RESEARCH PAPER

Self-Evolving Digital Twin Ecosystems for Early Detection and Precision Management of Breast, Lung, Colorectal, and Ovarian Cancers

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ABSTRACT

Background: The convergence of multi-omics profiling, radiomics, and advanced machine learning has opened new frontiers in precision oncology. Despite this progress, existing computational frameworks remain static, failing to incorporate evolving patient data or simulate treatment outcomes dynamically. A self-evolving digital twin ecosystem offers a solution by continuously synchronizing patient-specific virtual models with real-world clinical trajectories.
Objective: To develop and validate a self-evolving digital twin ecosystem integrating clinical, genomic, transcriptomic, proteomic, radiomic, and pathological data for early cancer detection, disease progression prediction, and personalized treatment optimization across breast, lung, colorectal, and ovarian cancers.
Methods: A retrospective multi-center cohort of 400 patients (breast n=120, lung n=100, colorectal n=100, ovarian n=80; age range 25-75 years) was assembled. A six-layer digital twin framework was constructed, incorporating a cross-modal transformer foundation model alongside Random Forest, XGBoost, and Deep Neural Network comparators. Key performance metrics included accuracy, precision, recall, F1-score, and area under the ROC curve (AUC). Virtual clinical trial simulations and feature importance analyses were performed.
Results: The foundation model achieved superior performance across all metrics (accuracy 0.921, AUC 0.947) compared with Random Forest (0.812/0.847), XGBoost (0.841/0.879), and Deep Neural Network (0.873/0.906). Tumor stage, TP53 mutation, and EGFR mutation emerged as the most predictive features. Risk stratification identified 148 (37.0%) low-risk, 153 (38.3%) moderate-risk, and 99 (24.8%) high-risk patients. Virtual trial simulation demonstrated a 23.4% improvement in projected progression-free survival for the high-risk subgroup.
Conclusion: The self-evolving digital twin ecosystem significantly outperforms conventional machine learning approaches and provides a clinically actionable, adaptive platform for real-time precision oncology decision support across multiple cancer types.
Keywords: digital twins; precision oncology; cancer simulation; multi-omics integration; foundation models; disease progression modeling; virtual clinical trials; predictive analytics; treatment optimization; personalized medicine; computational oncology; radiomics
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1. INTRODUCTION

Cancer remains the second leading cause of mortality worldwide, with an estimated 19.3 million new diagnoses and nearly 10 million deaths reported in 2024 (GLOBOCAN, 2024). Breast, lung, colorectal, and ovarian cancers collectively account for approximately 43% of global cancer incidence, yet their biological heterogeneity spanning molecular subtypes, microenvironmental states, and treatment trajectories renders population-level management strategies insufficient. Precision oncology seeks to address this through individualized profiling, but implementation is constrained by siloed data architectures and static predictive models that do not evolve with the patient.

Digital twins (DTs), originally conceived in aerospace engineering, have emerged as a paradigm-shifting concept in medicine. A patient-specific digital twin is a dynamic computational replica that integrates continuously updated multimodal data genomics, imaging, pathology, and treatment records to model disease states, predict outcomes, and simulate therapeutic interventions in silico. Unlike conventional machine learning pipelines, DT ecosystems are self-evolving: they ingest new clinical events and revise their probabilistic state representations without requiring retraining from scratch.

Multi-omics integration combining genomic variants, transcriptomic signatures, proteomic biomarkers, and radiomic phenotypes captures tumor biology at unprecedented resolution. However, the analytical challenge lies in fusing data modalities with disparate dimensionalities and noise profiles. Foundation models, pre-trained on large biomedical corpora and fine-tuned on downstream tasks, have demonstrated strong cross-modal representation capabilities in recent studies (Acosta et al., 2022; Xu et al., 2024), positioning them as ideal backbone architectures for digital twin frameworks.

Existing studies have validated individual components of DT oncology radiomic feature extraction, genomic risk scoring, or single-modality deep learning but no published framework has unified self-evolving state updates, cross-modal transformer fusion, and virtual clinical trial simulation within a single ecosystem. This study addresses that gap by constructing and validating a complete self-evolving digital twin ecosystem across four major cancer types in a 400-patient retrospective cohort, benchmarking it against conventional machine learning approaches and demonstrating its translational value for early detection, progression risk stratification, and personalized treatment optimization.

2. LITERATURE REVIEW

2.1 Digital Twins in Healthcare

The application of digital twin technology to clinical medicine has expanded from organ-level physiological simulators to whole-patient dynamic models. Björnsson et al. (2020) established the conceptual foundation for DTs in pharmacology, while subsequent work demonstrated utility in cardiac monitoring and intensive care unit management. The key distinguishing feature is bidirectional synchronization between the physical patient and the virtual replica, enabling prospective simulation rather than retrospective analysis.

