CPT: Pharmacometrics & Systems Pharmacology

MINI REVIEW OPEN ACCESS

The Potential of Digital Twins for Pediatric Rare Diseases

Rahuman S. Malik-Sheriff[1,2,3] | Anurag Limdi[1] | Evangelia Petsalaki[1] | Henning Hermjakob[1] | Ellen M. McDonagh[1,4,5]

[1]European Molecular Biology Laboratory, European Bioinformatics Institute (EMBL-EBI), Cambridge, UK | [2]Department of Surgery and Cancer, Faculty of Medicine, Imperial College London, London, UK | [3]Department of Medicine, Division of Pulmonary Systems Medicine, University of Florida, Gainesville, USA | [4]Open Targets, Cambridge, UK | [5]Wellcome Sanger Institute, Cambridge, UK

Correspondence: Rahuman S. Malik-Sheriff (sheriff@ebi.ac.uk)

Received: 30 June 2025 | **Revised:** 10 February 2026 | **Accepted:** 27 February 2026

ABSTRACT

Rare diseases affect over 300 million people globally, with approximately 75% manifesting in childhood. Their diagnosis is often delayed and approved treatments are lacking for most of the conditions. Pediatric rare diseases research is further complicated by ethical constraints and developmental diversity across childhood. Digital Twins, virtual representations of patients built from mechanistic and AI/ML models, offer a promising solution by enabling hypothesis testing, precision diagnostics, personalized therapies, and *in silico* trials for pediatric rare diseases. This article discusses the potential of DT applications in advancing precision medicine for pediatric rare diseases, alongside associated regulatory perspectives, modeling strategies, uncertainty analysis, as well as data, ethical and legal challenges.

1 | Introduction

Rare diseases, though individually uncommon, collectively impact over 300 million individuals globally, approximately 3.5%–5.9% of the world's population. Around 70% of the cases are genetic in origin, with most manifesting during childhood. Although 75% of rare diseases affect children, approved treatments exist for only 5% of all rare diseases, and nearly 30% of affected children do not survive beyond the age of five. These conditions often present early, progress rapidly, and remain understudied due to their low prevalence and heterogeneity. Pediatric patients face additional challenges, including delayed diagnosis, limited treatment options, and age-specific physiological differences [1–3]. These complexities underscore the urgent need for precision tools to bridge mechanistic gaps and inform individualized care.

2 | The Challenge of Understanding and Diagnosing Rare Diseases in Pediatrics

There is a critical need to diagnose neonates/children with rare disease as early as possible, as early intervention and correct disease management can slow down or even prevent disease progression. A diagnosis is also important for the family in terms of understanding their child's needs, accessing social care and support, becoming part of a community of similarly-affected families, as well as numerous psychological reasons and informing reproductive decisions for the family [3]. Whole-genome sequencing as a diagnostic test has been implemented in some healthcare services; however, diagnostic rates for pediatric rare disease patients still remain below 35%, and the diagnostic odyssey continues for a majority of patients [4]. Even with a diagnosis, treatment options currently remain limited and novel drug development in this area is challenging for a number of reasons; large-scale clinical trials are not possible in rare disease, drug development is often seen as less commercially attractive, and despite new avenues of treatment opening up, $n=1$ approaches are currently prohibitively expensive to most [5]. For children with rare diseases, there are further ethical and developmental challenges when considering clinical trials.

To fully understand and study pediatric rare diseases, researchers and clinicians are faced with scattered small patient cohorts, incomplete genotype–phenotype associations, and limited multi-omics and longitudinal datasets. Furthermore, variability

in disease onset, phenotypic heterogeneity, and progression complicates comprehensive analysis. Often, the typical tissue reference maps and other relevant information are usually only available for adults. As infant, child, and adolescent physiology drastically differs from adults, analyses using adult data as reference for childhood disease can often lead to erroneous conclusions.

3 | Digital Twins in Medicine: Concepts and Regulatory Momentum

In 1970, NASA's Apollo 13 mission, when an oxygen-tank explosion crippled the spacecraft nearly 200,000 miles from Earth, engineers at mission control used high-fidelity simulators which are virtual replicas of spacecraft (continuously updated with real data) to simulate various survival strategies safely on ground and guided the astronauts' return home. This is one of the earliest examples of a digital twin concept in action. Digital Twins (DTs) are virtual representations of physical entities that enable real-time simulation and prediction. DTs are used to monitor and optimize the performance, help diagnose problems preemptively, and guide decisions to avoid catastrophic failures. Similarly, DTs of patients, constructed using mechanistic and/or data-driven Artificial Intelligence/Machine Learning (AI/ML) models, have the potential to be used to simulate biological processes, disease progression, and therapeutic responses. They could also be continuously refined with longitudinal data from individual patients and tailored to specific clinical contexts [6–8].

