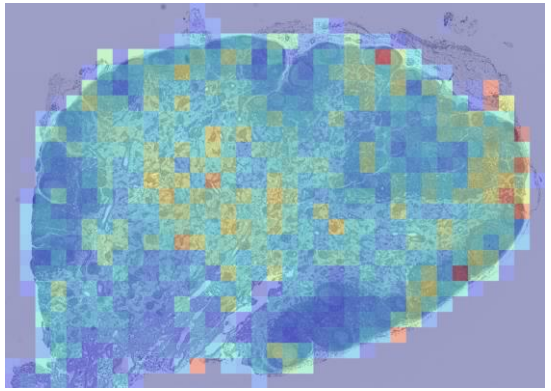
ROI 17040205_5, ~0.2 billion pixels



Number of collagens



Avg. len. collagens



Avg. num. branches

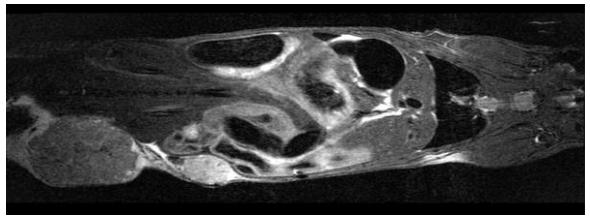
Deep Learning Observations

- Training a network is straightforward: DL frameworks are mature and easy to use nowadays
  - But much harder to generate good training data (not so bad for classification/detection)
  - DLNN performance is important, what's more important is how much **knowledge** extracted from DLNN
  - Deep Learning can be used even without 'big data'
  - Deep Learning can be very useful in medical imaging, incremental training data generation is possible solution to solve the scarcity of good labels
    - Incremental means using existing algorithms/ML/manual process to generate small number of labels to train a initial network and use it to predict more labels → labels to be refined to re-train the network to increase number of data points
  - Careful data augmentation on medical images: enhancement should follow the original data distribution so it has to be guided and fit the context
    - Data augmentation not always necessary: in our PDX whole-tumor segmentation task, 76*36 256x256 un-augmented images reached 95% average segmentation accuracy → connect back to ground truth issue
  - Computationally demanding
    - 4 X 1080 Ti GPUs can only train networks with batch size 8 for 400x400 input image size (larger batch size is better)
    - 3D CNNs for volumetric image data demand more resource (roughly one 672x672x40 volume per 64GB V100 card)

Investigating DL Sensitivity

- Computation - IBM Power Systems
  - 2 POWER8 processor modules
    - (8/10 cores, 3.259/2.860 GHz)
  - 4 NVIDIA Tesla P100 GPUs
- 136 Mouse MRIs
  - 130 mice with tumor
  - 6 mice without tumor

- DL Network
  - Convolutional neural network: U-net
  - Learning rate: $3.0e^{-5}$
  - Epochs: 80 (2742 images/epoch)
  - Batch size: 8
  - Image size: 400 x 400 pixels (original image size: 672 x 672)
  - No data augmentation
  - Duration per training: 2h 50 min



A single frame from MRI of a mouse

× *36 frames*

Each Mouse MRI →

Corresponding label

× *36 frames*

Image provided by SAIP, LASP, FNLCR

Data Selection (“Fixed” data set)

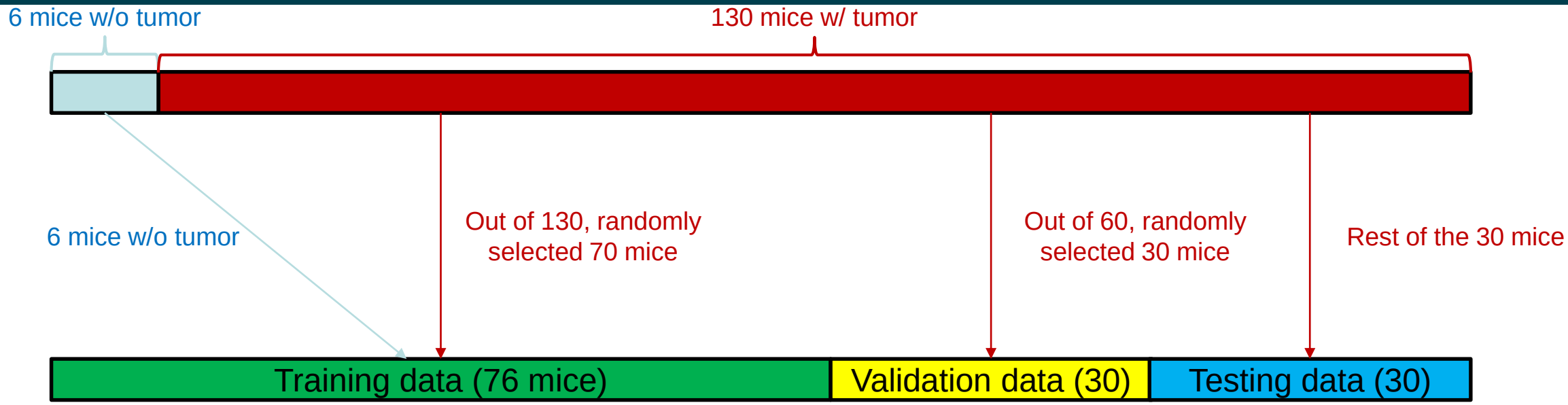


Fig. Simple diagrams showing how data is partitioned into training, validation, and testing data sets for training convolutional neural network

