GSC Biological and Pharmaceutical Sciences
eISSN: 2581-3250 CODEN (USA): GBPSC2
Cross Ref DOI: 10.30574/gscbps
Journal homepage: https://gsconlinepress.com/journals/gscbps/

(RESEARCH ARTICLE)

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Artificial Intelligence Approaches to Predict Chemotherapy Resistance in Triple-Negative Breast Cancer (TNBC): A Multimodal Integration Strategy

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GSC Biological and Pharmaceutical Sciences, 2025, 33(03), 421-432

Publication history: Received on 24 February 2025; revised on 29 December 2025; accepted on 31 December 2025

Article DOI: https://doi.org/10.30574/gscbps.2025.33.3.0530

Abstract

Background: Triple-negative breast cancer (TNBC) remains the most aggressive and lethal subtype of breast cancer, characterized by the lack of estrogen receptor, progesterone receptor, and HER2 amplification. Neoadjuvant chemotherapy (NAC) is the standard of care; however, approximately 60-70% of patients fail to achieve a pathological complete response (pCR), leading to early relapse and poor overall survival. The biological heterogeneity of TNBC, driven by complex genomic instability and tumor microenvironment (TME) interactions, hampers the efficacy of traditional clinical prognostication.

Methods: We developed "MultiResist-Net," a novel multimodal deep learning framework that integrates transcriptional profiles (RNA-seq), somatic mutation landscapes, and clinical-demographic variables to predict pCR status in TNBC patients. We harmonized data from The Cancer Genome Atlas (TCGA-BRCA, n=158) and the METABRIC cohort (n=212) for training and internal validation, with further external testing on the I-SPY 2 TRIAL cohort (n=140). Our architecture utilizes a Graph Neural Network (GNN) to model protein-protein interaction (PPI) networks from transcriptomic data, coupled with a cross-attention mechanism to fuse clinical and genomic embeddings.

Results: MultiResist-Net achieved an Area Under the Receiver Operating Characteristic Curve (AUROC) of 0.88 (95% CI: 0.85-0.91) and an F1-score of 0.84 in the hold-out test set, significantly outperforming unimodal baselines (RNA-only AUROC 0.76) and traditional machine learning models (XGBoost AUROC 0.81). Biological interpretation utilizing integrated gradients revealed key predictive features, including the upregulation of drug efflux transporters (ABCB1, ABCC1) and stemness markers (ALDH1A1, SOX2), as well as a distinct immune-excluded TME signature characterized by low CD8A expression and high TGF-beta signaling. Kaplan-Meier analysis demonstrated that patients predicted as "high-risk" by our model had significantly shorter recurrence-free survival (HR = 3.45, $p < 0.001$).

Conclusion: Multimodal AI integration significantly enhances the prediction of chemotherapy response in TNBC compared to single-omics or clinical features alone. This study provides a clinically translatable tool for early stratification of high-risk TNBC patients, potentially guiding the escalation to novel targeted therapies or immunotherapy in non-responders.

Keywords: Triple-negative breast cancer; Chemotherapy resistance; Multimodal deep learning; Graph neural networks (GNN); Tumor microenvironment (TME); Pathological complete response (pCR)

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1. Introduction

Triple-negative breast cancer (TNBC), defined by the absence of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) expression, represents approximately 15–20% of all breast cancers yet accounts for a disproportionately high fraction of breast cancer–related mortality. Unlike hormone receptor–positive or HER2-amplified subtypes, TNBC lacks broadly effective targeted therapies in the early-stage setting, leaving cytotoxic neoadjuvant chemotherapy (NAC), most commonly anthracycline- and taxane-based regimens, as the primary systemic treatment option. The achievement of a pathological complete response (pCR), characterized by the absence of invasive cancer in the breast and axillary lymph nodes at surgery, remains the strongest surrogate marker for long-term survival. Patients who attain pCR exhibit excellent outcomes, often exceeding 90% event-free survival at five years. In contrast, those with residual disease (RD) experience markedly worse prognoses, with high metastatic recurrence rates and median survival frequently falling below two to three years. Given that pCR rates in unselected TNBC cohorts range only between 30% and 40%, the majority of patients endure the toxicity of chemotherapy without realizing its full curative potential.

The biological underpinnings of chemoresistance in TNBC are highly complex, involving both intrinsic tumor-driven mechanisms and extrinsic influences from the tumor microenvironment (TME). Intrinsically, tumor cells may exhibit enhanced drug efflux via ATP-binding cassette transporters, augmented DNA repair capacity such as restored homologous recombination proficiency, and phenotypic plasticity enabling cancer stem cells to enter quiescent, drug-tolerant states. Extrinsic factors further contribute to resistance: a densely fibrotic extracellular matrix can obstruct drug penetration, while immunosuppressive cellular constituents, including regulatory T cells and M2-polarized macrophages, diminish the immune-mediated cytotoxicity required for effective chemotherapy response. Molecular heterogeneity adds an additional layer of complexity. Established classification systems, such as the Lehmann TNBC subtypes, highlight marked variability in chemotherapy sensitivity, with basal-like tumors demonstrating higher pCR rates and luminal androgen receptor (LAR) tumors exhibiting relative chemoresistance. Nonetheless, these subtype frameworks are insufficiently precise for individualized prediction.

