EDITORIAL

Digital Twins in Nuclear Medicine: A Pathway to Personalized Theranostics

Hossein Arabi [1*], Swagat Dash [2], Habibollah Dadgar [3], Majid Assadi [4]

[1] *Division of Nuclear Medicine and Molecular Imaging, Geneva University Hospital, CH-1211, Geneva 4, Switzerland*

[2] *Department of Nuclear Medicine & Molecular Theranostics, Sarvodaya Hospital, Faridabad, India*

[3] *Department of Nuclear Medicine and Molecular Imaging, Cancer Research Center, RAZAVI Hospital, Mashhad University of Medical Sciences, Mashhad, Iran*

[4] *The Persian Gulf Nuclear Medicine Research Center, The Persian Gulf Biomedical Research Institute, Department of Nuclear Medicine, Molecular Imaging, and Theranostics, Bushehr Medical University Hospital, School of Medicine, Bushehr University of Medical Sciences, Bushehr, Iran*

*Corresponding Author: Hossein Arabi
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Email: hossein.arabi@unige.ch

Abstract

Theranostics has revolutionized nuclear medicine by integrating diagnostic imaging and targeted radionuclide therapy, delivering precision oncology with proven survival benefits in cancers such as prostate cancer and neuroendocrine tumors. However, inter-patient variability in biodistribution, response, and toxicity remains a major challenge. This editorial explores the transformative potential of digital twins, dynamic virtual replicas of patients continuously updated with real-world data, as a natural synergy for theranostics. Theranostic digital twins enable predictive dosimetry, personalized treatment optimization, responder identification, and toxicity forecasting through hybrid AI-mechanistic models grounded in radiopharmacokinetics and radiobiology. Early development should prioritize clinically meaningful applications supported by comprehensive, harmonized multimodal datasets, robust hybrid modeling, and effective synchronization mechanisms. Large-scale collaboration and systematic evidence synthesis are essential to accelerate clinical translation. By bridging in-silico simulation with real-world theranostics, digital twins promise to evolve nuclear medicine toward truly proactive, equitable, and predictive personalized care.

Keywords: Theranostics; Digital Twins; Nuclear Medicine; Artificial Intelligence.

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1. The Promise of Theranostics in Nuclear Medicine

Theranostics represents a cornerstone of modern Nuclear Medicine (NM), seamlessly integrating diagnostic imaging and targeted therapy through radiopharmaceuticals that bind to specific molecular targets. This paradigm, rooted in the pioneering use of radioiodine for thyroid disorders in the 1940s, has evolved dramatically with agents like Prostate-Specific Membrane Antigen (PSMA)-targeted ligands for prostate cancer and somatostatin receptor analogs for neuroendocrine tumors [1]. Today, theranostics drives precision oncology, enabling clinicians to visualize disease extent via Positron Emission Tomography (PET) or Single-Photon Emission Computed Tomography (SPECT) and deliver therapeutic radiation using the same molecular scaffold, often with isotopes like Lutetium-177 [2]. Its importance cannot be overstated: landmark trials, such as VISION, have demonstrated significant survival benefits (median overall survival of 15.3 months vs. 11.3 months in metastatic castration-resistant prostate cancer treated with 177Lu-PSMA-617), while minimizing off-target effects [3]. However, challenges persist, including inter-patient variability in pharmacokinetics, tumor response, and toxicity, underscoring the need for tools to simulate and optimize treatments.

2. Linking Theranostics to Digital Twins: A Natural Synergy

One of the most meaningful and feasible applications of emerging technologies in clinical practice lies at the intersection of theranostics and Digital Twins (DTs). Theranostics generates rich, multimodal data, from pre-treatment PET scans quantifying target expression to post-therapy dosimetry assessments, providing an ideal foundation for DTs. Unlike broader oncology fields where data silos and heterogeneity hinder integration, theranostics' unified diagnostic-therapeutic workflow offers a streamlined entry point for DTs. By creating virtual patient replicas, DTs can "replay" theranostic scenarios in silico, forecasting outcomes like tumor regression or organ-at-risk toxicity before actual administration. This not only enhances personalization but also addresses ethical imperatives by reducing unnecessary radiation exposures and accelerating drug development through virtual trials [4, 5].

3. Defining Digital Twins and Their Advantages in Theranostics

A digital twin in medicine is a dynamic, virtual replica of a patient or biological system, continuously updated with real-time data to simulate physiological processes, disease progression, and therapeutic interventions [6]. Adapted from engineering origins (e.g., NASA's aerospace simulations), medical DTs incorporate five core elements: the physical patient as the data source, data connections for integration, an in-silico model for predictions, user interfaces for clinical interaction, and synchronization mechanisms for ongoing alignment [6]. In theranostics, DTs, often termed Theranostic Digital Twins (TDTs), extend this by embedding Physiologically-Based Radiopharmacokinetic (PBRPK) models with radiobiological and immunological modulators [7].

