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Opportunistic AI for Predicting Cancer Outcomes

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Conflict of Interest Disclosures

Anant Madabhushi, PhD

Picture Health – Founder, Equity

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Role of AI and Computational Imaging in developing Better Diagnostic, Prognostic, and 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*

MIT Technology Review

VOL. 120 NO. 3 MAY/JUNE 2017 US \$6.99/CAN \$7.99

Feature p. 42

**A 3-D Printer That
Really Matters**

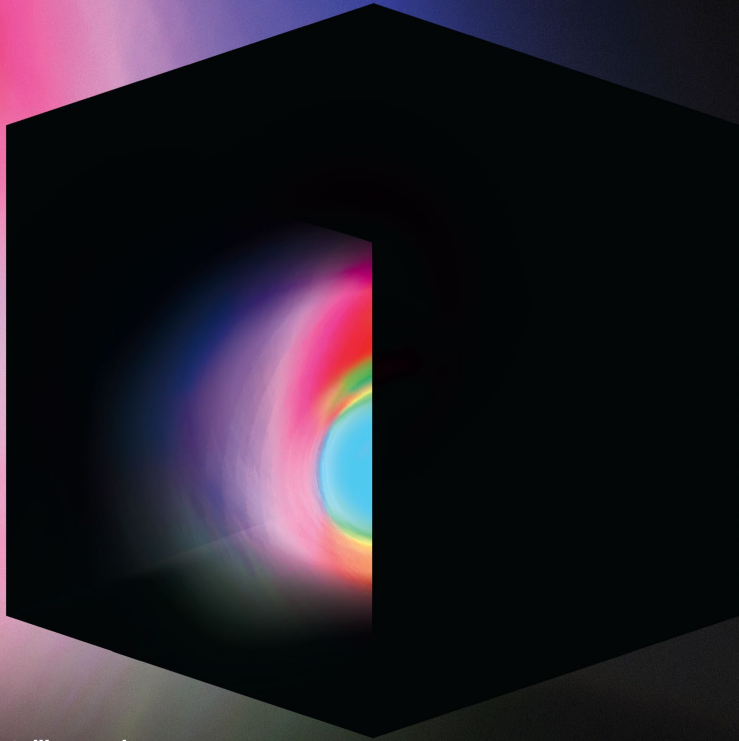
Feature p. 78

**Cancer Cures
For a Lucky Few**

Feature p. 28

**Time to Consider
Geoengineering?**

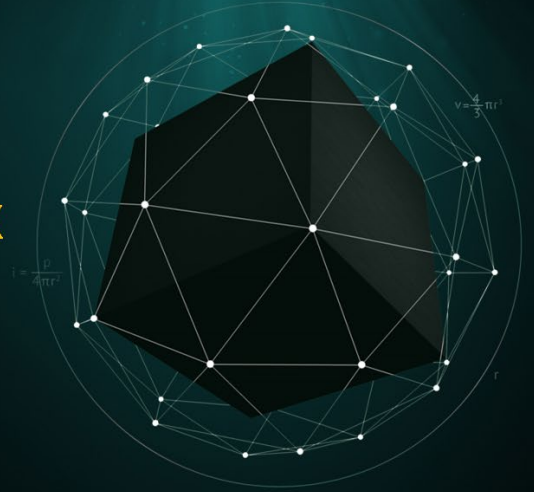
Mysterious Machines



Artificial intelligence is a
black box that thinks in ways
we don't understand. That's
thrilling and scary. p. 54

 Analytics Insight

What is Inside the **BLACK BOX**
of Artificial Intelligence?





Is AI leading crisis in science

Scientists worry that ill-informed use of AI is leading to unreliable or useless research

LIE TO ME | MAY 5, 4:04 PM EDT by VICTOR TANGERMANN

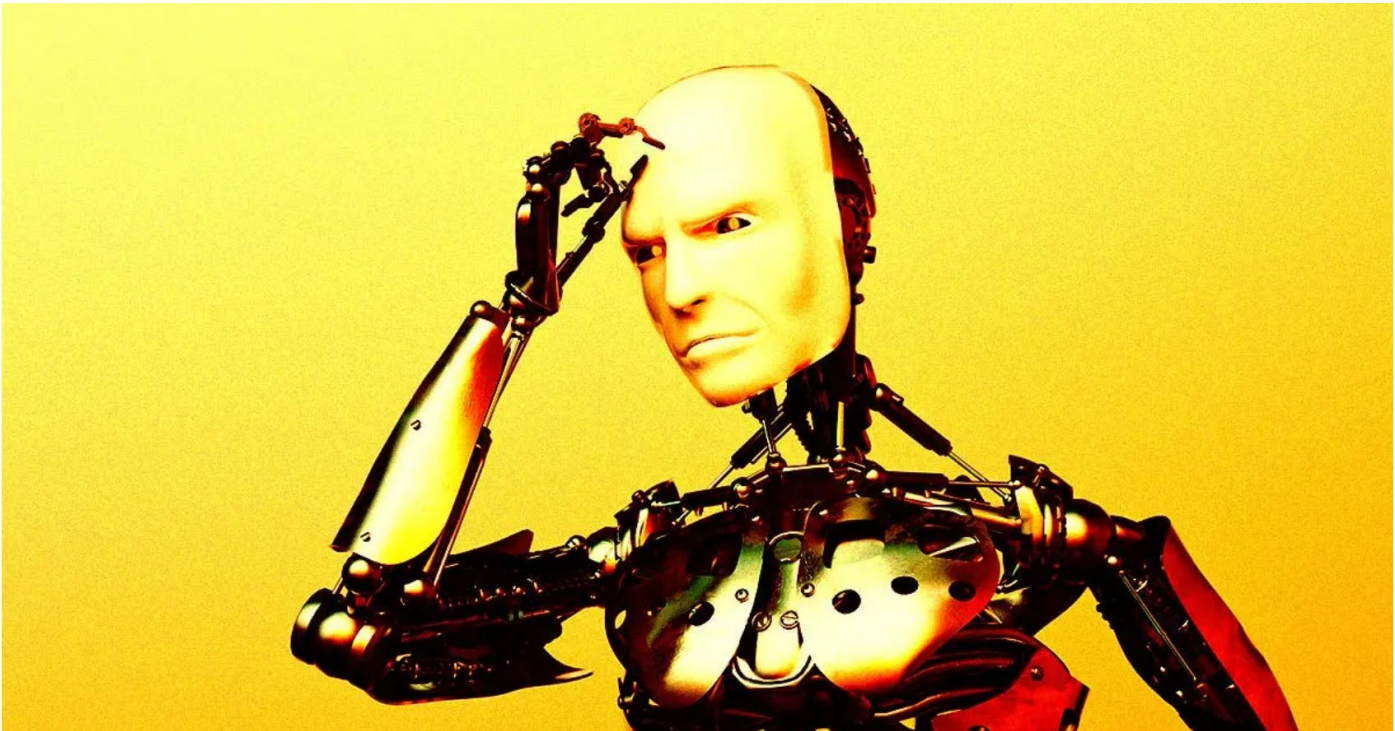
The AI Industry Has a Huge Problem: the Smarter Its AI Gets, the More It's Hallucinating

That's not good.

/ Artificial Intelligence / AI Chatbots / AI Hallucinations / ChatGPT

ty Crisis' in
sing a wave of spurious results.

