Digital Pathomics - An Alternative to Deep Learning to Prognosticating Disease Outcome

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

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The Lifetime Probability of Developing Cancer for Men, 2009-2011*

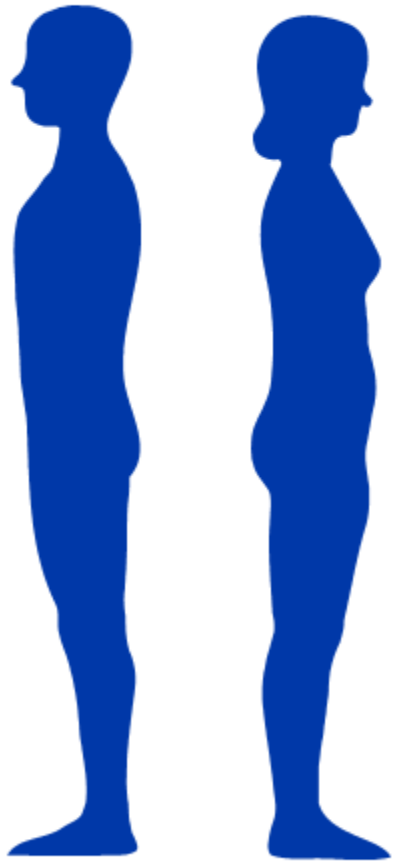
Site	Risk
All sites†	1 in 2
Prostate	1 in 7
Lung & bronchus	1 in 13
Colon & rectum	1 in 21
Urinary bladder‡	1 in 26
Melanoma of the skin §	1 in 34
Non-Hodgkin lymphoma	1 in 42
Kidney & renal pelvis	1 in 49
Leukemia	1 in 59
Oral cavity & pharynx	1 in 65
Pancreas	1 in 66

* For those free of cancer.
† All sites exclude basal cell and squamous cell skin cancers and in situ cancers except urinary bladder.
‡ Includes invasive and in situ cancer cases
§ Statistic for white men.

Source: DevCan: Probability of Developing or Dying of Cancer Software, Version 6.7.1 Statistical Research and Applications Branch, National Cancer Institute, 2014.

Estimated Cancer Deaths in the US in 2015

Men 312,150		Women 277,280	
Lung & bronchus	28%	26%	Lung & bronchus
Prostate	9%	15%	Breast
Colon & rectum	8%	9%	Colon & rectum
Pancreas	7%	7%	Pancreas
Liver & intrahepatic bile duct	5%	5%	Ovary
Leukemia	5%	4%	Leukemia
Esophagus	4%	4%	Uterine corpus
Urinary bladder	4%	3%	Non-Hodgkin lymphoma
Non-Hodgkin lymphoma	4%	3%	Liver & intrahepatic bile duct
Kidney & renal pelvis	3%	2%	Brain & other nervous system
All other sites	24%	23%	All other sites



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*

PATHOMICS

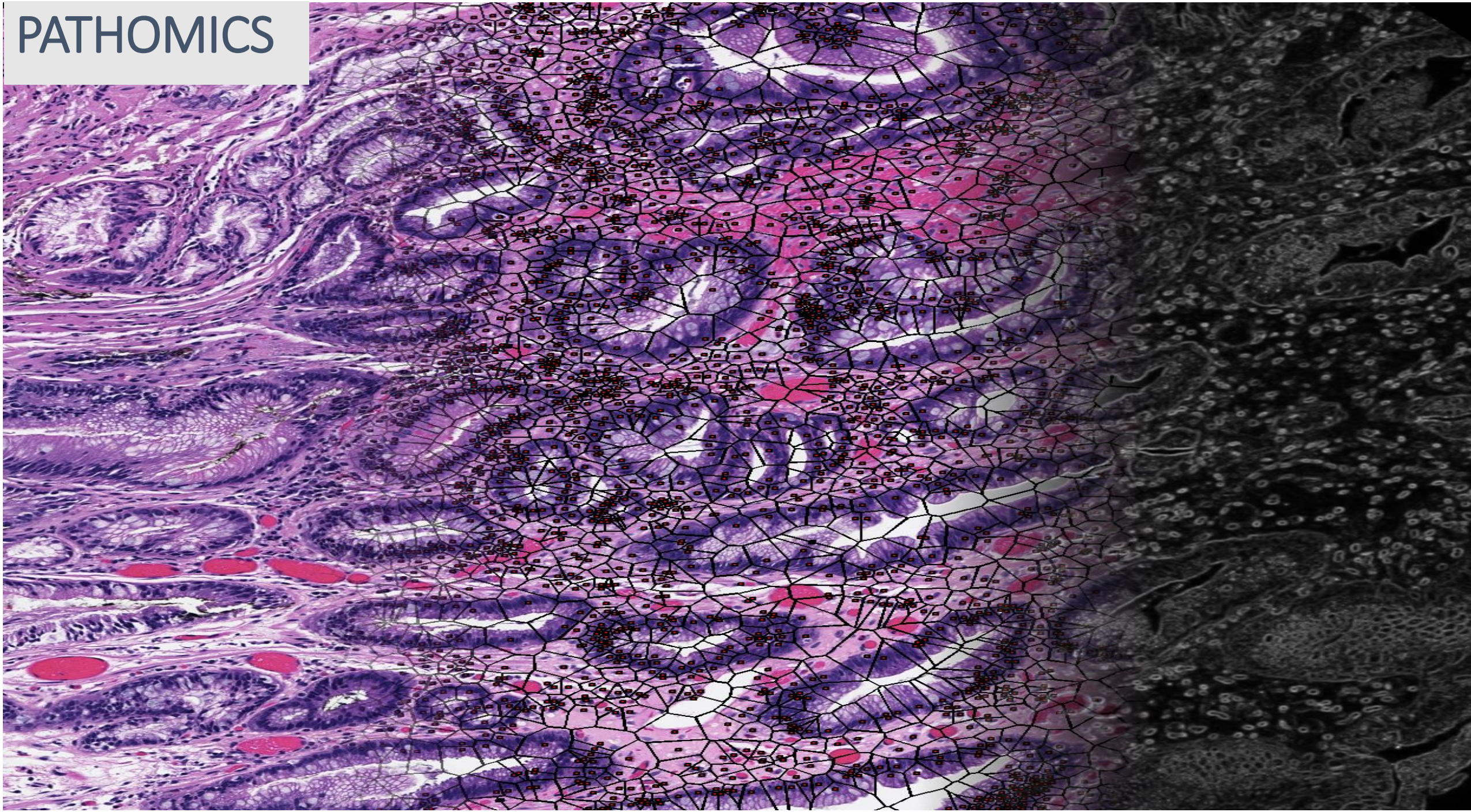
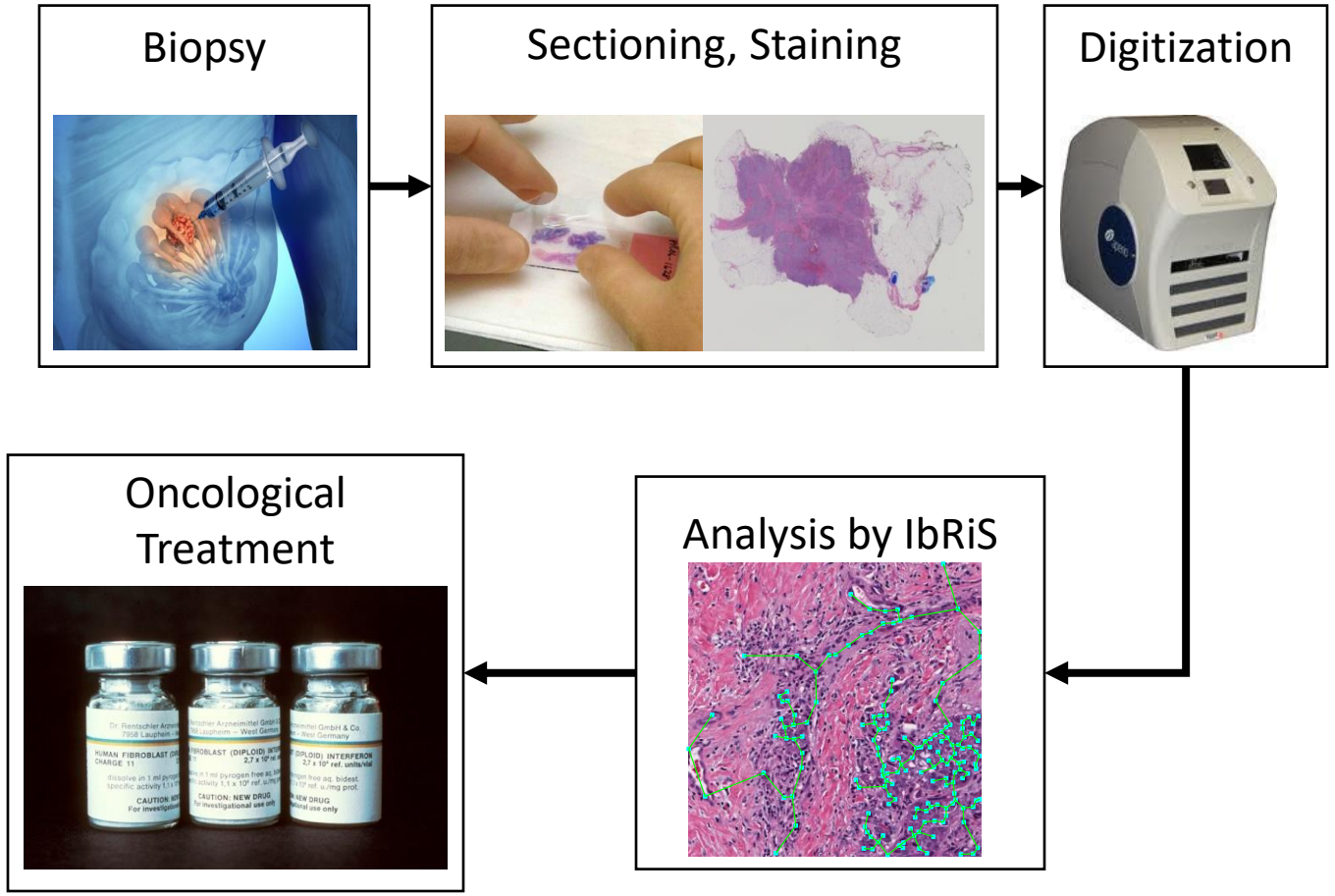
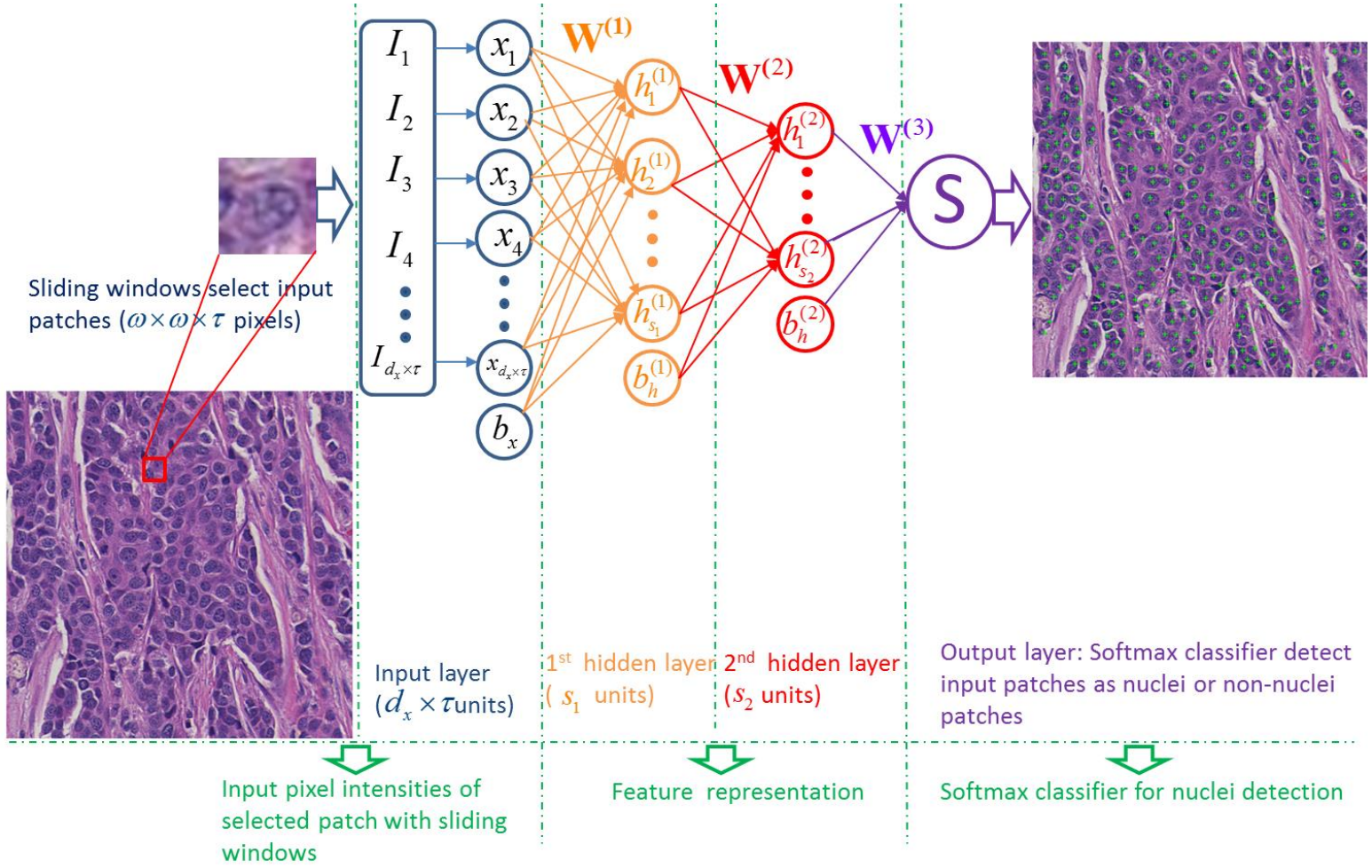


Image-based Risk Score (Ibris)



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.