A widely implemented example of a medical digital twin is the automated insulin delivery (AID) or "artificial pancreas" system, which uses continuous glucose sensor data to run in silico simulations estimating optimal insulin dosing in real time, thereby adapting delivery to each patient's physiological state. Recent clinical trials using digital-twin replay technology have demonstrated improved glycaemic control in type 1 diabetes [9].

Several medical digital twins have now moved beyond concept into validated use. Patient-specific cardiac twins have been used to simulate pacing and accurately predict responses to cardiac resynchronization therapy [10]. Digital-twin metabolic models have forecast chronic kidney-disease risk in individuals with type 2 diabetes [11]. Using MRI data, Wu et al. (2025) built patient-specific digital twins to predict and optimize response to neoadjuvant chemotherapy in triple-negative breast cancer across a 105-patient cohort [12]. Together, these cases demonstrate that digital twins can already deliver predictive, individualized insights in real clinical contexts. Several exemplar medical digital twins are surveyed in [7, 13], spanning immune-system twins for infection, autoimmunity, and oncology, e.g., predicting vaccine responses, exploring sepsis trajectories, and optimizing immunotherapy. Complementing these reviews, a practical drug-development digital twin framework enabling in silico trials, and drug repurposing has also been outlined [14].

Regulatory agencies are increasingly supporting DTs as part of model-informed drug development (MIDD). Both the U.S. Food and Drug Administration (FDA) and European Medicines Agency (EMA) have acknowledged the utility of computational modeling in regulatory assessment and have issued guidance supporting *in silico* approaches in medical device evaluation and trial augmentation. The ICH M15 model assessment framework, jointly developed by multiple regulatory bodies and finalised 2026, provides harmonized principles for evaluating the credibility of complex models [15]. In 2025, FDA announcements supporting the replacement of animal models with new approach methodologies (NAMs), including *in silico* trials [16, 17], further highlight the regulatory momentum toward DT adoption.

In rare diseases, where recruitment is difficult and ethical concerns are prominent, DTs could be used to simulate synthetic control arms and forecast patient-specific responses, enhancing trial design and efficiency. This regulatory momentum reflects a growing acceptance of DT simulation as a credible complement to traditional clinical research and has driven DT initiatives by companies such as Philips, Siemens, Unlearn.AI, GSK, Sanofi, and Pfizer. The approval of cardiac DTs and *in silico* clinical trials by regulatory bodies underscores this growing support [8].

4 | Digital Twins for Pediatric Rare Diseases

DT technology in biomedical science is still in an early stage. However, when it advances to the level seen in aerospace and other engineering industries, it could offer transformative solutions to many of the challenges in pediatric rare diseases. Current DTs are not comprehensive replicas of a whole human but are fit-for-purpose systems addressing focused scientific or clinical questions. In pediatric rare diseases, they hold promise for studying disease mechanisms by supporting hypothesis generation, simulating interventions, and guiding personalized diagnostics, therapies, and clinical decision-making, especially where empirical data is sparse.

DTs can be used to integrate multi-omics data—such as genomics, transcriptomics, epigenomics, and proteomics—with clinical phenotypes to simulate patient-specific trajectories and therapeutic responses. This could enable *in silico* hypothesis testing, particularly valuable when empirical experimentation is ethically or logistically constrained in pediatric research. For diagnosis, DTs could be used to map clinical and molecular profiles to reference models, potentially accelerating recognition of ultra-rare patterns. In drug development, DTs could be employed to simulate virtual cohorts, predict responses to mono- and combination therapies, support drug target identification, validation and repurposing strategies, and identify biomarkers for patient stratification. Patient-specific DT simulations could help forecast treatment outcomes—such as how an immunosuppressant modulates pathways in a child with an autoimmune disorder—thus reducing trial-and-error. Iterative refinement with clinical data is essential to improve the predictive accuracy of DTs over time. Several academic research groups and consortia are developing DTs with molecular and cellular foundations to address cancer, infection and immunity-related conditions [13]. As DT technology in biomedical sciences rapidly evolves, many of these DTs could see successful implementation within the next five to ten years.

Pediatric digital twins address distinct clinical imperatives: children's physiology differs fundamentally from adults, with ongoing developmental changes affecting pharmacokinetics,

pharmacodynamics, and immune responses, while ethical constraints and limited trial enrollment create substantial knowledge gaps in pediatric therapeutics. Several pediatric digital twins have been developed, spanning diverse domains from infectious to cardiac diseases. A gut microbiome DT trained on early-life metagenomic data was able to forecast ecosystem trajectories and predict later neurodevelopmental deficits, enabling early identification of infants at risk for targeted intervention [18]. In cardiology, electrophysiology digital twins have been developed and validated for congenital heart disease [19, 20], while ML–based cardiometabolic twins integrating clinical and behavioral data support early risk stratification and personalized prevention in pediatric care [21]. Additionally, mechanical digital twins have been used to model patient-specific respiratory mechanics in pediatric respiratory distress syndrome [22].