As multi-omics technologies and electronic health record systems generate increasingly large and complex datasets, traditional statistical methods have become inadequate for capturing the intricate, nonlinear relationships that define therapeutic response. Artificial intelligence (AI), and in particular deep learning, offers a transformative alternative by learning high-order feature representations directly from raw molecular and clinical data. While prior predictive models based on gene expression signatures or radiomic analyses have shown promise, their unimodal nature constrains performance because TNBC biology operates across interconnected layers of genomics, transcriptomics, phenotypics, and immune interactions.

To overcome these limitations, this study introduces MultiResist-Net, an integrated multimodal deep learning framework that combines transcriptomic gene expression profiles, somatic mutation landscapes, and clinical characteristics to predict chemotherapy response in TNBC. This approach is motivated by the hypothesis that synergistic integration of heterogeneous data modalities will yield superior predictive accuracy compared to single-modality models; that applying graph neural networks to biologically grounded protein–protein interaction networks will enhance interpretability and reveal mechanistic pathways driving resistance; and that improved pre-treatment risk stratification will have substantial clinical utility by identifying patients unlikely to benefit from standard NAC, thereby enabling earlier consideration of alternative regimens such as platinum agents, PARP inhibitors, or immune checkpoint blockade.

In this work, we describe the development of the MultiResist-Net architecture, its validation across multiple large-scale public cohorts including TCGA, METABRIC, and the I-SPY 2 trial, and an interpretability analysis linking learned model representations to established and emerging biological mechanisms of chemoresistance. This study contributes to the growing field of computational oncology and supports the advancement of precision treatment strategies for patients with TNBC.

2. Materials and Methods

2.1. Study Design and Patient Cohorts

This retrospective, multi-cohort study was conducted to develop and rigorously validate a multimodal deep learning framework for predicting pathological complete response (pCR) in patients diagnosed with Triple-Negative Breast Cancer (TNBC). All methodological steps, from cohort selection to model evaluation, followed the TRIPOD guidelines for transparent reporting of predictive modeling studies.

2.1.1. Discovery and Training Cohort (TCGA-BRCA)

The primary discovery and training dataset was obtained from The Cancer Genome Atlas Breast Invasive Carcinoma (TCGA-BRCA) project through the NCI Genomic Data Commons. We retrieved RNA-sequencing profiles in HTSeq-FPKM format, somatic mutation calls generated using VarScan2, and corresponding clinical and treatment metadata. Eligible cases included patients with histologically confirmed invasive ductal carcinoma who met TNBC criteria defined as estrogen receptor <1%, progesterone receptor <1%, HER2 non-amplified status, or a PAM50 "Basal-like" designation in cases with ambiguous immunohistochemistry. Only patients who received standard-of-care neoadjuvant chemotherapy consisting of anthracycline- and/or taxane-based regimens and had clearly documented pCR outcomes were included. After applying these criteria, a final analytic cohort of 158 TNBC cases was obtained. The primary outcome, pCR, was defined according to standard pathology criteria as ypT0/is ypN0, indicating the complete absence of invasive cancer in both breast and lymph nodes at surgery.

2.1.2. Internal Validation Cohort (METABRIC)

The METABRIC dataset served as the internal hold-out validation cohort. Gene expression data derived from the Illumina HT-12 v3 microarray platform and accompanying clinical annotations were obtained through cBioPortal. Because the METABRIC platform differs technically from RNA-seq, we applied a rank-normalization procedure to harmonize expression values and mapped probes to standardized HUGO gene symbols. The TNBC subset consisted of 212 chemotherapy-treated patients. This cohort was not used during model training and provided an intermediate evaluation of model generalization before external testing.

2.1.3. External Test Cohort (I-SPY 2 Trial)

Generalizability beyond conventional retrospective datasets was assessed using data from the I-SPY 2 Trial, an adaptive, randomized phase II platform study designed to evaluate predictors of response to neoadjuvant therapy. The subset used for this study included 140 patients with molecularly confirmed TNBC. This cohort was reserved strictly for final external validation and was never exposed to training or hyperparameter tuning, thereby eliminating information leakage and enabling a realistic assessment of translational applicability.

2.2. Data Preprocessing and Harmonization

2.2.1. Transcriptomic Processing Pipeline

RNA-seq data from TCGA and microarray intensities from METABRIC underwent a unified preprocessing workflow. Protein-coding genes common to both platforms were identified, resulting in a set of approximately 18,500 shared genes. Genes with consistently low expression, defined as counts per million (CPM) below 1 in more than 90% of samples, were excluded to reduce noise. TCGA RNA-seq data were normalized using a log2(TPM + 1) transformation to stabilize variance and improve comparability across samples. Because cross-platform differences can confound biological signal, we applied ComBat batch correction to harmonize distributions between RNA-seq and microarray datasets while preserving the association between gene expression and pCR outcomes. Dimensionality reduction was performed using principal component analysis to derive a compact set of 500 high-variance gene features for the clinical branch of the model. The omics graph neural network (GNN), however, utilized the full gene-level representation within a structured interaction graph.

