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State-of-the-Art

Digital twins for cardiopulmonary medicine: the case for pulmonary arterial hypertension

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Abstract

The management of pulmonary arterial hypertension (PAH), like so many diseases, currently relies on episodic data from clinic visits, which offers limited insight into a patient's disease trajectory and dynamic clinical decisions. Patient digital twins present a technological solution that combines hospital and community data into a single dynamic and predictive virtual representation of the patient. Digital twins operationalize real-world observational inference at the individual level, functioning as a complementary decision-support tool alongside trial evidence. This review introduces the concept of a patient digital twin and provides a roadmap for the development, evaluation, and potential implementation of a patient digital twin for PAH. The resulting twin has the potential to change PAH care pathways, shifting PAH care from reactive to proactive management.

Keywords digital twin, pulmonary arterial hypertension, machine learning, personalized medicine

Use of technology to capture health information

Clinicians typically make decisions based on episodic data from clinic visits, with limited insight into a patient's disease trajectory. These decisions are informed by studies of trial populations that rarely match an individual. There is growing interest in capturing ecologically valid, community-acquired data from remote monitoring technologies (eg, wearable devices, implanted sensors, connected sensors, and patient-reported outcomes) to inform and personalize care.[1-5] These data, which can encompass everything from physiological (eg, heart rate variability and blood pressure), functional (eg, movement and sleep patterns), to patient-reported outcomes, add to the corpus of knowledge that clinicians need to synthesize and act on but also offer the potential to revolutionize how we detect and manage disease.

Combining community-acquired sensor data with hospital measurements enables a shift from episodic to high-frequency or continuous evaluation. It can reduce the reliance on interval face-to-face consultations and reduce the travel burden for patients. Furthermore, it offers the potential to individualize treatment decisions and prioritize services by targeting resources to patients with the greatest need and potential benefit.[6,7] Whereas traditional healthcare delivery relies on standardized protocols applied broadly across patient populations, a data-based care approach enables personalization and predictive care at population scale.

The key challenge to delivering this vision of data-driven care that tracks a patient's trajectory is the integration and continuous analysis of vast streams of heterogeneous data. Digital twins offer a technological solution. Patient digital twins can combine disparate patient data sets in a virtual representation of the patient.[8] The twin provides a continuously updated dashboard accessible to doctors and patients (Figure 1)[9] that can be updated as patient data become available and may be used to inform treatment decisions.[10-13] This allows the patient trajectory to be mapped, simulations of different scenarios to guide procedures, forecasts to facilitate therapy selection, and insights to inform new therapies.[14-21]

Patient digital twins

Digital twins may be broadly categorized into knowledge-based (mechanistic), data-based representations,[22] and a combination

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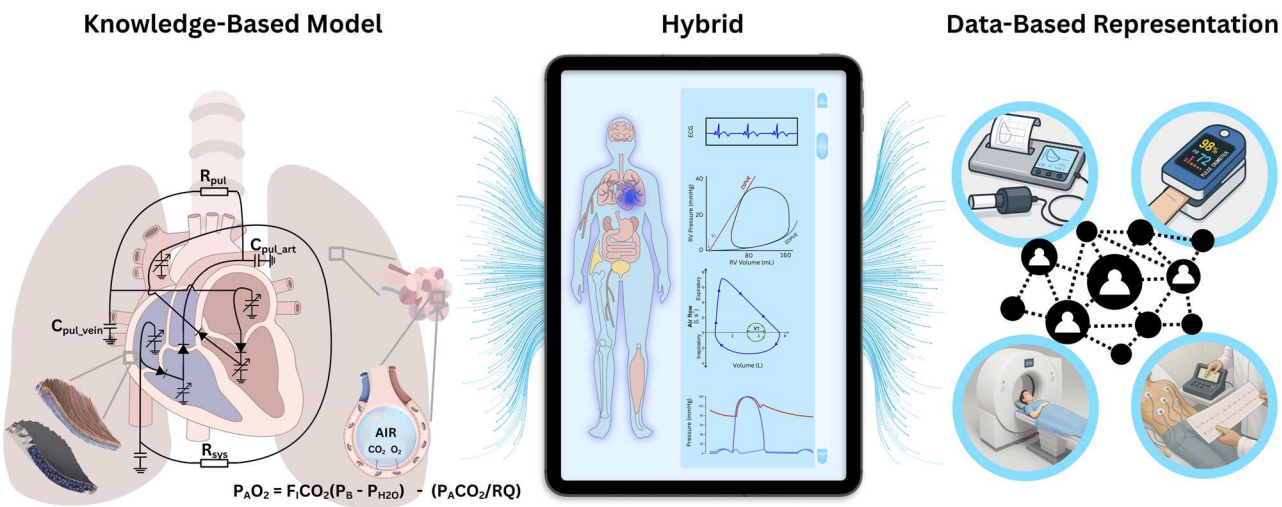