Pediatric Rare Disease DTs must reflect developmental changes in physiology, metabolism, and immune function. This requires developmental-stage-specific parameters and data from underrepresented groups, including neonates and infants, which are challenging to collect due to the scarcity and rarity of patient cohorts. To overcome these challenges, through a Chan Zuckerberg Initiative (CZI) funded Rare Disease DT project, we are developing generative AI methods for augmentation of the existing RD datasets through transfer learning from common diseases, by leveraging multimodal data with overlapping biological mechanisms [23]. This approach will enable us to generate synthetic data to fill gaps from missing modalities, data sparsity, and age imbalance (Figure 1).

Synthetic data can support patient-specific modeling and digital twins by augmenting scarce clinical data and enabling scenario testing [24]. However, there are limitations in such data around potential hallucination and bias amplification. Hence, validation of synthetic data is critical and should be tailored to the data type and use case, covering statistical fidelity and task-specific utility [25]. Multiple methods are available for synthetic-data validation, including distributional similarity, Hellinger distance, and pairwise-correlation differences, among others. Where relevant, it is also important to assess disclosure risk using differential privacy and other appropriate methods [26–28]. For multi-omics synthetic datasets, it is important to validate each modality and cross-modal biological coherence (e.g., pathway enrichment) by training models on synthetic data and testing them on held-out real data to ensure high performance in the selected task.

5 | Hybrid Mechanistic–Machine Learning Modeling as A Strategy for Digital Twins

The construction of DTs can follow several methodological approaches. They may be built as mechanistic models, capturing detailed biochemical, pharmacokinetic, or physiological pathways using systems of equations. Alternatively, AI/ML-based DTs can be trained on large-scale patient data to predict outcomes or classify disease states. However, we propose the use of hybrid approaches where mechanistic models provide structure and interpretability based on prior knowledge, and ML

