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VA | U.S. Department of Veterans Affairs
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Office of Research and Development

To Deep Learn or not Deep Learning

Computational Pathology for Precision Medicine

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Artificial Intelligence, Cancer imaging, Digital pathology, radiomics, pathomics, precision medicine

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Probability of Developing Invasive Cancer during Lifetime (2019)

	Male	Female
All sites†	1 in 2	1 in 3
Breast		1 in 8
Colon & rectum	1 in 23	1 in 25
Kidney & renal pelvis	1 in 46	1 in 82
Leukemia	1 in 54	1 in 77
Lung & bronchus	1 in 15	1 in 17
Melanoma of the skin‡	1 in 28	1 in 41
Non-Hodgkin lymphoma	1 in 41	1 in 52
Prostate	1 in 9	
Thyroid	1 in 144	1 in 52
Uterine cervix		1 in 159
Uterine corpus		1 in 33

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.7.7. Statistical Research and Applications Branch, National Cancer Institute, 2019.

Estimated Cancer Deaths in the US, 2020

Male			Female		
Lung & bronchus	72,500	23%	Lung & bronchus	63,220	22%
Prostate	33,330	10%	Breast	42,170	15%
Colon & rectum	28,630	9%	Colon & rectum	24,570	9%
Pancreas	24,640	8%	Pancreas	22,410	8%
Liver & intrahepatic bile duct	20,020	6%	Ovary	13,940	5%
Leukemia	13,420	4%	Uterine corpus	12,590	4%
Esophagus	13,100	4%	Liver & intrahepatic bile duct	10,140	4%
Urinary bladder	13,050	4%	Leukemia	9,680	3%
Non-Hodgkin lymphoma	11,460	4%	Non-Hodgkin lymphoma	8,480	3%
Brain & other nervous system	10,190	3%	Brain & other nervous system	7,830	3%
All sites	321,160		All sites	285,360	

2020, American Cancer Society, Inc., Surveillance Research

Overdiagnosis is harming patients and action is required, says chief medical officer

By Kate Aubusson

15 October 2018 — 12:00am

Australia's chief medical officer has backed moves to protect patients and safeguard the sustainability of the health system against the growing problem of too much medicine.

Overdiagnosis is exposing healthy people to tests and treatments that are at best useless, and at worst trigger aggressive procedures with devastating side effects, a formidable alliance of peak doctors colleges, researchers, advocates and public health experts warned.

Michael Shirley was diagnosed with prostate cancer and told he needed a radical prostatectomy. Thirteen years after saying no to the surgery he wants men to know they have other options. WOLTER PEETERS

Need for Better Diagnostic, Predictive Tools

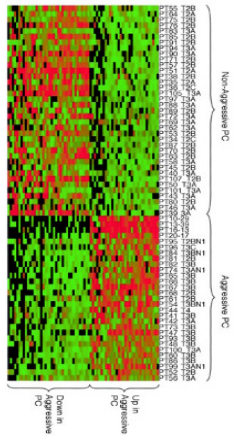
Diagnostic: *Identifying presence of disease*

Prognostic: *Predicting Disease Outcome, progression*

Predictive: *Predicting Response to treatment*

Precision Medicine: *Using Prognostic and Predictive Tools for Tailoring Therapy for a given patient based off specific risk profile*

Which cancer patients will receive added benefit from chemotherapy?



Oncotype DX molecular assay (Genomic Health, Inc.)

- For <u>early stage (LN-), ER+ patients</u>
- Recurrence Score (RS) between 0-100
- Predicts:
  - Likelihood for 10-year distant recurrence
  - Expected benefit from adjuvant chemotherapy

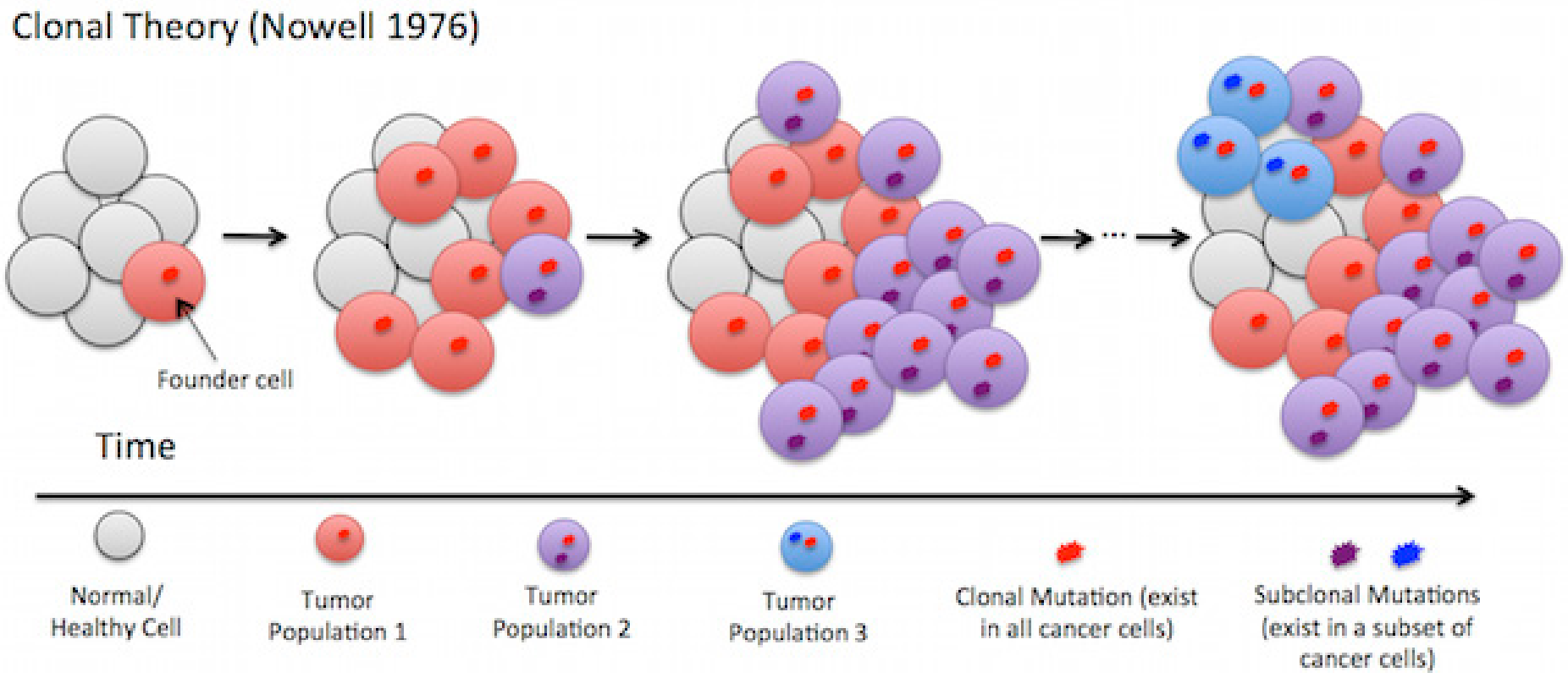
PROLIFERATION	INVASION	HER2
Ki-67 STK15 Survivin Cyclin B1 MYBL2	Stromelysin 3 Cathepsin L2	GRB7 HER2

ESTROGEN	REFERENCE	OTHER
ER PR Bcl2 SCUBE2	Beta-actin GAPDH RPLPO GUS TFRC	GSTM1 CD68 BAG1

Recurrence Score=
+0.47 x HER2 Group Score
-0.34 x ER Group Score
+1.04 x Proliferation group Score
+0.10 x Invasion Group Score
+0.05 x CD68
-0.08 x GSTM1
-0.07 x BAG1

Paik et al., N Engl J Med 2004 351: 2817-2826

Intra-tumoral heterogeneity



PATHOMICS

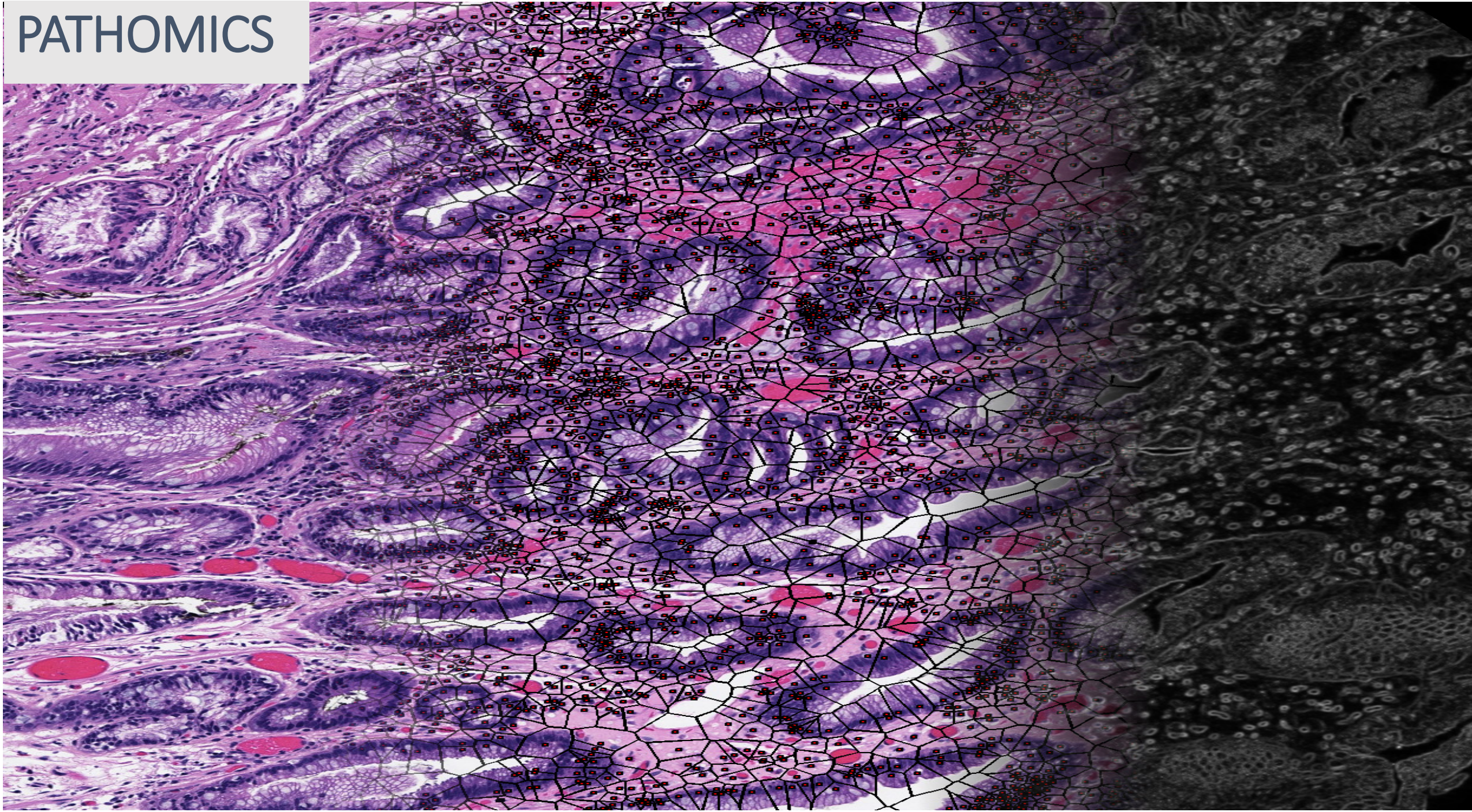
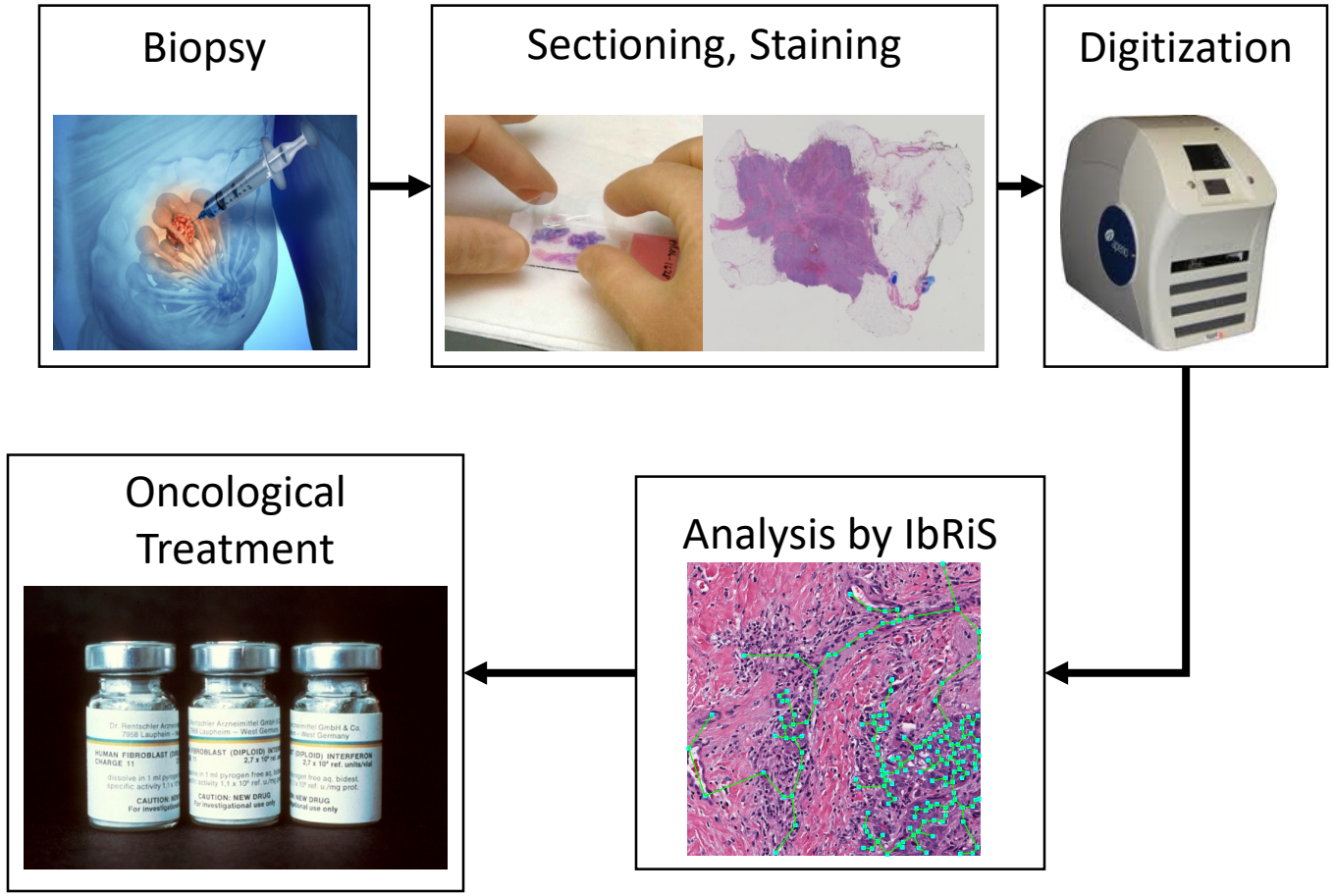
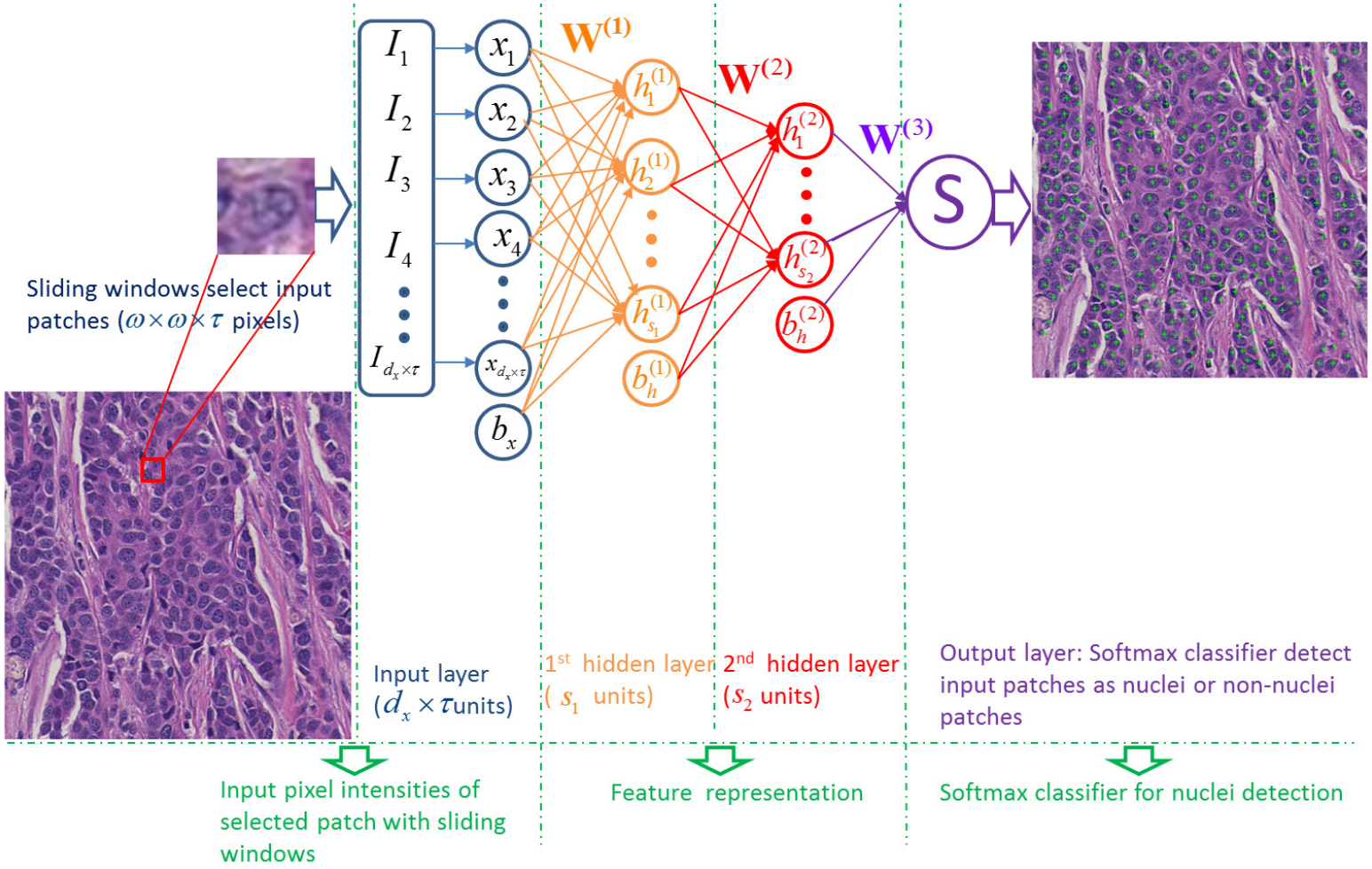


Image-based Risk Score (Ibris)



Academic Industry Partnership NIH 1R01CA202752-01A1

Stacked Sparse Auto-encoder for Nuclei Detection



***Xu J**, et al.* "Stacked Sparse Autoencoder (SSAE) based Framework for Nuclei Patch Classification on Breast Cancer Histopathology", ISBI2014.

