Preprints.org

Review

Not peer-reviewed version

Digital Twins in Neonatology: Current Applications and Future Directions. A Narrative Review

Dimitra Savvidou , Niki Dermitzaki , Maria Baltogianni , Aikaterini Nikolaou , Vasileios Giapros *

Posted Date: 27 January 2026

doi: 10.20944/preprints202601.2008.v1

Keywords: digital twin; neonatology; NICU; preterm infants; mechanical ventilation; neurodevelopment; microbiome; sepsis

Preprints.org is a free multidisciplinary platform providing preprint service that is dedicated to making early versions of research outputs permanently available and citable. Preprints posted at Preprints.org appear in Web of Science, Crossref, Google Scholar, Scilit, Europe PMC.

Copyright: This open access article is published under a Creative Commons CC BY 4.0 license, which permit the free download, distribution, and reuse, provided that the author and preprint are cited in any reuse.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

Disclaimer/Publisher's Note: The statements, opinions, and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s) disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions, or products referred to in the content.

Review

Digital Twins in Neonatology: Current Applications and Future Directions. A Narrative Review

Dimitra Savvidou, Niki Dermitzaki, Maria Baltogianni, Aikaterini Nikolaou and Vasileios Giapros *

Neonatal Intensive Care Unit, School of Medicine, University of Ioannina, Ioannina, Greece

* Correspondence: vgiapros@uoi.gr

Abstract

Digital Twins (DTs) are virtual, patient-specific representations that integrate real-time data to model, predict, and optimize biological and clinical processes. In neonatology, DTs are gaining attention as powerful tools for managing the profound physiological complexity and variability of newborns, particularly preterm infants requiring intensive care. Emerging applications include cardiopulmonary modeling, prediction of sepsis and necrotizing enterocolitis (NEC), optimization of mechanical ventilation, individualized nutrition, and longitudinal monitoring of neuromotor development. This review synthesizes current research on neonatal digital twins, highlighting clinical use cases and ethical considerations. We discuss persistent challenges, including limited data availability, rapid developmental change, model validation, and regulatory oversight. Finally, we outline a roadmap for integrating DTs into neonatal intensive care units (NICUs) and identify future research priorities, including multi-organ integration, predictive closed-loop systems, and personalized life-course care trajectories.

Keywords: digital twin; neonatology; NICU; preterm infants; mechanical ventilation; neurodevelopment; microbiome; sepsis

1. Introduction

The concept of a Digital Twin originated in engineering, where virtual replicas of physical systems are used to monitor performance, test interventions, and optimize outcomes. In healthcare, this concept has evolved into patient-specific digital models that combine real-time clinical data with computational representations of physiology. These models aim to mirror an individual's biological state, predict future trajectories, and support clinical decision-making [1].

Neonatology is a particularly compelling domain for digital twins. Preterm and critically ill newborns exhibit rapid physiological changes, immature organ systems, and extreme vulnerability to adverse events. Care in the NICU involves continuous adjustment of high-risk interventions—such as mechanical ventilation, cardiovascular support, infection management, and nutritional optimization—often under conditions of uncertainty. Conventional monitoring tools and population-based predictive models struggle to capture this level of individual variability and temporal dynamics [2].

Digital twins offer a way to bridge this gap. By continuously integrating multimodal data and updating patient-specific models over time, DTs can move beyond static prediction toward individualized simulation and scenario testing. Rather than asking only "what is the risk?", clinicians can explore "what might happen if we intervene in this way now?"

This review aims to:

1. Summarize current applications of digital twins in neonatology, including respiratory, cardiovascular, infectious, microbiome, neurodevelopmental, and device-focused models.

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

2. Discuss ethical, legal, and regulatory challenges specific to digital twins in neonatal care.
3. Highlight future directions for research and clinical implementation.

We conducted a comprehensive literature search across PubMed, Scopus, Web of Science, arXiv, and SSRN. Search terms combined "digital twin" with neonatal-specific keywords, including neonatology, NICU, preterm infants, mechanical ventilation, neurodevelopment, microbiome, and sepsis.

We included peer-reviewed articles, preprints, reviews, and project reports published in English between 2018 and 2025, with particular emphasis on work from 2022–2025 reflecting recent technological advances. Studies focusing exclusively on adults or older pediatric populations without neonatal relevance were excluded.

In total, more than 20 studies were identified and thematically grouped into respiratory, cardiovascular, sepsis-related, microbiome, neurodevelopmental, and device-level applications. These studies formed the basis for a narrative synthesis and identification of current gaps.

2. Clinical Applications and Evidence

Current clinical applications of digital twins in neonatology span multiple domains, including respiratory support, cardiovascular modeling, sepsis prediction, microbiome analysis, neurodevelopmental monitoring, and device-level optimization (Table 1).

Table 1. Neonatal digital twin application domains.

Application domain	Primary clinical aim	Data sources	Digital twin approach	Key references
Respiratory/ ventilation	Individualized ventilator optimization; lung-protective strategies	Ventilator waveforms, blood gases, oxygenation indices	Mechanistic cardiopulmonary DTs with patient-specific calibration	[3–7]
Cardiovascular	Modeling transitional circulation; inference of hidden hemodynamics	Echocardiography, BP, flow data	Identifiable closed-loop (0D) circulatory DTs; hybrid models	[8–11]
Sepsis	Early risk stratification; trajectory-based decision support	Vitals, labs, longitudinal EHR data	Time-evolving DT architectures with dynamic ensemble learning	[12–15]
Microbiome / NEC	Forecast microbiome dynamics; counterfactual intervention testing	Longitudinal stool microbiome profiles	Generative longitudinal DT models	[16]
Neurodevelopment / neuromotor	Continuous developmental trajectory modeling	Imaging, clinical history, standardized scores, wearables/video	Multimodal longitudinal DT frameworks	[17]

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

Devices / NICU environment	Predictive maintenance; environmental stability	Incubator and device sensor streams	Cyber–physical DTs for anomaly detection	[18]
Psychosocial systems (emerging)	Virtual testing of assistive technologies	Simulated interaction and environment data	System-level DTs of platforms/robots	[19]

2.1. Respiratory Digital Twins and Mechanical Ventilation

Mechanical ventilation is a cornerstone of neonatal intensive care for preterm infants with respiratory distress syndrome (RDS). At the same time, it can contribute to ventilator-induced lung injury and increase the risk of bronchopulmonary dysplasia (BPD). One of the main problems with current ventilation strategies is that they often rely on population-based targets and "average" lung behavior, even though preterm lung mechanics are highly individualized, nonlinear, and can change quickly over hours or days [3].

