Deep-learning And Digital Pathology

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Artificial Intelligence Resource, NCI

NCI/NIH

06/15/2021

- Introduction to Pathology
- Introduction to Digital Pathology
- Interesting publications
- Combining machine learning with pathology

AGENDA

INTRODUCTION TO PATHOLOGY

"The lab"

SURGICAL PATHOLOGY WORKFLOW

Formaldehyde
~1mm/hr

Accessioning

Gross Examination

Tissue Processing

Embedding

Cutting

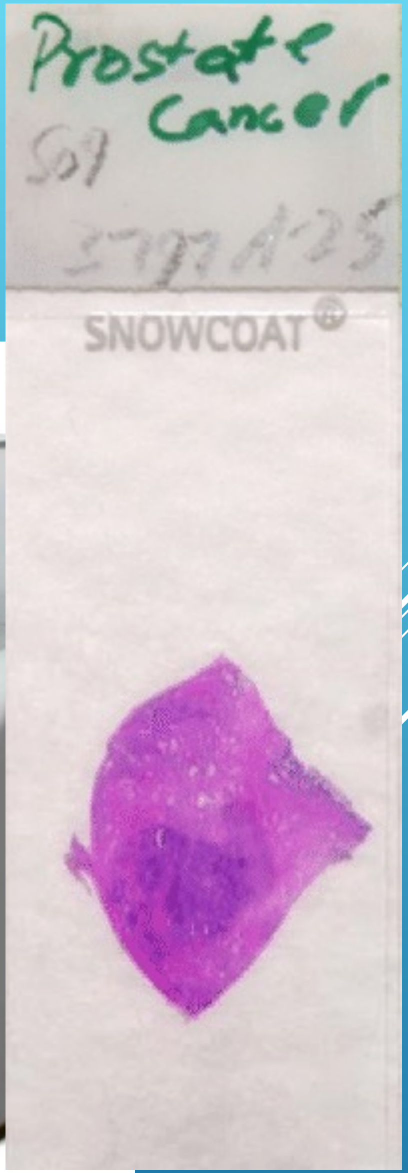
Staining

Microscopic Examination

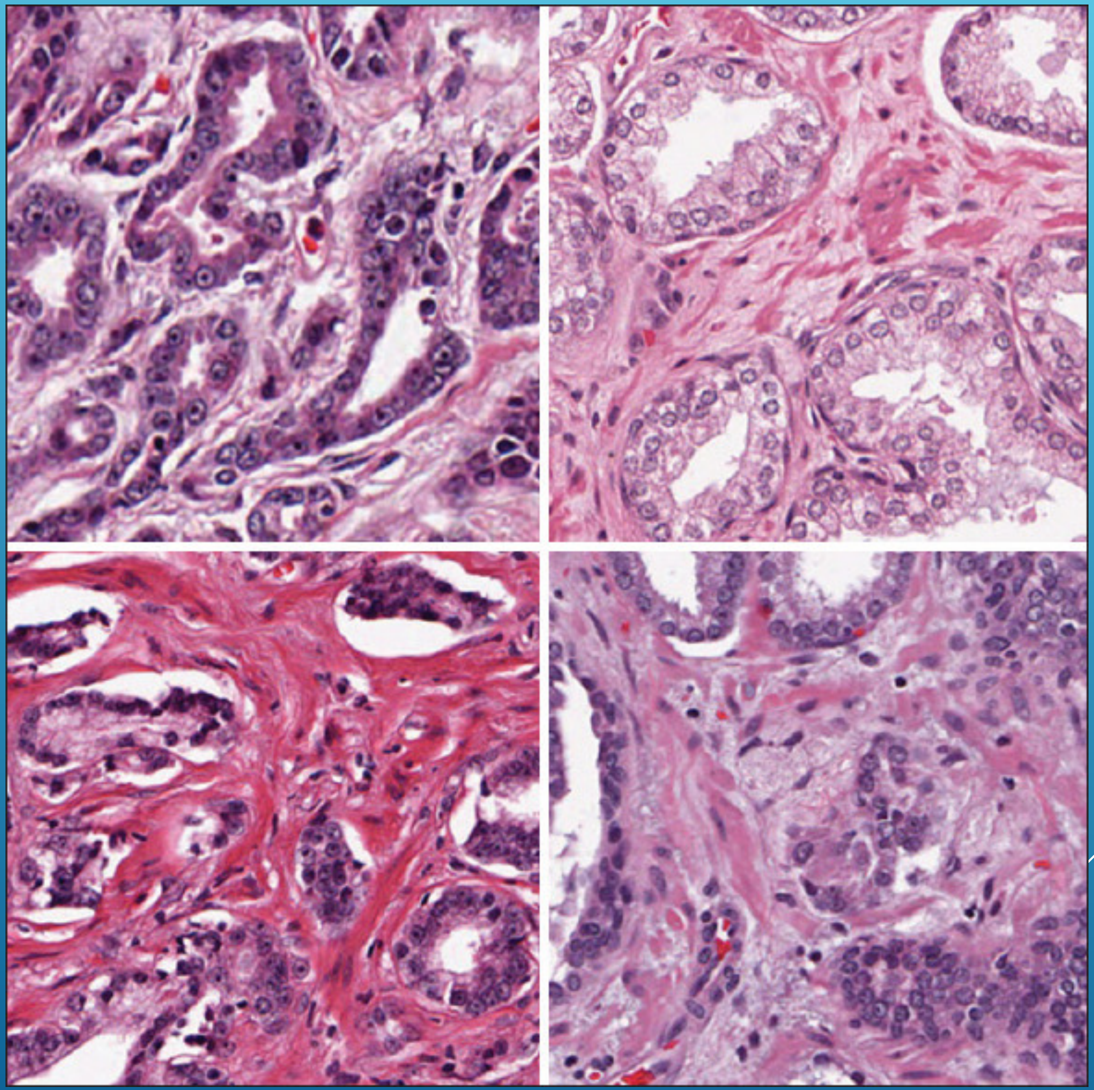
Ancillary Testing

TISSUE STAINING

- Hematoxylin & Eosin
- Mounting media
- Coverslip



COLOR VARIATION



DIGITAL PATHOLOGY

News & Events

FDA News Release

FDA allows marketing of first whole slide imaging system for digital pathology

For Immediate Release April 12, 2017

Release

The U.S. Food and Drug Administration today permitted marketing of the Philips IntelliSite Pathology Solution (PIPS), the first whole slide imaging (WSI) system that allows for review and interpretation of digital surgical pathology slides prepared from biopsied tissue. This is the first time the FDA has permitted the marketing of a WSI system for these purposes.

"The system enables pathologists to read tissue slides digitally in order to make diagnoses, rather than looking directly at a tissue sample mounted on a glass slide under a conventional light microscope," said Alberto Gutierrez, Ph.D., Director of the Office of In Vitro Diagnostics and Radiological Health in the FDA's Center for Devices and Radiological Health. "Because the system digitizes slides that would otherwise be stored in physical files, it also provides a streamlined slide storage and retrieval system that may ultimately help make critical health information available to pathologists, other health care professionals and patients faster."

Pathologists are medical doctors who specialize in understanding the cause and development of a disease or condition. In pathology, biopsied tissues are mounted onto glass slides and stained for viewing and evaluation. The PIPS uses proprietary hardware and software to scan and digitize conventional surgical pathology glass slides prepared from biopsied tissue at resolutions equivalent to 400 times magnification. These digitized images can then be reviewed and interpreted by

Inquiries

Media

Stephanie Caccomo
301-348-1956

Consumers

888-INFO-FDA

Related Information

- FDA: Medical Devices
- FDA: Office of In Vitro Diagnostics and Radiological Health

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Review finds more cases handled by impaired pathologist at VA clinic in Fayetteville, Ark.

Posted: Tue 1:53 PM, Jan 29, 2019

FAYETTEVILLE, Ark. (AP) — A pathologist accused of working while impaired at a Fayettevile, Ark. Veterans Affairs hospital handled 96 cases as a private consultant before he was hired, according to an independent review.

Dr. Robert Morris Levy has acknowledged that he once showed up to work at the Veterans Health Care System of the Ozarks drunk in 2016, but he denies working while impaired.

Kelvin Parks, the system's director told veterans at a town hall meeting on Monday that outside pathologists reviewed nearly 34,000 cases handled by Levy and found more than 3,000 errors or missed diagnoses, the Northwest Arkansas Democrat-Gazette reported. The cases date back to 2005.

Review finds more cases handled by impaired pathologist at VA clinic in Fayetteville, Ark.

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Review finds more cases handled by impaired pathologist at VA clinic in Fayetteville, Ark.

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FOR IMMEDIATE RELEASE

Friday, January 22, 2021

Fayetteville Doctor Sentenced To 20 Years In Federal Prison For Mail Fraud And Involuntary Manslaughter

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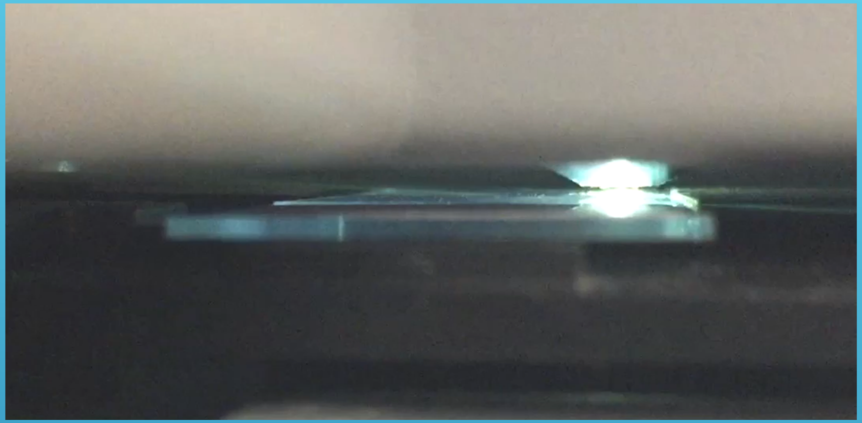
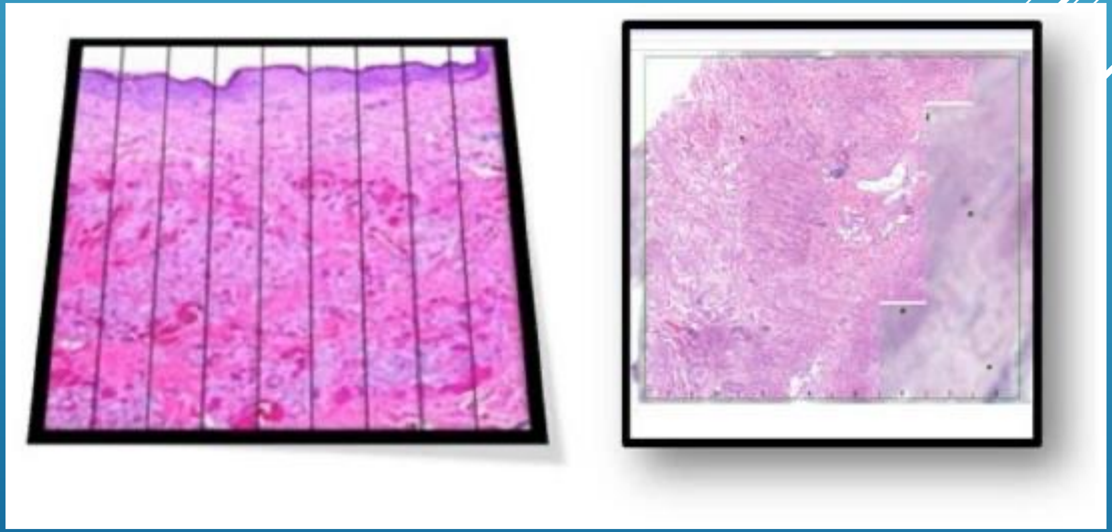
WHOLE-SLIDE IMAGING