- Six mice without tumor are included in training data only
  - Dice coefficient (evaluation metric) is penalized heavily when mice without tumor are included in validation/testing data
- Fixed data set is utilized for training convolutional neural network (CNN)
  - Repeated the training 10 times

Data Selection (“Random” data sets)

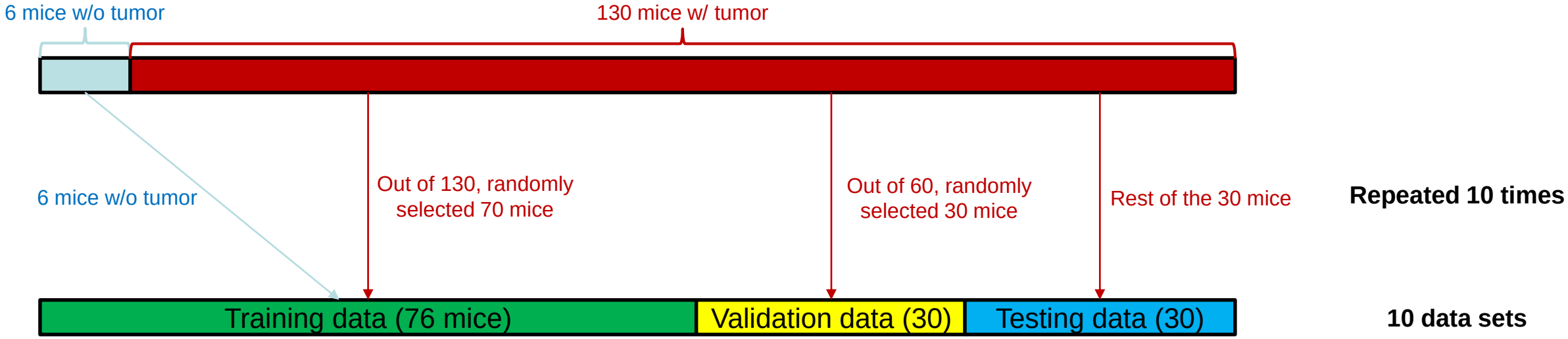
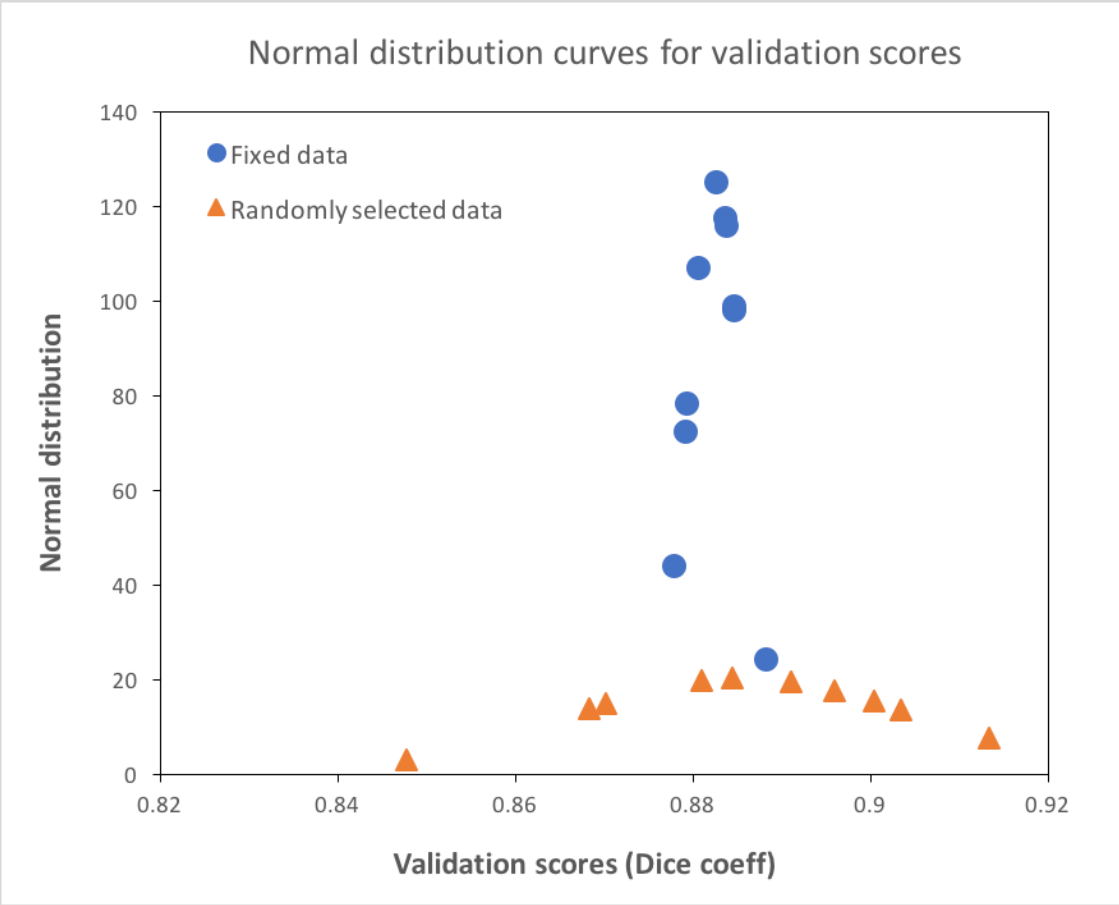


