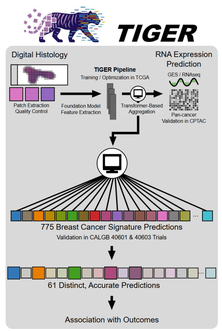
Digital Histology Models Predict Chemotherapy Benefit in Randomized Trials and Real-World Cohorts

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Background

- Gene expression signatures are widely used to predict prognosis and chemotherapy benefit for early HR+/HER2- breast cancer and are in development for other subtypes
- However – gene expression testing is **costly**, **time consuming** (can delay care), **depletes tissue**, and **is unavailable in low resource settings**
- Conversely, H&E stained histology is widely available worldwide
- We previously developed a pipeline - **TIGER** (Transformer-based hIstology-driven Gene Expression Regressor) that accurately reproduces 61 distinct signatures from histology (correlation > 0.5 with true signature)[1,2]
- **Hypothesis:** histology signatures predict recurrence / chemotherapy benefit



Pipeline for Breast Signature Prediction from Histology

Materials and Methods

- Patients enrolled from four cohorts: **CALGB 9344** (AC vs AC-T), **CALGB 9741** (dose dense vs standard density AC-T), cases of breast cancer from the **American Cancer Society** CPS-II/III studies, and real world cases from three **Chicago** hospitals
- Eligible patients had H&E histology images, recurrence data and clinical parameters (age, ER/PR status, tumor size, nodal status)
- 61 histology signatures tested in CALGB 9344; Most prognostic signature selected by concordance index
- Clinicopathologic Cox model fit in CALGB 9344, and validated externally for prognosis, incorporating signature, age, tumor size, number of nodes, and ER / PR
- Predictive value for chemotherapy benefit tested using interaction between tertiles / regimen
- Primary outcome: **distant recurrence free interval**

Results

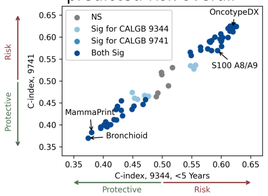
- We identified 7,501 patients across four cohorts for inclusion (**Table 1**)
- Patients from CALGB 9344 and CALGB 9741 had higher nodal burden and greater proportion of HR-negative disease than the ACS / Chicago cohorts
- A **bronchioid** signature (originally developed to identify a low risk lung adenocarcinoma subtype) best predicted DRFI in CALGB 9344 (**Fig 1**)
- Histology signatures had inverse relationships with early / late recurrence

Table 1. Demographics of Included Patients

		CALGB9344	CALGB9741	Chicago	ACS
n		2355	1460	2564	1122
Age, mean (SD)		48.5 (9.8)	50.6 (9.5)	58.3 (12.0)	61.2 (11.4)
Tumor Size in mm, mean (SD)		31.4 (18.9)	28.9 (17.8)	21.5 (18.7)	17.4 (14.5)
Involved nodes (SD)		5.0 (4.7)	4.3 (4.5)	0.6 (2.2)	0.7 (2.0)
HR Status	**Positive**	1585 (67.3)	1006 (68.9)	2244 (87.5)	1122 (100.0)
	Negative	770 (32.7)	454 (31.1)	320 (12.5)	0 (0)
HER2 Status	**Positive**			205 (8.0)	
	Negative			2062 (80.4)	850 (75.8)
	Unknown	2355 (100.0)	1460 (100.0)	297 (11.6)	272 (24.2)
Grade, n (%)	**1**			469 (18.3)	322 (28.7)
	2			1331 (51.9)	564 (50.3)
	3			709 (27.7)	191 (17.0)
	Unknown	2355 (100.0)	1460 (100.0)	55 (2.1)	45 (4.0)
Distant Recurrence, n (%)	**No**	1495 (63.5)	1262 (86.4)	2444 (95.3)	
	Yes	860 (36.5)	198 (13.6)	120 (4.7)	
	Unknown				1122 (100.0)
Survival, n (%)	**Alive**	1352 (57.4)	1322 (90.5)	2333 (91.0)	976 (87.0)
	Dead	1003 (42.6)	138 (9.5)	231 (9.0)	146 (13.0)

