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BRAVE: Predicting Treatment Outcomes in Breast Cancer from Pretreatment H&E Slides Using Pathology Foundation Models with Multiple Instance Learning

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BACKGROUND

Pathologic complete response (pCR):

- Absence of residual invasive cancer in breast and axillary nodes after neoadjuvant therapy.
- Serves as a surrogate endpoint for long-term outcomes in breast cancer.
- Current predictive models rely mainly on **clinical and molecular factors** (e.g., receptor status, gene expression, MRI).

Computational pathology + deep learning

- Prior models have successfully predicted tumor proliferation, molecular subtype, and genomic alterations directly from histology.
- **Multiple Instance Learning (MIL):** aggregates tile-level features to make slide-level predictions.
- Application of MIL for pCR prediction from frozen biopsy WSIs, particularly in large, multi-arm clinical trials, has not been well studied.

		pCR	No pCR
Subtype	HR+/HER2+	56	86
	HR+/HER2-	56	291
	HR-/HER2+	54	31
	HR-/HER2-	132	205
Race	White	237	483
	Black or African American	32	80
	Asian	22	42
	Other	7	8
Ethnicity	Hispanic or Latino	45	72
	Not Hispanic or Latino	251	537
Arm	Paclitaxel	26	138
	Paclitaxel + ABT 888 + Carboplatin	25	45
	Paclitaxel + AMG 386	30	70
	Paclitaxel + AMG 386 + Trastuzumab	6	13
	Paclitaxel + Ganetespib	25	66
	Paclitaxel + Ganitumab	22	74
	Paclitaxel + MK-2206	16	36
	Paclitaxel + MK-2206 + Trastuzumab	16	9
	Paclitaxel + Neratinib	38	70
	Paclitaxel + Pembrolizumab	31	33
	Paclitaxel + Pertuzumab + Trastuzumab	26	17
	Paclitaxel + Trastuzumab	7	20
	T-DM1 + Pertuzumab	30	22
Age	Mean ± SD	48.8 ± 10.1	48.7 ± 10.6
Total		298	613

Table 1. Patient Demographics

METHODS

We developed **BRAVE** (Breast cancer Response prediction using Attention-based Vision modEls) to predict pathologic complete response (pCR) from pre-treatment H&E-stained frozen tumor biopsies in the I-SPY2 neoadjuvant trial. A total of **3,306 WSIs** from **911 patients** across **13 treatment arms** were tiled (224 × 224 px), quality-controlled to exclude blank regions, and embedded using the **UNI pathology foundation model** to extract 1024-dimensional feature vectors per tile.

BRAVE applies **attention-based multiple instance learning (MIL)** to aggregate tile-level features and generate patient-level predictions of treatment response (**Figure 1**):

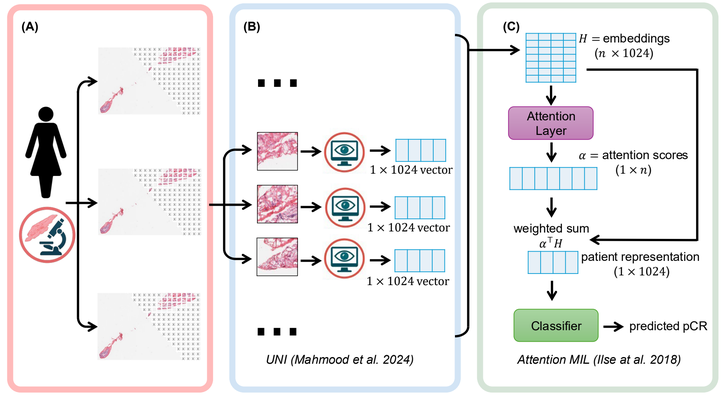


Figure 1. Overview of BRAVE framework.

The model was independently trained and evaluated using 3-fold cross-validation within each treatment arm and molecular subtype.

To contextualize performance, we benchmark BRAVE against two regression models:

1. A **histology-only** model using pathology report features (**tumor grade, DCIS, invasive histology subtype, lymphovascular invasion**).
2. A **clinical + histology** model incorporating additional predictors — **baseline MRI functional tumor volume (FTV)** and transcriptome-derived **response predictive subtypes (RPS).**

These comparisons evaluated whether BRAVE captures predictive morphologic signals beyond conventional pathology and established clinical and molecular predictors.

RESULTS

BRAVE Predicts Treatment Outcome in Specific Arms and in HR+ Subtypes

To identify regimen-specific predictors of response, **BRAVE** was independently trained and evaluated by **3-fold cross-validation** within each of the **13 I-SPY2 treatment arms** to predict pCR from baseline WSIs. Model performance was quantified by **AUROC** with **95% confidence intervals (CIs)** estimated via **1,000 bootstrap resamples**. Performance varied by arm (**AUROC range: 0.50–0.89**), with the highest accuracy observed in **HER2+ cohorts** receiving trastuzumab. Overall, BRAVE showed statistically significant prediction (AUROC 95% CI entirely > 0.5) in six treatment arms (**Table 2**). When grouped by molecular subtype, **BRAVE** demonstrated higher predictive performance in **hormone receptor–positive (HR+)** disease compared with HR– subtypes. These findings suggest that **morphologic correlates of treatment response** are more prominent in HR+ tumors.