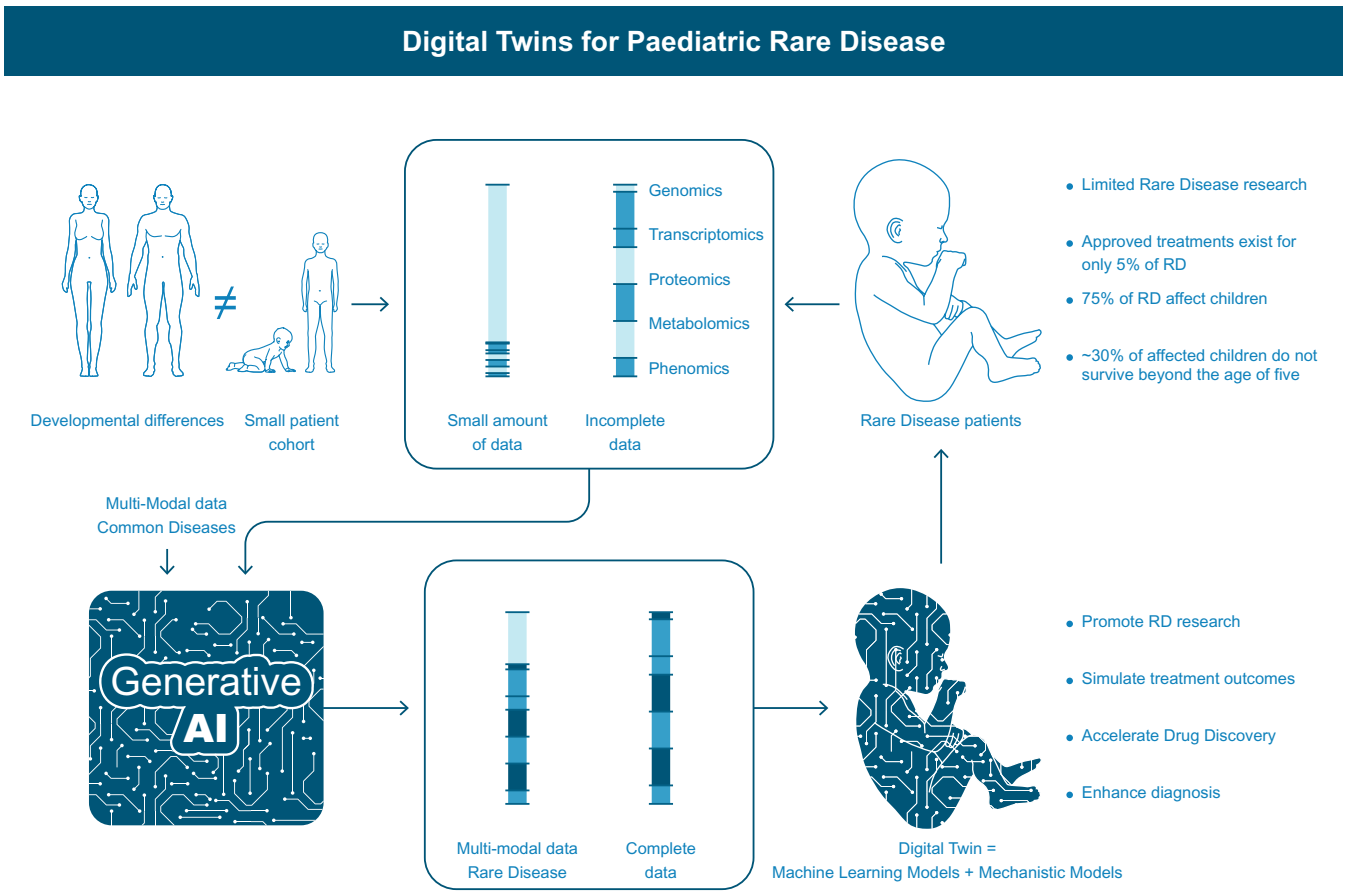

FIGURE 1 | Challenges and opportunities in building rare disease digital twins.

components enable scalability and adaptivity to account for the unknown knowledge. The hybrid model strategy is particularly well-suited for rare diseases, allowing integration of known biological mechanisms with ML from sparse, heterogeneous datasets.

Integrating mechanistic models with ML components into a hybrid framework raises important challenges around identifiability, interpretability, and uncertainty quantification (UQ). Identifiability refers to whether model parameters can be uniquely inferred from the available data, while UQ aims to characterize how confident we are in model predictions.

The mechanistic core of a hybrid model can be analyzed using well-established frameworks. These include global sensitivity analysis (e.g., Sobol methods, which quantify how much each parameter contributes to output variability), structural and practical identifiability analysis using profile likelihoods (to assess whether parameters are theoretically and empirically learnable), and Bayesian calibration with posterior predictive checks (which compare model predictions to observed data). Together, these approaches ensure that predictions are accompanied by confidence intervals and that the learnability of parameters is made explicit.

To address remaining *epistemic uncertainty* (uncertainty due to incomplete knowledge of the system), the mechanistic backbone can be coupled with ML components such as deep ensembles of multilayer perceptrons, Bayesian neural networks, Gaussian process surrogates, or neural differential equations. These elements can learn unknown or poorly characterized dynamics while preserving biophysical constraints imposed by the mechanistic model. The ML layers can then be analyzed using feature attribution methods (which identify which inputs drive predictions) and counterfactual tests (which probe how predictions change under hypothetical interventions). Anchoring these analyses in a validated mechanistic core helps retain causal interpretation and biological plausibility.

ML components are often weakly identifiable, meaning that multiple internal parameter configurations can produce similar outputs. In a hybrid setting, ML models may inadvertently replicate mechanistic behavior or absorb dynamics that would otherwise constrain mechanistic parameters, thereby undermining unique parameter inference (e.g., in neural ordinary differential equations [29]). This risk can be mitigated by restricting ML components to modeling *residuals* (i.e., discrepancies between mechanistic predictions and data) imposing biologically meaningful constraints, or enforcing orthogonality between mechanistic and ML components so that they capture complementary information.

Mechanistic models are typically interpretable by design, whereas ML models usually require post hoc explainability techniques, for example, SHapley Additive exPlanations (SHAP), which attribute a model's predictions to individual input features. In a hybrid model, such analyses can highlight discrepancies between known mechanisms and patterns learned by the ML component. Moreover, ML layers can be directly constrained by prior biological knowledge, for example by incorporating gene programs or pathway-activity constraints into their latent representations [30, 31].

Uncertainty estimation is especially critical for hybrid-model-based digital twins. Their predictions may be affected by multiple sources of uncertainty, including observation noise, limited data, and structural model error arising from simplifications in the mechanistic model or from how it is coupled to ML components [32]. Bayesian hierarchical models, ensemble methods, and related approaches can be applied to the full hybrid system to generate distributions over parameters and outputs. A key consideration is calibration, meaning that predicted uncertainties should accurately reflect real-world predictive performance. Comprehensive UQ strategies that jointly assess mechanistic and ML components therefore provide a coherent and auditable pathway toward credible hybrid digital-twin predictions.