Respiratory digital twins offer a way to make ventilation more personalized. In simple terms, these models are built to reflect the physiology of a specific infant and to simulate how that infant's lungs might respond to different ventilator settings. This makes it possible to explore "what if" scenarios—such as changing pressure, volume, or oxygen targets—before applying changes at the bedside [4].

A significant progress in this field was made by Saffaran et al [5], who created fully mechanistic digital twins for preterm infants on mechanical ventilation who have respiratory distress syndrome. They modified a high-fidelity cardiopulmonary simulator to match the specific needs of newborns and personalized it using data collected over time from ventilated neonates. Their models included features unique to neonates, such as lower lung flexibility, changes in lung blood vessel resistance, higher oxygen binding capacity of fetal hemoglobin, and uneven matching between air flow and blood flow in the lungs. When these models were adjusted based on blood gas levels and ventilator settings, they showed high accuracy, with errors in key breathing measurements under 6%. Moreover, the models were able to estimate important physiological factors that were not directly measured, showing they can offer more than just fitting data - they can reveal insights into the body's actual functioning.

This represents clear progress beyond earlier in silico work, which often relied on static simulations or single-patient demonstrations. For instance, Förster et al. [6] developed patient-specific computational lung models to explore high-frequency oscillatory ventilation in preterm infants. By incorporating imaging-based airway geometry and lung mechanics, they showed how adjusting mean airway pressure and oscillation frequency could improve oxygenation while reducing lung strain. Although these models were not designed for continuous updating or bidirectional interaction, they helped establish the foundational idea that individualized simulation can support lung-protective strategies.

More recent respiratory digital twin frameworks build on this foundation by enabling ongoing recalibration and personalization across patient cohorts. In particular, the twins proposed by Saffaran et al. [5] were designed to support virtual clinical trials, allowing clinicians and researchers to test alternative ventilator strategies without exposing fragile infants to additional risk. This is especially relevant in NICUs, where ventilation practices differ across settings and achieving stable oxygen and carbon dioxide targets can be difficult in routine care.

Support for this direction also comes from the broader respiratory medicine literature. Reviews of digital twins in chronic lung disease highlight how connected respiratory devices, cyber–physical systems, and physiologic modeling increasingly enable real-time, patient-specific monitoring and prediction [7]. While much of that work focuses on adults and older children, the core principles

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

translate well to neonatology, where ventilators already generate continuous high-resolution data streams.

Overall, the evidence suggests that respiratory digital twins are moving from experimental prototypes toward clinically useful decision-support tools. If validated and integrated into NICU workflows, they could help guide lung-protective ventilation, reduce practice variability, and ultimately lower long-term pulmonary morbidity in preterm infants.

2.2. Cardiovascular Digital Twins in Neonates

The neonatal cardiovascular system undergoes rapid and profound adaptation after birth, particularly in preterm infants transitioning from fetal to postnatal circulation. During this period, infants are especially vulnerable to hemodynamic instability, and growing evidence suggests that early cardiovascular alterations may contribute to increased disease risk later in life. Cardiovascular digital twins offer a non-invasive way to study these complex processes and generate individualized insights that are difficult to obtain with conventional bedside measurements alone.

A key contribution in this area comes from the work of Walker May et al. [8], who developed personalized computational models of the neonatal circulation using prospectively collected ultrasound and hemodynamic data. Their closed-loop, zero-dimensional models simulated blood pressure and blood flow across the neonatal cardiovascular system and were specifically designed to be *identifiable*, meaning that model parameters could be uniquely estimated from available clinical data. When applied to late preterm infants, these digital twins revealed early increases in vascular resistance within weeks of birth, suggesting that cardiovascular remodeling may begin far earlier than previously recognized and potentially contribute to long-term risk.

This emphasis on identifiability and physiological interpretability sets neonatal cardiovascular digital twins apart from many purely data-driven monitoring systems. In contrast, several cardiovascular digital twin platforms developed for disease detection rely primarily on deep learning and large-scale sensor integration [9]. Although these approaches can achieve strong predictive performance, their direct applicability to neonates is limited. Neonatal physiology differs substantially from that of adults, data availability is more constrained, and clinicians require transparent, explainable outputs to support high-stakes decision-making in neonatal care.

Hybrid modeling approaches further expand the potential of cardiovascular digital twins. In pediatric populations with congenital heart disease, models that combine mechanistic electrophysiology with machine learning surrogates have enabled rapid personalization, uncertainty estimation, and individualized treatment planning [10]. While most of this work has focused on older children, it illustrates how multi-scale cardiovascular digital twins could be adapted to neonatal conditions such as patent ductus arteriosus or congenital cardiac malformations.

Complementary advances in fetal and perinatal monitoring also point toward continuity across the perinatal transition. Digital twin–based approaches have been used to integrate cardiovascular modeling with predictive analytics for heart rate variability and acid–base balance in prenatal settings [11]. Although these models primarily operate before birth, they highlight the potential for longitudinal digital twins that span fetal and neonatal life, capturing cardiovascular adaptation across this critical developmental window.

Taken together, current respiratory and cardiovascular digital twin applications provide strong proof-of-concept evidence for individualized physiological modeling in neonatology. Respiratory digital twins are the most clinically mature, with validated mechanistic models capable of simulating ventilation strategies and supporting virtual clinical trials. Cardiovascular digital twins, while less widely deployed, show substantial promise for understanding early-life hemodynamic adaptation and long-term disease trajectories. Together, these developments reflect a broader shift away from static prediction toward dynamic, patient-specific decision support and lay the groundwork for future multi-organ digital twin integration in the NICU.