WHOLE-SLIDE IMAGING (WSI)



- Image capture device
  - Motorized
- Microscope objective



WSI FORMAT

- 20x or 40x magnification
  - 0.5 µm/pixel or 2.75 µm/pixel
- 1-5 minutes per glass slide
- ***Large*** file sizes
  - Gigapixel range, 0.5-2GB file sizes
- LZW/TIF or some lossless compression*
- Image tiling and image pyramids

**YMMV*

OPENSLIDE

- Open source C library
  - Java, python
- API
  - OpenSeaDragon
- Reverse engineered
  - Aperio
  - Hamamatsu
  - Leica
  - Phillips
  - Sakura
  - Ventana
  - 3DHISTECH MRXS ("MIRAX")
  - And more

TECHNICAL NOTE

J Pathol Inform 2013, 4:27

OpenSlide: A vendor-neutral software foundation for digital pathology

Adam Goode[1], Benjamin Gilbert[2], Jan Harkes[2], Drazen Jukic[3], Mahadev Satyanarayanan[2]

[1] School of Computer Science, Carnegie Mellon University; Google, Pittsburgh, PA, USA

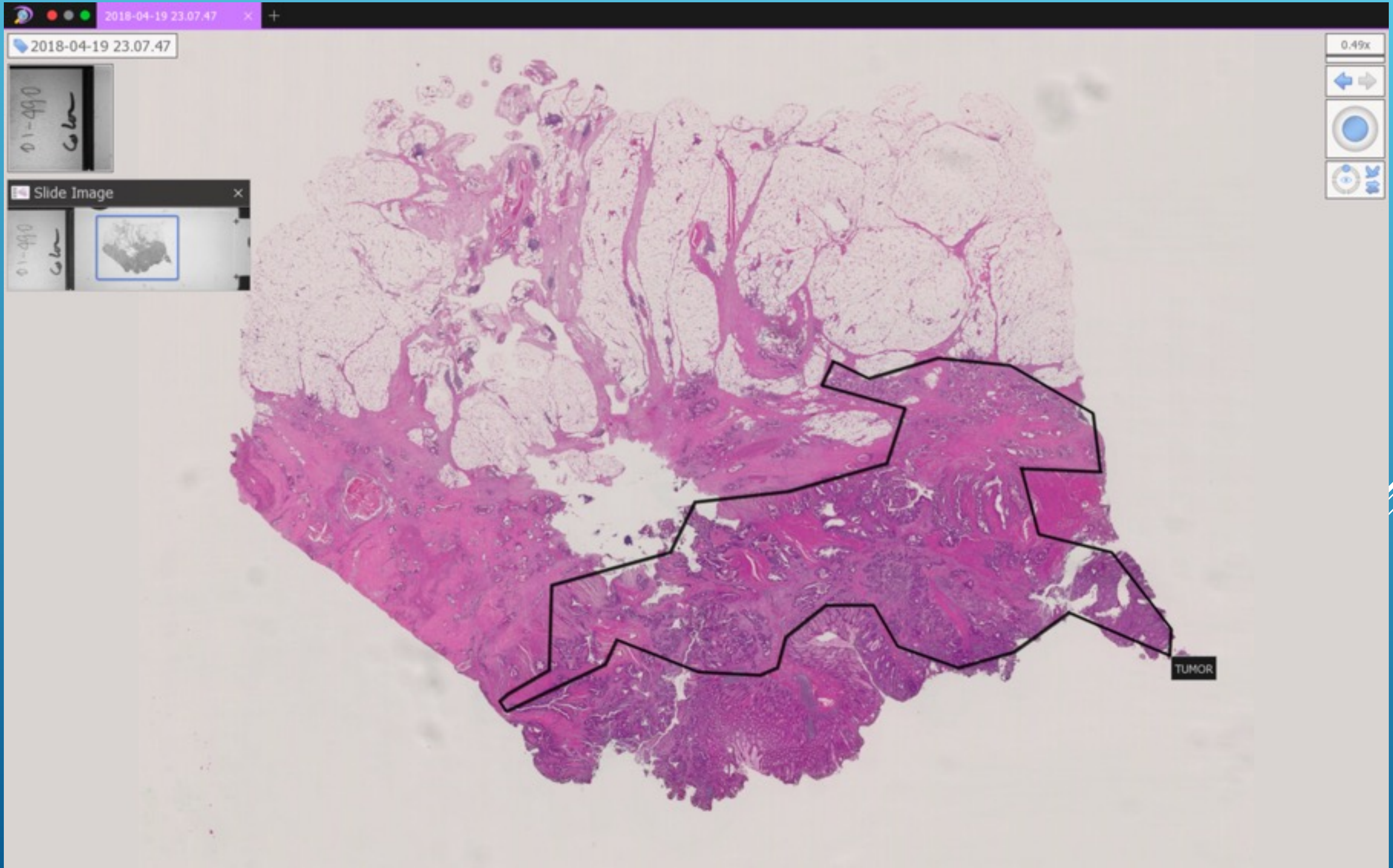
[2] School of Computer Science, Carnegie Mellon University, Pittsburgh, Pennsylvania, USA

[3] Department of Pathology and Dermatology, University of Pittsburgh, Pittsburgh, Pennsylvania; James A. Haley Veterans Hospital and University of South Florida, Tampa, FL, USA

BENEFITS OF NIH

- NCI / AIR – Computer vision expertise
  - DGX-A100 (8x A100's; 320GB VRAM)
  - Pathologists, Radiologists, Data Scientists
- NCI
  - CBIIT
    - HALO, Palantir, etc
- NIH Clinical Center – Rich source of medical samples
  - ~6-7k pathology cases per year
  - All cases research (IRB protocol)
- NIH-wide
  - Biowulf/Helix
    - Many V100's
    - Many A100's

ANNOTATING



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RESEARCH ARTICLE

Pigeons (*Columba livia*) as Trainable Observers of Pathology and Radiology Breast Cancer Images

Richard M. Levenson, Elizabeth A. Krupinski, Victor M. Navarro, Edward A. Wasserman

Published: November 18, 2015 • https://doi.org/10.1371/journal.pone.0141357

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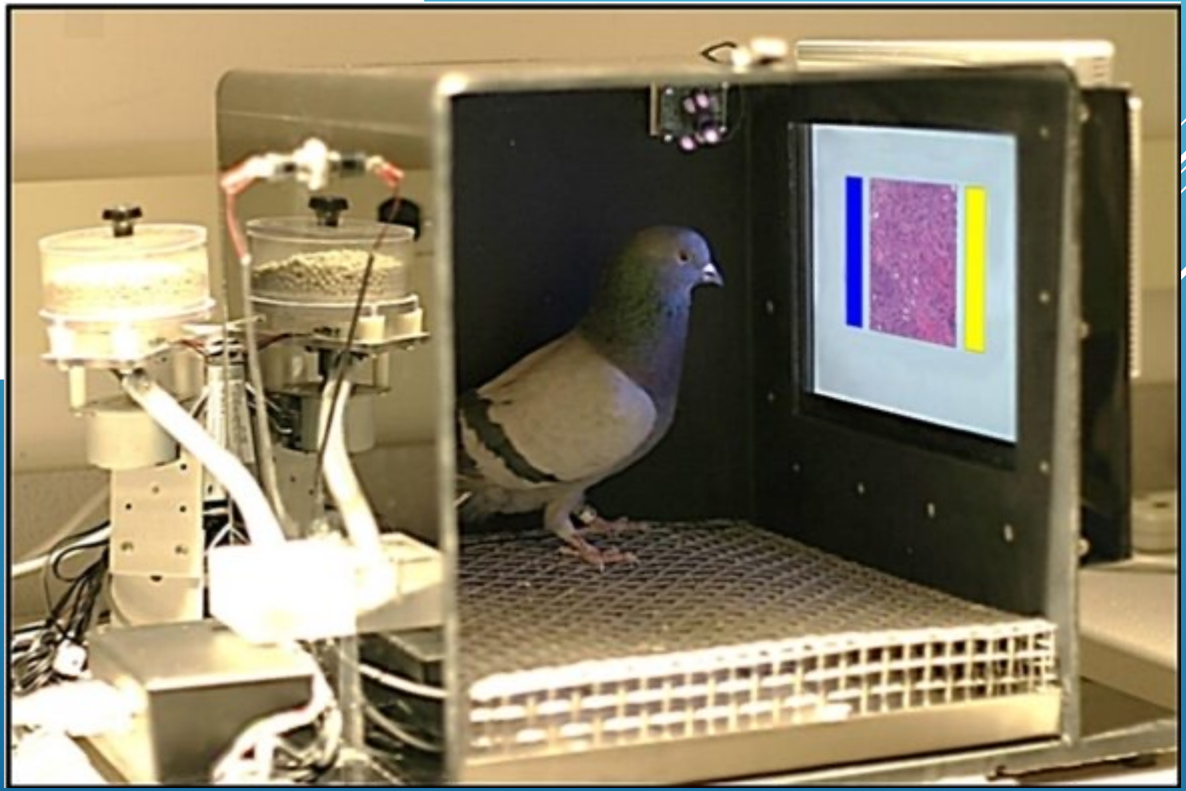

NO NEED FOR PATHOLOGIST ROI'S?

nature medicine

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Article | Published: 15 July 2019