WILL KNIGHT
BUSINESS AUG 18, 2022 7
sloppy Use of
science
AI hype has researche

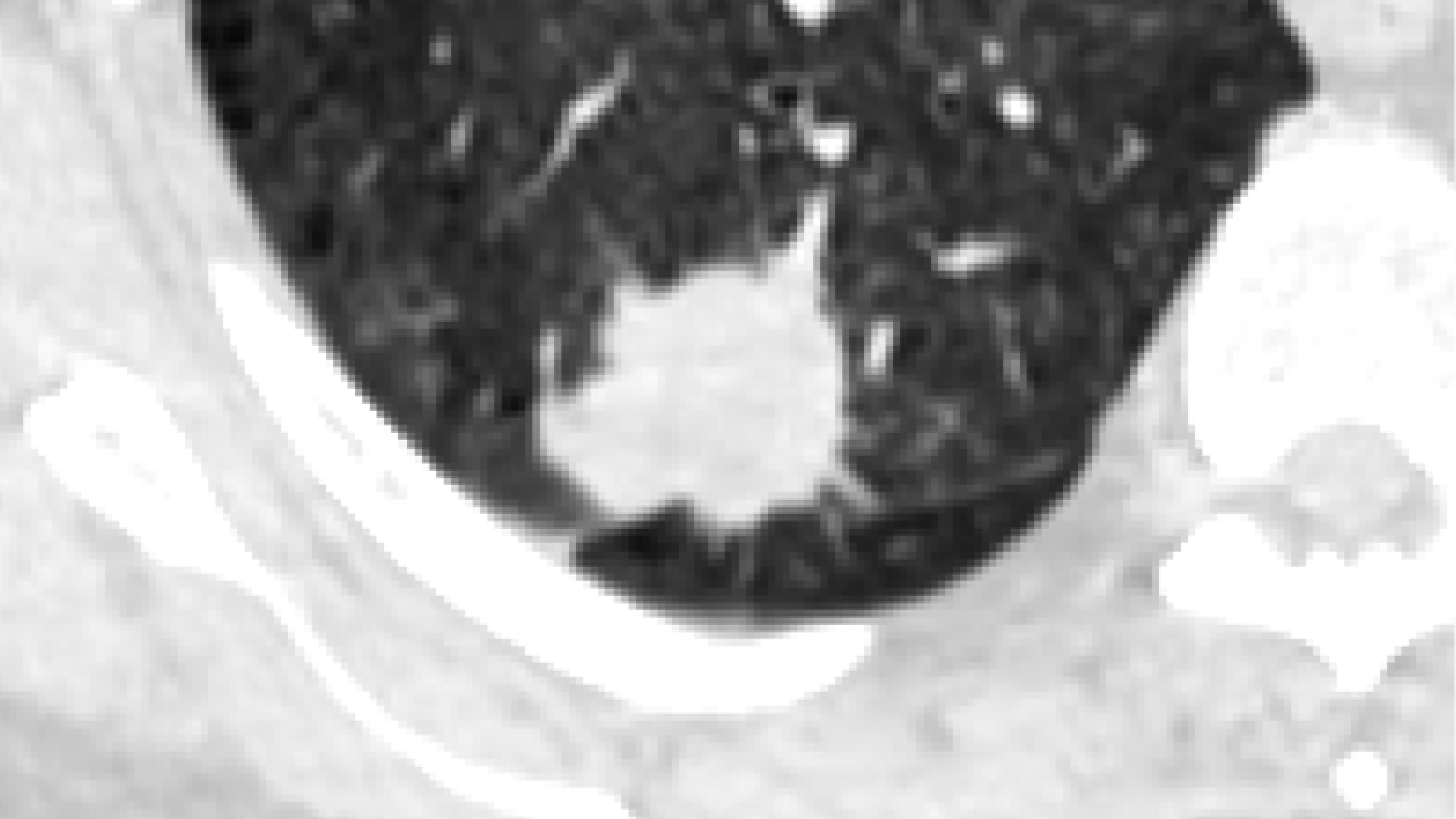


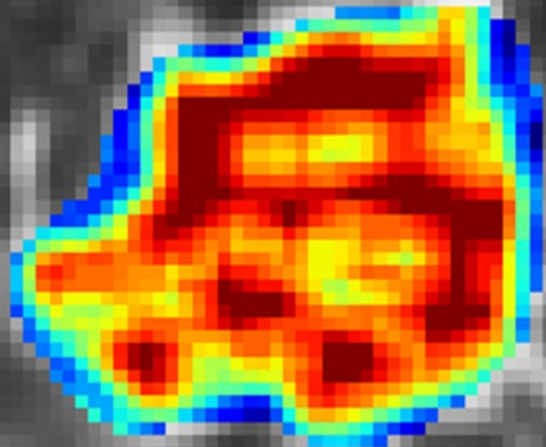
ing fuel a
in science?
earning use across disciplines,



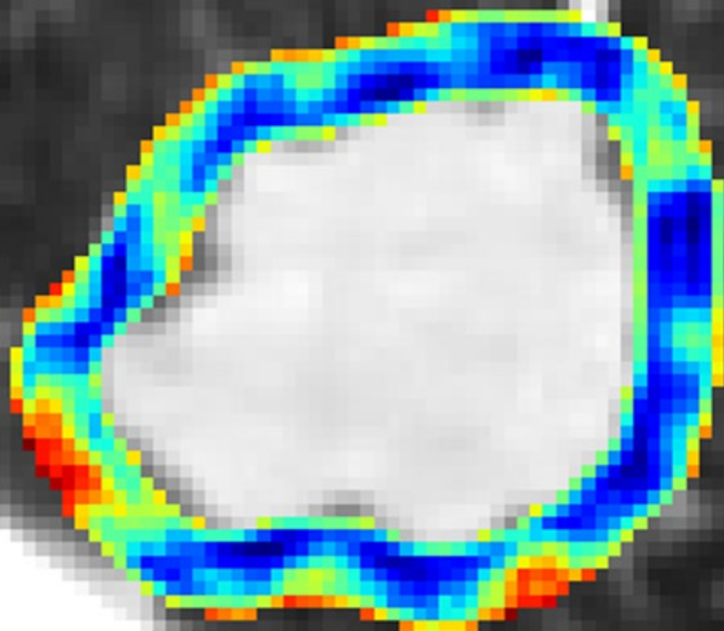
The individual in the photo is Anant Madabhushi, a renowned expert in the field of medical imaging and artificial intelligence. His work is highly recognized, particularly in developing AI algorithms for medical image analysis to predict disease progression and treatment outcomes. He has received numerous awards and honors for his contributions to the field. This headshot was taken at Emory University, as indicated by the background.

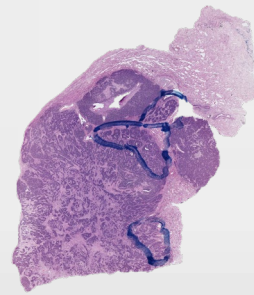




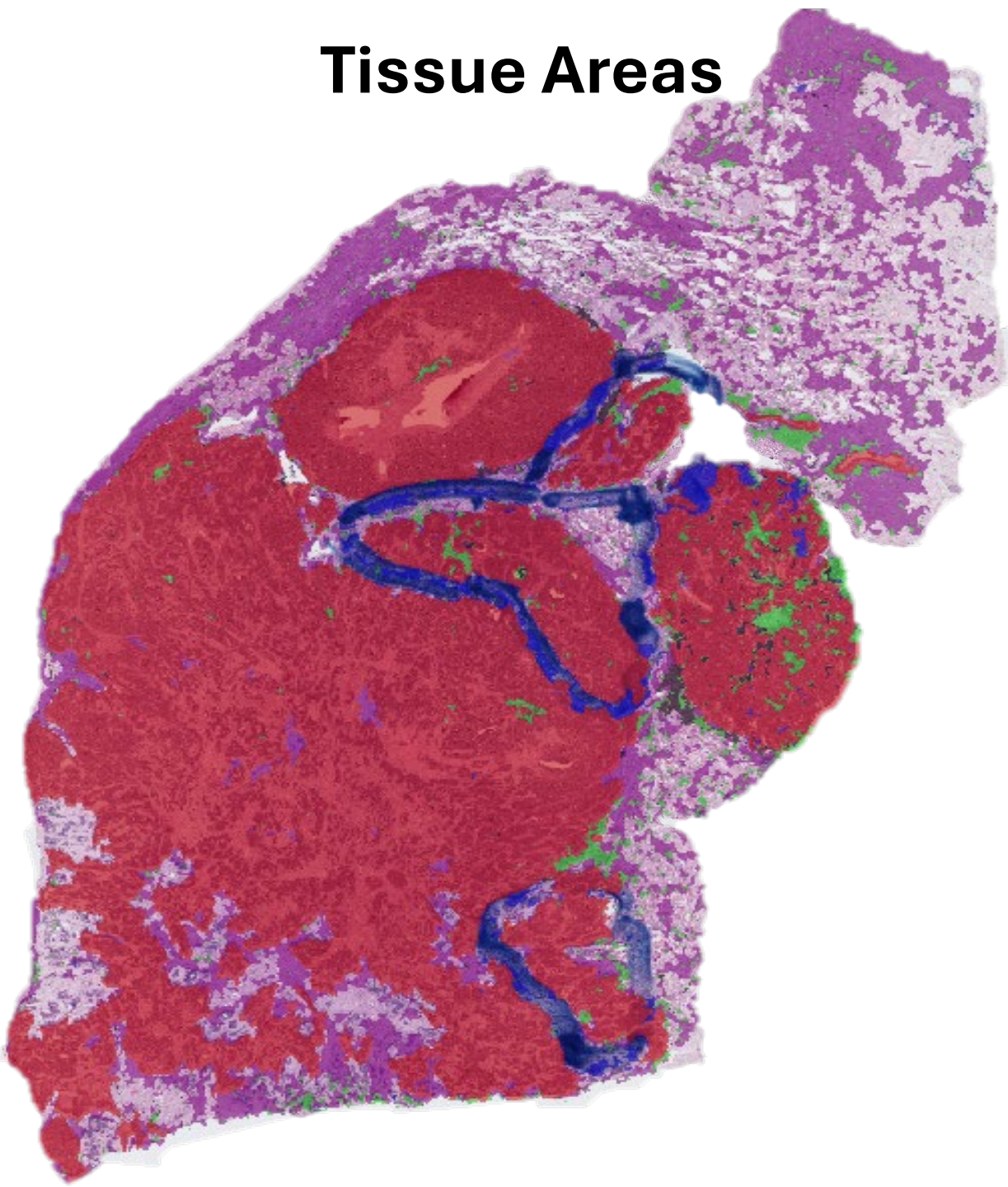


Intra-/Peri-tumoral Texture





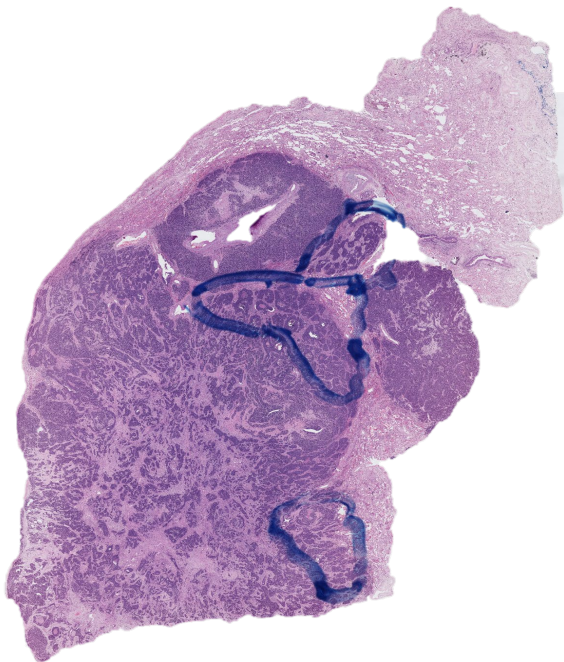
Tissue Areas



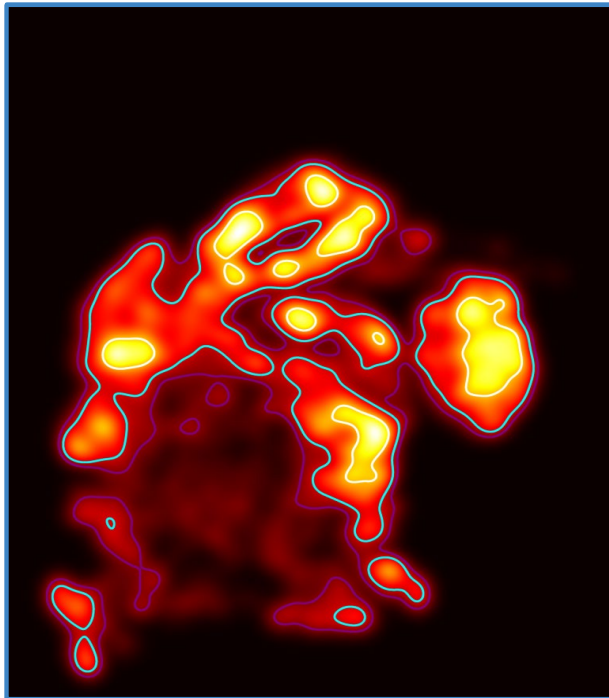
Single-cell Identification



H&E



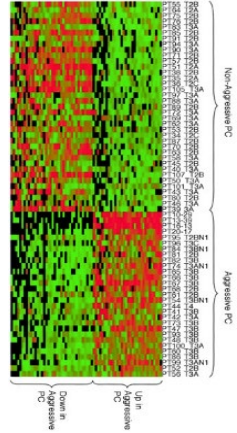
Immune Hotspots



Which breast cancer patients will receive added benefit from chemotherapy?

