Robust prediction of patients' response to neoadjuvant therapy across breast cancer subtypes using transcriptomics and histopathology

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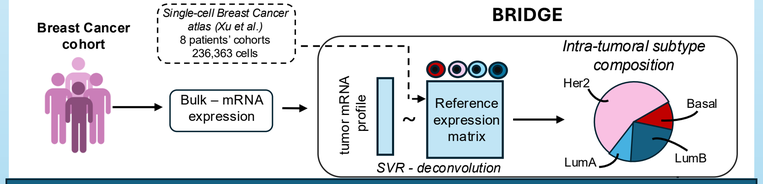
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BACKGROUND

Neo-adjuvant therapy response in breast cancer is highly variable and strongly influenced by intra-tumoral heterogeneity. Tumors frequently contain mixtures of molecular subtypes, each with distinct proliferation programs and treatment sensitivities. To address this challenge, we developed **BRIDGE** (**BR**east **I**ntratumoral **D**econvolution of **G**ene **E**xpression), a framework that quantifies intra-tumoral subtype composition from bulk transcriptomics and links these patterns to therapy response. Its histopathology-based extension, **BRIDGE-Slide**, applies the same biological principles directly to H&E slides, enabling subtype-informed prediction without sequencing.

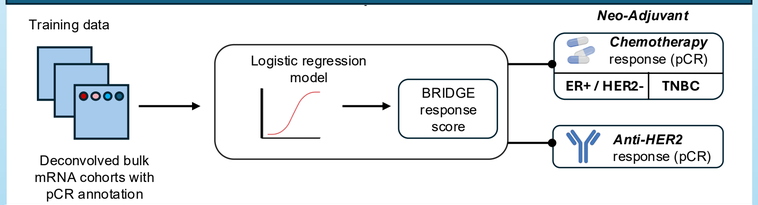
METHODS

(1) Deconvolution of Breast Cancer Molecular Subtypes



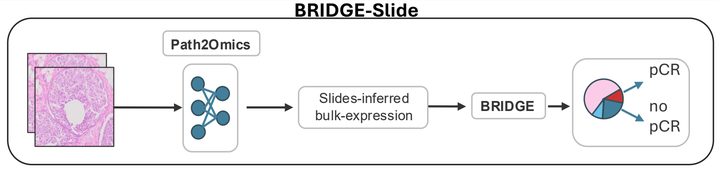
Given a cohort of patients with bulk mRNA expression data, BRIDGE quantifies each patient's subtype abundances through computational deconvolution. Each patient is then represented by a small set of values corresponding to these abundances.

(2) Pathological Complete Response prediction from bulk expression



Leveraging 9 datasets of breast cancer patients treated with neo-adjuvant therapies, a logistic regression model derives, from each patient's subtype composition, a therapy response score. BRIDGE implements indication-specific scores.

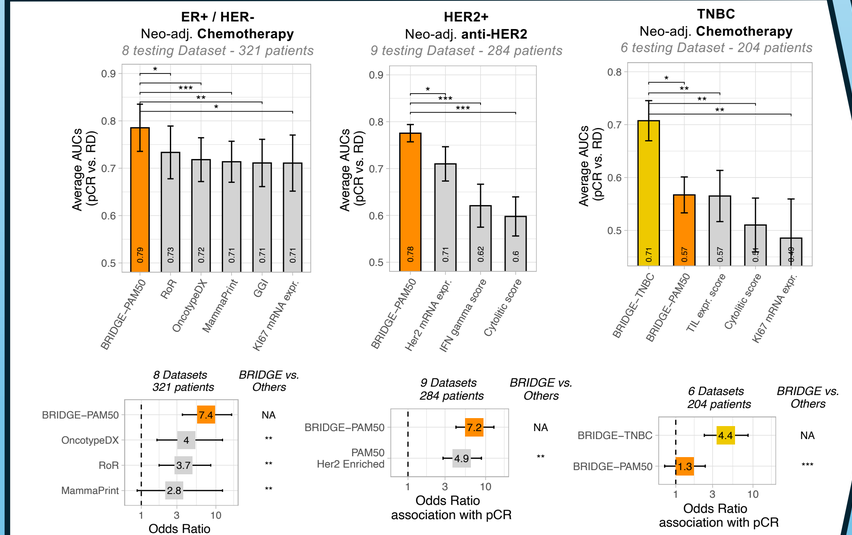
(3) Pathological complete Response prediction from Histopathology slides



By teaming up with Path2Omics[1], BRIDGE-Slide predicts bulk-expression profiles directly from whole-slide-images. These profiles are then taken as input by the BRIDGE pipeline (steps 1 and 2) to derive BRIDGE response scores.