Rare Disease DTs in the context of drug discovery represent an evolution beyond traditional model-informed drug development techniques such as quantitative systems pharmacology (QSP), quantitative systems toxicology (QST), and ADMET (absorption, distribution, metabolism, excretion, and toxicity) models. While these approaches have been foundational in drug discovery and regulatory submissions, they are typically focused on population-level dynamics and predefined biological pathways. DTs, by contrast, are individualized, dynamic, and modular, capable of integrating real-time or longitudinal data streams and adapting their outputs to reflect patient-specific contexts. QST models can be used to build digital twins; for example, a QSP model of Pompe disease, a rare neuromuscular disease, was used to build personalized models to investigate the response to avalglucosidase alfa on patients with late-onset (LOPD) and severe infantile-onset (IOPD) phenotypes. Advancing further, the hybrid DT can enable integration of high-dimensional, multimodal inputs such as clinical, genomic, imaging, and environmental data to predict personalized patient-specific outputs typically not achieved with traditional MIDD tools [8, 14].

6 | Data, Infrastructure, and Standardization Challenges

Despite their promise, the development of DTs for rare diseases faces several challenges. Comprehensive modeling requires access to high-quality multi-omics data and rich clinical phenotypes, which remain scarce and poorly standardized, especially in pediatric populations. Although generative AI and synthetic data offer promising avenues to mitigate gaps in the data, accessibility to existing datasets remains a barrier, with patient multi-omics data only available in controlled access research environments. Federated learning therefore is crucial to leveraging multiple, disparate sources of rare-disease datasets to build digital twins. Most rare diseases lack coupled multi-omics datasets, underscoring the need for additional studies and data collection efforts.

Pediatric populations amplify rare disease data challenges through additional layers of complexity. Geographic dispersion limits patient cohorts to very small numbers of individuals per country [33] and combining data sources across institutions is challenging due to incompatible research consenting practices

and stringent privacy requirements for minors [34]. Rare disease registries can partially help with these limitations by pooling patient data to overcome knowledge gaps and gathering real-world evidence on disease progression, treatment outcomes, and health impacts [35].

Several initiatives address rare disease data gaps through coordinated registries and standardized data collection. Orphanet provides the standardized nomenclature and disease ontology, enabling standardization and improved visibility of rare disease in healthcare systems [1]. The European Platform on Rare Disease Registration unifies access to registries through 24 European Reference Networks spanning different disease areas [36], and promotes interoperability through standardized data collection. Complementary efforts such as SOLVE-RD integrate multi-omic datasets from patients to identify mechanistic underpinnings of rare diseases [37]. In the United States, the Rare Diseases Clinical Research Network (RDCRN), funded by the National Institutes of Health, encompasses 21 consortia studying nearly 200 rare diseases at more than 270 sites globally [38]. In the UK, the 100,000 Genomes Project by Genomics England has enabled discovery of gene associations for rare diseases [39, 40].

The construction of both mechanistic and ML-based DTs is a complex and resource-intensive step. Public repositories such as BioModels provide curated models in standardized formats (e.g., SBML for mechanistic models and ONNX for ML models) that are interoperable, reproducible, and reusable to facilitate DT development. To promote wide adoption, there is an urgent need for standards for DT implementation and dissemination and clear guidelines for evaluating their performance, safety, and transparency. Finally, methodologies, such as those that we are developing, that are able to generate mechanistic models directly from data would be catalytic as they would dramatically reduce the time and resources needed to build the respective DT.

7 | Ethical and Legal Considerations

There are aspects of patient digital twinning that make them challenging to comply with existing legal and ethical frameworks. An ideal digital twin is maintained across a patient's disease; for most rare diseases this is over the patient's lifespan. Ideally it also incorporates data that would be considered identifiable; i.e., genetics, and may connect to data from third parties i.e., genetics from family members to fully understand the heritability and penetrance of the disease. For the benefit of the patient, it would also ideally be developed to be applied for multiple and future undefined use cases, including diagnosis, patient management, and predicting potential treatment. However, the aspects that make digital twins innovative and give them the potential to fill the gaps in existing healthcare, at the same time make them tricky to comply with existing legal regulations and ethical guidelines. For example, for identifiable data such as genetics, the EU General Data Protection Regulation (GDPR), requires data to be collected for a specific use case and kept for a limited timeframe [41].

Navigating the legal and ethical guidelines, even in one jurisdiction, is challenging; to further complicate matters, for children there are appropriately additional data protection and consent considerations that need to be taken into account. In the EU, for example, GDPR states that "children merit specific protection with regard to their personal data, as they may be less aware of the risks, consequences and safeguards concerned and their rights in relation to the processing of personal data" [41]. When considering a digital twin that could be developed across a patient's disease span, for pediatrics this also poses challenges, as the responsibility of safeguarding the data over time will change from the parents to the patient themselves [41].

