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Imaging AI to Predict Outcomes and Treatment Response for Breast Cancer

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Need for Better Diagnostic, Predictive Tools

Diagnostic: *Identifying presence of disease*

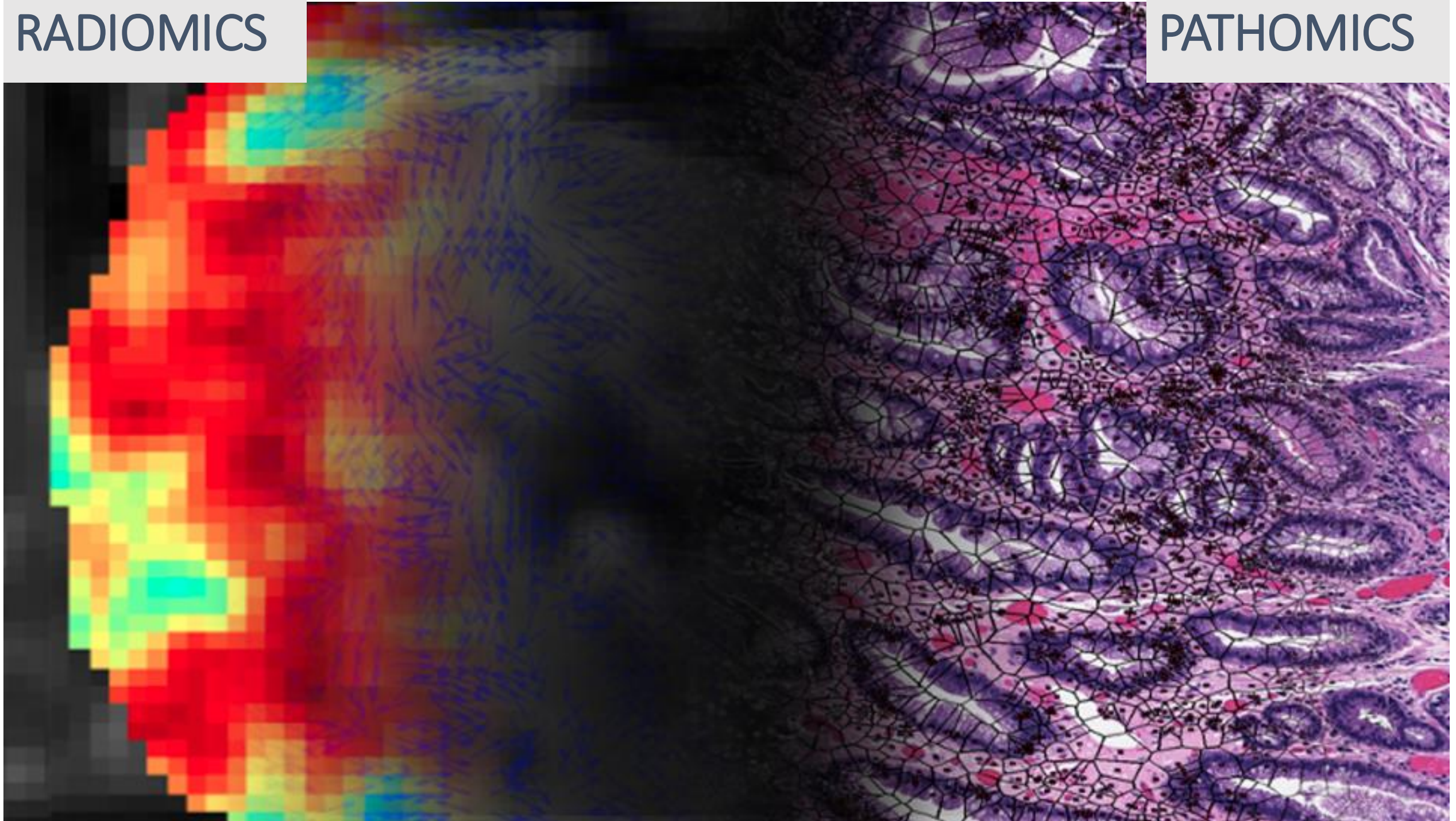
Prognostic: *Predicting Disease Outcome, progression*

Predictive: *Predicting Response to treatment*

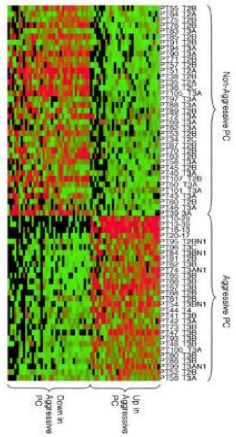
Precision Medicine*: Using Prognostic and Predictive Tools for Tailoring Therapy for a given patient based off specific risk profile*

RADIOMICS

PATHOMICS



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

Collagen fiber detection

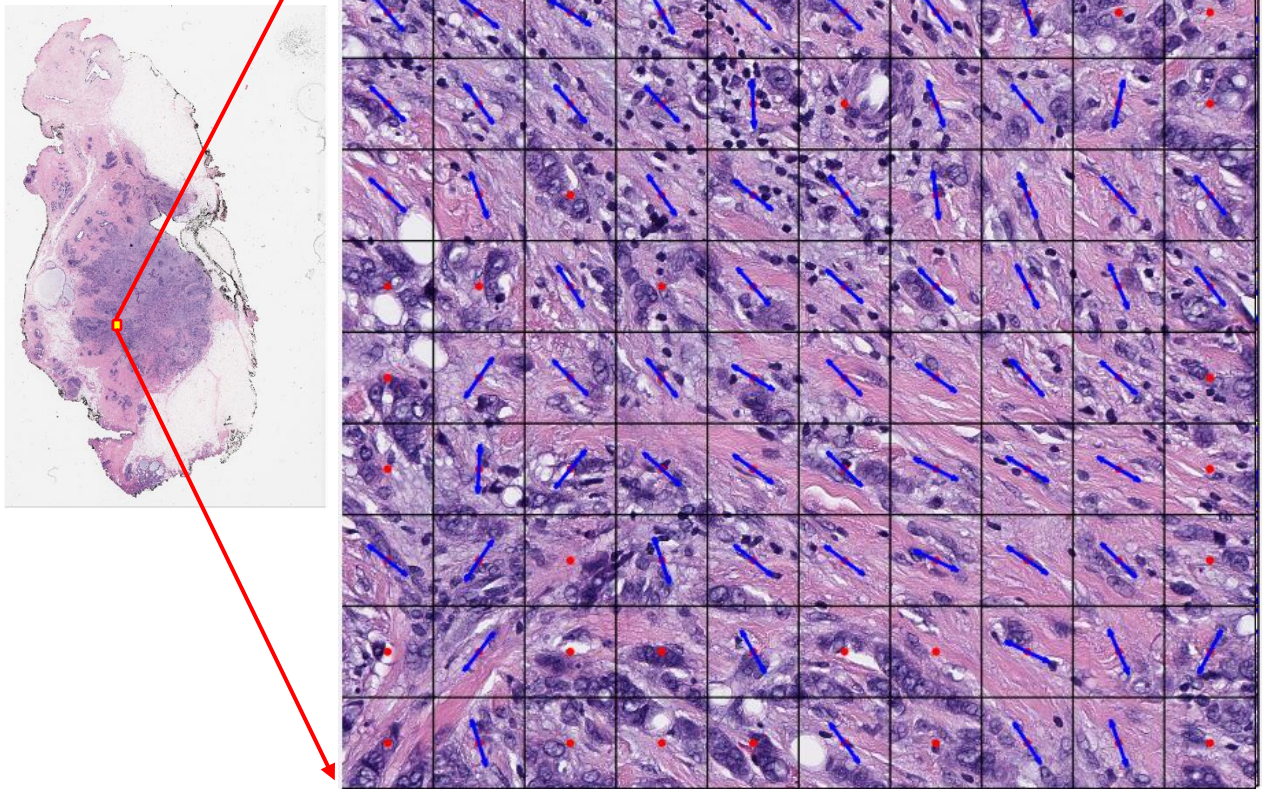
Epithelium segmentation

Collagen vectors in tumor-associated stroma

Collagen fiber orientation disorder calculation

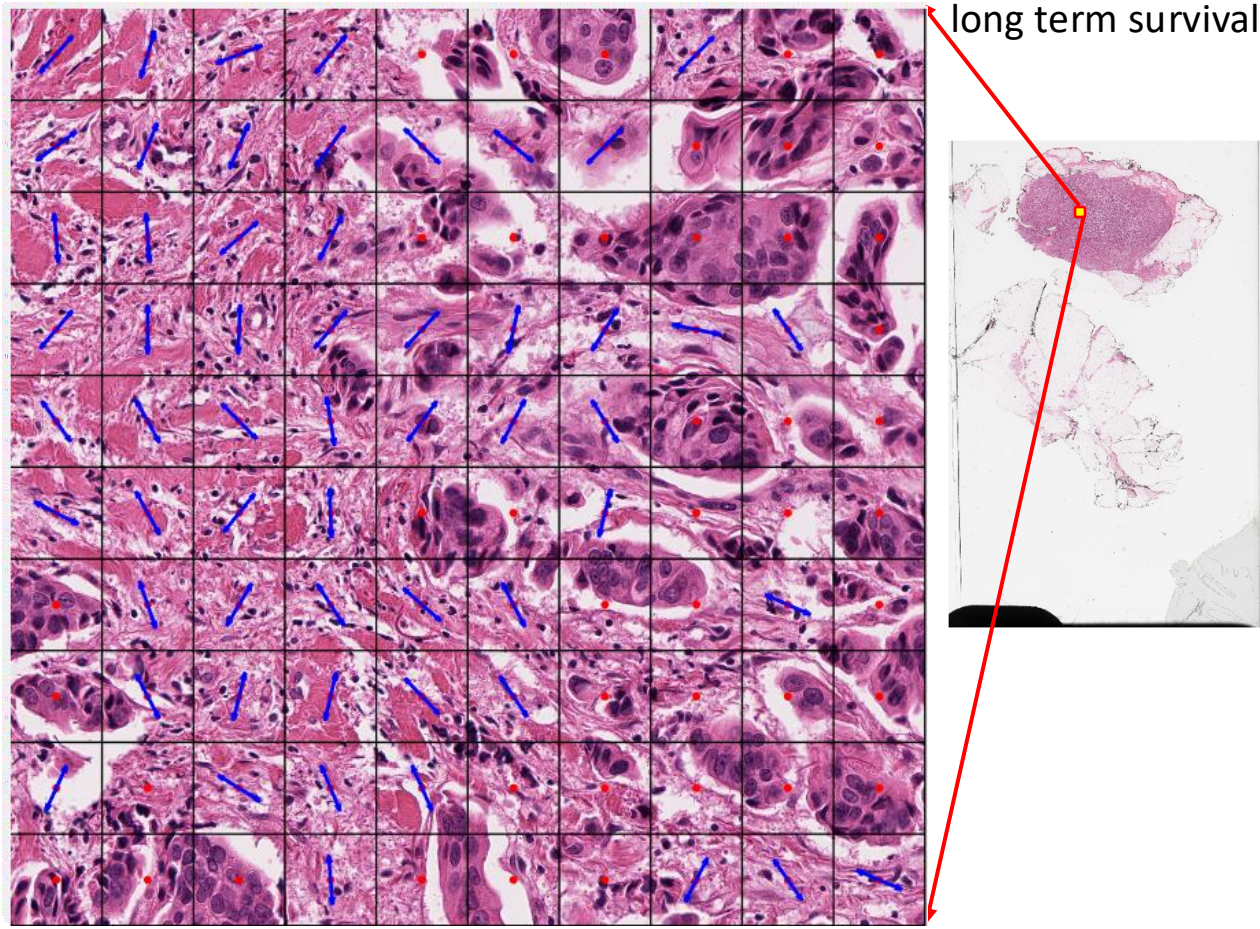
Low degree of disorder

Short term survival



High degree of disorder

long term survival



Li et al, npj Breast Cancer, 2021

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

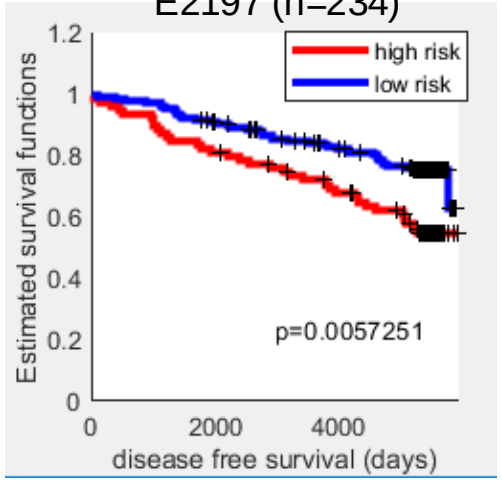
Unmet Clinical Need

- 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.