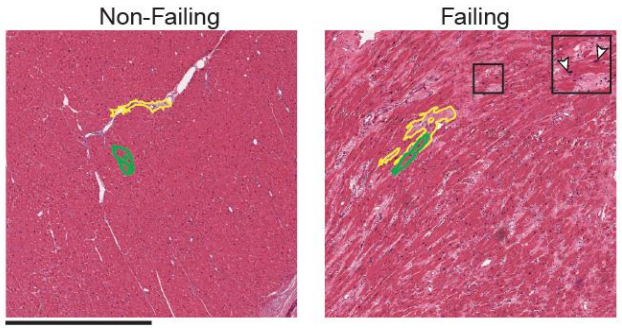
***Xu J**, et al.* "Stacked Sparse Autoencoder (SSAE) for Nuclei Detection on Breast Cancer Histopathology". *IEEE Trans. on Medical Imaging,* 2015

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

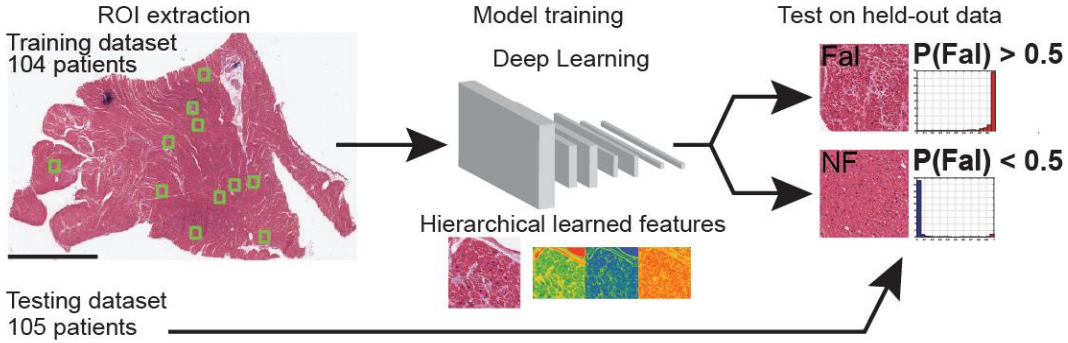
Lu C, Xu H, ***Xu J***, Mandal M, and Madabhushi A, "Multiple Passes Adaptive Voting for Nuclei Detection in Histopathlogical Images", *IEEE Journal of Biomedical and Health Informatics, (Under Preparing)*

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

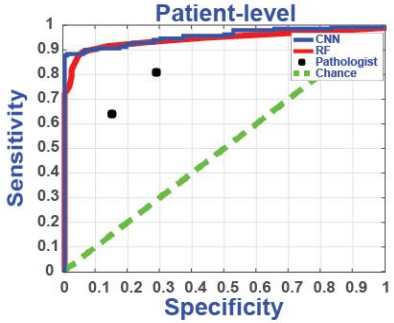
a Cardiac histopathology in heart failure



b Training a deep convolutional neural network



c Detection of clinical heart failure

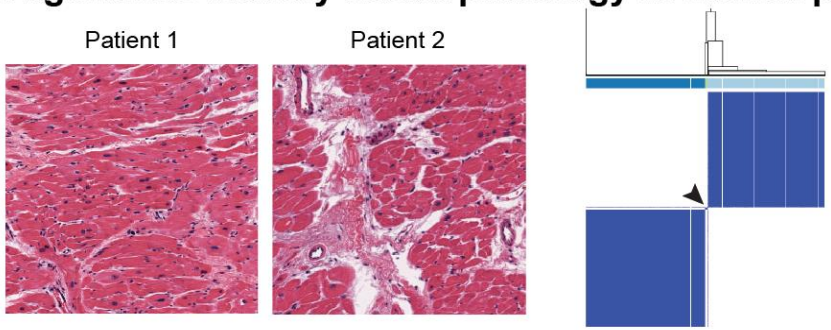


Performance evaluation

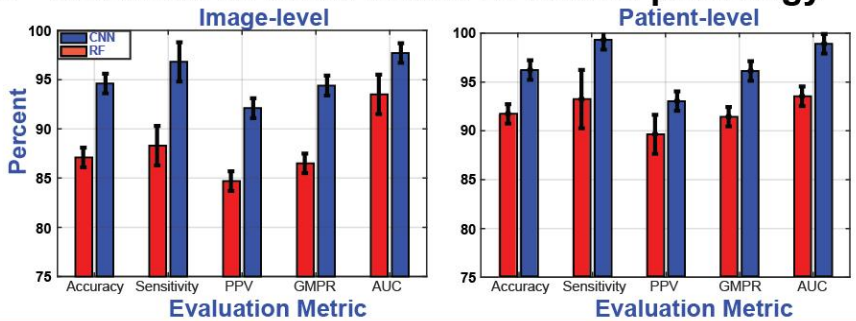
	CNN	Pathologists	
Accuracy	0.94±0.01	0.75	0.75
Sensitivity	0.99±0.01	0.81	0.64
Specificity	0.89±0.01	0.71	0.85
PPV	0.88±0.01	0.69	0.77
AUC	0.97±0.01	0.75	0.73

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

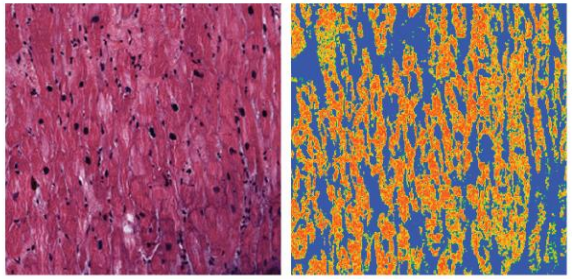
d Algorithms identify tissue pathology in normal patients



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

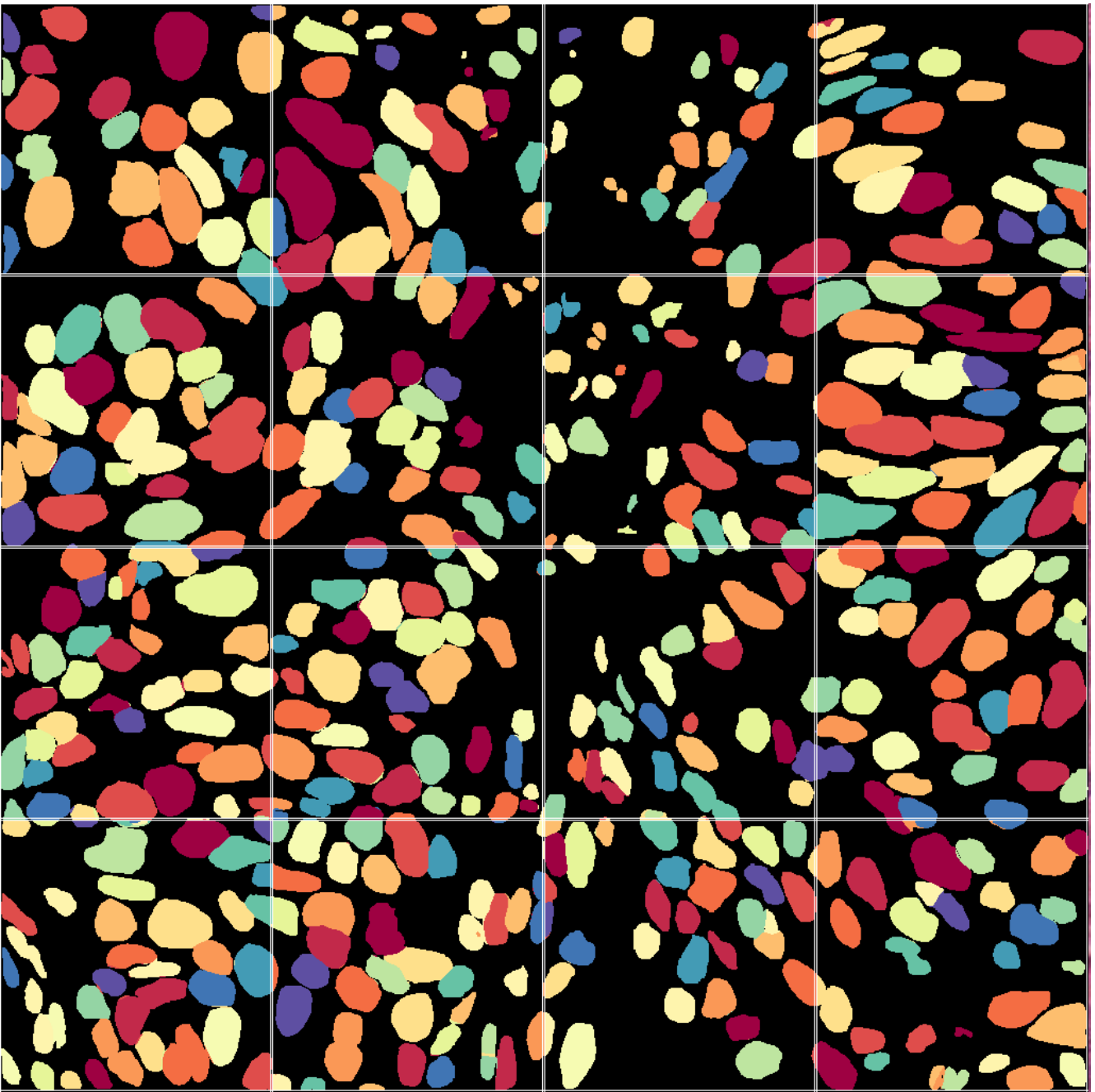
Husky or Wolf? Using a Black Box Learning Model to Avoid Adoption Errors

