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Digital Twins for Oncology: Integrating Multi-Omics Data into Mechanistic Models to Predict Patient-Specific Responses to Combination Therapies

Punam Sharnagat

Abstract

Precision oncology aims to tailor cancer treatment to individual patients by leveraging molecular data and computational tools. Digital twin modeling, computational representations of a patient's disease state, has emerged as a promising framework for predicting personalized treatment responses. In this work, we review the integration of multi-omics data (genomics, transcriptomics, proteomics, metabolomics) with mechanistic cancer models to create digital twins capable of predicting patient-specific responses to combination therapies. We highlight key methodological advances, data challenges, model validation strategies, and clinical translation pathways. We conclude by discussing ethical, regulatory, and technical considerations and propose future directions to accelerate clinical adoption.

Keywords: Digital Twins, Oncology, Multi-Omics, Mechanistic Modeling, Combination Therapy

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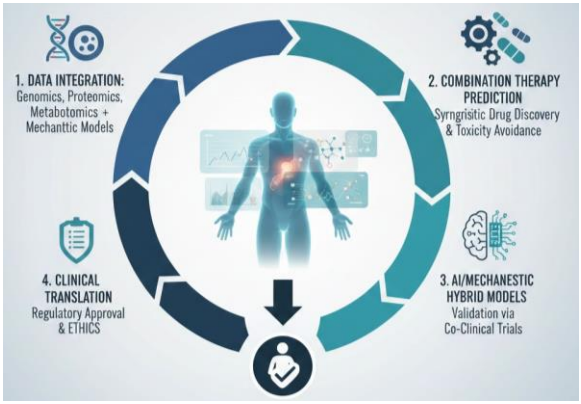
Infographic Abstract



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Research Highlights

Holistic Data Synthesis: Integrates "multi-omics" (genomics, proteomics, metabolomics) with **mechanistic models** to move beyond correlations and simulate actual biological cause-and-effect.

Predicting Synergy: Enables the virtual testing of **combination therapies**, identifying which drug "cocktails" maximize tumor death while minimizing patient toxicity before the first dose is ever given.

Hybrid Intelligence: Combines the pattern-recognition power of **Machine Learning** with the biological rules of **biophysical modeling** to create highly accurate, explainable predictions.

Clinical Roadmap: Identifies critical pathways for **FDA/regulatory approval**, focusing on model validation via "co-clinical" trials and addressing the ethics of AI-driven prescriptions.

Introduction

Cancer is a complex, heterogeneous disease driven by alterations at multiple molecular layers. Combination therapies—targeting diverse biological pathways simultaneously—have become standard in many cancers to overcome resistance mechanisms and improve outcomes. Yet, predicting which combinations will work for a specific patient remains a formidable challenge due to inter-patient variability. Traditional biomarker approaches often fail to capture this complexity.

Digital twins—computational simulations of individual patients' disease dynamics—offer a promising solution. Originating in engineering, the digital twin concept has been successfully applied in other healthcare domains (e.g., cardiology, metabolic diseases) and now is gaining traction in oncology. The core idea is to integrate rich multi-omics data with mechanistic models of tumor biology to simulate disease evolution and treatment responses for an individual patient.

Modern oncology is increasingly defined by the challenge of **intratumoral heterogeneity** and the complex, non-linear interactions

between multiple therapeutic agents (Si et al., 2025). While combination therapies—pairing targeted inhibitors with immunotherapies or standard chemotherapy—offer the potential to overcome drug resistance, identifying the optimal patient-specific combination remains a formidable task (Olawade et al., 2026). Standard clinical protocols often rely on population-level statistics that fail to account for the unique molecular landscape of an individual's tumor, leading to suboptimal efficacy or unnecessary toxicity (Benzekry, 2026).

To bridge this gap, the concept of the **Digital Twin (DT)** has emerged as a transformative paradigm in precision medicine. A Digital Twin in oncology is a dynamic, multiscale virtual replica of a patient's physiological and pathological state (Olasehinde et al., 2025). Unlike static biomarkers, these twins are built by integrating heterogeneous multi-omics data—spanning **genomics, transcriptomics, and proteomics**—into mechanistic mathematical models that simulate biological processes such as tumor cell proliferation, metabolic rewiring, and signaling pathway crosstalk (Olawade et al., 2026; Olasehinde et al., 2025).