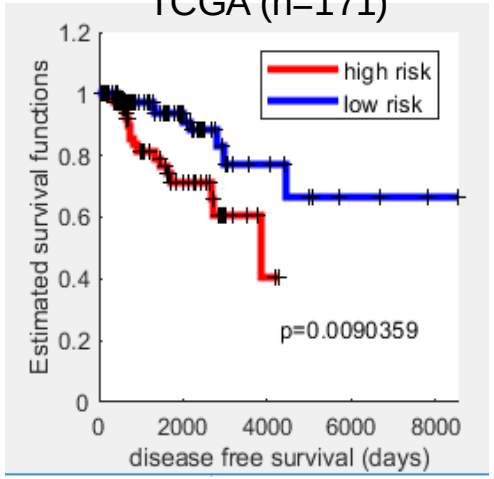
Results:

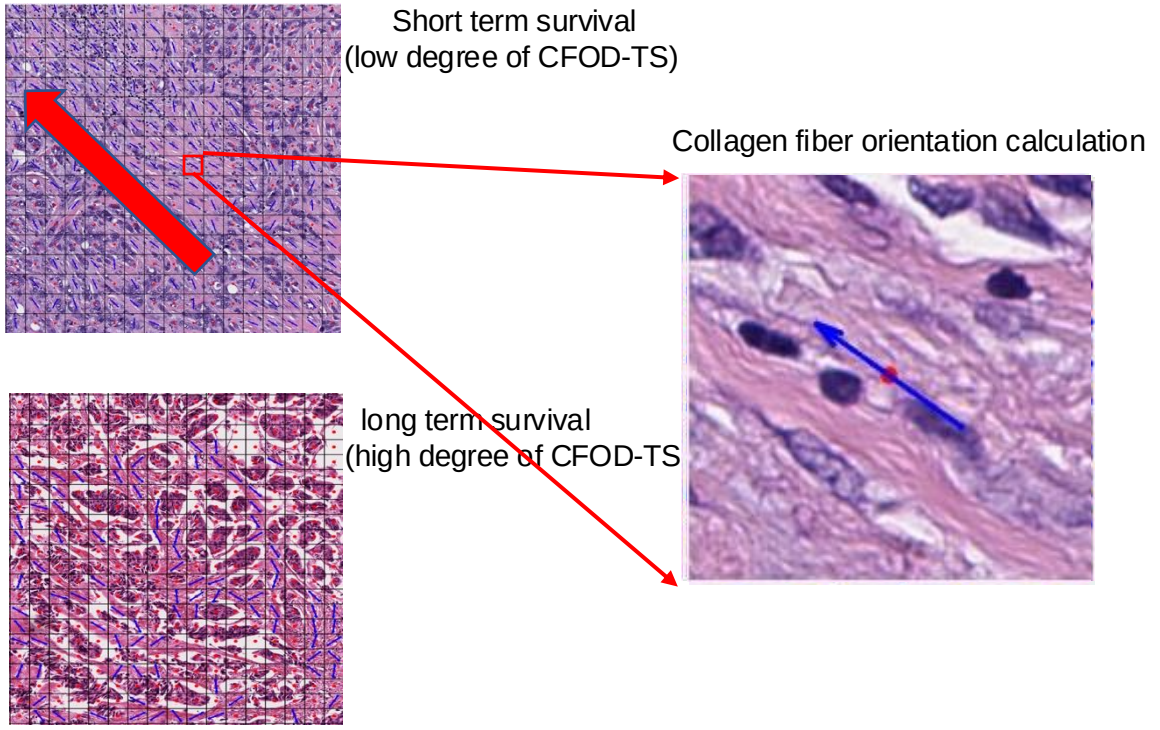
- Collagen Fiber Orientation Disorder in Tumor associated Stroma (CFOD-TS) was independently prognostic for ER+ BCs in E2197 and TCGA.

E2197 (n=234)



TCGA (n=171)

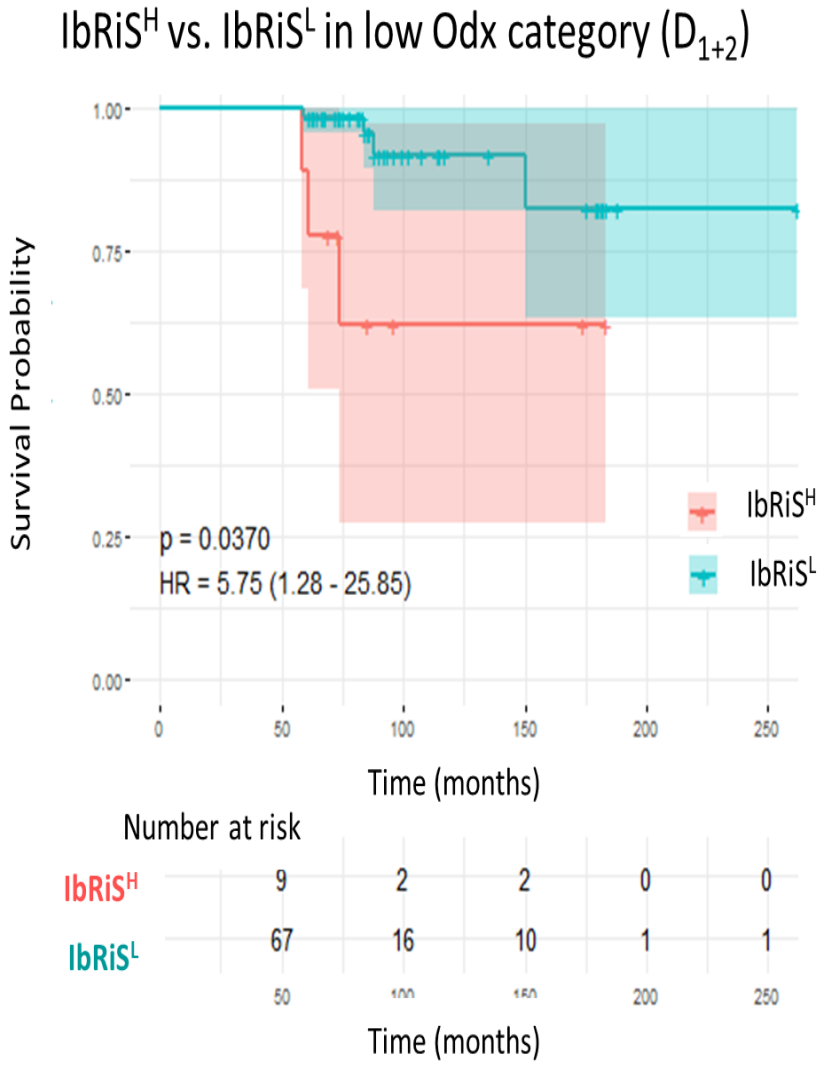


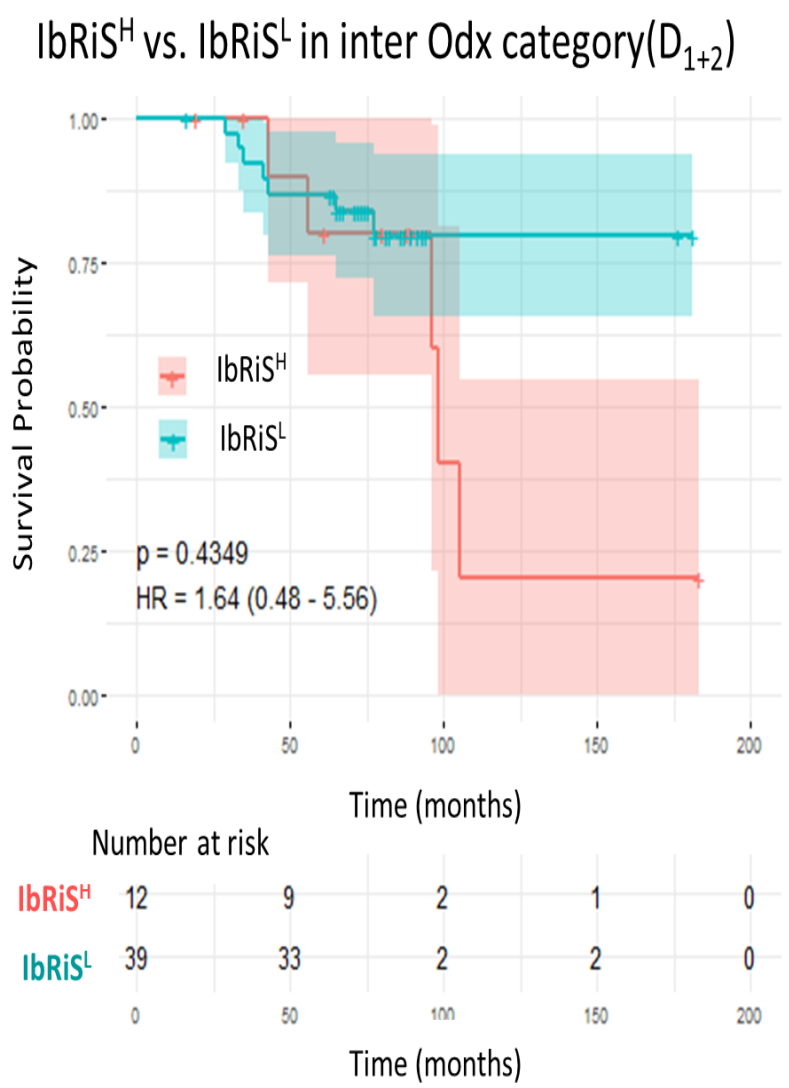


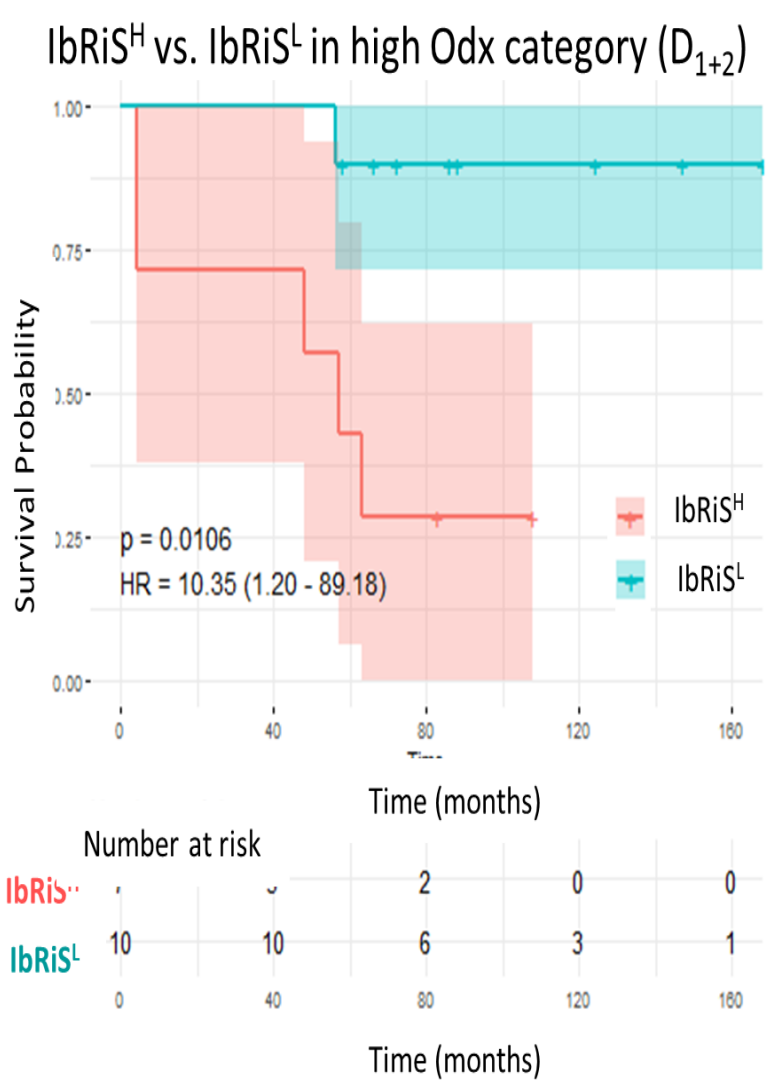
Take away:

