Multimodal Deep Learning for Recurrence Stratification for Early-Stage Breast Cancer in Resource-Constrained Environments: Genomics-grade recurrence stratification directly from H&E images - no sequencing required.

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SAN ANTONIO BREAST CANCER SYMPOSIUM®
UT Health San Antonio Mays Cancer Center
AACR American Association for Cancer Research®

95% Specificity

92% NPV

3.8x Recurrence Risk

Introduction

Genomic assays (e.g., Oncotype DX, MammaPrint) guide adjuvant chemotherapy in early-stage breast cancer.

Challenges:

- High-cost limits accessibility in low- and middle-income settings
- Long turnaround delays treatment decisions
- Dependence on sequencing infrastructure not available in many hospitals

Our solution: TRINITY AI

A multimodal deep-learning platform that integrates:

- Tissue morphology from standard H&E slides
- Clinical variables (e.g. tumor size, grade, patient features)
- AI-inferred transcriptomic signature

TRINITY AI generates a BreastRS score (0-100) that provides:

- "Virtual genomics-grade" recurrence stratification
- **Rapid, affordable**, and **scalable** deployment.
- Broader access to de-escalation/escalation decisions.

Methods and Materials

Model development

- TRINITY AI was trained on 1219 early-stage breast cancer cases from TCGA and CPTAC.
- A self-supervised transformer foundation model infers transcriptomic signatures directly from digitized H&E whole-slide images (WSI), integrating these with clinical variables (age, tumour size, grade, nodal status) and tissue morphology.

Diagnostic validation

Three external cohorts (n=146) with matched Oncotype DX scores were used for validation, with strict slide QC and pathologist review.

Prognostic Validation

Prognostic utility was assessed in **1051 TCGA cases** with ≥5-year follow-up using multivariable Cox models for **distant recurrence-free interval (DRFI),** adjusted for clinicopathologic factors.

TRINITY AI BreastRS Workflow

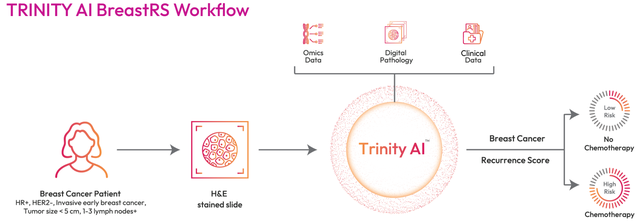


Figure 1: Trinity AI inference workflow for a Standard H&E stained WSI

Patient Demographics and Clinical Characteristics (N = 1219)

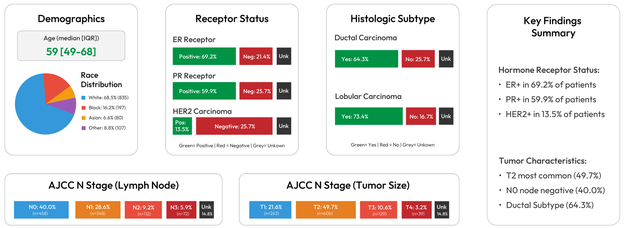


Figure 2A: Demographic and Clinical Characteristics of Patients in Training Cohort (TCGA/CPTAC)

Spatial Omics based Explainable AI (xAI)

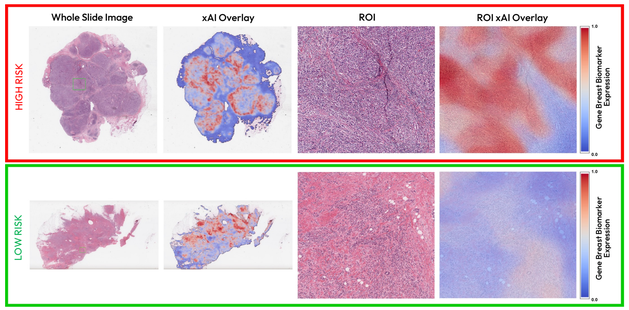


Figure 2B: Visualization of the expression levels of Breast Cancer recurrence genes on H&E WSI.