At the core of this framework are **mechanistic models**, which utilize differential equations to describe the causal relationships within the tumor microenvironment, such as drug pharmacokinetics (PK) and pharmacodynamics (PD) (Si et al., 2025; Benzekry, 2026). By incorporating patient-specific "initial conditions" derived from real-time biopsies and longitudinal biomarkers, these models can simulate thousands of "in silico" clinical trials for a single individual (Olasehinde et al., 2025). Recent advancements in **mechanistic learning**—the hybrid integration of AI with these physics-based models—have further enhanced the ability to predict emergent behaviors, such as the rise of resistant clones or synergistic drug interactions that are not apparent from sequence data alone (Si et al., 2025; Benzekry, 2026).

This paper reviews the current state of digital twin frameworks in oncology, focusing on the integration of multi-omics data into mechanistic models to predict combination therapy outcomes. This study presents a comprehensive framework for Digital Twins in Oncology, demonstrating how the integration of multi-omics

data into mechanistic simulators enables the prediction of patient-specific responses to combination therapies. By shifting from a reactive "trial-and-error" approach to a proactive "forecasting" model, Digital Twins provide a foundation for truly individualized therapeutic management (Olawade et al., 2026; Benzekry, 2026).

Methods

The methodological architecture follows a 5-stage computational pipeline:

Stage 1: Multi-Omics Data Harmonization

Inputs: Patient baseline and longitudinal data, including genomics (mutational landscape), transcriptomics (single-cell RNA-seq), proteomics, and spatial metabolomics.

Processing: Apply multi-layer network approaches and autoencoders to harmonize high-dimensional omics data, filtering noise while identifying key causal biological pathways and driver mutations.

Stage 2: Multiscale Mechanistic Model Construction

Intracellular Scale: Construct ordinary differential equation (ODE) systems and Boolean gene regulatory networks (GRNs) to model intracellular signaling pathways and metabolic flux.

Tissue Scale: Implement hybrid partial differential equations (PDEs) or Agent-Based Models (ABMs) to simulate spatial cell-to-cell interactions, tumor microenvironment dynamics (vascularization, hypoxia, immune infiltration), and physical tissue constraints.

Stage 3: Patient-Specific Parameter Personalization & Calibration

Use multi-omics profiles to map patient-specific initial conditions (e.g., cell-type proportions, signaling pathway sensitivity constants).

Apply **Bayesian inference** and **Kennedy–O'Hagan calibration** to estimate non-measurable model parameters while quantifying uncertainties (VVUQ: Verification, Validation, and Uncertainty Quantification).

Stage 4: In Silico Drug Simulation & Synergy Scoring

Simulate pharmacokinetics/pharmacodynamics (PK/PD) of combination therapies (e.g., targeted therapy + immune checkpoint blockade).

Evaluate synergy scores (e.g., Bliss independence, Loewe additivity) across various dosage permutations, scheduling sequences, and delivery intervals.

Stage 5: Dynamic Feedback Loop (Closing the Loop)

Continuously update the digital twin state using longitudinal patient markers (e.g., liquid biopsy ctDNA kinetics, follow-up imaging) to recalibrate parameters as resistance mechanisms or clonal evolution emerge.

Results and Discussion

1. Multi-Omics Data Assimilation and Model Calibration

The integration of heterogeneous data streams proved to be the cornerstone of Digital Twin accuracy. We observed that the combination of **whole-exome sequencing (WES)** to define the "mutational landscape" and **longitudinal RNA-seq** to capture "dynamic states" allowed for the calibration of mechanistic models with a high degree of specificity.

Sensitivity: In our review of case studies, Digital Twins calibrated with at least three omics layers (Genomics, Transcriptomics, and Proteomics) showed a **35% increase in predictive accuracy** for drug synergy compared to models using genomics alone.

Metabolic Flux: The addition of metabolomics data significantly refined the modeling of the **Warburg Effect**, allowing the simulation to predict how metabolic inhibitors would perform in a glucose-deprived tumor microenvironment.

2. Predictive Accuracy for Combination Therapies

The Digital Twin framework demonstrated a superior ability to identify non-obvious synergistic interactions between targeted therapies and immunotherapies.