Clinical-grade computational pathology using weakly supervised deep learning on whole slide images

Gabriele Campanella, Matthew G. Hanna, Luke Geneslaw, Allen Miraflor, Vitor Werneck Krauss Silva, Klaus J. Busam, Edi Brogi, Victor E. Reuter, David S. Klimstra & Thomas J. Fuchs

Nature Medicine **25**, 1301–1309 (2019) | Cite this article

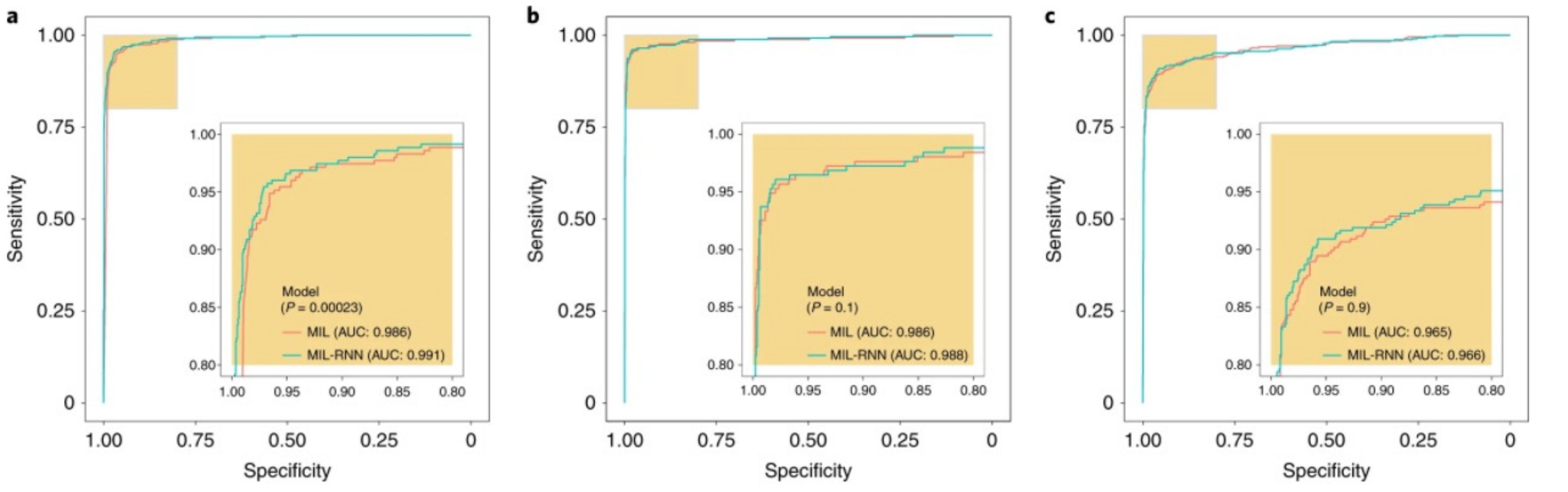
Abstract

The development of decision support systems for pathology and their deployment in clinical practice have been hindered by the need for large manually annotated datasets. To overcome this problem, we present a multiple instance learning-based deep learning system that uses only the reported diagnoses as labels for training, thereby avoiding expensive and time-consuming pixel-wise manual annotations. We evaluated this framework at scale on a dataset of 44,732 whole slide images from 15,187 patients without any form of data curation. Tests on prostate cancer, basal cell carcinoma and breast cancer metastases to axillary lymph nodes resulted in areas under the curve above 0.98 for all cancer types. Its clinical application would allow pathologists to exclude 65–75% of slides while retaining 100% sensitivity. Our results show that this system has the ability to train accurate classification models at unprecedented scale, laying the foundation for the deployment of computational decision support systems in clinical practice.

Fig. 3: Weakly supervised models achieve high performance across ~~all~~ tissue types.

^
a few

From: Clinical-grade computational pathology using weakly supervised deep learning on whole slide images



Prostate

BCC (skin)

Breast mets

Gleason score? Why only in the supplemental?

Mortality *very* low

Interesting, but very specific. Also, many previously trained models:
doi:10.1001/jama.2017.14585
doi:10.1093/gigascience/giy065
doi:10.1001/jama.2017.14585
doi:10.1109/TMI.2018.2867350

npj | digital medicine

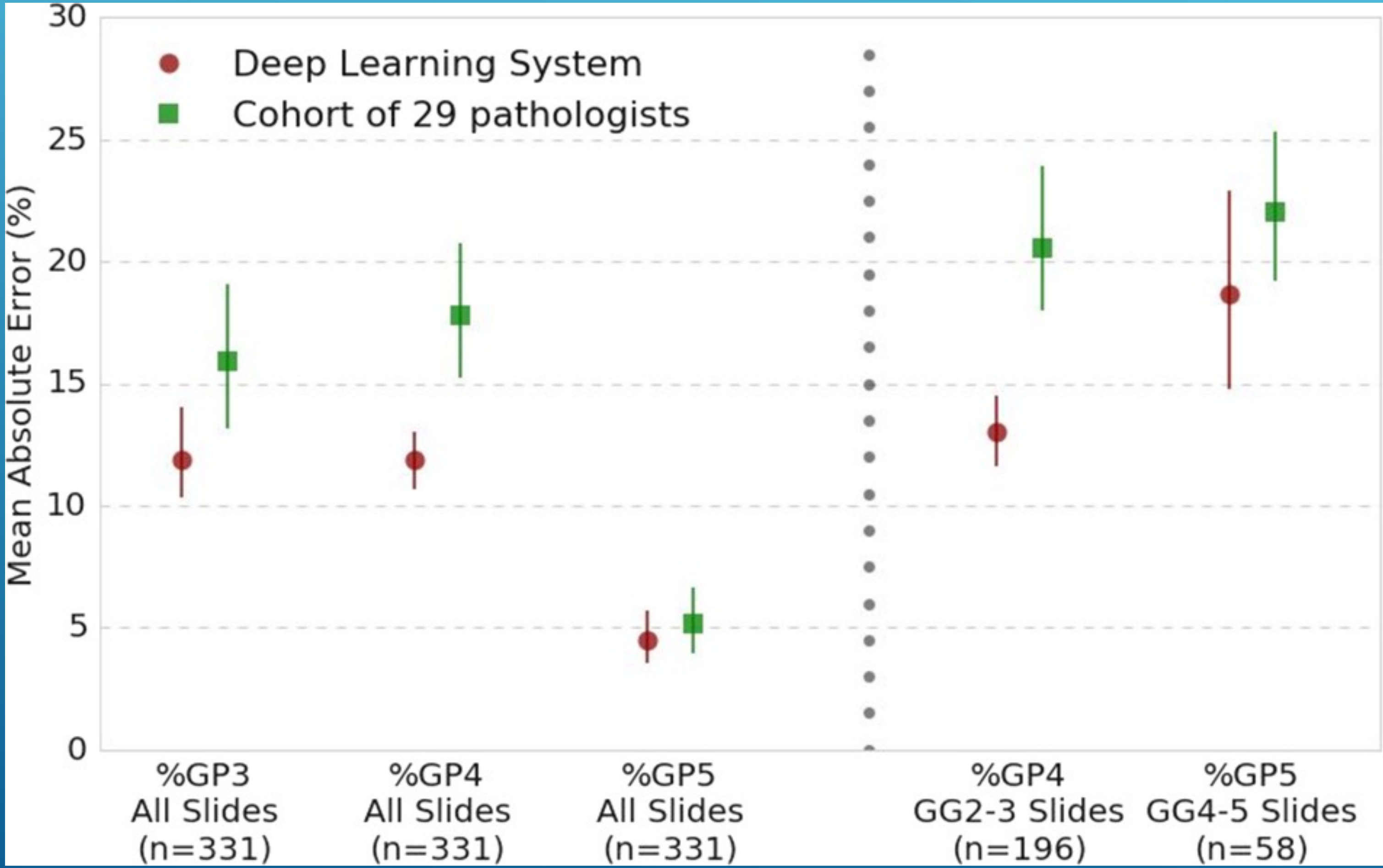
Article | Open Access | Published: 07 June 2019

Development and validation of a deep learning algorithm for improving Gleason scoring of prostate cancer

Kunal Nagpal, Davis Foote, Yun Liu, Po-Hsuan Cameron Chen, Ellery Wulczyn, Fraser Tan, Niels Olson, Jenny L. Smith, Arash Mohtashamian, James H. Wren, Greg S. Corrado, Robert MacDonald, Lily H. Peng, Mahul B. Amin, Andrew J. Evans, Ankur R. Sangoi, Craig H. Mermel ✉, Jason D. Hipp & Martin C. Stumpe ✉

npj Digital Medicine **2**, Article number: 48 (2019) | Cite this article

HUMAN COMPARISON



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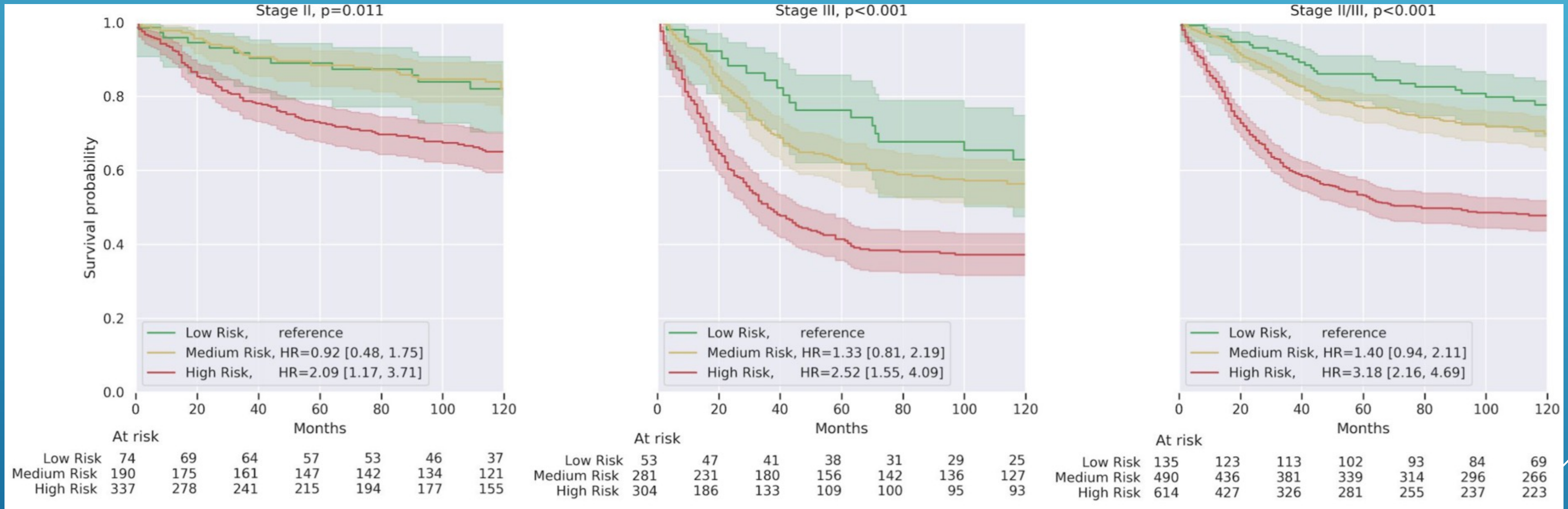
Article | Open Access | Published: 19 April 2021