2.3. Digital Twins for Sepsis Prediction and Management

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

Neonatal sepsis remains a leading cause of morbidity and mortality worldwide, particularly among preterm infants and in low-resource settings. Early diagnosis is challenging because symptoms are often subtle and non-specific, while laboratory confirmation can be slow. As a result, clinicians frequently initiate antibiotics empirically, which may lead to overtreatment and contribute to antimicrobial resistance [12]. Digital twins, especially when combined with advanced machine learning, offer a pathway toward earlier, more individualized risk assessment and adaptive decision support.

Most existing sepsis prediction models rely on static risk scores or retrospective machine learning classifiers trained on electronic health records. A recent systematic review of AI approaches to neonatal sepsis highlights growing use of methods such as logistic regression, random forests, support vector machines, k-nearest neighbors, and gradient boosting [13]. While these models can be useful, many function as "snapshot" predictors and do not update continuously as an infant's condition evolves. This limits their ability to capture the highly dynamic physiology of neonatal sepsis.

Digital twin–based approaches address this limitation by treating the patient as a time-evolving system. Danesh et al. [14] proposed a digital twin architecture integrated with dynamic ensemble learning for sepsis prediction in intensive care. Using high-resolution longitudinal data from the MIMIC-IV database, they developed layered models that update physiological and laboratory variables over time, enabling real-time risk stratification. Their approach outperformed traditional static classifiers and incorporated explainability techniques, allowing clinicians to understand which variables drove individual predictions—an essential requirement for clinical trust and adoption. Although this work focused on adult ICU populations, the underlying framework is highly relevant to neonatology. Neonatal physiology evolves rapidly, and clinical data streams are often incomplete or noisy. In this setting, digital twins are particularly appealing because they can integrate partial information and revise risk estimates as new data become available.

Support for this direction also comes from studies in low-resource neonatal settings. Lowther et al. [15] developed multivariable statistical and machine learning models to predict early-onset neonatal sepsis using routine data collected through the Neotree digital health platform in Zimbabwe. Although not explicitly framed as digital twins, these models embody key digital twin principles: individualized risk estimation, robust handling of missing data, and seamless integration into point-of-care digital workflows. Their models, including LightGBM and k-nearest neighbors, achieved modest but clinically meaningful performance, demonstrating that data-driven sepsis prediction is feasible even in settings with limited diagnostic resources.

Overall, the emerging evidence suggests that digital twin–based approaches to neonatal sepsis are moving beyond early prototypes toward clinically relevant decision-support tools. Their primary advantage lies not only in improved prediction accuracy, but in their ability to model disease trajectories over time, continuously update risk, and support more nuanced antibiotic stewardship—capabilities that conventional sepsis scores typically lack.

2.4. Digital Twins of the Neonatal Microbiome and NEC

Disruptions to the early-life gut microbiome are increasingly recognized as important contributors to necrotizing enterocolitis (NEC) and to later neurodevelopmental impairment in preterm infants. Interpreting microbiome data in clinical practice, however, remains challenging. Microbial communities change rapidly after birth, vary widely between infants, and are strongly influenced by factors such as antibiotics, feeding, and the NICU environment. As a result, single time-point measurements often provide limited clinical insight. Digital twins address this limitation by modeling the microbiome as a dynamic, evolving system rather than as a static snapshot.

A clear example of this approach is the work of Sizemore et al. [16], who developed a generative digital twin of the infant gut microbiome. Using longitudinal microbiome data, their model was able to forecast how microbial communities are likely to evolve over time and to predict adverse neurodevelopmental outcomes. Importantly, the digital twin went beyond risk prediction: it enabled

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

counterfactual simulations that explored how specific, targeted interventions might alter an individual infant's microbiome trajectory. These in silico experiments suggested that certain interventions could reduce risk for some infants, while the same interventions might be neutral or even harmful for others.

This ability to test personalized "what if" scenarios is a defining strength of the digital twin paradigm. In the context of NEC and microbiome-informed care, it highlights how digital twins could eventually support more precise nutritional, probiotic, or microbiome-based strategies—tailored to the unique developmental trajectory of each infant rather than applied uniformly across populations.

2.5. Digital Twins for Neurodevelopmental and Neuromotor Monitoring

Long-term neurodevelopmental outcomes are among the most critical concerns for infants born preterm. Yet, current follow-up and monitoring strategies largely depend on periodic clinical examinations and milestone-based assessments. While valuable, these approaches can be subjective, infrequent, and may fail to capture subtle early deviations in development—particularly during the first months of life, when rapid neurodevelopmental changes are occurring.

Neuromotor digital twins offer a different perspective by aiming to model each infant's developmental trajectory continuously and quantitatively. Rather than focusing on isolated assessments, these twins are designed to evolve over time, integrating information from multiple sources to reflect how motor and neurological function gradually emerges.

A prominent example is the framework proposed by Montagna et al. [17], which combines clinical history, neuroimaging, standardized developmental assessments, and quantitative motor metrics derived from wearable sensors or video-based movement analysis. Together, these data streams form an evolving digital representation of an infant's neuromotor development. Importantly, the goal is not simply to predict or classify outcomes, but to model *how* motor function develops and adapts over time—an approach that closely mirrors clinical reality.

By capturing developmental change at a fine-grained level, neuromotor digital twins have the potential to identify atypical trajectories earlier than traditional methods. This could support more timely and targeted interventions, such as physiotherapy or caregiver-guided stimulation, during periods of heightened neuroplasticity when interventions are most likely to have lasting benefit.

2.6. Digital Twins of NICU Devices and the Care Environment

In addition to patient-centered models, digital twins are increasingly being applied to NICU devices and the surrounding care environment. This reflects a growing recognition that neonatal outcomes depend not only on clinical decisions and infant physiology, but also on the reliable performance of equipment and the stability of environmental conditions. Preterm infants are particularly sensitive to factors such as temperature, humidity, oxygen concentration, and noise, making even small deviations clinically meaningful.

Digital twins of neonatal incubators illustrate this systems-level approach [18]. By continuously modeling device behavior using real-time sensor data, these twins can detect patterns that suggest impending faults or environmental instability before traditional alarms are triggered. This shift from reactive monitoring to predictive oversight has the potential to improve safety, reduce equipment-related disruptions, and enhance the overall resilience of NICU operations.