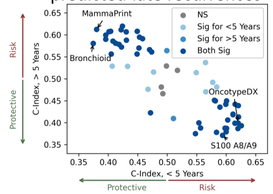
Fig 1. Time Dependence of Signature Predictions and Recurrence Risk

A **Bronchioid** signature best predicted risk overall



Early Recurrence Predictions Highly Consistent Across Trials

An **S100 A8/A9** signature best predicted late recurrences



Histologic Features have Inverse Associations with Early / Late Risk

Results

- A Cox model was fit in CALGB 9344 to predict risk of distant recurrence using the histology signature and clinical factorsTertiles of Cox model predicted risk consistently identified groups of low / medium / high recurrence risk across cohorts (**Fig 2**)
- An optimized cutoff of the bronchioid signature, but not clinical factors (or combined clinical + pathologic risk) **predicted benefit from taxane** in CALGB 9344 (interaction $p < 0.05$ for DRFI, DRFS, and OS; **Fig 3**)
  - This cutoff identified a group with 3.7% reduction in distant recurrence with dose dense (vs standard density) chemotherapy in CALGB 9741 and predicted chemotherapy benefit in the Chicago cohort
- Synthetic histology demonstrated features associated with low risk had more extensive tubule formation and less tumor cell pleomorphism[3] (**Fig 4**)

Fig 2. Tertiles of Scores from Clinicopathologic Model Accurately Stratify Patient Recurrence Risk

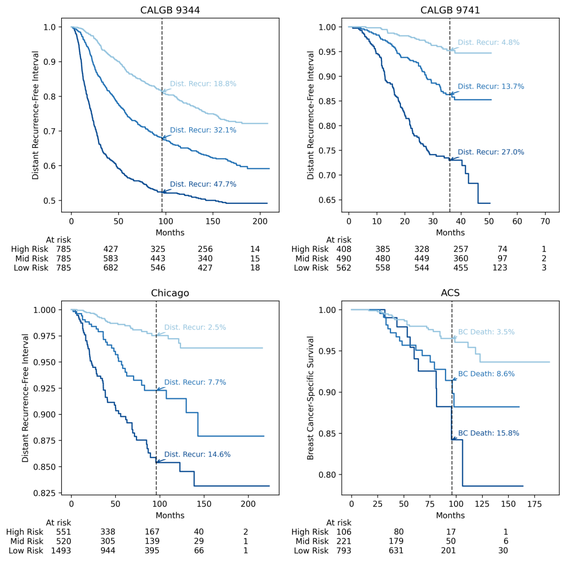


Fig 3. Histology Signature Identifies Group with No Benefit from Chemotherapy Intensification

Significant Interaction of Signature with DRFI, DRFS, OS in CALGB 9344

High risk group benefits from dose dense chemo in CALGB 9741

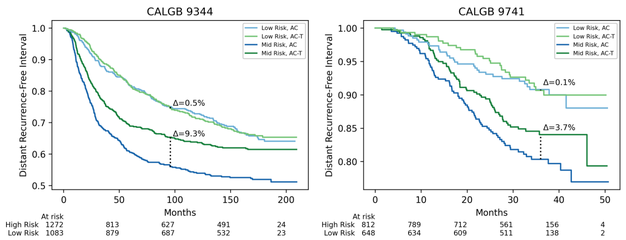
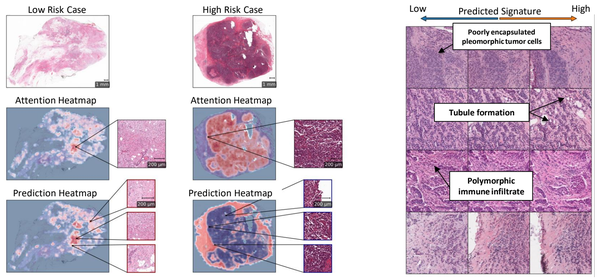


Fig 4. Explainability Analysis of Model Predictions and Synthetic Histology Illustrating High / Low Risk

Representative High / Low Risk Cases per Bronchioid Signature

Synthetic Images with Low → High Prediction for Signature



Conclusions

- A histologic signature can accurately predict risk of recurrence and chemotherapy benefit in multiple trial and real world cohorts
- Histology-based, rather than clinical + histology models, are more likely to identify patients with early breast cancer who benefit from chemotherapy

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