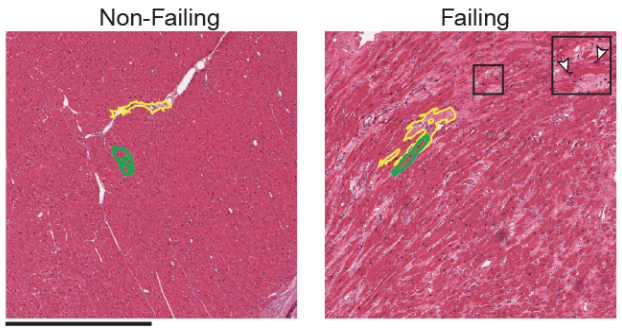
***Xu J**, et al.* "Stacked Sparse Autoencoder (SSAE) for Nuclei Detection on Breast Cancer Histopathology". *IEEE Trans. on Medical Imaging,* 2015

*Zhang X, Dou H, **Xu J,** Zhang S,* "Fusing Heterogeneous Features for the Image-Guided Diagnosis of Intraductal Breast Lesions", *IEEE Journal of Biomedical and Health Informatics,* 2015

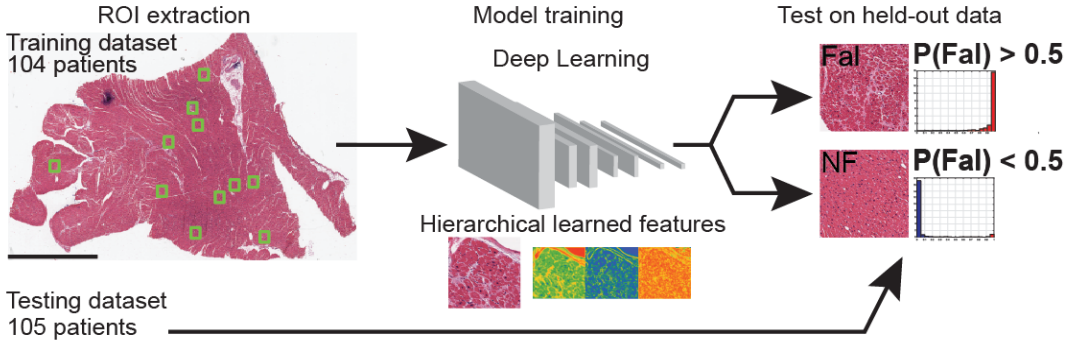
Lu C, Xu H, ***Xu J***, Mandal M, and Madabhushi A, "Multiple Passes Adaptive Voting for Nuclei Detection in Histopathlogical Images", *IEEE Journal of Biomedical and Health Informatics, (Under Preparing)*

A deep learning classifier identifies patients with heart failure using WSI of H&E tissue biopsies

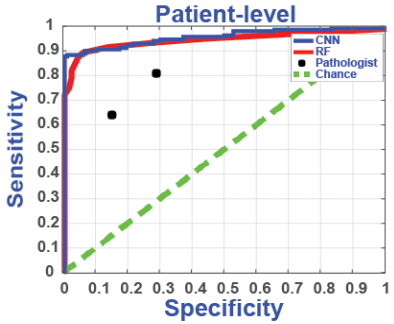
a Cardiac histopathology in heart failure



b Training a deep convolutional neural network



c Detection of clinical heart failure

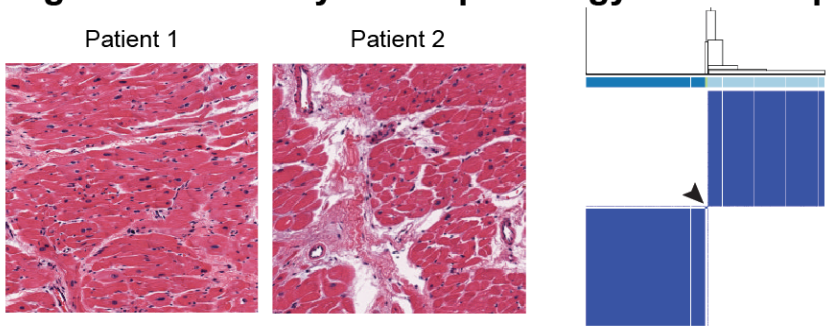


Performance evaluation

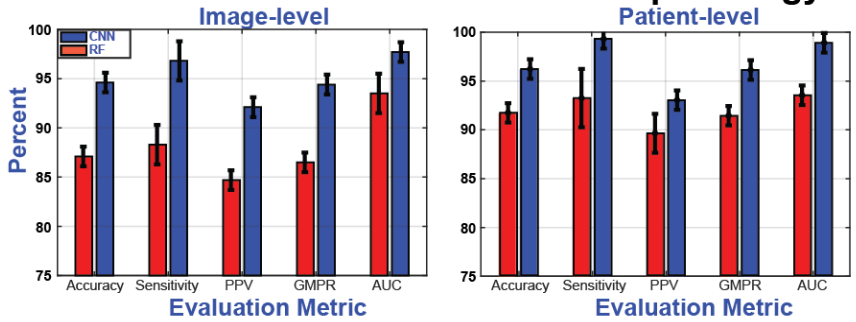
	CNN	Pathologists	
Accuracy	0.94±0.01	0.75	0.75
Sensitivity	0.99±0.01	0.81	0.64
Specificity	0.89±0.01	0.71	0.85
PPV	0.88±0.01	0.69	0.77
AUC	0.97±0.01	0.75	0.73

Table 1. Patient level performance metrics on the test set (105 patients). Mean ± SD of three models or individual results from each pathologist.

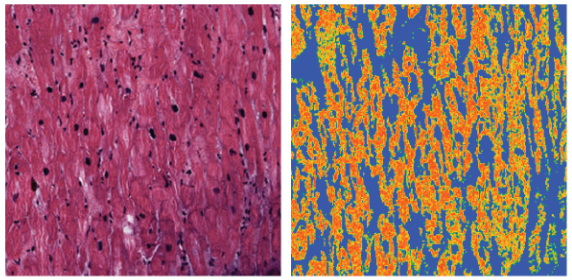
d Algorithms identify tissue pathology in normal patients



e Detection of heart failure or severe pathology



f An example of a feature learned from the CNN



The original H&E stained image is shown on the left. The hidden layer activations for one feature, shown on the right, is strongest in myocyte tissue. Thus, the CNN learned that segmenting myocyte tissue is a useful feature to detect patients with heart failure

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Business | Technology

Is there a smarter path to artificial intelligence? Some experts hope so

Originally published June 24, 2018 at 5:00 pm | *Updated June 25, 2018 at 12:59 am*

But now some scientists are asking whether deep learning is really so deep after all.

In recent conversations, online comments and a few lengthy essays, a growing number of AI experts are warning that the infatuation with deep learning may well breed myopia and overinvestment now — and disillusionment later.

"There is no real intelligence there," said Michael I. Jordan, a professor at the University of California, Berkeley, and the author of an essay published in April intended to temper the lofty expectations surrounding AI.

"And I think that trusting these brute-force algorithms too much is a faith misplaced."

More on AI

IBM's robot debater is ready to convince you that you're wrong

IBM pits computer against human debaters

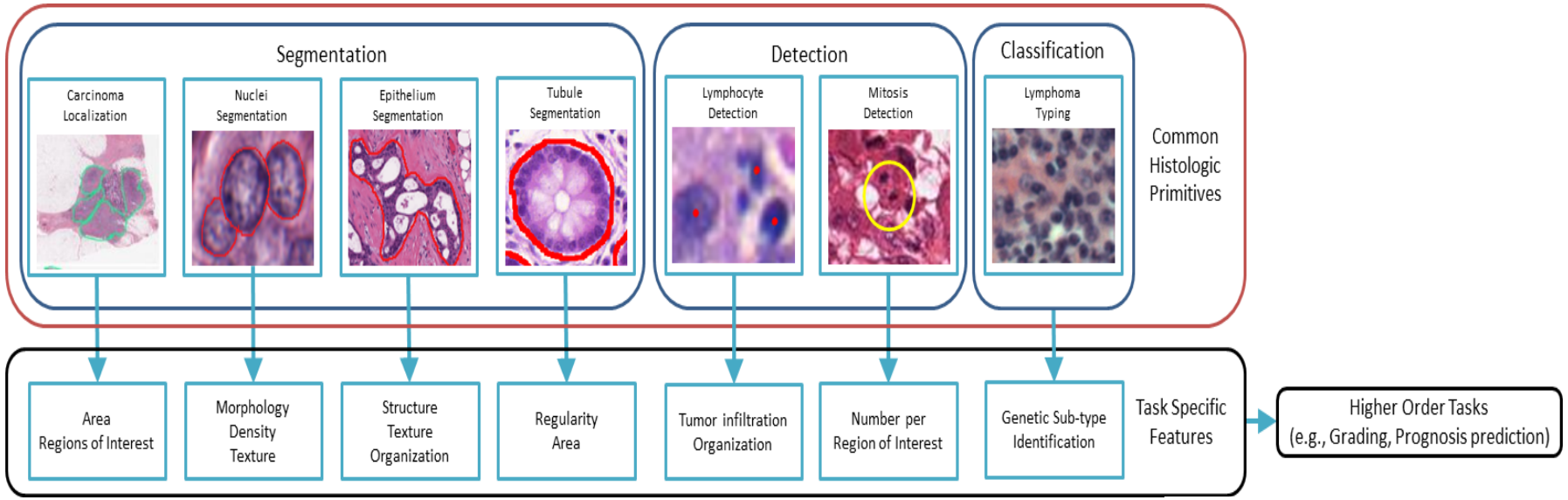
Husky or Wolf? Using a Black Box Learning Model to Avoid Adoption Errors

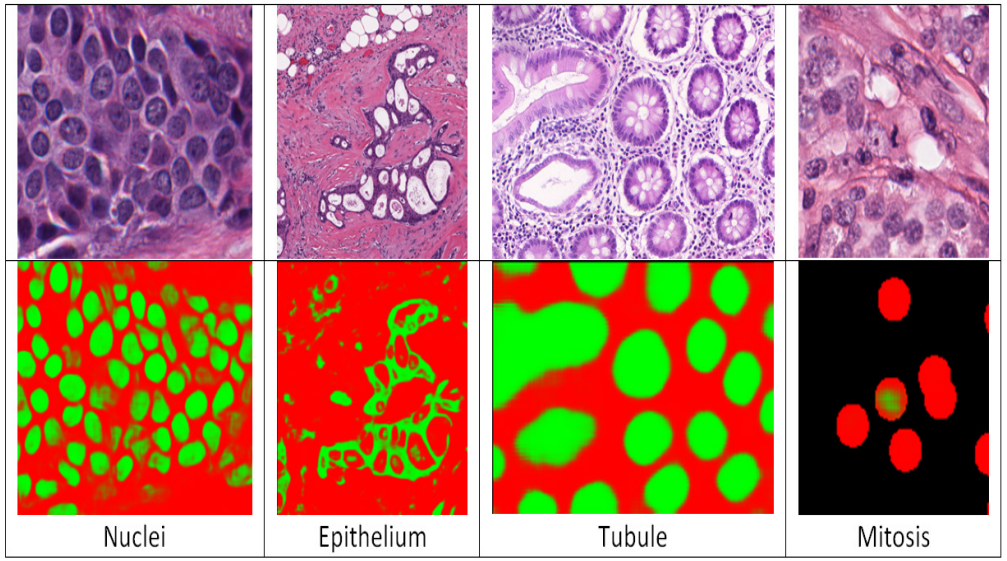
Past Tides

August 24, 2017 By Wendy Wolfson

Say you want to adopt a dog, from a picture, and you task your machine learning system to classify the image as either a husky, which would be safe to adopt, or a wolf, which probably is not a good idea. Can you get that photograph classified with certainty? "Because researchers don't have insights into what is going on they can easily be misled," said Sameer Singh, assistant professor in the UCI Department of Computer Science. "Classification is core to machine learning," said Singh, describing 'black box' machine learning predictions at the Association for Computing Machinery (ACM) July 12 meeting at the Cove. Machine learning is pervasive in our lives—from email to games. "It's in our phones," said Singh, a machine learning and natural language processing expert. "It is in our houses. It is basically everywhere."One of his students created a wolf/dog classifier in a few hours that seemed to work—at first.

Deep Learning can be extremely useful for segmentation of individual Histologic Primitives and structures





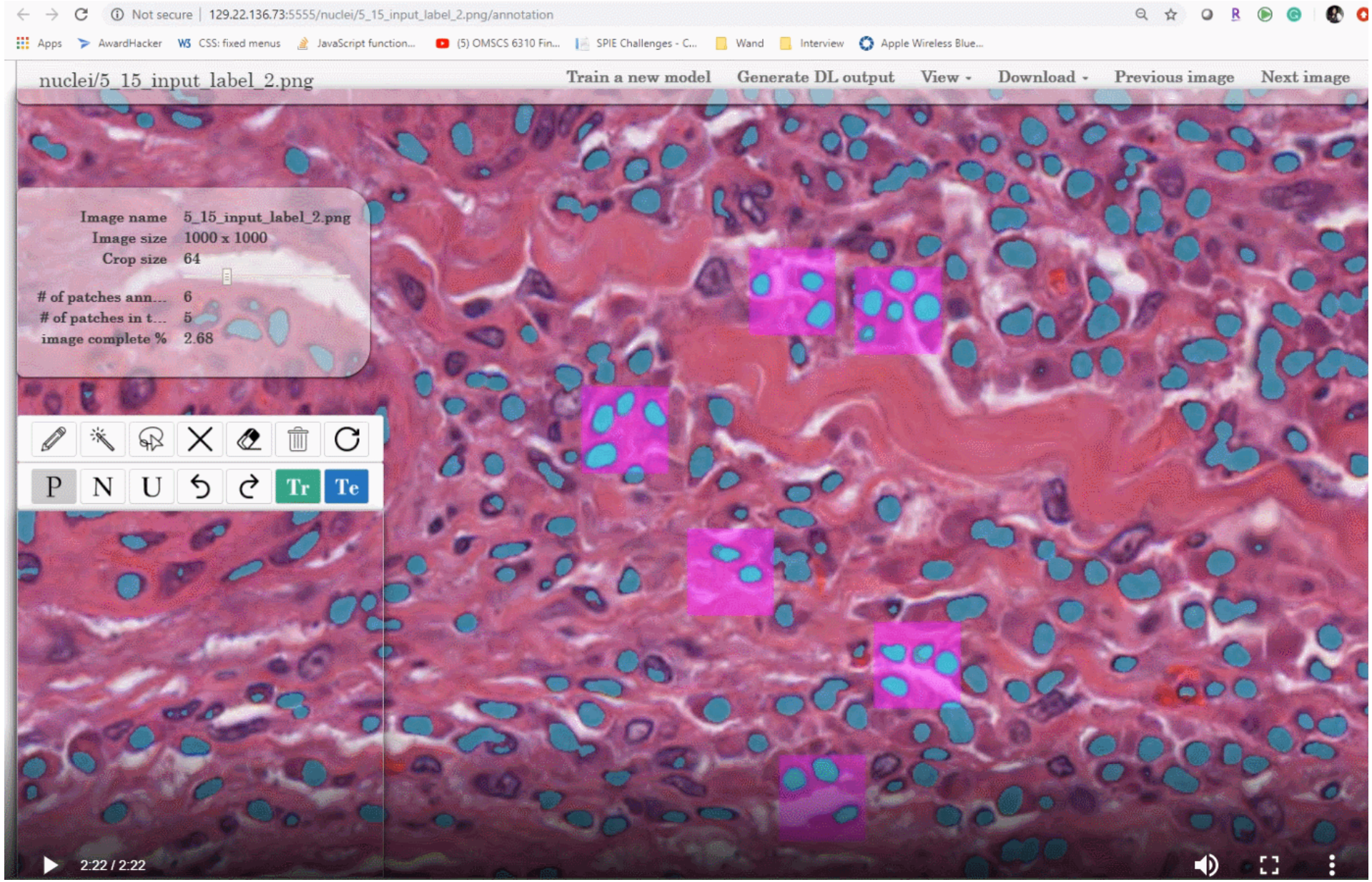
Flowchart of typical workflow for digital pathology research. Histologic primitives (e.g., nuclei, lymphocytes, mitosis, etc.) are identified, after which biologically relevant features are extracted use in downstream applications.

Janowczyk and Madabhushi, JPI 2016

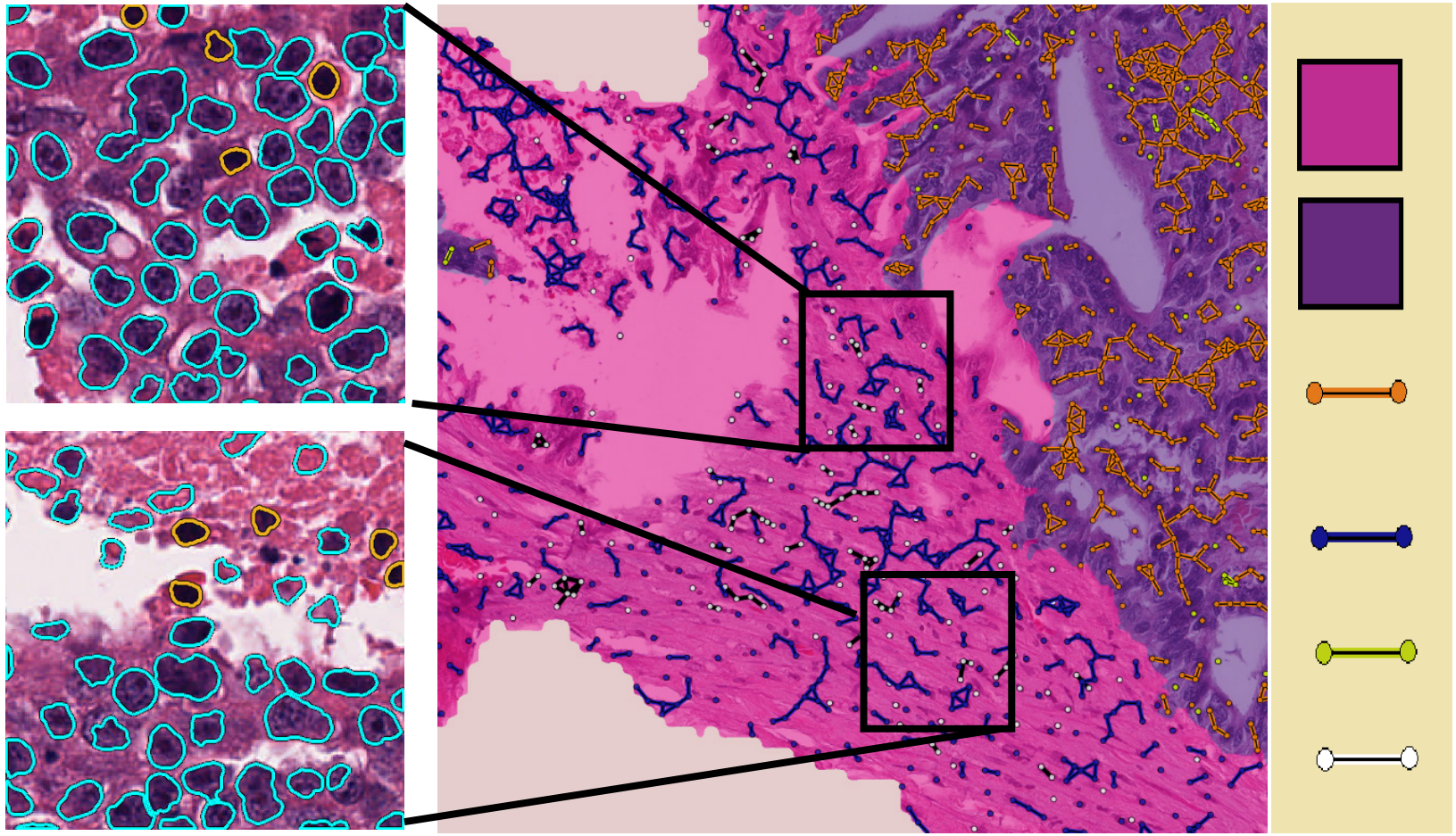
PATHOMICS

1U24CA199374-01

Quick annotator



Nuclei segmentation and sub graph constitution



Stromal region

Epithelial region

Cancer cell clusters

Stromal cell clusters

Tumor infiltrating lymphocytes

Stromal tumor infiltrating lymphocytes

Collagen fiber detection

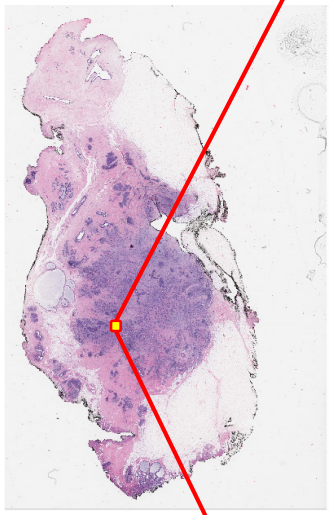
Epithelium segmentation

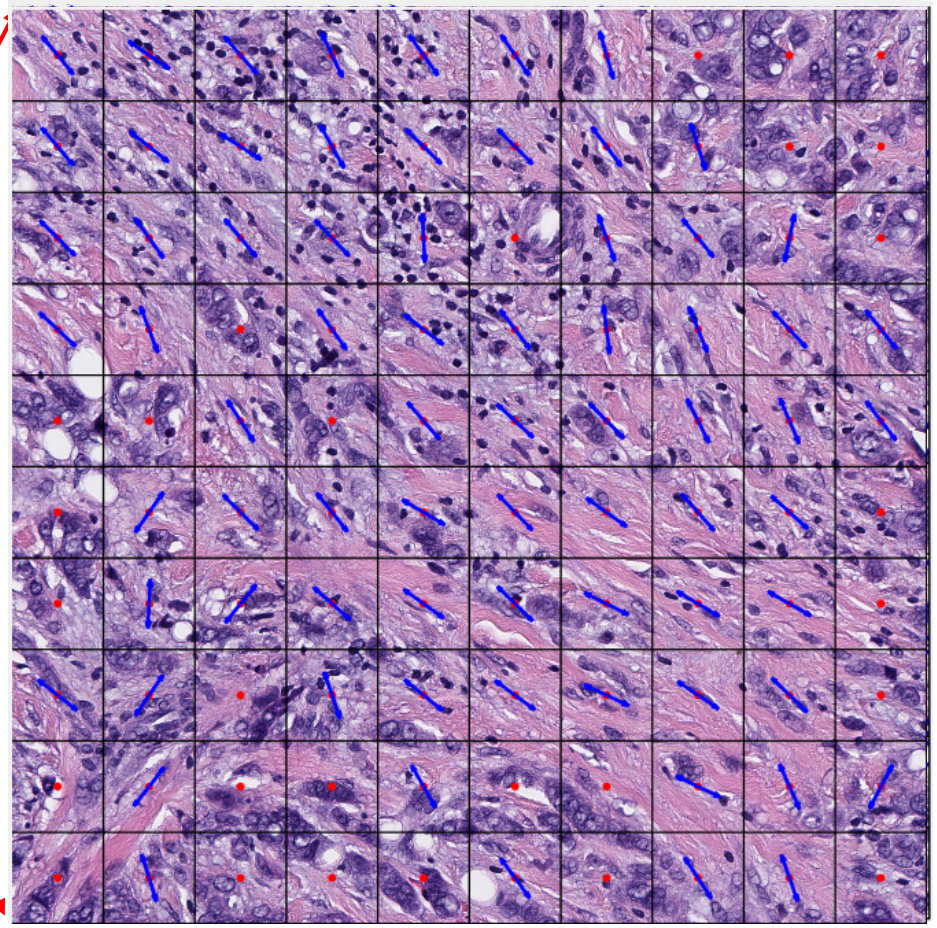
Collagen vectors in tumor-associated stroma