Results

- Across the pooled external validation set, TRINITY AI identified low-risk disease with **95% specificity, 92% negative predictive value, and AUC= 0.88**, outperforming clinicopathologic nomograms and approximating Oncotype DX.
- In cohort-specific analysis, TRINITY AI maintained a **NPV >87%** and **specificity >92%.**
- High-risk classification was associated with a **3.8-fold higher distant recurrence risk** (95 % CI 2.08–7.18), independent of size, grade, nodal status, and subtype (**C-index = 0.698**, 95% CI: 0.622–0.770).

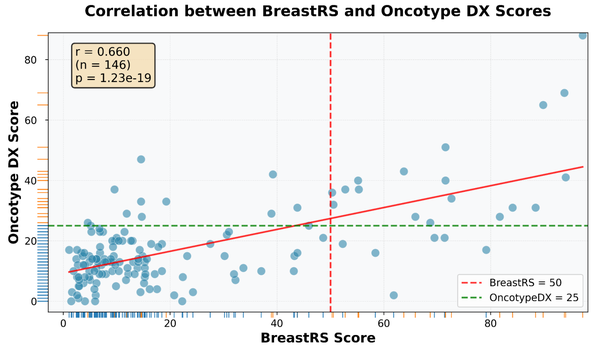


Figure 3: Scatterplot to Show Correlation Between BreastRS and Oncotype DX Scores

BreastRS vs. Oncotype Dx

Metrics	Cohort 1 (n=65)	Cohort 2 (n=43)	Cohort 3 (n=38)	Combined (n=146)
Sensitivity	86.67%	44.44%	25%	64.29%
Specificity	92%	97.06%	97.06%	94.92%
PPV	76.47%	80%	50%	75%
NPV	95.83%	86.84%	91.67%	91.8%
Num of samples	65	43	38	146
Num Positive (n,%)	15 (23.08%)	9 (20.93%)	4 (10.53%)	28 (19.18%)
Num Negative (n,%)	50 (76.92%)	34 (79.07%)	34 (89.47%)	118 (80.82%)

Table 1: Comparative Performance of BreastRS against Oncotype DX Scores in Independent Clinical Validation Cohorts

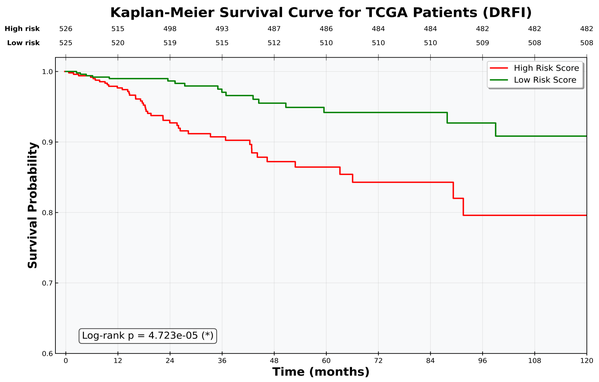


Figure 4: Kaplan-Meier Analysis of Primary Endpoint (Distant Recurrence-Free Interval, DRFI) in TCGA Cohort

Discussion

- **TRINITY AI** acts as a rule-out test to help low-risk HR+/HER2- patients **avoid unnecessary chemotherapy**.
- Demonstrates **independent prognostic value** beyond clinicopathologic and genomic markers.
- **AI insights align with known molecular biology**, supporting interpretability.
- **Limitations:** Incremental contribution of AI-inferred transcriptomics has not been formally quantified, and survival data were not available for external cohorts; primary survival analyses relied on TCGA.

Conclusions

- **TRINITY AI** transforms the ubiquitous H&E slide into a **genomics-grade breast cancer recurrence assay** that resides within the pathologist's digital workflow.
- Offers fast, affordable, and accessible precision oncology, no sequencing required.
- Early results on TCGA support its potential prognostic value, pending broader validation

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