Refining adjuvant CDK4/6 inhibitor eligibility in early HR+ HER2- breast cancer with artificial intelligence

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Introduction

- CDK4/6 inhibitors have demonstrated efficacy in reducing disease recurrence among HR+ HER2- breast cancer patients meeting certain risk of recurrence (RoR) criteria.
- These RoR criteria, defined in trials such as NATALEE[1], use stage, Ki-67, G3, or Oncotype DX/PAM50/MammaPrint/EndoPredict.
- However, the predictive value of these RoR criteria is limited, potentially missing patients who may benefit from CDK4/6 inhibitors.

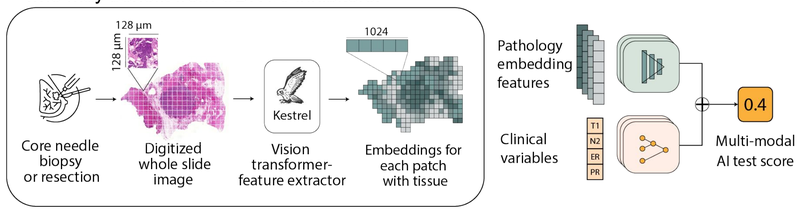


Figure 1: Schematic of ATX pipeline integrating pathology and clinical variables.

- ATX[2] is an artificial intelligence tool that integrates morphological features extracted from H&E-stained slides with clinical features to generate risk scores.
- We evaluated ATX's ability to:
  1. Establish the RoR in patients with early stage HR+ HER2- breast cancer.
  2. Assess ATX-based RoR performance within risk groups defined by NATALEE criteria.

Methods

- ATX risk scores were generated from 2,228 HR+ HER2- patients across 6 datasets.
  - Basel (n=266), Karmanos (n=161), Providence Health (n=1012), TCGA (n=312), UChicago (n=395), and UChicago Neoadjuvant (n=82).
- Patients received standard of care treatment which did not include CDK4/6 inhibitors as they were not available at the time of collection.
- Clinical High-Risk and Low-Risk groups were defined according to NATALEE trial CDK4/6 inhibitor eligibility criteria.
- The ATX model generated 5-year RoR scores, using a primary cut-off of 10% to classify patients into ATX-high and ATX-low risk groups.
- The model was not trained with any data used in this analysis.
- The primary endpoint was disease-free interval, evaluated using hazard ratios (HR per 0.1 increase in ATX score) and Harrell's concordance-index.

Patients

- Of the 2,228 patients, 918 (41%) were classified as Clinical High-Risk, and therefore eligible for adjuvant CDK4/6 inhibitors according to NATALEE criteria, and 1,310 were Clinical Low-Risk.
- 1,596 (72%) patients were classified as ATX-low and 632 (28%) patients were classified as ATX-high.

Results

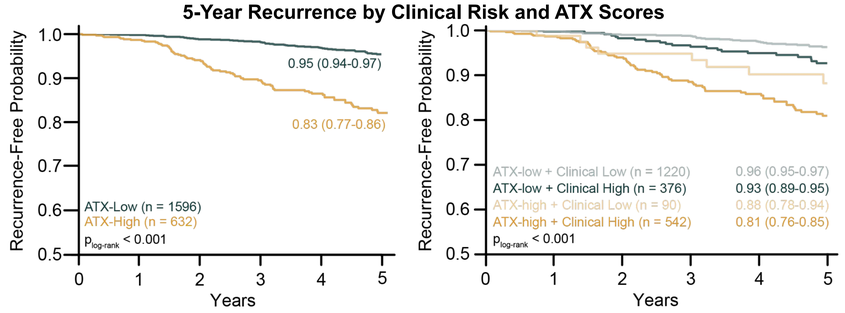
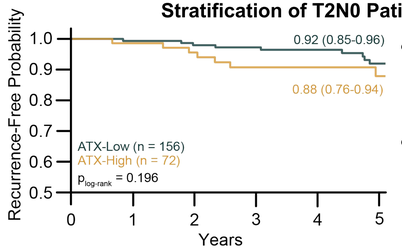


Figure 2: Kaplan-Meier analysis stratified by ATX and Clinical Risk

- ATX score-stratified patients show significant differences in disease-free interval regardless of Clinical Risk.