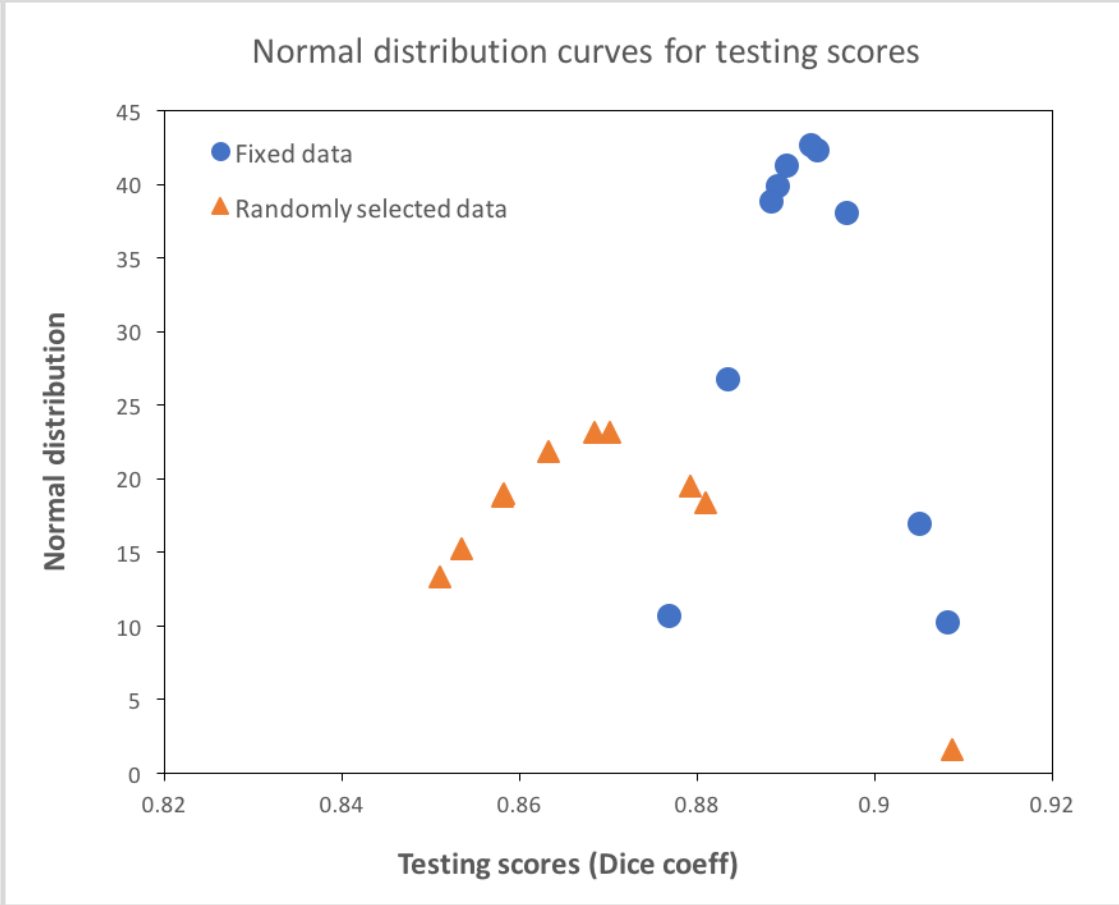
Fig. Simple diagrams showing how 10 different data sets are created for training convolutional neural network