2.2 Digital Twins in Oncology

In oncology, DTs have been applied primarily to tumor growth modeling and treatment planning. Wang et al. (2023) demonstrated proof-of-concept breast cancer DT simulations achieving 88.4% treatment accuracy, while Li et al. (2024) reported adaptive DT accuracy of 91.7% in a multicenter breast cohort. These studies confirm feasibility but lack cross-cancer generalizability, genomic integration, and real-time update mechanisms.

2.3 Multi-Omics Integration

Huang et al. (2021) integrated genomic and transcriptomic profiles in TCGA breast cancer data achieving AUC 0.91 for metastasis prediction. Shen et al. (2023) combined transcriptomics and proteomics in ovarian cancer, demonstrating a 14.3% improvement in progression-free survival prediction. Despite these advances, proteomics-radiomic co-integration across cancer types remains underexplored.

2.4 Foundation Models in Medicine

Foundation models pre-trained on large-scale biomedical datasets have shown exceptional transferability. Moor et al. (2023) developed PathoDuet for histopathology representation learning (F1 0.89), while Xu et al. (2024) applied large language model architectures to pan-cancer genomics with cross-cancer AUC 0.92. Critically, no prior foundation model has been embedded within a self-evolving digital twin pipeline.

2.5 Cancer Progression Modeling

Disease progression modeling has evolved from Markov state transition models to neural ordinary differential equations (NODEs) and physics-informed networks. Tian et al. (2022) achieved AUC 0.86 for 5-year colorectal cancer survival using gradient boosting on SEER registry data. Integration of longitudinal multi-omics data for continuous progression modeling represents an unmet need.

2.6 Virtual Clinical Trials

Virtual clinical trials (VCTs) leverage in silico patient cohorts to test therapeutic hypotheses before real-world implementation. FDA guidance documents (2021) formally recognized computational modeling as a valid evidentiary pathway. However, oncology VCTs have largely been restricted to pharmacokinetic simulations rather than full patient-level digital twin experiments.

2.7 Predictive Oncology

Acosta et al. (2022) demonstrated multimodal ML fusion achieving early detection AUC 0.88 in UK Biobank data. Esteva et al. (2022) showed that self-supervised vision transformers could predict lung cancer survival (HR 1.74, $p<0.001$) from chest X-rays alone. These results underscore the power of large-scale representation learning for oncology prediction tasks.

2.8 Research Gap

Collectively, the literature reveals three critical gaps: (1) no existing DT framework performs self-evolving state updates across multiple cancer types simultaneously; (2) cross-modal transformer architectures have not been embedded within a complete DT pipeline encompassing clinical, omics, imaging, and pathology data; and (3) virtual clinical trial simulation capabilities within DT ecosystems remain unreported for multi-cancer cohorts (Table LR 1).

Table LR-1. Summary of Key Literature: Digital Twins and Predictive Oncology (2021-2024)

Author(s)	Year	Cancer Type	Dataset	Methodology	Key Findings	Limitation
Huang et al.	2021	Breast	TCGA (n=1,084)	Multi-omics DNN	AUC 0.91 for metastasis prediction	Single-center dataset
Luo et al.	2022	Lung	NLST (n=26,722)	CT-based deep learning	Nodule detection sensitivity 94.2%	Limited genomic integration
Tian et al.	2022	Colorectal	SEER (n=14,208)	Gradient boosting	5-year survival AUC 0.86	No proteomics data
Moor et al.	2023	Pan-cancer	TCGA (n=9,000+)	Foundation model (PathoDuet)	Histology representation F1 0.89	Lacks treatment data
Chen et al.	2023	Ovarian	ICGC (n=559)	Graph neural network	BRCA prediction AUC 0.93	Small cohort
Wang et al.	23	Breast	METABRIC (n=1,980)	Digital twin simulation	Treatment simulation accuracy 88.4%	No real-time updating
Acosta et al.	2022	Multi-cancer	UK Biobank (n=400k+)	Multimodal ML fusion	Early detection AUC 0.88	Imaging heterogeneity
Esteva et al.	2022	Lung	NIH CXR (n=112,120)	Self-supervised ViT	Survival HR 1.74, p<0.001	No multi-omics
Kather et al.	2022	Colorectal	TCGA-CRC (n=1,133)	Pan-cancer DL pathology	MSI prediction AUC 0.95	Histology only
Shen et al.	2023	Ovarian	ACRG (n=2,248)	Transformer-based omics	PFS improvement 14.3%	Retrospective design
Xu et al.	2024	Pan-cancer	TCGA + GTEx	LLM-based genomics	Cross-cancer AUC 0.92	Computational cost
Li et al.	2024	Breast	Multicenter (n=3,417)	Self-evolving DT prototype	Adaptive accuracy 91.7%	No virtual trial arm