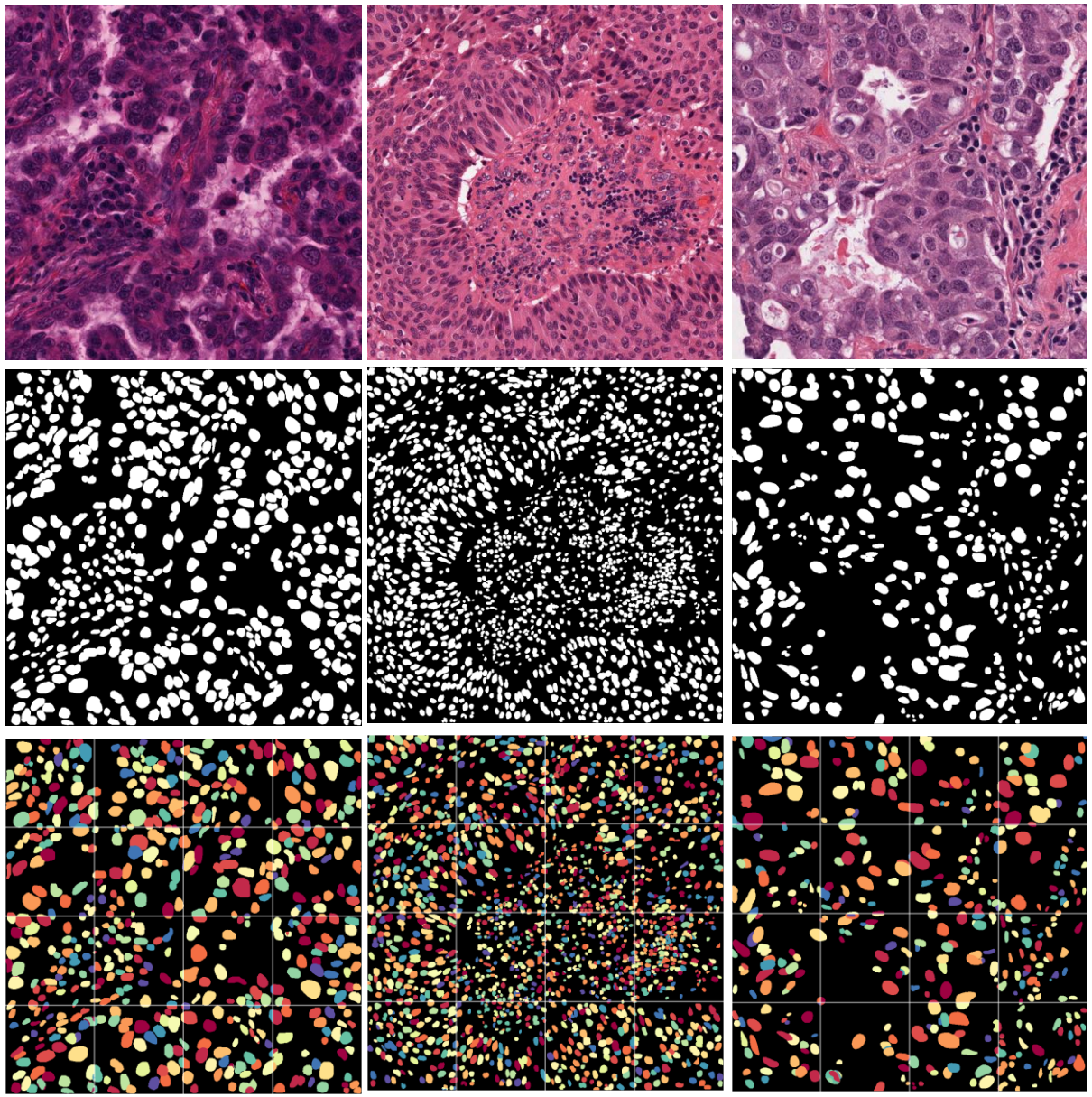
Past Tides

August 24, 2017 By Wendy Wolfson

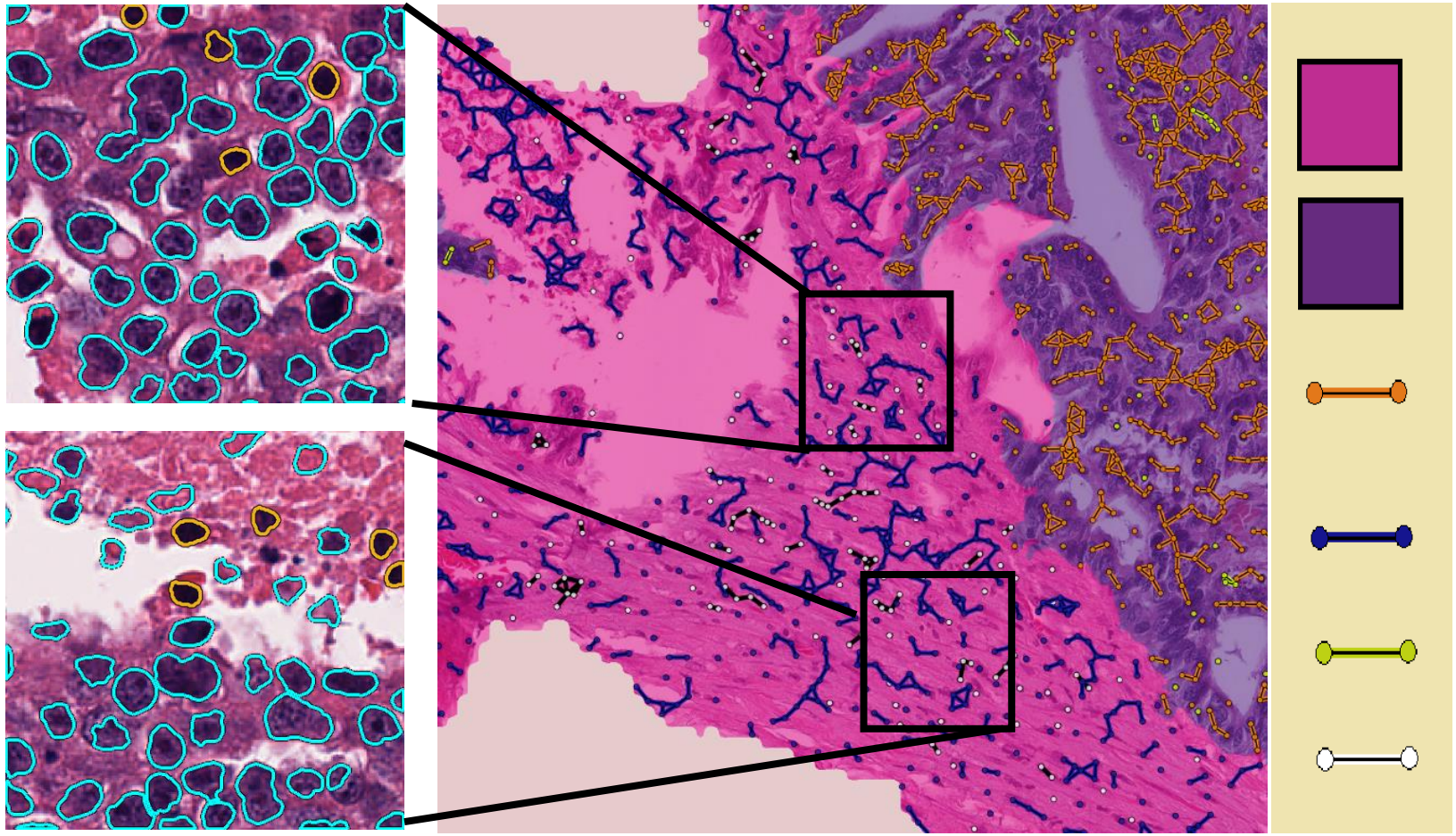
Say you want to adopt a dog, from a picture, and you task your machine learning system to classify the image as either a husky, which would be safe to adopt, or a wolf, which probably is not a good idea. Can you get that photograph classified with certainty? “Because researchers don’t have insights into 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.

Instance Segmentation and GANs





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

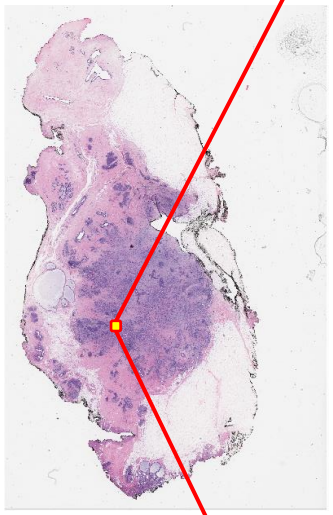
Epithelium segmentation

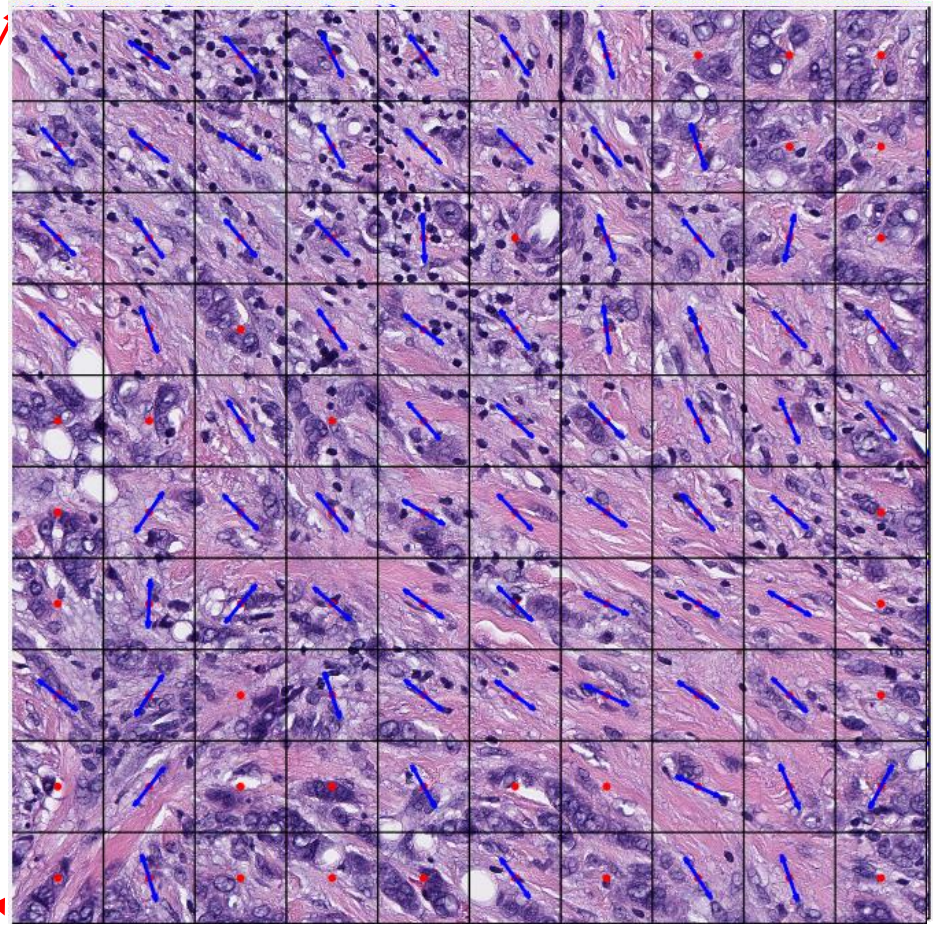
Collagen vectors in tumor-associated stroma

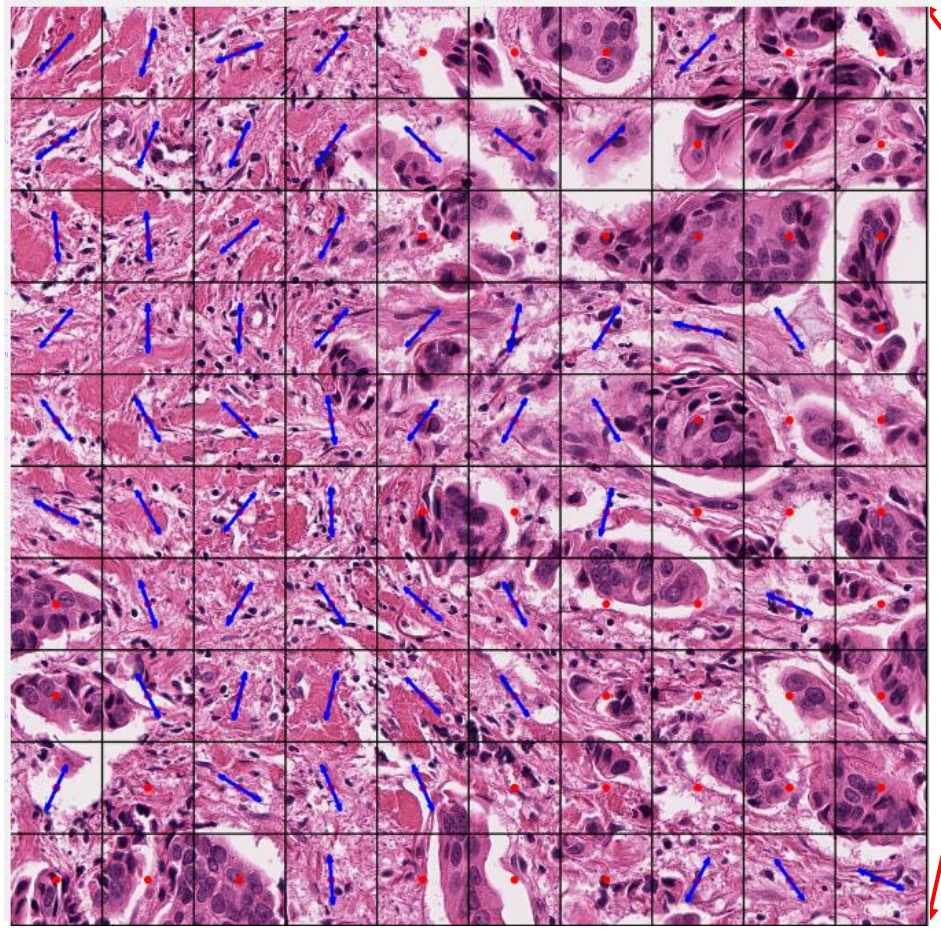
Collagen fiber orientation disorder calculation

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

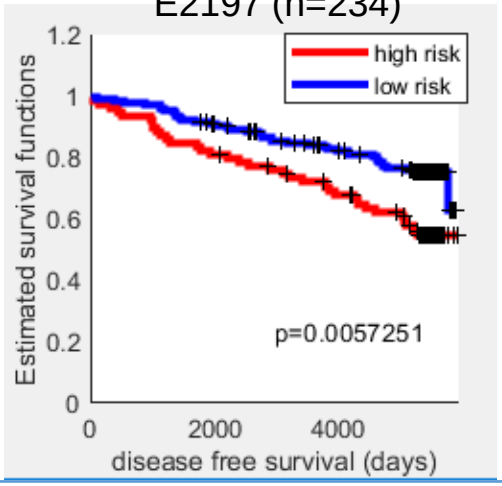
Unmet Clinical Need

- 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.