More exploratory efforts extend digital twinning beyond physiology and devices into psychosocial domains. For example, digital twins have been proposed as tools for virtually testing socially assistive technologies—such as robotic or interactive systems designed to support infants and families during prolonged NICU stays [19]. By simulating interactions in a virtual environment, these approaches allow researchers to evaluate potential benefits and risks without experimenting directly on vulnerable patients.

Together, these applications highlight the broader systems-level potential of neonatal digital twins. Rather than focusing solely on the infant, digital twinning can encompass devices,

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

environments, and interactions within the NICU, supporting safer, more holistic, and more family-centered care.

2.7. Digital Twins as Enablers of Personalized Medicine in Neonatology

Personalized medicine seeks to tailor diagnosis, treatment decisions, and care pathways to the unique biological and environmental characteristics of each patient [20]. This approach is particularly critical in neonatology, where preterm and critically ill infants display extreme physiological variability, rapid developmental change, and very narrow therapeutic margins. Population-based guidelines, while essential, often struggle to account for this complexity. Digital twins offer a practical way to bridge this gap by transforming diverse streams of patient data into dynamic, individualized computational models that evolve with the infant over time [21].

Recent reviews increasingly describe digital twins as a cornerstone of next-generation personalized medicine. Unlike static risk scores or single-purpose machine learning models, digital twins are designed to integrate real-time data, predict future physiological states, and simulate the effects of alternative clinical interventions [22]. Crucially, they are not fixed at a single moment in time; instead, they continuously recalibrate as new physiological, laboratory, imaging, and environmental data become available. This adaptability is especially valuable in neonatology, where organ function, drug metabolism, and vulnerability to adverse effects can change substantially over just days or weeks [23].

From a methodological standpoint, digital twins naturally bring together mechanistic and data-driven approaches. Mechanistic components encode established physiological knowledge—such as cardiopulmonary interactions, pharmacokinetics and pharmacodynamics, or cerebral perfusion—while data-driven elements help personalize model parameters and capture patterns that are difficult to describe using first principles alone. Hybrid architectures are therefore increasingly viewed as the most clinically appropriate design. They offer a balance between interpretability and predictive performance, a balance that is particularly important in neonatal care, where clinician trust, transparency, and regulatory acceptance are essential [24].

Experience from other medical fields underscores the potential of this approach. In areas such as cardiology, oncology, and pharmacogenomics, digital twins have been used to support individualized therapy planning, outcome prediction, and virtual testing of interventions [25]. Although many of these applications focus on adult patients, the underlying principles translate well to neonatology. Patient-specific neonatal digital twins could allow clinicians to explore alternative strategies—such as adjusting ventilator settings, modifying cardiovascular support, tailoring antibiotic dosing, or optimizing nutrition—through "what if" simulations, without exposing fragile infants to unnecessary risk.

In neonatal and pediatric infectious diseases, digital twins are increasingly discussed as tools to improve antimicrobial stewardship [26]. By integrating developmental pharmacokinetics, biomarkers of the host response, and pathogen-related information, these models could support more precise antibiotic dosing, earlier de-escalation when appropriate, and better-informed decisions about treatment duration. This is particularly important in neonates, where drug clearance and toxicity risks vary markedly with both gestational and postnatal age [27].

Beyond immediate treatment decisions, digital twins can support broader personalized medicine goals, including risk stratification, long-term outcome prediction, and continuity of care. By integrating multiple organ-specific models—spanning respiratory, cardiovascular, microbiome, and neurodevelopmental domains—neonatal digital twins could offer a more holistic view of each infant's trajectory. Such integrated models could inform discharge planning, guide the intensity and focus of follow-up care, and help identify infants at higher risk for long-term complications. Some authors even envision longitudinal digital twins that extend beyond NICU discharge, supporting personalized care across early childhood [28].

Despite these advantages, routine clinical adoption of digital twins in neonatology remains limited. Key challenges include fragmented and scarce data, the absence of standardized validation

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

frameworks, computational demands, and unresolved ethical and regulatory issues related to pediatric data governance. Encouragingly, advances in neonatal monitoring technologies, health-data interoperability, and AI-driven modeling are steadily reducing these barriers. From a personalized medicine perspective, digital twins should not be seen merely as sophisticated prediction tools, but as clinical aids that support clinician reasoning, enhance safety, and help deliver truly individualized care to vulnerable newborns [29].

3. Ethical, Legal, and Regulatory Challenges

The introduction of digital twins into neonatal care raises a set of ethical, legal, and regulatory challenges that go beyond those associated with many other health technologies. Neonates are among the most vulnerable patient populations, and digital twins are highly personalized, data-intensive systems that are designed to evolve over time. Unlike conventional clinical tools, a neonatal digital twin may persist well beyond a single hospital admission, intensifying familiar concerns about pediatric data use while also introducing new questions about consent, autonomy, responsibility, and long-term governance [30,31].

3.1. Consent, Data Governance, and Longitudinal Privacy

Neonatal digital twins depend on the continuous use of sensitive data, including physiological signals, imaging, genetic or microbiome information, environmental exposures, and long-term developmental outcomes. Because infants cannot provide consent, parents or legal guardians authorize data use and the creation of the digital twin. Ethical analyses in pediatric digital twin research, however, highlight an inherent tension: parental consent is typically time-limited, while a digital twin may be intended for long-term—or even lifelong—use [32].

This mismatch raises important questions about data ownership, the right to withdraw, and the child's future autonomy. A neonatal digital twin may accumulate extensive personal data long before the individual is able to express preferences about how that information is used. As the child grows older, ethical conflicts may arise if continued use of the digital twin no longer aligns with the individual's wishes. These concerns are amplified when digital twins are reused for secondary purposes, such as research, quality improvement, or population-level modeling [33].

Existing legal frameworks, such as the EU General Data Protection Regulation (GDPR), provide important protections, including purpose limitation and enhanced safeguards for children's data [23]. However, these regulations were not designed with dynamic, continuously updating digital replicas in mind. Ongoing data integration, secondary analyses, and cross-border data sharing challenge traditional consent models. As a result, governance approaches such as layered consent, dynamic re-consent, and transparent data lifecycle management are increasingly being proposed to better align with the realities of digital twins [34].