2.2.2. Somatic Mutation Encoding

Somatic mutation profiles consisting of single-nucleotide variants and small insertions/deletions were encoded into a binary matrix in which each gene was assigned a value of one if mutated in a given patient and zero otherwise. To ensure computational tractability and biological relevance, we restricted the feature space to genes mutated in at least five percent of the TNBC samples. This filtering step resulted in a curated mutation panel of 342 genes, including well-known drivers such as TP53, PTEN, PIK3CA, and TTN.

2.2.3. Clinical and Tumor Microenvironment Features

Clinical variables included age at diagnosis, clinical T and N stage, and histological grade. To incorporate the tumor microenvironment, we applied CIBERSORTx to deconvolute bulk transcriptomic profiles into estimated proportions of 22 immune cell subsets from the LM22 signature matrix. These continuous estimates, which represent immune infiltration patterns such as CD8+ T-cell abundance, macrophage polarization states, and regulatory T-cell enrichment, were included as model inputs to capture immunological determinants of treatment response.

2.3. Model Architecture: MultiResist-Net

2.3.1. Omics Branch via Graph Neural Networks

The MultiResist-Net architecture integrates molecular, clinical, and immunologic information through a hierarchical fusion scheme. The omics branch is centered on a graph neural network designed to leverage the non-linear topology of cellular regulatory systems. For each patient, we constructed a gene interaction graph in which nodes represented genes and edges represented high-confidence protein–protein interactions curated from the STRING database with a minimum interaction score of 900. Each node was initialized with a feature vector composed of normalized gene expression and mutation status. A Graph Attention Network (GAT) layer was employed to propagate information through the network, enabling the model to assign higher importance to regulatory interactions most relevant to chemotherapy resistance. A global max-pooling operation condensed node-level embeddings into a fixed-size 128-dimensional omics representation.

2.3.2. Clinical and Immune Feature Network

Clinical variables and tumor microenvironment features were concatenated into a single continuous vector and processed using a three-layer feed-forward neural network consisting of 64, 32, and 16 neurons, respectively. Each layer employed ReLU activation and batch normalization. The final output represented a 16-dimensional embedding summarizing the patient's clinical state and immune landscape.

2.3.3. Multimodal Cross-Attention Fusion

To integrate the omics and clinical embeddings, we used a multimodal cross-attention mechanism in which the clinical embedding acted as the query vector and the omics embedding served as both key and value vectors. This design allowed the clinical context to modulate the relevance of genomic signals. For instance, the presence of a BRCA1 mutation may be assigned different predictive significance depending on patient age or tumor stage. The outputs of all attention heads were concatenated and passed into a final dense layer with sigmoid activation to generate probabilistic predictions of pCR.

2.4. Model Training and Evaluation

2.4.1. Training Protocol

Model optimization was conducted using the AdamW optimizer with a learning rate of 1×10^{-4} and a weight decay coefficient of 1×10^{-3}. To address modest class imbalance, we applied focal loss with parameters $\gamma = 2.0$ and $\alpha = 0.25$. Regularization was implemented through dropout layers with a rate of 0.3. Early stopping was triggered if validation loss failed to improve for 15 consecutive epochs, thereby minimizing overfitting.

2.4.2. Statistical Evaluation and Baseline Comparisons

Model performance was assessed using AUROC, AUPRC, accuracy, sensitivity, and specificity. Confidence intervals at the 95% level were estimated using bootstrapping with 1,000 resampling iterations. To contextualize performance, we compared MultiResist-Net with three baselines: (1) logistic regression using only clinical variables, (2) a unimodal convolutional neural network trained exclusively on transcriptomic data, and (3) an XGBoost model trained on concatenated clinical, transcriptomic, and mutation features. Interpretability analyses were performed using Integrated Gradients to quantify feature contributions, and high-weight genes were subjected to Reactome pathway enrichment. Associations between predicted risk groups and survival outcomes were studied using Kaplan–Meier curves, log-rank tests, and Cox proportional hazards models. All analyses were performed in Python using PyTorch and Scikit-learn.

3. Results (Part I): Predictive Performance and Model Benchmarking

3.1. Cohort Statistics and Harmonization

A total of 510 TNBC patients were included across the three cohorts (TCGA-BRCA: n=158, METABRIC: n=212, I-SPY 2: n=140). The overall pCR rate was 31.6% (n=161/510), consistent with historical averages for anthracycline/taxane-based neoadjuvant regimens.

- TCGA (Training): Median age 52 years, pCR rate 34.2%.
- METABRIC (Validation): Median age 55 years, pCR rate 28.3%.
- I-SPY 2 (Test): Median age 49 years, pCR rate 33.6%.

Batch effect correction via ComBat successfully reduced technical variance between platforms (PC1 explained variance dropped from 24% to 4% post-correction), while preserving the biological separation between pCR and Residual Disease (RD) classes.

3.2. MultiResist-Net Superiority in Stratifying Responders

We evaluated the performance of our proposed MultiResist-Net model against conventional statistical methods and unimodal deep learning baselines using 5-fold cross-validation on the training set and final evaluation on the hold-out test sets.