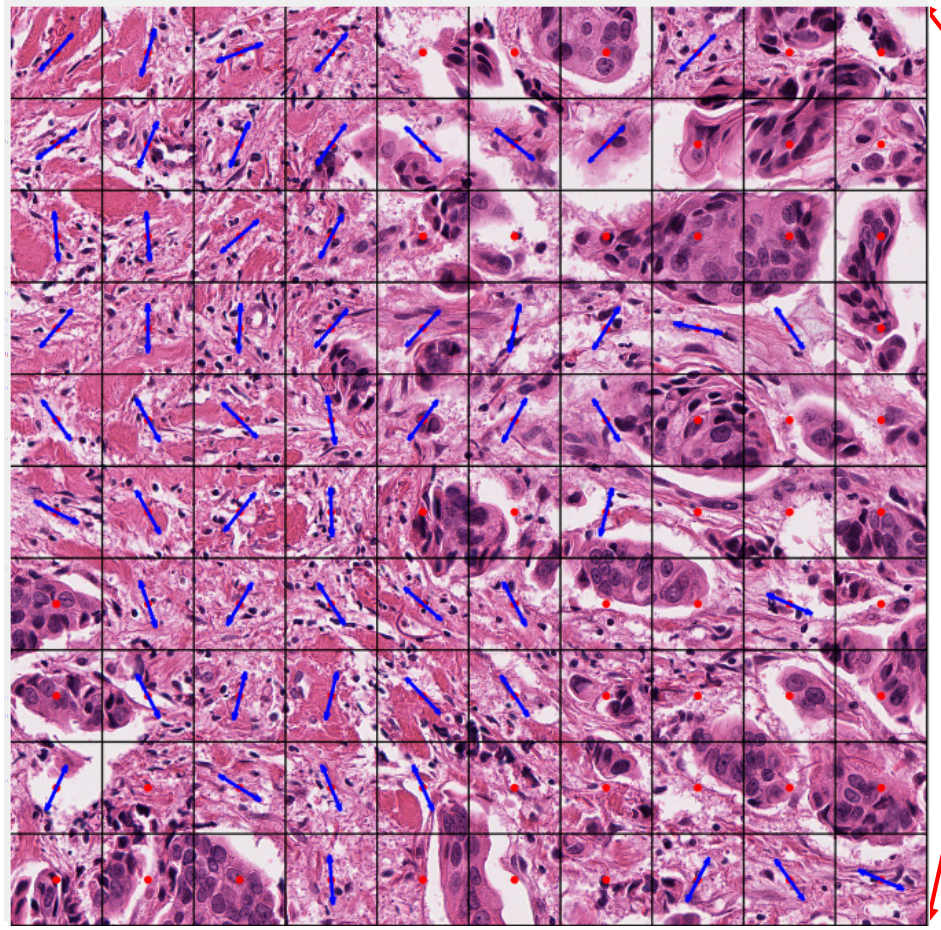
Collagen fiber orientation disorder calculation

Low degree of disorder

Short term survival







High degree of disorder

long term survival

Disorder of collagen fiber orientation associated with risk of recurrence in ER+ breast cancers in ECOG-ACRIN E2197 & TCGA

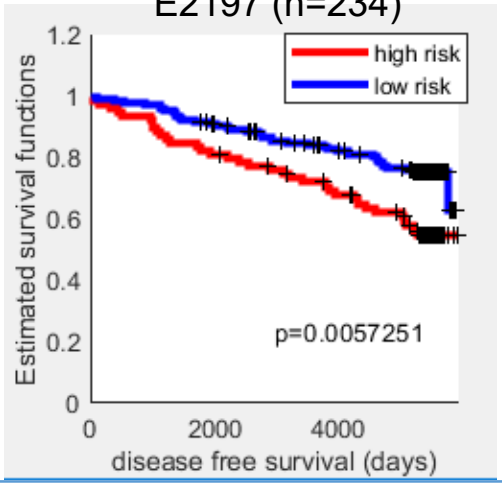
Unmet Clinical Need

- Early stage ER+ breast cancer (BC) is the most common type of breast cancer in the United States
- Predicting the likelihood of recurrence for patients helps physicians plan more tailored treatment strategy to improve survival rate.

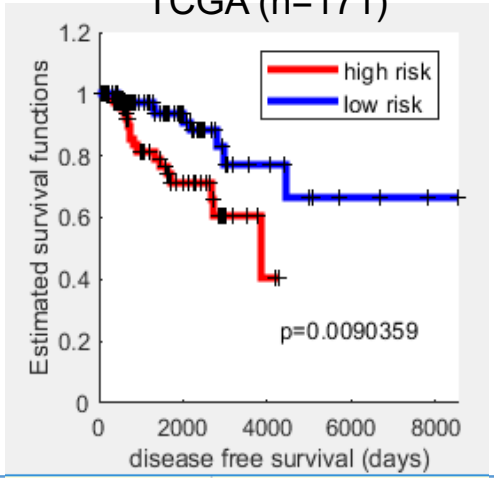
Results:

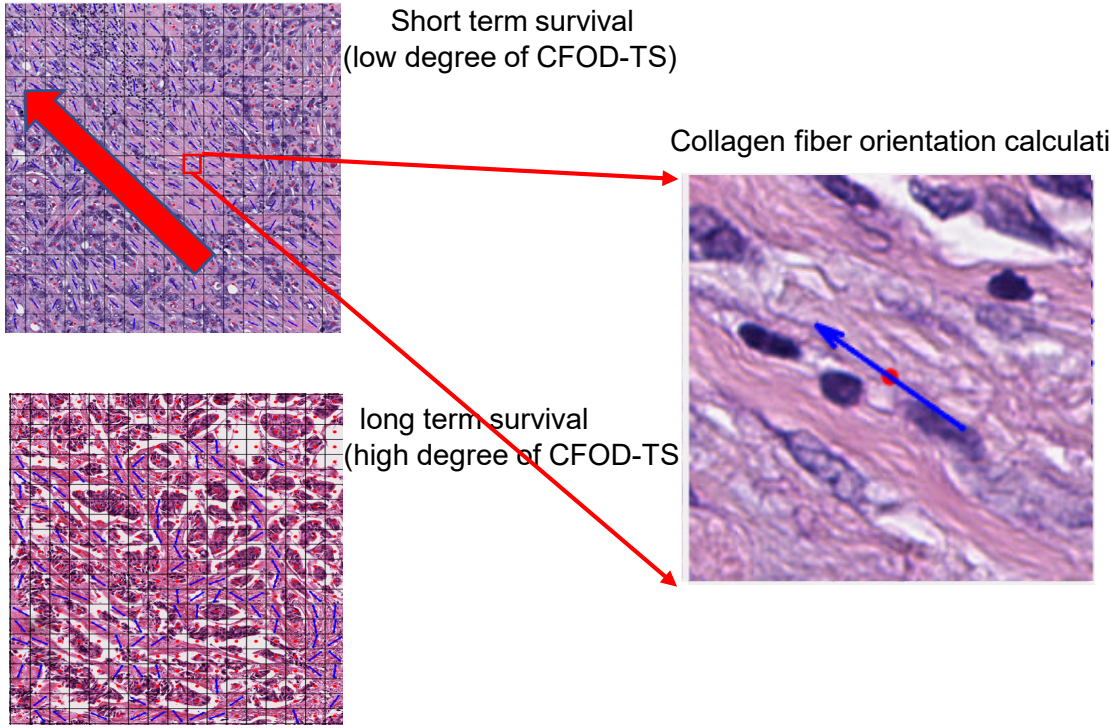
- Collagen Fiber Orientation Disorder in Tumor associated Stroma (CFOD-TS) was independently prognostic for ER+ BCs in E2197 and TCGA.

E2197 (n=234)



TCGA (n=171)





Take away:

- Over-expression of CFOD-TS was be independently associated with lower likelihood of recurrence and could potentially serve as a prognostic marker of outcome for ER+ invasive breast cancer.

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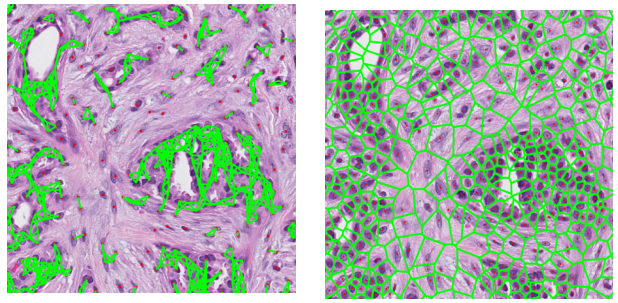
The Center for Computational Imaging & Personalized Diagnostics

Combination of Computer Extracted Features of Nuclear morphology, Tubular Formation, and Mitotic Count from H&E Images Predict Disease Free Survival in Estrogen Receptor Positive (ER+) Breast Cancer

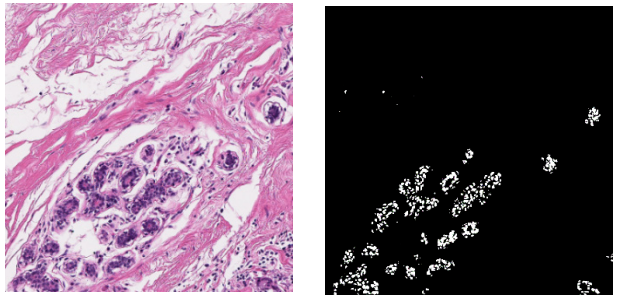
Background

- ER+ breast cancer (BCa) is the most common type of breast cancer in the United States
- Nottingham combined histologic grade reflects how far the tumor architecture and cytology deviate from normal, and how rapidly the tumor proliferates.

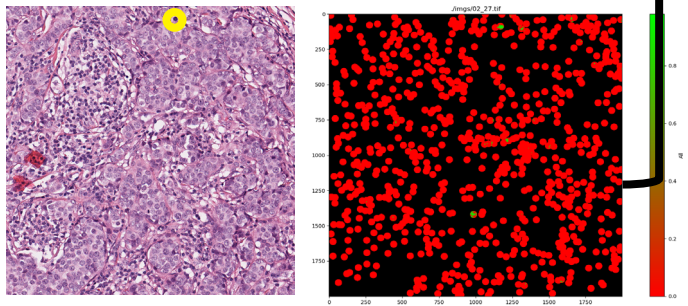
Nuclear morphology



Tubule formation



Mitotic count



Model construction for LN-

Feature combination

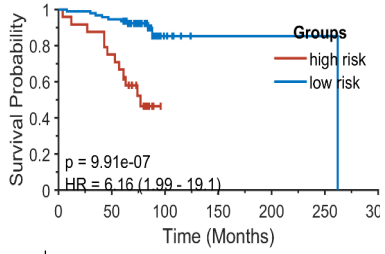
Model construction for LN+

Results

Independent validation on 2 sites

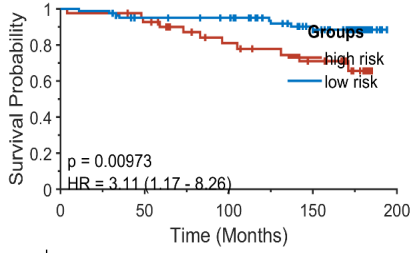
- **LN-**

Train on UH (116 patients)



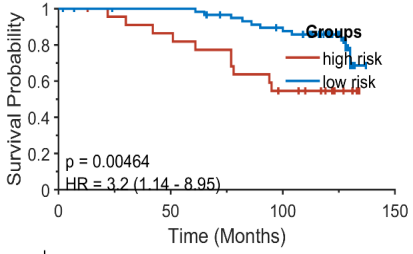
high risk	24	18	0	0	0	0	0
low risk	92	87	6	1	1	1	0

ECOG2197 (121 patients)



high risk	41	37	26	20	0
low risk	80	72	68	51	0

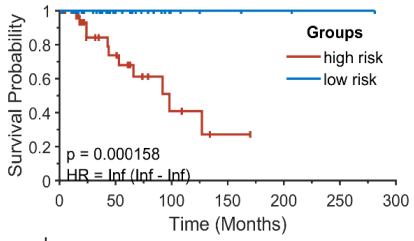
Tata (85 patients)



high risk	23	19	11	0
low risk	61	58	49	0

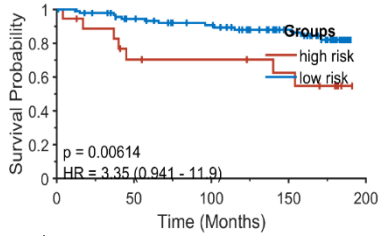
- **LN+**

Train on TCGA (83 patients)



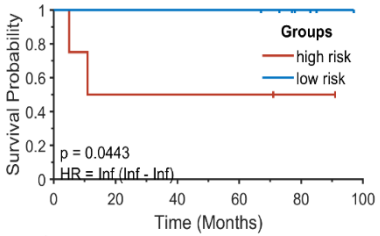
high risk	41	14	4	1	0	0	0
low risk	42	18	5	3	2	1	0

ECOG2197 (112 patients)



high risk	18	11	10	8	0
low risk	94	80	69	49	0

UH (11 patients)



high risk	4	2	2	2	1	0
low risk	7	7	7	7	3	0

Takeaway

The combination of nuclear, tubule, and mitotic features is prognostic of disease-free survival (DFS) for the ER+ breast cancer patients.

A Head-to-Head Comparison

	Oncotype DX	IbRiS
Cost of test:	$4,600	$4.60
Waiting for results:	2 weeks	20 minutes
Tissue specimen:	Destroyed	Digitized
Accessibility:	USA only	Worldwide

An inexpensive, fast, reliable, accessible prognostic breast cancer test: **PRICELESS**

For everything else… there's Mastercard

Combining IbRiS+Oncotype DX: ECOG2197

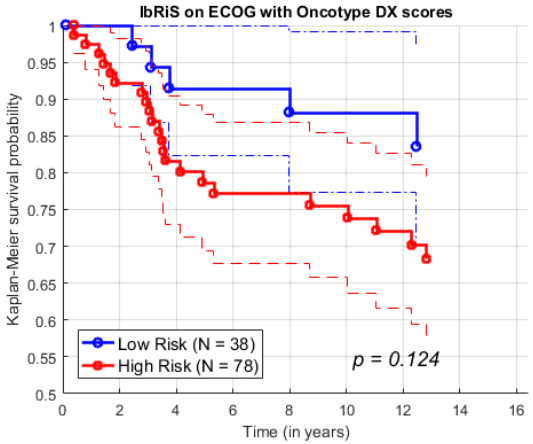
- 378 ER+ breast cancer patients (60 recurrences)
- Node positive, negative axillary lymph nodes, primary tumors at least 1.1 cm
- Endocrine therapy plus chemotherapy
- 116 with Oncotype DX (ODx) scores (27 recurrences)

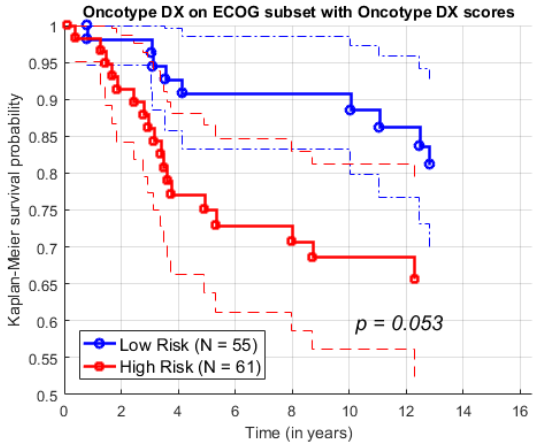
Assay	% of patients with no recurrence after 10 years classified as low-risk	10-year recurrence rate in low-risk group	% of HER2- patients with no recurrence after 10 years classified as low-risk	10-year recurrence rate in low-risk HER2- group
IbRiS	35.34%	10.87%	37.11%	10.0%

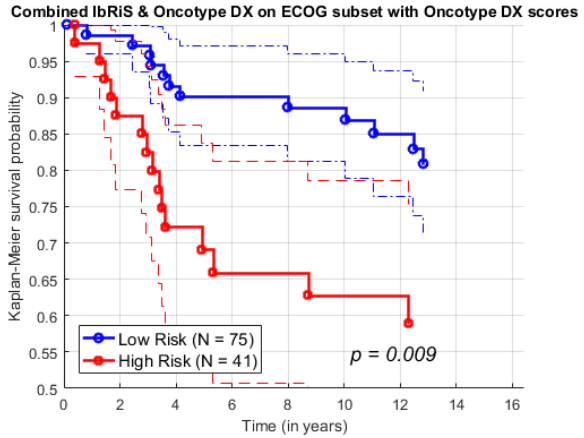
IbRiS performance over all 378 cases

Assay	% of patients with no recurrence after 10 years classified as low-risk	10-year recurrence rate in low-risk group	% of HER2- patients with no recurrence after 10 years classified as low-risk	10-year recurrence rate in low-risk HER2- group
IbRiS	37.5%	17.2%	50.0%	13.3%
ODx	56.3%	20.0%	53.8%	26.3%
IbRiS + ODx	75.0%	20.0%	84.6%	21.4%

Comparison of IbRiS to Onctoype DX over 116 cases with ODx scores







Verma et al ASCO 2018

Computer extracted features of nuclear shape, orientation disorder and texture from H&E Whole slide images are associated with disease-free survival in Ductal Carcinoma in situ (DCIS)

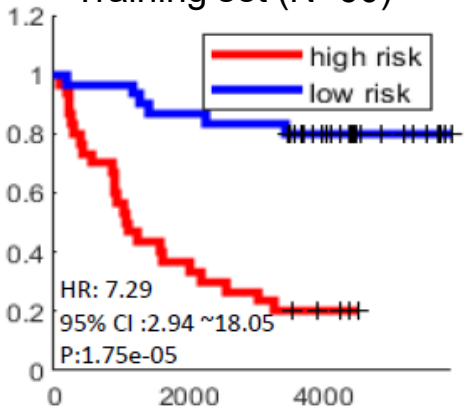
Unmet Clinical Need

- Gold standard treatment: lumpectomy + adjuvant radiation.
- Identify patients with low-risk DCIS, for whom radiotherapy can often be omitted.
- Gene assays such as Oncotype DX: expensive, time-consuming and tissue destructive.

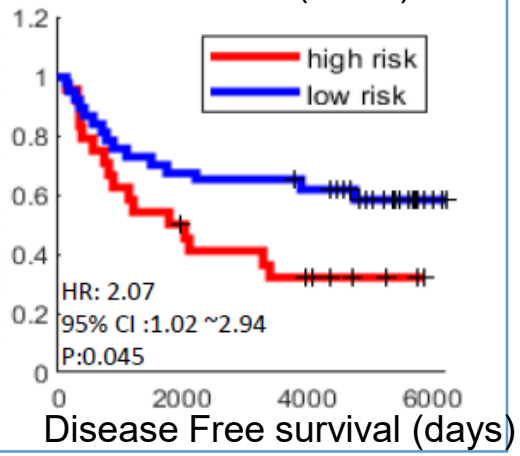
Results

The Cox regression model built with nuclear morphologic features is prognostic of DCIS

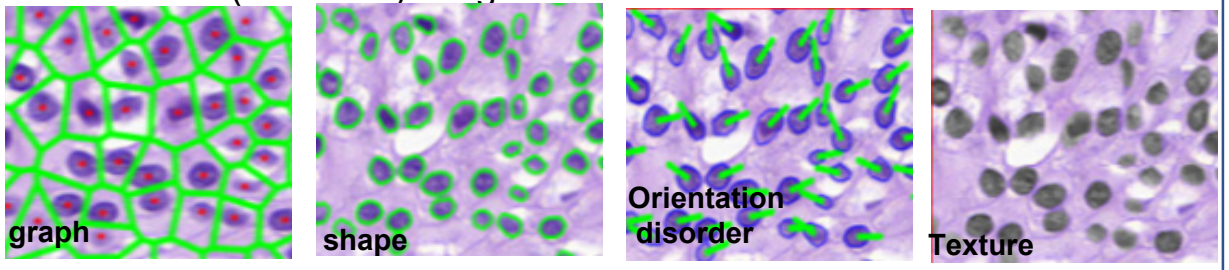
Training set (N=60)

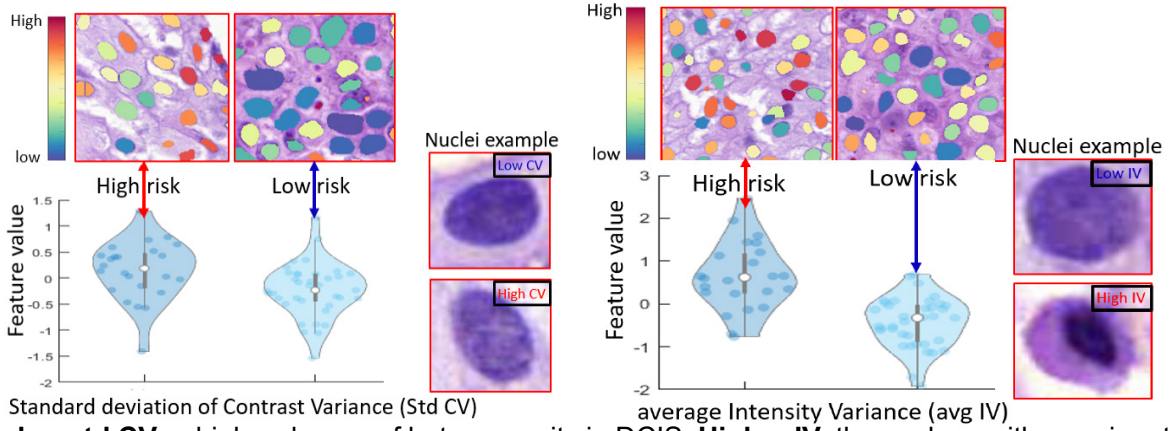


Validation set (N=61)



Computationally derived morphometric features in histological (resection) images to assess recurrence risk.





Higher std CV: a higher degree of heterogeneity in DCIS **Higher IV**: the nucleus with prominent nucleolus

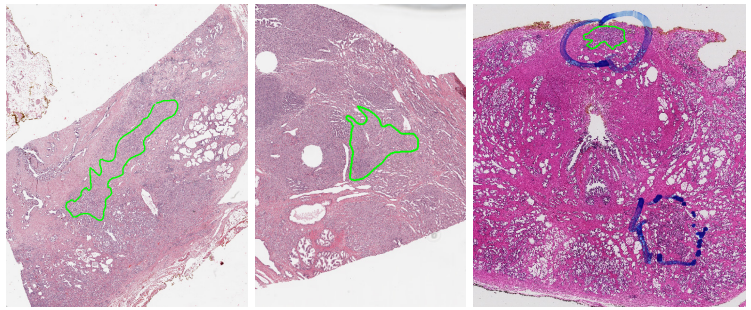
Take Away: Combination of the quantitative nuclear histomorphometric features pertaining to nuclear shape, orientation disorder and Haralick textures is prognostic for DCIS.