Oncotype DX molecular assay (Genomic Health, Inc.)

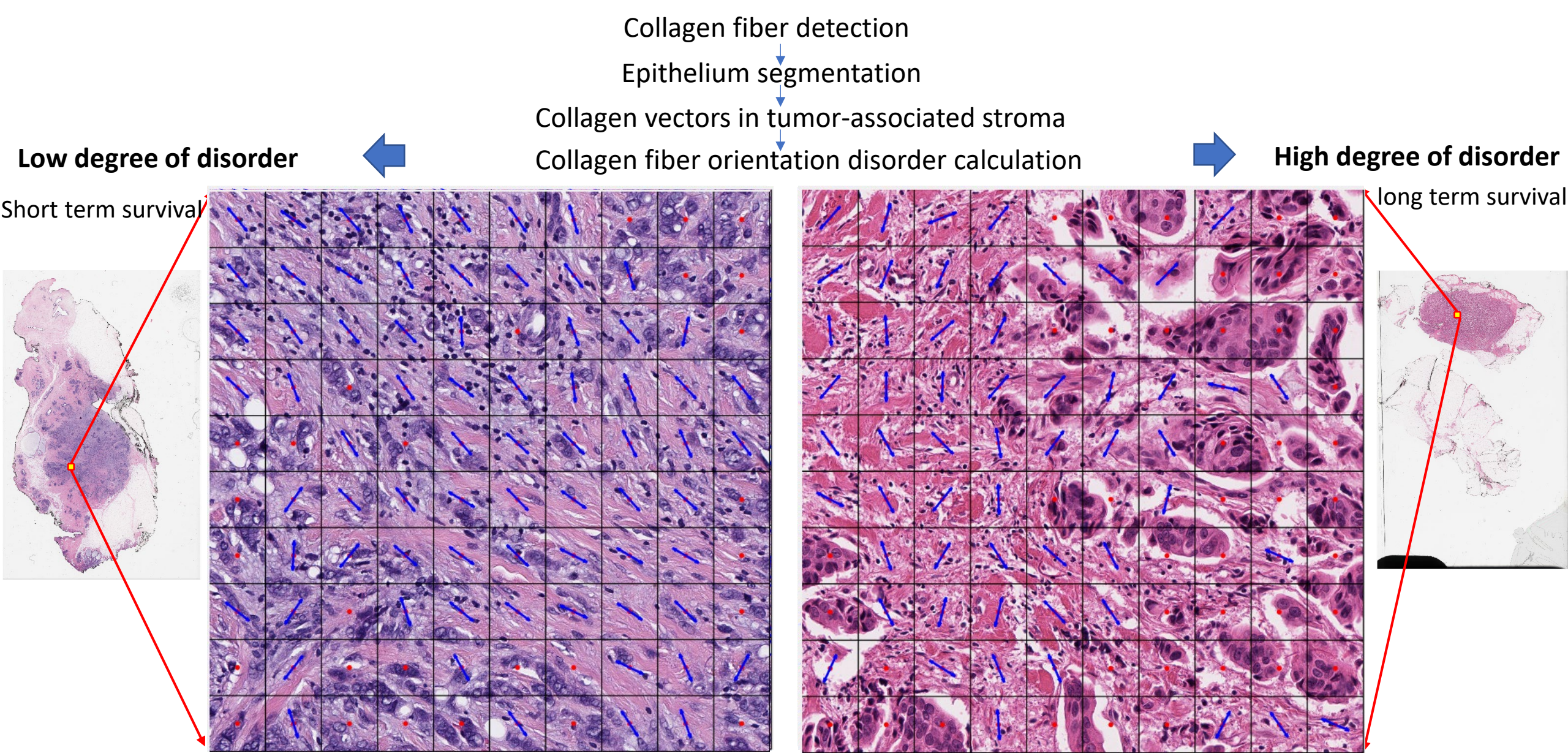
- For early stage (LN-), ER+ patients
- Recurrence Score (RS) between 0-100
- Predicts:
 - Likelihood for 10-year distant recurrence
 - Expected benefit from adjuvant chemotherapy



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

$$\begin{aligned}\text{Recurrence Score} = & +0.47 \times \text{HER2 Group Score} \\ & - 0.34 \times \text{ER Group Score} \\ & + 1.04 \times \text{Proliferation group Score} \\ & + 0.10 \times \text{Invasion Group Score} \\ & + 0.05 \times \text{CD68} \\ & - 0.08 \times \text{GSTM1} \\ & - 0.07 \times \text{BAG1}\end{aligned}$$

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



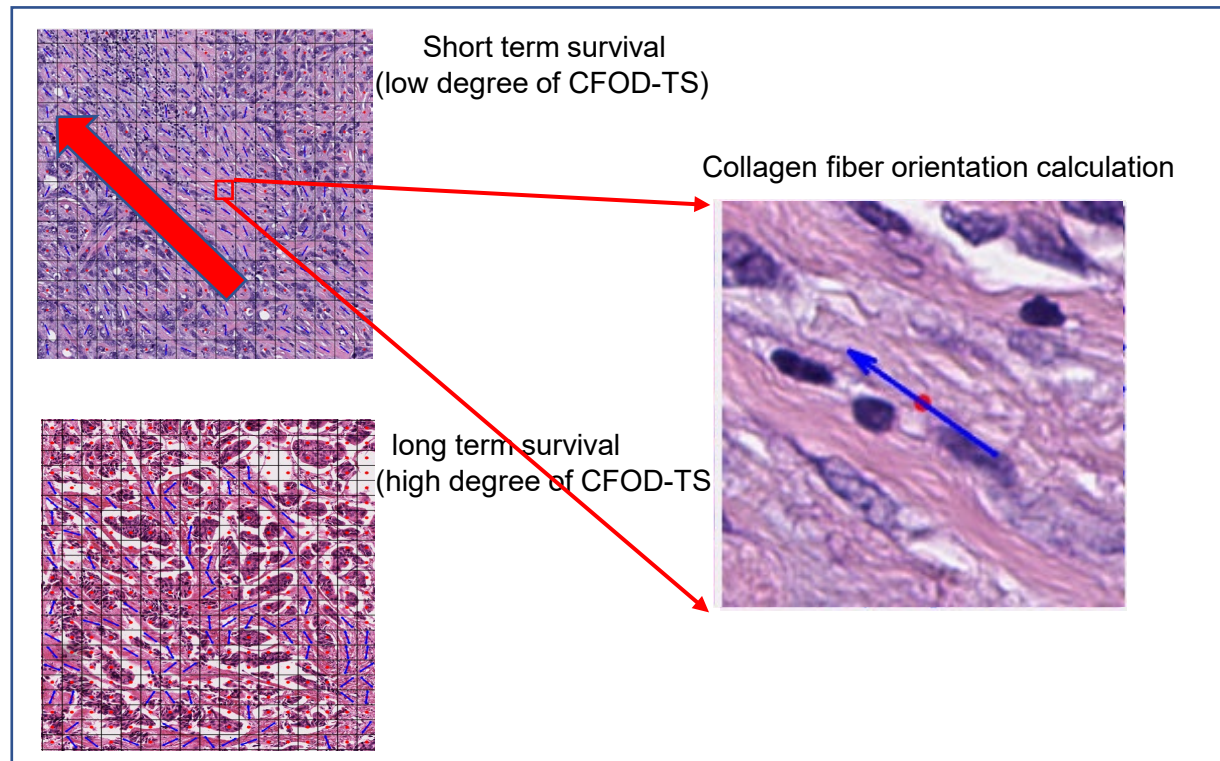
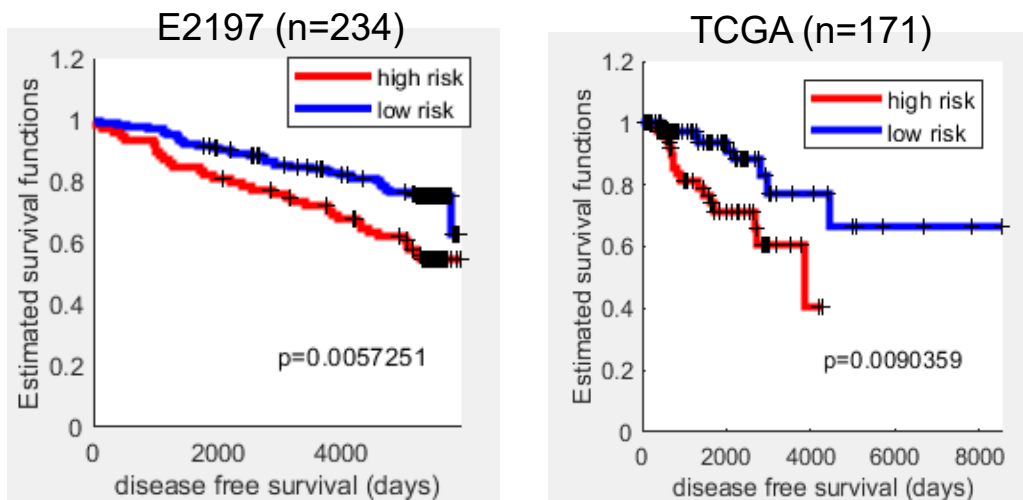
Disorder of collagen fiber orientation associated with risk of recurrence in ER+ breast cancers in ECOG-ACRIN E2197 & TCGA

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.