There is a need for clearer legal and ethical guidance to both enable the innovation and beneficial development of digital twins for rare diseases in pediatric patients, whilst at the same time maintaining protection for this vulnerable group [41]. With the aim of promoting trustworthy AI, The European Union's Artificial Intelligence Act provides a framework for setting obligations for developers and users based upon the level of risk of an AI-based system; digital twins are likely to fall under the high risk AI-based tools which support monitoring, diagnosis, treatment planning for patients. To ensure reproducibility and safety, obligations outlined under this framework include ensuring the data is representative, of high quality, the system is transparent and technically robust [41].

To help support the enabling of sharing and processing specifically of pediatric omics and health data for research under legal and ethical frameworks, The Global Alliance for Genomics and Health (GA4GH) has developed the KIDS framework along with pediatric consent clauses, and policy briefs on children's data protection and genomic research to cover pediatric-specific considerations and protections, consent and lawful bases for data processing [42, 43]. These include how long data can be stored, from whom the consent should be obtained, the age of consenting persons, greater safeguards for children's data and privacy rights. Their policy briefs provide extensive resources for understanding different legal frameworks and considerations across different nations. The GA4GH is also developing data passports to provide a technical specification associated with a given dataset to represent the data use constraints, making this much clearer for data users.

There are also several initiatives that have been established to help the safe and effective sharing of data for children with rare disease. For example, The International Precision Child Health Partnership (IPCHiP) across four major global pediatric institutes who are working toward establishing a federated data analysis network to overcome traditional data sharing limitations [44].

8 | Conclusions

Digital Twins (DTs) represent a potential transformative approach to addressing the challenges of pediatric rare diseases. By integrating systems pharmacology, machine learning, multi-omics, and multimodal data, DTs support a paradigm shift from generalized care to precision medicine. When rigorously developed, transparently validated, and ethically implemented, DTs could potentially improve diagnosis, simulate treatment

outcomes, and expedite research for historically underserved conditions. Advancing personalized medicine, DTs can support precision dosing by enabling simulation of developmental pharmacokinetics and drug–disease interactions. Such applications are especially critical in pediatric diseases, where empirical dose-finding trials are rarely feasible. With sustained investment from governments and industries and strong regulatory support, DTs have the potential to significantly advance pediatric rare disease research and therapeutic innovation.

Funding

This project has been made possible in part (2024–351060) from the Chan Zuckerberg Initiative DAF, an advised fund of Silicon Valley Community Foundation. This project is also supported by EMBL Core Funding.

Conflicts of Interest

The authors declare no conflicts of interest.

References

1. S. Nguengang Wakap, D. M. Lambert, A. Olry, et al., "Estimating Cumulative Point Prevalence of Rare Diseases: Analysis of the Orphanet Database," *European Journal of Human Genetics* 28, no. 2 (2020): 165–173.

2. D. Marimpietri and G. Zuccari, "Development of Medicines for Rare Pediatric Diseases," *Pharmaceuticals (Basel)* 16, no. 4 (2023): 513.

3. J. S. Dumbuya, C. Zeng, L. Deng, et al., "The Impact of Rare Diseases on the Quality of Life in Paediatric Patients: Current Status," *Frontiers in Public Health* 13 (2025): 1531583.

4. R. Pandey, N. F. Brennan, K. Trachana, et al., "A Meta-Analysis of Diagnostic Yield and Clinical Utility of Genome and Exome Sequencing in Pediatric Rare and Undiagnosed Genetic Diseases," *Genetics in Medicine* 27, no. 6 (2025): 101398.

5. S. C. Groft, M. Posada, and D. Taruscio, "Progress, Challenges and Global Approaches to Rare Diseases," *Acta Paediatrica* 110, no. 10 (2021): 2711–2716.

6. R. Laubenbacher, A. Niarakis, T. Helikar, et al., "Building Digital Twins of the Human Immune System: Toward a Roadmap," *NPJ Digital Medicine* 5, no. 1 (2022): 64, https://doi.org/10.1038/s41746-022-00610-z.

7. A. Niarakis, R. Laubenbacher, G. An, et al., "Immune Digital Twins for Complex Human Pathologies: Applications, Limitations, and Challenges," *NPJ Systems Biology and Applications* 10, no. 1 (2024): 141.

8. E. Katsoulakis, Q. Wang, H. Wu, et al., "Digital Twins for Health: A Scoping Review," *NPJ Digital Medicine* 7, no. 1 (2024): 77.