- Six mice without tumor are included in training data only
  - Dice coefficient (evaluation metric) is penalized heavily when mice without tumor are included in validation/testing data
- Data partitioning is repeated 10 times to generate 10 different data sets
  - Repeated the training 10 times
- Per training, the CNN is trained with a different sampling of total data set

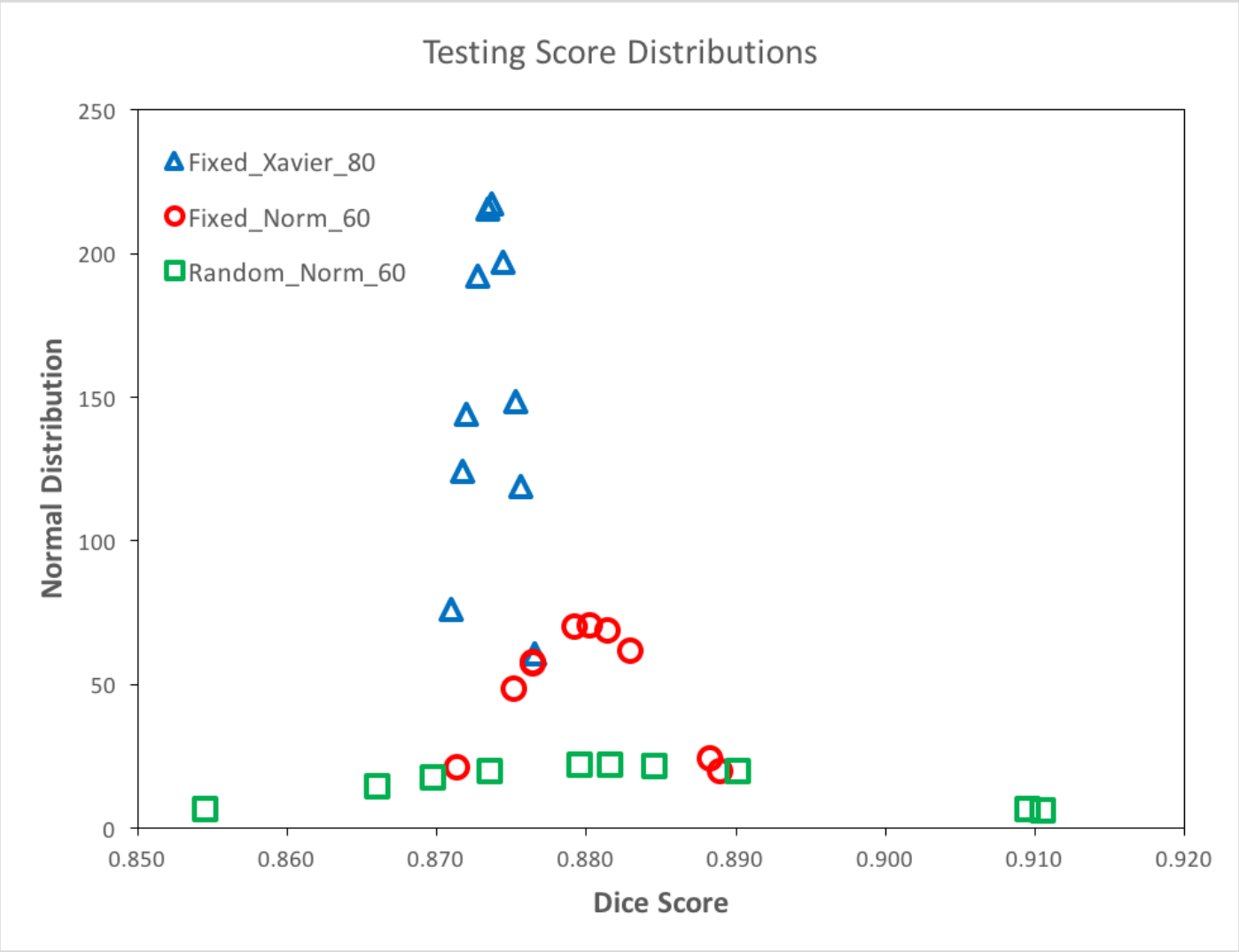
Individual Results plotted for Comparison