Interpretable survival prediction for colorectal cancer using deep learning

Ellery Wulczyn, David F. Steiner, Melissa Moran, Markus Plass, Robert Reihs, Fraser Tan, Isabelle Flament-Auvigne, Trissia Brown, Peter Regitnig, Po-Hsuan Cameron Chen, Narayan Hegde, Apaar Sadhwani, Robert MacDonald, Benny Ayalew, Greg S. Corrado, Lily H. Peng, Daniel Tse, Heimo Müller, Zhaoyang Xu, Yun Liu ✉, Martin C. Stumpe, Kurt Zatloukal & Craig H. Mermel ✉

npj Digital Medicine **4**, Article number: 71 (2021) | Cite this article

PREDICTING RISK!



nature medicine

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Article | Published: 17 September 2018

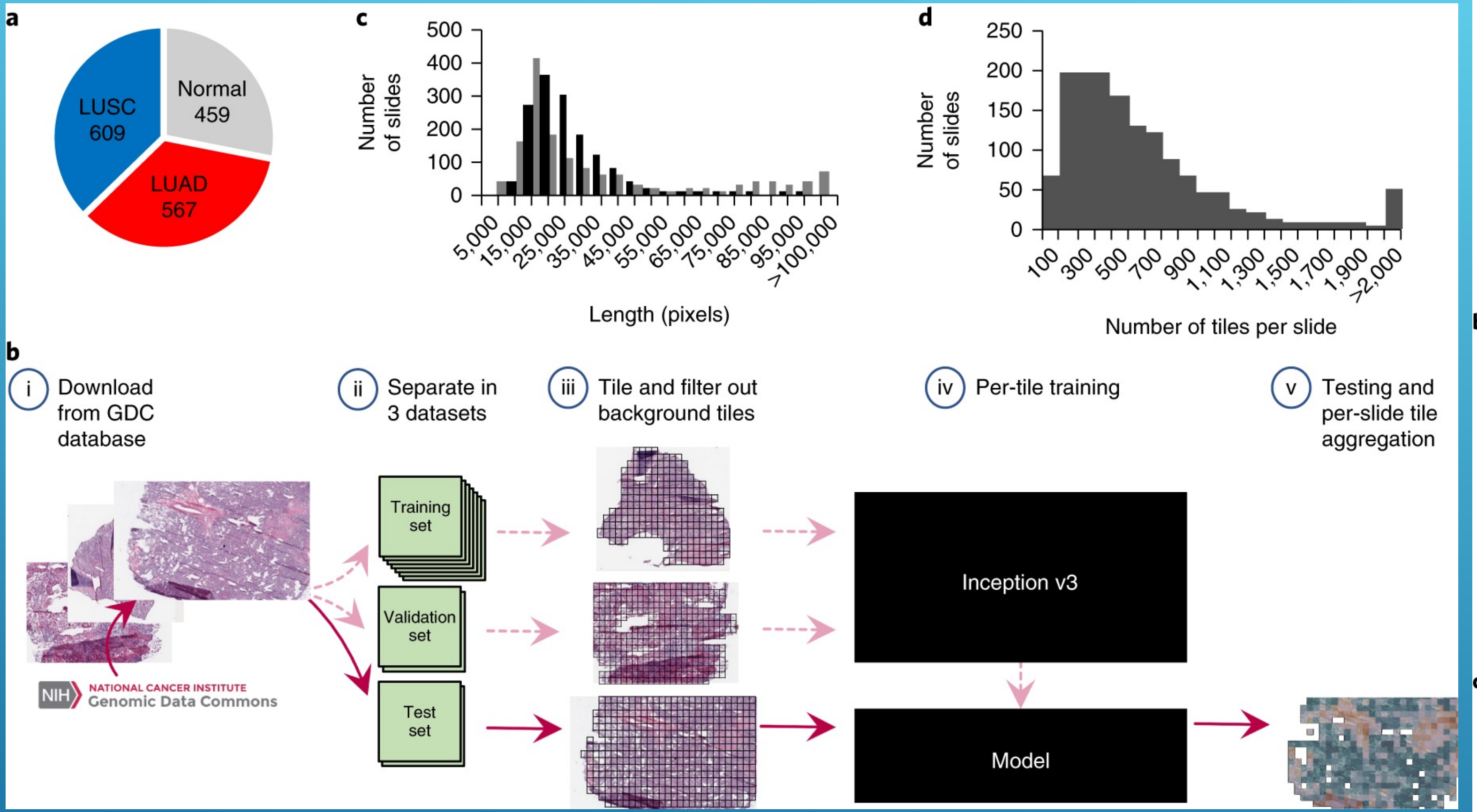
Classification and mutation prediction from non–small cell lung cancer histopathology images using deep learning

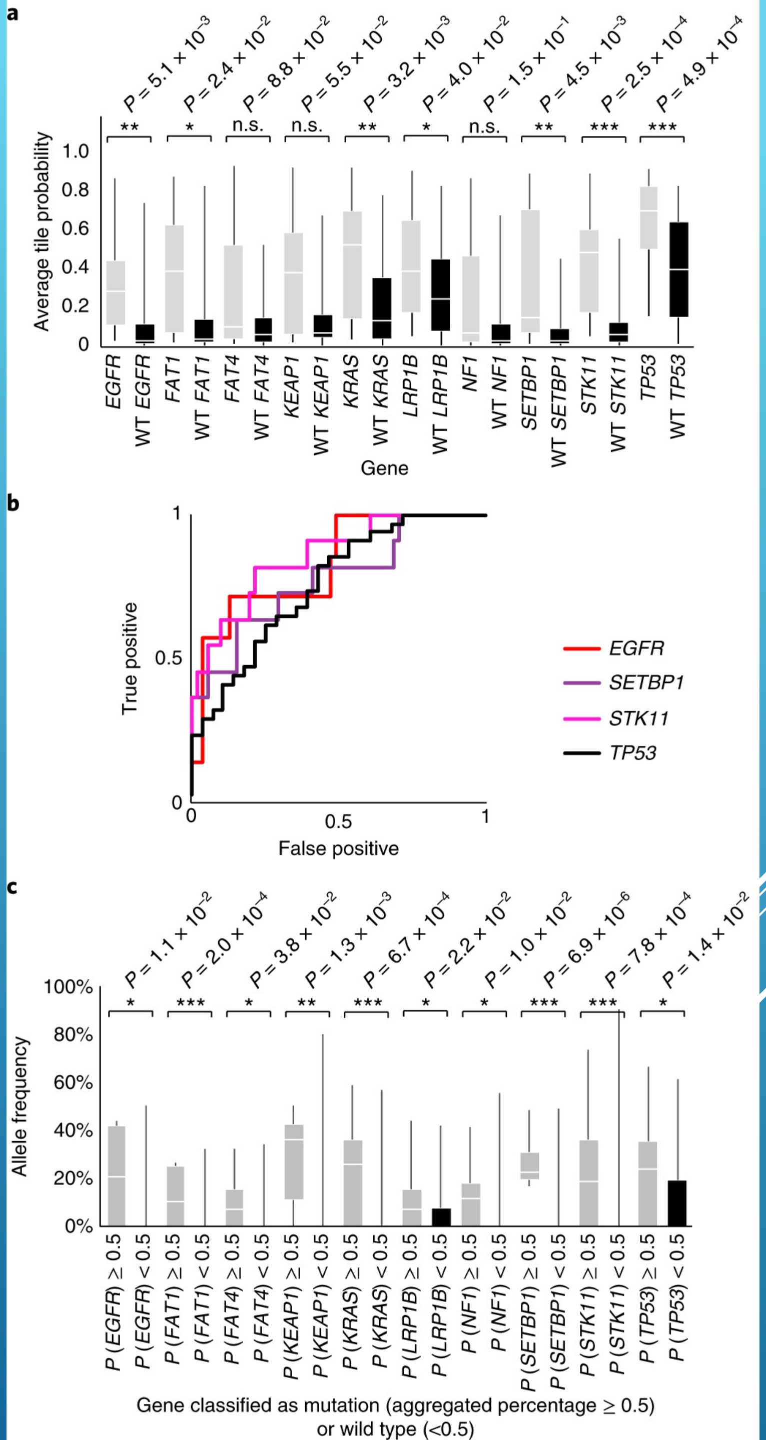
Nicolas Coudray, Paolo Santiago Ocampo, Theodore Sakellaropoulos, Navneet Narula, Matija Snuderl, David Fenyö, Andre L. Moreira, Narges Razavian & Aristotelis Tsirigos

Nature Medicine **24**, 1559–1567 (2018) | Cite this article

Abstract

Visual inspection of histopathology slides is one of the main methods used by pathologists to assess the stage, type and subtype of lung tumors. Adenocarcinoma (LUAD) and squamous cell carcinoma (LUSC) are the most prevalent subtypes of lung cancer, and their distinction requires visual inspection by an experienced pathologist. In this study, we trained a deep convolutional neural network (inception v3) on whole-slide images obtained from The Cancer Genome Atlas to accurately and automatically classify them into LUAD, LUSC or normal lung tissue. The performance of our method is comparable to that of pathologists, with an average area under the curve (AUC) of 0.97. Our model was validated on independent datasets of frozen tissues, formalin-fixed paraffin-embedded tissues and biopsies. Furthermore, we trained the network to predict the ten most commonly mutated genes in LUAD. We found that six of them—STK11, EGFR, FAT1, SETBP1, KRAS and TP53—can be predicted from pathology images, with AUCs from 0.733 to 0.856 as measured on a held-out population. These findings suggest that deep-learning models can assist pathologists in the detection of cancer subtype or gene mutations. Our approach can be applied to any cancer type, and the code is available at https://github.com/ncoudray/DeepPATH.


a
LUSC 609
Normal 459
LUAD 567
c
Number of slides
Length (pixels)
d
Number of slides
Number of tiles per slide
b
i Download from GDC database
ii Separate in 3 datasets
iii Tile and filter out background tiles
iv Per-tile training
v Testing and per-slide aggregation
Training set
Validation set
Test set
Inception v3
Model
NIH NATIONAL CANCER INSTITUTE Genomic Data Commons


a
Average tile probability
Gene
EGFR
WT EGFR
FAT1
WT FAT1
FAT4
WT FAT4
KEAP1
WT KEAP1
KRAS
WT KRAS
LRP1B
WT LRP1B
NF1
WT NF1
SETBP1
WT SETBP1
STK11
WT STK11
TP53
WT TP53
b
True positive
False positive
EGFR
SETBP1
STK11
TP53
c
Allele frequency
Gene classified as mutation (aggregated percentage ≥ 0.5) or wild type (<0.5)

INTRODUCTION

- Cervical Cancer
  - One of the most common cancer among women.
  - 2018 US Statistics ᐞ
    - 13,240 diagnosed cases.
    - 4,170 women die from cervical cancer.
  - Cervical cancer that is detected early is more likely to be treated successfully.

