To Deep Learn or not Deep Learning

Computational Pathology for Precision Medicine

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Biomedical Engineering Department
Case Western Reserve University

Research Health Scientist
Louis Stokes Cleveland Veterans Administration Medical Center
@anantm
<table>
<thead>
<tr>
<th>Cancer Type</th>
<th>Male</th>
<th>Female</th>
</tr>
</thead>
<tbody>
<tr>
<td>All sites†</td>
<td>1 in 2</td>
<td>1 in 3</td>
</tr>
<tr>
<td>Breast</td>
<td></td>
<td>1 in 8</td>
</tr>
<tr>
<td>Colon &amp; rectum</td>
<td>1 in 23</td>
<td>1 in 25</td>
</tr>
<tr>
<td>Kidney &amp; renal pelvis</td>
<td>1 in 46</td>
<td>1 in 82</td>
</tr>
<tr>
<td>Leukemia</td>
<td>1 in 54</td>
<td>1 in 77</td>
</tr>
<tr>
<td>Lung &amp; bronchus</td>
<td>1 in 15</td>
<td>1 in 17</td>
</tr>
<tr>
<td>Melanoma of the skin‡</td>
<td>1 in 28</td>
<td>1 in 41</td>
</tr>
<tr>
<td>Non-Hodgkin lymphoma</td>
<td>1 in 41</td>
<td>1 in 52</td>
</tr>
<tr>
<td>Prostate</td>
<td>1 in 9</td>
<td></td>
</tr>
<tr>
<td>Thyroid</td>
<td>1 in 144</td>
<td>1 in 52</td>
</tr>
<tr>
<td>Uterine cervix</td>
<td></td>
<td>1 in 159</td>
</tr>
<tr>
<td>Uterine corpus</td>
<td></td>
<td>1 in 33</td>
</tr>
</tbody>
</table>

## Estimated Cancer Deaths in the US, 2020

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

2020, American Cancer Society, Inc., Surveillance Research
Overdiagnosis is harming patients and action is required, says chief medical officer

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. WALTER PETERS
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 early stage (LN-), ER+ patients
- Recurrence Score (RS) between 0-100
- Predicts:
  - Likelihood for 10-year distant recurrence
  - Expected benefit from adjuvant chemotherapy

Intra-tumoral heterogeneity

Clonal Theory (Nowell 1976)

- Founder cell
- Normal/Healthy Cell
- Tumor Population 1
- Tumor Population 2
- Tumor Population 3
- Clonal Mutation (exist in all cancer cells)
- Subclonal Mutations (exist in a subset of cancer cells)
Image-based Risk Score (Ibris)

Biopsy → Sectioning, Staining → Digitization

Oncological Treatment → Analysis by IbRiS

Academic Industry Partnership NIH 1R01CA202752-01A1
Stacked Sparse Auto-encoder for Nuclei Detection


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

a Cardiac histopathology in heart failure

Non-Failing  
Failing

b Training a deep convolutional neural network

ROI extraction  
Model training  
Deep Learning  
Hierarchical learned features  
Test on held-out data  
Failure  
\text{P(Fal) > 0.5}  
Non-Failure  
\text{P(Fal) < 0.5}

c Detection of clinical heart failure

Performance evaluation

\begin{tabular}{lccc}
& CNN & Pathologists \\
\hline
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 \\
\end{tabular}

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

Patient 1  
Patient 2

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.
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
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.

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.
**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.