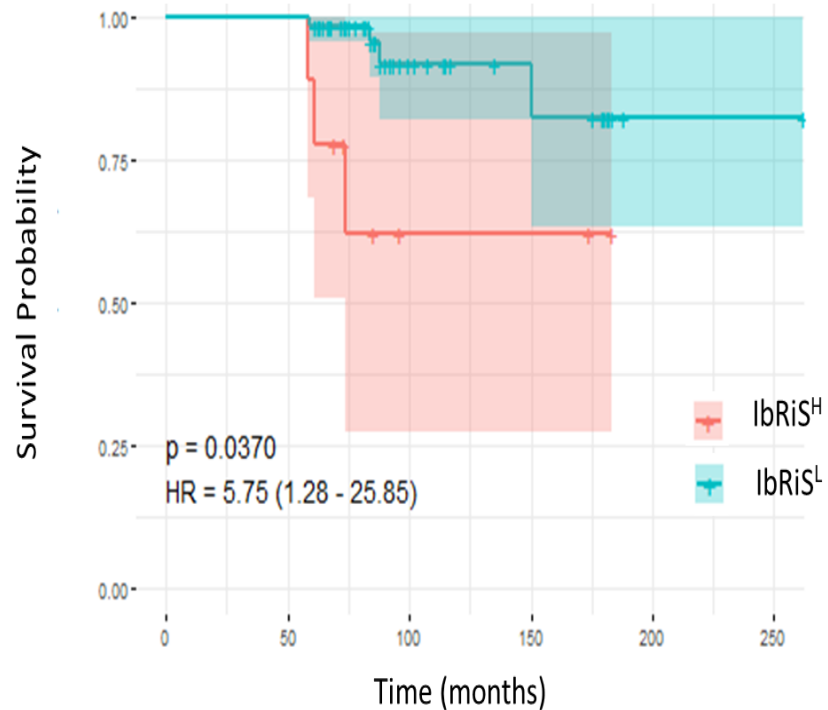


Take away:

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

IbRiS adds prognostic value to Oncotype DX Risk Categories in Estrogen Receptor Positive (ER+) Breast Cancer

IbRiS^H vs. IbRiS^L in low Odx category (D₁₊₂)

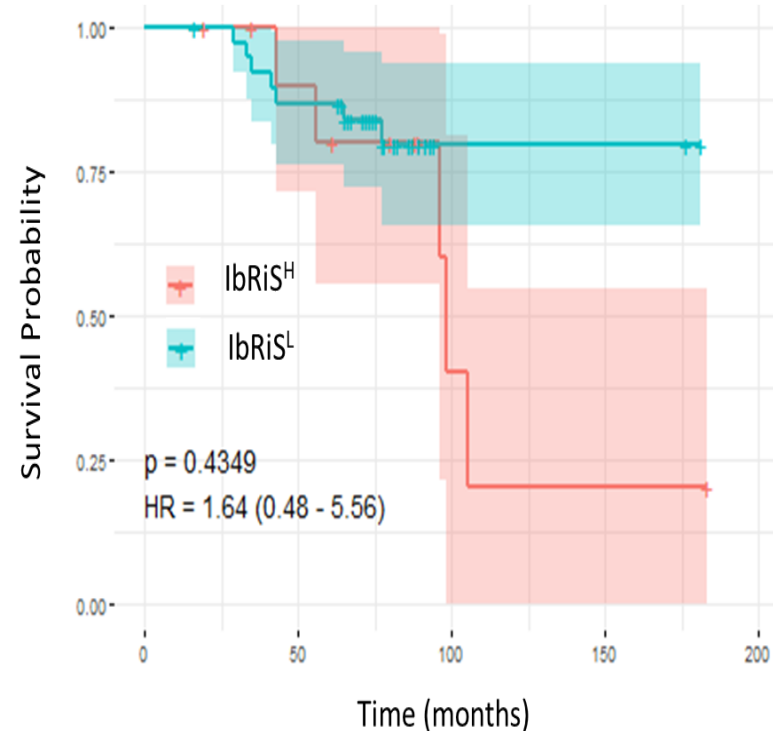


Number at risk

	0	50	100	150	200	250
IbRiS ^H	9	2	2	0	0	0
IbRiS ^L	67	16	10	1	1	1

Time (months)

IbRiS^H vs. IbRiS^L in inter Odx category (D₁₊₂)

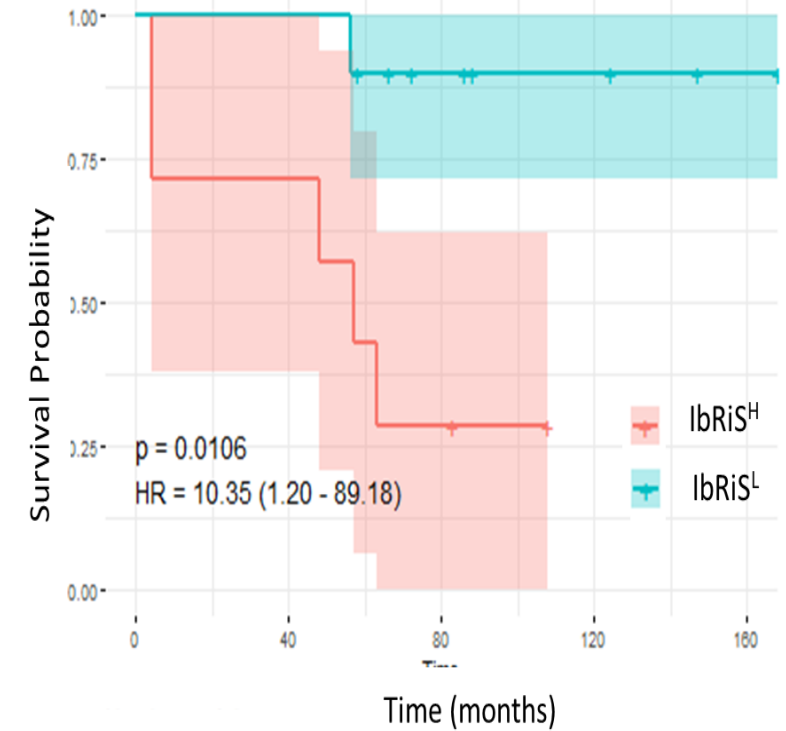


Number at risk

	0	50	100	150	200
IbRiS ^H	12	9	2	1	0
IbRiS ^L	39	33	2	2	0

Time (months)

IbRiS^H vs. IbRiS^L in high Odx category (D₁₊₂)

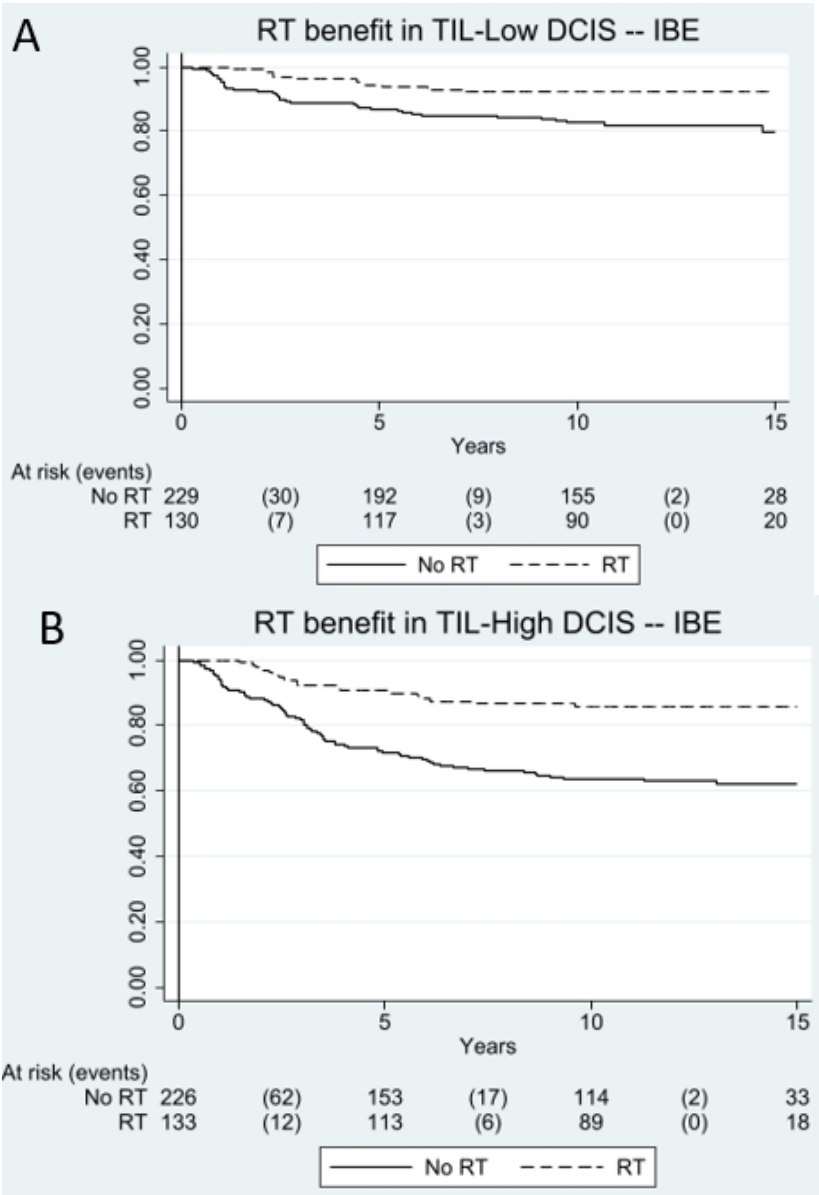
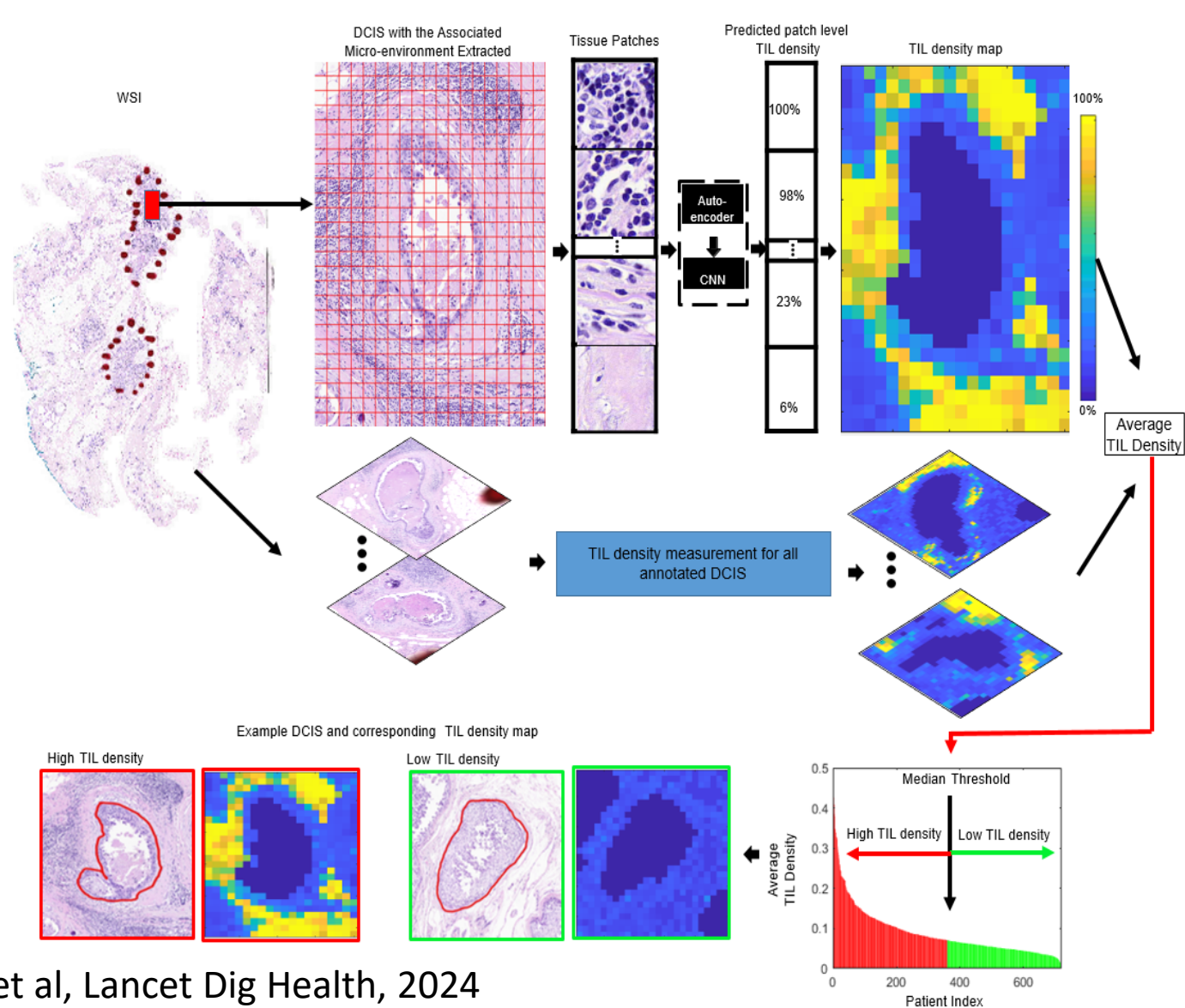