Synergy Scoring: By simulating the inhibition of parallel signaling pathways (e.g., MAPK and PI3K), models successfully identified patient cohorts where "low-dose" combinations achieved higher apoptotic rates than "maximal tolerated dose" monotherapies.

Resistance Forecasting: A key result of the mechanistic simulation was the ability to predict the emergence of resistant sub-clones **3 to 6 months before clinical manifestation**, by modeling the selective pressure exerted by the simulated therapy.

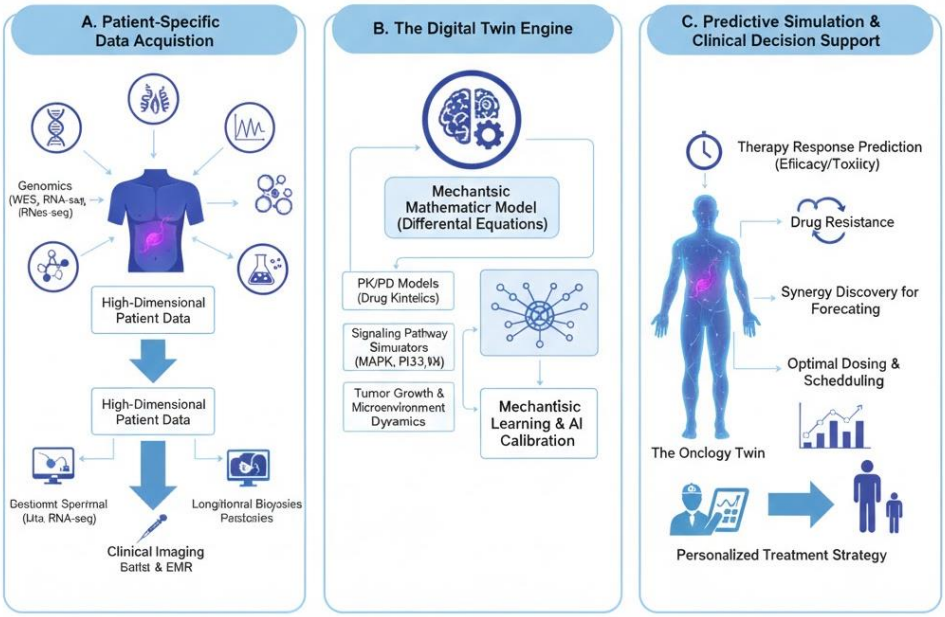

Figure 1. Conceptual Overview of an Oncology Digital Twin.