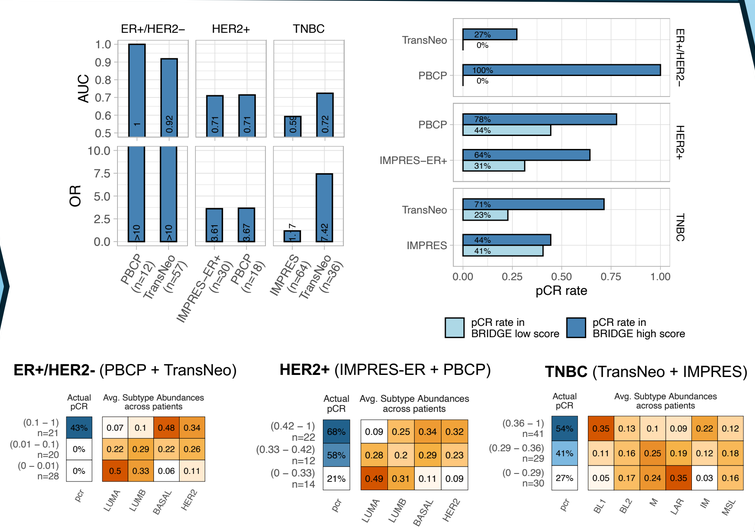
RESULTS

BRIDGE robustly predicts Neo-Adjuvant therapy from bulk-transcriptomics



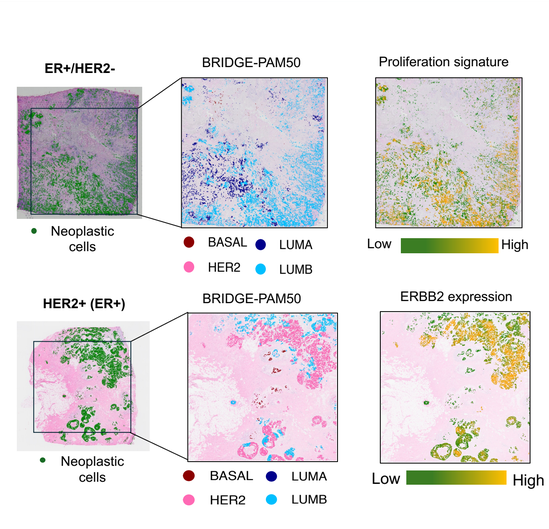
(Top) Average AUCs across ER+/HER2–, HER2+, and TNBC test datasets. BRIDGE consistently ranks among the highest-performing predictors (paired Wilcoxon tests). **(Bottom)** Odds ratios (ORs) for pathological complete response (pCR) using dichotomized BRIDGE scores. BRIDGE shows strong association with pCR compared to established biomarkers. BRIDGE-TNBC is designed to exploit Lehman's molecular subtypes rather than PAM50 (BRIDGE-PAM50).

BRIDGE-Slide predicts response to Neo-Adjuvant therapy from histopathology slides



(Top) BRIDGE-Slide scores derived from H&E images (via Path2Omics) stratify patients into low- and high-response groups across ER+/HER2–, HER2+, and TNBC cohorts reaching AUCs > .70 and ORs > 3.6 in 5 out of 6 cohorts. **(Bottom)** High-score groups (divided into low-medium-high) consistently show higher pCR rates, mirroring predictions from bulk RNA-seq. Subtypes composition varies according to response-score groups.

BRIDGE identifies spatially cohesive molecular subtypes in breast cancer



Representative Visium sections illustrating neoplastic regions **(left)**, BRIDGE-PAM50 subtype predictions **(middle)** on spatial transcriptomics data, and either proliferation signature or ERBB2 expression **(right)**. **(Top)** ER+/HER2– tumor showing predominantly Luminal A/B states with spatially high-proliferation regions corresponding enriched for BRIDGE LUMB. **(Bottom)** HER2+ (ER+) tumor displaying strong HER2-enriched subtype localization and concordant high ERBB2 expression in neoplastic areas.

CONCLUSIONS

BRIDGE is a biologically grounded framework that predicts neoadjuvant therapy response by quantifying intra-tumoral subtype composition. It is validated across diverse patient cohorts and consistently generalizes across treatments and platforms. Its histopathology-based version, BRIDGE-Slide, enables fast, low-cost prediction directly from H&E images. With further prospective validation, it could support real-time response stratification in routine clinical practice.

REFERENCES

1. Hoang, Danh-Tai, et al. "Path2Omics Enhances Transcriptomic and Methylation Prediction Accuracy from Tumor Histopathology." *Cancer Research* (2025).