Over-expression of CFOD-TS 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 in Estrogen Receptor Positive (ER+) Breast Cancer

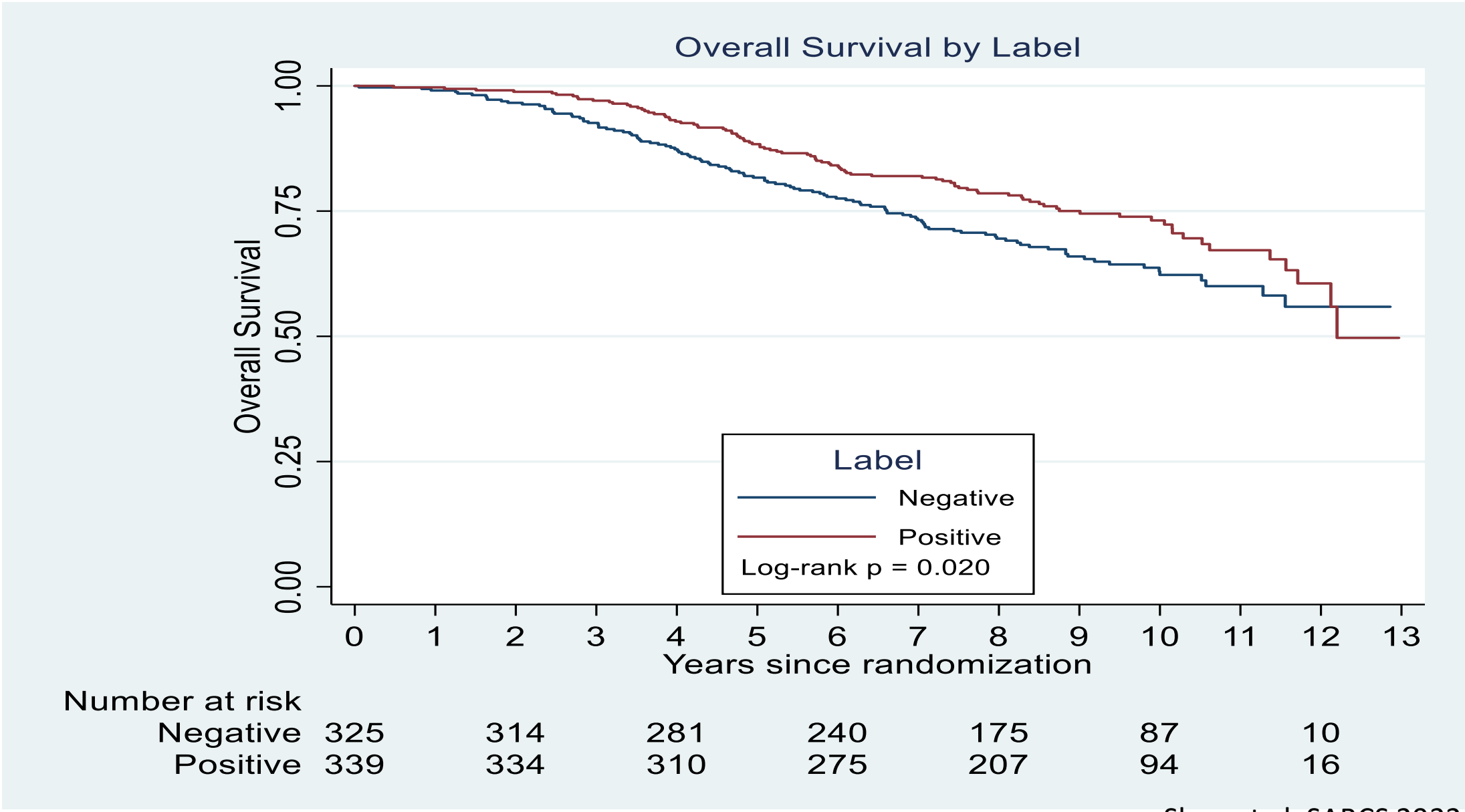






Chen et al, npj Breast Cancer 2023.

Independent Validation on SWOG S8814



Shao et al, SABCS 2022

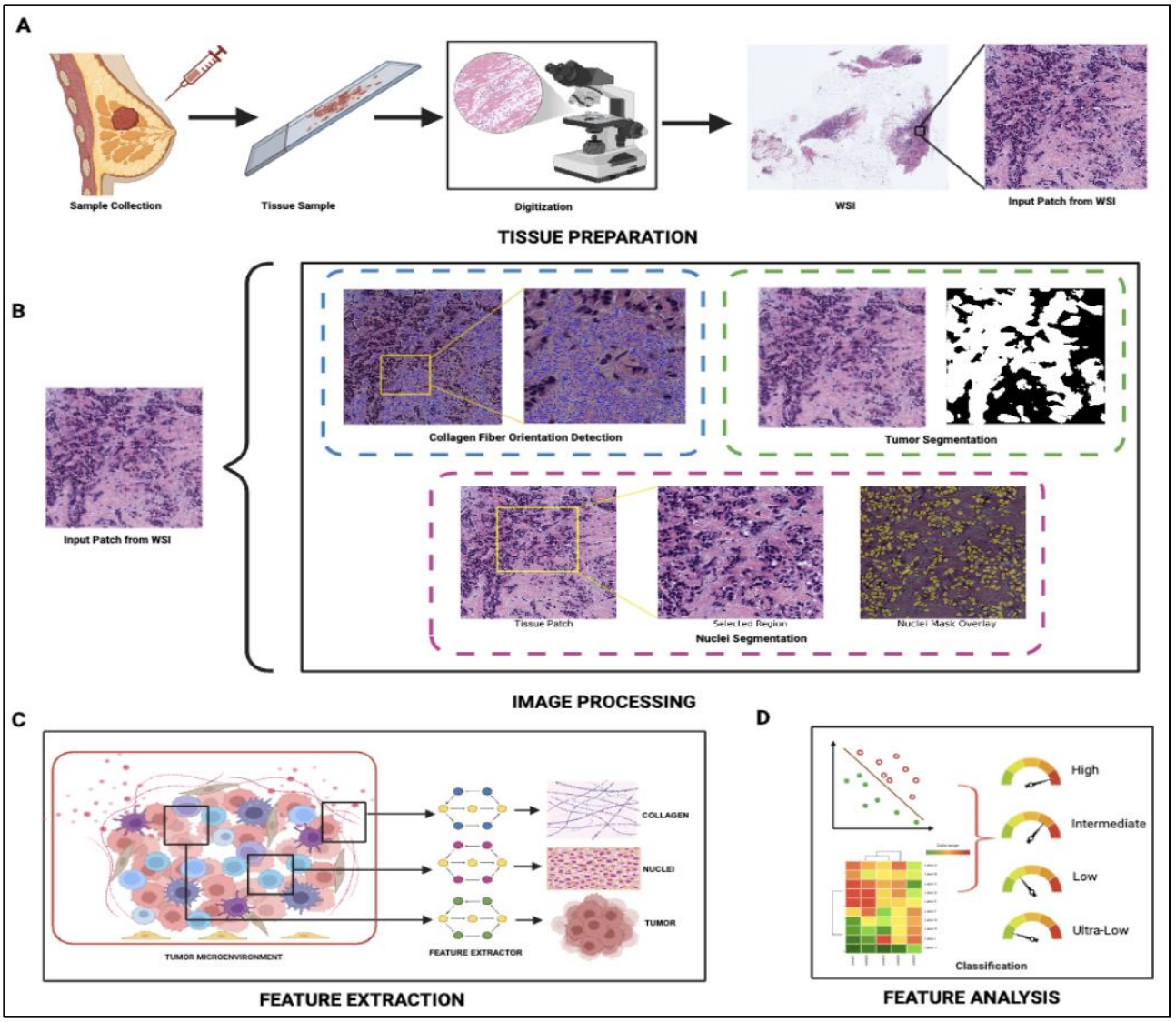
MammaPrint Ultra-Low Luminal A Stratification Based-on Histopathology Images

Objective
To stratify MammaPrint genomic assay-derived Ultra-Low Risk Luminal A patients from Low-Risk Luminal A patients using histopathology features.

Experiment
A computational pathology method was developed to quantitatively characterize collagen and nuclei histomorphometry as well as tumor components of the TME, analyzed on 218 H&E biopsy slides from UH (145 for training and 73 for testing).

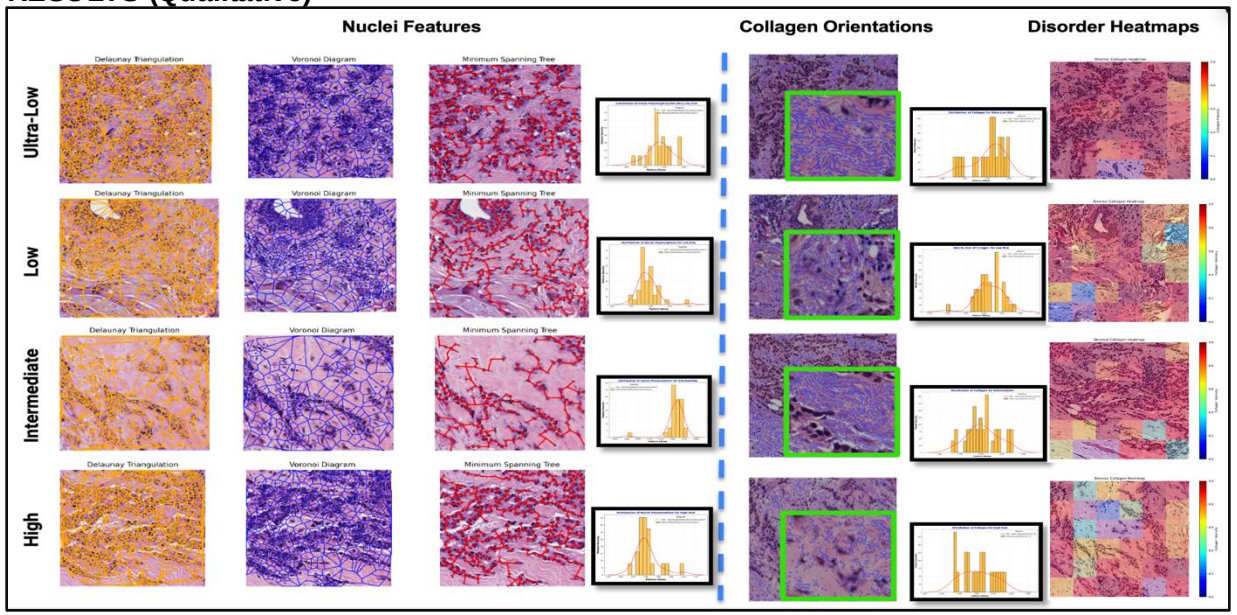
Results
Our patient-level analysis demonstrated that histopathology features can distinguish Ultra-Low risk patients from Low-risk patients with 74% accuracy.