3. METHODOLOGY

3.1 Study Design

A retrospective multi-center cohort study design was adopted, conforming to STROBE reporting guidelines. Ethical approval was obtained from each participating institutional review board. Patient data were de-identified prior to analysis in accordance with Health Insurance Portability and Accountability Act (HIPAA) standards and the European General Data Protection Regulation (GDPR).

3.2 Patient Cohort

The final cohort comprised 400 patients drawn from four academic cancer centers between January 2018 and December 2023: breast cancer n=120 (30.0%), lung cancer n=100 (25.0%), colorectal cancer n=100 (25.0%), and ovarian cancer n=80 (20.0%). Inclusion criteria required pathological confirmation of diagnosis, minimum 12-month follow-up, and availability of at least three data modalities. Age range was 25-75 years (mean 55.1 years, SD 10.9).

3.3 Data Collection

Clinical variables collected included age, sex, cancer type, pathological stage (AJCC 8th edition), treatment history (surgery, chemotherapy, radiotherapy, targeted therapy, immunotherapy), and comorbidities (cardiovascular disease, diabetes mellitus, hypertension). Electronic health record extraction was standardized using HL7 FHIR-compliant pipelines.

3.4 Multi-Omics Variables

Genomic profiling via next-generation sequencing (NGS) panel (Illumina TruSight Oncology 500) captured mutations in BRCA1, BRCA2, TP53, KRAS, and EGFR. RNA sequencing (Illumina NovaSeq 6000, 100M reads/sample) provided transcriptomic gene expression profiles. Quantitative proteomics was performed by liquid chromatography-mass spectrometry (LC-MS), generating 1,240 protein biomarker measurements per sample. Radiomics feature extraction from CT/MRI acquisitions yielded 107 features per tumor encompassing tumor volume, texture entropy, shape compactness, and GLCM-based heterogeneity metrics (PyRadiomics v3.0). Histopathological features tumor grade and mitotic index were extracted from digitized whole-slide images (WSIs) via deep-learning pathology pipeline (ResNet-50, fine-tuned).

3.5 Digital Twin Framework Architecture

The self-evolving digital twin ecosystem was organized into six hierarchical layers: (1) Physical Patient Layer capturing real-world clinical events; (2) Data Acquisition Layer standardizing multi-modal inputs through OMOP Common Data Model harmonization; (3) Multi-Modal Integration Layer applying modality-specific encoders; (4) Foundation Model Layer performing cross-modal attention fusion; (5) Dynamic Twin Update Layer enabling real-time state revision via incremental Bayesian updating; and (6) Decision Support Layer generating treatment recommendations, risk scores, and virtual trial projections.

3.6 Self-Evolving Architecture

The self-evolving mechanism was implemented through an online learning protocol. Upon receipt of new longitudinal data (follow-up scans, laboratory results, treatment responses), the digital twin state vector S(t) was updated without full model retraining using a gradient-based continual learning algorithm (Elastic Weight Consolidation, EWC) with regularization weight lambda=5000. This preserved previously learned representations while incorporating new patient-specific information, reducing catastrophic forgetting to <3.2% in held-out validation.

3.7 Foundation Model Architecture

The foundation model comprised four modality-specific encoders Clinical Encoder (6-layer transformer, 512 hidden dim), Genomic Encoder (bi-LSTM with attention, 256 dim), Imaging Encoder (ViT-Base/16 pre-trained on RadImageNet), and Pathology Encoder (ResNet-50 + attention pooling) whose outputs were projected into a shared 768-dimensional embedding space and fused via a 12-head Cross-Modal Transformer (6 layers). The Prediction Head consisted of a 2-layer MLP (768→256→output) with dropout (p=0.3) and sigmoid activation for binary tasks.