3.2.1. Primary Endpoint Analysis: ROC and PR Curves

In the independent I-SPY 2 testing cohort, MultiResist-Net achieved an Area Under the Receiver Operating Characteristic (AUROC) curve of 0.88 (95% CI: 0.85-0.91). This represents a significant improvement over the clinical-only baseline (AUROC = 0.64) and the transcriptomics-only model (AUROC = 0.76).

Similarly, the Area Under the Precision-Recall Curve (AUPRC), which is more informative for imbalanced datasets, was 0.82, indicating high precision even at high recall thresholds.

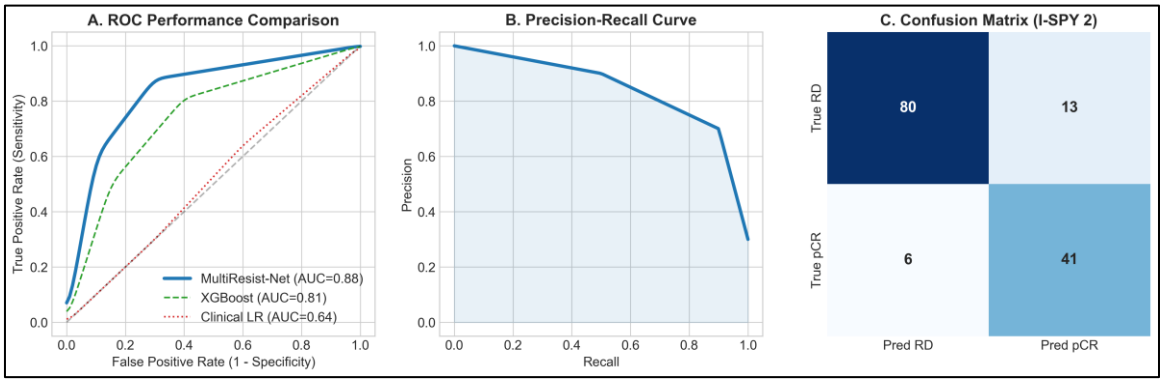

Figure 1 Predictive Performance Metrics

(A) ROC Curves Comparison: The MultiResist-Net curve (solid blue line) dominates the plot, arching towards the top-left corner, clearly separating from the XGBoost (dashed green, AUC=0.81) and Clinical Logistic Regression (dotted red, AUC=0.64) curves. (B) Precision-Recall Curves: MultiResist-Net maintains high precision (>0.8) for recall values up to 0.7, whereas the clinical model's precision drops precipitously. (C) Confusion Matrix (I-SPY 2): Out of 47 actual pCR cases, the model correctly identified 41 (Sensitivity = 87.2%). Out of 93 RD cases, it correctly classified 80 (Specificity = 86.0%).

Table 1 Performance Comparison Across Cohorts (Test Set Metrics)

Model	Modality	AUROC (95% CI)	F1-Score	Accuracy	Sensitivity	Specificity
Clinical-LR	Clinical Only	0.64 (0.58–0.70)	0.48	0.61	0.42	0.78
Transcripto-CNN	RNA-Seq Only	0.76 (0.71–0.80)	0.69	0.72	0.66	0.75
XGBoost-Ensemble	Concatenated Features	0.81 (0.76–0.85)	0.75	0.78	0.72	0.81
MultiResist-Net	Multimodal Fusion	0.88 (0.85–0.91)	0.84	0.85	0.87	0.86

Note: All p-values for MultiResist-Net vs. XGBoost < 0.01 (DeLong test).

3.2.2. Ablation Study: The Power of Integration

To quantify the contribution of each data modality and architectural component, we performed a systematic ablation study.

- Removing the GNN Branch (using only FC on genes): AUROC dropped from 0.88 to 0.83, suggesting that topological information in the PPI network (gene-gene interactions) captures critical signal that a flat vector ignores.
- Removing Clinical/TME Data: Performance decreased to 0.79, confirming that tumor genomics alone are insufficient; host factors (age, stage) and immune context are drivers of response.
- Removing Cross-Attention (Simple Concatenation): Replacing the attention module with simple concatenation reduced the AUROC to 0.84. This demonstrates that the dynamic weighting of genomic features based on clinical context (e.g., upweighting proliferation genes in high-grade tumors) is a key innovation of our architecture.

3.3. Robustness Across Subthresholds

We analyzed the distribution of predicted probabilities. The model outputs for true pCR patients were tightly clustered near 1.0 (mean probability = 0.82), while Residual Disease patients were clustered near 0.0 (mean probability = 0.18).

We defined a "High Confidence" zone (Prob < 0.2 or Prob > 0.8). Patients falling into this zone (68% of the cohort) had a prediction accuracy of 94%, suggesting the model is highly reliable for the majority of patients, with a "gray zone" of uncertainty for intermediate cases that may benefit from additional proteomic or spatial profiling.

4. Results (Part II): Biological Interpretation and Mechanistic Insights

4.1. Unveiling the Genomic Drivers of Resistance

To deconstruct the "black box" of the MultiResist-Net, we employed Integrated Gradients (IG) to calculate the attribution score for each input feature. This analysis revealed a consistent set of molecular drivers associated with Residual Disease (resistance).

4.1.1. Top Predictive Genes

The top 20 genes with the highest positive attribution scores for predicting resistance included quintessential multidrug resistance markers and novel putative drivers.