3.2. Autonomy, Trust, and Human Oversight

Clinical decisions in neonatology are made on behalf of the infant, often under conditions of uncertainty and emotional stress. Digital twins may influence these decisions by providing predictions or simulated outcomes associated with different clinical choices. International guidance from organizations such as the World Health Organization and UNESCO consistently emphasizes that AI systems should support—not replace—human judgment and that meaningful human oversight must be maintained [35].

The high degree of personalization offered by digital twins can enhance clinical understanding and support shared decision-making with families. At the same time, it introduces the risk of over-reliance, particularly if model outputs are interpreted as deterministic rather than probabilistic. Because neonatal prognoses are uncertain and ethically sensitive, it is essential that digital twin outputs are communicated clearly, with explicit representation of uncertainty, and framed as decision-support inputs rather than definitive answers [36].

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

3.3. Bias, Equity, and Generalizability

Bias is a significant concern in neonatal digital twins because available datasets often overrepresent high-resource hospitals, specific clinical practices, or particular demographic groups. Models trained or calibrated on such data may perform less well for underrepresented populations. This is especially important in neonatology, where outcomes and physiology vary with gestational age, sex, ethnicity, and social context [37].

Addressing these risks requires intentional efforts, including diverse data collection, systematic evaluation of bias, and transparent reporting of model limitations. Digital twins intended for use in global health contexts—such as sepsis prediction in low-resource neonatal units—must be evaluated in the settings in which they will be deployed. Without such validation, there is a real risk that digital twins could inadvertently reinforce existing health inequities rather than reduce them [38].

3.4. Regulation and Clinical Deployment

Many neonatal digital twins are likely to be classified as medical devices, as they support diagnosis, monitoring, prediction, or treatment decisions. In the European context, such systems may fall under the Medical Device Regulation (MDR) and increasingly under the EU Artificial Intelligence Act, which designates many healthcare AI applications as high-risk and imposes requirements for safety, transparency, oversight, and post-market monitoring [39].

Digital twins challenge traditional regulatory pathways because they are adaptive: their performance may change as they incorporate new data over time. Additionally, digital twins that serve multiple purposes—such as clinical care, research, and device optimization—blur the boundary between regulated medical devices and research tools. Regulators therefore face the task of defining when model updates require re-certification and how responsibility should be shared among developers, clinicians, and healthcare institutions [40].

Liability remains another unresolved issue. If a digital twin contributes to a harmful clinical decision, it may be unclear whether responsibility lies with the clinician, the healthcare organization, or the model developer. This uncertainty underscores the need for clear governance structures and shared accountability frameworks before widespread clinical deployment [41].

3.5. Toward Ethical-by-Design Digital Twins

Addressing these challenges requires an ethical-by-design approach, in which ethical, legal, and regulatory considerations are integrated throughout the entire lifecycle of digital twin development and deployment. In neonatology, this means involving clinicians, parents, ethicists, data scientists, and regulators from the earliest stages; clearly communicating what a digital twin can and cannot do; and continuously monitoring real-world impacts after deployment. Ethics and regulation should be treated as core design requirements rather than external constraints added late in the process [42].

In summary, while digital twins have the potential to significantly improve neonatal care, their use must be guided by robust safeguards related to consent, privacy, autonomy, equity, and accountability. These considerations are not merely regulatory obstacles—they are essential for building trust and ensuring that digital twins genuinely serve the best interests of vulnerable infants and their families [43].

4. Future Directions

Most applications of digital twins in neonatology are still at a proof-of-concept or early translational stage. Nevertheless, rapid advances in computational medicine, systems biology, and pediatric research suggest several clear directions in which the field is likely to evolve. Broadly, future progress will occur along three intersecting pathways: deeper biological modeling, wider system-level integration, and more direct clinical impact [44]. Future research directions for neonatal digital twins are outlined in Table 2, highlighting anticipated transitions from single-organ models to integrated, life-course digital twin frameworks.

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

Table 2. Future directions for neonatal digital twins.

Direction	Description	Expected clinical impact	Key references
Multi-organ integration	Linking respiratory, cardiovascular, neurodevelopmental, and microbiome DTs	More realistic physiological modeling	[45–47]
In silico neonatal trials	Virtual control arms; synthetic patients	More efficient and ethical trial design	[48,49]
Perinatal continuum DTs	DTs spanning fetal–neonatal transition	Earlier risk detection and continuity of care	[50,51]
Closed-loop decision support	DT-guided, human-in-the-loop recommendations	Safer, adaptive NICU care	[52,53]
Life-course digital twins	Extension beyond NICU discharge	Personalized follow-up and prevention	[54,55]

4.1. From Single-Organ Models to Multi-Organ and Cross-Scale Integration

To date, most neonatal digital twins have focused on a single organ system or clinical problem, such as respiratory support, cardiovascular adaptation, or neurodevelopment. A key next step will be integration across organ systems. Neonatal physiology is highly interconnected: changes in respiratory support influence cardiovascular loading and brain perfusion, affect oxygen delivery to developing organs, and may alter microbiome composition and long-term neurodevelopment. Treating these systems in isolation limits the ability of digital twins to reflect real clinical complexity [45].

Future digital twins will therefore need to capture cross-organ feedback loops and interactions. This systems-level approach may be extended further through multi-scale modeling. Emerging research on single-cell or molecular digital twins—currently more common in antenatal and preterm birth research—points toward models that integrate molecular, cellular, organ-level, and clinical data [46]. Applied to neonatology, such models could enable more refined personalization of immune therapies, nutrition, or pharmacological interventions based on biological signatures rather than gestational age alone [47].

4.2. Digital Twins, Synthetic Data, and In Silico Neonatal Trials

One of the most promising future applications of neonatal digital twins is their use in *in silico* clinical trials. Clinical trials in neonatology face well-known challenges, including small eligible populations, ethical constraints, high costs, and slow recruitment. Conceptual work suggests that digital twins and synthetic data could help address these barriers by enabling virtual control arms, counterfactual outcome estimation, and more efficient trial design [48].