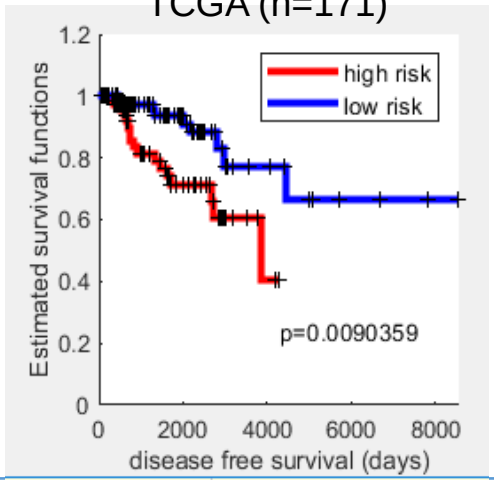
Results:

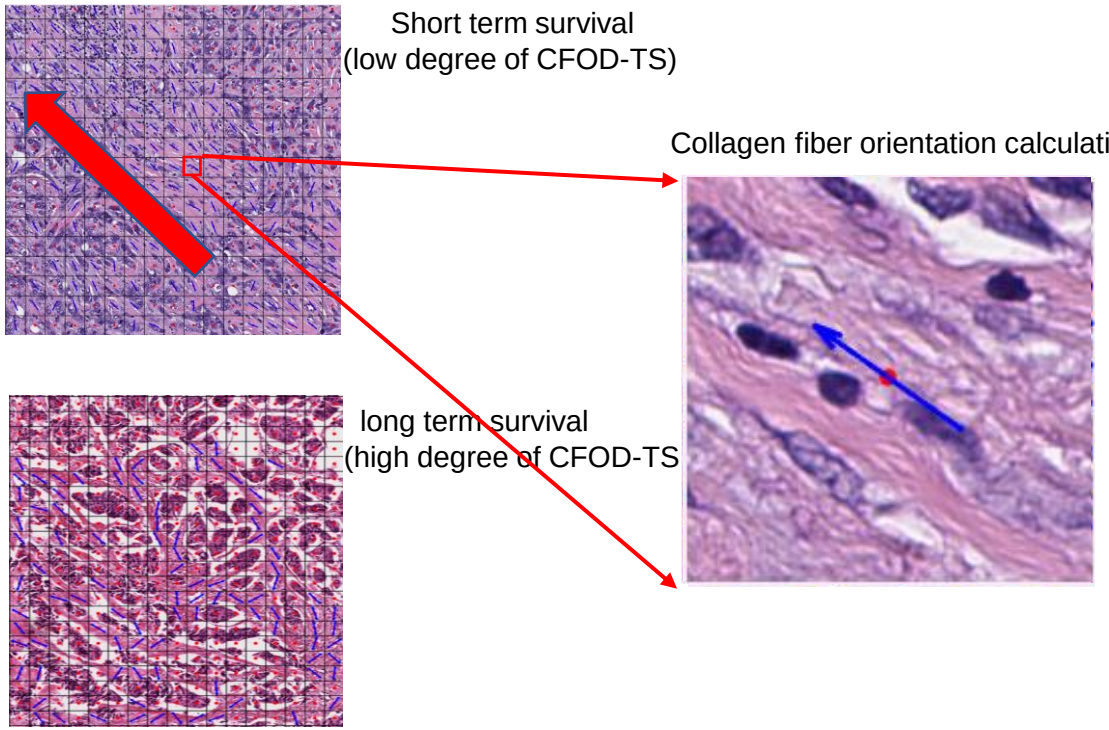
- Collagen Fiber Orientation Disorder in Tumor associated Stroma (CFOD-TS) was independently prognostic for ER+ BCs in E2197 and TCGA.

E2197 (n=234)



TCGA (n=171)





Take away:

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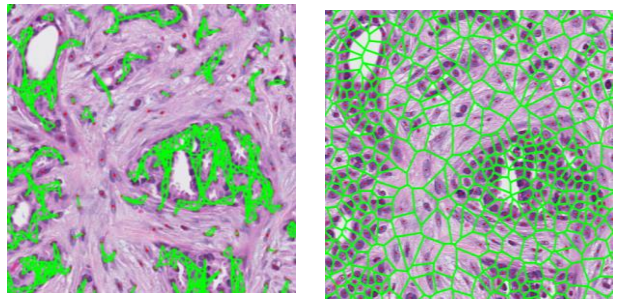
Combination of Computer Extracted Features of Nuclear morphology, Tubular Formation, and Mitotic Count from H&E Images Predict Disease Free Survival in Estrogen Receptor Positive (ER+) Breast Cancer

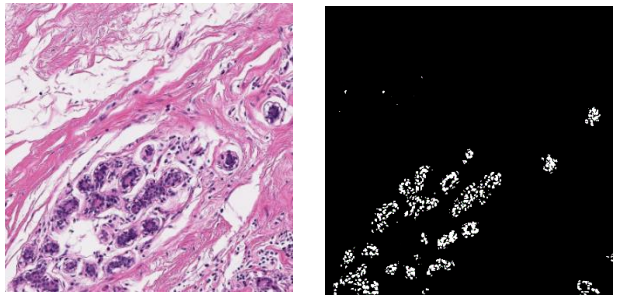
Background

- 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.

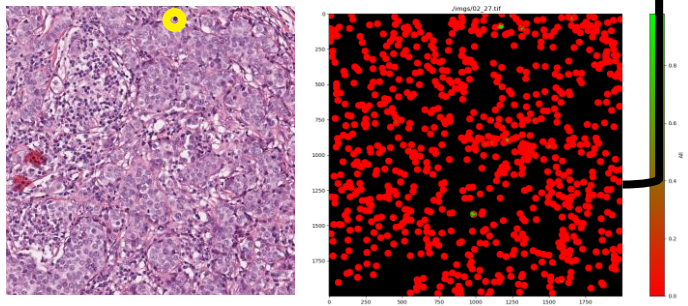
Nuclear morphology



Tubule formation



Mitotic count



Model construction for LN-

Feature combination

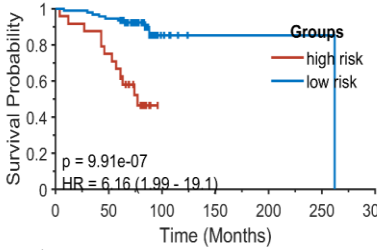
Model construction for LN+

Results

Independent validation on 2 sites

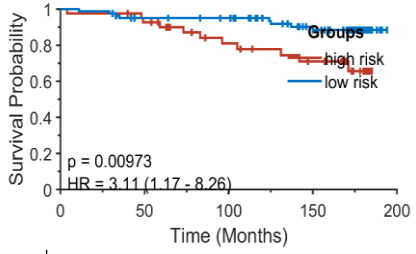
- **LN-**

Train on UH (116 patients)



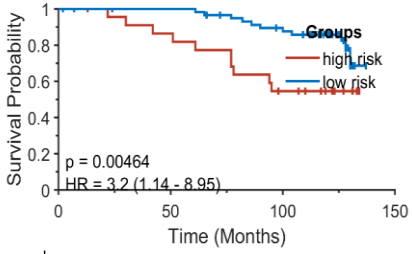
high risk	24	18	0	0	0	0	0
low risk	92	87	6	1	1	1	0

ECOG2197 (121 patients)



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

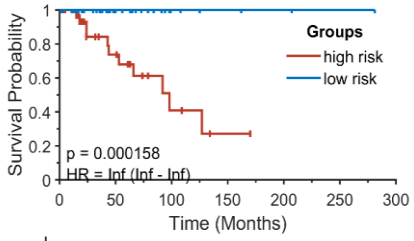
Tata (85 patients)



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

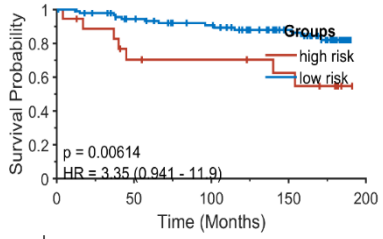
- **LN+**

Train on TCGA (83 patients)



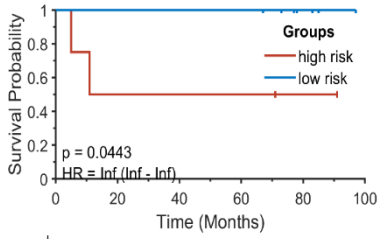
high risk	41	14	4	1	0	0	0
low risk	42	18	5	3	2	1	0

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.

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)

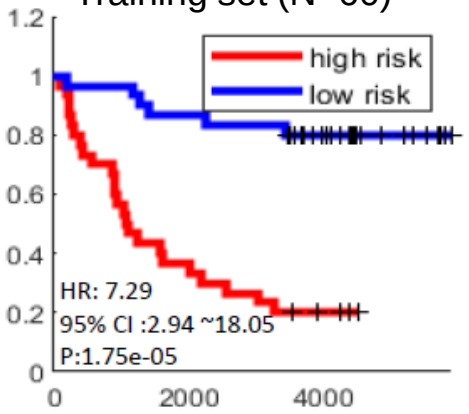
Unmet Clinical Need

- 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

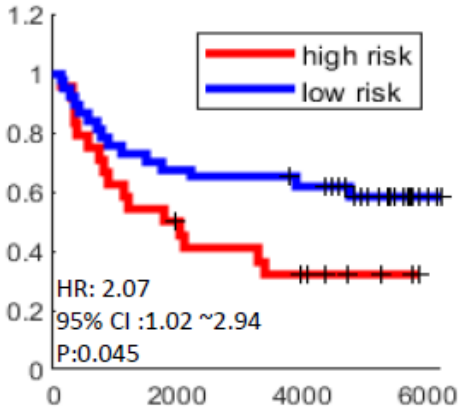
The Cox regression model built with nuclear morphologic features is prognostic of DCIS

Training set (N=60)



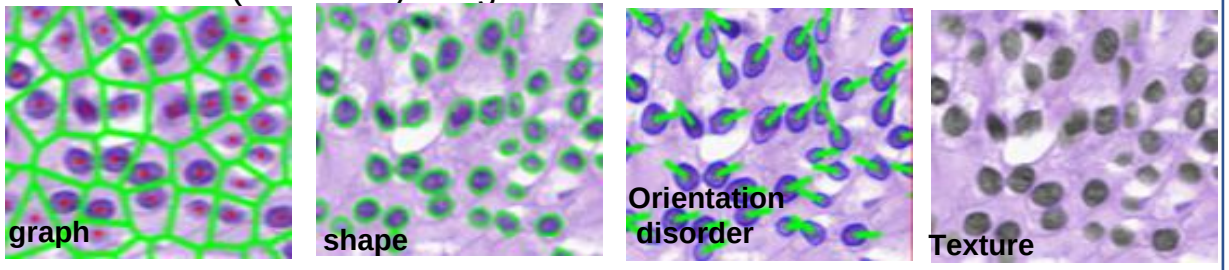
Disease Free survival (days)

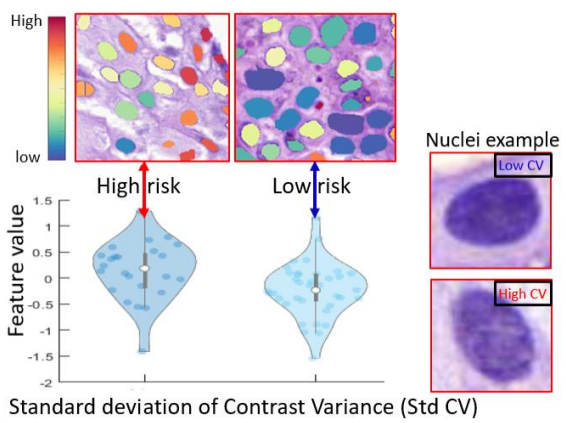
Validation set (N=61)

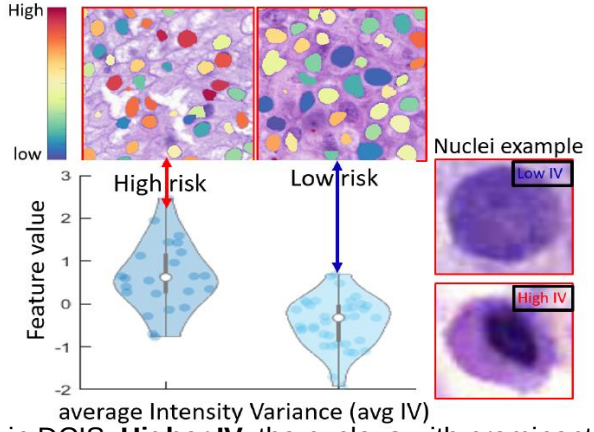


Disease Free survival (days)

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.