The advantages are profound. DTs enable predictive dosimetry, optimizing injected activity and cycles to maximize tumor kill while sparing healthy tissues, potentially improving response rates from ~50% in current trials. They facilitate cost savings (virtual trials could reduce patient recruitment by 30–50%, per U.S. FDA estimates) and ethical gains by simulating underrepresented populations. In prostate cancer, for instance, a DT could integrate PSMA-PET uptake with renal function to predict nephrotoxicity, transforming NM from reactive to proactive care. Broader benefits include enhanced equity, as DTs can model global variations in disease presentation, and regulatory acceleration through in-silico evidence for approvals [8].

4. Focusing Early Development on Clinically Meaningful Applications

Given that DTs in theranostics are in early stages, with prototypes like TDTs for 177Lu-PSMA showing promise but lacking routine clinical integration [7], early efforts must prioritize clinically meaningful, technically feasible applications. These include patient stratification (e.g., identifying responders via baseline imaging), treatment response prediction (e.g., tumor shrinkage post-therapy), and toxicity forecasting (e.g., renal or bone marrow risks in radionuclide therapy). Such focus ensures tangible impact, like reducing futile treatments in non-responders, while building on existing data infrastructures.

To realize these, three major components of a theranostic DT must be developed: comprehensive datasets, robust models simulating biological dynamics, and effective synchronization mechanisms.

5. Comprehensive Datasets: The Foundation

High-quality, multimodal data are essential for DT fidelity. Requirements include longitudinal records (pre- and post-treatment), diversity (to mitigate bias), standardization, and integration of clinical variables (e.g., biomarkers, genomics). Data must be harmonized across sites to account for scanner variability, ensuring reproducibility. For example, in prostate cancer theranostics, pre-treatment 68Ga-PSMA PET images (e.g., SUVmean ≥10 indicating high uptake) can predict 177Lu-PSMA response (PSA response rates 91% in high-uptake vs 52% in low-uptake cases) and toxicity (e.g., mean eGFR decline of ~11%, with grade 3–4 renal events in ~9% of patients) [3, 9]. A DT dataset might combine these with blood-based markers (e.g., PSA kinetics) and patient demographics, enabling simulations that forecast individualized outcomes and refine inclusion criteria for trials.

6. Model Development: Hybrid AI and Mechanistic Approaches

The modeling core simulates complex interactions, blending Artificial Intelligence (AI) for data-driven insights with mechanistic approaches for biological realism [6]. AI components, such as machine learning or deep neural networks, excel at pattern recognition from large datasets, predicting outcomes like tumor response from imaging features. However, they risk "black box" opacity and poor generalization without vast data [10]. Mechanistic models, grounded in pathophysiology (e.g., ordinary/partial differential equations for pharmacokinetics or tumor growth), provide interpretable simulations but struggle with incomplete biological knowledge or parameter estimation.

Hybrids could address these: AI augments mechanistic frameworks by estimating parameters (e.g., via physics-informed neural networks, PINNs) or generating synthetic data to train models. In theranostics, a hybrid TDT might use mechanistic PBRPK equations to simulate 177Lu distribution, with AI refining predictions based on PET-derived biodistribution patterns [7]. This synergy enhances accuracy, interpretability, and applicability in data-scarce rare cancers.

7. Twin Synchronization: Ensuring Dynamic Relevance

Synchronization maintains the DT's alignment with the real patient, enabling iterative refinements. This component is crucial for upgrading the system, incorporating new data (e.g., post-therapy scans) to recalibrate predictions and adapt to changes like tumor evolution. In prostate theranostics, after the first 177Lu cycle, synchronization could update the DT with reduced PSMA uptake on interim PET, adjusting subsequent doses to mitigate emerging toxicity risks.

Mechanistically, synchronization operates event-based (e.g., after each cycle) or continuously (via wearables monitoring biomarkers), using data fusion algorithms to reconcile discrepancies [6]. This feedback loop, akin to closed-loop systems in engineering, ensures the DT evolves, improving precision over treatment courses.

8. The Path Forward: Collaboration and Evidence-Based Advancement

Realizing theranostic DTs demands large-scale collaboration. Data collection must be consistent, harmonized, and standardized across centers, adhering to frameworks like FAIR principles (Findable, Accessible, Interoperable, Reusable) and EANM/IAEA guidelines for NM imaging. Privacy and data-sharing issues should be effectively addressed to enable development of comprehensive and unified models. For model development, dedicated AI algorithms are needed to process multimodal inputs (e.g., PET, clinical labs, genomics) efficiently, with seamless connections to mechanistic simulators via hybrid architectures.

Systematic reviews and meta-analyses of existing literature and data are essential to define clinically meaningful DT applications. For instance, meta-analyses of PSMA trials could reveal promises (e.g., 60–70% response rates), gaps (e.g., inconsistent dosimetry reporting), limitations (e.g., bias in trial demographics), and requirements (e.g., standardized uptake metrics). These syntheses would guide dedicated AI (e.g., for uncertainty quantification) and mechanistic models (e.g., incorporating immunological modulators for immune responses to radiation).

While challenges like regulatory hurdles (e.g., FDA qualification for medical device DTs) and computational demands persist, the potential is immense. By 2030, DTs could enable "what-if" scenarios in theranostics DT, transforming NM into truly predictive medicine.

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