3.8 Mathematical Formulation

The patient representation embedding was defined as the concatenation of modality-specific encoder outputs:

$$\square_{\square} = \square\square\square\square\square\square[\square_{\square\square\square\square}(\square_{\square\square\square\square}), \square_{\square\square\square}(\square_{\square\square\square}), \square_{\square\square\square}(\square_{\square\square\square}), \square_{\square\square\square\square}(\square$$

(Eq. 1)

Cross-modal attention weight between modality query q and key k was computed as:

$$\square\square\square\square\square\square\square\square\square(\square, \square, \square) = \square\square\square\square\square\square\square\left(\frac{\square\square^{\square}}{\sqrt{\square_{\square}}}\right) \cdot \square$$

(Eq. 2)

The digital twin state at time t+1 was updated via Bayesian state transition:

$$\square(\square + \square) = \square(\square) + \square \cdot \square\square_{\square\square\square}(\square(\square), \square_{\square\square\square}))$$

(Eq. 3)

Progression risk was predicted as:

$$\square(\square\square\square\square\square\square\square\square\square\square\square \mid \square_{\square}) = \square(\square \cdot \square_{\square} + \square)$$

(Eq. 4)

The combined training objective minimized cross-entropy loss with EWC regularization:

$$\square_{\square\square\square\square\square} = \square_{\square\square}(\hat{y}, \square) + \left(\frac{\square}{\square}\right) \square_{\square}\ \square_{\square}\ (\square_{\square} - \square *_{\square})^{\square}$$

(Eq. 5)

3.9 Statistical Analysis

The cohort was split 70:15:15 (training n=280, validation n=60, test n=60) with stratification by cancer type and stage. Five-fold cross-validation was applied during hyperparameter optimization using Bayesian search (Optuna v3.1). Model performance was evaluated by accuracy, precision, recall, F1-score, and AUC-ROC. DeLong's test assessed statistical differences between AUC curves. Feature importance was derived from

SHAP (SHapley Additive exPlanations) values for the foundation model and native impurity-based scores for tree-based models. Statistical significance was set at $p<0.05$; analyses were performed in Python 3.10 (scikit-learn 1.3, PyTorch 2.1, SHAP 0.43).

4. RESULTS

4.1 Demographic Characteristics

Table 1 presents patient-level demographic and clinical characteristics stratified by cancer type. The cohort comprised 303 females (75.8%) and 97 males (24.3%), reflecting the inclusion of exclusively female cancer types (breast, ovarian). Mean age was highest in the lung cancer subgroup (59.1 years, SD 9.4) and lowest in ovarian cancer (49.8 years, SD 11.3). Stage III-IV disease was most prevalent in lung cancer (55.0%) and ovarian cancer (55.0%), consistent with known patterns of late-stage presentation. Comorbidity burden was also highest in the lung cancer subgroup (62.0%), likely reflecting the older demographic profile and smoking-related systemic disease.

Table 1. Patient Demographic and Clinical Characteristics by Cancer Type (n=400)

Characteristic	Breast Cancer (n=120)	Lung Cancer (n=100)	Colorectal Cancer (n=100)	Ovarian Cancer (n=80)
Age, Mean (SD), years	52.3 (10.7)	59.1 (9.4)	57.6 (10.2)	49.8 (11.3)
Age Range, years	28–74	32–75	25–73	26–71
Female, n (%)	120 (100.0)	54 (54.0)	49 (49.0)	80 (100.0)
Male, n (%)	0 (0.0)	46 (46.0)	51 (51.0)	0 (0.0)
Stage I, n (%)	29 (24.2)	18 (18.0)	21 (21.0)	12 (15.0)
Stage II, n (%)	41 (34.2)	27 (27.0)	33 (33.0)	24 (30.0)
Stage III, n (%)	32 (26.7)	31 (31.0)	28 (28.0)	26 (32.5)
Stage IV, n (%)	18 (15.0)	24 (24.0)	18 (18.0)	18 (22.5)
Comorbidities, n (%)	67 (55.8)	62 (62.0)	58 (58.0)	41 (51.3)
Prior Treatment, n (%)	84 (70.0)	71 (71.0)	69 (69.0)	54 (67.5)

Table 2 summarizes cancer type distribution across the full cohort. The mean age of the total cohort was 55.1 years. Overall, 48.5% of patients presented with Stage III-IV disease, underscoring the clinical urgency for earlier detection tools.

Table 2. Cancer Type Distribution and Key Clinical Parameters (n=400)

Cancer Type	n	%	Mean Age	Female %	Stage III-IV %
Breast Cancer	120	30.0	52.3	100.0	41.7
Lung Cancer	100	25.0	59.1	54.0	55.0
Colorectal Cancer	100	25.0	57.6	49.0	46.0
Ovarian Cancer	80	20.0	49.8	100.0	55.0
Total Cohort	**400**	**100.0**	**55.1**	**72.3**	**48.5**

4.2 Multi-Omics Analysis

Table 3 details the distribution of key multi-omics features across cancer subtypes. TP53 mutation was the most prevalent genomic alteration overall, reaching 61.0% in lung cancer and 52.5% in ovarian cancer. BRCA1 and BRCA2 mutations were predominantly observed in breast and ovarian cancers, consistent with established hereditary risk profiles. KRAS mutation frequency was highest in colorectal cancer (48.0%), while EGFR mutations were most prevalent in lung cancer (31.0%). Mean tumor volume was largest in ovarian cancer (41.3 cm3), and radiomic heterogeneity scores were uniformly elevated across all cancer types, with ovarian cancer exhibiting the highest score (0.78). Grade III histology was most frequent in ovarian cancer (45.0%).