**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**

**Results**

- **LN-**
  - Train on UH (116 patients)
  - ECOG2197 (112 patients)
  - Tata (85 patients)

- **LN+**
  - Train on TCGA (83 patients)
  - ECOG2197 (112 patients)
  - UH (11 patients)

**Independent validation on 2 sites**

**Takeaway**

- The combination of nuclear, tubule, and mitotic features is prognostic of disease-free survival (DFS) for the ER+ breast cancer patients.
<table>
<thead>
<tr>
<th>Feature</th>
<th>Oncotype DX</th>
<th>IbRiS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cost of test</td>
<td>$4,600</td>
<td>$4.60</td>
</tr>
<tr>
<td>Waiting for results</td>
<td>2 weeks</td>
<td>20 minutes</td>
</tr>
<tr>
<td>Tissue specimen</td>
<td>Destroyed</td>
<td>Digitized</td>
</tr>
<tr>
<td>Accessibility</td>
<td>USA only</td>
<td>Worldwide</td>
</tr>
</tbody>
</table>

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)

<table>
<thead>
<tr>
<th>Assay</th>
<th>% of patients with no recurrence after 10 years classified as low-risk</th>
<th>10-year recurrence rate in low-risk group</th>
<th>% of HER2- patients with no recurrence after 10 years classified as low-risk</th>
<th>10-year recurrence rate in low-risk HER2- group</th>
</tr>
</thead>
<tbody>
<tr>
<td>IbRiS</td>
<td>35.34%</td>
<td>10.87%</td>
<td>37.11%</td>
<td>10.0%</td>
</tr>
<tr>
<td>ODx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IbRiS + ODx</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

IbRiS performance over all 378 cases

Comparison of IbRiS to Oncotype 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)

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

Added value in margin-negative patients

Independent from clinical markers

<table>
<thead>
<tr>
<th>Covariate</th>
<th>p</th>
<th>HR</th>
</tr>
</thead>
<tbody>
<tr>
<td>Risk score (per 0.1 increase)</td>
<td>&lt;.01</td>
<td>1.33</td>
</tr>
<tr>
<td>Grade group &gt;2</td>
<td>&lt;.01</td>
<td>3.05</td>
</tr>
<tr>
<td>Positive margins</td>
<td>&lt;.01</td>
<td>2.21</td>
</tr>
<tr>
<td>Log2 pre-op PSA</td>
<td>0.24</td>
<td>1.13</td>
</tr>
<tr>
<td>Stage &gt;T2a</td>
<td>0.63</td>
<td>1.42</td>
</tr>
</tbody>
</table>

Npj Precision Oncology, In Press
Image based risk score versus Decipher: Head to Head Comparison

**BCR-free survival**

- **p = 0.0047**
- **HR = 2.60 (1.41 - 4.81)**

**Number at risk (number censored)**

- **Low-risk**: 79 (0), 41 (32), 1 (68)  
- **High-risk**: 88 (0), 41 (24), 6 (53), 1 (56)

**Histotyping Decipher**

- **p = 1.1e-05**
- **HR = 4.49 (2.43 - 8.32)**

**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
Tiling at 40x

MuNI calculation

MN masks

Tiles

G_{MN}

G_{EP}

EP masks

\[ \text{MuNI} = \frac{\sum_{i=1}^{m} \text{(# of MN)}}{\sum_{i=1}^{m} \text{(# of EP cells)}} \]
KM-DMFS curves for patients in training/validation cohorts for different cancer stage groups according to AJCC 8th edition definition.
Computerized tumor multinucleation index (MuNI) is prognostic in p16+ oropharyngeal carcinoma: A multi-site validation study

Can F. Koyuncu,1 Cheng Lu,1 Kaustav Bera,1 Zelin Zhang,2 Jun Xu,2 Paula Andrea Toro Castaño,1 Germán Corredor,1 Deborah Chute,3 Pingfu Fu,4 Wade L. Thorstad,5 Farhoud Faraji,6 Justin A. Bishop,7 Mitra Mehrad,8 Patricia D. Castro,9 Andrew G. Sikora,10 Lester D. R. Thompson,11 R. D. Chernock,12 Krystle A. Lang Kuhls,13 Jingxin Luo,14 Vlad C. Sandulache,10 David J. Adelstein,15 Shlomo Koyfman,16 James S. Lewis Jr.,17 and Anant Madabhushi1