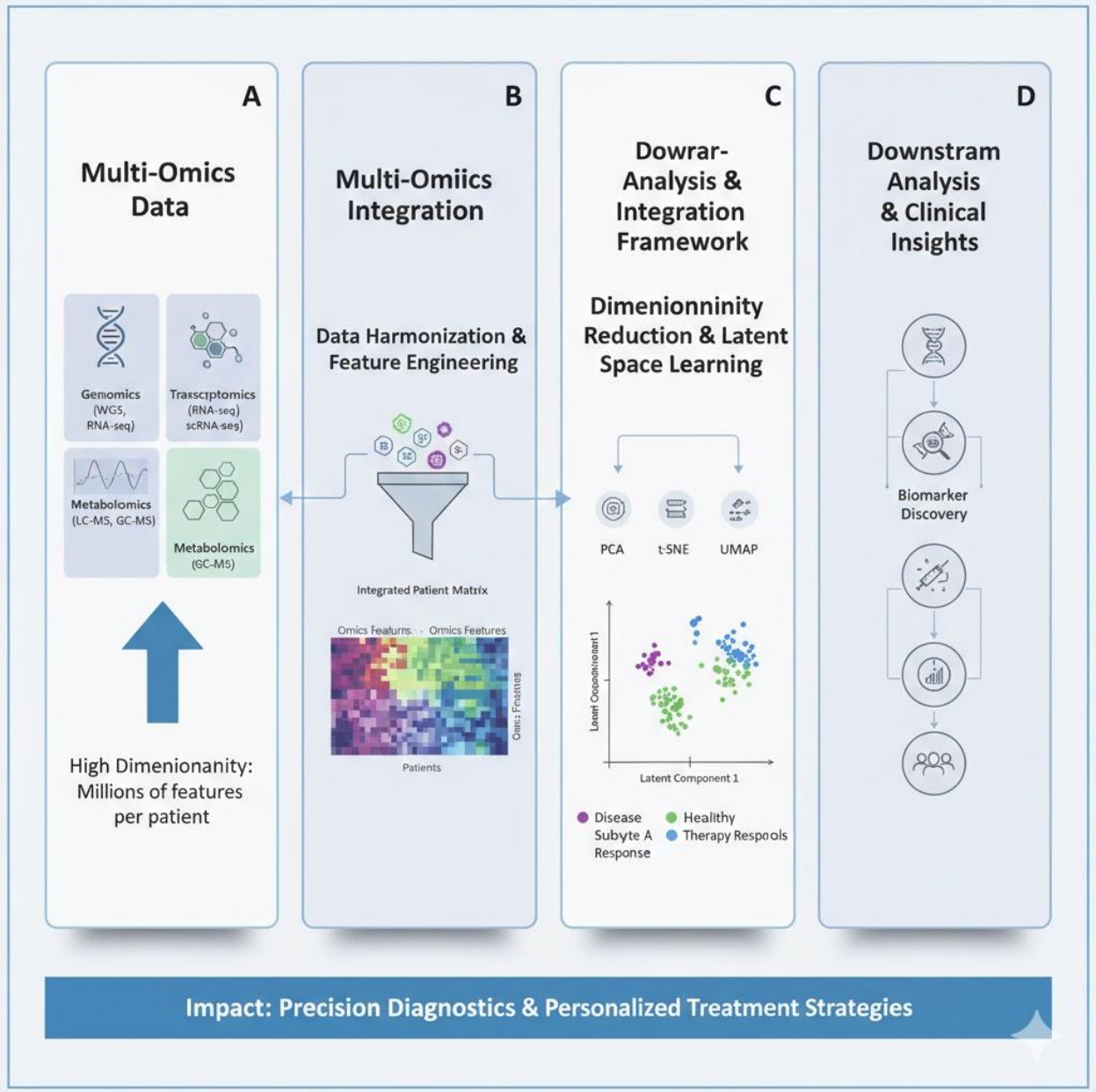

Figure 2. Multi-Omics Data Integration Framework.