WORKFLOW

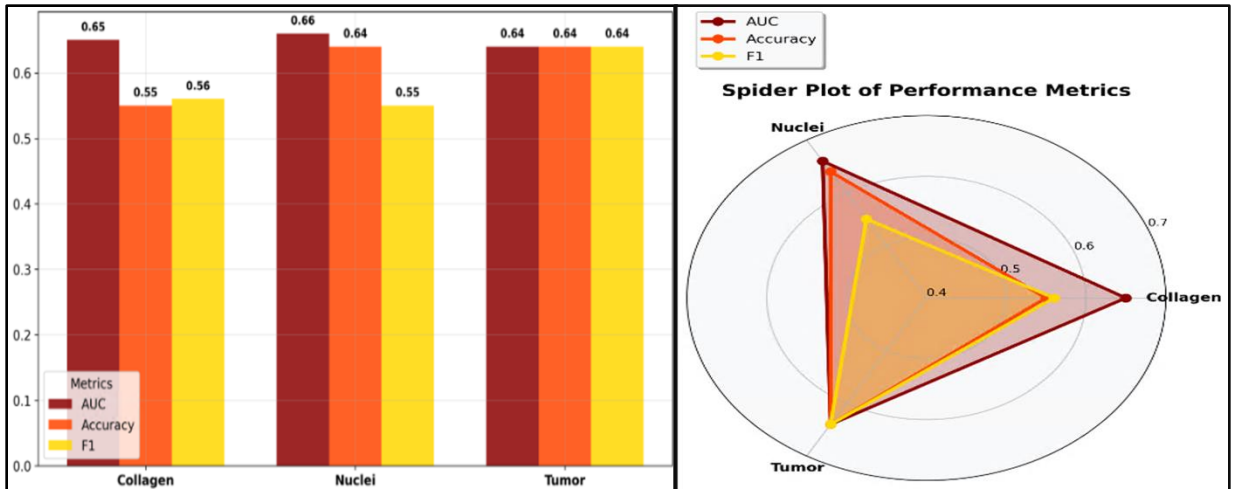


*Unpublished work do not circulate

RESULTS (Qualitative)



RESULTS (Quantitative)



HAI-Score, An Objective Image-Based Method for Accurate HER2 H-Score Estimation from IHC-Stained Breast Cancer Samples

Objective: To develop an objective, accurate, cost-effective, alternative to evaluate HER2 expression

Cohorts: Tissue microarray cores stained with HercepTest (S1 dataset, n=566) and Ventana Pathway 4B5 (S2 dataset, n=580) assays, accompanied by ground truth HER2 RNA levels measured via RNAscope, an in-situ hybridization test

Results: The HAI-Score strongly correlated with HER2 RNA levels and was superior to AHSQ (SOTA), an expert breast cancer pathologist, and current hospital-standard assays (HercepTest and Ventana)

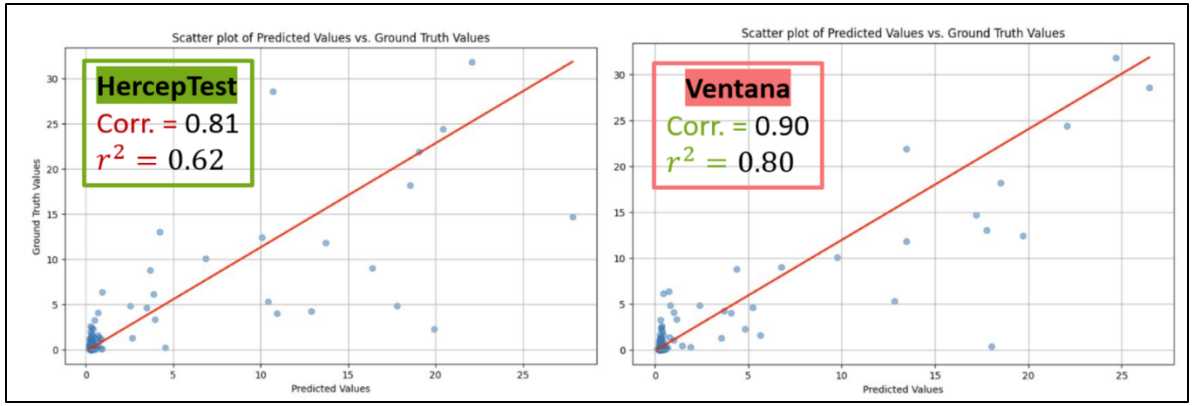


Fig 2. HAI-Score correlation with RNA values on the test dataset for HercepTest and Ventana assays

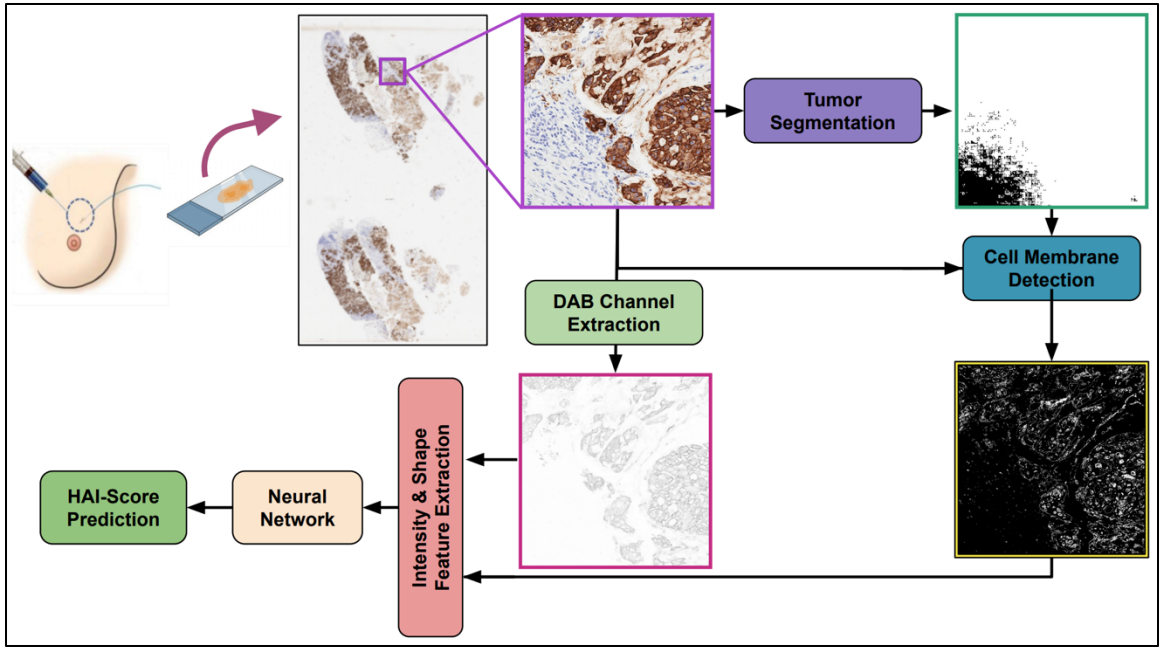


Fig 1. Workflow of HAI-Score development: tumor detection, cell membrane Detection, feature extraction, and neural network training

Holdout set (N=231)		
Method	**Pearson Correlation**	**R-Squared Error**
Ventana PATHWAY 4B5	0.580	0.330
HercepTest	0.760	0.570
Pathologist	0.760	0.580
AHSQ	0.827	0.685
HAI-Score	**0.850**	**0.710**

*** Unpublished work, please do not circulate**

Predictive image biomarker for benefit of Trastuzumab-based regimens in HER2+ breast cancer patients validated on NSABP B41 clinical trial

An image biomarker, **based on the density and spatial arrangement of tumor-infiltrating lymphocytes**, was trained on the HER2+ *TCGA cohort (n=298)* and validated for its ***prognostic*** ability on *ECOG 2197 (n=54),* Her2+ dataset from University Hospitals, Cleveland *(n=193)*, while also demonstrating its ***predictive*** ability in the NSABP B-41 clinical trial *(n=310).*

Image biomarker low

Trastuzumab dominating regimen vs Lapatinib alone

(interaction term p = 0.022*)

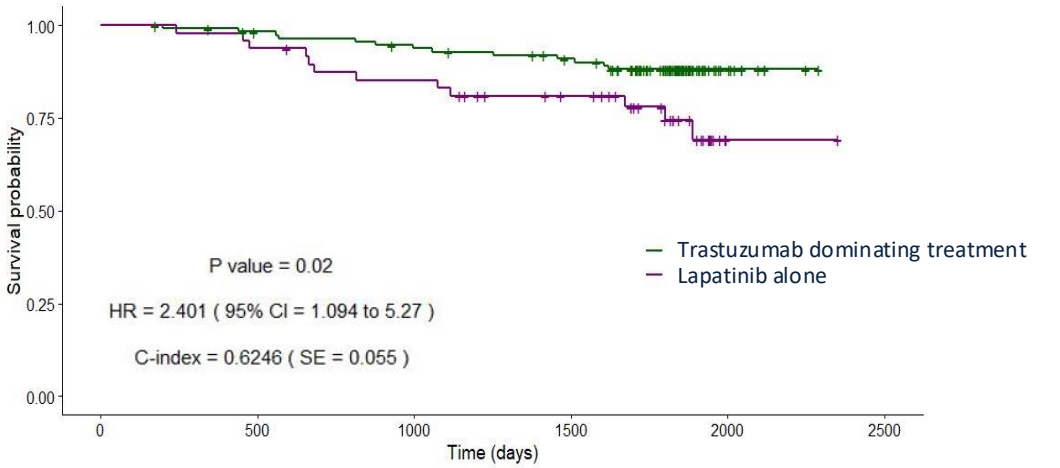
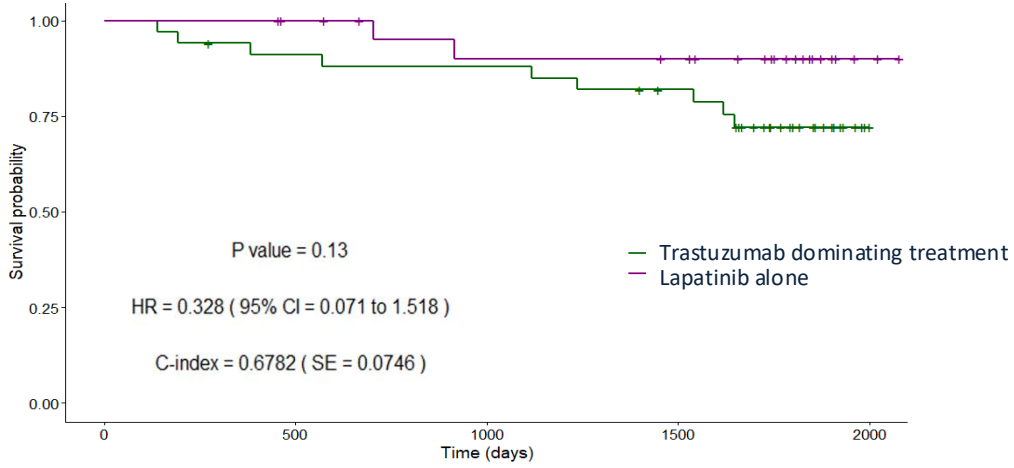


Image biomarker high

Trastuzumab dominating regimen vs Lapatinib alone



The image biomarker identifies a subset of patients who significantly benefit from Trastuzumab-containing regimens *compared to Lapatinib alone, while* ***the image biomarker-high does not show*** *a significant benefit associated for the same regimen.*