Number at risk

	0	40	80	120	160
IbRiS ^H	10	10	2	0	0
IbRiS ^L	10	10	6	3	1

Time (months)

Computer extracted features of immune architecture from H&E Whole slide images are associated with disease-free survival and benefit of radiotherapy in Ductal Carcinoma in situ (DCIS)

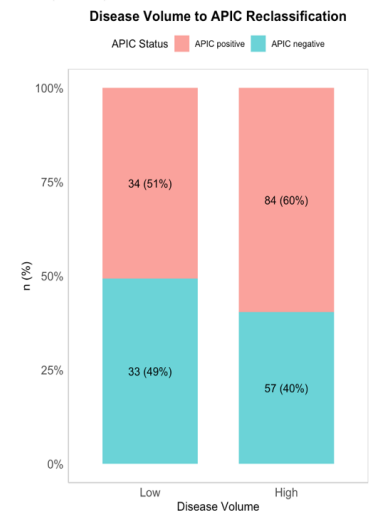
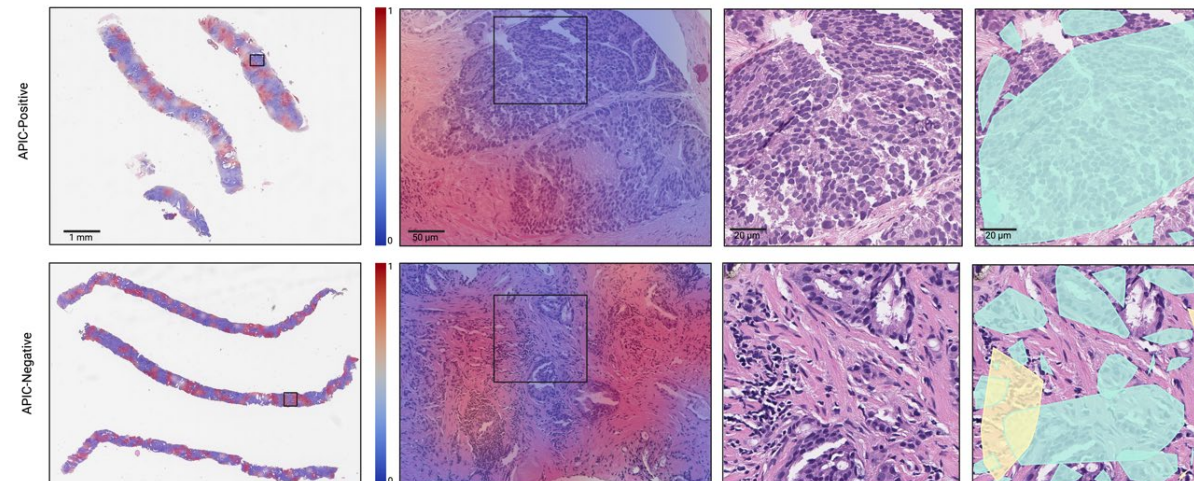
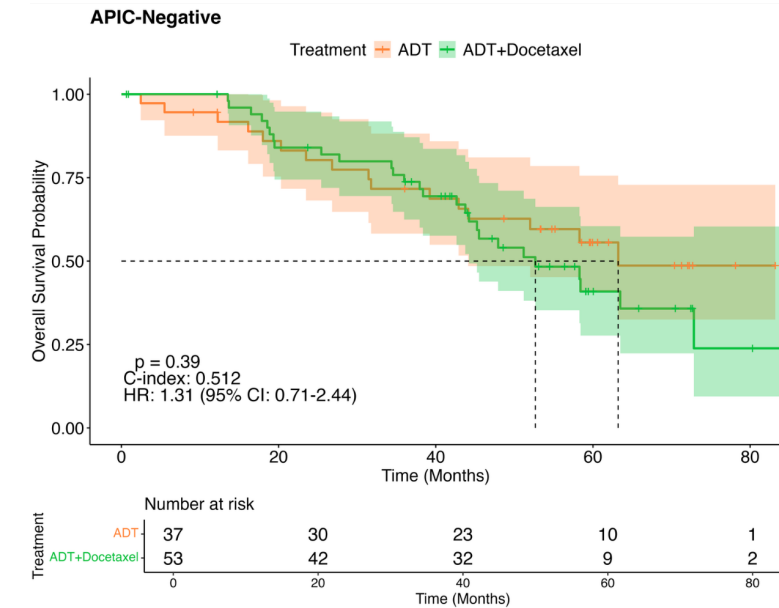
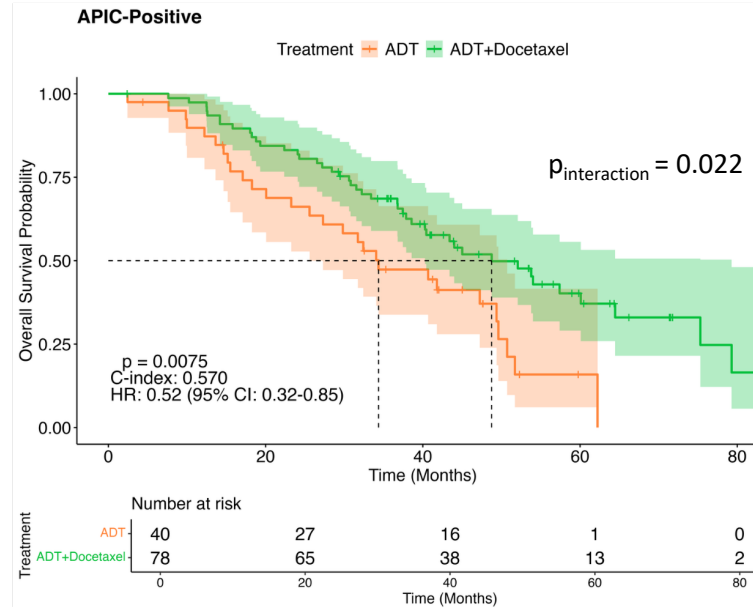
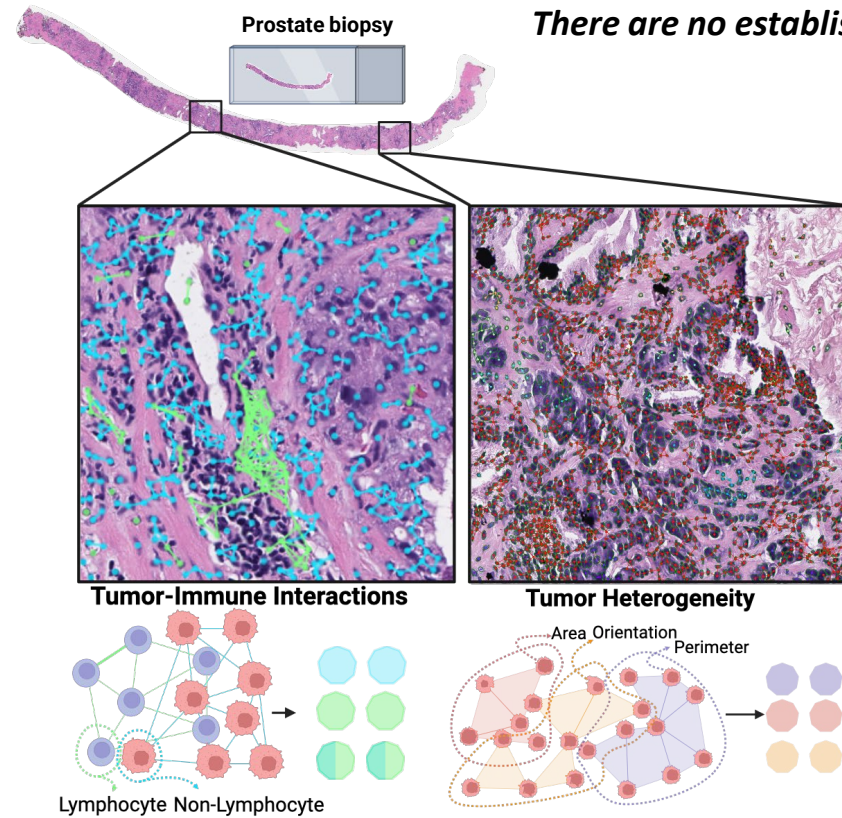


A predictive biomarker of docetaxel benefit in metastatic castration-sensitive prostate cancer (mCSPC)

Validation in the CHARTED phase III randomized controlled trial

- Docetaxel has proven survival benefit in metastatic disease, however benefit is heterogeneous
- Clinical trials show variable benefit when combined with ADT or ARPIs, especially in low volume metastasis

