Transcriptomics-Guided AI Outperforms and Expands on OncotypeDX to Predict Hormonal Therapy Response and Chemotherapy Benefit from H&E-Stained Whole Slide Images in ER+/HER2- Breast Cancer

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Introduction

- Oncotype DX (ODX) is one of the most widely used genomic tests for risk stratification and prediction of response to hormonal therapy (HT) of early stage ER+/HER2- node-negative breast cancer.
- However, this test is not specific in predicting chemotherapy (CT) failure.
- We developed an AI-based model that predicts response to HT and failure of CT followed by HT (HT+CT) directly from H&E-stained whole slide images (WSI) of the breast tumor in surgical resections through inferring underlying genomic and signaling pathway gene expression changes directly from morphology.
- Our model was developed to improve upon the performance of ODX in risk stratification and prediction of recurrence and distant metastasis. It also extends its clinical utility by predicting HT+CT failure to enable consideration of other therapy options.

Method

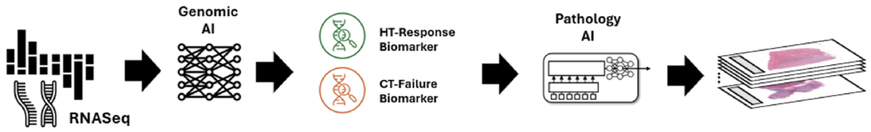


Figure 1. Overall functional diagram. A genomic signature is created to predict response to hormone therapy (HT) and chemotherapy (CT). Once validated, this genomic signature is translated to be predicted from a WSI.

- Our AI technology leverages cross-modality transfer learning (Figure 1) to infer transcriptomic signals from morphological features.
- We first developed a biomarker for HT-response and combined HT+CT-failure using only genomic data by mapping RNA-Seq to recurrence outcomes from ScaB cohort (Staaf J. et al. npj Breast Cancer. 2022;8:94.), using PathwayNet (Figure 2). These biomarkers integrated thousands of gene expressions from genes that belong to various signaling pathways.
- After validating the predictive accuracy of these genomic biomarkers, we trained a deep learning model to infer the biomarkers directly from H&E WSIs of the invasive breast tumor.
- For external validation, we used our AI model to predict on H&E-stained WSIs from 290 early stage ER+/HER2- node-negative breast cancer patients where most patients received treatment according to ODX recommendations.
- For each WSI, we predicted the presence or absence of our HT-response and HT+CT-failure biomarkers, enabling further stratification of patients within their respective groups.
- Kaplan-Meier survival estimation and log-rank statistical testing were used to measure the magnitude and significance of stratification in the HT and HT+CT treated groups.
- Finally, to interpret our markers, we used the gene expression data along with the gene-pathway weights assigned by our model, to quantify each of the pathways' contributions towards outcome.
- We then used these contributions in a differential (weighted) pathway analysis setting across the two risk groups to derive insights into the pathways that are statistically dysregulated in each of the cohorts revealing the inherent biological mechanism that is represented by these markers. (Fig. 7)

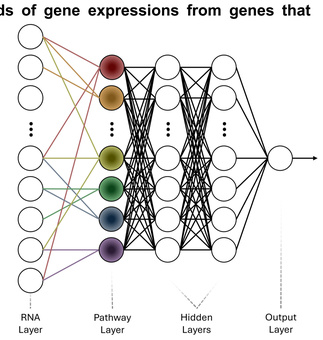


Figure 2. Architecture of Pathway net. Input to the model is gene expressions. Sparse connections simulate known signaling pathways. Model output is predictive score.

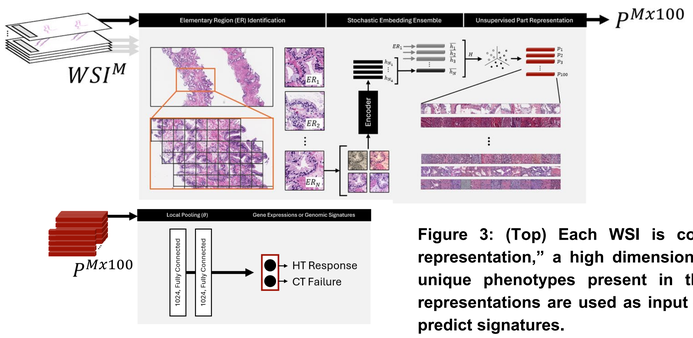


Figure 3: (Top) Each WSI is converted to a "part representation," a high dimensional representation of unique phenotypes present in the WSI. (Left) Part representations are used as input data into an MLP to predict signatures.