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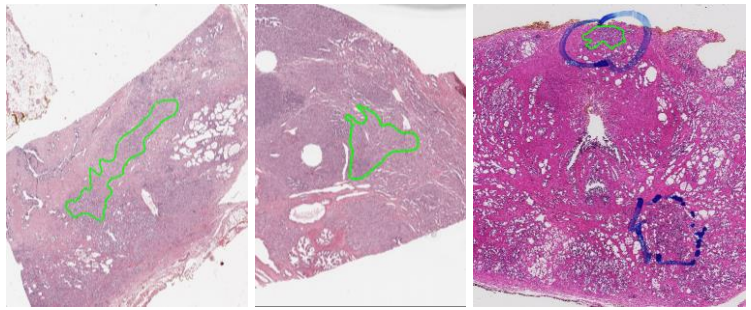
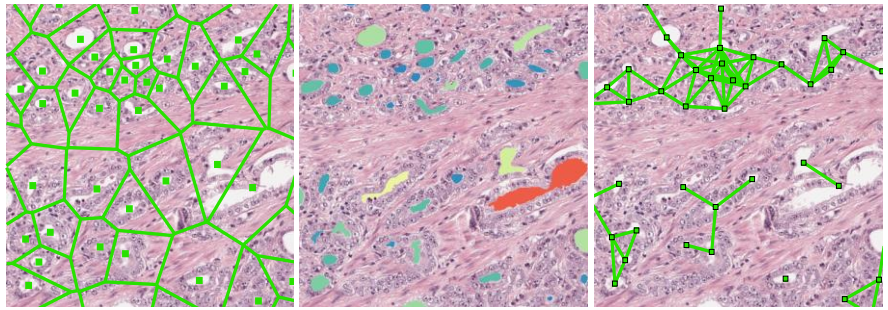
Predicting post-surgical recurrence in prostate cancer

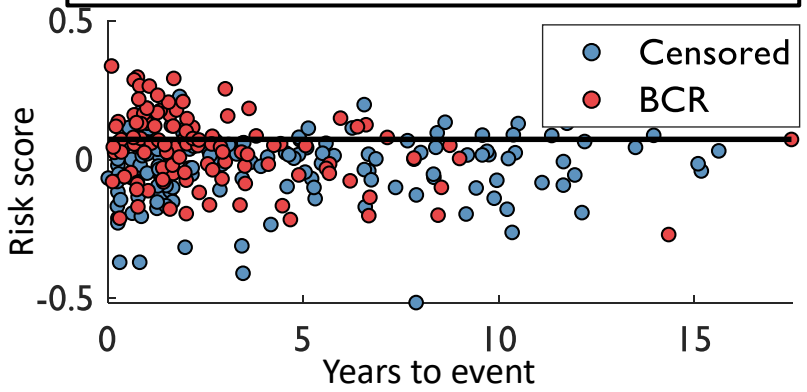
N=907 diagnostic slides from 6 sites



Extract 216 gland lumen features

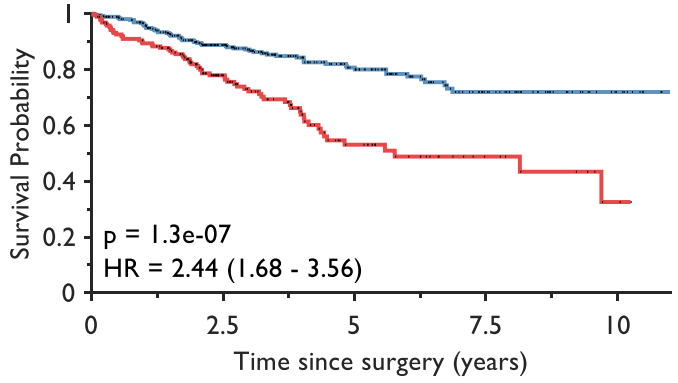


Train on 263 patients from one site



Results

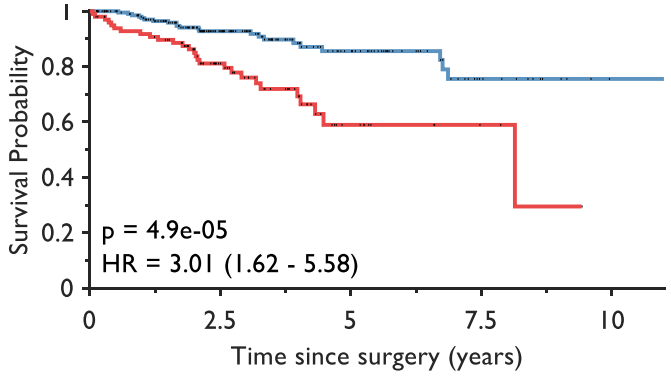
Prognostic in independent validation



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



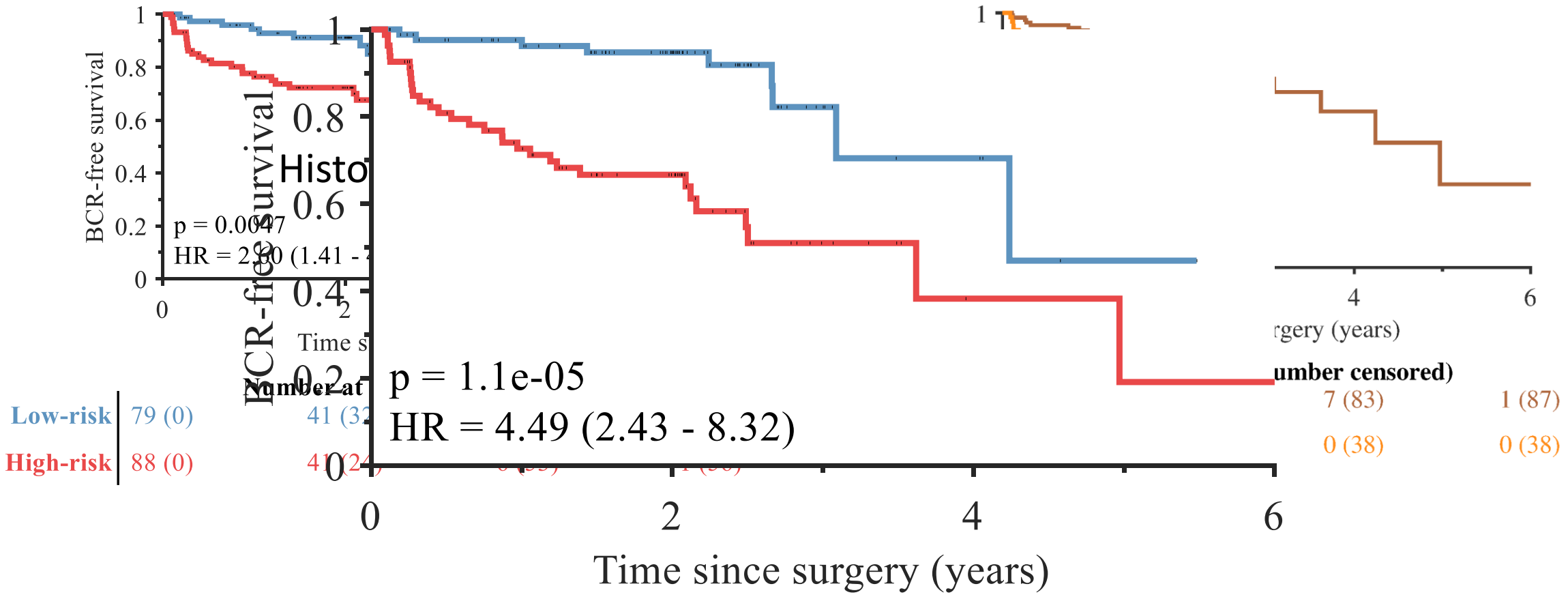
Number at risk (number censored)

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

Image based risk score versus Decipher: Head to Head Comparison



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

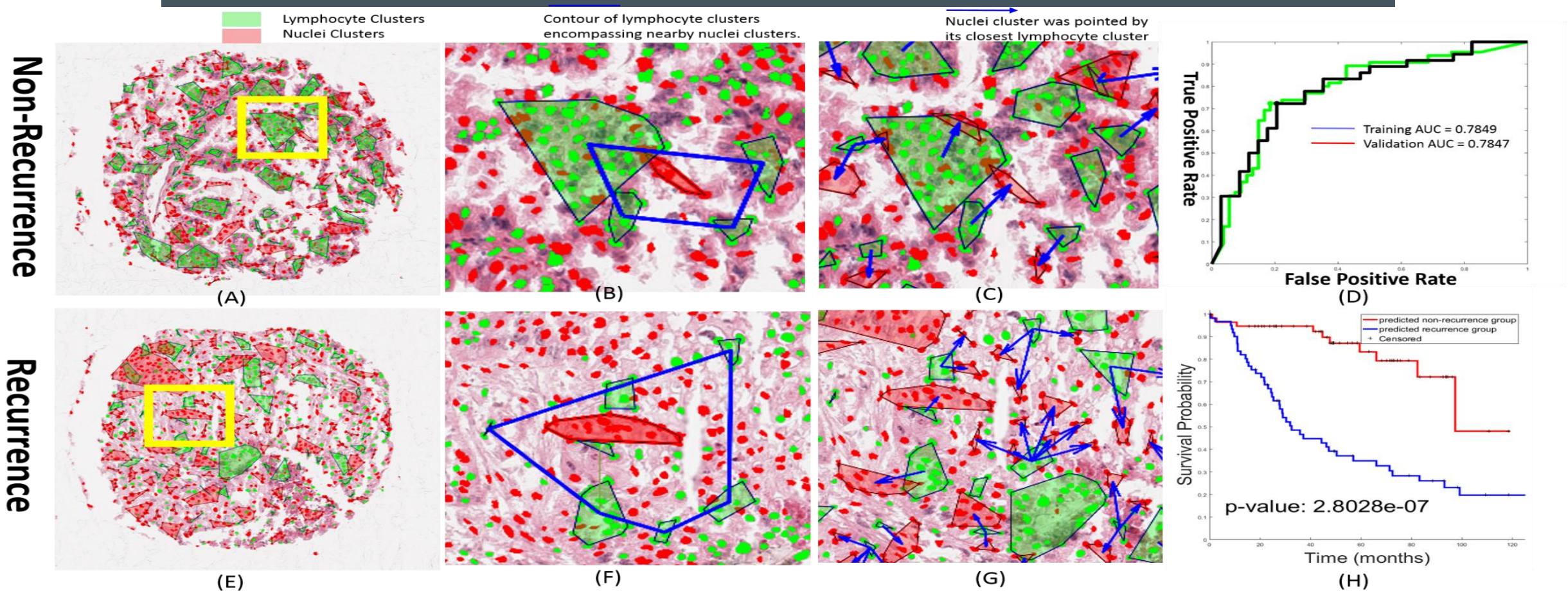


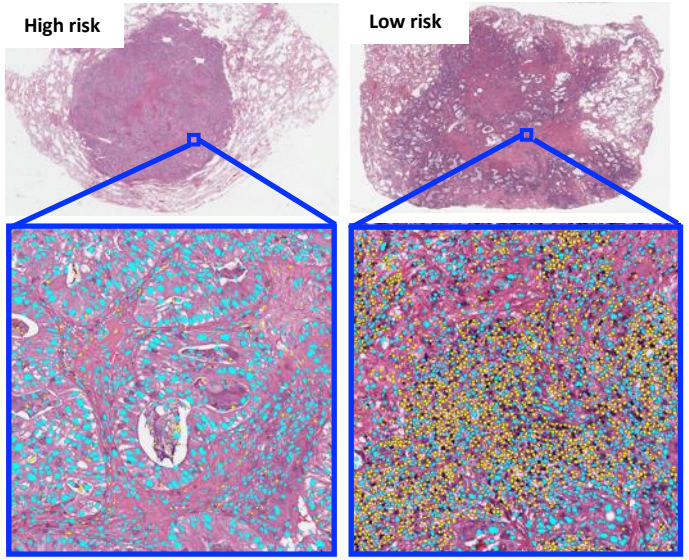
Figure 1. (A) Non-recurrent and (E) Recurrent NSCLC patient images. (A, E) TIL (green) and cancer nuclei cluster (red) construction, (B, F) number of proximal TIL clusters circumscribing each nuclear cluster, (C, G) Arrows show location of closest TIL cluster with respect to each cancer nuclei cluster, (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).*