CASE SCHOOL OF ENGINEERING
CASE WESTERN RESERVE UNIVERSITY

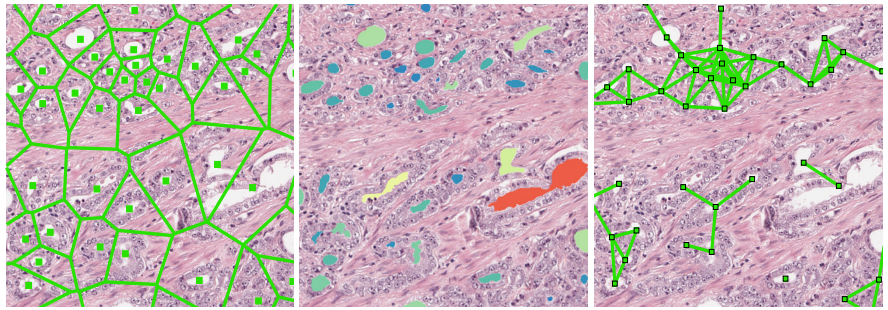
The Center for Computational Imaging & Personalized Diagnostics

Predicting post-surgical recurrence in prostate cancer

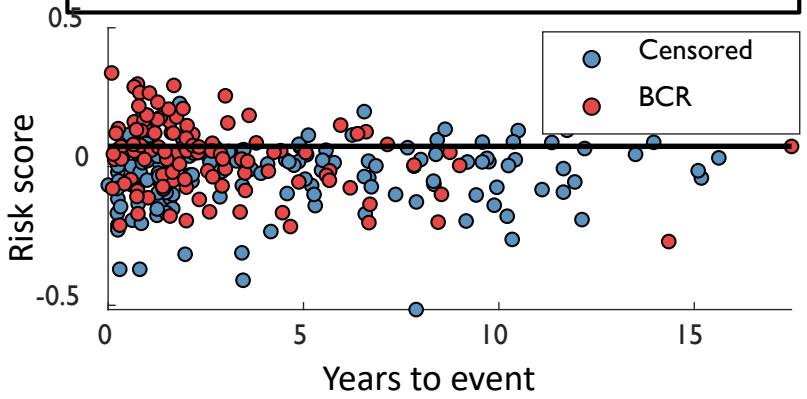
N=907 diagnostic slides from 6 sites



Extract 216 gland lumen features

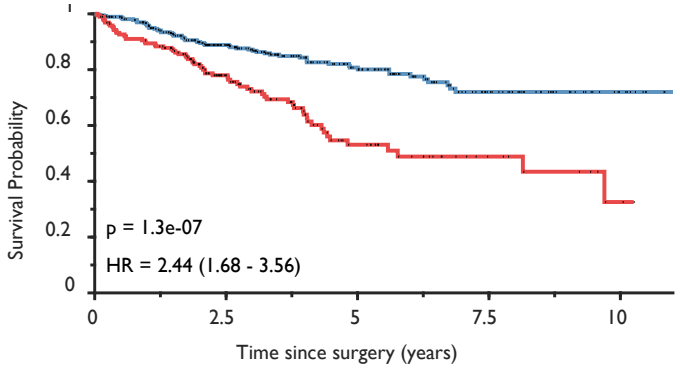


Train on 263 patients from one site



Results

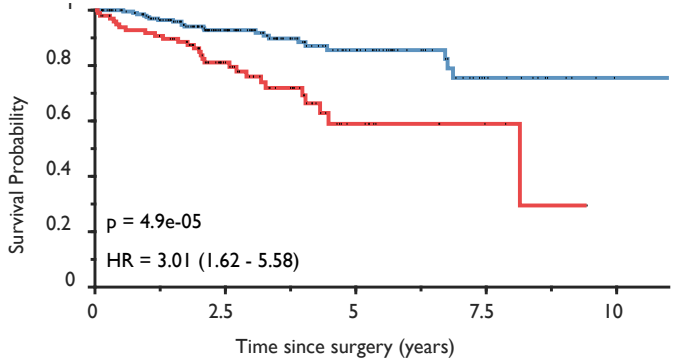
Prognostic in independent validation



Number at risk (number censored)

Low-risk	381 (0)	229 (115)	121 (207)	48 (271)	15 (304)
High-risk	193 (0)	99 (55)	33 (98)	11 (118)	2 (125)

Added value in margin-negative patients



Number at risk (number censored)

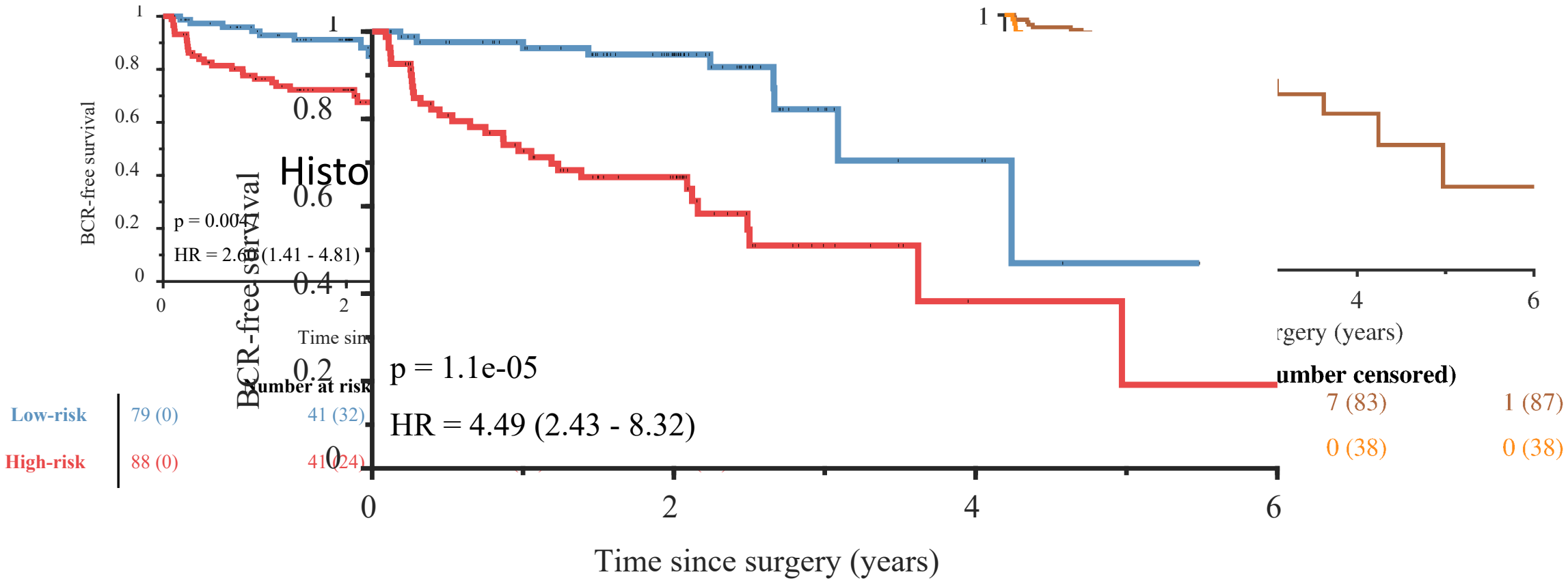
Low-risk	224 (0)	118 (93)	51 (154)	15 (187)	4 (198)
High-risk	100 (0)	51 (32)	11 (63)	3 (71)	0 (73)

Independent from clinical markers

Covariate	p	HR
Risk score (per 0.1 increase)	<.01	1.33
Grade group >2	<.01	3.05
Positive margins	<.01	2.21
Log2 pre-op PSA	0.24	1.13
Stage >T2a	0.63	1.42

Npj Precision Oncology, In Press

Image based risk score versus Decipher: Head to Head Comparison



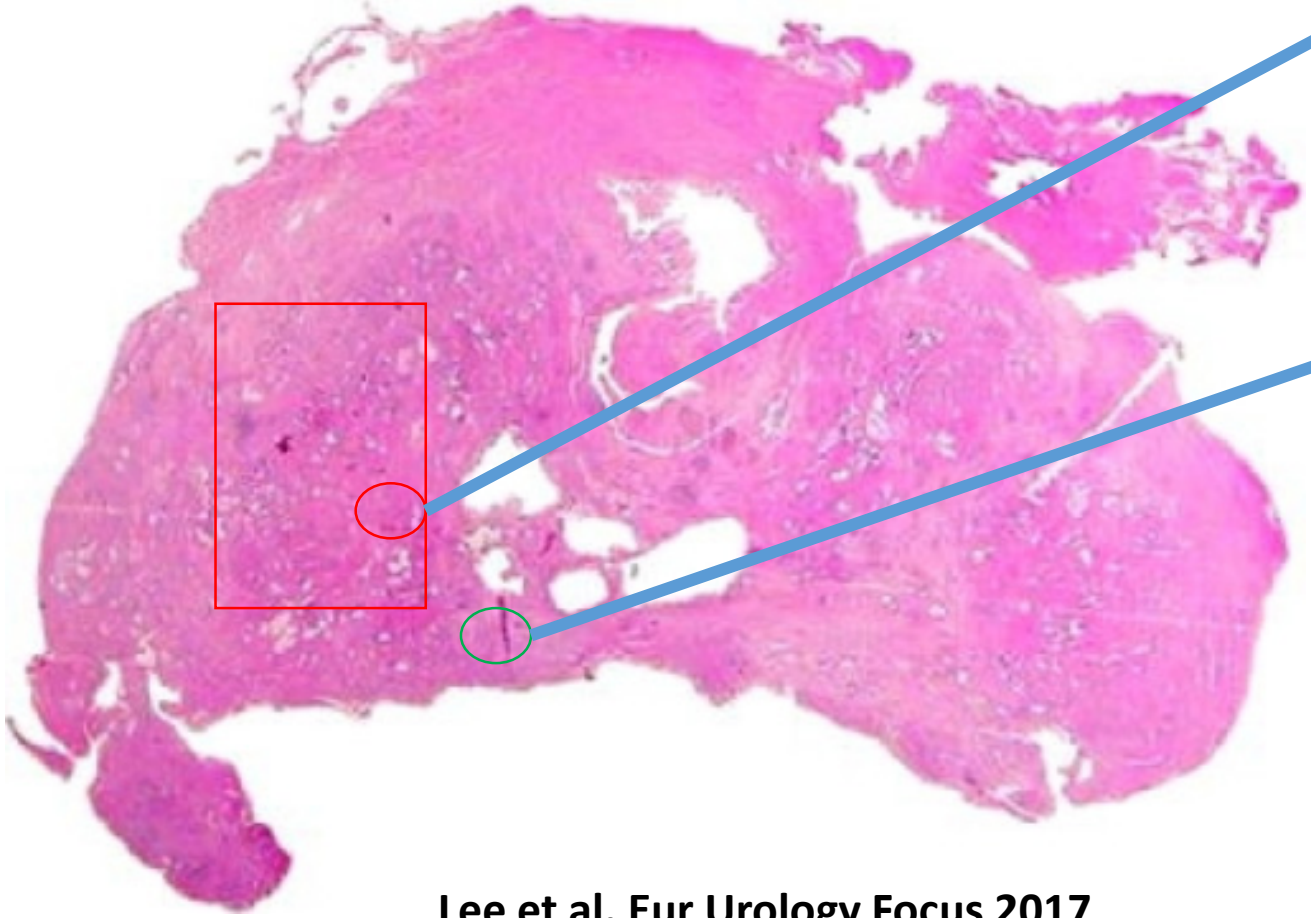
Number at risk (number censored)

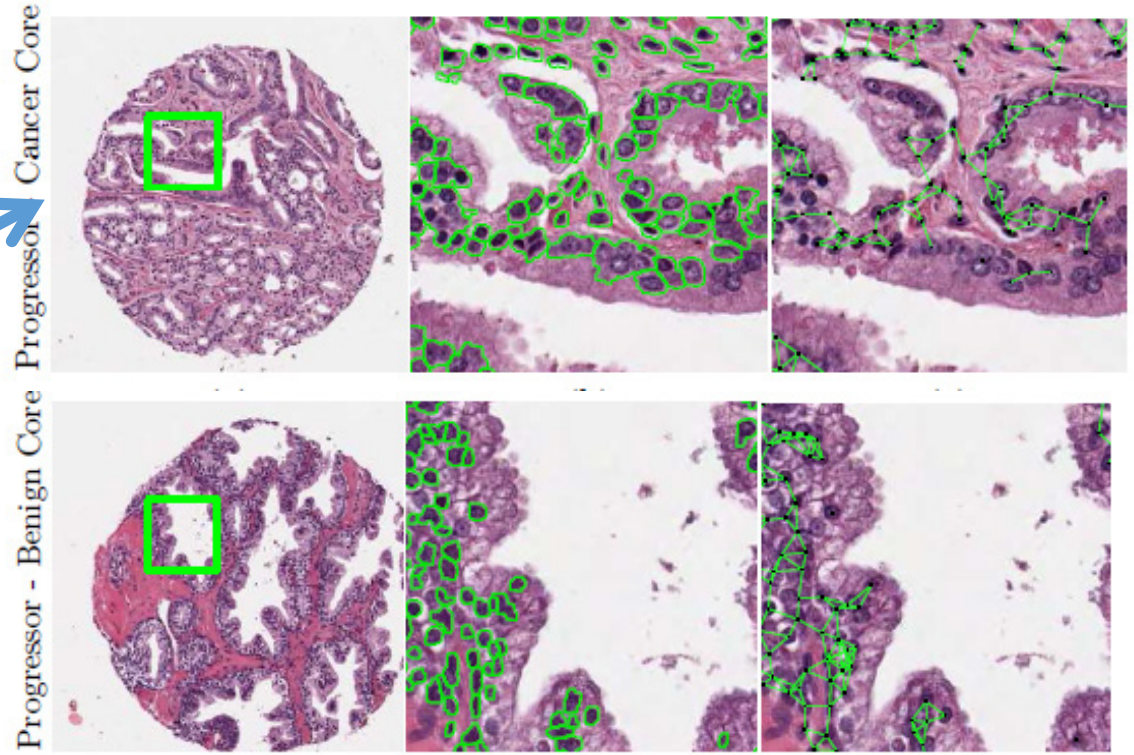
Low-risk	86 (0)	47 (35)	5 (73)	0 (77)
High-risk	81 (0)	35 (21)	2 (48)	1 (48)

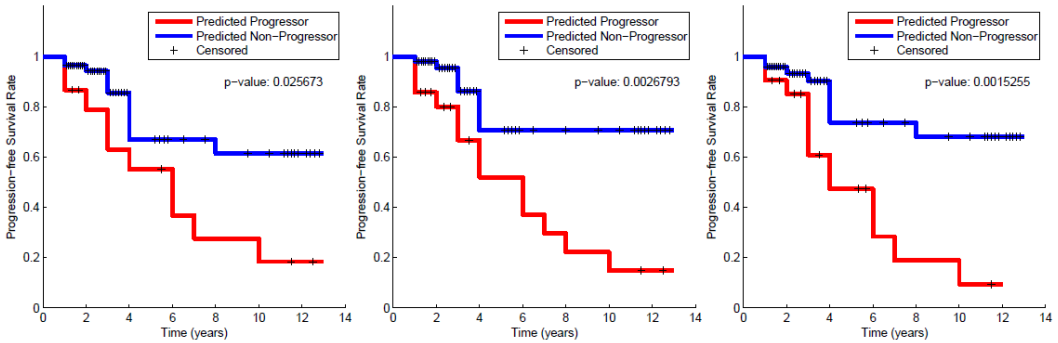
Npj Precision Oncology, In Press

Features from benign regions on surgical specimens of the prostate predict likelihood of cancer recurrence after surgery

- Field effect provides clues on cancer progression
- Tumor + Adjacent Benign Signature (TABS) outperforms prediction from cancerous regions alone