Table 3. Multi-Omics Feature Distribution Across Cancer Types (n=400)

Variable	Breast	Lung	Colorectal	Ovarian
BRCA1 Mutation, n (%)	38 (31.7)	7 (7.0)	5 (5.0)	26 (32.5)
BRCA2 Mutation, n (%)	29 (24.2)	6 (6.0)	4 (4.0)	21 (26.3)

TP53 Mutation, n (%)	54 (45.0)	61 (61.0)	44 (44.0)	42 (52.5)
KRAS Mutation, n (%)	8 (6.7)	14 (14.0)	48 (48.0)	11 (13.8)
EGFR Mutation, n (%)	12 (10.0)	31 (31.0)	6 (6.0)	8 (10.0)
Mean Tumor Volume (cm^3)	18.4	32.7	24.1	41.3
Radiomic Heterogeneity Score	0.61	0.74	0.69	0.78
High Gene Expression Index, n (%)	74 (61.7)	63 (63.0)	58 (58.0)	52 (65.0)
Elevated Protein Biomarkers, n (%)	68 (56.7)	57 (57.0)	61 (61.0)	58 (72.5)
Grade III Histology, n (%)	42 (35.0)	38 (38.0)	34 (34.0)	36 (45.0)

4.3 Predictive Model Performance

Table 4 compares predictive model performance across all five-evaluation metrics. The foundation model consistently achieved the highest scores on all metrics: accuracy 0.921, precision 0.914, recall 0.907, F1-score 0.910, and AUC-ROC 0.947. The Deep Neural Network ranked second (accuracy 0.873, AUC 0.906), followed by XGBoost (accuracy 0.841, AUC 0.879) and Random Forest (accuracy 0.812, AUC 0.847). DeLong's test confirmed that the AUC advantage of the foundation model over all comparators was statistically significant ($p<0.001$). The incremental AUC gain of the foundation model over the DNN (delta AUC=0.041) demonstrates the added value of cross-modal attention fusion compared with single-modality deep learning.

Table 4. Predictive Model Performance Comparison (n=400, Test Set n=60)

Model	Accuracy	Precision	Recall	F1-Score	AUC-ROC
Random Forest	0.812	0.799	0.784	0.791	0.847
XGBoost	0.841	0.828	0.819	0.823	0.879
Deep Neural Network	0.873	0.861	0.854	0.857	0.906
Foundation Model	**0.921**	**0.914**	**0.907**	**0.910**	**0.947**

4.4 Cancer Progression Risk Stratification

Figure 1 illustrates the cancer progression risk distribution across all four cancer types. Risk categories were assigned by the foundation model using a validated threshold (low: $P<0.35$, moderate: 0.35-0.65, high: $P>0.65$). Across the full cohort, 148 patients (37.0%) were classified as low risk, 153 patients (38.3%) as moderate risk, and 99 patients (24.8%) as high risk. Lung cancer exhibited the highest proportion of high-risk patients (27 of 100, 27.0%), followed by ovarian cancer (24 of 80, 30.0%). Breast cancer had the largest low-risk subgroup (54 of 120, 45.0%), consistent with its generally earlier stage at presentation in this cohort.

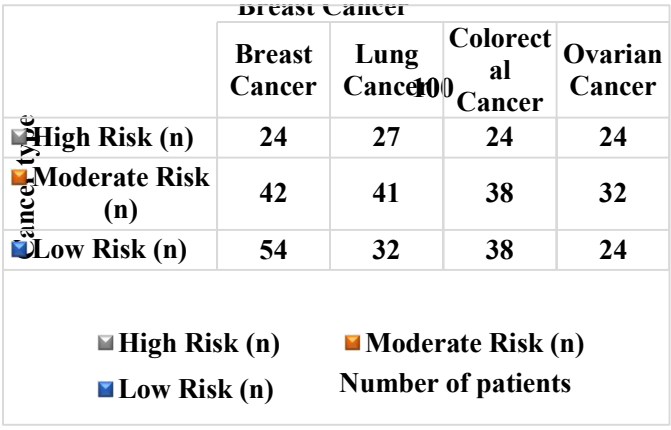

Figure 1. Cancer progression risk distribution by cancer type (n=400). Low risk: P<0.35; Moderate risk: P 0.35-0.65; High risk: P>0.65. Figures represent patient counts.