Published March 2, 2021. More Info

View PDF

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, R01CA208236-01A, R01CA216579-01A, R01CA220581-01A, 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 Research Program Breakthrough Level 1 Award (W81XWH-15-1-0668), and the DOD Breast Cancer Research Program Breakthrough Level 1 Award (W81XWH-15-1-0668).
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

Univariate survival analysis
- Overall survival: p = 0.000103, HR = 1.88 (1.28 - 2.76)
- Event-free survival: p = 1.24e-07, HR = 1.97 (1.51 - 2.57)

Multivariate survival analysis

Variable | Overall Survival p-value | HR (CI) | Event-free Survival 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)

Feature discovery and model training

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

DFS - MuN1+SpaTIL

Groups
- High-Risk
- Low-Risk

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

DFS - MuN1+SpaTIL (Stage I)

Groups
- High-Risk
- Low-Risk

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

DFS - MuN1+SpaTIL (Stage II)

Groups
- High-Risk
- Low-Risk

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

DFS - MuN1+SpaTIL (Stage III)

Groups
- High-Risk
- Low-Risk

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 cancer.

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

Two Years Survival in D₃ PDL1 Low

Groups
- high risk
- low risk

Probability of DFS
- p = 0.016
- HR $\frac{1}{2.59}$ (1.35, 4.99)

Survival Probability

10 years survival in

Time (Months)

N = 47

<table>
<thead>
<tr>
<th>Months after Treatment</th>
<th>high risk</th>
<th>low risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>36</td>
<td>11</td>
</tr>
<tr>
<td>1</td>
<td>12</td>
<td>8</td>
</tr>
<tr>
<td>2</td>
<td>7</td>
<td>7</td>
</tr>
<tr>
<td>3</td>
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<td>3</td>
<td>0</td>
</tr>
<tr>
<td>7</td>
<td>0</td>
<td>0</td>
</tr>
</tbody>
</table>

Validation set, D3

p = 0.0295
HR = 4.12 (1.87, 9.09)
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**
  - High risk
  - Low risk

- **TIL spatial distribution on LUSC**
  - High risk
  - Low risk

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

- **CD4+ vs CD8+ spatial interaction on LUSC**
  - High risk
  - Low risk

**Prognostic density features on LUAD**

- Yellow: TILs
- Blue: non TILs

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

**Enrichment scores of pathways implicated immune response**

- **(N = 859) Association between Prognostic Signatures and 1) Biological Pathways 2) Immune Scores**
Predicting overall survival in Ovarian Cancer using SpaTIL

- Tile and Epithelial extraction
- Slicing of the WSI in 2000 x 2000 patches
- Segmenting the epithelial by DL model

- Feature extraction
- LASSO feature selection

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

- Interaction between TIL and nonTIL clusters in each patch
- TILs and nonTILs segmented patches

- Feature extraction
- Interaction between TIL and nonTIL clusters in each patch

- Random patches within epithelial region
- Segmented patches

- Survival Analysis

- Distribution plots for low-risk and high-risk patients
- Scatter and distribution plots for survival time

- Training HR=2.81
- Test HR=2.06

- LASSO feature selection
- Extracting top features and calculating risk score

- Predicting overall survival in Ovarian Cancer using SpaTIL
Predicting overall survival in Endometrial and Cervical Cancers using SpaTIL
Spatial arrangement of TILs for predicting response to IO in gynecological cancers

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 administering therapy.
- Imaging features could potentially identify patients who are likely to derive clinical benefit from immunotherapy beyond clinical data.

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)

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)

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.
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.
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

Shape Cell orientation Disorder (CORE)
Global graph Cell Cluster Graph (DGG)
Texture

Model construction on training set
Validation on SA in testing set

Model trained with North American (MNA)
Model trained with North American + South Asian (MNA+SA)
Model trained with South Asian (MSA)

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.
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

Better Gleason score definition in 3D space [2]


[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
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Are you concerned about the increase in artificial intelligence?

No, but I'm concerned about the decrease in real intelligence.