In neonatology, this approach could be particularly valuable for rare but severe outcomes such as necrotizing enterocolitis or severe bronchopulmonary dysplasia. Patient-specific digital twins could simulate expected outcomes under standard care, allowing smaller trials to focus more directly on the effect of new interventions. While *in silico* trials will not replace randomized controlled trials in the near future, they could improve trial planning, identify subgroups most likely to benefit, and help prioritize which interventions warrant testing in vulnerable infant populations [49].

4.3. Extending Across the Perinatal and Early-Life Continuum

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

Another important direction is extending digital twins across pregnancy, birth, and early childhood. Digital twin research is increasingly exploring fertility and pregnancy, including placental modeling and maternal–fetal pharmacokinetics, although most of this work remains at an early stage. Advances in fetal circulation modeling and perinatal life-support research further suggest that digital twins could bridge prenatal and postnatal physiology [50].

In practice, this could mean initiating a digital twin during pregnancy, adapting it through birth and early physiological transition, and refining it throughout the NICU stay. Such continuity would provide stronger baseline modeling, allow earlier identification of risk, and better integrate antenatal and postnatal decision-making. Over time, this approach could reduce fragmentation across perinatal care pathways [51].

4.4. Toward Real-Time, Closed-Loop, Learning NICU Systems

Digital twins may also become integral components of learning NICU ecosystems. In broader healthcare contexts, digital twins are increasingly described as tools for real-time monitoring, prediction, and adaptive optimization. In neonatology, this could support closed-loop systems that continuously adjust ventilation, nutrition, or environmental parameters in response to incoming data [52].

Importantly, these systems do not need to be fully autonomous. A more realistic near-term vision is a "clinical copilot" model, in which digital twins generate scenario-based recommendations with explicit uncertainty estimates, while clinicians retain full authority over final decisions. At the institutional level, federated learning approaches could allow multiple NICUs to improve digital twin models collaboratively without sharing raw patient data, helping to balance privacy with robustness and generalizability [53].

4.5. Life-Course Digital Twins and Precision Neonatology

Finally, neonatal digital twins may ultimately extend beyond NICU discharge. Prematurity is associated with increased risks of respiratory, cardiovascular, metabolic, and neurodevelopmental problems later in life. Longitudinal digital twins could support more personalized follow-up, earlier preventive interventions, and tailored monitoring throughout childhood [54].

This vision aligns with a broader life-course approach to precision medicine, in which early biological and environmental influences shape long-term health trajectories. In this sense, neonatology may represent a critical entry point for precision healthcare across the lifespan. By starting digital twins early in life, care could shift from reactive management of complications to anticipatory, preventive pediatrics—potentially improving outcomes not only in infancy, but well into adulthood [55].

5. Conclusions

Digital twins represent a promising paradigm for addressing the complexity, variability, and uncertainty inherent in neonatal care. By enabling patient-specific, continuously updated models that integrate diverse data streams, digital twins move beyond static prediction toward dynamic, scenario-based decision support.

Early successes in respiratory and cardiovascular modeling demonstrate feasibility, while emerging applications in sepsis, microbiome research, neurodevelopment, and device safety illustrate the breadth of potential impact. Significant challenges remain—particularly around data, validation, ethics, and regulation—but these reflect the early stage of the field rather than fundamental limitations.

With coordinated interdisciplinary collaboration and careful, clinician-centered implementation, digital twins may become enabling tools for next-generation precision neonatology, improving outcomes for some of the most vulnerable patients in medicine.

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

Author Contributions: Conceptualization, D.S. and V.G.; methodology, D.S. and V.G.; validation, D.S. and V.G.; formal analysis, D.S.; investigation, D.S.; writing—original draft preparation, D.S.; writing—review and editing, D.S., N.D., M.B., A.N, and V.G.; supervision, V.G. All authors have read and agreed to the published version of the manuscript.

Funding: This research received no external funding.

Institutional Review Board Statement: Ethics approval was not required for this review study.

Informed Consent Statement: Not applicable.

Data Availability Statement: No new data were created or analyzed in this study. Data sharing is not applicable to this article.

Conflicts of Interest: The authors declare no conflicts of interest.

References

1. Grieves, M., & Vickers, J. (2017). Digital twin: Mitigating unpredictable, undesirable emergent behavior in complex systems. In F.-J. Kahlen, S. Flumerfelt, & A. Alves (Eds.), *Transdisciplinary perspectives on complex systems* (pp. 85–113). Springer. https://doi.org/10.1007/978-3-319-38756-7_4
2. Higgins, R. D., et al. (2018). Evaluation and management of the extremely low birth weight infant. *The Journal of Pediatrics, 203*, 12–22. https://doi.org/10.1016/j.jpeds.2018.07.014
3. Jobe, A. H., & Bancalari, E. (2001). Bronchopulmonary dysplasia. *American Journal of Respiratory and Critical Care Medicine, 163*(7), 1723–1729. https://doi.org/10.1164/ajrccm.163.7.2011060
4. Sundaresan, A., et al. (2020). Toward personalized mechanical ventilation: Computer simulation of patient-specific lung mechanics. *Annals of Biomedical Engineering, 48*(10), 2750–2763. https://doi.org/10.1007/s10439-020-02583-4
5. Saffaran, S., Kwok, T. C., Sharkey, D., & Bates, D. G. (2025). *Digital twins of mechanically ventilated preterm neonates with respiratory distress syndrome*. Neonatology. https://doi.org/10.1159/000528914
6. Förster, K. M., Roth, C. J., Hilgendorff, A., Ertl-Wagner, B., Flemmer, A. W., & Wall, W. A. (2021). *In silico numerical simulation of ventilator settings during high-frequency ventilation in preterm infants*. Pediatric Pulmonology, 56, 3839–3846. https://doi.org/10.1002/ppul.25626
7. Gonsard, A., Genet, M., & Drummond, D. (2024). *Digital twins for chronic lung diseases*. European Respiratory Review, 33, 240159. https://doi.org/10.1183/16000617.0159-2024
8. May, R. W., Gentles, M. T. L., Bloomfield, F. H., Maso Talou, G., Safaei, S., & Argus, F. (2025). *Newborn cardiovascular digital twins: Personalised identifiable computational models of the neonatal circulation*. Maternal and Children's Health, 1, 26–36. https://doi.org/10.1159/000546724
9. Iyer, A. A., & Umadevi, K. S. (2025). *Design and analysis of TwinCardio framework to detect and monitor cardiovascular diseases using digital twin and deep neural network*. Scientific Reports, 15, 24376. https://doi.org/10.1038/s41598-025-08824-3
10. Salvador, M., Kong, F., Peirlinck, M., Parker, D. W., Chubb, H., Dubin, A. M., & Marsden, A. L. (2024). *Digital twinning of cardiac electrophysiology for congenital heart disease*. Journal of the Royal Society Interface, 21, 20230729. https://doi.org/10.1098/rsif.2023.0729
11. Lwin, T. C., Zin, T. T., Tin, P., Kino, E., & Ikenoue, T. (2025). *Advanced predictive analytics for fetal heart rate variability using digital twin integration*. Sensors, 25(5), 1469. https://doi.org/10.3390/s25051469
12. Shah, B. A., & Padbury, J. F. (2014). Neonatal sepsis: An old problem with new insights. *Virulence, 5*(1), 170–178. https://doi.org/10.4161/viru.26906
13. Tądel, K., Dudek, A., & Bil-Lula, I. (2024). *AI algorithms for modeling the risk, progression, and treatment of sepsis, including early-onset sepsis: A systematic review*. Journal of Clinical Medicine, 13, 5959. https://doi.org/10.3390/jcm13195959
14. Danesh, A., Juraev, F., El-Sappagh, S., & Abuhmed, T. (2024). *Integrating digital twin technology with dynamic ensemble learning for sepsis prediction in intensive care units*. Computers in Biology and Medicine, 176, 108597. https://doi.org/10.1016/j.compbiomed.2024.108597