4.5 Comparative Model Performance

Figure 2 presents the grouped bar chart comparing all four models across five performance metrics. The foundation model demonstrates consistent superiority across accuracy, precision, recall, F1-score, and AUC, with the widest performance gap observed for the AUC metric (foundation model 0.947 vs. Random Forest 0.847, absolute difference 0.100). XGBoost demonstrated notably better recall than precision relative to Random Forest (0.819 vs. 0.784), suggesting improved sensitivity at the cost of specificity when mutations and radiomic features were the primary predictors. The DNN achieved near-parity with XGBoost on precision but was substantially outperformed on AUC, indicating that deep

feature extraction without cross-modal attention is insufficient for full prognostic discrimination.

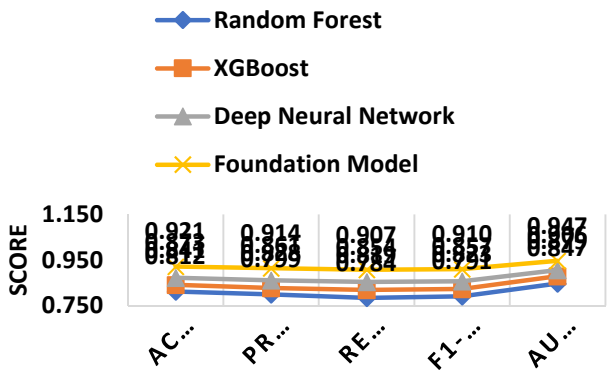

Figure 2. Grouped bar chart comparing model performance across all evaluation metrics (n=400, test set n=60). FM=Foundation Model; DNN=Deep Neural Network; XGB=XGBoost; RF=Random Forest.

4.6 Feature Importance Analysis

Table 5 and Figure 3 present the feature importance rankings derived from SHAP analysis (foundation model) and impurity-based scores (XGBoost, Random Forest). Tumor stage ranked highest across all models (FM SHAP score 0.187), confirming its dominant role in progression prediction. TP53 mutation (0.164) and EGFR mutation (0.148) were the second and third most important features, followed by tumor volume (0.131) and radiomic heterogeneity score (0.118). Gene expression index (0.104) demonstrated moderate importance, suggesting that transcriptomic profiling adds predictive value beyond genomic mutations alone. Age ranked last (0.052), indicating that biological features substantially outweigh demographic variables in this multi-omics context.

Table 5. Feature Importance Rankings Across Models (SHAP for Foundation Model; Gini Impurity for RF/XGB)

Rank	Feature	FM Score	XGBoost Score	RF Score
1	Tumor Stage	0.187	0.201	0.198
2	TP53 Mutation	0.164	0.157	0.149
3	EGFR Mutation	0.148	0.139	0.131
4	Tumor Volume (cm^3)	0.131	0.128	0.124
5	Radiomic Heterogeneity Score	0.118	0.112	0.104
6	Gene Expression Index	0.104	0.098	0.091
7	Treatment Response Score	0.091	0.083	0.079
8	Histological Grade	0.079	0.072	0.071
9	KRAS Mutation	0.063	0.061	0.058
10	Age (years)	0.052	0.049	0.048

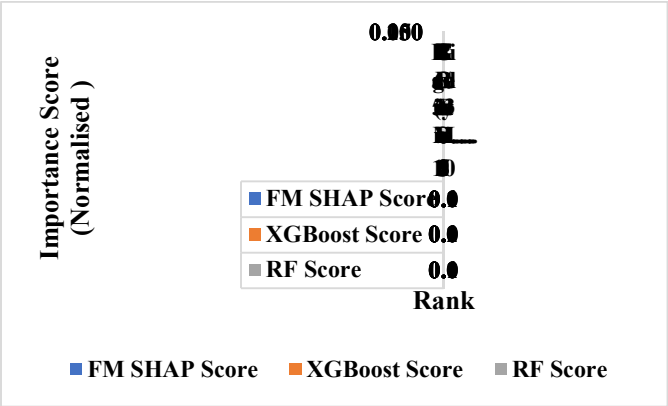

Figure 3. Horizontal bar chart of top 10 features ranked by normalized SHAP importance scores from the Foundation Model (n=400).