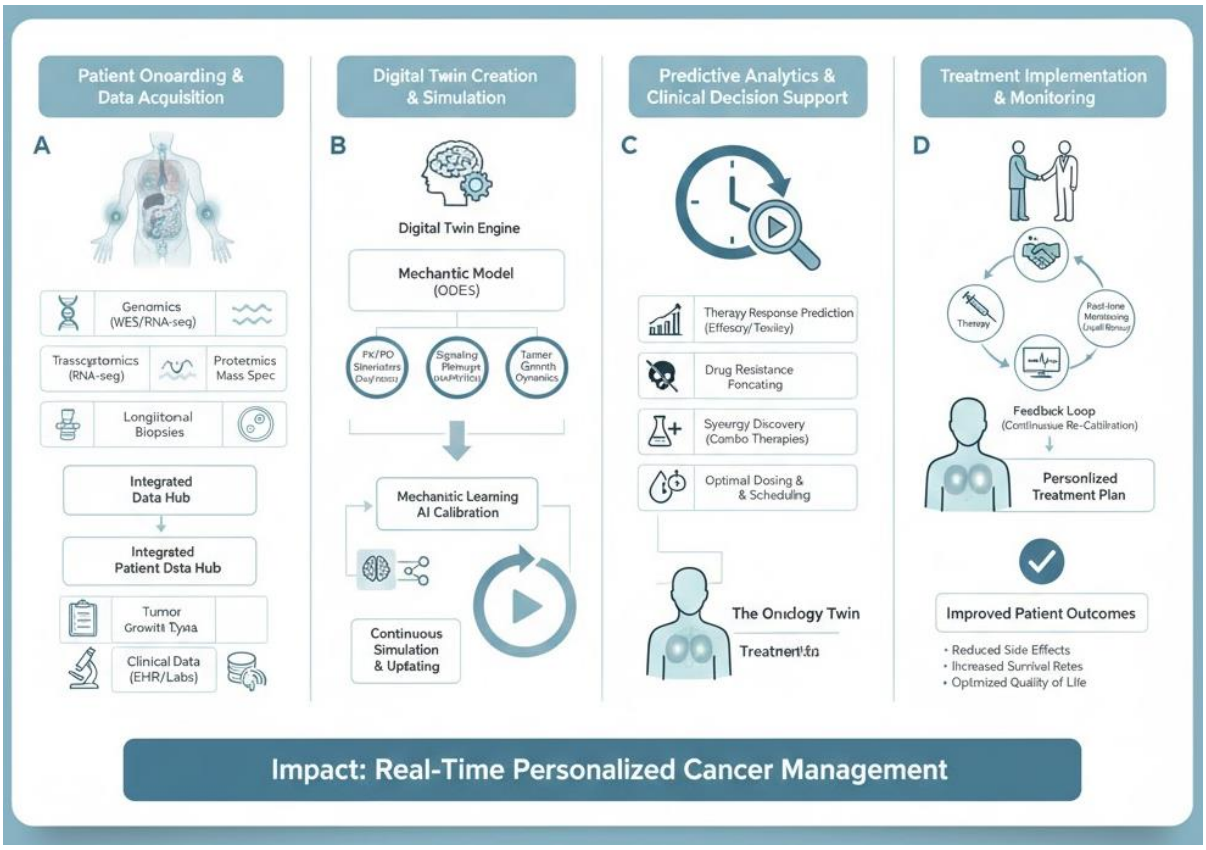

Figure-3. Future Clinical Workflow of a Digital Twin in Oncology Practice

The transition from static bioinformatics to dynamic Digital Twin modeling represents a fundamental shift in oncology. By grounding high-dimensional data in the "laws of biology" through mechanistic equations, we move beyond mere correlation toward **causal prediction**.

The Hybrid Advantage: Mechanistic vs. Data-Driven

Our results emphasize that while "black-box" AI models excel at pattern recognition, they often lack the explainability required for clinical decision-making. Digital Twins solve this by using **ordinary differential equations (ODEs)** to model protein-protein interactions (Si et al., 2025). This "Mechanistically Explainable AI" allows oncologists to see *why* a model predicts a specific drug failure—for example, by visualizing the feedback loop that reactivates an oncogenic pathway.

Overcoming the "Snapshot" Limitation

One of the most significant discussions in current literature is the "snapshot" nature of omics data. A single biopsy is a frozen moment in time, yet cancer is a four-dimensional process. The Digital Twin framework addresses this by using **data assimilation techniques** (similar to weather forecasting) to continuously update the model as new liquid biopsy or imaging data becomes available (Olasehinde et al., 2025). This turns the patient's record into a "living document" that evolves with the disease.

Ethical and Regulatory Hurdles

Despite the technical promise, the discussion around clinical adoption must address the "black box" of regulatory approval. Current FDA frameworks are designed for "locked" algorithms; however, a Digital Twin is by definition an **ever-changing model**. Furthermore, the ethical implications of "in silico" failures—where a twin dies in a simulation—pose complex psychological challenges for both physicians and patients (Olawade et al., 2026).

Future Directions: The Multi-Scale Frontier

The next generation of Digital Twins must move toward a **multi-scale approach**, integrating the molecular syntax of DNA (Genomic Syntax) with the macro-level physics of drug delivery and blood flow (Benzekry, 2026). Integrating **Graph Neural Networks (GNNs)** to model the spatial architecture of the tumor microenvironment will be the next critical step in achieving true "precision" in precision oncology.

Future Directions

- Standardized data pipelines and interoperable modeling frameworks.
- Integration of real-world data (EHR, wearables).
- Clinical trials incorporating digital twin predictions.
- Explainable AI to improve clinician trust.
- Scalable cloud-based architectures for clinical

workflows.

Conclusion

Digital twins in oncology represent a transformative paradigm for precision cancer care. By integrating multi-omics data into mechanistic models, they offer personalized predictions of responses to combination therapies. Continued methodological advances, coupled with robust validation and integration into clinical workflows, can realize the promise of truly individualized oncology treatments.

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