Dataset

		Train (n=2608)	Validation (n=1097)
Age, Median (Range), y		61-65 (21-99)	61-65 (31-99)
Histological Grade (%)	Grade 1	431 (17.2)	183 (17.2)
	Grade 2	1440 (57.3)	645 (60.5)
	Grade 3	642 (25.5)	238 (22.3)
Tumor size, Median (Range), mm		17 (0-126)	17 (2-125)
Menopausal Status (%)		Not Available	
Lymph Node Positive		1001 (39.1)	398 (36.9)
#Distant Recurrence Events (%)		170 (6.5)	73 (6.7)
Treatment (%)	HT	1774 (68.0)	756 (69.2)
	HT + CT	834 (32.0)	337 (30.9)
Follow up, Median (Range), months		63 (1-131)	63 (1-129)
Recurrence Free Rate	at 5 years	94.7%	94.6%
	at 10 years	89.5%	89.6%

		All (n=290)	ODX High (n=140)	ODX Low (n=150)
Age, Median (Range), y		54 (26-82)	56 (26-82)	52 (28-77)
Histological Grade (%)	Grade 1	47 (16.2)	5 (3.6)	42 (28.0)
	Grade 2	147 (50.7)	61 (43.6)	86 (57.3)
	Grade 3	96 (33.1)	74 (52.9)	22 (14.7)
Tumor size, Median (Range), mm		17 (3-90)	18 (3-90)	16 (6-90)
Menopausal Status (%)	Post	186 (64.1)	100 (71.4)	86 (57.8)
	Pre	95 (32.8)	35 (25.0)	60 (40.3)
	Peri	7 (2.4)	4 (2.9)	3 (2.0)
Lymph Node Positive (%)		0 (0)		
#Distant Recurrence Events (%)		56 (19.4)	34 (24.3)	22 (14.8)
Treatment (%)	HT	165 (56.9)	19 (13.6)	146 (97.3
	HT + CT	120 (41.4)	120 (85.8)	0 (0)
	Missing	5 (1.7)	1 (0.1)	4 (2.7)
Follow up, Median (Range), mo.		66 (1-227)	63 (1-227)	70 (1-201)
Recurrence Free Rate	at 5 yrs	85.6%	80.2%	91.2%
	at 10 yrs	64.1%	55.4%	72.3%

Table : Patient Characteristics of ScanB cohort (left) and MDA cohort (right)

Results

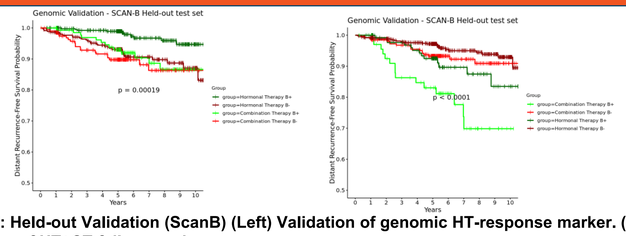


Figure 4: Held-out Validation (ScanB) (Left) Validation of genomic HT-response marker. (Right) Validation of HT+CT-failure marker.

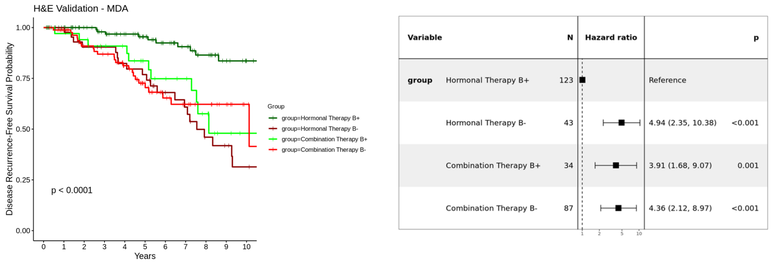


Figure 5: External Validation (Left) Kaplan-meier model of patients stratified into HT-response biomarker positive and negative and treatment groups. (Right) Cox-proportional model-based hazard ratios of HT-treated biomarker negative and HT+CT-treated groups against HT-treated b