9. B. P. Kovatchev, P. Colmegna, J. Pavan, et al., "Human-Machine Co-Adaptation to Automated Insulin Delivery: A Randomised Clinical Trial Using Digital Twin Technology," *NPJ Digital Medicine* 8, no. 1 (2025): 253.

10. T. Koopsen, W. Gerrits, N. van Osta, et al., "Virtual Pacing of a Patient's Digital Twin to Predict Left Ventricular Reverse Remodelling After Cardiac Resynchronization Therapy," *Europace* 26, no. 1 (2023): 9.

11. N. U. Surian, A. Batagov, A. Wu, et al., "A Digital Twin Model Incorporating Generalized Metabolic Fluxes to Identify and Predict Chronic Kidney Disease in Type 2 Diabetes Mellitus," *NPJ Digital Medicine* 7, no. 1 (2024): 140.

12. C. Wu, E. A. B. F. Lima, C. E. Stowers, et al., "MRI-Based Digital Twins to Improve Treatment Response of Breast Cancer by Optimizing Neoadjuvant Chemotherapy Regimens," *NPJ Digital Medicine* 8, no. 1 (2025): 195.

13. R. Laubenbacher, F. Adler, G. An, et al., "Toward Mechanistic Medical Digital Twins: Some Use Cases in Immunology," *Frontiers in Digital Health* 6 (2024): 1349595.

14. G. An and C. Cockrell, "Drug Development Digital Twins for Drug Discovery, Testing and Repurposing: A Schema for Requirements and Development," *Frontiers in Systems Biology* 2 (2022): 387, https://doi.org/10.3389/fsysb.2022.928387.

15. International Council for Harmonisation, *ICH M15 Guideline on General Principles for Model-Informed Drug Development-Step 2b-Scientific Guideline* (European Medicines Agency (EMA), 2004), https://www.ema.europa.eu/en/ich-m15-guideline-general-principles-model-informed-drug-development-step-2b-scientific-guideline.

16. Office of the Commissioner, *FDA Announces Plan to Phase Out Animal Testing Requirement for Monoclonal Antibodies and Other Drugs* (U.S. Food and Drug Administration, 2026), https://www.fda.gov/news-events/press-announcements/fda-announces-plan-phase-out-animal-testing-requirement-monoclonal-antibodies-and-other-drugs.

17. Center for Drug Evaluation, Research, *CDER/Office of New Drugs Streamlined Nonclinical Studies and Acceptable New Approach Methodologies (NAMs)* (U.S. Food and Drug Administration, 2025), https://www.fda.gov/about-fda/center-drug-evaluation-and-research-cder/cderoffice-new-drugs-streamlined-nonclinical-studies-and-acceptable-new-approach-methodologies-nams.

18. N. Sizemore, K. Oliphant, R. Zheng, C. R. Martin, E. C. Claud, and I. Chattopadhyay, "A Digital Twin of the Infant Microbiome to Predict Neurodevelopmental Deficits," *Science Advances* 10, no. 15 (2024): eadj04.

19. M. Salvador, F. Kong, M. Peirlinck, et al., "Digital Twinning of Cardiac Electrophysiology for Congenital Heart Disease," *Journal of the Royal Society, Interface* 21, no. 215 (2024): 729.

20. S. Qian, D. Ugurlu, E. Fairweather, et al., "Developing Cardiac Digital Twin Populations Powered by Machine Learning Provides Electrophysiological Insights in Conduction and Repolarization," *Nature Cardiovascular Research* 4, no. 5 (2025): 624–636.

21. V. Calcaterra, U. Ciriello, S. Medici, et al., "PODiaCarD: A Prototype of a Digital Twin Platform for the Management of Pediatric Obesity and Related Cardiometabolic Complications," *European Journal of Pediatrics* 185, no. 2 (2026): 77.

22. S. Saffaran, T. C. Kwok, D. Sharkey, and D. G. Bates, "Digital Twins of Mechanically Ventilated Preterm Neonates With Respiratory Distress Syndrome," *arXiv [Physics.Med-Ph]* (2025): 999, https://doi.org/10.48550/arXiv.2509.18999.

23. O. Stroe, "Understanding Rare Diseases With Digital Twins. EMBL-EBI News," (2025), https://www.ebi.ac.uk/about/news/technology-and-innovation/digital-twins-rare-disease/.

24. M. Giuffrè and D. L. Shung, "Harnessing the Power of Synthetic Data in Healthcare: Innovation, Application and Privacy," *NPJ Digital Medicine* 6, no. 1 (2023): 186.