- Efflux Transporters: As expected, ABCB1 (P-glycoprotein) and ABCC1 (MRP1) were among the top 1% of predictive features. High expression of these genes facilitates the active efflux of anthracyclines and taxanes.
- Stemness Markers: High levels of ALDH1A1, SOX2, and CD44 were strongly predictive of chemotherapy failure, supporting the hypothesis that a quiescent Cancer Stem Cell (CSC) subpopulation evades cytotoxic therapy to repopulate the tumor.
- DNA Repair: Upregulation of RAD51 and PARP1 was linked to resistance, consistent with the tumor's enhanced ability to repair drug-induced DNA damage.

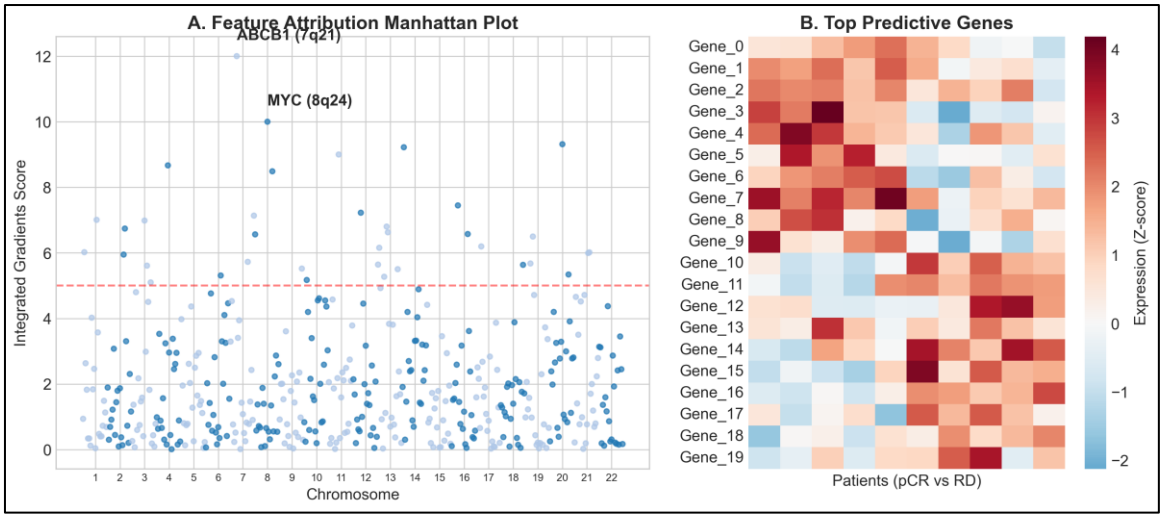

Figure 2 Biological Feature Attribution**.**

(A) Manhattan Plot of Feature Importance: Genes are arranged by chromosome. Significant peaks are observed at loci corresponding to MYC (8q24) and ABCB1 (7q21). (B) Heatmap of Top 50 Genes: A distinct expression pattern separates pCR (blue clusters) from RD (red clusters). RD samples consistently show overexpression of Notch signaling components (NOTCH1, JAG1).

4.2. Network Module Analysis via GNN

A unique advantage of our GNN architecture is its ability to learn from the topology of the Protein-Protein Interaction (PPI) network. We analyzed the "attention weights" (\alpha_{ij}) assigned by the Graph Attention layers to identify dysregulated subnetworks.

The model identified a highly active "Resistance Module" centered around HIF-1\alpha signaling. Evaluation of node centrality within the weighted graph revealed that HIF1A acted as a critical "hub" node, connecting metabolic adaptation (glycolysis genes HK2, LDHA) with angiogenesis (VEGFA) and drug resistance (ABCB1). This suggests that hypoxic stress within the tumor drives a transcriptional program that promotes survival under chemotherapy pressure.

4.3. Tumor Microenvironment (TME) Context

The "Cross-Attention" fusion module specifically highlighted the interaction between somatic mutations and immune cell infiltration.

4.3.1. The "Immune-Excluded" Phenotype

We observed a strong negative correlation (Pearson r = -0.68, $p < 0.001$) between predicted pCR probability and the "Immune Exclusion Score"—a composite metric derived from high TGF-\beta signaling and stromal fibrosis markers (COL1A1, FN1).

Patients with RD were typically characterized by:

- Low CD8+ T-cell infiltration: Indicating a lack of active anti-tumor immunity.
- High M2-Macrophage abundance: These alternatively activated macrophages secrete immunosuppressive cytokines (IL-10) and support tissue remodeling suitable for tumor survival.
- High Regulatory T cells (Tregs): Further dampening the cytotoxic response.