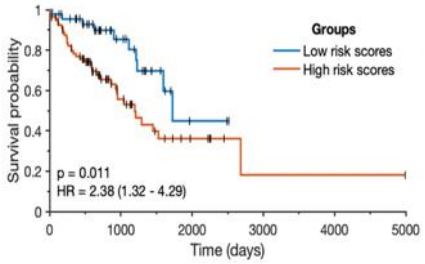
Clinical Cancer Research 2018

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)

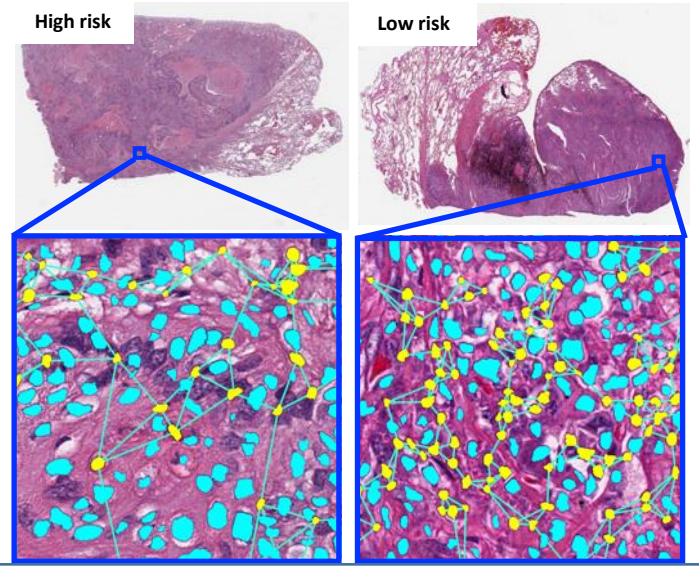
TIL density measures on LUAD

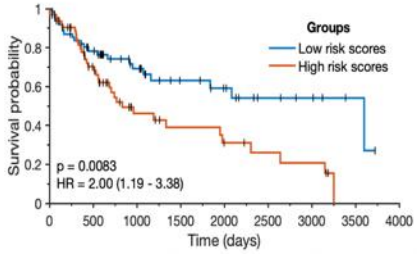




Yellow: TILs
Blue: non TILs

TIL spatial distribution on LUSC

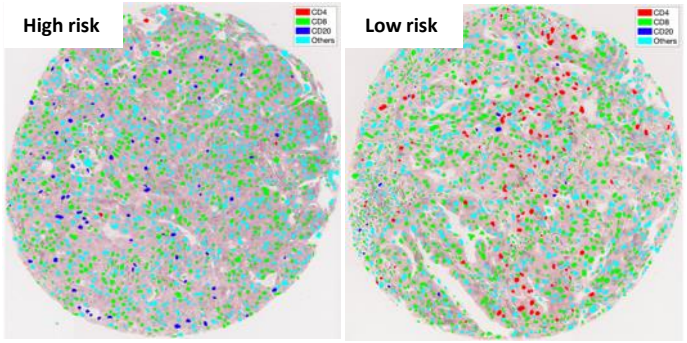


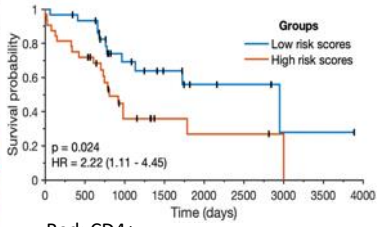


Yellow: TILs
Blue: non TILs

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

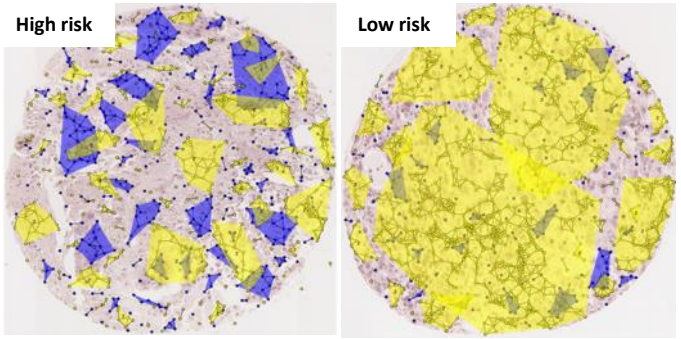
CD4+ density on LUAD

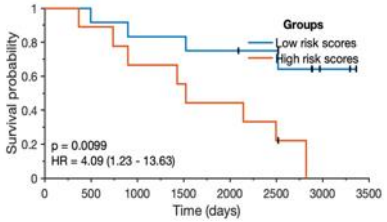




Red: CD4+
Green: CD8+
Blue: CD20+
Cyan: Other types

CD4+ vs CD8+ spatial interaction on LUSC



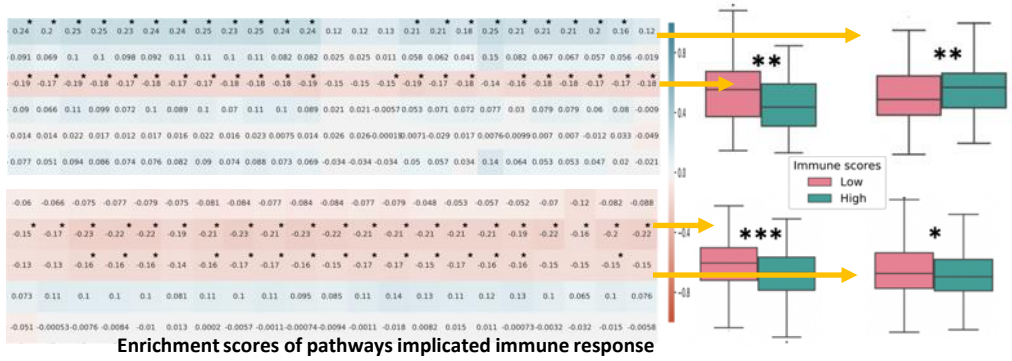


Yellow: CD8 clusters
Purple: CD4 clusters

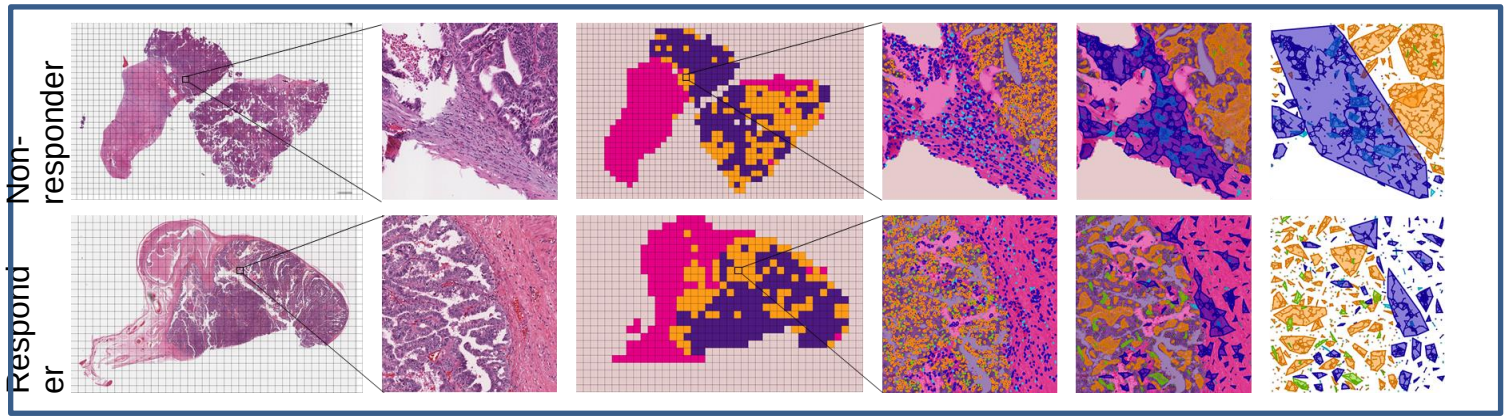
(N = 859) Association between Prognostic Signatures and 1) Biological Pathways 2) Immune Scores

Prognostic density features on LUAD

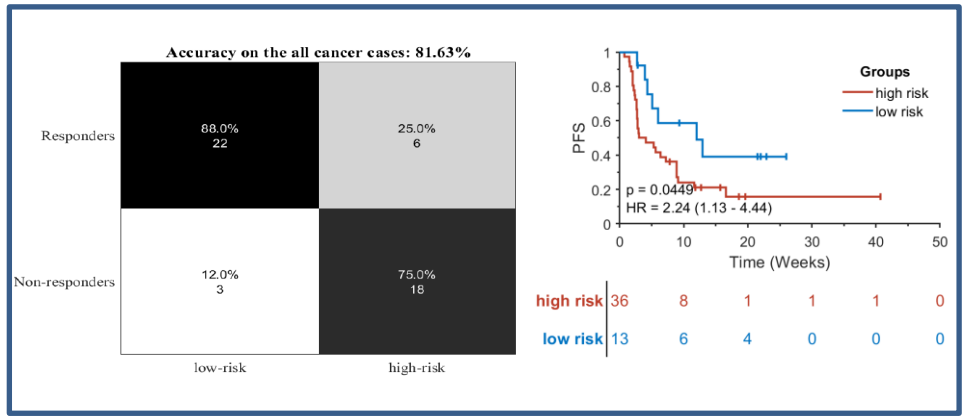
Prognostic spatial features on LUSC



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.**

CASE SCHOOL OF ENGINEERING
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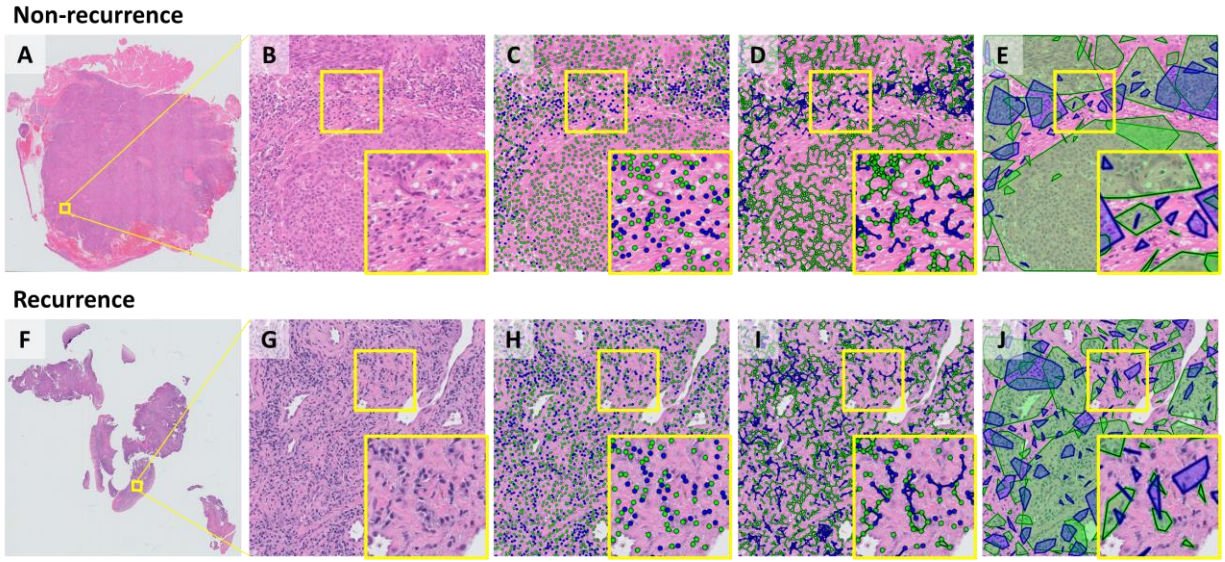
Center for Computational Imaging & Personalized Diagnostics