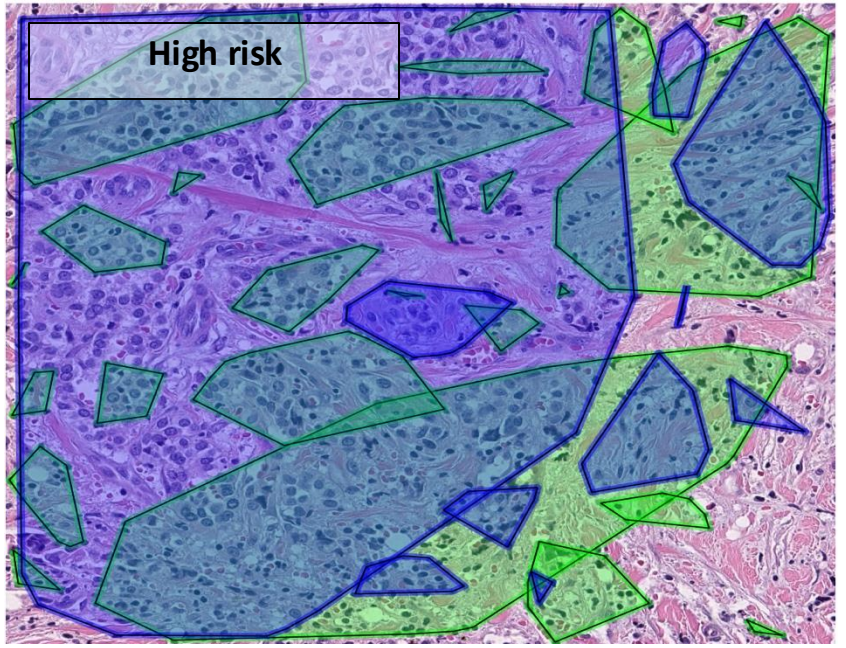
Spatial TIL architecture associated with outcome in Early-Stage TNBC

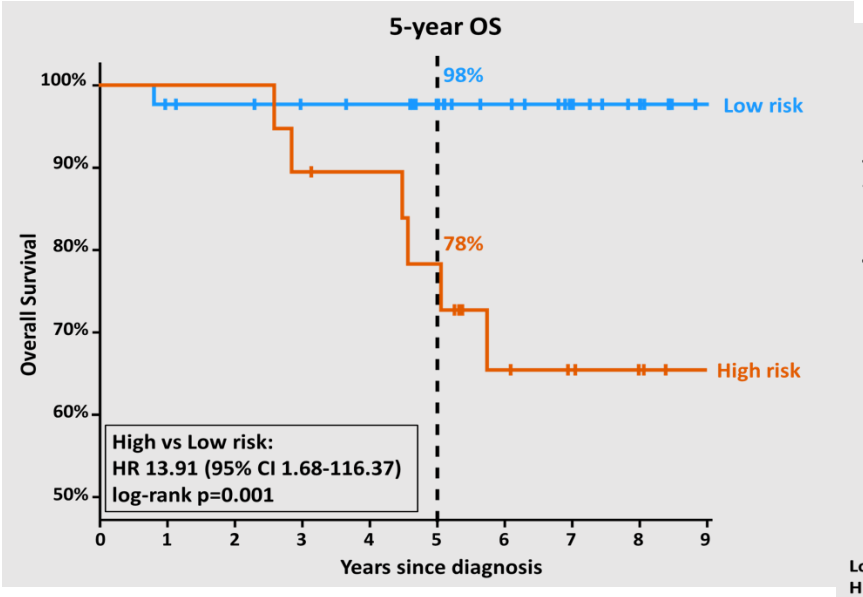
Aim: Evaluate prognostic utility of features derived from spatial architecture of TILs in H&E slides in early-stage TNBC

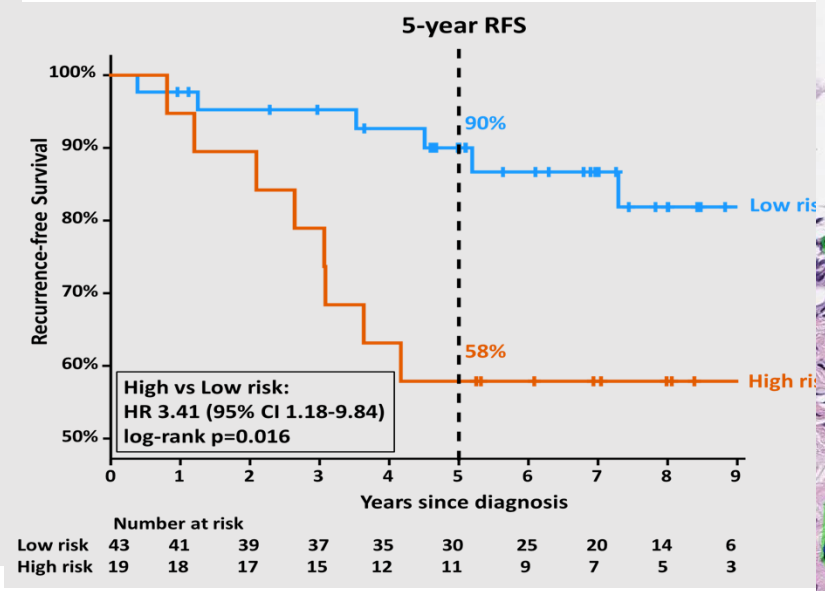
Datasets	# Cases
Instituto Nacional de Enfermedades Neoplásicas, Peru	26
University of Kansas	62
Total	88

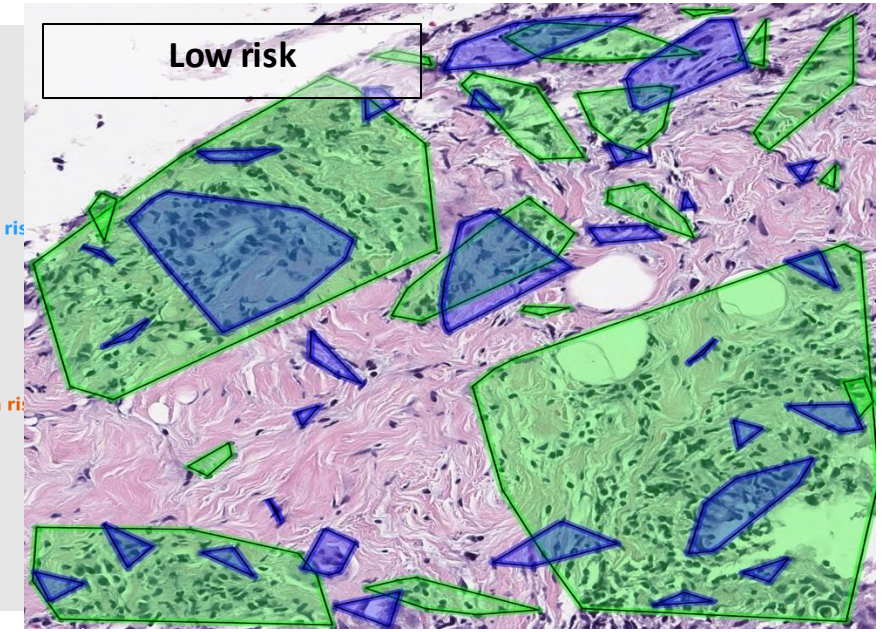
Feature discovery and model training

Independent validation



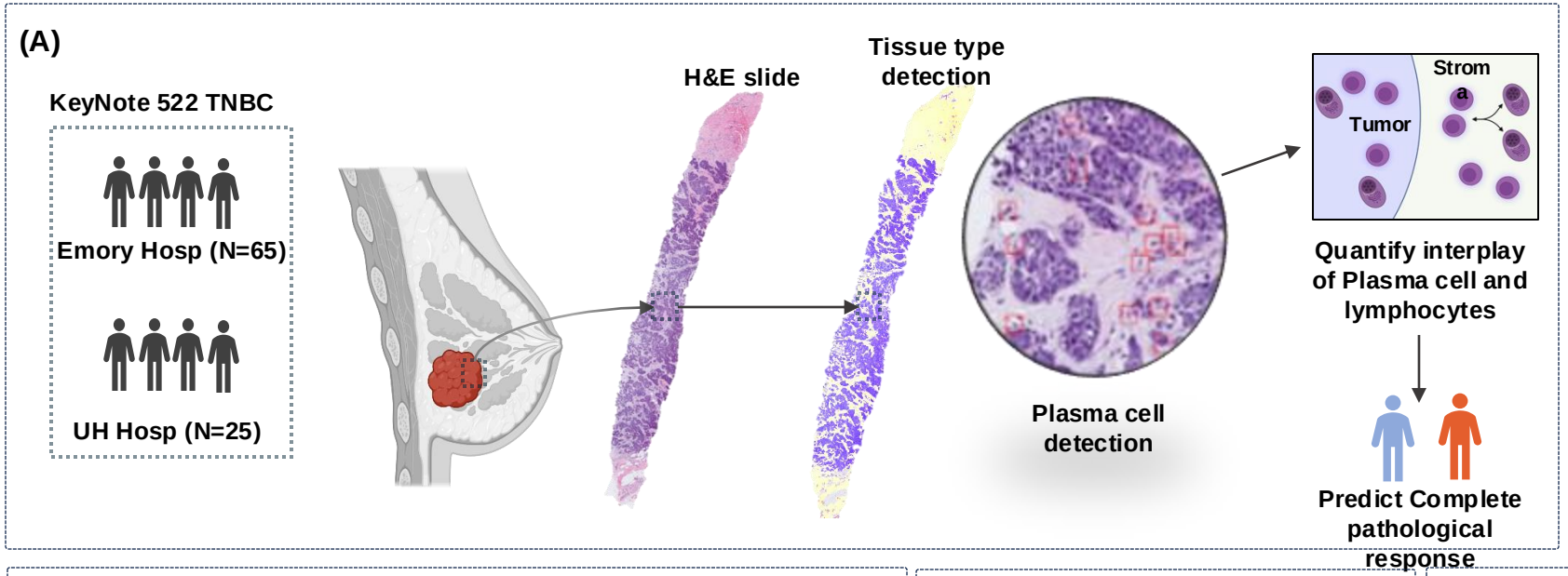






Corredor et al AACR 2023

Tumor-Infiltrating Plasma Cells on H&E Predictive of Complete Pathological Response in Triple Negative Breast Cancer: KEYNOTE-522



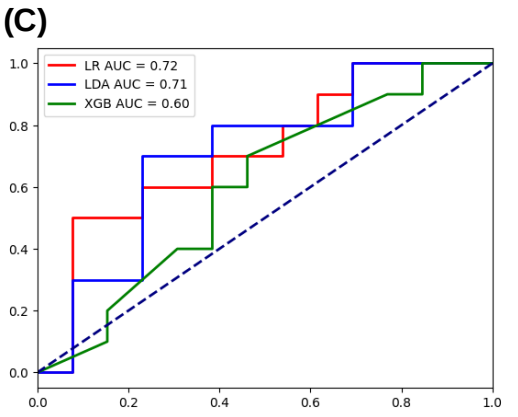
Objective: Predict complete pathological response, via interaction of tumor-infiltrating plasma cells and lymphocytes

Cohort: Stage I-III TNBC patients from KeyNote 522 trial (NCT03036488), who received pembrolizumab plus chemo

Results: Interplay of tumor-infiltrating plasma cells and lymphocytes is predictive of complete pathological response. (Holdout AUC=0.72).