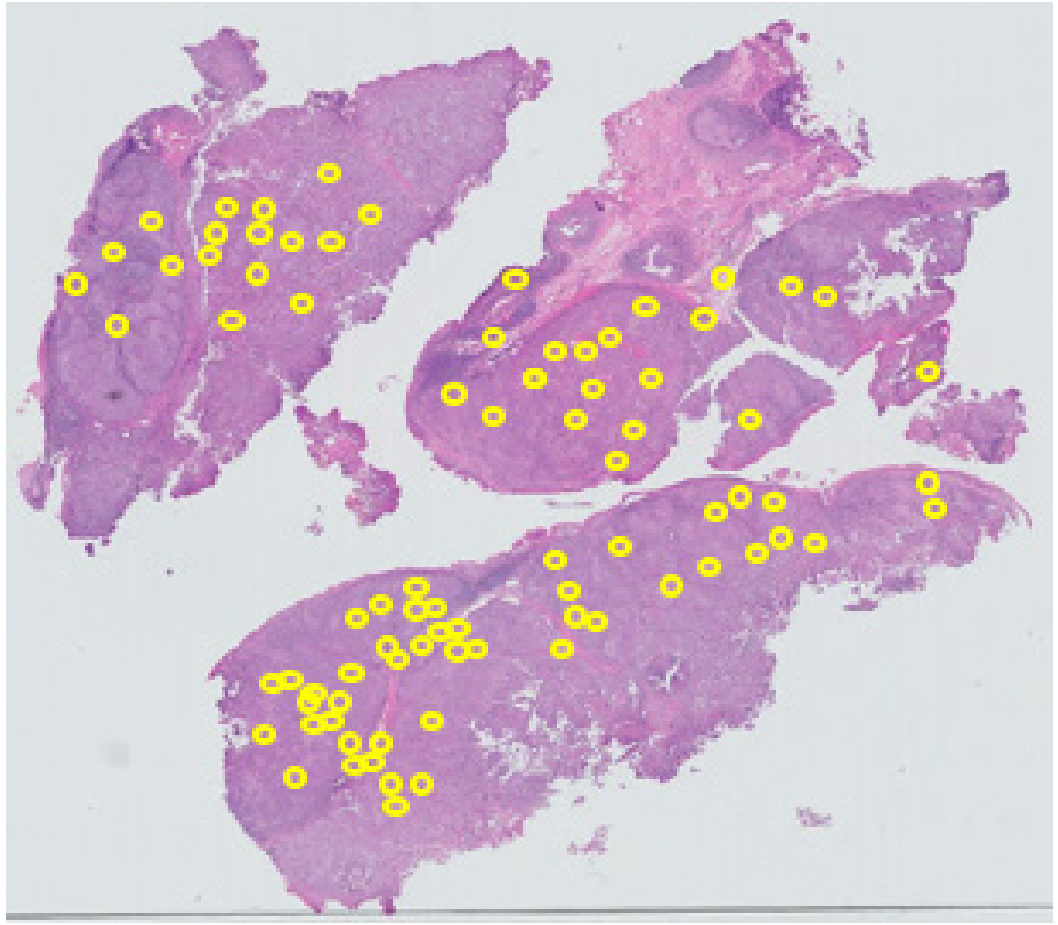




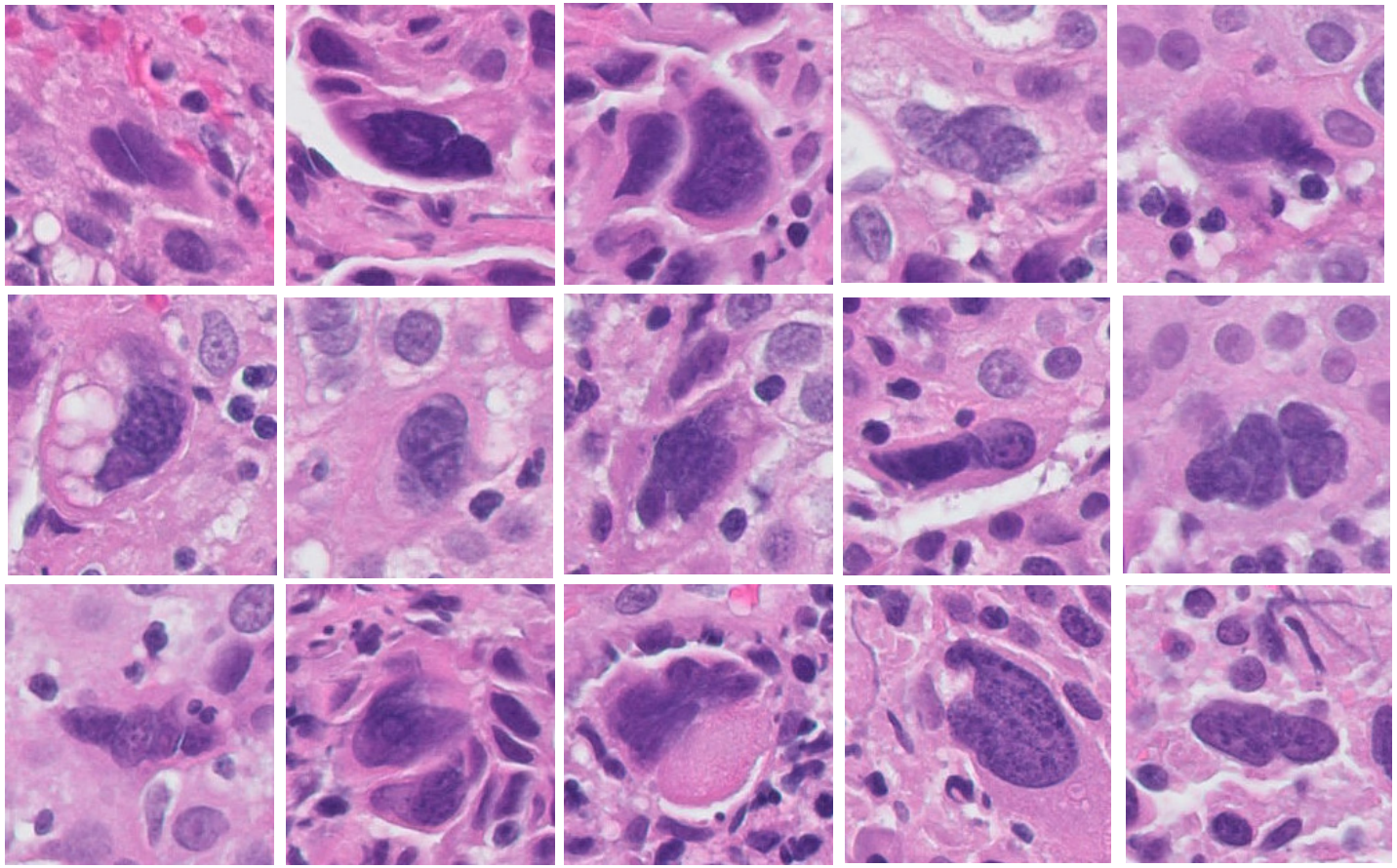


Lee et al. Eur Urology Focus 2017

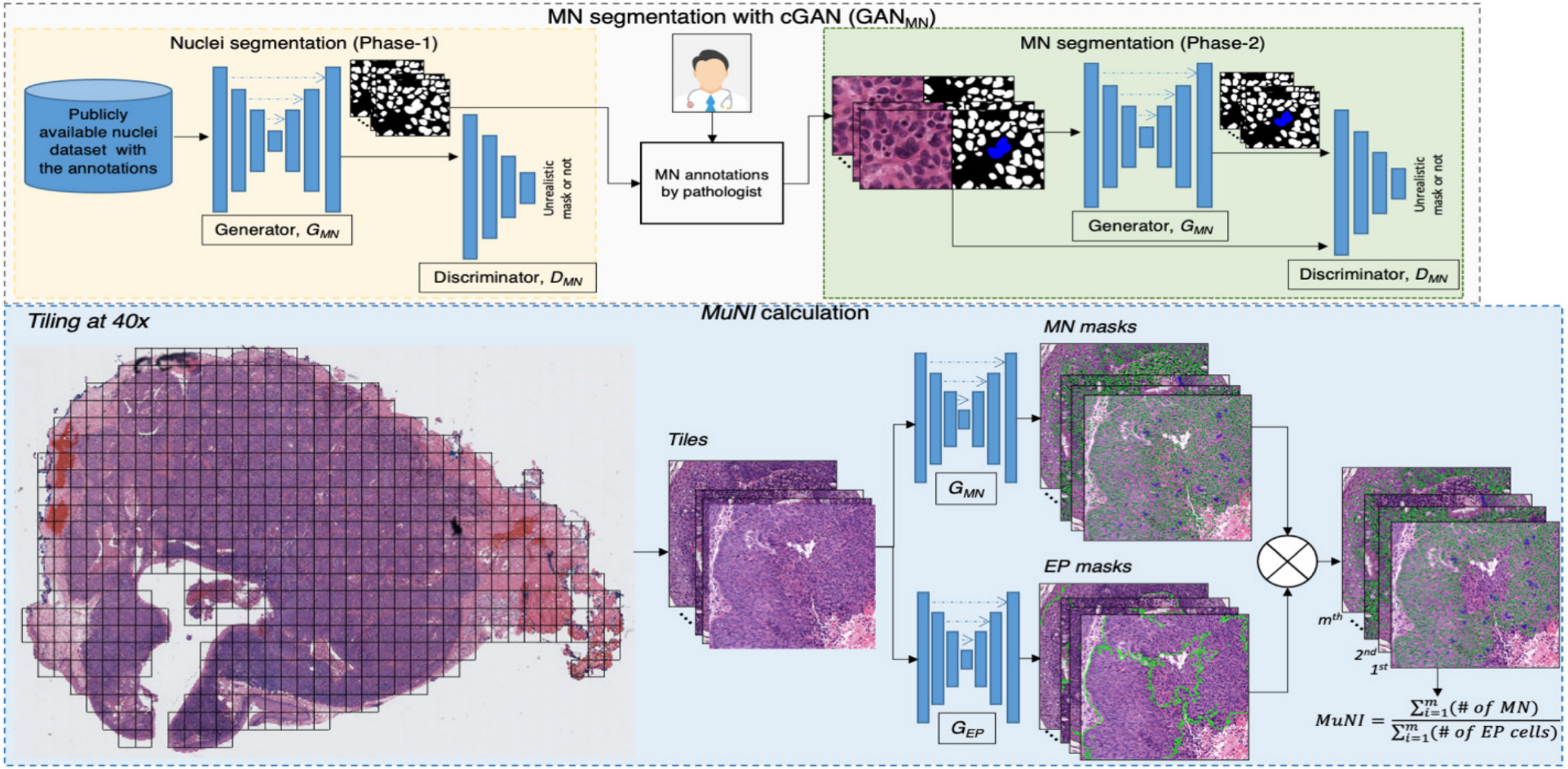
Computerized Quantitation of Tumor Cell Multinucleation is Strongly Prognostic for p16-Positive Oropharyngeal Squamous Cell Carcinoma

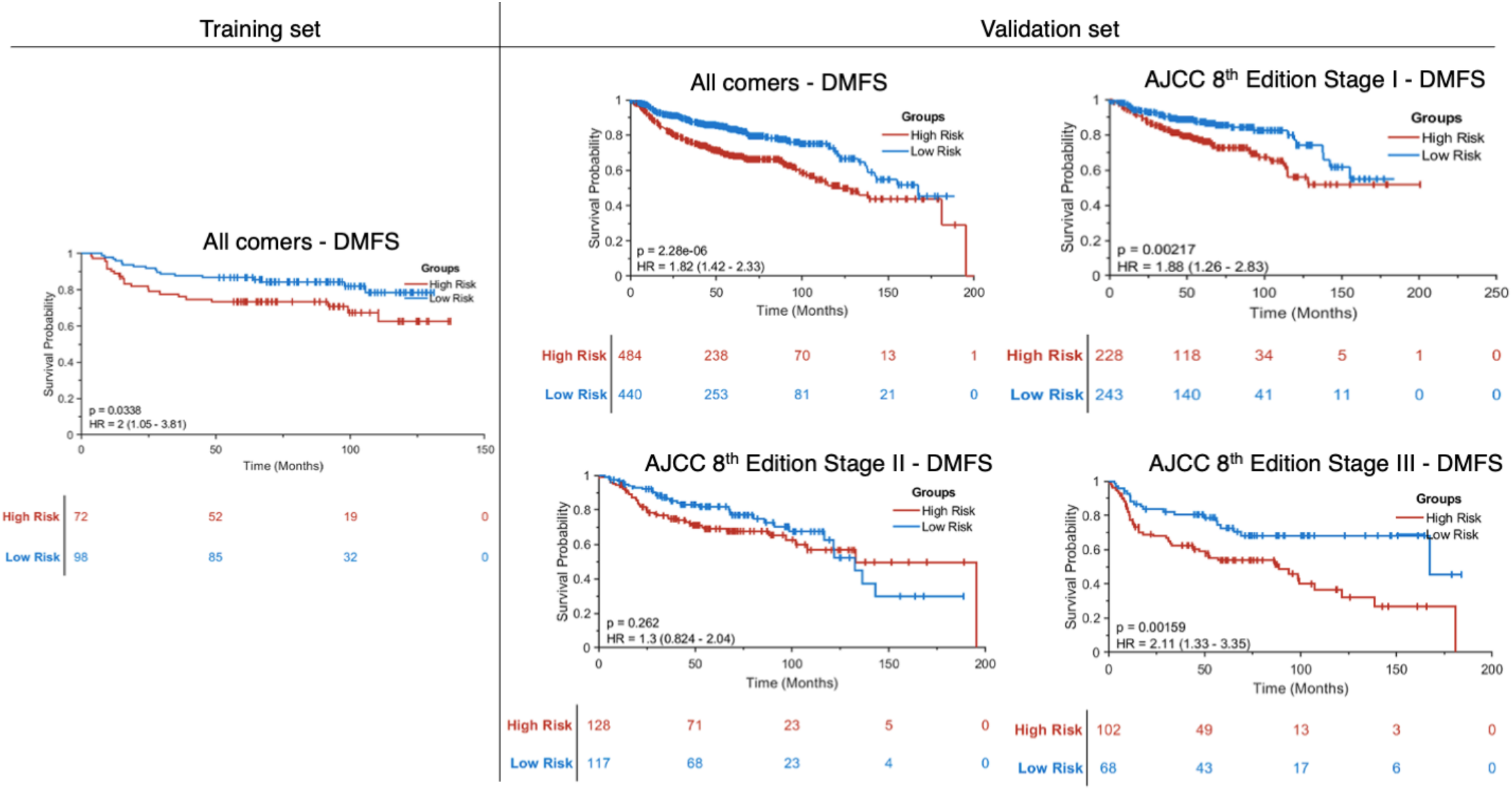


Yellow spots indicates the locations of multinucleation



Zoomed in Multinucleation figures


MN segmentation with cGAN (GAN_{MN})
Nuclei segmentation (Phase-1)
Publicly available nuclei dataset with the annotations
Generator, G_{MN}
Discriminator, D_{MN}
Unrealistic mask or not
MN annotations by pathologist
MN segmentation (Phase-2)
Generator, G_{MN}
Discriminator, D_{MN}
Unrealistic mask or not
Tiling at 40x
MuNI calculation
Tiles
G_{MN}
MN masks
G_{EP}
EP masks
m^{th}
2nd
1st
$MuNI = \frac{\sum_{i=1}^{m}(\#\ of\ MN)}{\sum_{i=1}^{m}(\#\ of\ EP\ cells)}$



KM-DMFS curves for patients in training/validation cohorts for different cancer stage groups according to AJCC 8th edition definition.

JCI The Journal of Clinical Investigation

Clinical Medicine In-Press Preview Oncology Free access | 10.1172/JCI145488

Computerized tumor multinucleation index (MuNI) is prognostic in p16+ oropharyngeal carcinoma: A multi-site validation study

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Published March 2, 2021 - More info

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Abstract

BACKGROUND. p16 positive oropharyngeal squamous cell carcinoma (OPSCC) patients are potentially cured with definitive treatment. However, there are currently no reliable biomarkers of treatment failure in p16 positive OPSCC. Pathologist-based visual assessment of tumor cell multinucleation has been shown to be independently prognostic of disease-free survival in p16 positive OPSCC. However, its quantification is time-intensive, subjective, and at risk of interobserver variability.

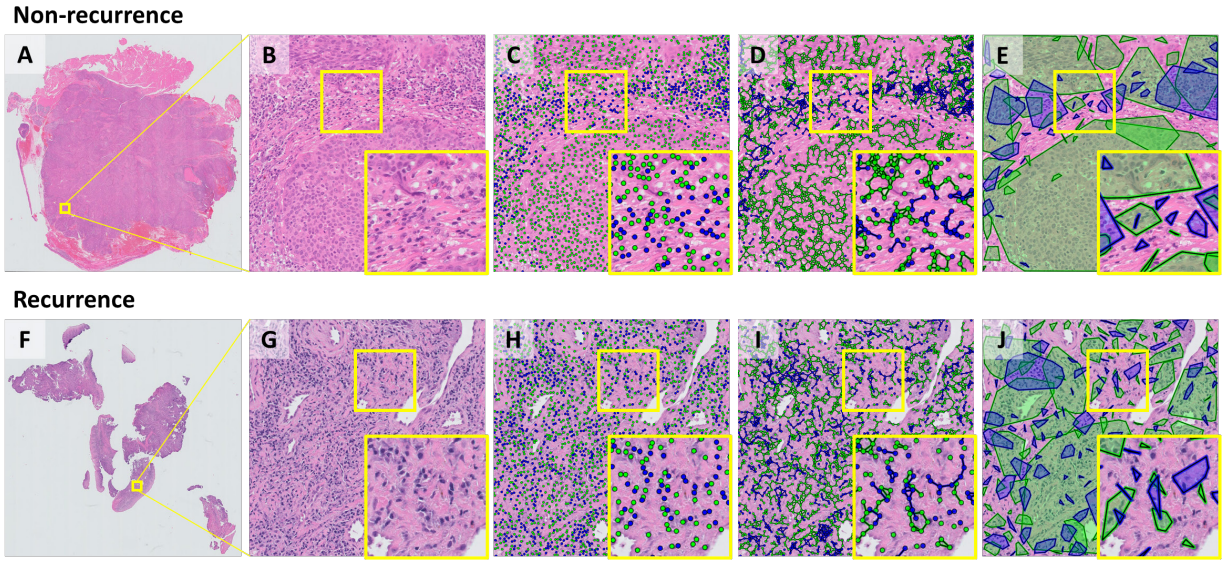
METHODS. We present a deep learning-based metric, the multi-nucleation index (MuNI), for prognostication in p16 positive OPSCC. This approach quantifies tumor multi-nucleation from digitally scanned hematoxylin eosin (H&E)-stained slides. Representative H&E whole slide images from 1,094 previously untreated p16 positive OPSCC patients were acquired from six institutions for optimizing and validating MuNI.

RESULTS. MuNI was prognostic for disease-free (DFS), overall (OS), or distant metastasis-free (DMFS) survival in p16 positive OPSCC with HRs of 1.78(95%CI:1.37-2.30), 1.94(1.44-2.60), and 1.88(1.43-2.47), respectively, independent of age, smoking status, treatment type, and T/N-categories in multivariable analyses. It was also prognostic for DFS, OS, and DMFS in OPSCC patients at stages I and III.

CONCLUSION. MuNI holds promise as a low-cost, tissue non-destructive, H&E stain based digital biomarker test for counseling, treatment, and surveillance of p16 positive OPSCC patients. These data support further confirmation of MuNI in prospective trials.

FUNDING. This work was supported by the National Cancer Institute of the National Institutes of Health (under award numbers 1U24CA199374-01, R01CA202752-01A, R01CA208236-01A1, R01CA216579-01A1, R01CA220581-01A1, 1U01CA239055-01), the National Institute for Biomedical Imaging and Bioengineering (1R43EB028736-01), the National Center for Research Resources (1C06RR12463-01), the VA Merit Review Award (IBX004121A) from the United States Department of Veterans Affairs Biomedical Laboratory Research and Development Service, the DoD Breast Cancer Research Program Breakthrough Level 1 Award (W81XWH-19-1-0668), the DOD Prostate Cancer Idea Development Award (W81XWH-15-1-0558), the DOD Lung Cancer

Predicting prognosis in Head and Neck Cancers by characterizing the interplay between TILs and surrounding cancer cells

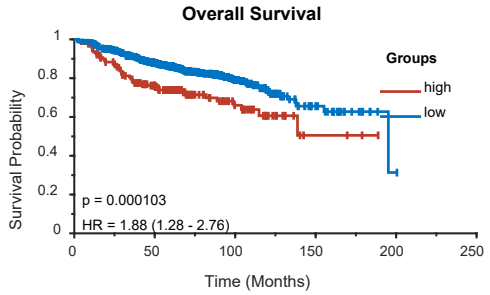


Datasets	# Cases	# Recurrences	# Deaths
Houston VA (D1)	94	30	61
JHU (D2)	121	33	13
WU (D3)	107	16	21
Kaiser (D4)	169	30	37
CCF (D5)	336	55	74
VUMC (D6)	158	17	29
Total	**985**	**181**	**235**

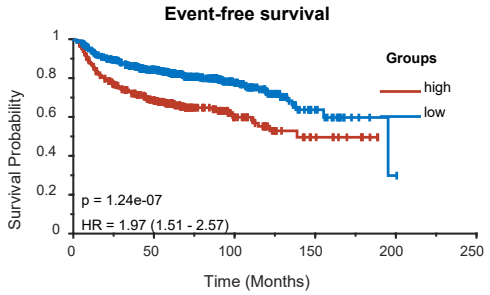
Feature discovery and model training

Independent validation

Univariable survival analysis

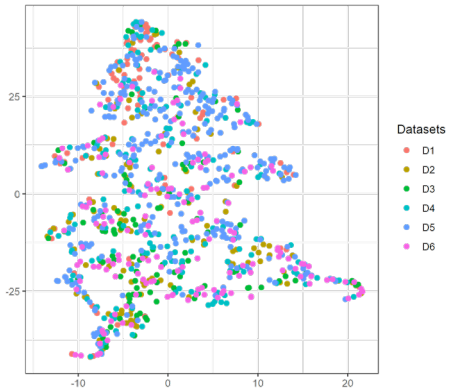


high	183	108	30	3	0	0
low	708	459	148	26	1	0



high	359	184	49	11	0	0
low	532	340	122	18	1	0

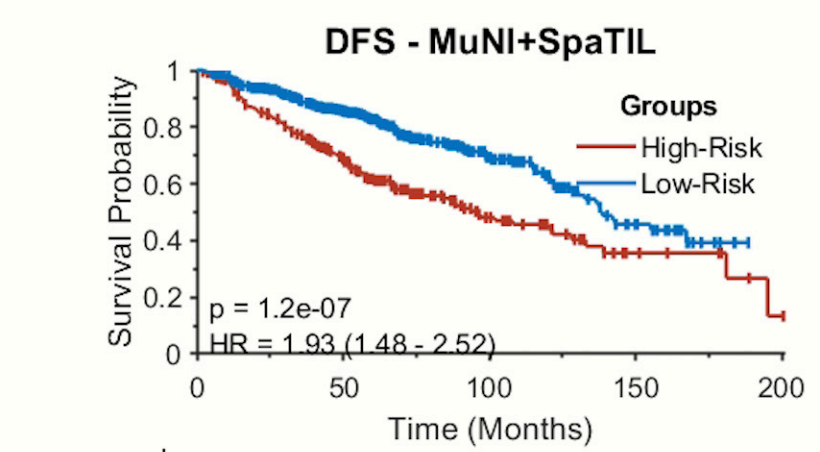
Unsuperv. Clustering of Features



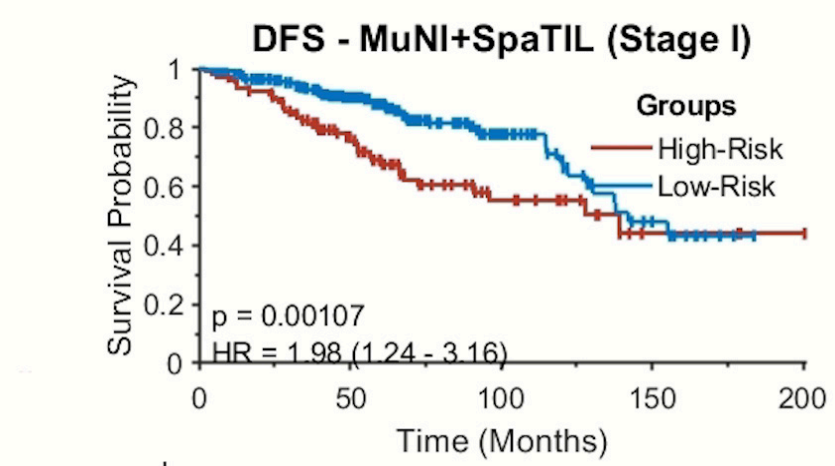
Multivariable survival analysis

Variable	Overall Survival		Event-free Survival	
	p-value	HR (CI)	p-value	HR (CI)
Age	**8.04E-07**	1.05(1.03-1.07)	**1.00E-05**	1.04 (1.02-1.05)
Race	0.3385	0.73(0.39-1.38)	0.1919	0.68 (0.38-1.21)
Sex	0.624	0.88(0.53-1.47)	0.793	1.06 (0.67-1.69)
Smoking	**0.0176**	1.56(1.08-2.24)	0.198	1.22 (0.90-1.64)
Overall st.	**0.1389**	0.74(0.49-1.10)	**0.0331**	0.68 (0.47-0.97)
T-stage	**0.0012**	1.60(1.21-2.13)	**0.0001**	1.68 (1.31-2.16)
N-stage	**0.0126**	1.42(1.08-1.86)	**0.0017**	1.47 (1.16-1.87)
OP-TIL	**0.008**	1.60(1.13-2.26)	**0.0001**	1.74 (1.32-2.28)

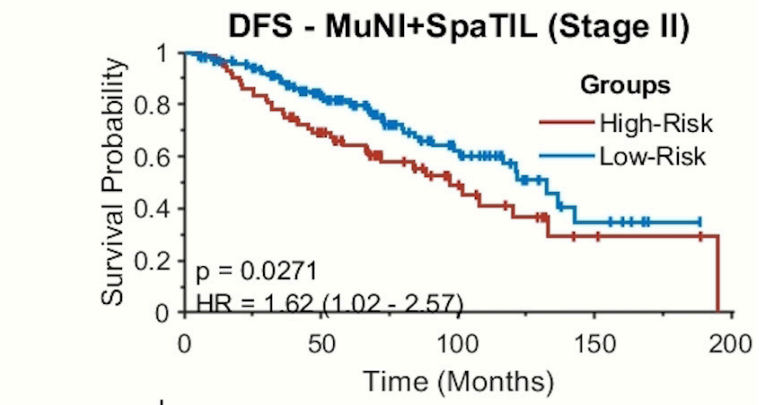
Combining biomarkers results in even better prognosis – even within individual stage groups



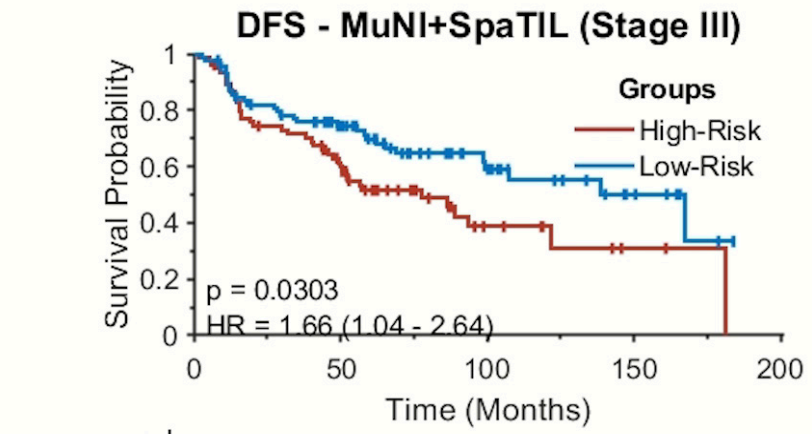
High-Risk	267	146	43	8	1
Low-Risk	532	323	101	24	0