ᐞ "Cancer Facts & Figures 2018," *American Cancer Society*, 2018.

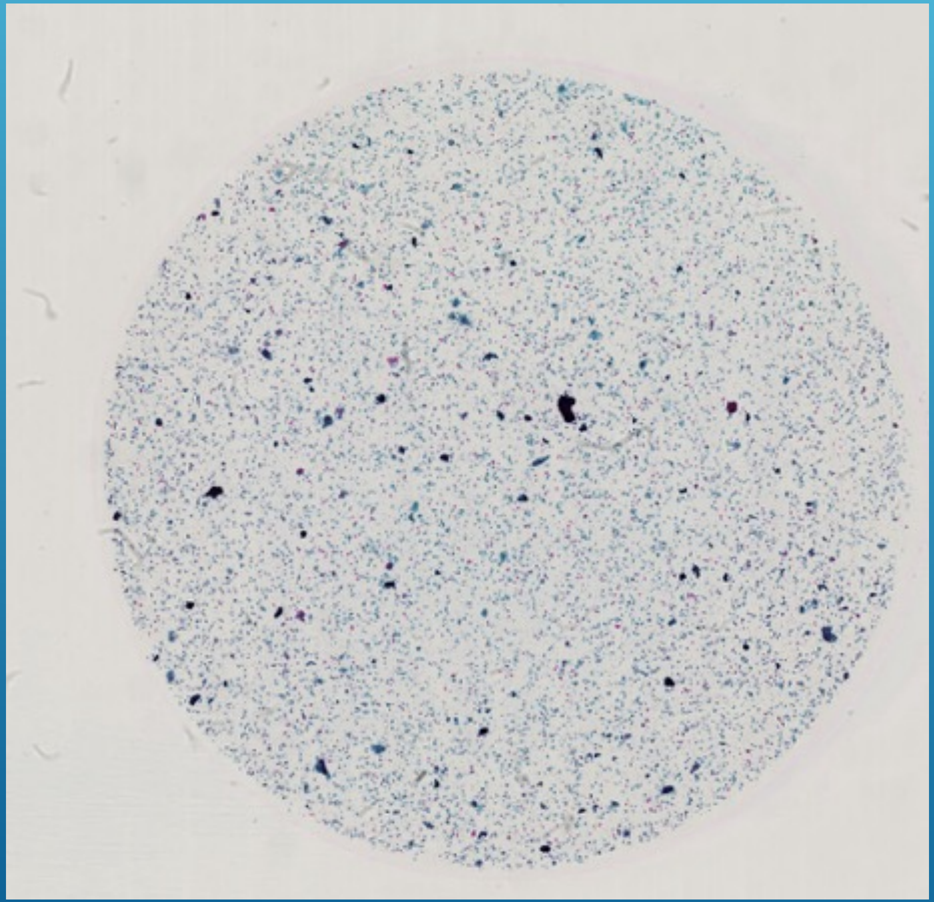
DATASETS

- NLM Data
  - 25 cytology slides.
    - Provided by BD (Becton-Dickinson) Corporation.
    - The slides are prepared using Sure Path.
- Herlev Pap Smear Dataset
  - 917 cervical cell images

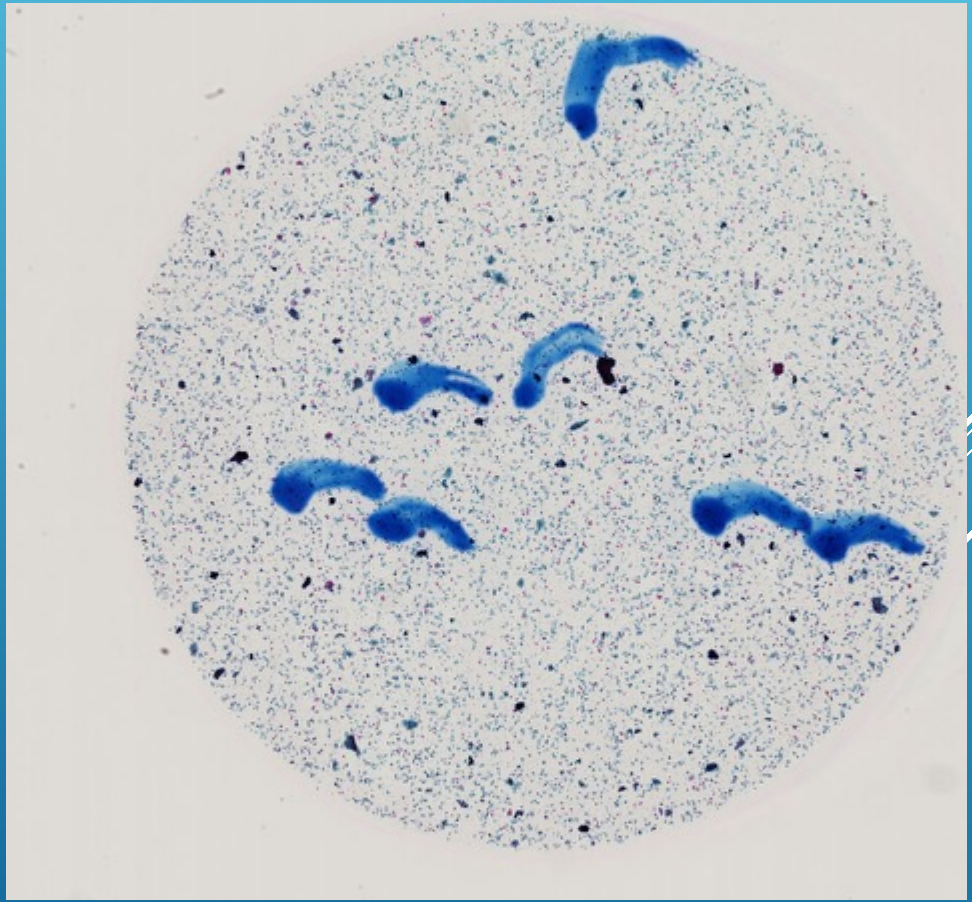
Δ http://mde-lab.aegean.gr/downloads

NLM DATA

Clean Slide image



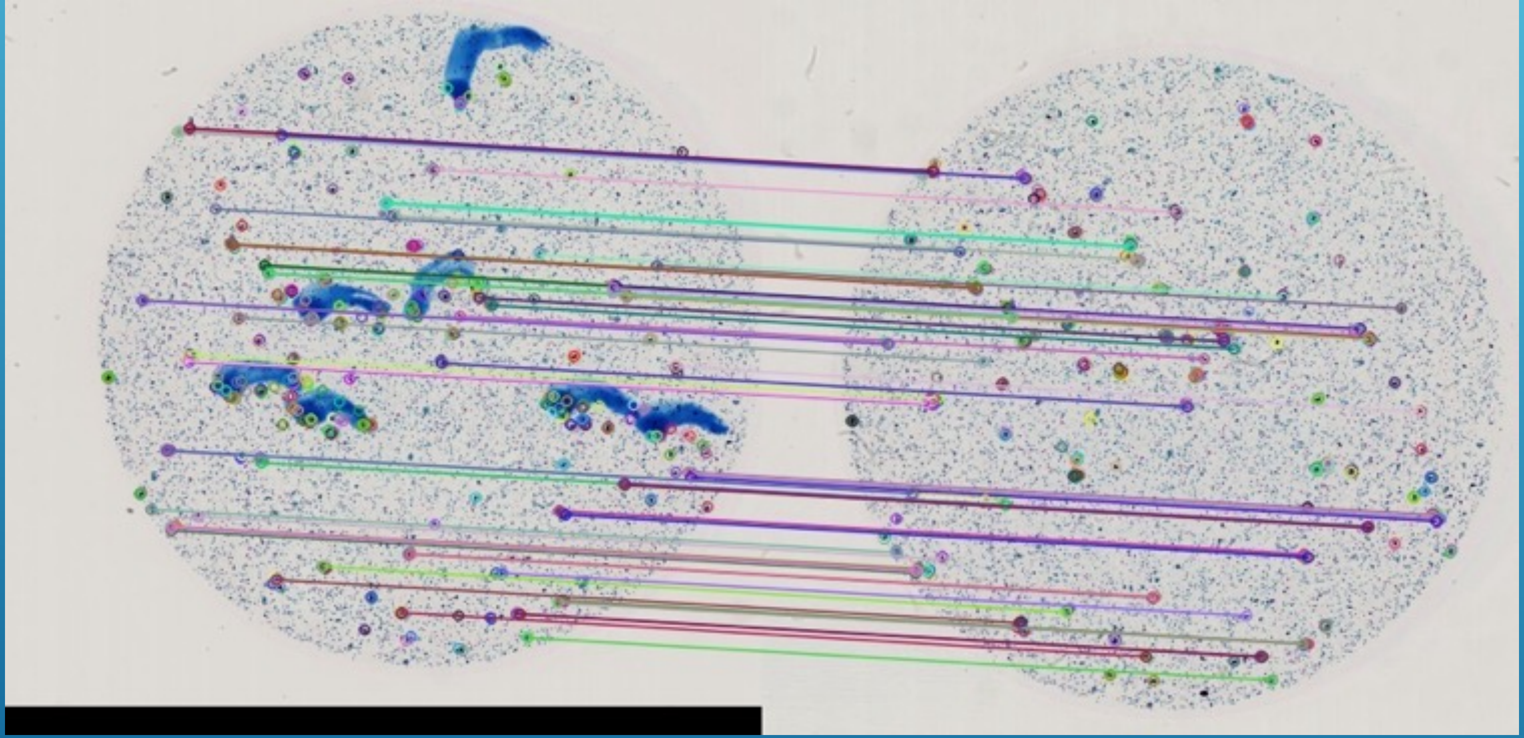
Annotated Slide image



Note: Displayed images are from level 7

ROI DETECTION

- **Image Registration**
  - **ORB feature detector Δ**
  - **Match features**
  - **Calculate Homography**
    - **Uses RANSAC* estimation technique**