There are no established biomarkers to identify patients who will benefit from docetaxel

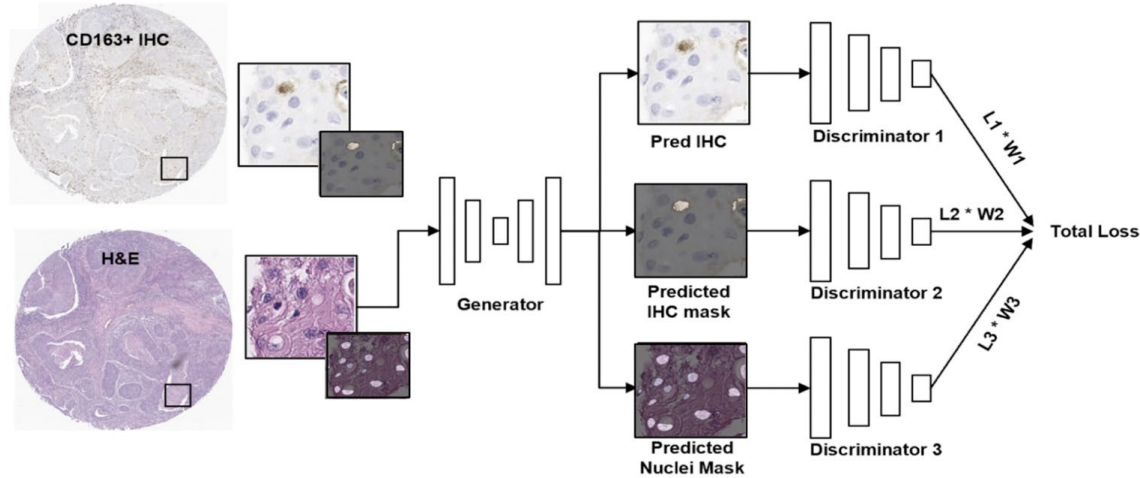


Median Overall Survival

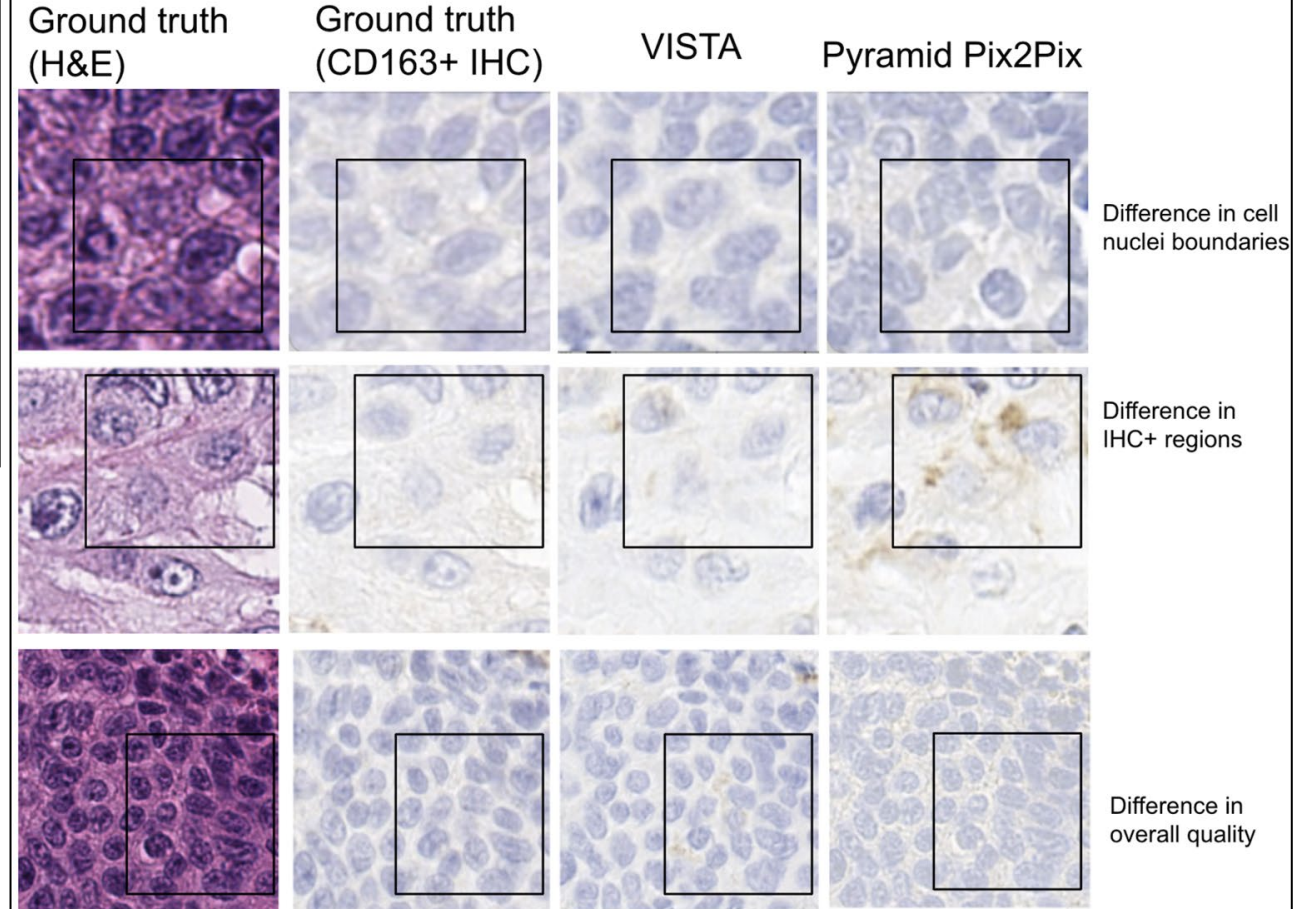
Therapy	APIC +	APIC -
ADT	2.9 years	5.3 years
ADT + Docetaxel	4.1 years	4.4 years

AI Virtual Staining for Identifying Tumor-Associated Macrophages from H&E: Prognosis of Head and Neck Cancer

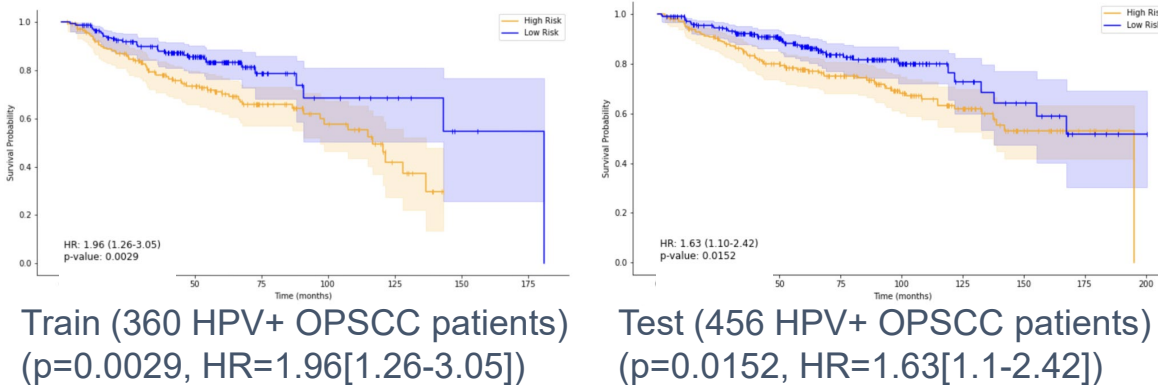
VISTA framework for H&E to IHC image translation