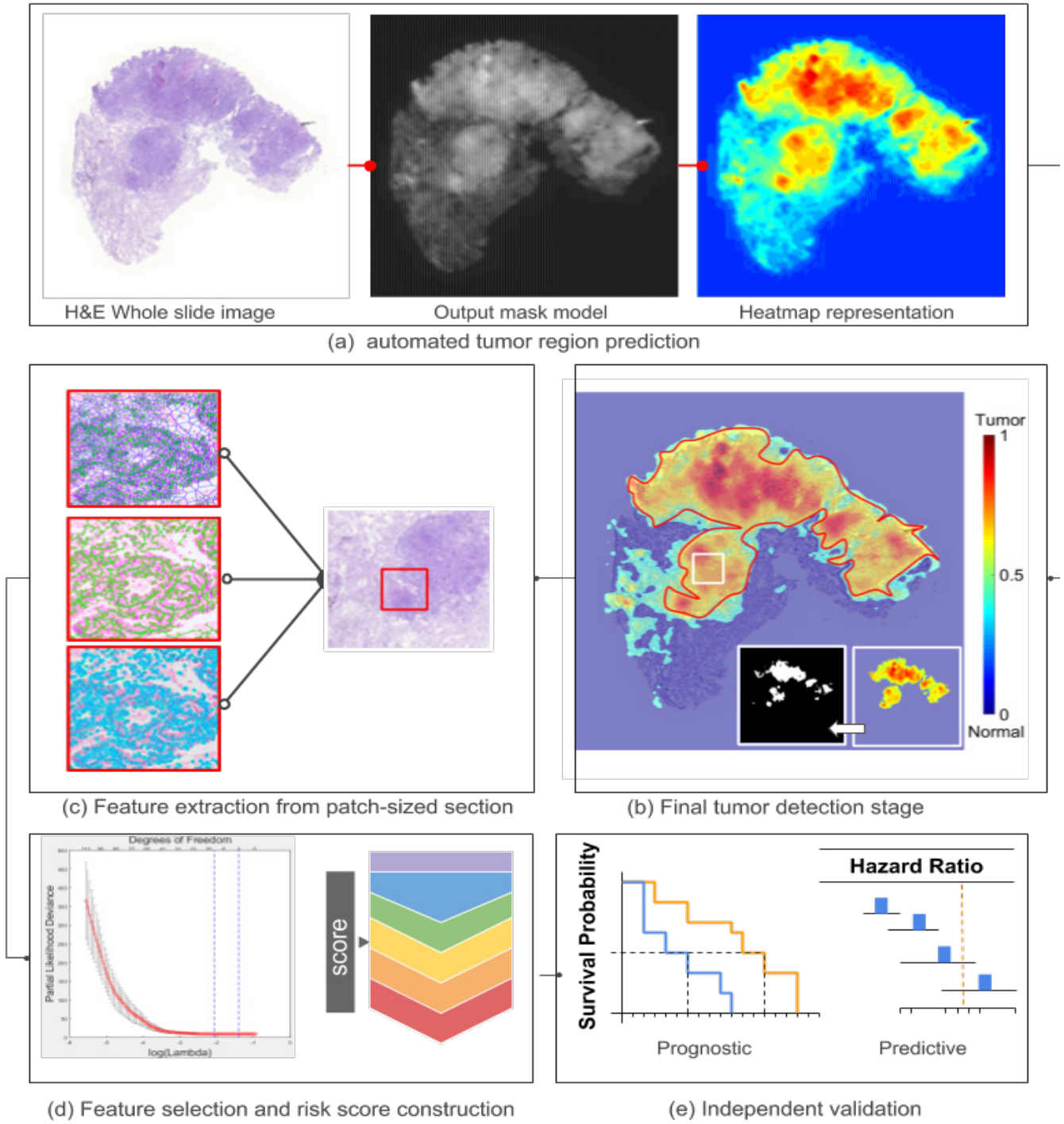
High-Risk	106	61	20	3	1
Low-Risk	286	173	49	11	0



High-Risk	73	46	14	3	0
Low-Risk	151	96	31	6	0



High-Risk	76	39	9	2	0
Low-Risk	85	53	21	7	0



IbRiS is prognostic and predictive for added benefit for adjuvant chemotherapy in early stage non-small cell lung cancer

Spatial arrangement of clusters of tumor infiltrating lymphocytes and cancer nuclei is predictive of recurrence in early stage non-small cell lung caner

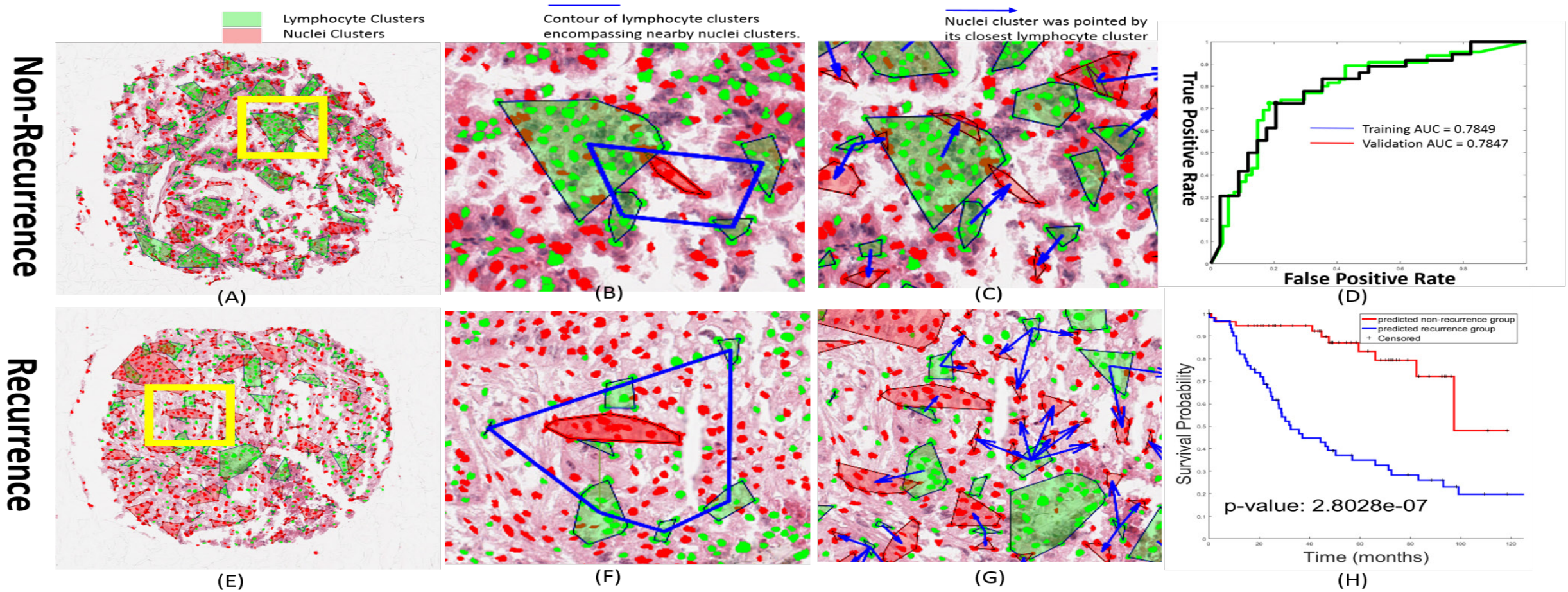
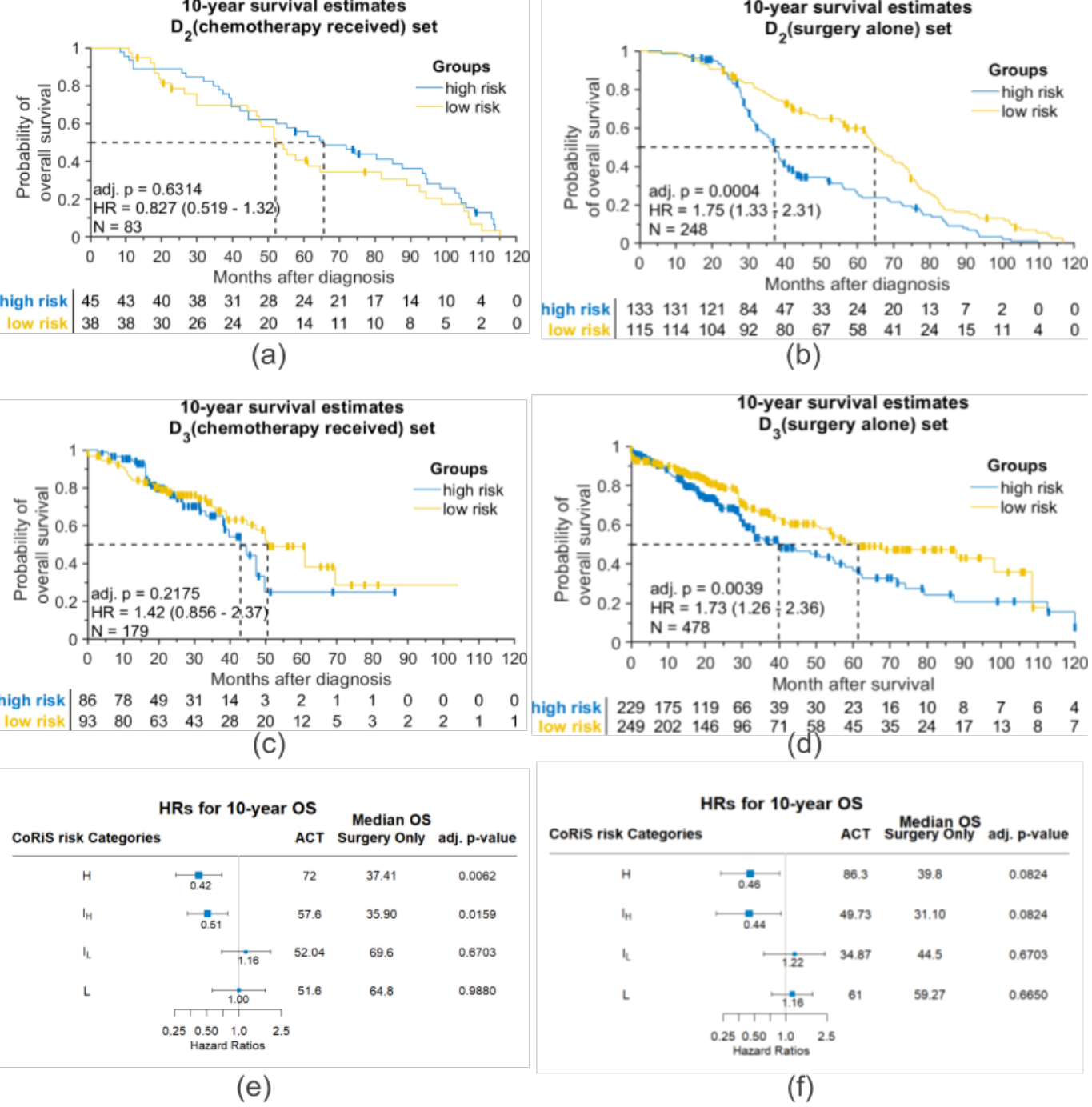


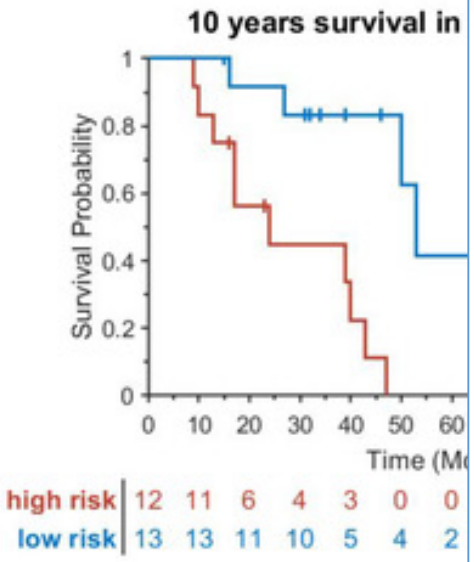
Figure 1. (A) Non-recurrent and (E) Recurrent NSCLC patient images. (A, E) TIL (green) and cancer nuclei cluster (red) construction, (B, F) number of proximal TIL clusters circumscribing each nuclear cluster, (C, G) Arrows show location of closest TIL cluster with respect to each cancer nuclei cluster, (D) receiver operating curve for both training and validation sets (AUC=0.78 for both sets) for the quadratic discriminant analysis in conjunction with the 12 most predictive features. (H) Kaplan-Meier curves showing separation between the recurrent and non-recurrent cases on the test set via the quadratic discriminant analysis in conjunction with the 12 most predictive features ($p < 10^{-7}$). *Note: nuclei cluster are closely encompassed by proximal lymphocyte clusters for patients with better outcome (see area and vertex of blue contour in B and F); nuclei cluster are guarded tightly by surrounding lymphocyte cluster (see the arrow source point in C and G).*

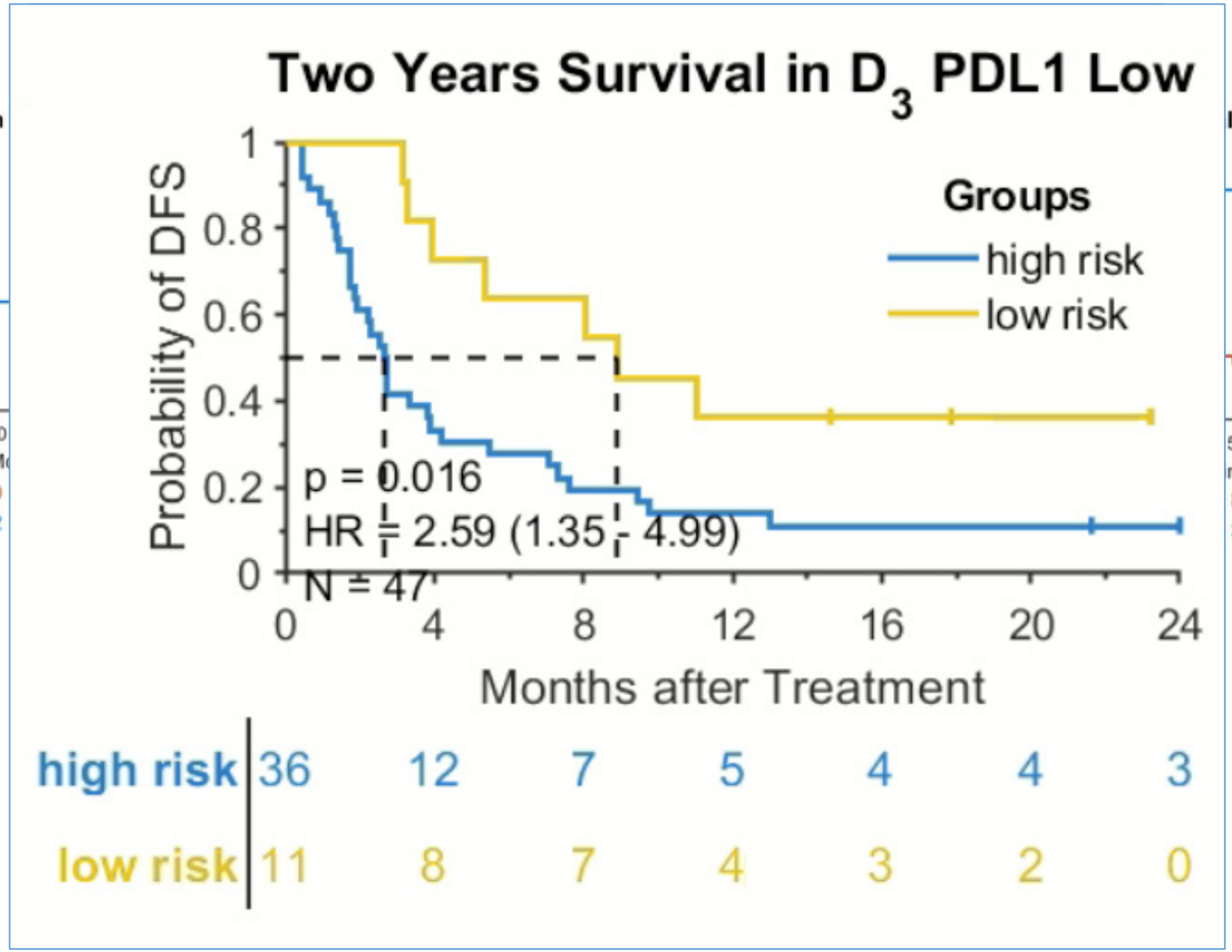
IbRiS is predictive of added benefit of adjuvant chemotherapy in early stage lung cancer

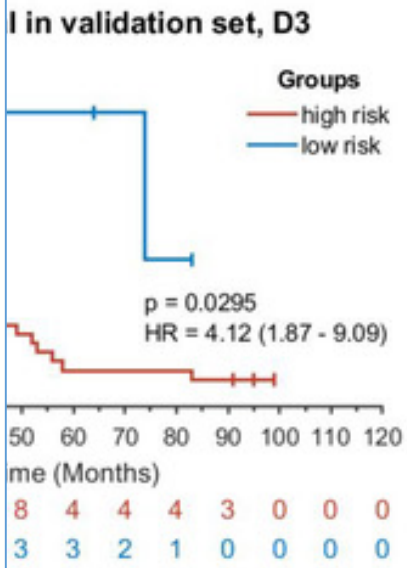


Kaplan-Meier plots showing predictive effect in CoRiS defined different risk of overall survival groups: (a) patients received adjuvant chemotherapy in D2; (b) patients only received surgery in D2; (c) patients received adjuvant chemotherapy in D3; (d) patients only received surgery in D3. Forest plots of different CoRiS defined risk of overall survival groups in (e) D2 and (f) D3.

Architecture of Tumor-Infiltrating Lymphocyte on H&E Slides Associated with Response and Outcome in IO Treated Lung Cancer



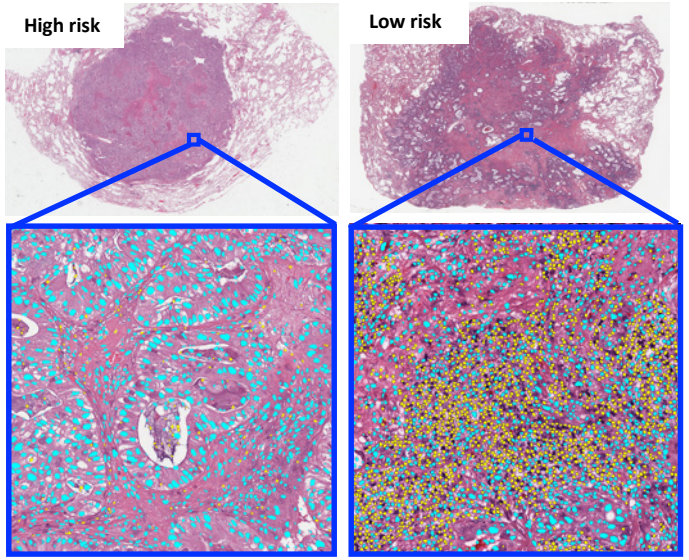


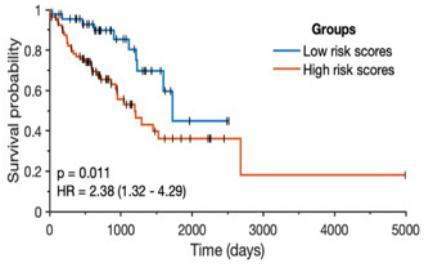


Computational Image Analysis of H&E and QIF Tissue Slides Reveals Morphologically and Molecularly Distinct Prognostic Patterns of Tumor Infiltrating Lymphocytes between Adenocarcinoma and Squamous Cell Carcinomas in Non-Small Cell Lung Cancer

Prognostic Model Construction Using TIL Features (N = 859)

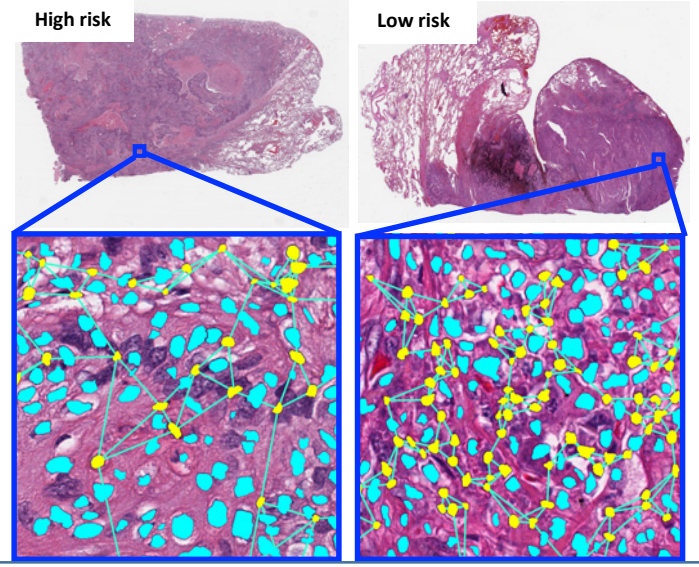
TIL density measures on LUAD

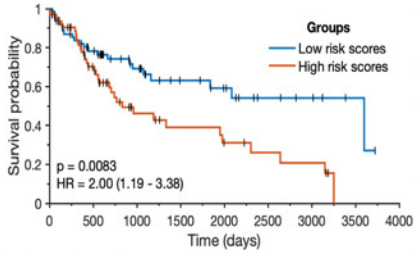




Yellow: TILs
Blue: non TILs

TIL spatial distribution on LUSC

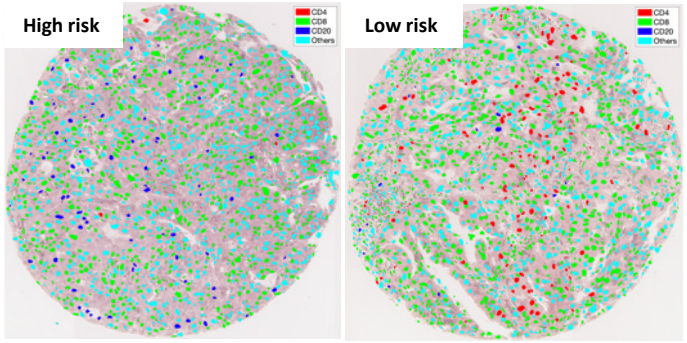


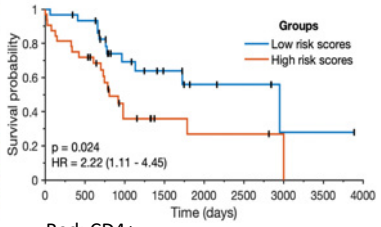


Yellow: TILs
Blue: non TILs

Contribution of TIL Subtypes to Prognostic Signatures (N = 83)