Group (Arm or Subtype)	BRAVE AUROC (95% CI)	Histology Variables EN AUROC (95% CI)	Histology+FTV+RPS EN AUROC (95% CI)
Paclitaxel + Trastuzumab	0.893 (0.730–1.000)	0.358 (0.119–0.614)	0.438 (0.175–0.707)
Paclitaxel + Pertuzumab + Trastuzumab	0.785 (0.640–0.905)	0.683 (0.505–0.844)	0.829 (0.669–0.961)
Paclitaxel + Ganitumab	0.709 (0.564–0.841)	0.431 (0.307–0.565)	0.556 (0.420–0.690)
Paclitaxel	0.702 (0.585–0.809)	0.541 (0.429–0.659)	0.559 (0.442–0.668)
T-DM1 + Pertuzumab	0.683 (0.534–0.825)	0.517 (0.365–0.670)	0.774 (0.636–0.897)
Paclitaxel + ABT 888 + Carboplatin	0.662 (0.537–0.790)	0.607 (0.469–0.738)	0.846 (0.745–0.934)
Paclitaxel + Neratinib	0.618 (0.496–0.725)	0.425 (0.327–0.532)	0.549 (0.437–0.660)
Paclitaxel + Pembrolizumab	0.616 (0.473–0.757)	0.440 (0.300–0.585)	0.868 (0.762–0.958)
Paclitaxel + AMG 386 + Trastuzumab	0.615 (0.249–0.949)	0.400 (0.103–0.737)	0.446 (0.156–0.750)
Paclitaxel + AMG 386	0.602 (0.490–0.716)	0.755 (0.644–0.853)	0.827 (0.730–0.913)
Paclitaxel + MK-2206	0.582 (0.397–0.764)	0.509 (0.342–0.689)	0.683 (0.510–0.827)
Paclitaxel + MK-2206 + Trastuzumab	0.549 (0.278–0.795)	0.621 (0.368–0.840)	0.634 (0.359–0.873)
Paclitaxel + Ganetespib	0.501 (0.369–0.633)	0.586 (0.463–0.699)	0.533 (0.396–0.668)
HR+/HER2-	0.706 (0.636–0.773)	0.594 (0.505–0.669)	0.698 (0.603–0.780)
HR+/HER2+	0.677 (0.576–0.769)	0.518 (0.426–0.612)	0.645 (0.548–0.734)
HR-/HER2-	0.548 (0.482–0.614)	0.569 (0.514–0.629)	0.662 (0.603–0.717)
HR-/HER2+	0.533 (0.395–0.664)	0.463 (0.343–0.585)	0.597 (0.455–0.720)

Table 2. AUROC of MIL vs benchmark models.

Comparison with Clinical and Histology Models

To benchmark performance, BRAVE was compared with two **elastic-net logistic regression models**. All models were evaluated by **AUROC**, with **DeLong's test** used for paired comparisons. BRAVE **significantly outperformed** the histology-only model in:

- **HR+/HER2+** (P = 0.0215)
- **HR+/HER2–** (P = 0.0309)
- **Paclitaxel + Trastuzumab** (P = 0.00055)
- **Paclitaxel + Ganitumab** (P = 0.00081)
- **Paclitaxel + Neratinib** (P = 0.023)

BRAVE also outperformed the **clinical + histology model** in the **Paclitaxel + Trastuzumab** arm (P = 0.0037).

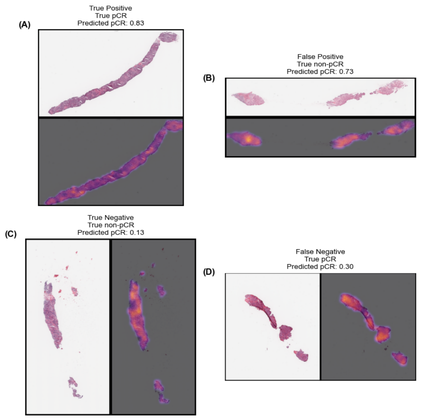


Figure 2. Representative BRAVE attention heatmap examples from the Paclitaxel + Trastuzumab Arm

CONCLUSIONS

These findings demonstrate the feasibility of applying MIL vision models to predict treatment-specific response in breast cancer, even with frozen section WSIs and limited data. MIL detects important histology patterns not captured by conventional pathology reports. This approach enables early, accurate predictions from routine histology and supports personalized, less toxic treatment—particularly in under-resourced settings.

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