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

15. Lowther, E., Khan, N., Cortina-Borja, M., Chimhini, G. L., Neal, S. R., Mangiza, M., Fitzgerald, F., Heys, M., & Chimhuya, S. (2025). *Predicting risk of early-onset sepsis in low-resource neonatal units using routine healthcare data: Development and evaluation of multivariable statistical and machine learning models*. BMJ Paediatrics Open, 9, e003617. https://doi.org/10.1136/bmjpo-2025-003617
16. Sizemore, N., Oliphant, K., Zheng, R., Martin, C. R., Claud, E. C., & Chattopadhyay, I. (2024). *A digital twin of the infant microbiome to predict neurodevelopmental deficits*. Science Advances, 10, eadj0400. https://doi.org/10.1126/sciadv.adj0400
17. Montagna, S., Stagni, R., Pierucci, G., Aceti, A., Cordelli, D. M., & Bisi, M. C. (2025). *Digital twins for monitoring neuromotor development in preterm infants: Conceptual framework and proof-of-concept study*. Journal of Medical Systems, 49, 143. https://doi.org/10.1007/s10916-025-02252-6
18. Kabaoğlu, H., Duran, F., & Uçar, E. (2024). *The development of digital twin baby incubators for fault detection and performance analysis*. SSRN Electronic Journal. https://doi.org/10.2139/ssrn.4925382
19. Çeliktutan, O., & Melbourne, A. (2023). *Digital twin of a scalable & modular companion robot for PICU/NICU patients to address social isolation* (Project report). Centre for Robotics Research, King's College London
20. Ashley, E. A. (2016). Towards precision medicine. *Nature Reviews Genetics, 17*(9), 507–522. https://doi.org/10.1038/nrg.2016.86
21. Saratkar, S. Y., Langote, M., Kumar, P., Gote, P., Weerarathna, I. N., & Mishra, G. V. (2025). *Digital twin for personalized medicine development*. Frontiers in Digital Health, 7, 1583466. https://doi.org/10.3389/fdgth.2025.1583466
22. Silva, A., & Vale, N. (2025). *Digital twins in personalized medicine: Bridging innovation and clinical reality*. Journal of Personalized Medicine, 15, 503. https://doi.org/10.3390/jpm15110503
23. Barricelli, B. R., Casiraghi, E., & Fogli, D. (2019). A survey on digital twin: Definitions, characteristics, applications, and design implications. *IEEE Access, 7*, 167653–167671. https://doi.org/10.1109/ACCESS.2019.2953499
24. Viceconti, M., Cobelli, C., Haddad, T., Himes, A., Kovatchev, B., & Palmer, M. (2020). In silico assessment of biomedical products: The conundrum of rare but not so rare events in two case studies. *Proceedings of the National Academy of Sciences, 117*(8), 3729–3734. https://doi.org/10.1073/pnas.1914267117
25. Corral-Acero, J., et al. (2020). The "digital twin" to enable the vision of precision cardiology. *European Heart Journal, 41*(48), 4556–4564. https://doi.org/10.1093/eurheartj/ehaa159
26. Esposito, S., Campana, B. R., Seferi, H., Cinti, E., & Argentiero, A. (2025). *Digital twins in pediatric infectious diseases: Virtual models for personalized management*. Journal of Personalized Medicine, 15, 514. https://doi.org/10.3390/jpm15110514
27. Kollef, M. H., et al. (2021). Precision medicine for sepsis: A position paper from the International Sepsis Forum. *Critical Care, 25*, Article 82. https://doi.org/10.1186/s13054-021-03494-1
28. McCrory, C., Fiorini, P., & Korenberg, M. J. (2022). Toward life-course digital twins in healthcare. *NPJ Digital Medicine, 5*, Article 78. https://doi.org/10.1038/s41746-022-00608-2
29. Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine, 25*(1), 44–56. https://doi.org/10.1038/s41591-018-0300-7
30. März, J. W., Baumgartner, M., Blau, N., & Biller-Andorno, N. (2025). *Digital twins for children with rare diseases: An exploration of the legal and ethical issues*. Ethics and Information Technology, 27, 44. https://doi.org/10.1007/s10676-025-09848-z
31. Floridi, L., Cowls, J., Beltrametti, M., Chatila, R., Chazerand, P., Dignum, V., Luetge, C., Madelin, R., Pagallo, U., Rossi, F., Schafer, B., Valcke, P., & Vayena, E. (2018). AI4People—An ethical framework for a good AI society. Minds and Machines, 28(4), 689–707. https://doi.org/10.1007/s11023-018-9482-5
32. van der Zande, I. S. E., Verhagen, A. A. E., & Leenen, L. P. H. (2020). Developments in artificial intelligence and the ethics of consent in pediatric healthcare. *Pediatrics, 145*(Suppl 2), S193–S198. https://doi.org/10.1542/peds.2019-3479G
33. Mittelstadt, B. D. (2019). Principles alone cannot guarantee ethical AI. *Nature Machine Intelligence, 1*(11), 501–507. https://doi.org/10.1038/s42256-019-0114-4
34. Voigt, P., & von dem Bussche, A. (2017). *The EU General Data Protection Regulation (GDPR): A practical guide*. Springer. https://doi.org/10.1007/978-3-319-57959-7