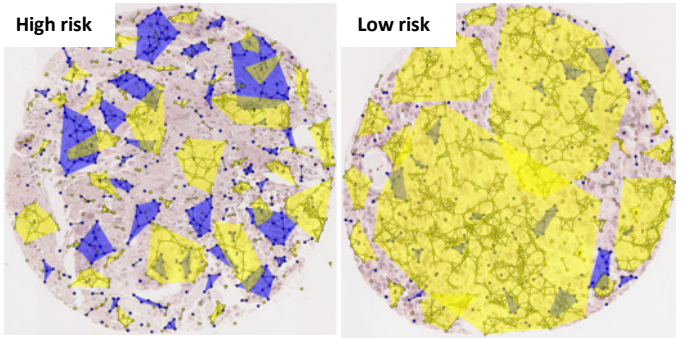
CD4+ density on LUAD

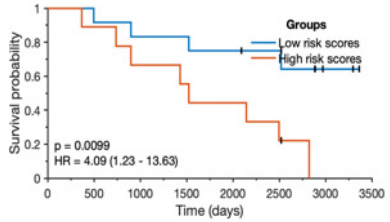




Red: CD4+
Green: CD8+
Blue: CD20+
Cyan: Other types

CD4+ vs CD8+ spatial interaction on LUSC



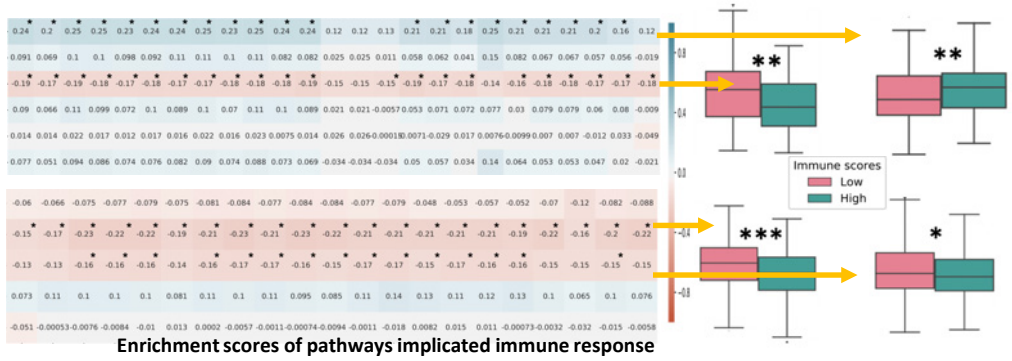


Yellow: CD8 clusters
Purple: CD4 clusters

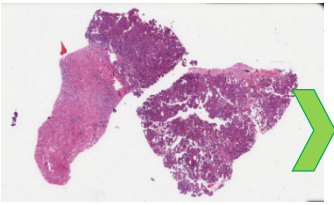
(N = 859) Association between Prognostic Signatures and 1) Biological Pathways 2) Immune Scores

Prognostic density features on LUAD

Prognostic spatial features on LUSC



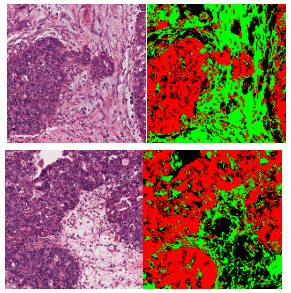
Predicting overall survival in Ovarian Cancer using SpaTIL



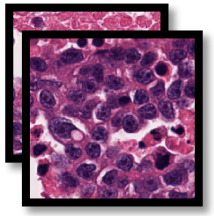
WSI

- Tile and Epithelial extraction

- Slicing of the WSI in 2000 x 2000 patches
- Segmenting the epithelial by DL model



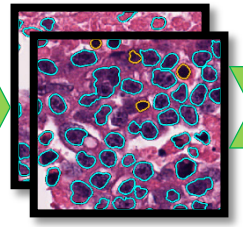
Segmented patches



Random patches within epithelial region

- Nuclei Detection
- Lymphocyte Identification

- Watershed nuclei segmentation
- Lymphocyte identification using shape features and SVM classifier



TILs and nonTILs segmented patches

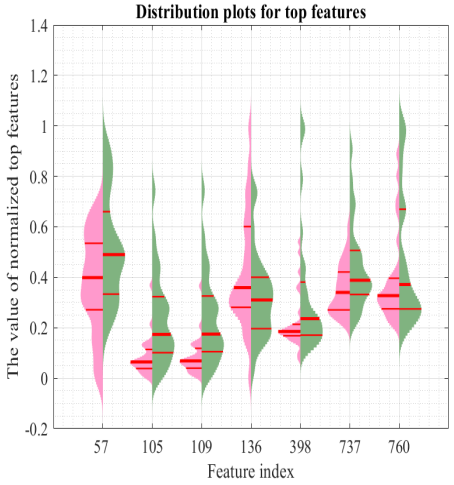
- Feature extraction

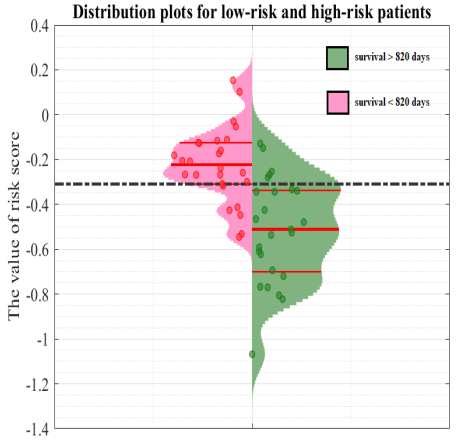
Interaction between TIL and nonTIL clusters in each patch

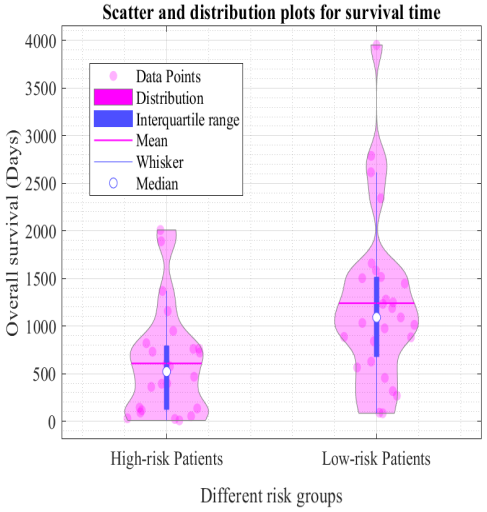
- LASSO feature selection

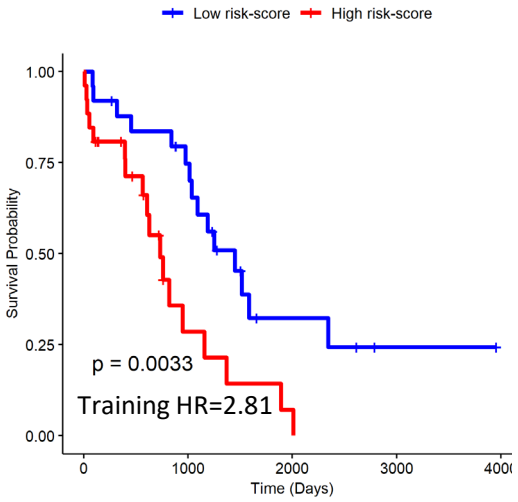
Extracting top features and calculating risk score

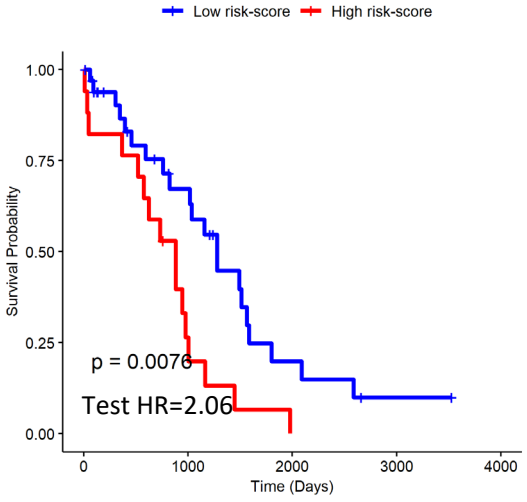
survival Analysis



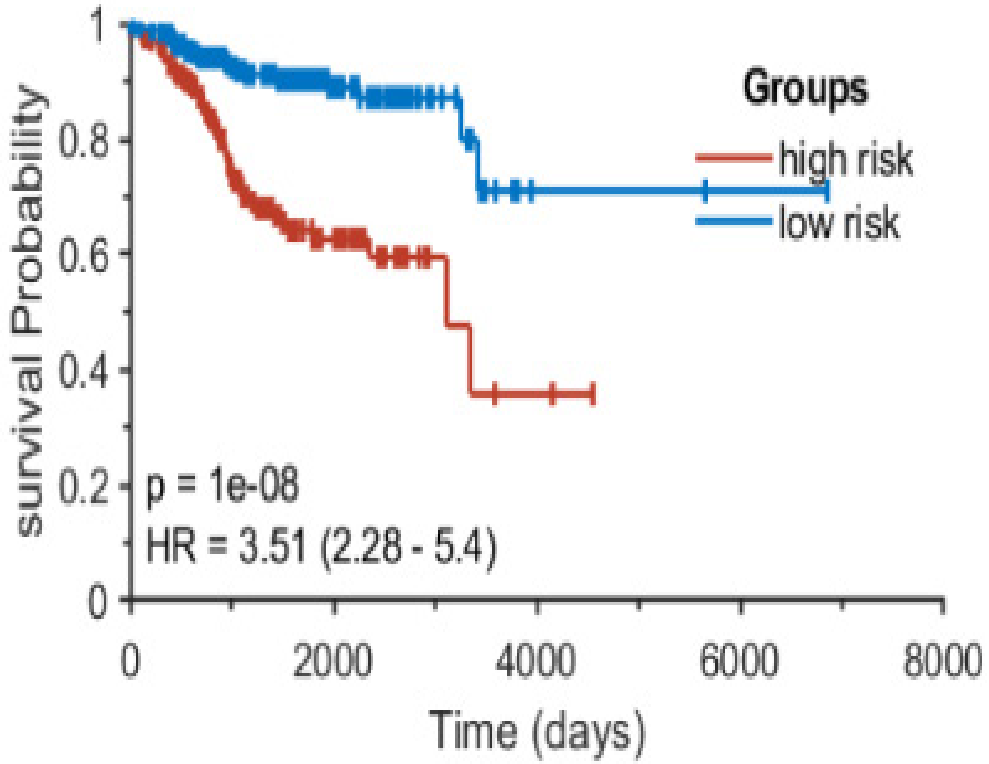




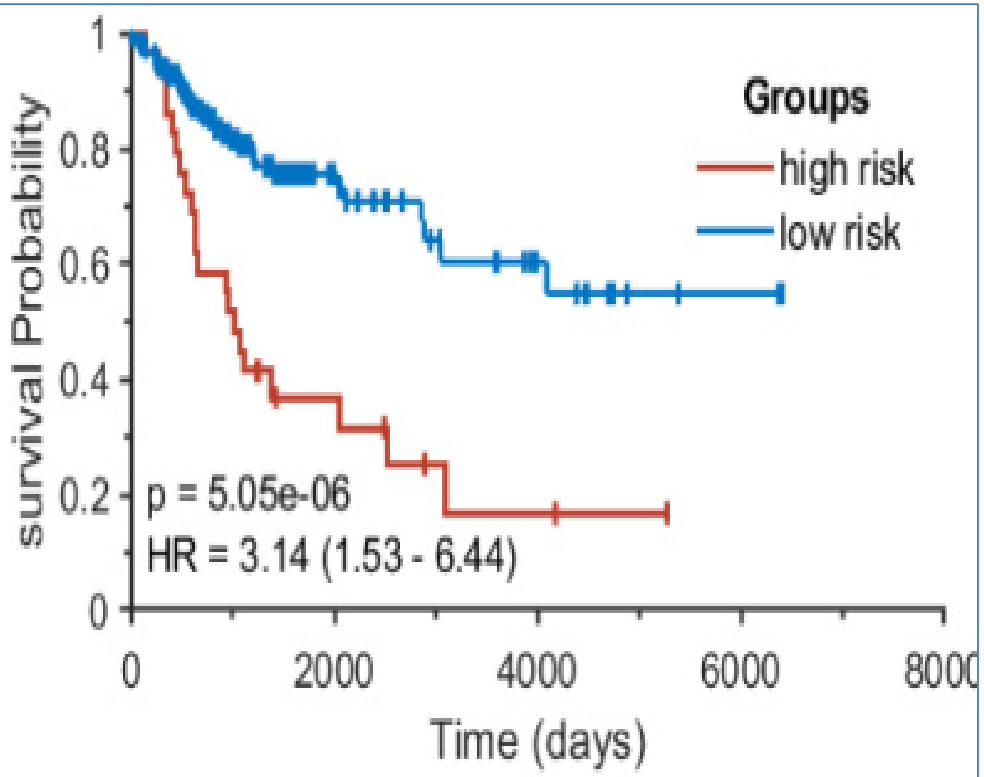




Predicting overall survival in Endometrial and Cervical Cancers using SpaTIL

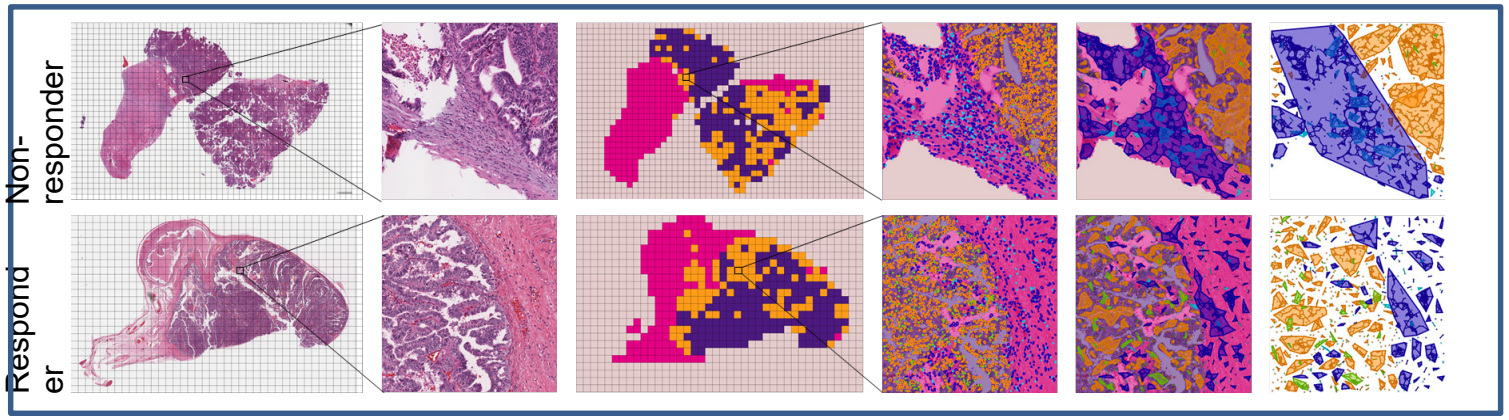


high risk	255	32	2	0	0
low risk	311	66	2	1	0

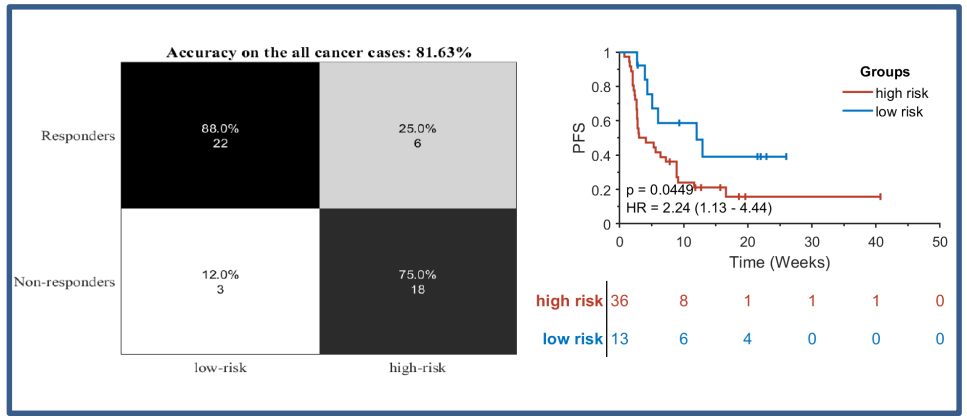


high risk	33	7	2	0	0
low risk	245	33	11	2	0

Spatial arrangement of TILs for predicting response to IO in gynecological cancers



A. Representative patch of short- (top) and long-term survivor (bottom). (cyan: stromal TILs, blue: stromal non-lymphocyte cells, green: epithelial TILs, orange: cancer-cells)



Confusion matrix and KM curves of high- (red) and low-risk groups (blue) in PFS of GC ICI-treated cohort (N=49, HR=2.24, CI=[1.13–4.44], p=0.045). (epithelial ovarian cancer: 14, endometrial: 28, cervical cancer: 7)

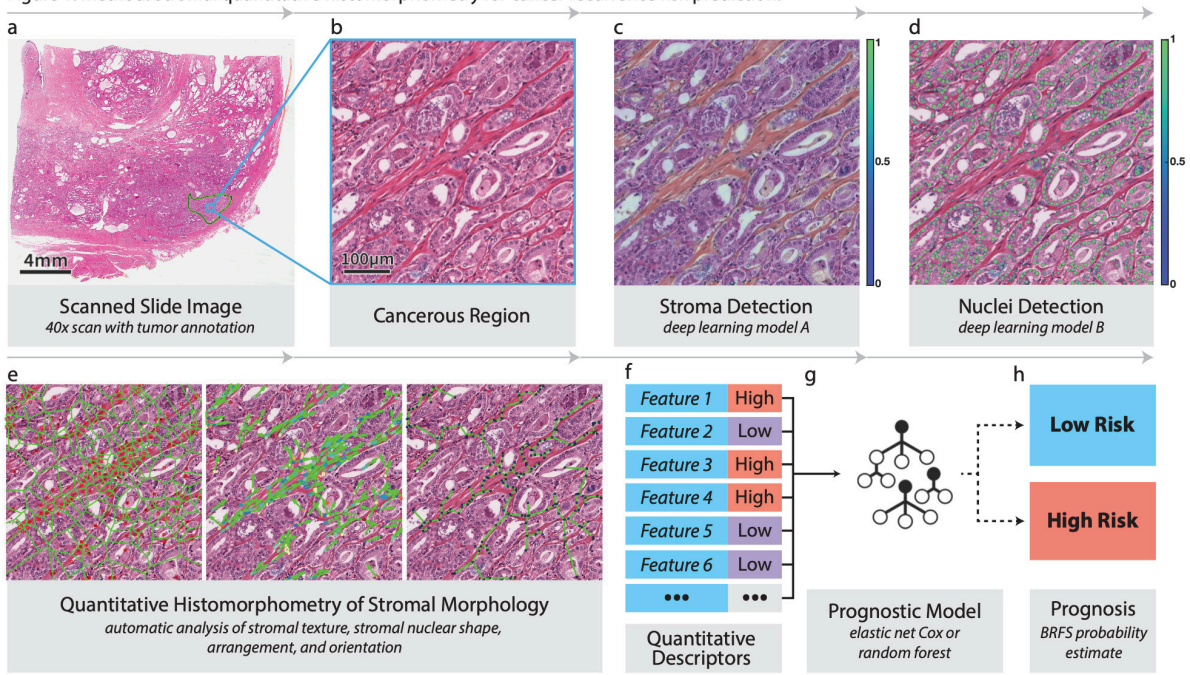
In non-responders, the epithelial TILs are scarce, but the stromal compartment contains groups of stromal TILs (cyan), resulting in larger areas of cell cluster graphs. However, in responders, the presence of epithelial TILs dispersed among cancer cells caused highly fragmented cluster graphs.