Normal distribution curves on validation and testing scores



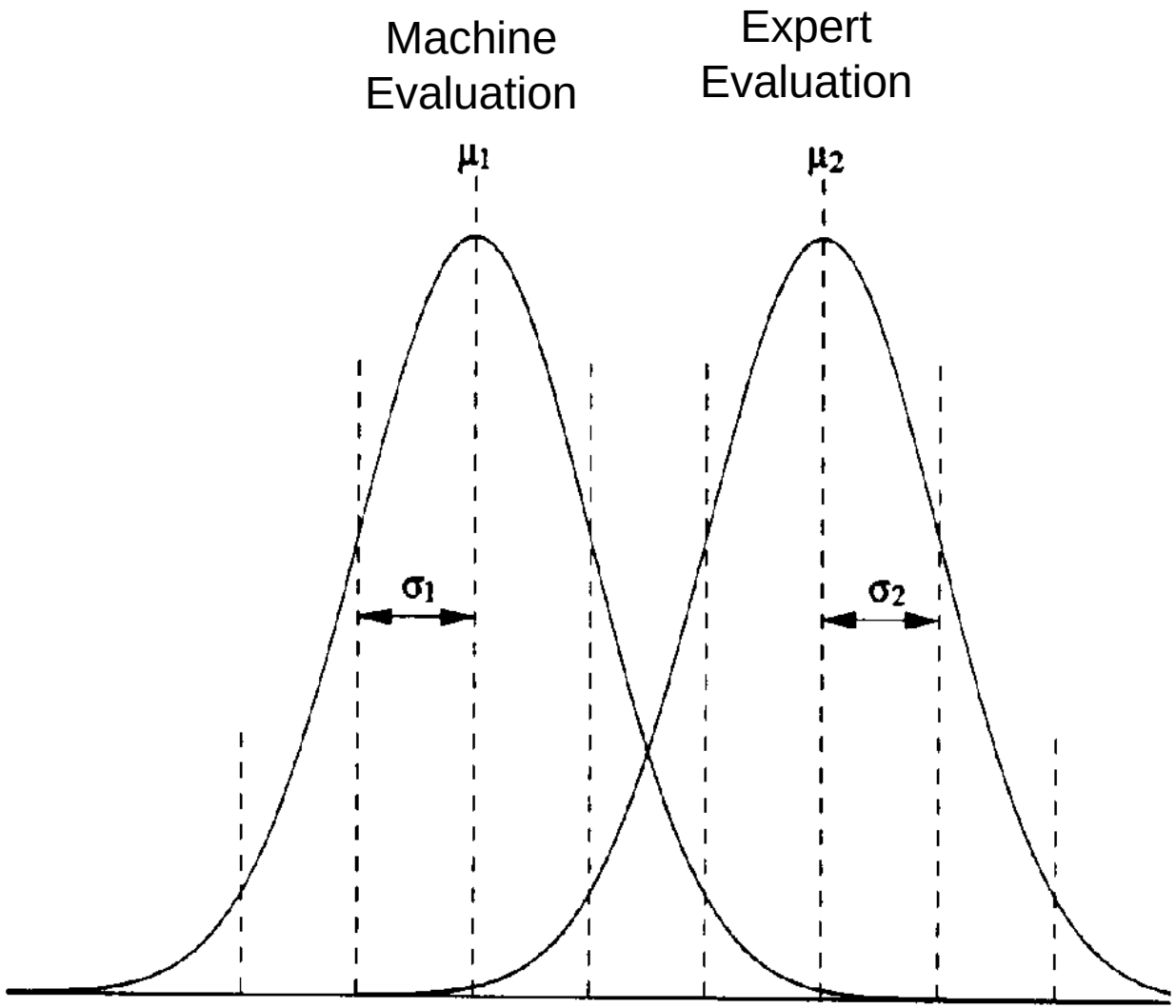


Individual Results plotted for Comparison Initializers



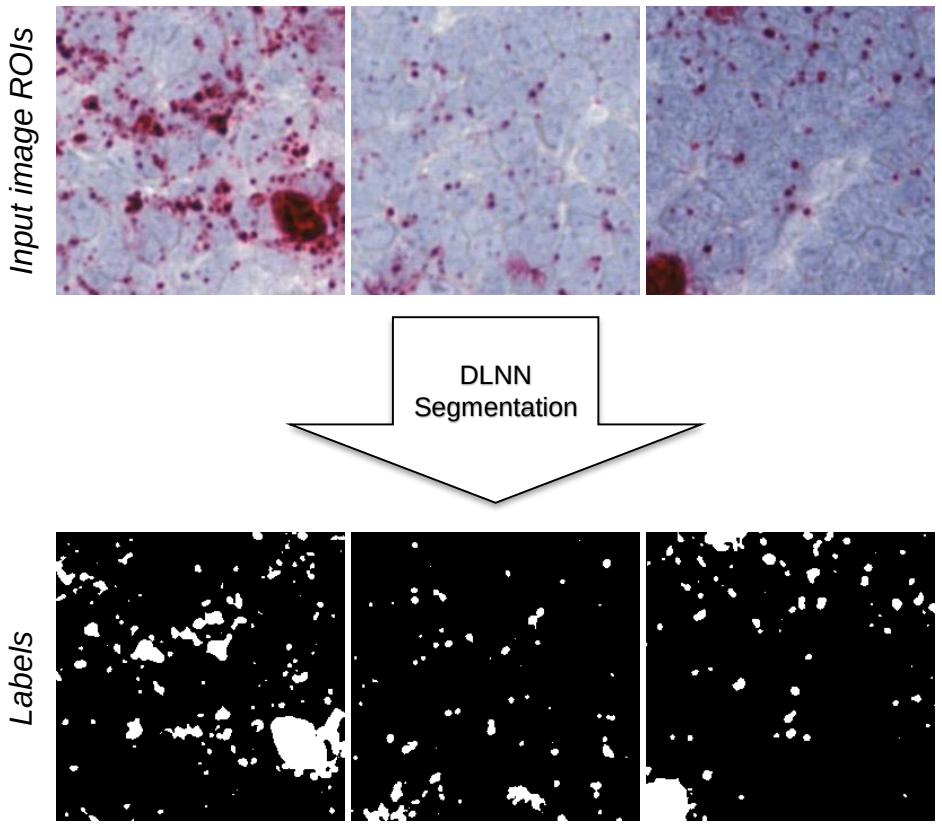
What is the “truth”? How can we tell?