Matching Keypoints

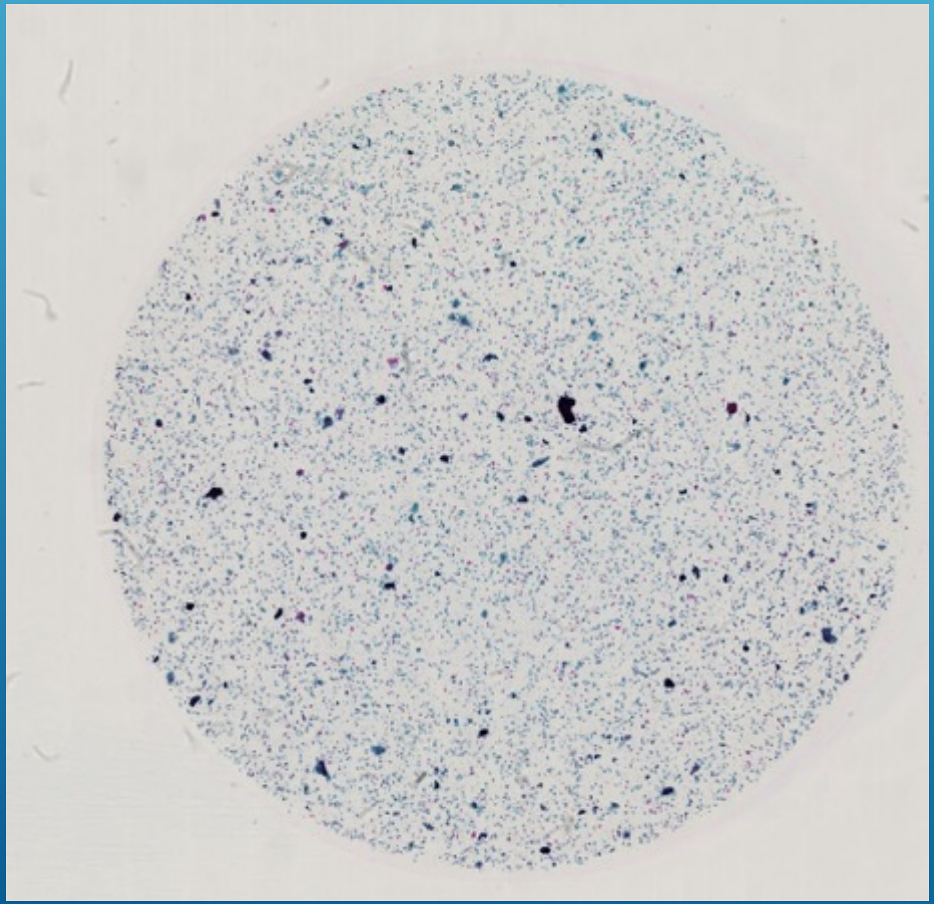
Δ Ethan Rublee, Vincent Rabaud, Kurt Konolige, Gary R. Bradski: ORB: An efficient alternative to SIFT or SURF. ICCV 2011: 2564-2571

* Random sample consensus (**RANSAC**) is an iterative method to estimate parameters of a mathematical model from a set of observed data that contains outliers