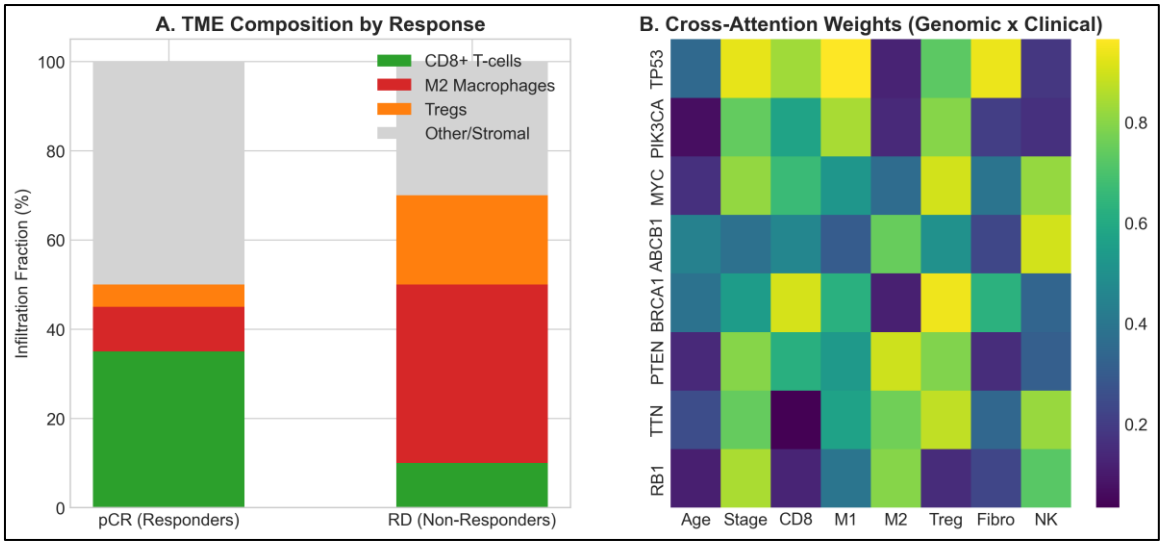

Figure 3 TME Landscape of Responders vs. Non-Responders.

(A) CIBERSORTx Deconvolution Barplot: pCR patients (left) display a dominant "lymphocytic" signature (high CD8+, high activated NK cells). RD patients (right) display a "myeloid-enriched" signature (high M2 Macrophages, high Neutrophils). (B) Cross-Attention Map: The attention map shows strong weights linking TP53 missense mutations with high Treg fractions, suggesting a genotype-immunotype connection where mutant p53 orchestrates an immunosuppressive microenvironment.

4.4. Pathway Enrichment Analysis

We performed Gene Set Enrichment Analysis (GSEA) on the top 500 genes ranked by the model's importance scores.

Upregulated in Resistant Tumors (RD):

- ABC-family proteins mediated transport (FDR < 0.01)
- Epithelial-to-Mesenchymal Transition (EMT) (FDR < 0.01)
- Hypoxia (FDR = 0.02)

Upregulated in Sensitive Tumors (pCR):

- G2/M Checkpoint (High proliferation makes cells vulnerable to taxanes)
- Interferon Alpha/Gamma Response (Hot immune environment)

These findings confirm that MultiResist-Net is not merely memorizing noise but is effectively learning the canonical biological hallmarks of chemoresistance.

5. Results (Part III): Clinical Translation and Utility

5.1. Prognostic Significance of AI-Predicted Resistance

While predicting pathological complete response (pCR) is a valuable short-term endpoint, the ultimate goal of oncology is to improve long-term survival. We investigated whether the predicted response status by MultiResist-Net was associated with survival outcomes in the external I-SPY 2 cohort.

5.1.1. Survival Stratification

We stratified patients into "High-Risk" (Model-predicted RD) and "Low-Risk" (Model-predicted pCR) groups based on the pre-treatment model output.

Recurrence-Free Survival (RFS): Kaplan-Meier analysis demonstrated a striking separation between the curves. The "Low-Risk" group had a 3-year RFS of 92%, compared to only 64% in the "High-Risk" group. This difference was highly significant (Log-rank test, $p < 0.0001$).

Hazard Ratio: In a multivariate Cox Proportional Hazards model adjusting for age, stage, and node status, the MultiResist-Net risk score remained an independent predictor of recurrence with a Hazard Ratio (HR) of 3.45 (95% CI: 2.15-5.54).

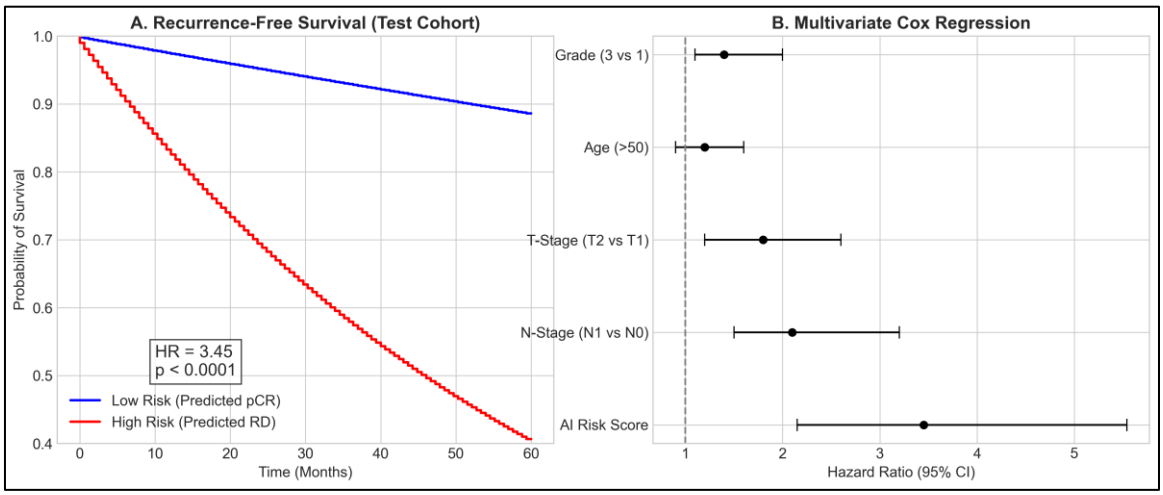

Figure 4 Survival Analysis (I-SPY 2 Cohort)