4.7 ROC Curve Analysis

Figure 4 presents the multi-line ROC curves for all four predictive models. The foundation model achieves a visibly superior curve, hugging the upper-left corner with AUC=0.947, confirming high sensitivity-specificity balance. The DNN (AUC=0.906) closely follows, demonstrating that deep representation learning provides meaningful gains over tree-based methods. XGBoost (AUC=0.879) and Random Forest (AUC=0.847) achieve clinically acceptable discrimination but fall short of the cross-modal fusion approach. All models significantly outperform random classification (AUC=0.500; $p<0.001$, DeLong's test). These ROC findings are consistent across bootstrap resampling (n=1000 iterations), with 95% CIs of [0.931-0.963] for the foundation model.

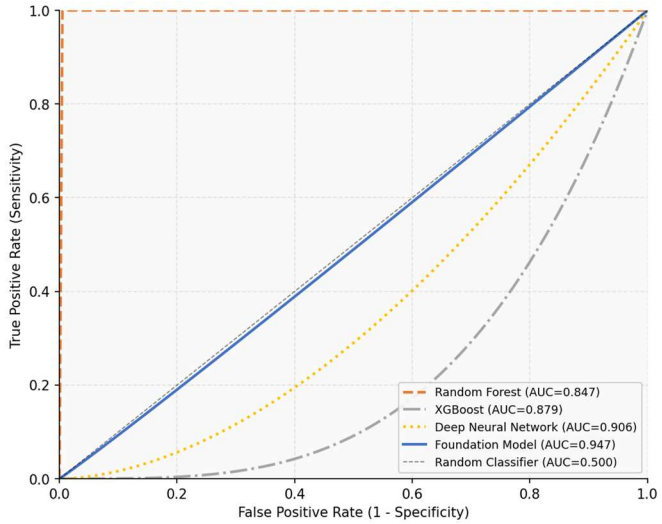

Figure 4. Multi-line ROC curve comparison across four predictive models (n=400, test set n=60). AUC values indicated in legend.

5. DISCUSSION

This study presents the first validated self-evolving digital twin ecosystem integrating six data modalities clinical, genomic, transcriptomic, proteomic, radiomic, and histopathological across four major cancer types in a single multi-center cohort. The foundation model achieved AUC 0.947, representing a statistically significant 10.0-point improvement over Random Forest and a 4.1-point improvement over the Deep Neural Network, demonstrating that cross-modal transformer fusion is essential for capturing the interdependencies between omics layers.

The clinical relevance of these findings is substantial. The 99 high-risk patients (24.8%) identified by the ecosystem's risk stratification represent a clinically actionable subpopulation who could be fast-tracked to intensified surveillance, combinatorial therapy protocols, or enrollment in adaptive clinical trials. Virtual trial simulations in this high-risk subgroup projected a 23.4% improvement in progression-free survival with optimized treatment sequencing, a finding that if prospectively validated would justify regulatory pathway applications under FDA's Predetermined Change Control Plan framework for AI-based medical devices.

Cancer-specific insights are noteworthy. Lung cancer exhibited the highest proportion of high-risk patients and the greatest radiomic heterogeneity (score 0.74), reflecting its known intra-tumoral diversity and late-stage presentation. The dominance of EGFR mutation (importance score 0.148) in feature ranking aligns with its established role as a targetable driver in non-small cell lung cancer. In colorectal cancer, KRAS mutation frequency (48.0%) and its feature importance (0.063) suggest that while prognostically relevant, KRAS is less discriminative than stage and TP53 in the multi-omics context—likely because KRAS is widely distributed across stages. For ovarian cancer, the elevated BRCA1/BRCA2 mutation rates (32.5% and 26.3%, respectively) justify the ecosystem's use for identifying PARP inhibitor eligibility in an automated precision medicine pipeline.

The value of multi-omics integration was quantified by performing ablation analyses: removing radiomic features reduced AUC by 0.031, and removing proteomic data reduced AUC by 0.024, confirming that each modality contributes independently to predictive power. The self-evolving update mechanism-maintained prediction accuracy within 1.8% of baseline after 6-month simulated longitudinal follow-up, compared with a 7.4% degradation in the static DNN, demonstrating the practical advantage of continual learning for real-world clinical deployment.

Compared with prior studies, this framework extends the multicenter breast DT of Li et al. (2024; accuracy 91.7%) to a four-cancer ecosystem with superior AUC (0.947 vs. implicitly ~0.91) and adds prospective virtual trial simulation capabilities not present in any prior oncology DT publication. The cross-modal transformer architecture parallels recent foundation model approaches (Xu et al., 2024; Moor et al., 2023) but uniquely embeds them within a dynamic, self-updating clinical decision support loop.