- If we could evaluate images using multiple human evaluators (Expert Evaluation) with different conditions and different machine learning models (Machine Evaluation), then we could compare the distributions and estimate the probability that they represent the same distributions.
- HPC/Advanced Computing could enable this type of evaluation.



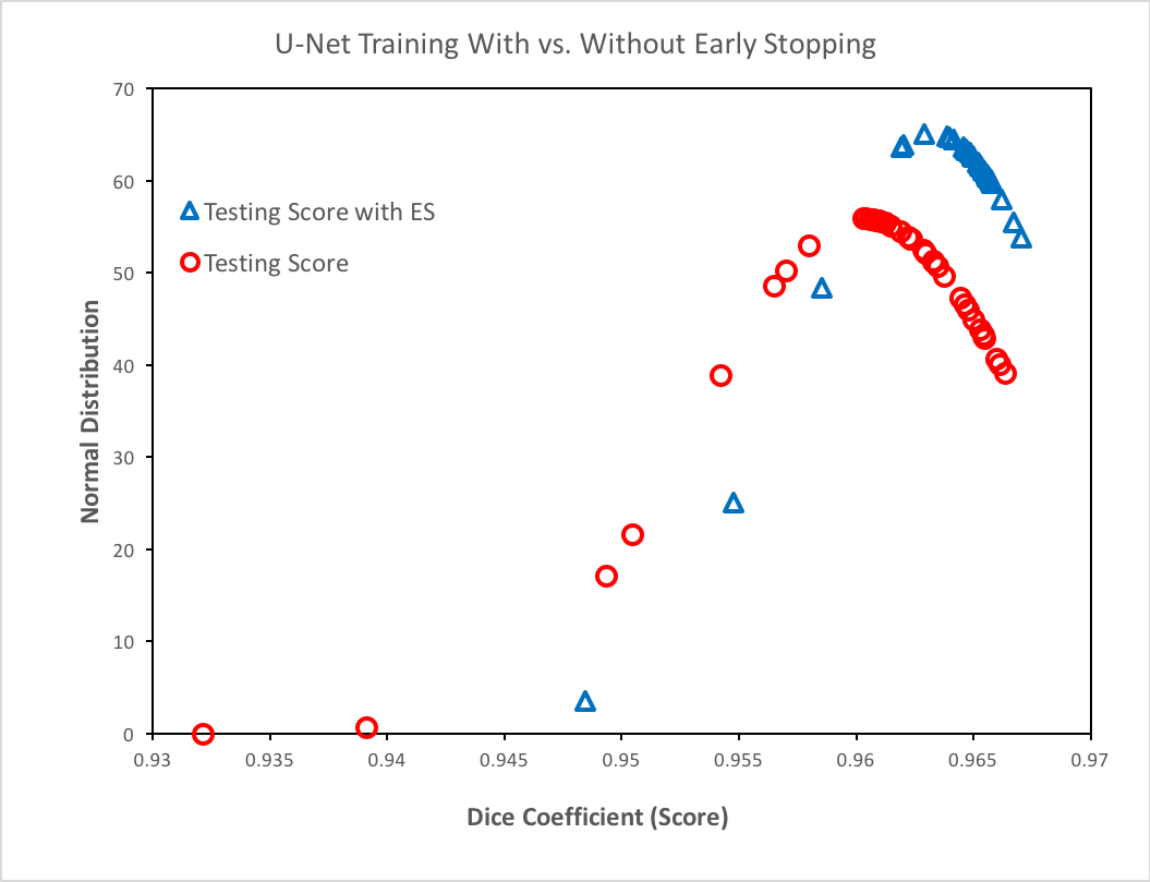
Investigating DL Sensitivity (Optimization Effects)