Qualitative results on H&E to CD163+ IHC image translation



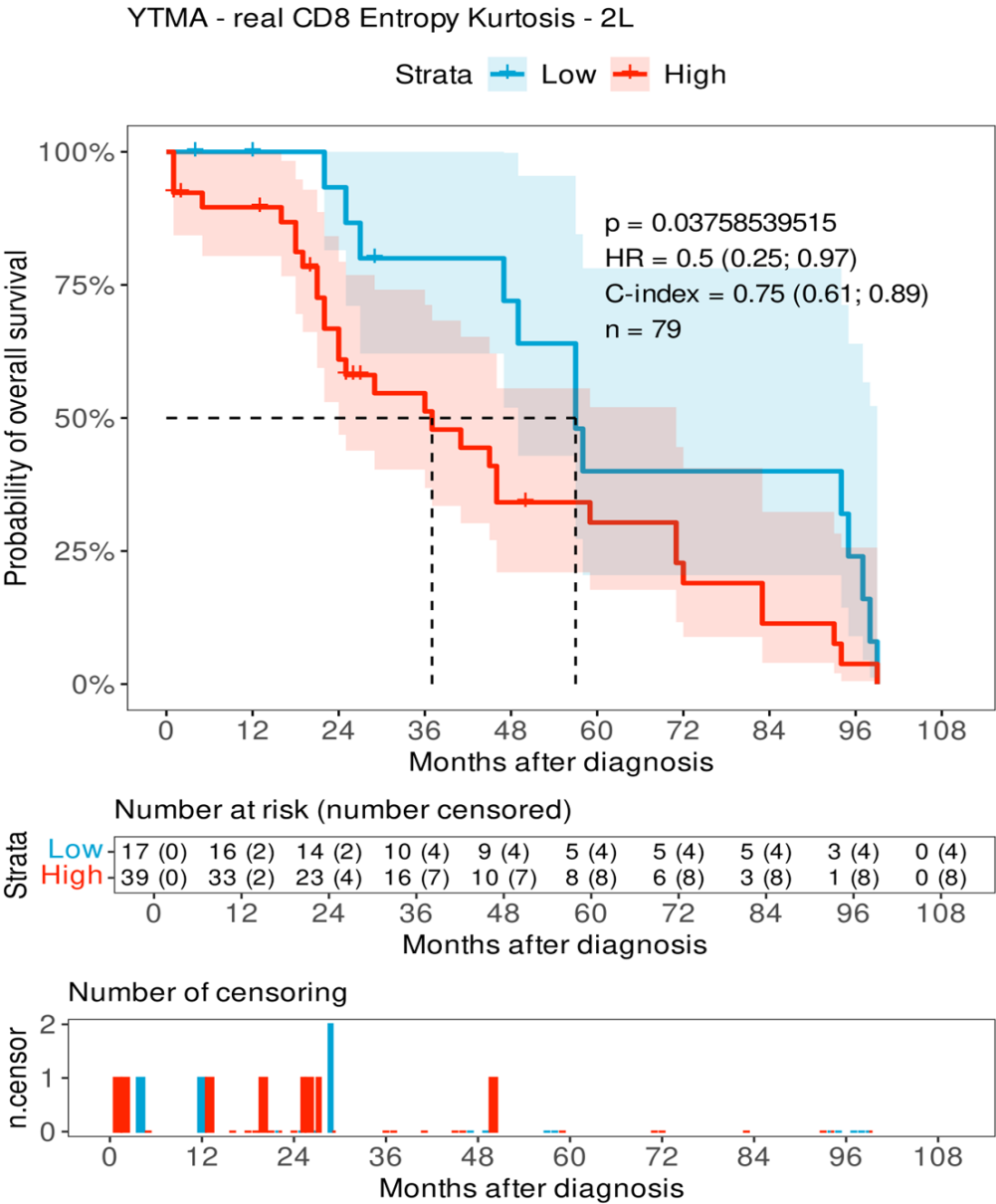
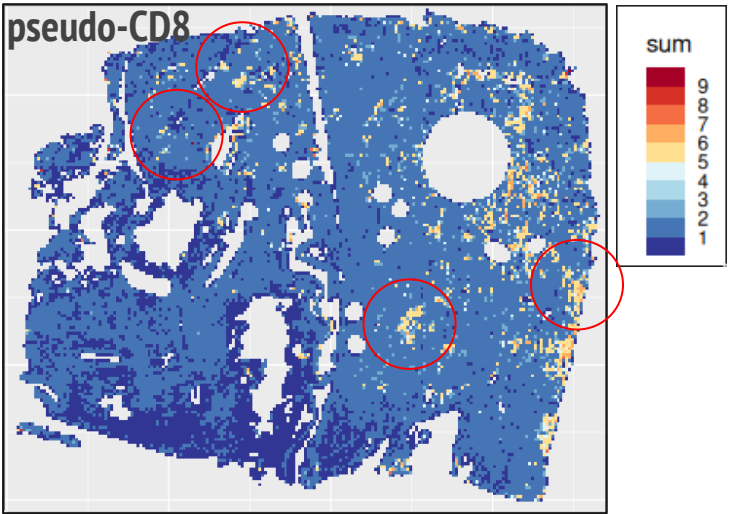
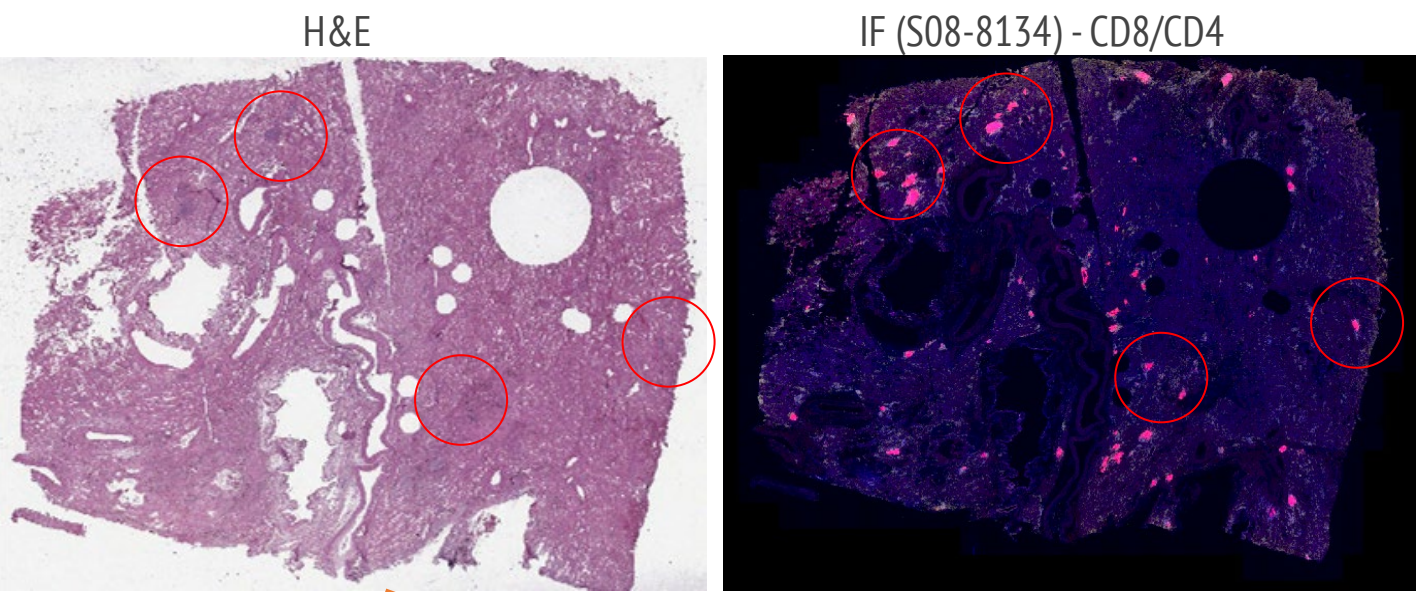
Association of VISTA-derived M2-TAM density biomarker with OS



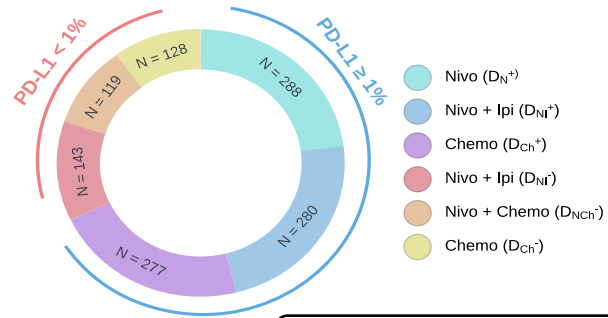
Methods

- Analysis on 968 HPV+ OPSCC patients - Train -> 102 co-registered H&E & CD163+ IHC
- Validate -> 50 co-registered H&E & CD163+ IHC - Validate -> 816 H&E WSIs with OS available

Virtual AI Staining for CD8+ Immune Cells on H&E Predicts Survival in Lung Cancer Patients Treated with Immunotherapy



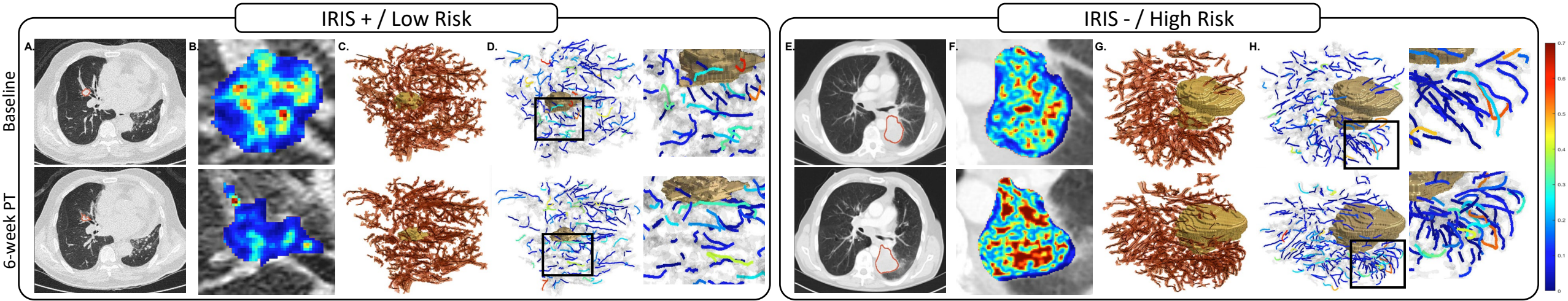
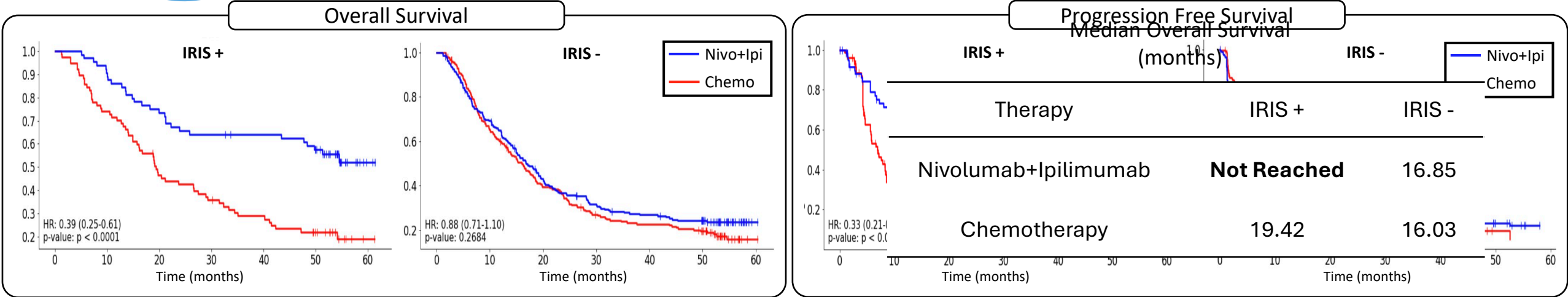
Predicting immunotherapy response using biology inspired AI biomarkers



Randomized Phase III Trial Evaluating Immunotherapy Compared to Chemotherapy in First Line Metastatic NSCLC

N = 1739 patients, 5-year follow-up

IRIS Predictive of IO benefit over Chemotherapy



Prospective Observational Validation: Preliminary Findings in INSIGNA/EA5163

INSIGNA/EA5163

- Ongoing Prospective Randomized Phase III Trial
- Formal exploratory endpoint
- Preliminary Association with Tumor Volume Change at 6-weeks

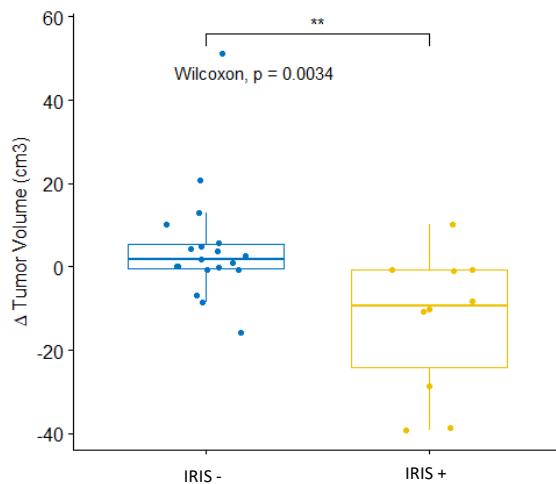
Trial Design



INSIGNA (D₃)

- 1L: ICI, 2L: Chemo
- 1L: ICI, 2L: ICI+Chemo
- 1L: ICI+Chemo, 2L: N.D.