(B)

	Holdout set (N=25)			
	AUC	F1	Sensitivity	Specificity
Logistic Reg	**0.715**	0.636	**0.7**	0.615
LDA	0.708	**0.667**	**0.7**	**0.69**
XGboost	0.6	0.571	0.6	0.615



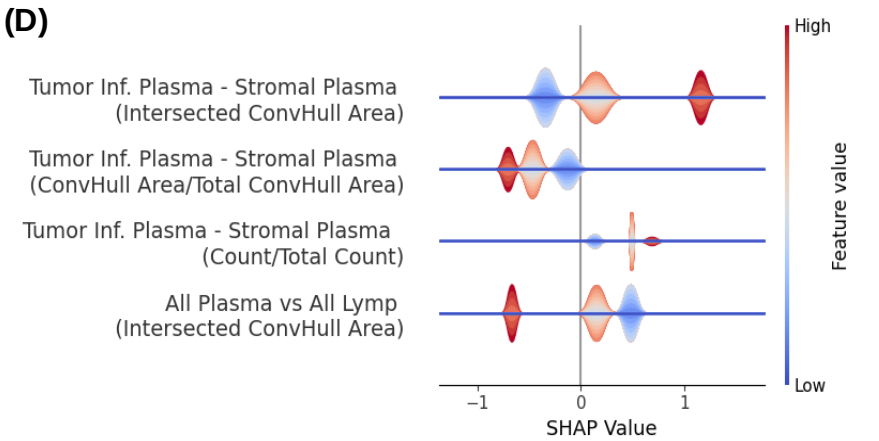
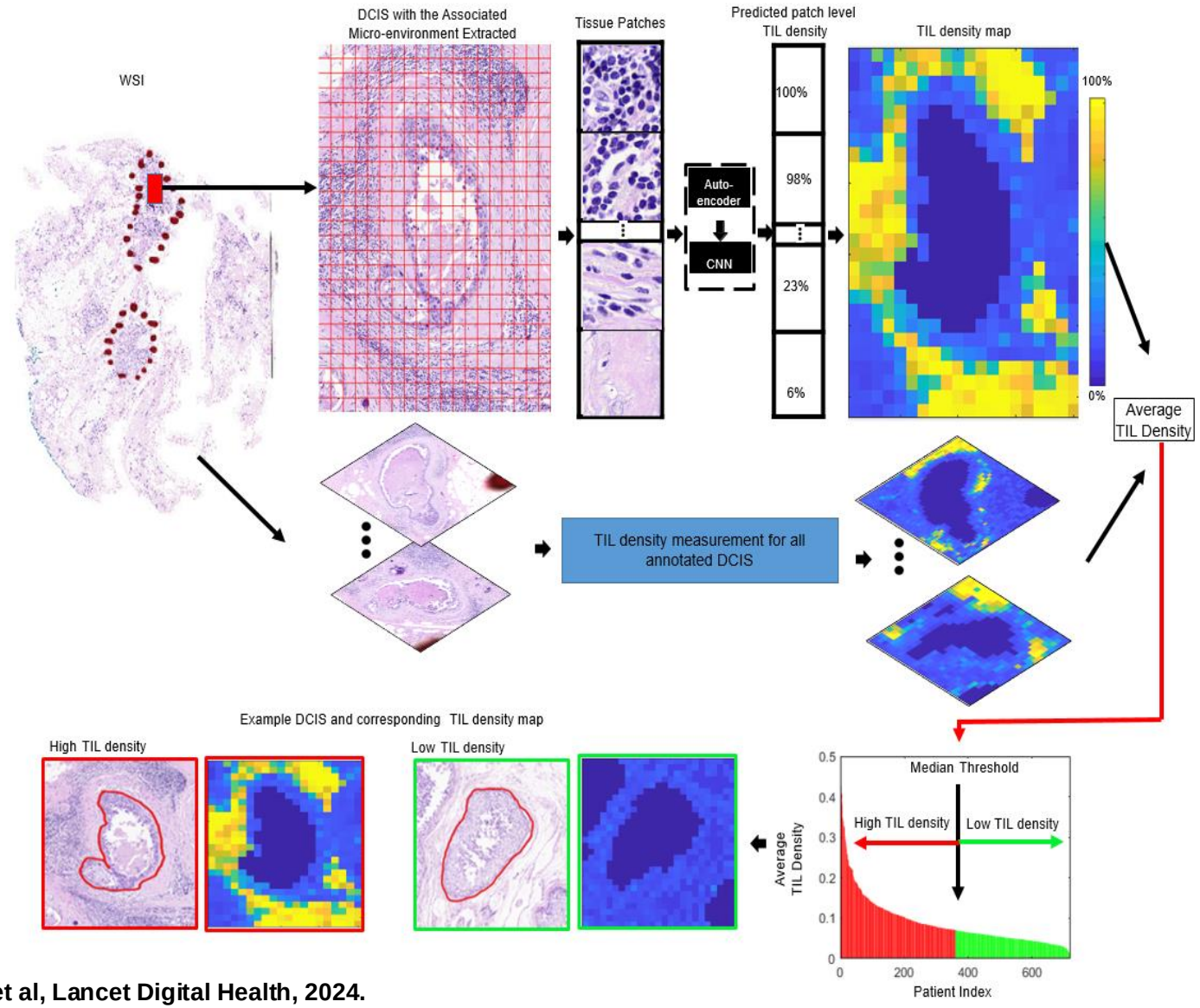
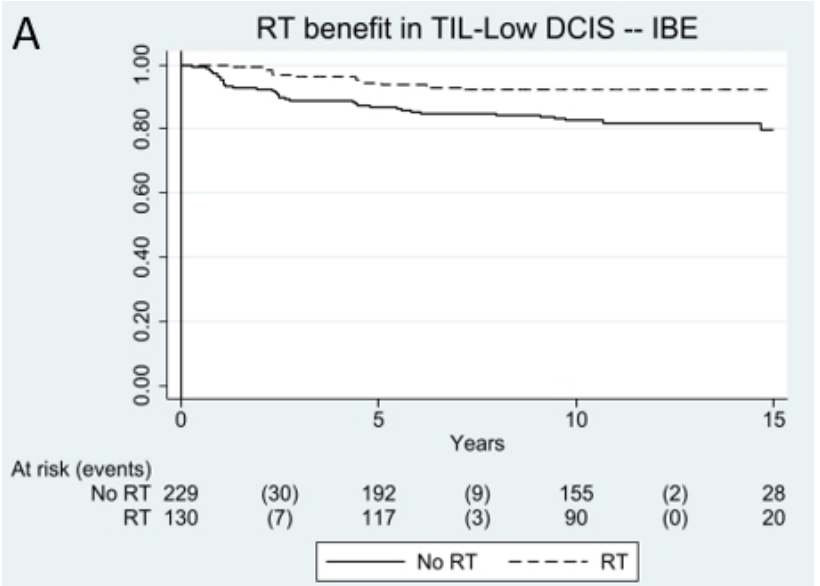


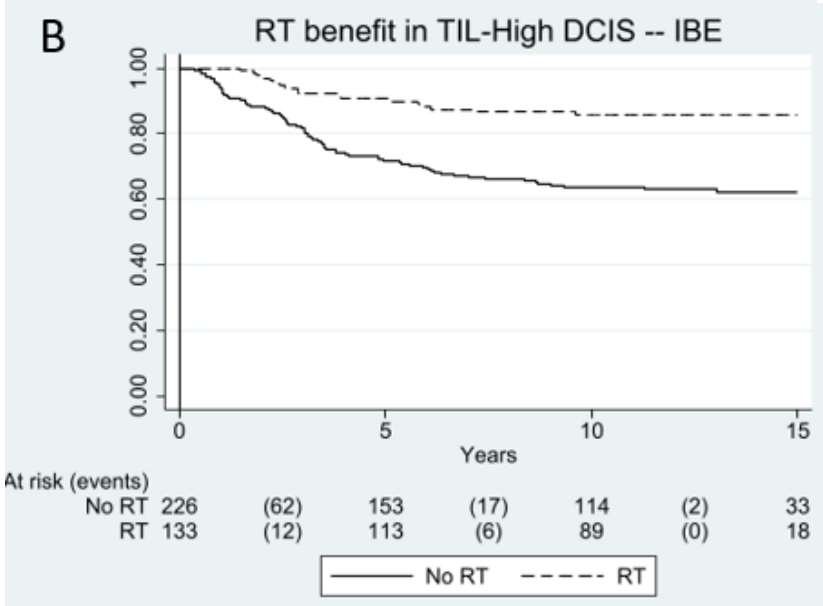
Fig 2: (A) Workflow figure for extraction of tumor-infiltrating plasma cells (TIPs) **(B)** Holdout set performance: Tumor-infiltrating plasma cell (TIPs), **(C)** AUC-ROC plot and **(D)** SHAP values

***Unpublished work, please don't circulate**

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): UK/ANZ Trial



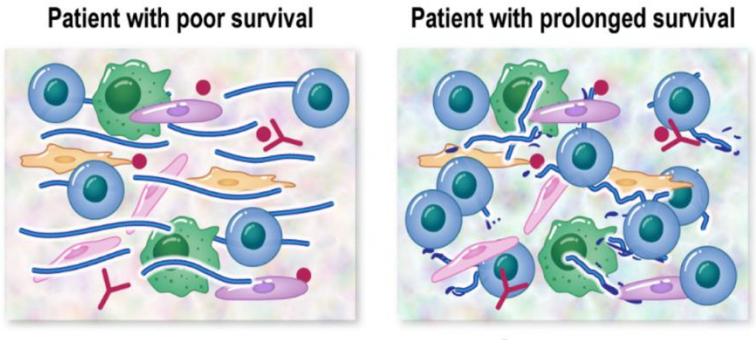




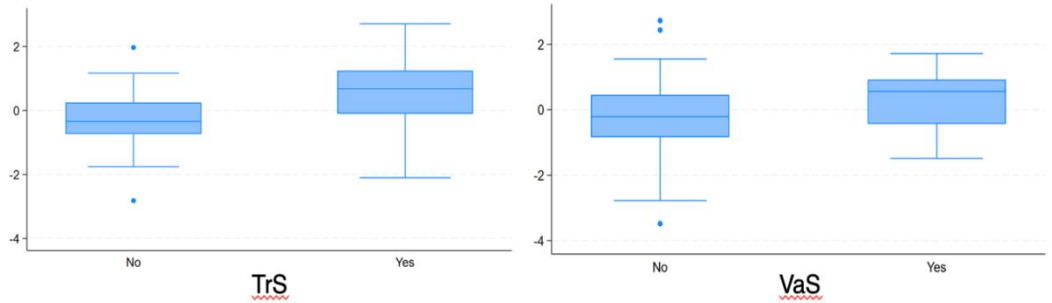
Li et al, Lancet Digital Health, 2024.