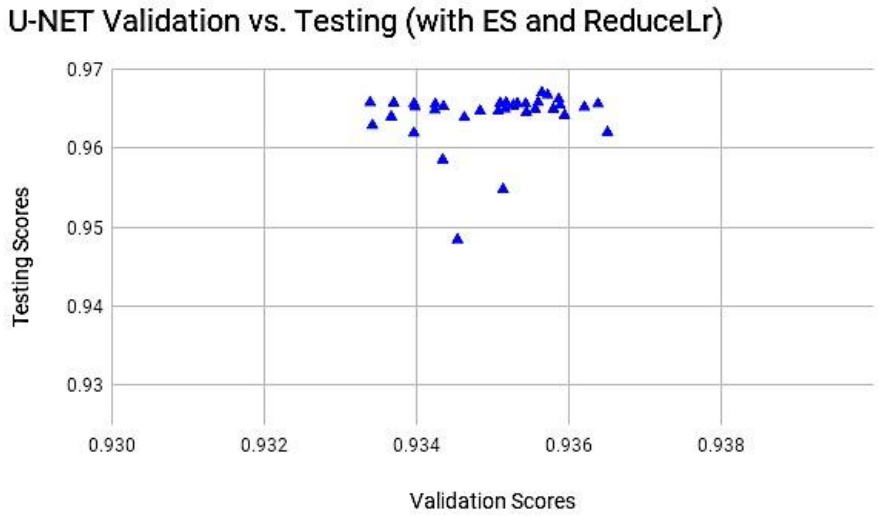
- Training data
  - 3184 256x256 RGB training patches
  - B&W training labels created using semi-manual methods
  - No data augmentation
- Testing data
  - 120 256x256 manually annotated patches
- Training Strategy (DLNN tested: U-Net)
  - Repeat training multiple times (~40) and up to 50 epochs each time
    - In each run, randomly select 75% for training and 25% for validation
    - Other parameters kept the same across multiple runs
  - With vs. without Early Stopping and Reduce Learning Rate on Plateau
    - Learning rate starting at 1e-4
  - Trained networks with <0.9 validation score excluded in reporting