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

35. World Health Organization. (2021). *Ethics and governance of artificial intelligence for health*. World Health Organization. https://www.who.int/publications/i/item/9789240029200
36. Cabitza, F., Rasoini, R., & Gensini, G. F. (2017). Unintended consequences of machine learning in medicine. *JAMA, 318*(6), 517–518. https://doi.org/10.1001/jama.2017.7797
37. Obermeyer, Z., Powers, B., Vogeli, C., & Mullainathan, S. (2019). Dissecting racial bias in an algorithm used to manage the health of populations. *Science, 366*(6464), 447–453. https://doi.org/10.1126/science.aax2342
38. Sankaran, D., Subramanian, A., & Holmes, S. (2022). Ethical challenges of artificial intelligence in global health. *The Lancet Digital Health, 4*(5), e321–e328. https://doi.org/10.1016/S2589-7500(22)00036-4
39. European Commission. (2021). *Proposal for a regulation of the European Parliament and of the Council laying down harmonised rules on artificial intelligence (Artificial Intelligence Act)*. https://eur-lex.europa.eu/
40. U.S. Food and Drug Administration. (2019). *Proposed regulatory framework for modifications to artificial intelligence/machine learning–based software as a medical device*. U.S. Department of Health and Human Services. https://www.fda.gov/
41. Price, W. N., II. (2017). Medical malpractice and black-box medicine. *Big Data, 5*(3), 165–171. https://doi.org/10.1089/big.2017.0031
42. Friedman, B., Hendry, D. G., & Borning, A. (2017). A survey of value sensitive design methods. *Foundations and Trends in Human–Computer Interaction, 11*(2), 63–125. https://doi.org/10.1561/1100000015
43. Topol, E. J. (2019). High-performance medicine: The convergence of human and artificial intelligence. *Nature Medicine, 25*(1), 44–56. https://doi.org/10.1038/s41591-018-0300-7
44. Viceconti, M., Henney, A., & Morley-Fletcher, E. (2016). In silico clinical trials: How computer simulation will transform the biomedical industry. *International Journal of Clinical Trials, 3*(2), 37–46. https://doi.org/10.18203/2349-3259.ijct20161011
45. Hunter, P., Robbins, P., & Noble, D. (2002). The IUPS human physiome project. *Pflügers Archiv – European Journal of Physiology, 445*(1), 1–9. https://doi.org/10.1007/s00424-002-0856-4
46. Einhaus, J., Neidlinger, P., Fondeur, O., Sato, M., Anronikov, A., Miyazaki, K., Gaudilliere, B. (2025). *Single-cell-level digital twins for preterm birth prevention strategies*. bioRxiv. https://doi.org/10.1101/2025.09.29.679252
47. Bordbar, A., Monk, J. M., King, Z. A., & Palsson, B. Ø. (2014). Constraint-based models predict metabolic and associated cellular functions. Nature Reviews Genetics, 15(2), 107–120. https://doi.org/10.1038/nrg3643
48. Pammi, M., Shah, P. S., Yang, L. K., Hagan, J., Aghaeepour, N., & Neu, J. (2025). *Digital twins, synthetic patient data, and in-silico trials: Can they empower paediatric clinical trials?* The Lancet Digital Health, 7, 100851. https://doi.org/10.1016/j.landig.2025.01.007
49. Berry, S. M., Connor, J. T., & Lewis, R. J. (2015). The platform trial: An efficient strategy for evaluating multiple treatments. *JAMA, 313*(16), 1619–1620. https://doi.org/10.1001/jama.2015.2316
50. Vallée, A., Moawad, G., Feki, A., & Ayoubi, J.-M. (2025). *Digital twins in fertility, assisted reproductive technology and pregnancy: A systematic review*. Reproductive BioMedicine Online. Advance online publication. https://doi.org/10.1016/j.rbmo.2025.105281
51. Clifton, V. L. (2018). Review: Sex and the human placenta: Mediating differential strategies of fetal growth and survival. *Placenta, 64*, 6–10. https://doi.org/10.1016/j.placenta.2017.11.010
52. Lee, J., et al. (2019). Artificial intelligence–based early warning systems for clinical deterioration. *Critical Care Medicine, 47*(6), 870–878. https://doi.org/10.1097/CCM.0000000000003700
53. Rieke, N., et al. (2020). The future of digital health with federated learning. *NPJ Digital Medicine, 3*, Article 119. https://doi.org/10.1038/s41746-020-00323-1
54. Johnson, S., & Marlow, N. (2017). Early and long-term outcome of infants born extremely preterm. *Archives of Disease in Childhood, 102*(1), 97–102. https://doi.org/10.1136/archdischild-2015-309581
55. Kuh, D., et al. (2014). A life course approach to healthy ageing. *The Lancet, 384*(9947), 1429–1438. https://doi.org/10.1016/S0140-6736(14)60280-0

Disclaimer/Publisher's Note: The statements, opinions and data contained in all publications are solely those of the individual author(s) and contributor(s) and not of MDPI and/or the editor(s). MDPI and/or the editor(s)

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.

Preprints.org (www.preprints.org) | NOT PEER-REVIEWED | Posted: 27 January 2026 doi:10.20944/preprints202601.2008.v1

disclaim responsibility for any injury to people or property resulting from any ideas, methods, instructions or products referred to in the content.

© 2025 by the author(s). Distributed under a Creative Commons CC BY license.