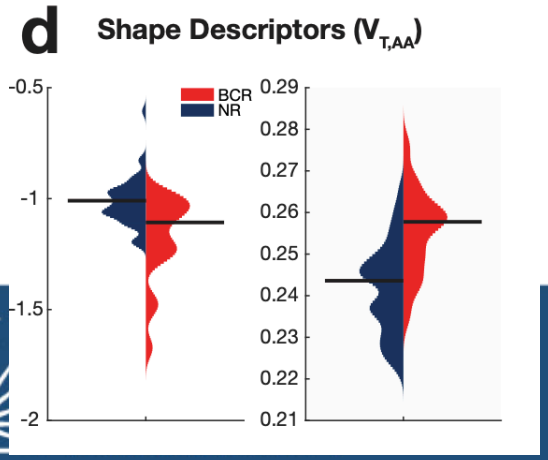
Takeaways

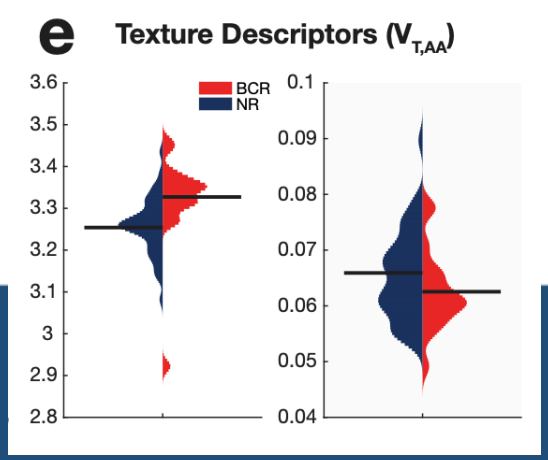
- **Arrangement of cell families appeared significantly different between responders and non-responders. There are generally more evenly-distributed and smaller clusters in responders.**
- **Sub-visual cell arrangement could potentially be used to identify early clinical response before administrating therapy**
- **Imaging features could potentially identify patients who are likely to derive clinical benefit from immunotherapy beyond clinical data.**

Prediction of Prostate Cancer Recurrence across Racial Groups using Computer-Extracted Features from Stromal Regions of Radical Prostatectomy H&E Slides

Figure 1. Method: Stromal quantitative histomorphometry for cancer recurrence risk prediction.







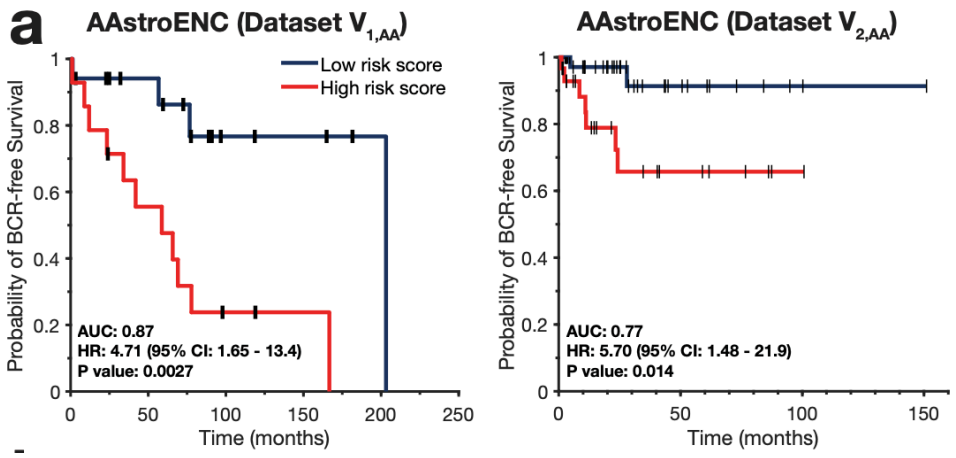


Figure 3. Association of stromal image features with IHC-derived tumor biomarker expression levels.

a

Marker Expression
immunohistochemistry

PTEN	TMPRSS2-ERG
PSMA	P-53
Racemase	C-MYC
Androgen Rec.	Ki-67
EZH2	Retinoblastoma

Stromal Features
quant. histomorphometry

- Texture
- Shape
- Orientation
- Arrangement

b

Biomarker-Correlated Stromal Descriptors

Biomarker	Stromal Feature	Corr.	P value	Prognostic?
Retinoblastoma	Shape: Mean Fract. Dimension	0.606	4.97E-04	Yes
TMRPSS2-ERG	Texture: Mean Info. Measure 1	-.447	3.26E-02	Yes
Androgen Rec.	Shape: Mean Fract. Dimension	0.414	4.12E-04	Yes
Retinoblastoma	Shape: Mean Invar. Moment 2	-.601	5.59e-04	No
PTEN	Shape: Fourier Descriptor 4	-.623	7.56E-03	No
PTEN	Shape: Fourier Descriptor 3	-.605	1.01E-02	No
ERG	Arrang: Triangle Area Disorder	-.557	5.72E-03	No
C-Myc	Arrang: STDEV Edge Length	.446	2.38E-03	No
•••				

Conclusion: A model trained on AA patients to distinguish BCR+/- performs better on the AA validation set than one trained on a mixture of AA+CA patients.

Center for Computational Imaging & Personalized Diagnostics

Clinical Cancer Research, 2020

Computerized image analysis reveals differences in early stage ER+ breast cancer phenotype of South Asian and North American women

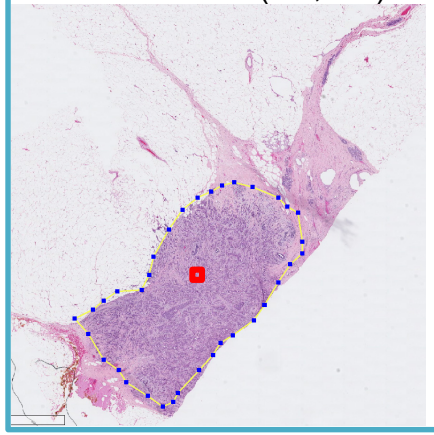
Unmet Clinical Need

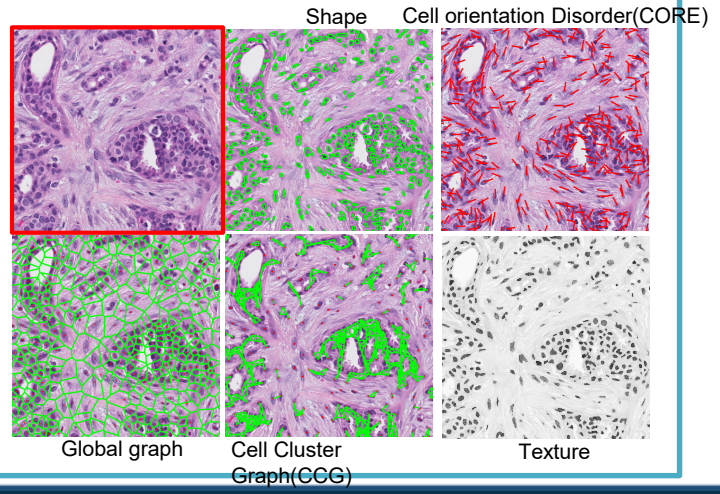
- Racial/ethnic disparity in incidence and mortality in breast cancers.
- Indian women more likely to be diagnosed with advanced breast cancer despite lower incidence than American women.
- The studies of digital pathology in breast cancer prognosis were mostly focused on American women.

Methods and Results

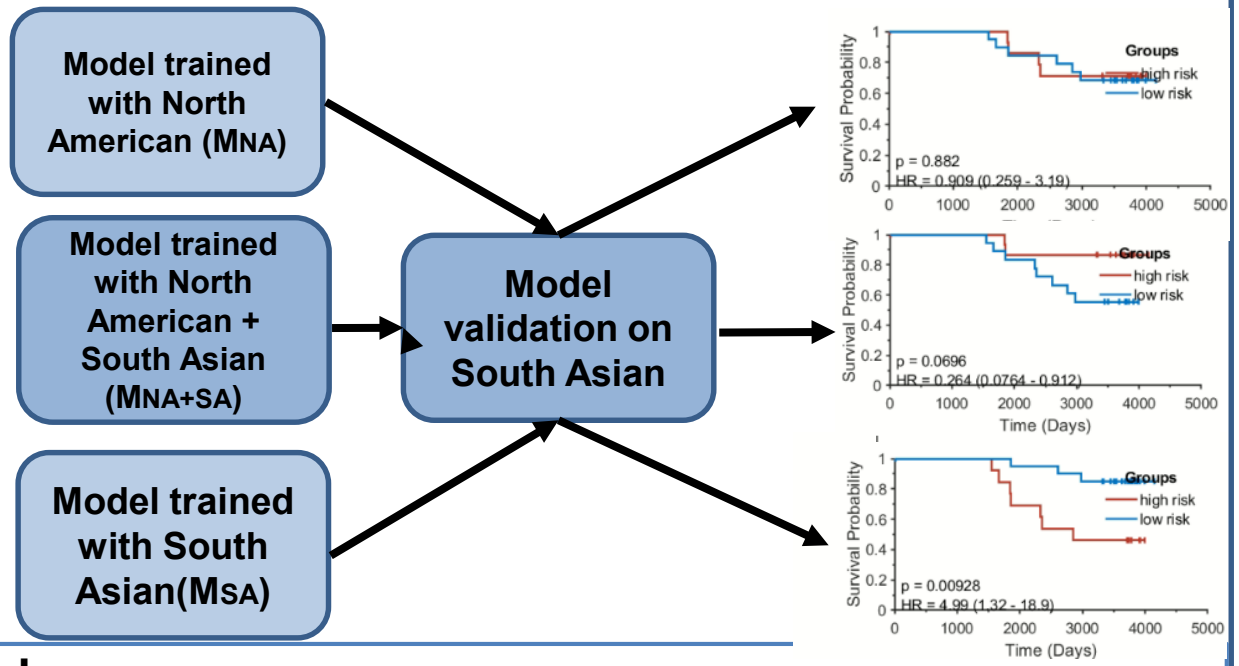
Data Description → Extraction of nuclear morphological features

South Asian (SA, Indian): N=69
North American (NA, US): N=121





Model construction on training set → Validation on SA in testing set



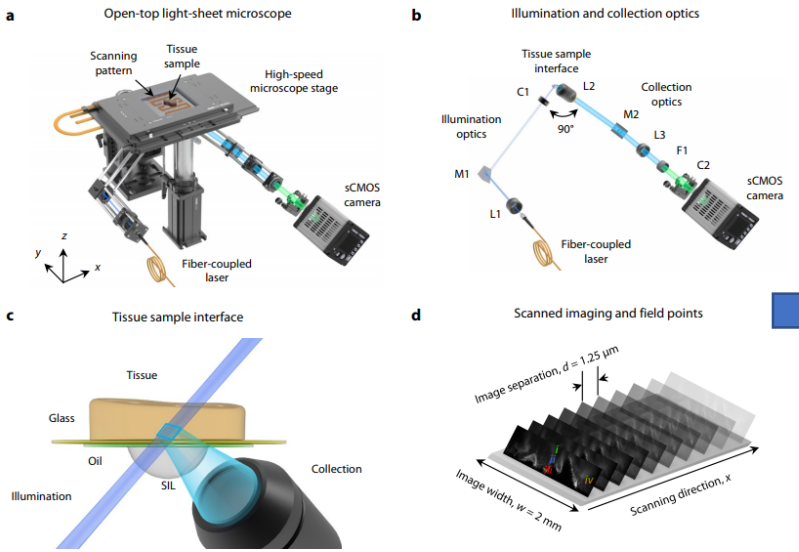
Take away:

Prognostic ability of the computational pathology based models for South Asian women with breast cancer could be significantly improved by taking into account of population-specific information.

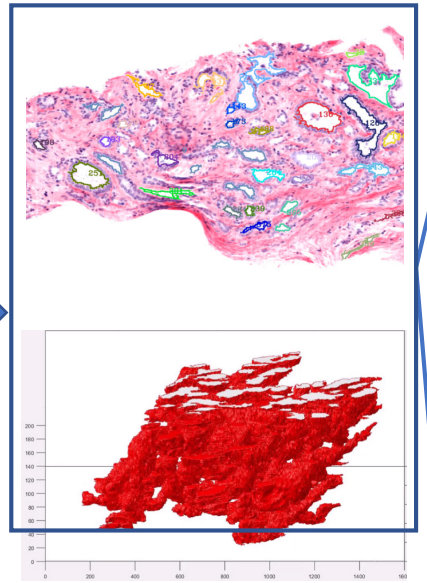
CASE SCHOOL OF ENGINEERING
CASE WESTERN RESERVE UNIVERSITY

The Center for Computational Imaging & Personalized Diagnostics

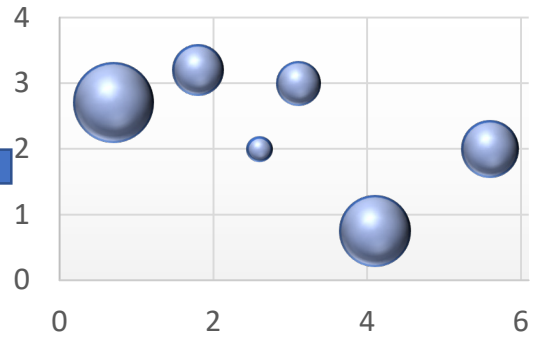
3D lumen-feature extraction from prostate pathology images of light-sheet microscopy for better Gleason score definition



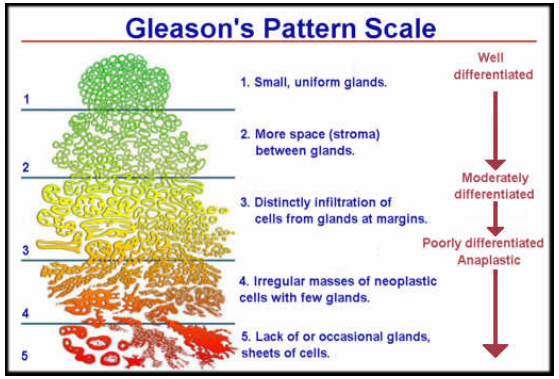
3D image acquisition from light-sheet microscopy [1]



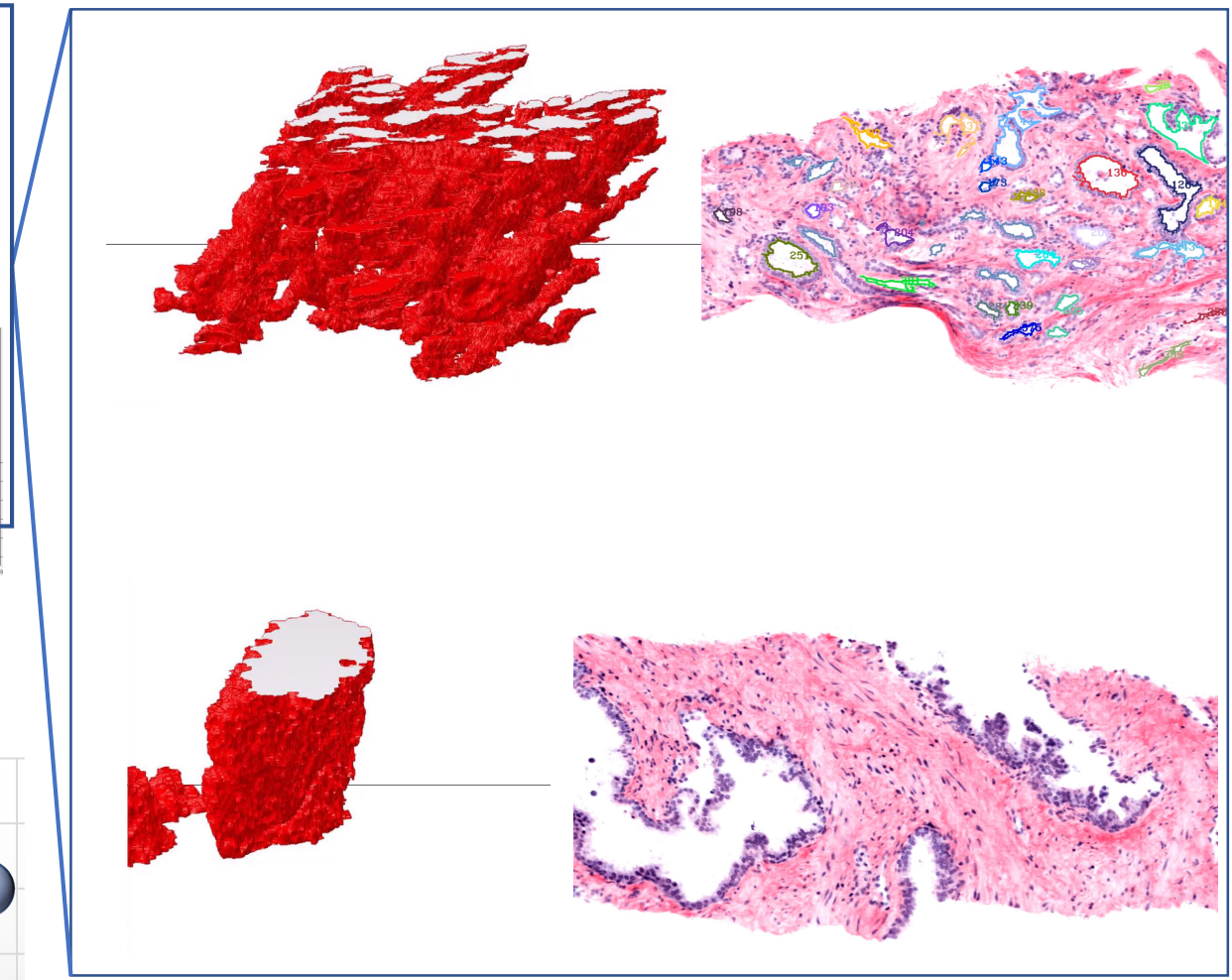
3D lumen segmentation



3D feature extraction



Better Gleason score definition in 3D space [2]



[1] ***Glaser A. K., et al.***, *Light-sheet microscopy for slide-free non-destructive pathology of large clinical specimens*, Nat. Biomed. Eng.2017, 1, 0084.
[2] *Image is obtained from the link:* https://www.prostateconditions.org/about-prostate-conditions/prostate-cancer/newly-diagnosed/gleason-score

Take Away

- **Computational Analytics with routine imaging** could help address questions in precision medicine, specifically prognosis and predicting response to therapy
- **Low cost** computational diagnostics
- **Global impact**, especially **low and middle income** countries.
- Multi-scale disease associations, looking to establish the morphologic and molecular basis of the imaging features. Need an intuitive basis to drive clinical adoption

Acknowledgements

- National Cancer Institute: U24CA199374-01, R01CA202752-01A1, R01CA208236-01A1, R01 CA216579-01A1, R01 CA220581-01A1
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- the Ohio Third Frontier Technology Validation Fund
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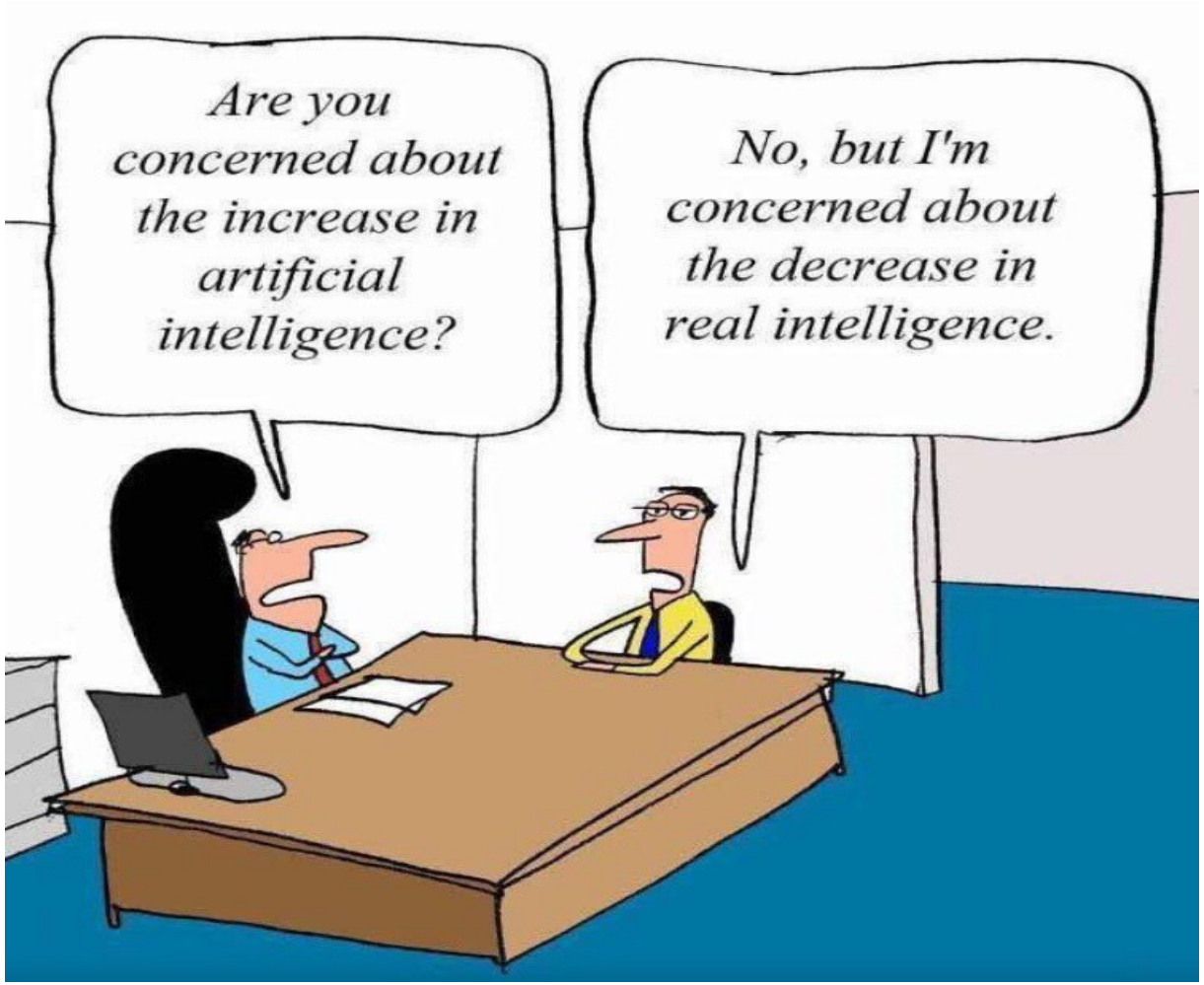
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No, but I'm concerned about the decrease in real intelligence.


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