- ATX score stratified patients demonstrate a non-significant difference in disease-free interval within T2N0 patients.
- ATX can meaningfully stratify risk within ambiguous T2N0 population, and guide selection of patients who are eligible for adjuvant CDK4/6 inhibitor treatment.

Figure 3: Kaplan-Meier analysis in T2N0 borderline patients.

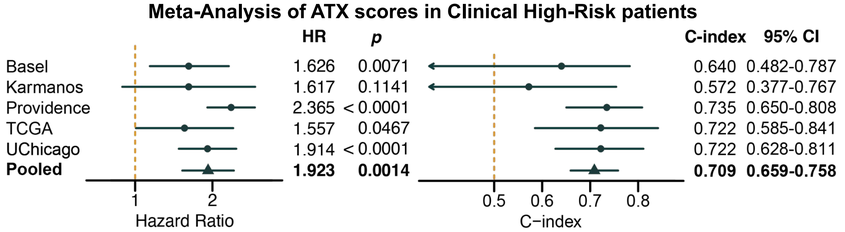


Figure 4: Meta-analysis of ATX scores across Clinical High-Risk patients in 5 cohorts.

- The predictive performance of ATX score was analyzed in Clinical High-Risk patients across 5 institutions to assess its association with 5-year recurrence risk.
- ATX risk scores demonstrated significant association with disease-free interval.

Results Continued

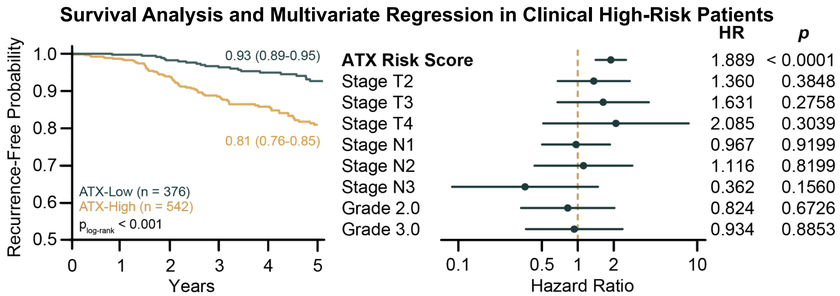


Figure 5: ATX performance in Clinical High-Risk patients.

- ATX score significantly stratifies recurrence-free survival in Clinical High-Risk patients.
- After controlling for tumor stage, nodal stage, and grade, ATX score remains prognostic..

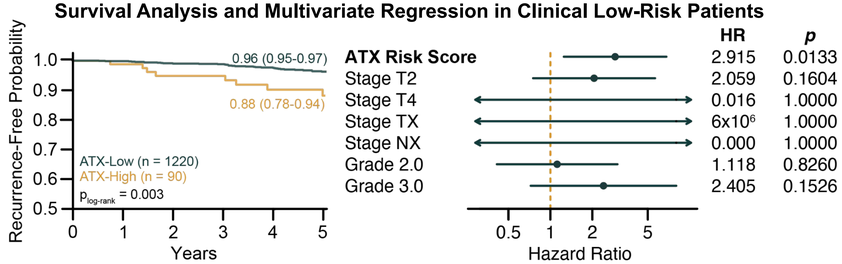


Figure 6: ATX performance in Clinical Low-Risk patients.

- Clinical Low-Risk patients show significantly different recurrence-free survival when stratified by ATX score.
- After multivariate regression, ATX score remains prognostic.

Conclusions

- ATX score enhances risk stratification beyond the risk criteria defined in the NATALEE trial in early-stage HR+ HER2- breast cancer patients.
- ATX score may identify both high-risk CDK4/6 inhibitor-eligible patients and those unlikely to benefit based on clinical features alone.
- This may potentially redefine which patients are eligible for adjuvant CDK4/6 inhibitors relative to the current criteria.

References

1. Slamon et al., The New England Journal of Medicine, 2024
2. Witowski et al., arxiv, 2024

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