A Computational Pathology Collagen Signature Predictive of Tamoxifen Benefit in Ductal Carcinoma in Situ: Results from a Cohort within the UK/ANZ DCIS Randomized Trial

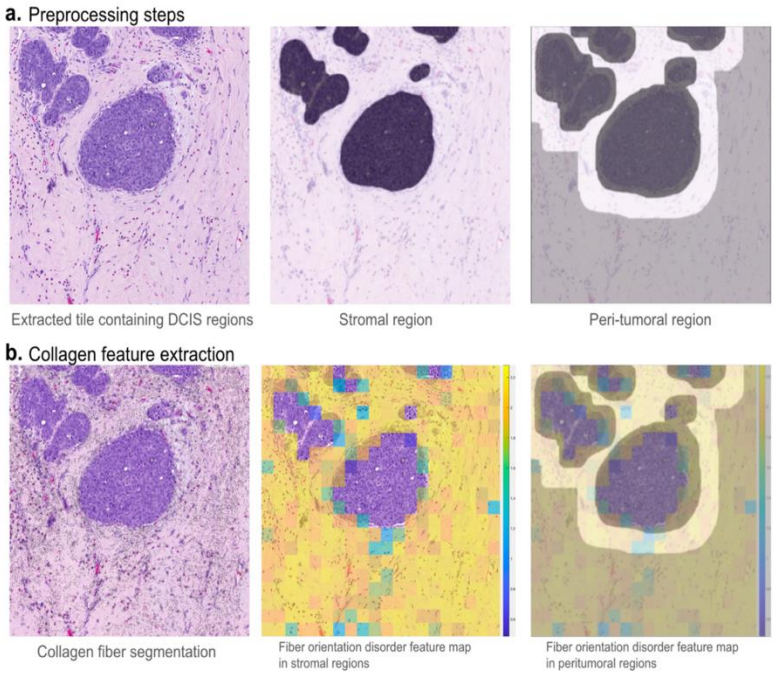
Hypothesis



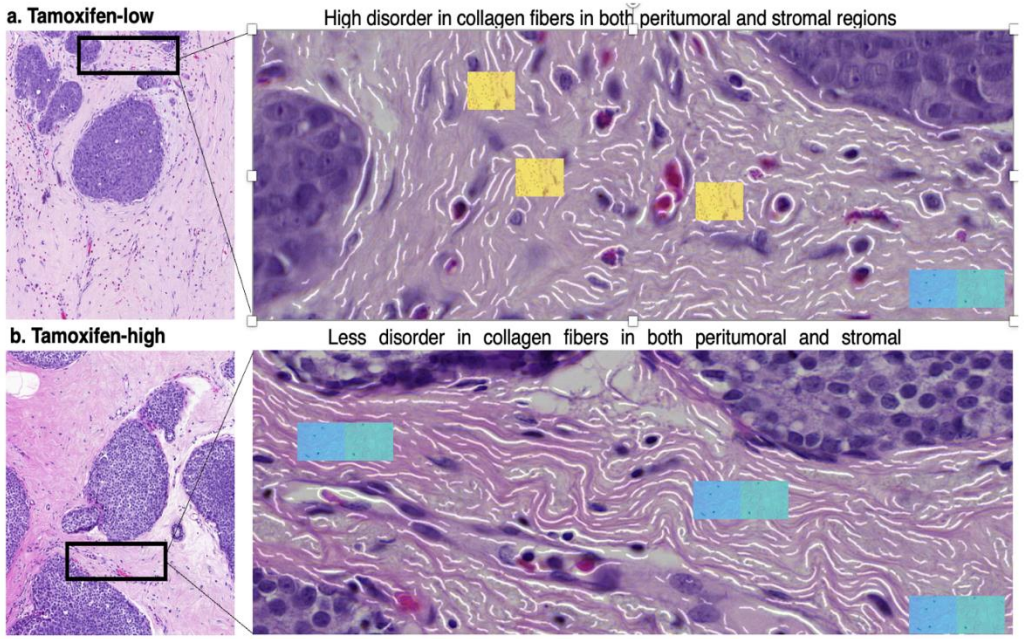
Results (Quantitative)



Workflow



Results (Qualitative)



Objective

Understand the association of collagen fiber architecture with tamoxifen benefit in the UK/ANZ DCIS randomized trial.

Experiment

- Computational pathology method that quantitativ characterizes the collagen components of the TME

- Analysis on 242 H&E slides from the UK/ANZ DCIS randomized trial with patients underg tamoxifen treatment
(102 for training and 140 for validation)

Results

- Our analysis on patient-level basis revealed disord collagen fiber architecture
associated with tamoxifen resistance in DCIS.
(Train (TrS): $p<0.001$, HR=4.54 [2.27-9.06],
Val (VaS): $p=0.006$, HR=3.46 [1.41-8.48])

- Our computational pathology collagen-tamoxifen score has a role, independent of ER status, in predicting tamoxifen benefit in DCIS.

***Reference**: Aggarwal, A. 171P A computational pathology collagen signature predictive of tamoxifen benefit in ductal carcinoma in situ: R esults from a cohort within the UK/ANZ DCIS randomized trial. Annals of Oncology **35**, S284 (2024).*

Original Investigation

FREE

January 21, 2021

Association of Race/Ethnicity and the 21-Gene Recurrence Score With Breast Cancer–Specific Mortality Among US Women

Kent F. Hoskins, MD[1,2]; Oana C. Danciu, MD[1,2]; Naomi Y. Ko, MD, MPH, AM[3]; Gregory S. Calip, PharmD, MPH, PhD[4,5,6]

» Author Affiliations | Article Information

JAMA Oncol. 2021;7(3):370-378. doi:10.1001/jamaoncol.2020.7320

Conclusions and Relevance In this cohort study, Black women in the US were more likely to have a high-risk recurrence score and to die of axillary node–negative breast cancer compared with non-Hispanic White women with comparable recurrence scores. The Oncotype DX Breast Recurrence Score test has lower prognostic accuracy in Black women, suggesting that genomic assays used to

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

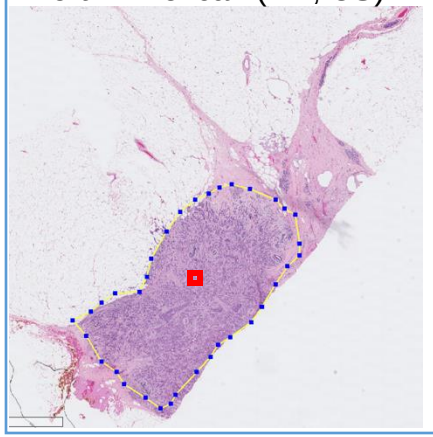
Unmet Clinical Need

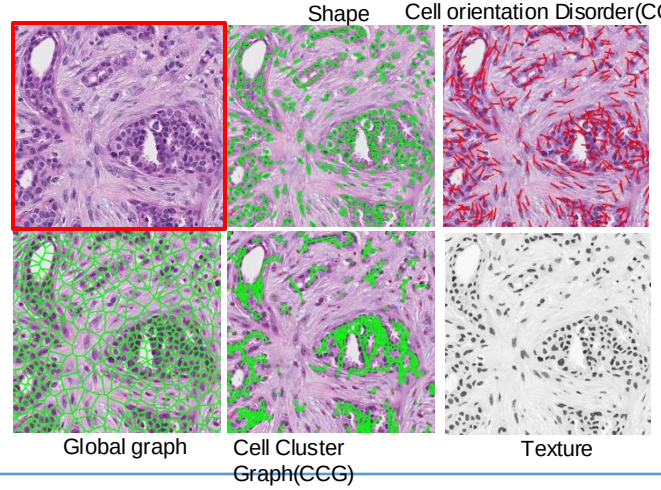
- Racial/ethnic disparity in incidence and mortality in breast cancers.
- Indian women more likely to be diagnosed with advanced breast cancer despite lower incidence than American women.
- The studies of digital pathology in breast cancer prognosis were mostly focused on American women.

Methods and Results

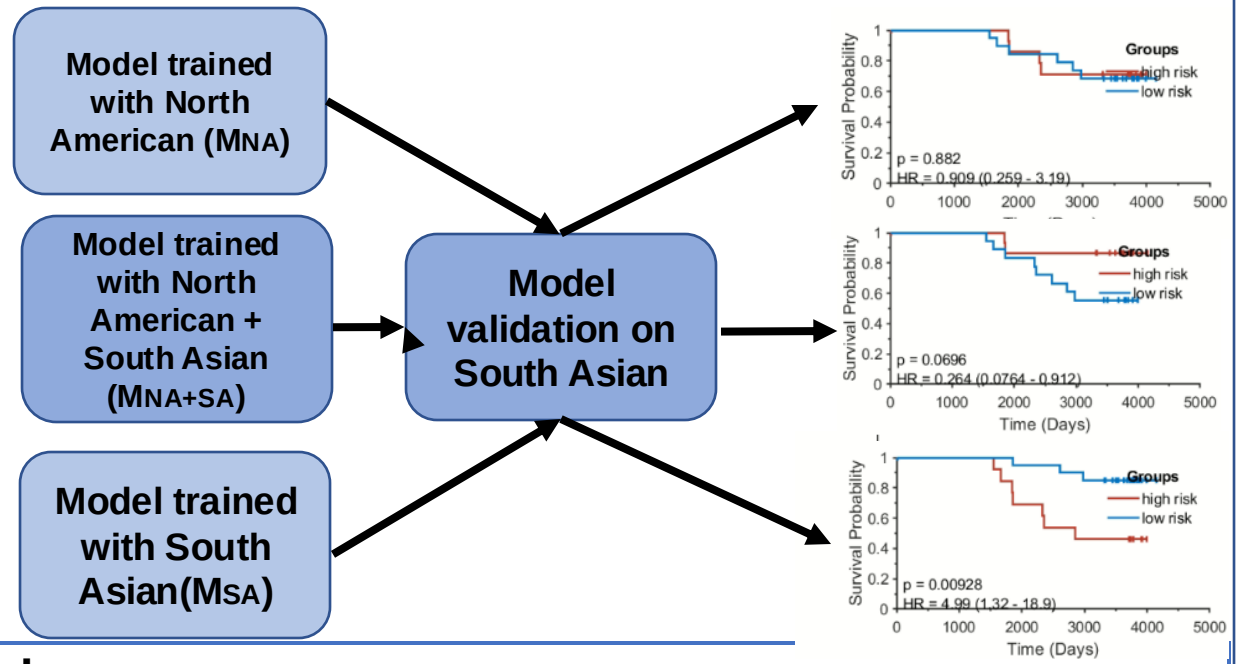
Data Description → Extraction of nuclear morphological features

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





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

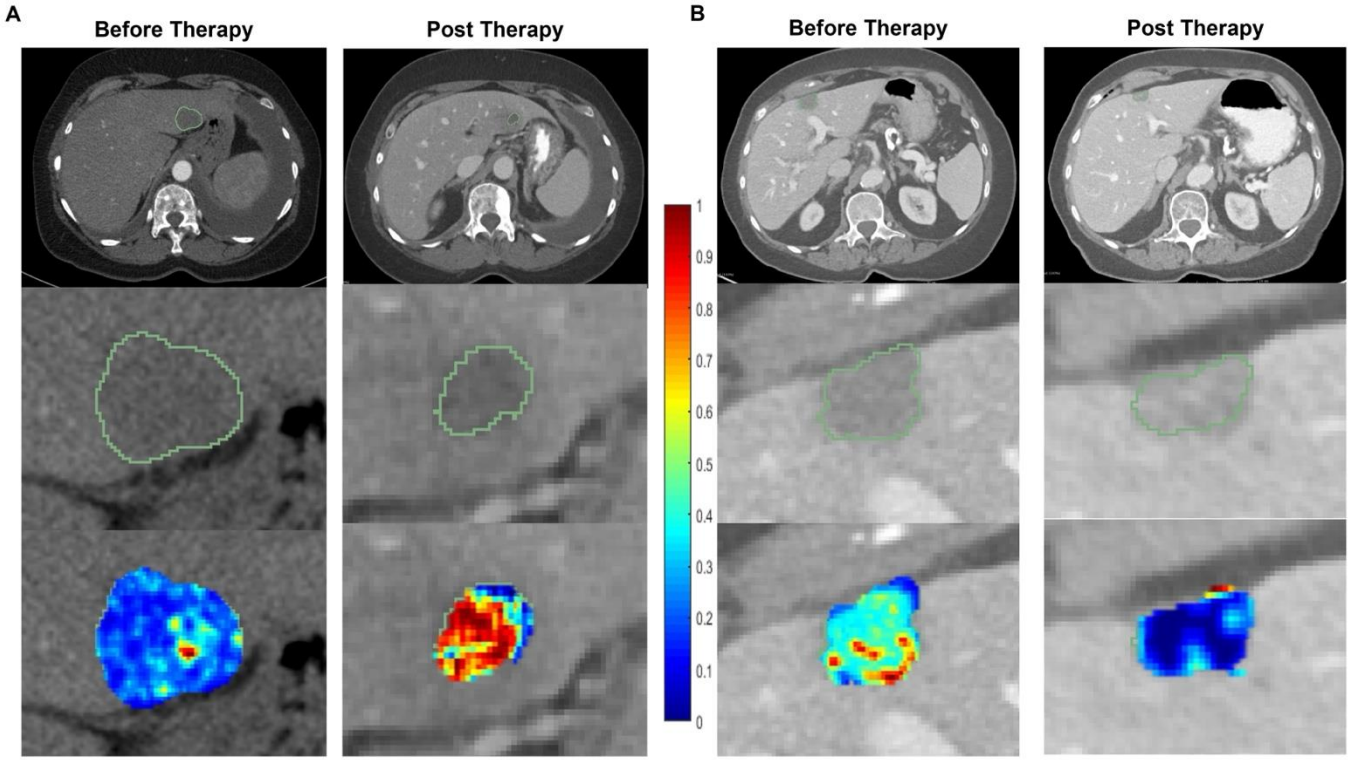


Take away:

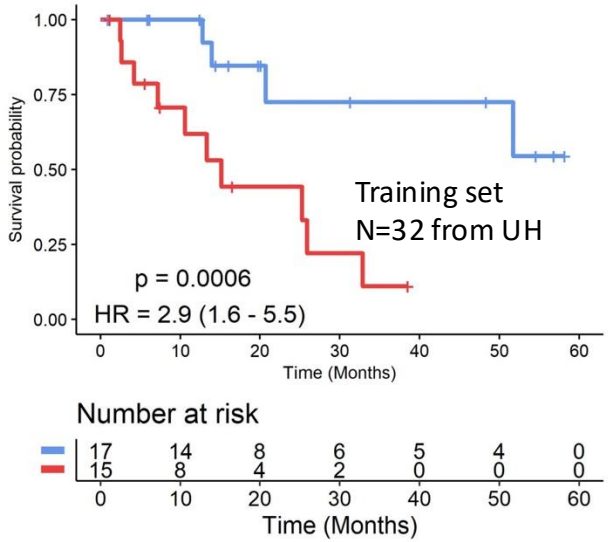
Prognostic ability of the computational pathology based models for South Asian women with breast cancer could be significantly improved by taking into account of population-specific information.

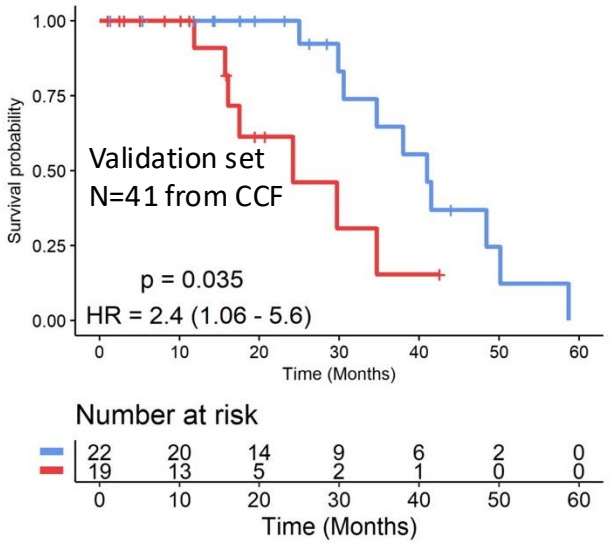
Li et al San Antonio 2021

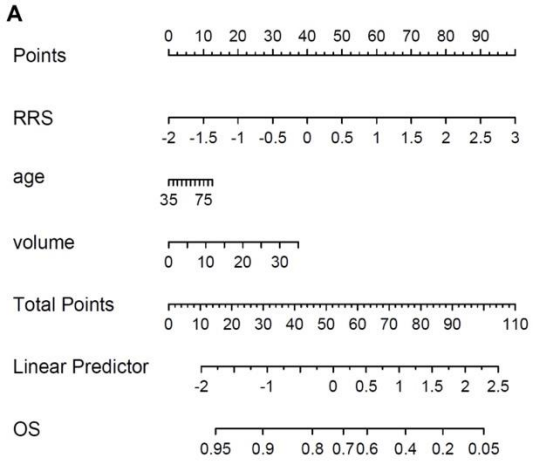
Radiomics to Predict Response to CDK 4/6 Inhibitors to Metastatic HER2+ Breast Cancer

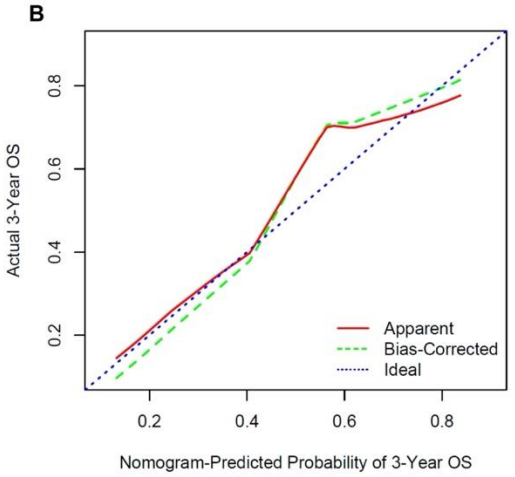


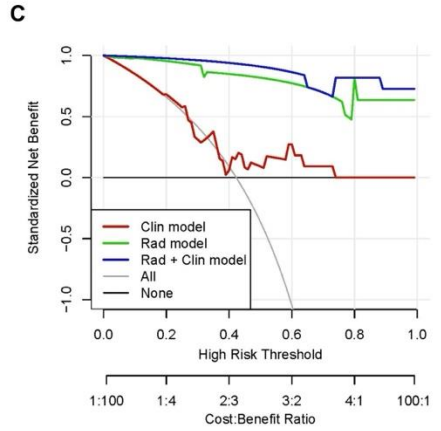
Delta radiomic features predict response to CDK4/6i therapy. (A) Axial contrast enhanced CT images (top row), liver tumor segmentations (middle row), and heatmaps (lower row) of intra-tumoral Haralick (entropy) feature in the representative pre- and post-treatment CT scans of a non-responder (A) and a responder (B).











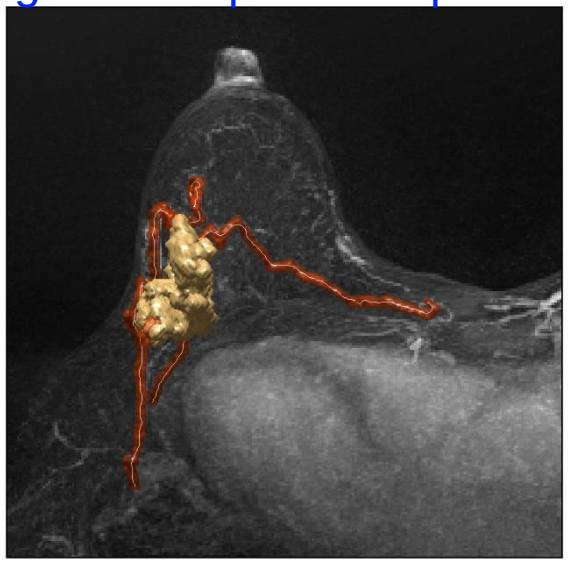
(A) A nomogram that shows the probability of 3-year surviving in breast cancer patients treated with CDK4/6i. (B) Calibration curve for survival. (C) Decision curve analysis (DCA) for three models (clinical, radiomic, and integrated radiomic+clinical).

Khorrami et al, npj Breast Cancer, 2023

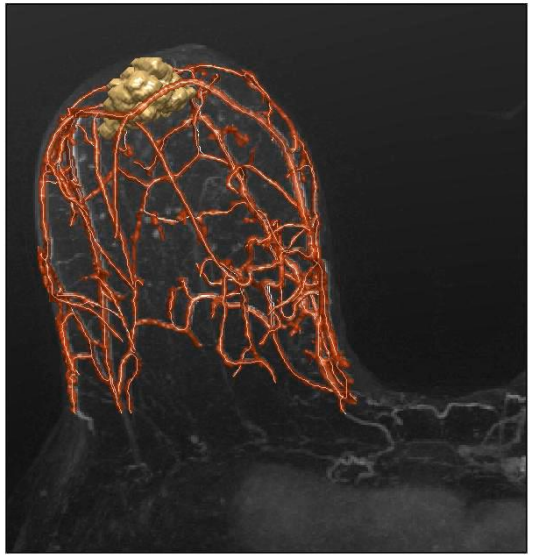
Clin Cancer Res 2022

Chaotic vessel architecture and reduced vascular function associated with poor therapeutic response

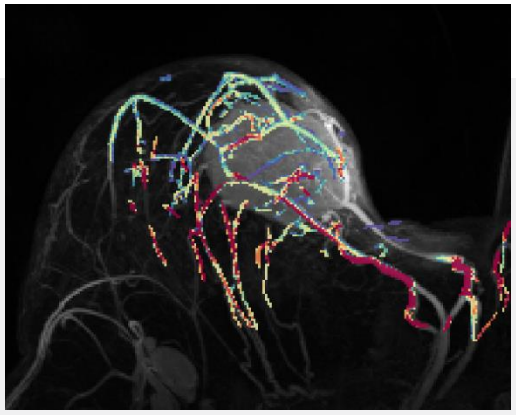
Pathological Complete Response (pCR)

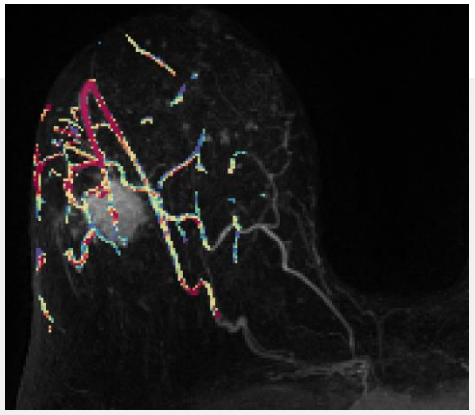


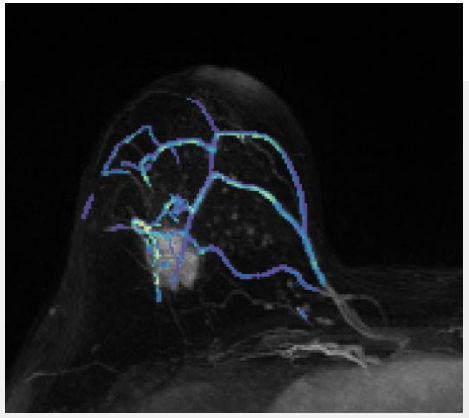
Non-pCR

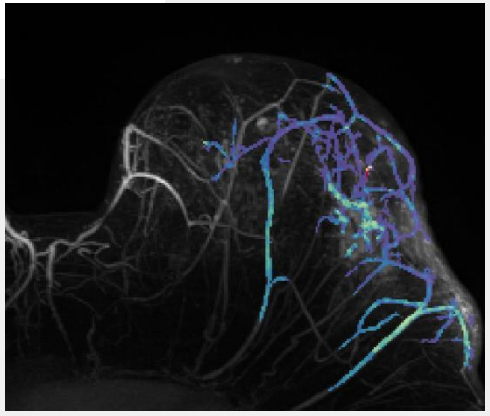


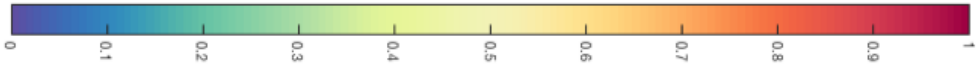
- Breast cancer patients who do not respond to chemotherapy are distinguished by
  - Twisted vessels, reduced structural organization
  - Reduced measures of vessel function, such as slow uptake in the vessels near the tumor
- AUC = 0.70, accuracy = 67% on 121 patient multi-institutional validation dataset











Uptake Rate

Emory researchers awarded up to $17.6M from ARPA-H to innovate cancer surgery, improve outcomes

January 6, 2025

Take Away

- **Computational Analytics with routine imaging** could help address questions in precision medicine, specifically prognosis and predicting response to therapy
- AI is not magic. Need to be intentional and focused on interpretable computational based biomarkers.
- Retrospective and Prospective Clinical Trial Validation Critical to Ensure Reproducibility

Acknowledgements

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