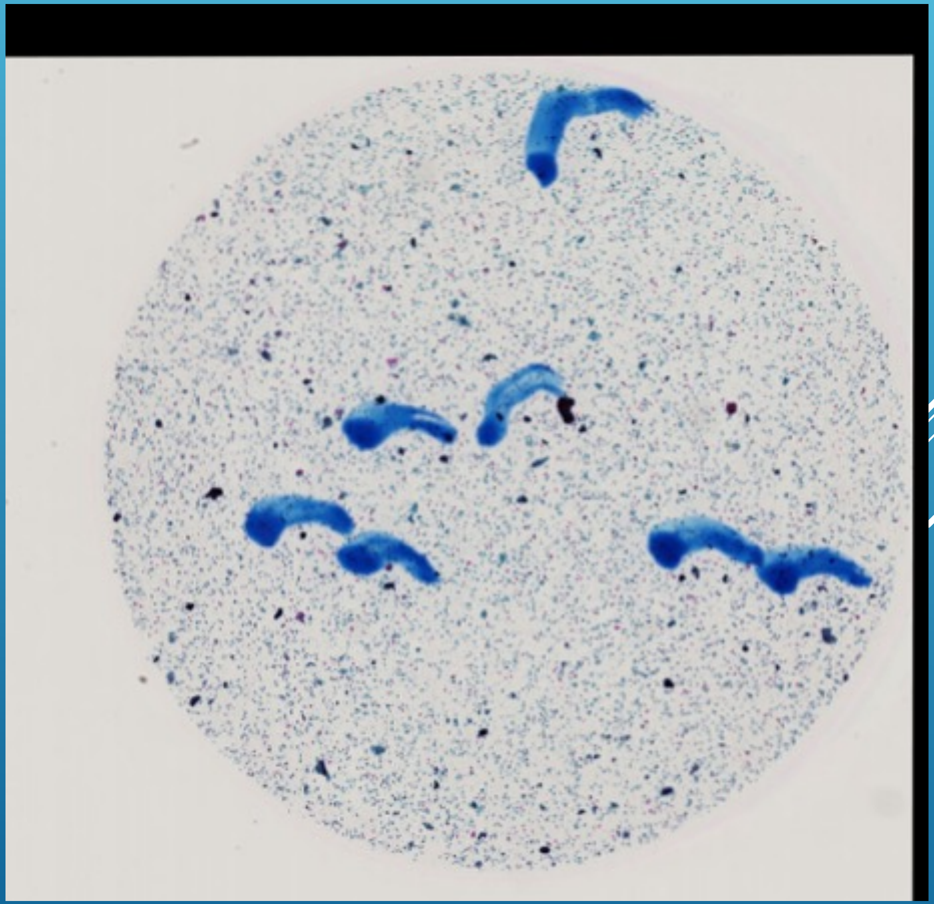
ROI DETECTION

- **Image Registration**

Reference Image

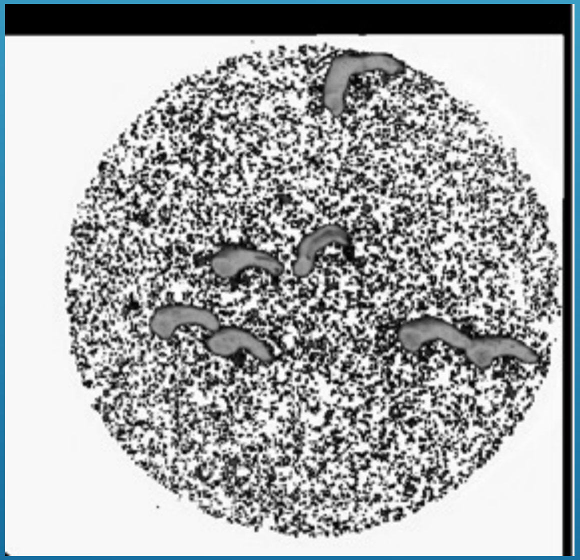


Aligned Image



ROI DETECTION

B_color_space – R_color_space

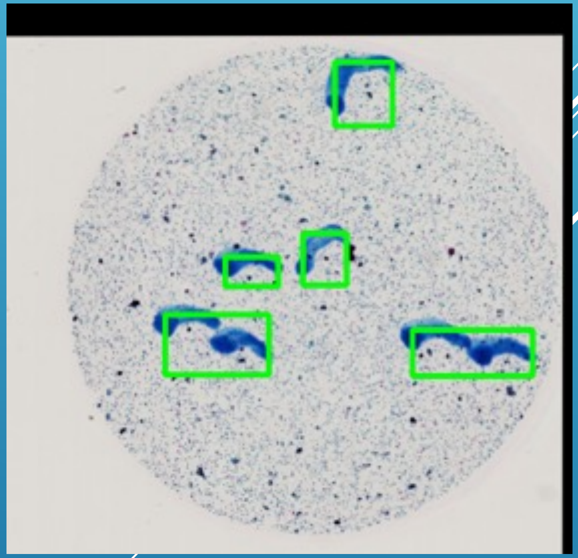


Threshold
+
Morphological operations

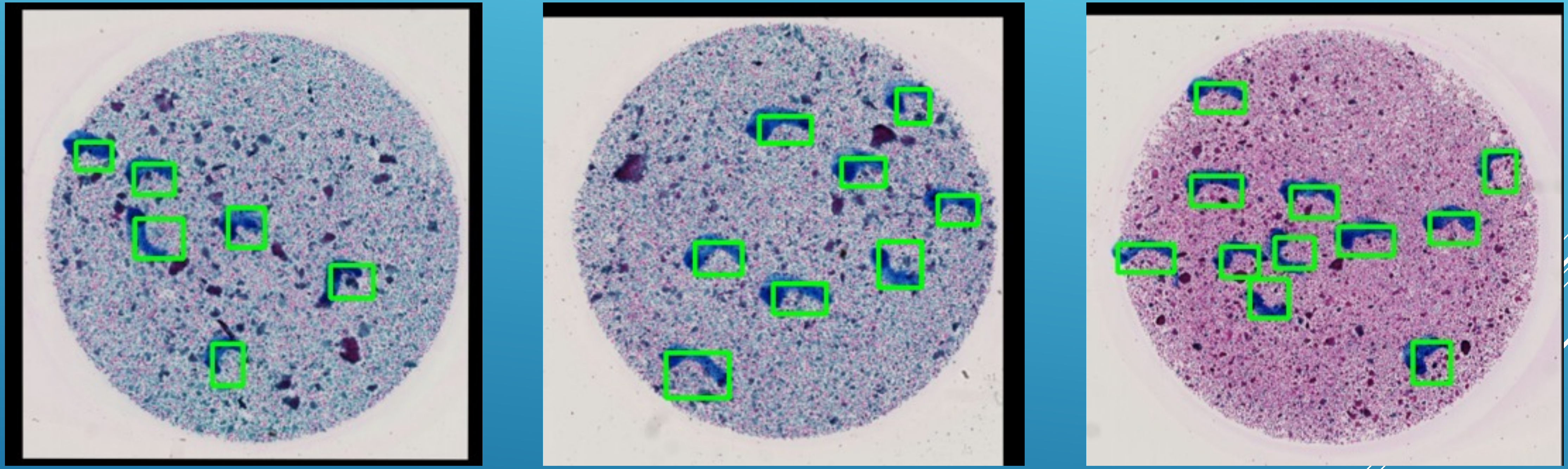
Mask output

Skeletonize
+
Refine boundaries

ROIs detected



ROI DETECTION RESULTS



LOCATING ABNORMAL CELLS

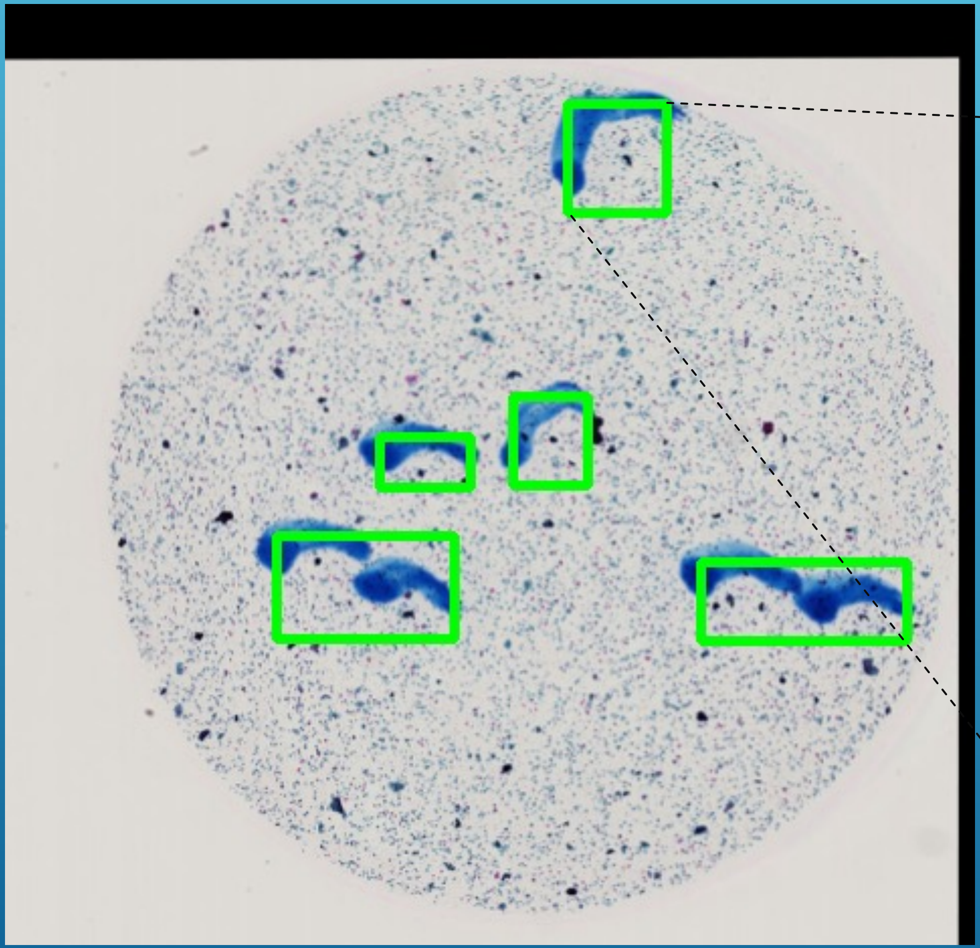


Image from level 7

Size: 3400x3079

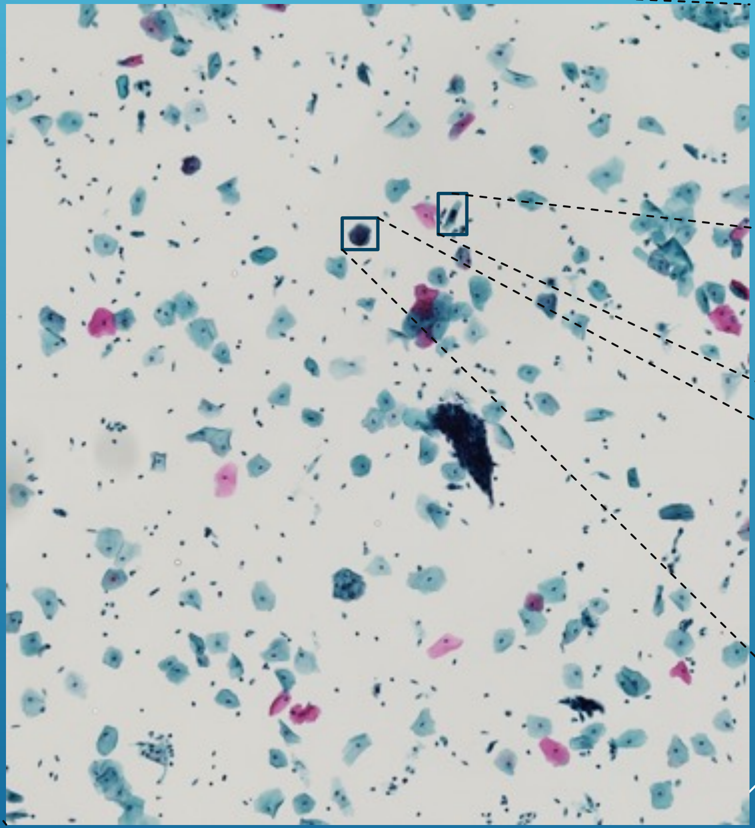
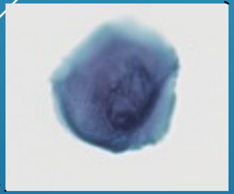


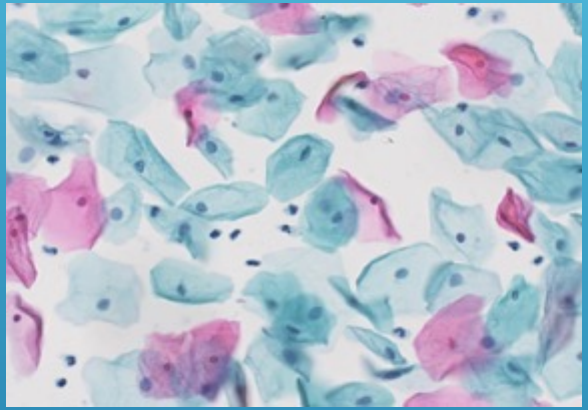
Image from level 1

Abnormal cells



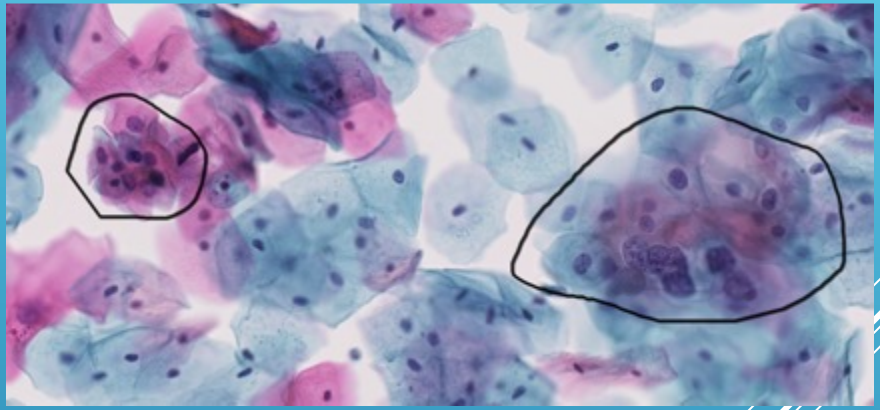
SLIDE CLASSIFICATION

- NILM (Negative for Intraepithelial Lesion or Malignancy)

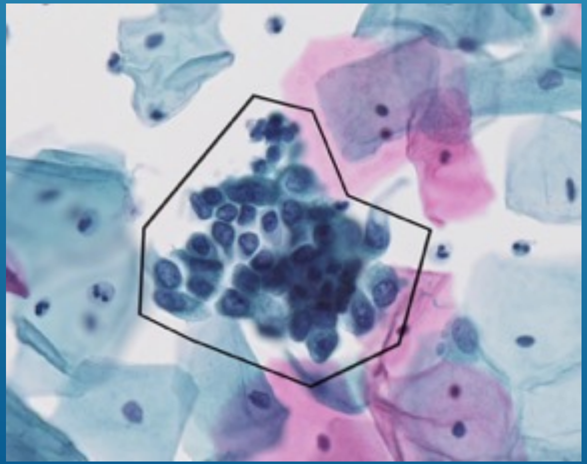


- **ASCUS (Atypical squamous cells of undetermined significance)**

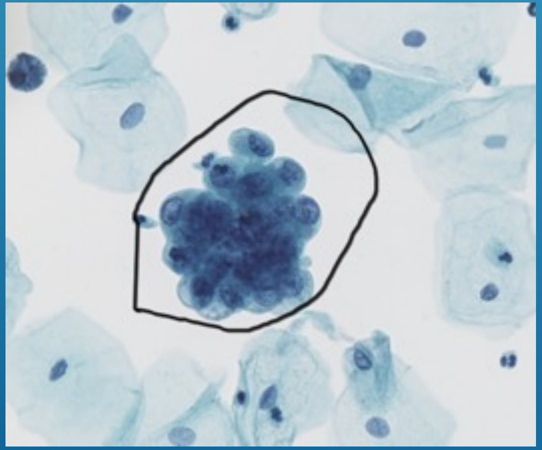
- **LSIL (Lower-grade Squamous intraepithelial lesion)**



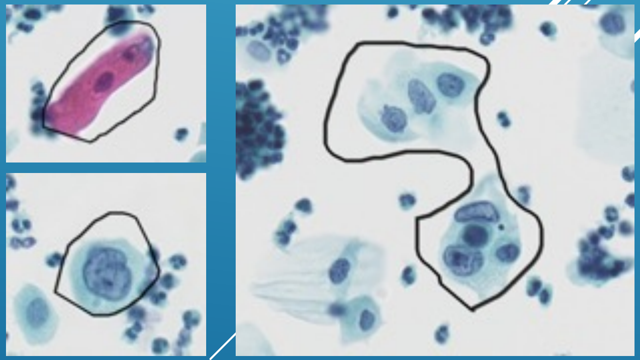
- **HSIL (Higher-grade Squamous intraepithelial lesion)**