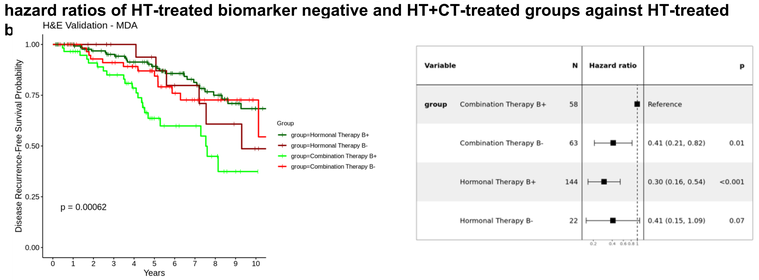


Figure 6: External Validation (Left) Kaplan-meier model of patients stratified into CT-response biomarker positive and negative and treatment groups. (Right) Cox-proportional model-based hazard ratios of HT+CT-treated biomarker negative and HT-treated groups against HT-treated biomarker positive group.

Results (Continued)

Distant Recurrence in 5 years

	Recur	No Recur	Total
Oncotype High	3	12	15
Oncotype Low	10	83	93
Total	13	95	108

SEN: 0.23 SPE: 0.87 PPV: 0.20 NPV: 0.89

	Recur	No Recur	Total
AI Group HT B-	9	28	37
AI Group HT B+	4	67	71
Total	13	95	108

SEN: 0.69 SPE: 0.71 PPV: 0.24 NPV: 0.94

Distant Recurrence in 10 years

	Recur	No Recur	Total
Oncotype High	7	4	11
Oncotype Low	21	25	46
Total	28	29	57

SEN: 0.25 SPE: 0.86 PPV: 0.64 NPV: 0.54

	Recur	No Recur	Total
AI Group HT B-	19	7	26
AI Group HT B+	9	22	31
Total	28	29	57

SEN: 0.68 SPE: 0.76 PPV: 0.73 NPV: 0.71

Table 2. Comparison of ODX and the AI HT marker groups in predicting distant recurrence under HT alone. The results suggest that our AI HT marker may better identify patients at risk of failing to respond to HT compared with ODX.

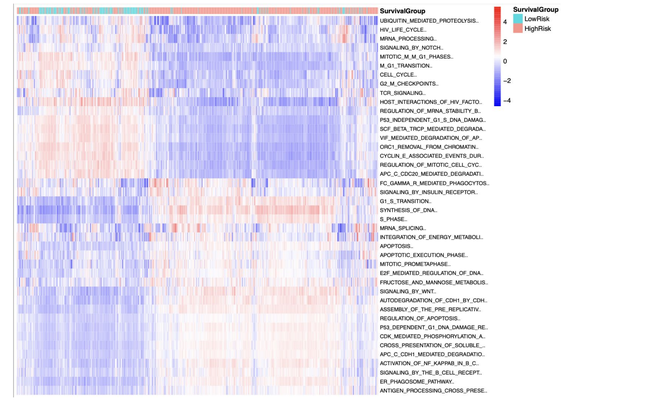


Figure 7: Unsupervised clustering of the weighted differential pathways revealed coherent grouping of patients by risk groups (horizontal bar). The heatmap highlights pathway-level differences across groups (vertical bar), with the high-risk cohort showing enrichment of biologically aggressive cancer pathways, such as Wnt signaling.

MVA	HR	p
HT-Response Marker	0.25 (0.11 – 0.57)	<0.001
Oncotype	1.05 (1.00 – 1.11)	0.04

MVA	HR	p
HT+CT Failure Marker	2.48 (1.22-5.02)	0.01
Age	0.97 (0.94 – 0.99)	0.03

Table 3: In an experimental multivariate analysis, Oncotype score added significant predictive information to the HT-response marker. Age added significant predictive information to the HT+CT-failure marker.

Conclusion & Discussion

- We introduced a novel method to translate predictive information from RNA-Seq to whole slide images, potentially overcoming hurdles introduced by pure genomic tests.
- PathwayNet's architecture enables us to identify and interpret the biological functions the model relies on to predict treatment response.
- To our knowledge, we have developed the first AI models that predict response to HT and HT+CT in early stage ER+/HER2- node-negative breast cancer.
- Further validation studies need to be completed to build further evidence of these findings.

Funding & COI

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