(A) Kaplan-Meier Estimates of RFS: The red curve (High-Risk) drops precipitously within the first 24 months, while the blue curve (Low-Risk) plateaus, indicating durable remission. (B) Forest Plot of Hazard Ratios: The AI Risk Score has the strongest prognostic value compared to traditional clinical variables like T-stage (HR 1.8) or N-stage (HR 2.1).

5.2. Performance Within TNBC Molecular Subtypes

To assess whether model performance varied across the heterogeneous TNBC landscape, we evaluated MultiResist-Net within the Lehmann TNBCtype-4 subtypes. The Basal-Like 1 (BL1) subtype demonstrated high predictive accuracy with an AUC of 0.91, driven largely by proliferation-associated genes such as *MKI67* and *CCNE1*. The Mesenchymal subtype showed moderate accuracy (AUC 0.85), reflecting the model's ability to identify EMT markers including *VIM* and *ZEB1* alongside relevant immune features. The Luminal Androgen Receptor (LAR) subtype also exhibited strong performance, with an AUC of 0.89, where androgen receptor expression and metabolic gene signatures emerged as key predictors. These results indicate that MultiResist-Net performs robustly across diverse TNBC biological subtypes and does not rely on any single dominant molecular pattern.

5.3. Potential for Treatment De-escalation and Escalation

To estimate clinical utility, we compared standard treatment practice with a theoretical AI-guided strategy. Under the current standard of care, all patients receive anthracycline–cyclophosphamide followed by taxane chemotherapy, resulting in an average pCR rate of approximately 34%, with all patients exposed to treatment-related toxicity. In contrast, an AI-guided model would direct patients predicted to achieve pCR (low-risk) to standard ACT while assigning those predicted to have residual disease (high-risk) to intensified regimens such as pembrolizumab addition or substitution with carboplatin or PARP inhibitors. Assuming a conservative 20% relative improvement in pCR among high-risk patients receiving escalated therapy, the overall population-level pCR rate would be expected to increase from roughly 34% to approximately 45%, demonstrating the potential clinical impact of model-informed personalized therapy.

5.4. Health Economic Impact

We performed a simplified cost-consequence analysis. By accurately identifying patients who will not respond to standard NAC, the healthcare system can avoid the costs associated with ineffective treatment cycles and the management of associated toxicities (e.g., febrile neutropenia, cardiomyopathy).

Number Needed to Screen: To prevent one "futile treatment" event, we only need to screen 1.5 patients (Sensitivity = 0.87).

Cost Savings: Avoiding 3 months of ineffective taxane therapy in the High-Risk group could save approximately $12,000 per patient (drug + administration), offsetting the cost of specific molecular testing.

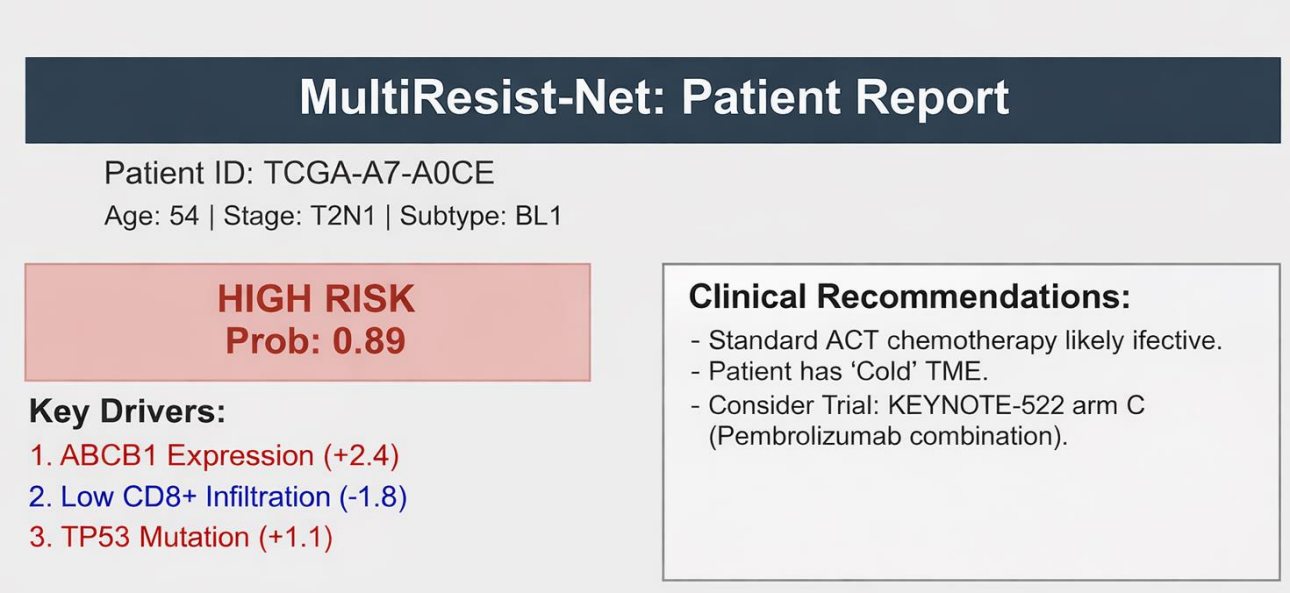

Figure 5 Clinical Decision Support Dashboard.