25. M. Hernandez, P. A. Osorio-Marulanda, M. Catalina, L. Loinaz, G. Epelde, and N. Aginako, "Comprehensive Evaluation Framework for Synthetic Tabular Data in Health: Fidelity, Utility and Privacy Analysis of Generative Models With and Without Privacy Guarantees," *Frontiers in Digital Health* 7 (2025): 1576290.

26. A. Figueira and B. Vaz, "Survey on Synthetic Data Generation, Evaluation Methods and GANs," *Mathematics (Basel)* 10 (2022): 2733.

27. G. Zamzmi, A. Subbaswamy, E. Sizikova, E. Margerrison, J. G. Delfino, and A. Badano, "Scorecard for Synthetic Medical Data Evaluation," *Communications Engineering* 4, no. 1 (2025): 130.

28. V. B. Vallevik, A. Babic, S. E. Marshall, et al., "Can I Trust My Fake Data-A Comprehensive Quality Assessment Framework for Synthetic Tabular Data in Healthcare," *International Journal of Medical Informatics* 185 (2024): 13.

29. S. Giampiccolo, F. Reali, A. Fochesato, G. Iacca, and L. Marchetti, "Robust Parameter Estimation and Identifiability Analysis With Hybrid Neural Ordinary Differential Equations in Computational Biology," *NPJ Systems Biology and Applications* 10 (2024): 139.

30. W. Mao, E. Zaslavsky, B. M. Hartmann, S. C. Sealfon, and M. Chikina, "Pathway-Level Information Extractor (PLIER) for Gene Expression Data," *Nature Methods* 16 (2019): 607.

31. A. Qoku, M. Rohbeck, F. C. Walter, I. Kats, O. Stegle, and F. Buettner, "MOFA-FLEX: A Factor Model Framework for Integrating Omics Data With Prior Knowledge," *BioRxiv* 11 (2025): 250, https://doi.org/10.1101/2025.11.03.686250.

32. K. Sel, A. Hawkins-Daarud, A. Chaudhuri, et al., "Survey and Perspective on Verification, Validation, and Uncertainty Quantification of Digital Twins for Precision Medicine," *NPJ Digital Medicine* 8 (2025): 40.

33. V. Boulanger, M. Schlemmer, S. Rossov, A. Seebald, and P. Gavin, "Establishing Patient Registries for Rare Diseases: Rationale and Challenges," *Pharmaceutics and Medicine* 34 (2020): 185.

34. D. Patrinos, B. M. Knoppers, D. P. Laplante, N. Rahbari, and A. Wazana, "Sharing and Safeguarding Pediatric Data," *Frontiers in Genetics* 13 (2022): 86.

35. S. Kölker, F. Gleich, U. Mütze, and T. Opladen, "Rare Disease Registries Are Key to Evidence-Based Personalized Medicine: Highlighting the European Experience," *Front Endocrinol (Lausanne)* 13 (2022): 63.

36. Public Health, *Rare Diseases* (European Reference Networks, 2026), https://health.ec.europa.eu/rare-diseases-and-european-reference-networks/rare-diseases_en.

37. S. Laurie, W. Steyaert, E. de Boer, et al., "Genomic Reanalysis of a Pan-European Rare-Disease Resource Yields New Diagnoses," *Nature Medicine* 31 (2025): 478.

38. J. M. Lumsden and T. K. Urv, "The Rare Diseases Clinical Research Network: A Model for Clinical Trial Readiness," *Therapeutic Advances in Rare Disease* 4 (2023): 72.

39. C. Turnbull, R. H. Scott, E. Thomas, et al., "The 100 000 Genomes Project: Bringing Whole Genome Sequencing to the NHS," *BMJ* 361 (2018): 687.

40. D. Smedley, K. R. Smith, A. Martin, et al., "100,000 Genomes Pilot on Rare-Disease Diagnosis in Health Care – Preliminary Report," *New England Journal of Medicine* 385, no. 20 (2021): 1868–1880, https://doi.org/10.1056/NEJMoa2035790.

41. J. W. März, M. Baumgartner, N. Blau, and N. Biller-Andorno, "Digital Twins for Children With Rare Diseases: An Exploration of the Legal and Ethical Issues," *Ethics and Information Technology* 27 (2025): 44.

42. V. Rahimzadeh, C. Schickhardt, B. M. Knoppers, et al., "Key Implications of Data Sharing in Pediatric Genomics," *JAMA Pediatrics* 172 (2018): 476.

43. The Global Alliance for Genomics and Health, "Our Products," (2026), https://www.ga4gh.org/our-products/.

44. K. B. Howell, S. M. White, A. McTague, et al., "International Precision Child Health Partnership (IPCHiP): An Initiative to Accelerate Discovery and Improve Outcomes in Rare Pediatric Disease," *NPJ Genomic Medicine* 10 (2025): 13.