Risk Stratification



Net decrease in
tumor volume in
IRIS-positive group

Illustrative Examples

↓ tumor volume

↑ tumor volume

Baseline

6-Week Post Treatment



AI-Informed Retinal Biomarkers Predict 10-Year Risk of Onset of Hematological Malignancies

Study design

1237 Patients

10-year follow-up

3 cancer types

Leukemia (N= 440)

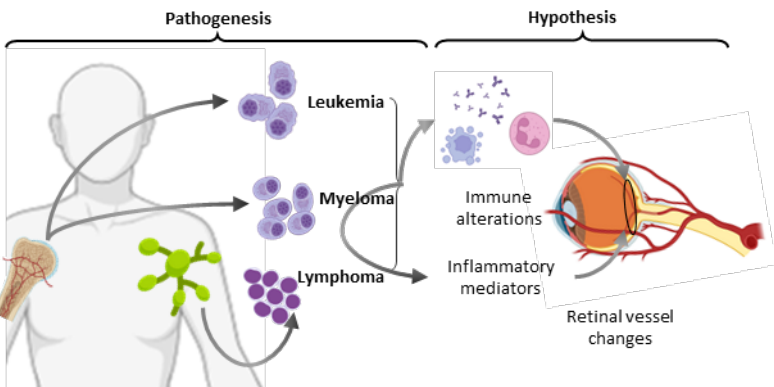
Myeloma (N = 314)

Lymphoma (N=483)

To reduce confounders:

Patient matched for
Age, Sex, HTN, Diabetes

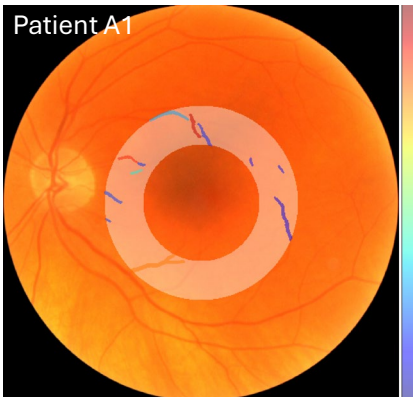
Patients with Existing
Cardiovascular event
removed



Results (Qualitative)

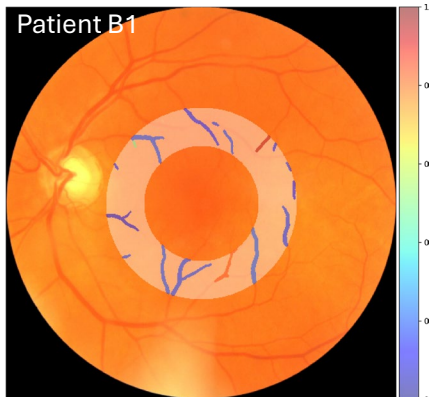
High risk for Leukemia

Patient A1

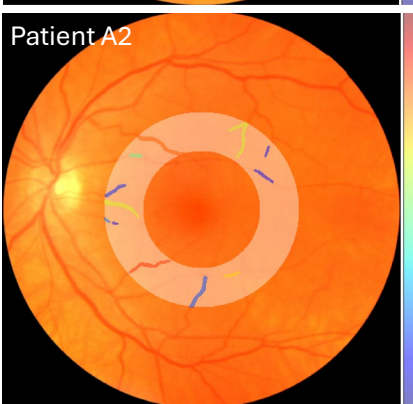


Low risk for Leukemia

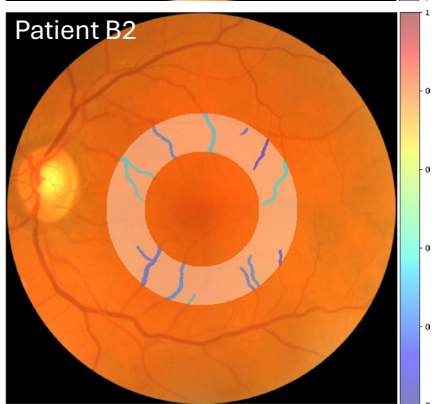
Patient B1



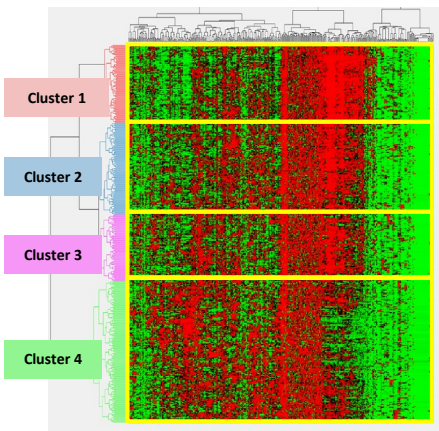
Patient A2



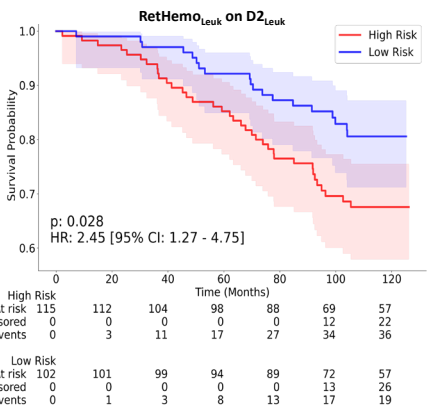
Patient B2



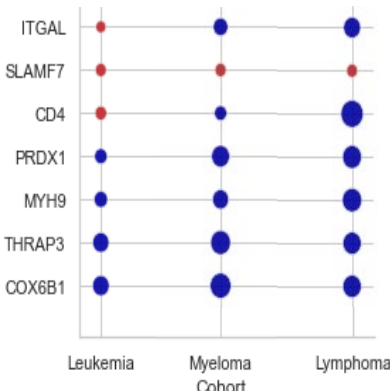
Results (Quantitative)



**Retinal features based
clusters have difference
in risk of developing
cancer**



**Risk stratification upto
10 years prior to onset of
cancer**



**Retina based High risk
patients had elevated
levels of inflammatory
proteins (proteomics)**

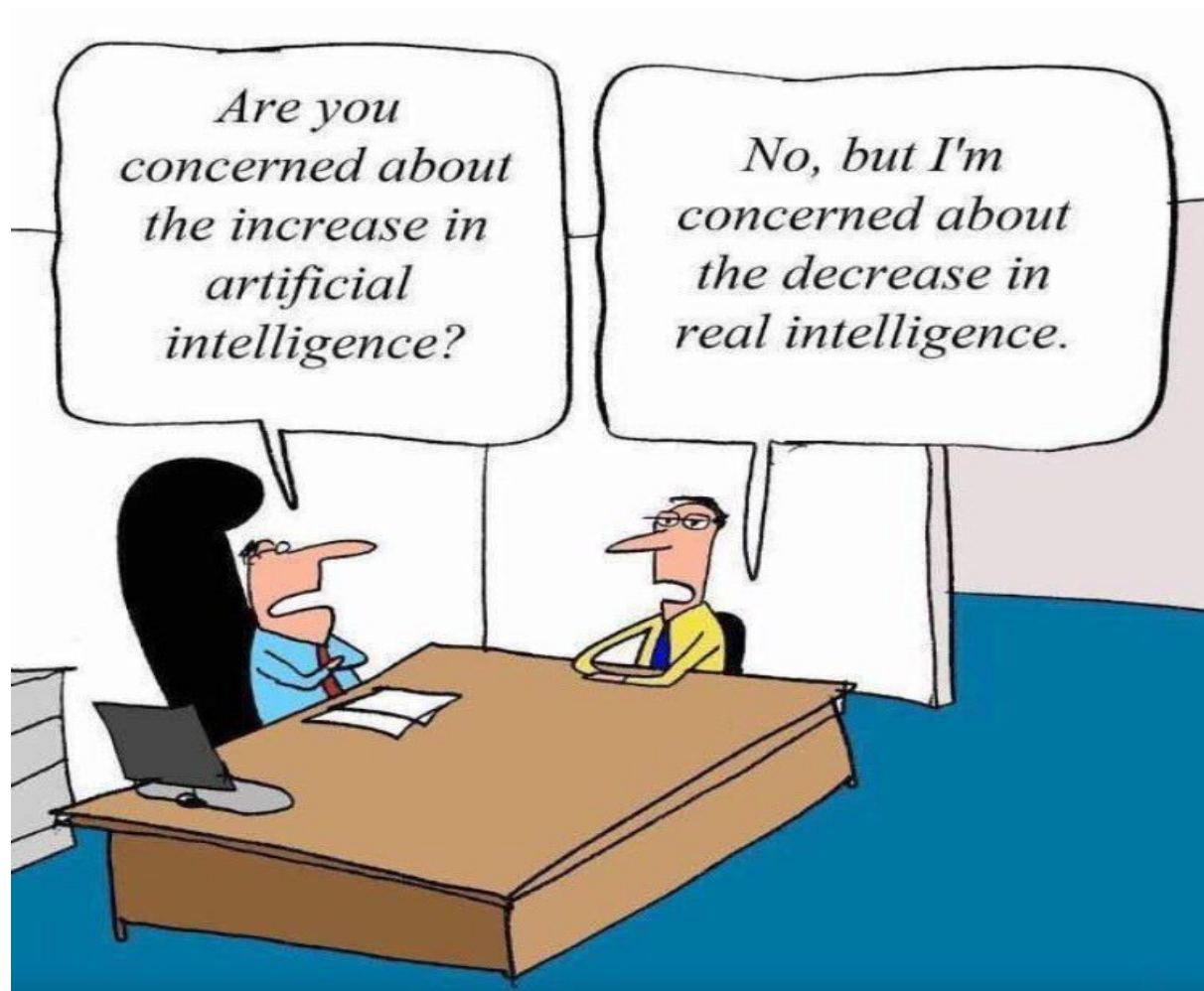
Take Away

- **AI is not magic** – Need to be thoughtful and intentional in developing algorithms.
- **Computational Analytics with routine imaging** and data could help address questions in precision medicine, specifically prognosis and predicting response to therapy
- **Low cost** computational diagnostics, need to be intentional in addressing **equity. Global impact**, especially **low and middle income** countries.
- Critical need to validate on completed and prospective clinical trials to establish predictive validity and establish higher levels of evidence.

Acknowledgements

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- W81XWH-20-1-0851
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