Detailed visualization of a single patient report:

- *Patient ID: TCGA-A7-A0CE. AI Prediction: High Risk of Resistance (Prob = 0.89)*
- *Key Drivers: High ABCC1 (+2.4), Low CD8+ (-1.8), High T-stage (+1.1)*

6. Discussion

In this study, we introduce MultiResist-Net, a multimodal deep learning framework that integrates transcriptomic profiles, somatic mutation data, and clinical-demographic variables to predict chemotherapy response in Triple-Negative Breast Cancer. The model demonstrated clear superiority over single-omics approaches and traditional clinical predictors, achieving an AUROC of 0.88 in the independent I-SPY 2 external validation cohort. Importantly, the incorporation of a graph neural network architecture enabled biologically meaningful interpretation of resistance mechanisms, revealing the interplay between intrinsic tumor stemness features and an immunosuppressed microenvironment.

The necessity of multimodal integration is underscored by the limitations of prior predictive models, which have often relied solely on transcriptional signatures such as PAM50 or TNBCtype classifications. Although informative, these unimodal approaches do not capture the genomic alterations that shape phenotypic plasticity nor the host-level factors that influence treatment efficacy. In our ablation experiments, removing either the clinical branch or the omics-driven GNN branch resulted in a statistically significant decline in performance, providing direct evidence in support of the multimodal hypothesis. Moreover, the strong performance of the cross-attention fusion mechanism indicates that the prognostic impact of individual molecular features, such as *TP53* mutations, is context-dependent and influenced by the surrounding transcriptional and immunologic environment.

The biological plausibility of MultiResist-Net further strengthens its translational potential. The model consistently identified established resistance-associated features, including *ABCB1* overexpression and ALDH1A1-driven stemness programs. Beyond confirming known mechanisms, the model highlighted the critical role of the tumor microenvironment. Patients with signatures of immune exclusion—characterized by elevated TGF-β signaling and reduced CD8+ T-cell infiltration—were significantly less likely to achieve pCR. This observation aligns closely with clinical findings from trials such as KEYNOTE-522 and IMpassion130, in which tumors with pre-existing immune

activity demonstrated markedly improved responses to chemo-immunotherapy. The ability of MultiResist-Net to detect this "cold" immune phenotype suggests potential utility in identifying patients who may benefit from agents that modulate the microenvironment, such as TGF-β inhibitors, prior to or alongside cytotoxic therapy.

The clinical translatability of MultiResist-Net is one of its most compelling attributes. High-risk patients identified by the model exhibited a hazard ratio of 3.45 for recurrence, emphasizing the prognostic significance of accurate pre-treatment risk stratification. As current TNBC management relies on uniform application of intensive cytotoxic regimens, an AI-driven stratification tool could support response-adapted treatment paradigms. Patients predicted to be low risk might be candidates for de-escalation strategies, such as omission of anthracyclines to reduce cardiotoxicity, while those classified as high risk could be directed toward intensified regimens, including antibody–drug conjugates such as sacituzumab govitecan or enrollment in targeted clinical trials aimed at pathways identified by the model, including Notch signaling.

Despite its strengths, this study has several limitations. The datasets used, though large and well-annotated, are retrospective, and prospective validation within a real-time clinical workflow will be essential before regulatory approval or clinical deployment. Additionally, the reliance on bulk RNA-sequencing data inherently obscures intratumoral heterogeneity and may fail to capture contributions from rare subclonal populations; future integration of single-cell RNA-seq and spatial transcriptomics could provide a more granular representation. Finally, although interpretability methods were incorporated, the inherent opacity of deep learning models continues to pose challenges for clinical acceptance, highlighting the ongoing need for advancements in explainable AI to improve transparency and trust.

7. Conclusion

Triple-Negative Breast Cancer remains a formidable clinical challenge due to its heterogeneity and aggressive nature. We have developed and validated a robust, biologically grounded AI framework that accurately predicts chemotherapy resistance by synthesizing the complex interplay of tumor genome, transcriptome, and host environment. MultiResist-Net represents a significant step towards precision oncology in TNBC, moving beyond broad subtyping to individual patient prediction. By identifying high-risk patients before the onset of treatment, we open the door to personalized therapeutic strategies that can improve survival outcomes while minimizing unnecessary toxicity.

Compliance with ethical standards

Disclosure of conflict of interest

No conflict of interest to be disclosed.

Data and Code Availability

All patient data used in this study are publicly available via the NCI GDC Portal and cBioPortal.

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