Predicting prognosis in p16+ OPSCC by characterizing the interplay between TILs and surrounding cells

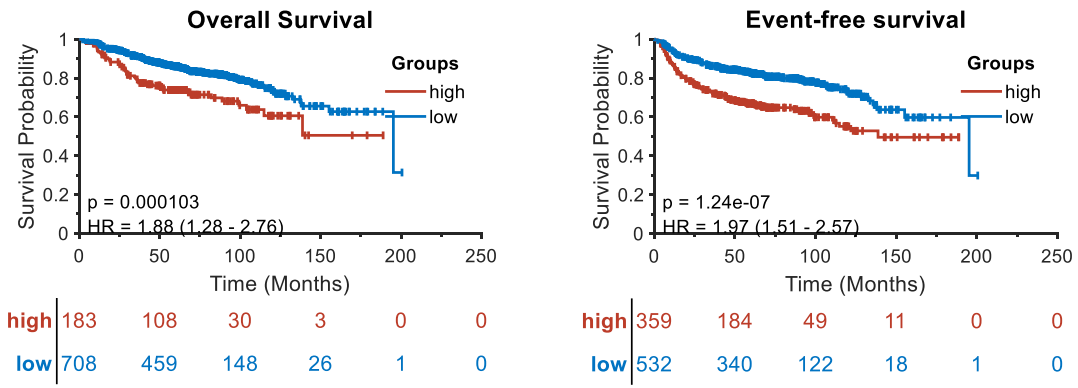


Datasets	# Cases	# Recurrences	# Deaths
Houston VA (D1)	94	30	61
JHU (D2)	121	33	13
WU (D3)	107	16	21
Kaiser (D4)	169	30	37
CCF (D5)	336	55	74
VUMC (D6)	158	17	29
Total	**985**	**181**	**235**

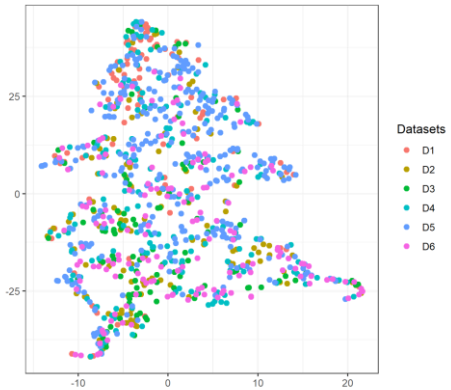
Feature discovery and model training

Independent validation

Univariable survival analysis



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)

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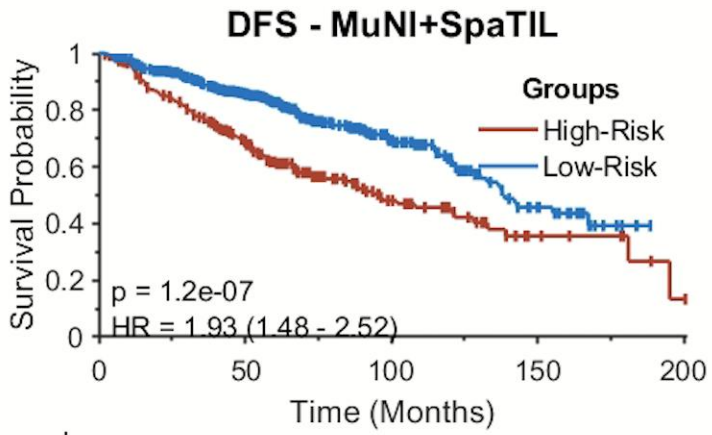
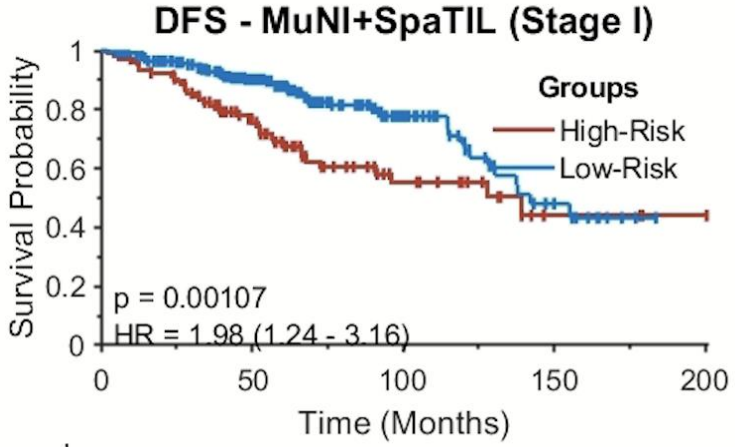
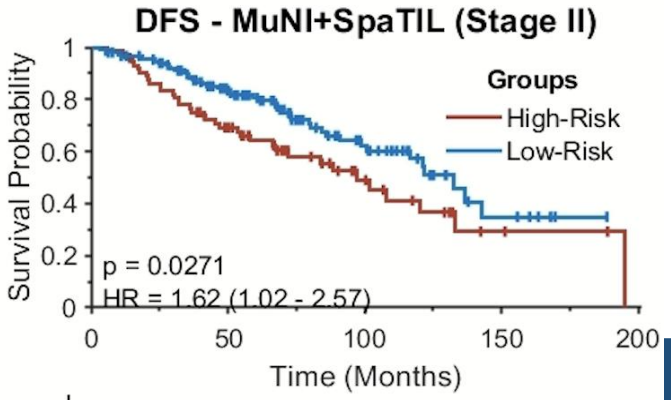
Combining biomarkers results in even better prognosis – even within individual stage groups



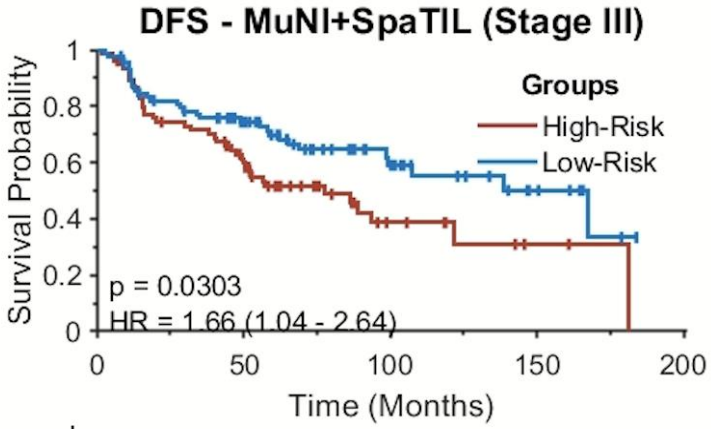
High-Risk	267	146	43	8	1
Low-Risk	532	323	101	24	0



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



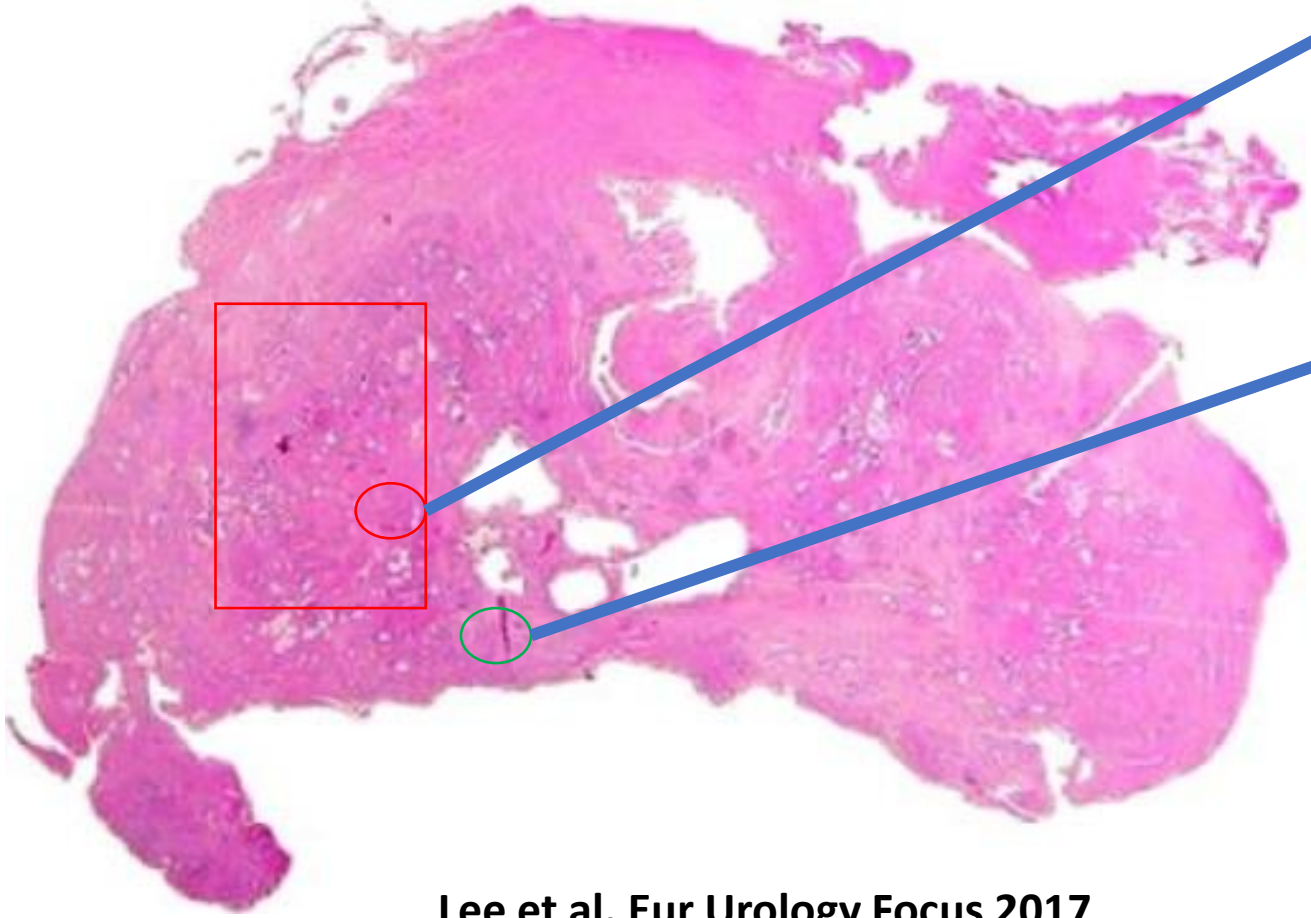
High-Risk	73	46	14	3	0
Low-Risk	151	96	31	6	0