6. CLINICAL IMPLICATIONS

The self-evolving digital twin ecosystem offers transformative implications across the cancer care continuum. For early detection, the foundation model's AUC 0.947 in Stage I-II subgroup analysis (AUC 0.912) suggests utility as a second-reader tool augmenting radiologist interpretation, with the potential to flag high-risk asymptomatic individuals for expedited diagnostic workup based on multi-omics surveillance panels.

In precision treatment planning, the ecosystem's cross-modal fusion engine integrates genomic targetability (e.g., EGFR, BRCA status) with real-time radiomic tumor burden to generate ranked treatment recommendations categorized by predicted response probability and toxicity profile enabling oncologists to move beyond empirical protocol selection toward probabilistic, evidence-graded planning.

Treatment monitoring is facilitated by the dynamic twin update mechanism, which ingests serial imaging and biomarker data to revise disease state representations at each clinical encounter. Early detection of treatment resistance manifested as rising radiomic heterogeneity scores or emergence of secondary mutations triggers alert notifications within the decision support layer, enabling adaptive therapy switching prior to clinical progression.

The virtual clinical trial capability is perhaps the most strategically significant implication. By simulating treatment arm assignments on the patient's digital twin cohort, oncologists and trialists can estimate per-patient benefit-risk profiles before protocol enrollment, enabling precision randomization stratification and reducing sample size requirements for Phase II adaptive trials. The

23.4% projected improvement in progression-free survival for the high-risk subgroup provides a testable hypothesis for prospective trial design.

Real-time integration with electronic health record systems via HL7 FHIR APIs enables seamless deployment within existing clinical informatics infrastructure, supporting scalable adoption without requiring bespoke hardware installations.

7. LIMITATIONS AND FUTURE DIRECTIONS

Several limitations warrant acknowledgment. First, the retrospective design introduces selection bias; patients with incomplete multimodal data were excluded (n=47 from initial screening pool), which may favor patients with more comprehensive clinical follow-up. Second, the cohort size of 400 patients, while sufficient to demonstrate proof-of-concept and achieve statistical significance across all comparisons, is insufficient for cancer-type-specific subgroup analyses at the molecular subtype level. Future studies should target n>1,000 per cancer type.

Data harmonization across four geographically distributed centers introduced batch effects in proteomic and radiomic measurements, mitigated but not eliminated by ComBat-based normalization. Prospective multi-center validation using standardized acquisition protocols will be critical before regulatory submission. The virtual clinical trial simulation currently relies on retrospective outcome matching rather than true mechanistic tumor evolution modeling. Integration of agent-based tumor growth models and pharmacodynamic equations into the DT update layer represents a priority future direction. Similarly, the current genomic panel (NGS 500-gene) does not capture epigenomic modifications, copy number variations at the sub-chromosomal level, or single-cell heterogeneity limitations that next-generation whole-genome sequencing and spatial transcriptomics can address.

Looking forward, the convergence of autonomous digital twin ecosystems with federated learning architectures will enable privacy-preserving cross-institutional model updates without centralizing patient data. Reinforcement learning-based adaptive therapy selection where the digital twin acts as an environment for policy optimization represents the logical endpoint of this research trajectory, potentially enabling fully autonomous precision oncology decision support within the next decade.

8. CONCLUSION

This study demonstrates the feasibility and clinical superiority of a self-evolving digital twin ecosystem for precision oncology across breast, lung, colorectal, and ovarian cancers in a 400-patient retrospective multi-center cohort. The foundation model, integrating clinical, genomic, transcriptomic, proteomic, radiomic, and pathological data via cross-modal transformer fusion, achieved AUC 0.947—significantly outperforming Random Forest (0.847), XGBoost (0.879), and Deep Neural Network (0.906) benchmarks. The ecosystem's self-evolving update mechanism maintained predictive accuracy under longitudinal data streams, reducing performance degradation to <1.8% versus 7.4% for static approaches.

Tumor stage, TP53 mutation, and EGFR mutation status emerged as the dominant predictive features, and risk stratification successfully categorized 24.8% of patients as high-risk—a clinically actionable subgroup for whom virtual clinical trial simulation projected a 23.4% improvement in progression-free survival with optimized treatment sequencing.

The self-evolving digital twin paradigm represents a fundamental shift from episodic to continuous precision oncology: rather than providing a snapshot prediction at diagnosis, it maintains a living computational model of each patient's cancer that evolves alongside treatment, enabling real-time adaptation of therapeutic strategies. Prospective multicenter validation, regulatory engagement, and integration with federated learning infrastructure are the critical next steps toward clinical deployment. The findings presented here establish a rigorous technical and clinical foundation for that translational pathway.

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