PS3-04-04: AI Predicts Response to Neoadjuvant Therapy in Breast Cancer Across Diverse Cohorts

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Introduction

- Neoadjuvant therapy has become the standard of care for many early-stage breast cancer patients to shrink or eradicate tumors before surgery.
- Despite its promise, only a subset of patients truly benefit from neoadjuvant therapy.
- Current prediction methods rely on broad clinical categories (ER/PR/HER2 status, tumor size) and basic histologic features that lack sufficient accuracy to guide individualized treatment planning.
- AI can reveal subtle morphological patterns in pathology slides to guide personalized treatment decisions for neoadjuvant therapy.

Methods

- We developed an AI model that integrates digital pathology with clinical information to predict the response to neoadjuvant therapy, specifically the probability of reaching pathological complete response (pCR).
- We extracted pathology imaging features using our AI foundation model, Kestrel [1].
- To enhance performance, we applied transfer learning from a previously developed model [2] that was trained to predict the risk of cancer recurrence using imaging features from Kestrel.

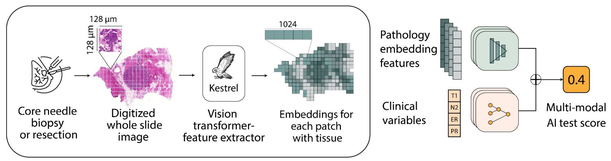


Figure 1: Imaging-based features from Kestrel were combined with clinical information to generate our multimodal AI test score.

Patients

The external evaluation sets included four cohorts (n=563):

- UChicago (n=257), Providence (n=65) and Jagiellonian (n=115) cohorts comprised all invasive breast cancer molecular subtypes
- IMPRESS (n=126) cohort included only TNBC and HER2+ patients.
- The pCR rates are 36.6%, 46.2%, 32.2%, 51.6% for UChicago, Providence, Jagiellonian, and IMPRESS cohorts respectively.

Results

AI prediction is independently predictive of pCR after adjusting for clinical features

- Multivariate logistic regression analysis demonstrated that the AI model was significantly associated with pCR, after adjusting for molecular subtype, TNM staging, patient age, and tumor grade.
- The adjusted odds ratio was 1.54 (95% CI, 1.27–1.88; $p < 0.01$), indicating that the AI model remained an independent predictor of pCR.

Performance robust in all external validation cohorts & across subgroups

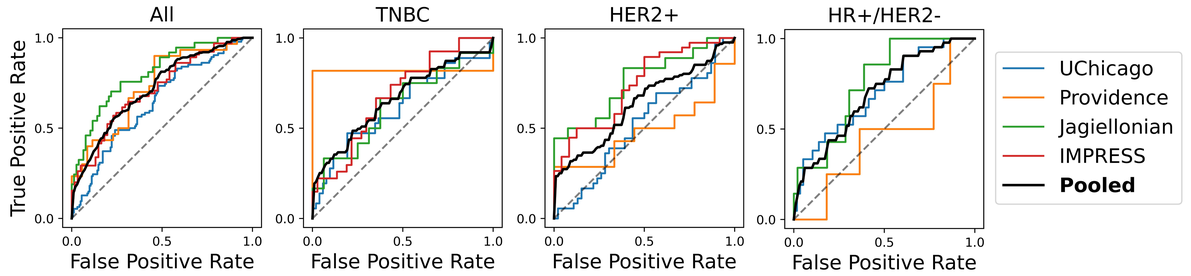


Figure 2: AI model generalizes well across four independent neoadjuvant cohorts and molecular subtypes for pCR prediction, as shown by Receiver-Operating Characteristic (ROC) curves. Pooled results represent weighted-averaged ROC curves, where the weights are computed using random effects model.

Predictions align with clinical outcomes across subgroups

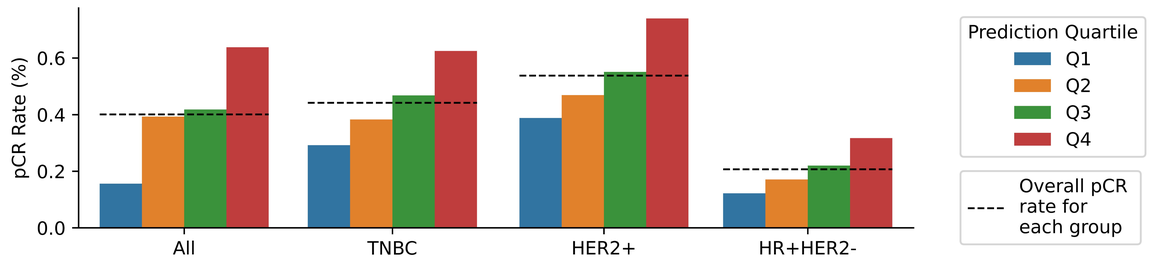


Figure 3: Distribution of pCR rates across subsets split by quartiles. Quartiles were computed with respect to the corresponding test datasets. Higher model-predicted pCR probability quartiles correspond to higher observed pCR rates, confirming predictive stratification performance. When stratifying all patients based on model predictions, the bottom quartile (Q1) had 15.6% pCR rate whereas the top quartile (Q4) had 63.8% pCR rate.

Significance

For patients likely to respond to neoadjuvant therapy:

- Enables less invasive surgery or skipping surgery entirely.

For patients unlikely to respond:

- Avoids weeks of toxic, ineffective therapy and accelerates access to alternative treatments or clinical trials.

For clinicians:

- Improves treatment planning for neoadjuvant therapy.

Scientific Innovation

- Instead of hand-engineered features, our AI model leverages an AI foundation model trained on a massive collection of pathology images to extract rich, generalizable morphological features.
- The AI model integrates morphological features with clinical information to further improve its performance.
- Our AI model is trained on a diverse dataset and validated on four independent cohorts.

Conclusion

The AI test:

- Shows promising performance in predicting the response to neoadjuvant therapy.
- Demonstrates strong generalization across patient cohorts and molecular subtypes (TNBC, HER2+, and HR+ HER2-).
- Has potential to improve personalized treatment decisions for neoadjuvant therapy.

References

[1] J. Cappadona, K. G. Zeng, C. Fernandez-Granda, J. Witowski, Y. LeCun, and K. J. Geras, “Squeezing performance from pathology foundation models with chained hyperparameter searches,” in NeurIPS 2024 Workshop: Self-Supervised Learning - Theory and Practice, 2024.

[2] Jan Witowski, Ken Zeng, Joseph Cappadona, Jailan Elayoubi, Elena Diana Chiru, Nancy Chan, Young-Joon Kang et al. "Multi-modal AI for comprehensive breast cancer prognostication." *arXiv preprint arXiv:2410.21256* (2024).

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