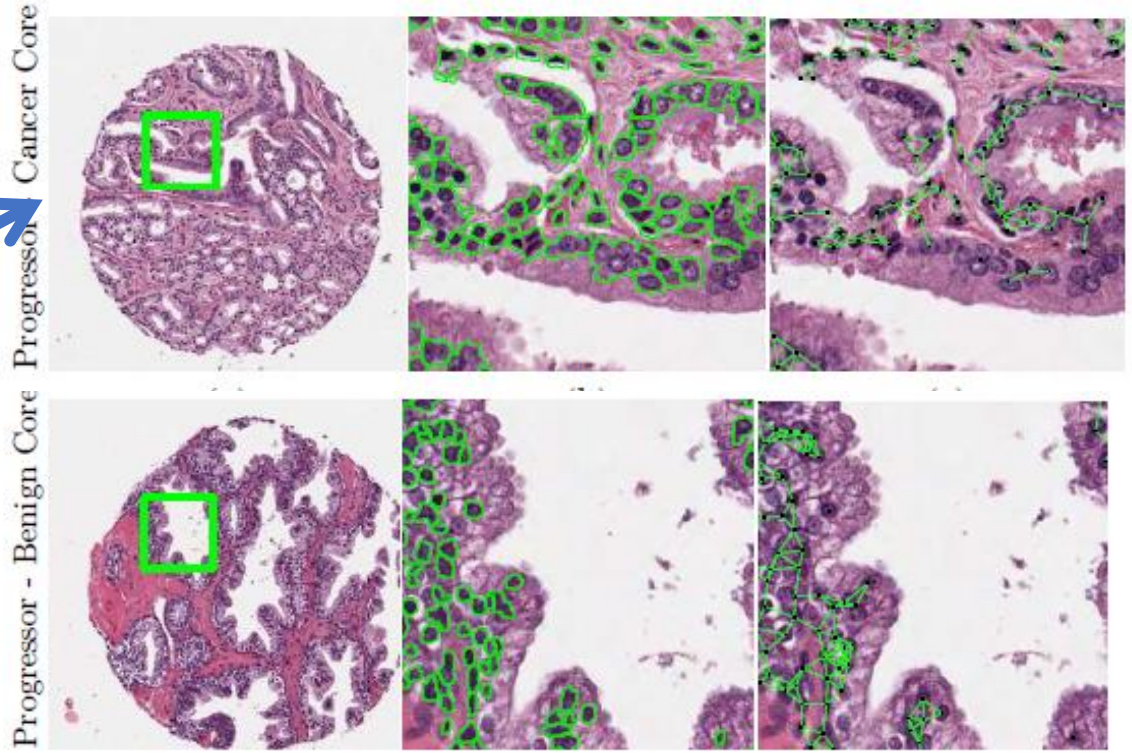


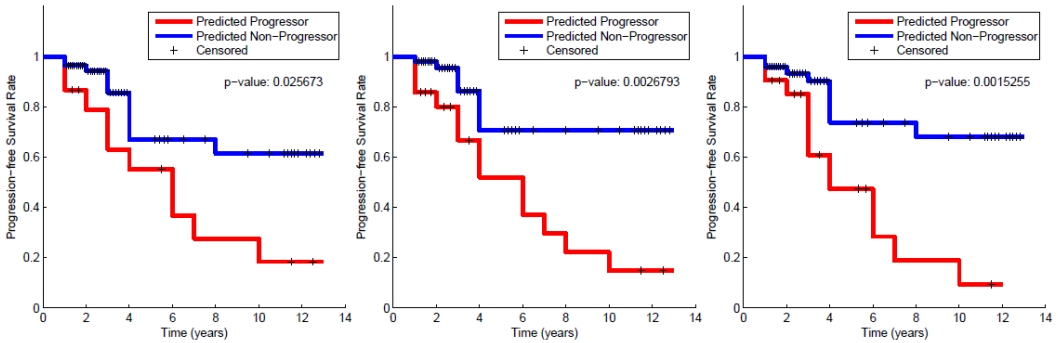
High-Risk	76	39	9	2	0
Low-Risk	85	53	21	7	0

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



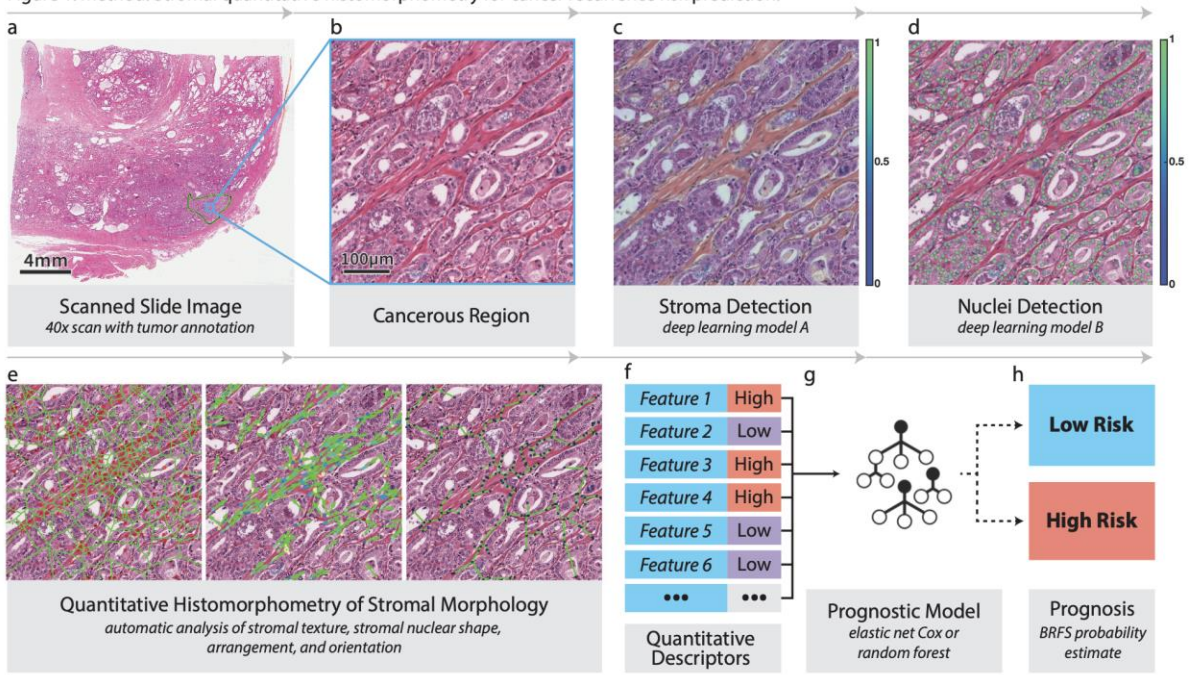


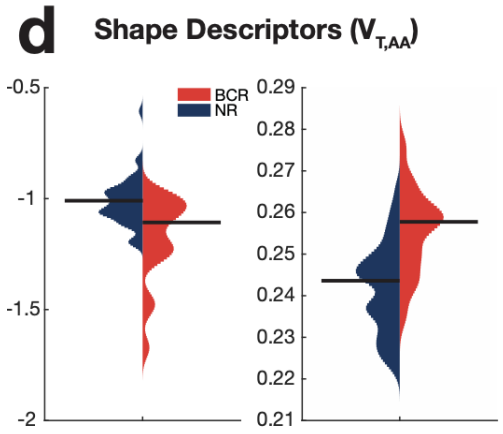


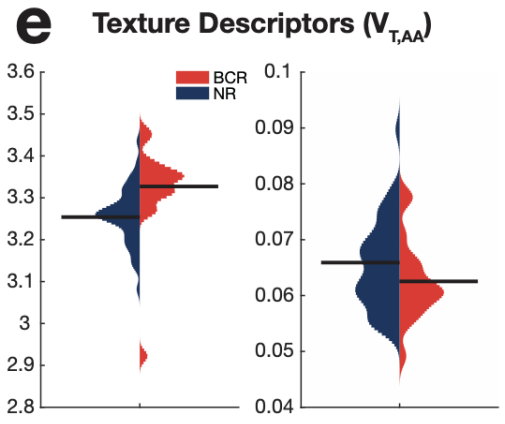
Lee et al. Eur Urology Focus 2017

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.







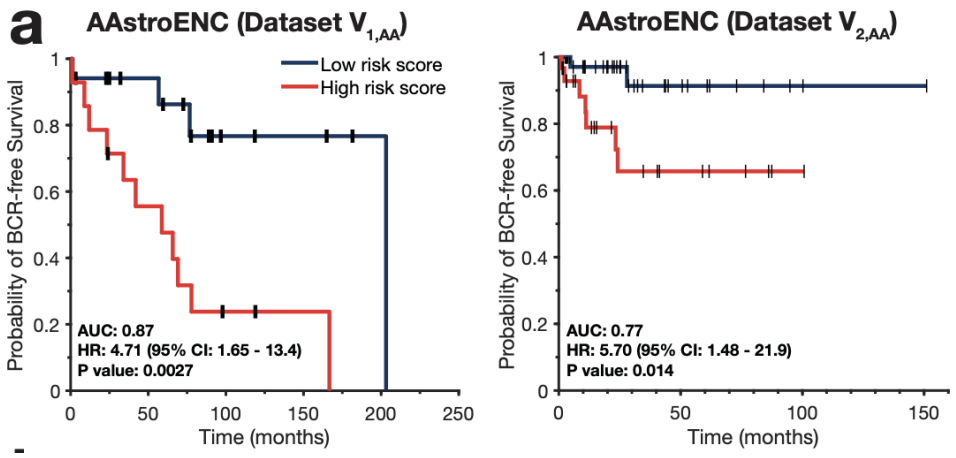


Figure 3. Association of stromal image features with IHC-derived tumor biomarker expression levels.

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.

Clinical Cancer Research, 2020

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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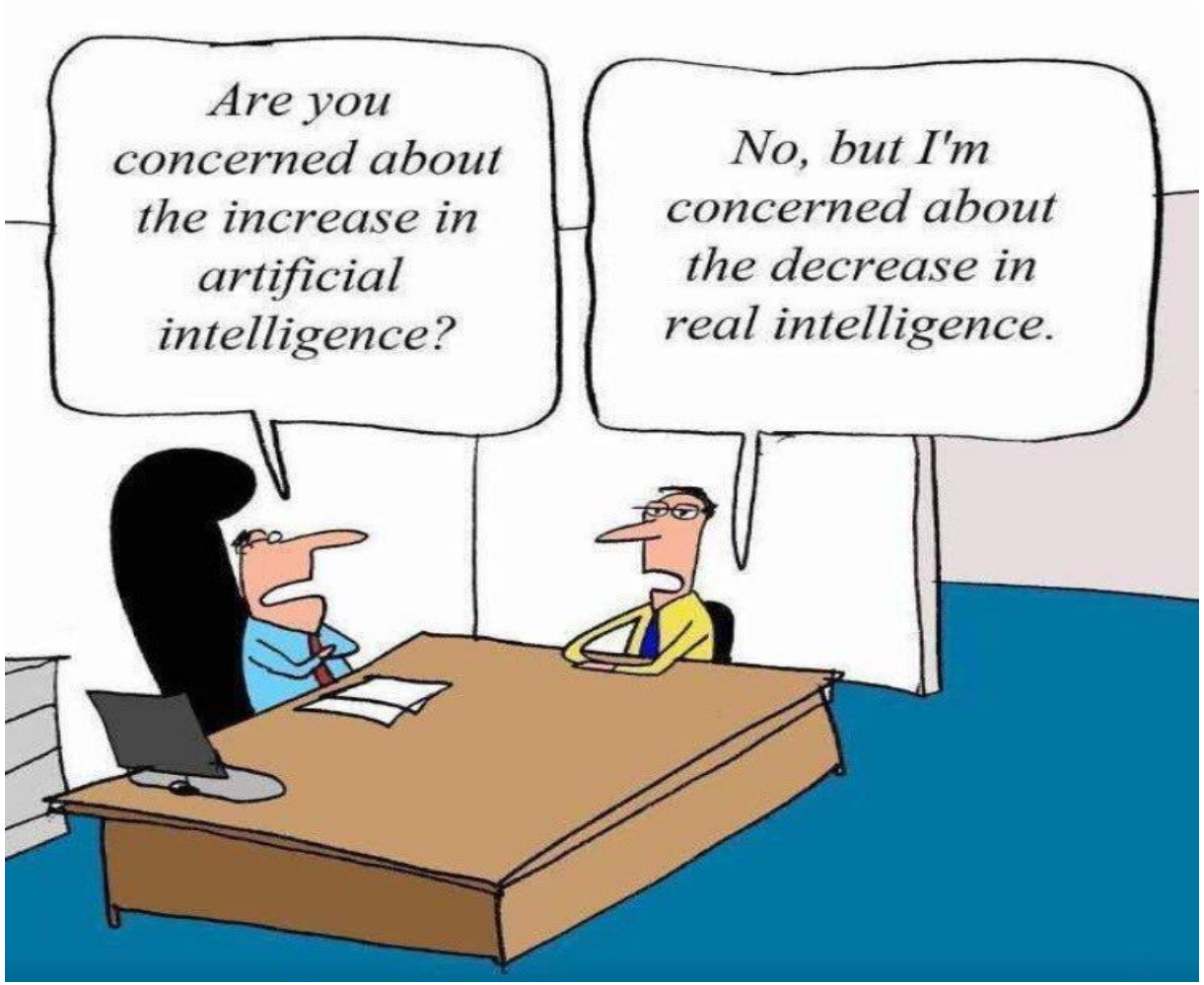
- the DOD Prostate Cancer Synergistic Idea Development Award (PC120857); the DOD Lung Cancer Idea Development New Investigator Award (LC130463), the DOD Prostate Cancer Idea Development Award; the DOD Peer Reviewed Cancer Research Program W81XWH-16-1-0329
- the Ohio Third Frontier Technology Validation Fund
- the Wallace H. Coulter Foundation Program and the Clinical and Translational Science Award Program (CTSA) at Case Western Reserve University.


Are you concerned about the increase in artificial intelligence?
No, but I'm concerned about the decrease in real intelligence.

Anant Madabhushi
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