- **Adeno (Adenocarcinoma)**



- **SCC (Squamous cell carcinoma)**

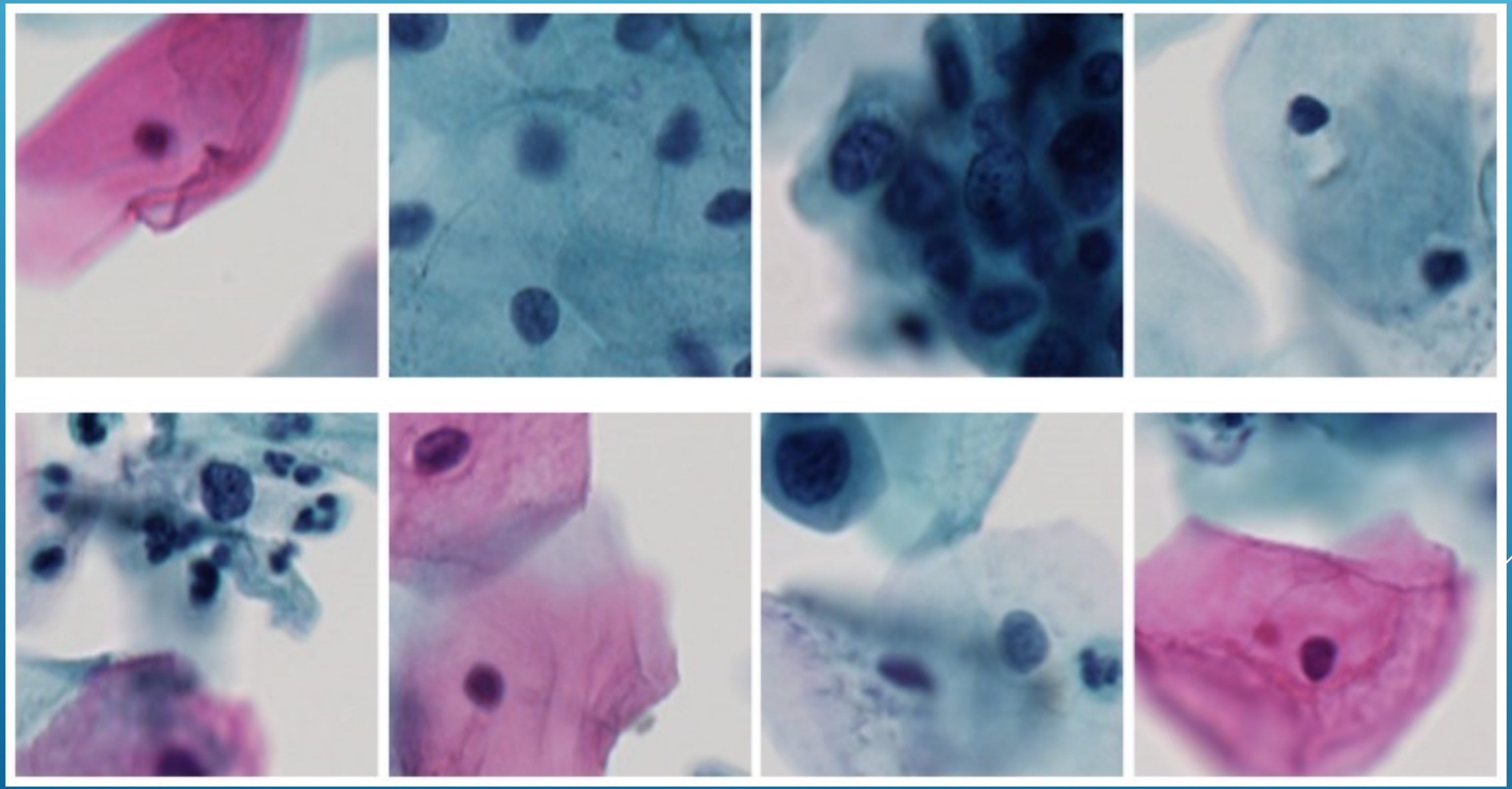


PATCH BASED DATA GENERATION

128x128 patch images

Normal

Abnormal



CLASSIFICATION

- This is a Bi-classfication
- Train, Test Dataset
  - Training Dataset (Herlev Pap Data)
    - Training: Normal – 196, Abnormal – 560
    - Validation: Normal – 46, Abnormal – 115
  - Testing Dataset (12XS12118 Patch data)
    - Testing: 15,035 patch (128x128) images

CLASSIFICATION

- CNN based Classifier
- Fine-tuning models initialized with pre-trained ImageNet weights.
- No. of Epochs = 200
- Batch Size = 32
- Optimizer: Stochastic Gradient Descent
  - Lr = 0.001, Momentum = 0.9
- Loss Function: Cross Entropy Loss

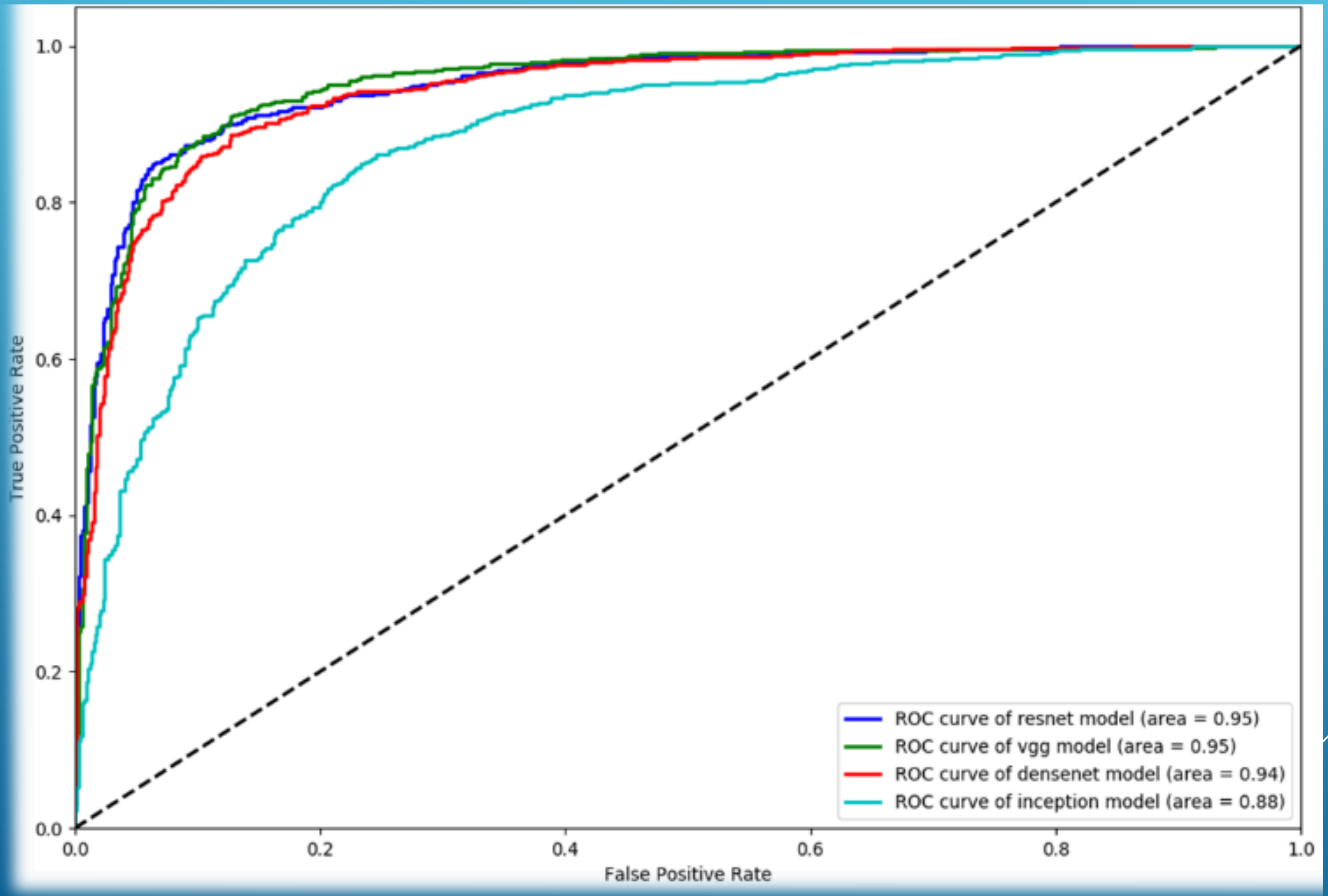
CLASSIFICATION RESULTS

- **Pytorch Deep Learning Platform.**
- **Models run on Nvidia DGX station.**
- **Evaluation results for normal class detection**

Model	Confusion matrix $\begin{bmatrix} TN & FP \\ FN & TP \end{bmatrix}$	ACC	PREC	REC	F1-Score	MCC
Resnet-50	$\begin{bmatrix} 589 & 71 \\ 78 & 582 \end{bmatrix}$	0.8871	0.8913	0.8818	0.8865	0.7742
VGG-19	$\begin{bmatrix} 581 & 79 \\ 68 & 592 \end{bmatrix}$	0.8886	0.8823	0.8970	0.8896	0.7773
Densenet-121	$\begin{bmatrix} 611 & 49 \\ 131 & 529 \end{bmatrix}$	0.8636	0.9152	0.8015	0.8546	0.7329
Inception_v3	$\begin{bmatrix} 429 & 231 \\ 57 & 603 \end{bmatrix}$	0.7818	0.7230	0.9136	0.8072	0.5843

https://pytorch.org/docs/stable/torchvision/models.html

CLASSIFIER COMPARISON



SUMMARY

- Digital pathology images are large
- Color variation, magnification should be considered
- Deep learning and pathology can assess diagnosis AND:
  - Assist with grading (Gleason, Elston, Weiss, etc)
  - Predict outcomes
  - Predict molecular mutations
- Collecting and curating dataset is extremely important
- Evaluate models thoroughly
- Different architectures can use more computer power, ie take longer to train

RESOURCES

- Courses:
  - THIS lecture series!
  - Fast AI : https://course.fast.ai/
  - Coursera
  - Khan Academy
- Challenges:
  - Grand-challenge.org
  - Nuclear segmentation
  - Tumor segmentation

ACKNOWLEDGMENTS

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  - Stephanie Harmon, PhD
  - Nathan Lay, PhD
  - Baris Turkbey, MD
  - Peter Choyke, MD
- Collaborators
  - Stephen Hewitt, MD, PHD
  - Sameer Antani, PHD
  - Paul Fontelo, MD, MPh
- Helpful people
  - Sudhir Sornapudi (Missouri S&T)

QUESTIONS?