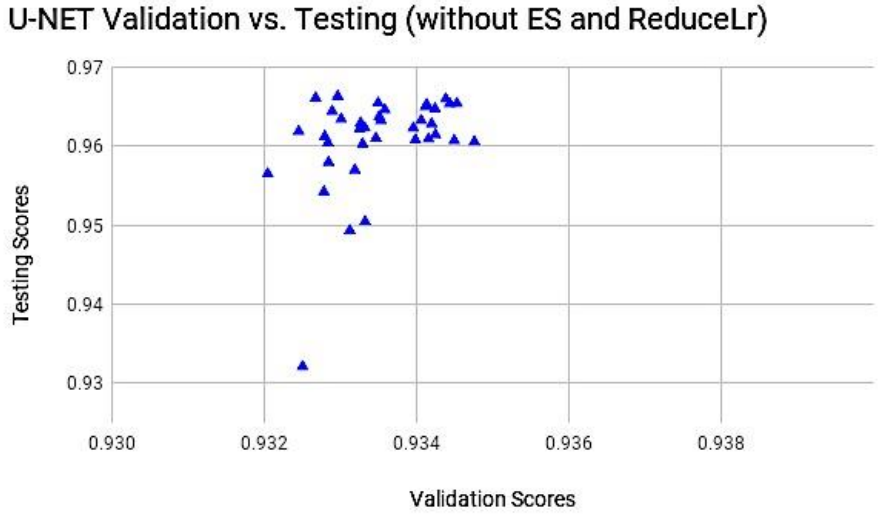


Individual Results plotted for Comparison

Normal distribution curves on testing scores



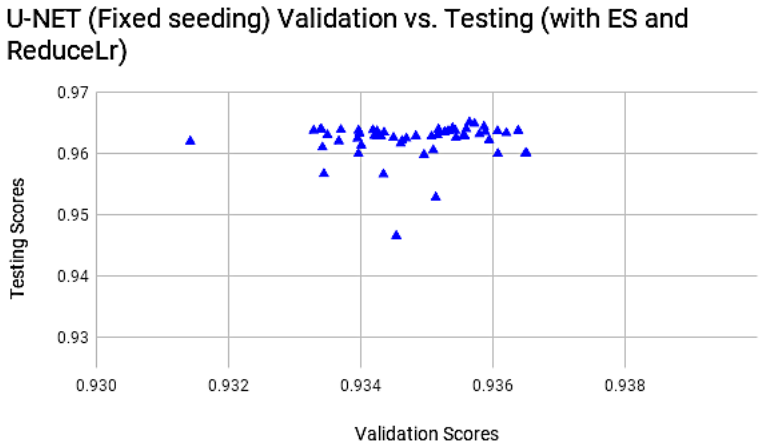


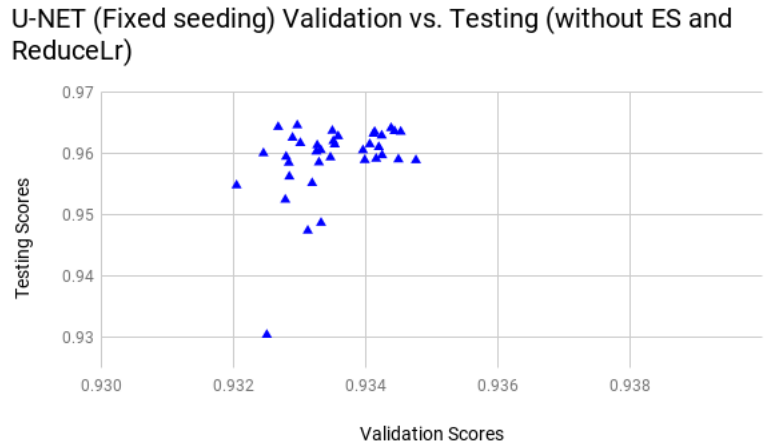


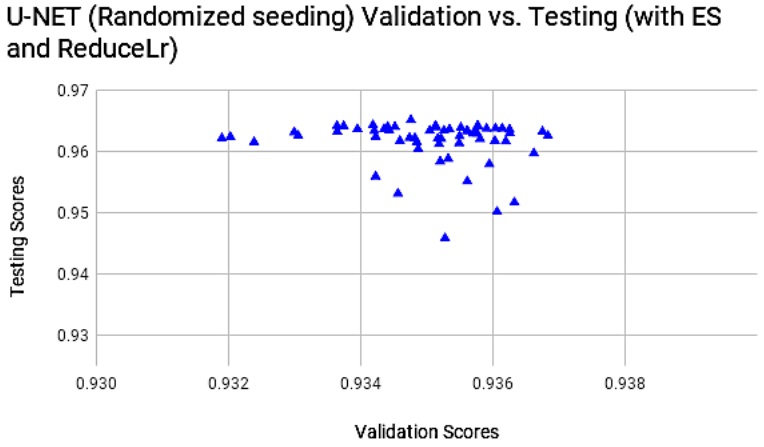
Early Stopping and Reduce Learning Rate help to reduce variations in testing scores

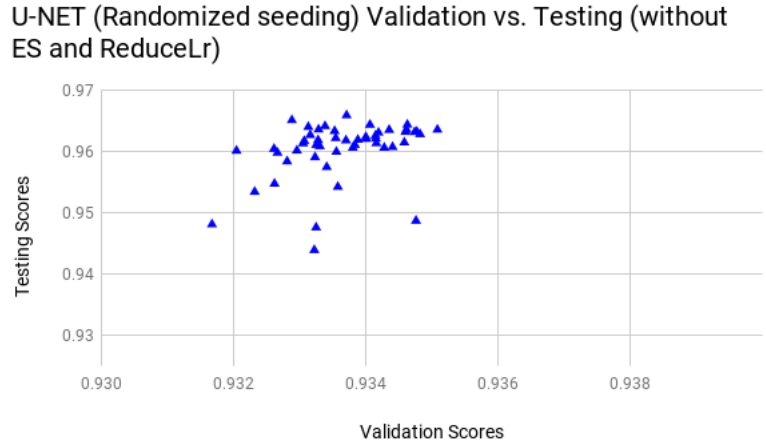
Investigating DL Sensitivity (Random Seeds)

- Machine learning algorithms are stochastic in practice
- Fixed seeding
  - Use an arbitrarily selected random seed across all trainings
- Randomized seeding
  - Restart training from the beginning every 10 runs to use new random seeds









Acknowledgements

- Imaging and Visualization Group
  - Hyun Jung
  - Christian Suloway
  - Tianyi Miao
  - Curtis Lisle, KnowledgeVis
  - Xinlian Liu, Hood College

- Our Collaborators at FNLCR, NCI/NIH

Thank you

Questions?

Deep Learning Questions

- **How robust / sensitive are the models with respect to training parameters**
- Image Augmentation
  - Currently ad-hoc “black box” used to improve training accuracy
  - Research really needed to determine the effect of different augmentation techniques on training accuracy, specificity in biomedical imaging
- Neural Network Architectures
  - Innovation with different connectivity
- Standards
  - Open Neural Network Exchange (onnx) format proposed for support across libraries (https://github.com/onnx/onnx)