Figure 1 Comparison of knowledge models and data-based representations: Knowledge-based models (left) use physiological principles and equations (eg, alveolar gas equation) for mechanistic insights. Data-based representations (right) leverage ML on diverse data (clinical, wearable, imaging) to find patterns. An integrated digital twin (Centre) ideally combines both for robust, personalized patient models.

of both (Figure 1). Knowledge-based models encode established physical and physiological principles, ensuring predictions adhere to known biological constraints, for example mathematical models of blood flow or mass action models of pharmacokinetics. Conversely, data-based models are developed from observed data, enabling them to capture patterns and relationships that may not yet be well-understood mechanistically, particularly in complex outcomes such as exercise tolerance or quality of life. Within this data-based category, statistical or machine learning (ML) models can be developed to operate on these data for forecasting and scenario testing.[16,23]

In most healthcare applications, a hybrid digital twin is likely to be required, integrating both knowledge and data-based approaches. This combination allows for the representation of both the well-understood and the less defined or poorly characterized elements of the system of interest (Figure 1).[11,12,24-26] For instance, even a predominantly knowledge-based model may require certain parameters to be estimated from observed data, highlighting the need to combine approaches in real-world medical applications.

Knowledge-based techniques

This approach relies on integrating prior knowledge from physics, biology, anatomy, genetics, and physiology into mathematical models. These models provide a coherent framework for combining diverse sources of patient information, ranging from imaging and physiological signals to laboratory data and genomic profiles. By incorporating established mechanistic relationships, such models can be used to infer unmeasured properties, estimate functional parameters, and simulate how changes at one level of the system, for example, changes in cell function, might affect outcomes at another, for example, whole heart physiology. This physics- and physiology-based approach forms the foundation for constructing interpretable and personalized digital representations of a patient, which can then be tailored to specific conditions in later stages of model development.

Data-based techniques

As an alternative to knowledge-based methods, we can build a data-based model of the patient's condition. This requires the patient's condition to be represented by expert-selected or learned features. To model the heart specifically, expert-selected features could include left ventricle volume, myocardial mass, QRS duration, QT interval, and diastolic and systolic pressure. In contrast to using knowledge-based techniques, learned features may involve statistical or ML approaches to create a compact representation of an output of the patient's condition. These learned features become a compressed code that describes the state of the patient at a particular time.

In the case of an abundance of relevant data, the data-based approach can be very effective, but the incorporation of even a limited understanding of the physiology or pathology can improve predictions.[27] This has been demonstrated in complex biological contexts where cellular-level data and dynamic regulatory networks are used to prioritize disease drivers and therapeutic targets.[28] In contrast, in the case of limited data and deeper understanding of the underlying system, a knowledge-based approach may be more appropriate. The two approaches may be applied synergistically, integrating data within a physics-based model built from expert or learned features to create a hybrid digital representation of each patient.[16,26,29,30]

Technical barriers to realizing the patient digital twin

Significant technical challenges need to be addressed to realize a patient digital twin.[11]

Data availability

Patient-specific data collection and use is constrained by ethical, logistical, and practical considerations.[18] Repeated sampling to reduce measurement noise, or other statistical design

considerations is not always acceptable, particularly when this involves radiation or invasive measurements.[31]

Unstructured data

Patient digital twins must be built dynamically from diverse, incomplete, and often unstructured clinical data. For example, imaging, outputs from a variety of medical devices, genomic information, and sporadic medical assessments collected based on clinical need rather than predefined schedules. To ensure robust processes, patient digital twin workflows need to manage missing data, inherently noisy signals, and integrate diverse data sources at intermittent periods.

Providing continuous updates

The statistical process of tuning a patient-specific model, based on static data, to receive continuously streamed patient data is expensive, both in terms of computational resources and often labor-intensive steps.[32-34] This can be further complicated by the need for robust probabilistic tuning methods to account for inherent uncertainties.

Scale up

Delivering digital twins at scale requires a robust, rapid, secure, and efficient process to build, run, and host the twins. Even a rare disease presents a scalability challenge requiring automation of the twin creation and updating process to ensure a precise, rapid, tested, and verified development of a deployable patient digital twin.

Privacy and security

Ensuring patient privacy is essential for digital twin deployment, particularly as models integrate clinical and real-time sensor-derived data. Privacy-preserving approaches, such as federated learning, encrypted computation, and trusted research environments,[35] enable multi-center collaboration and continual learning, while maintaining data confidentiality and regulatory compliance.

Economics of digital twins

Digital twins may require extensive computational investment. However, these costs are modest compared with the high lifelong clinical cost of some conditions, such as pulmonary arterial hypertension (PAH), dominated by hospitalization and advanced therapies. Even small reductions in unplanned admissions or optimization of therapy could generate net cost savings. Moreover, costs can be further reduced by leveraging existing registries[36] to reduce new data-acquisition requirements, and through the use of pre-computed template twins and improved priors for calibration that accelerate personalization. Falling compute costs, surrogate modeling, and reuse of trained models further reduce expense, making digital twins economically favorable in chronic, high-burden conditions.

The case for digital twins for PAH

PAH is a chronic, high-burden condition, characterized by increased pulmonary arterial pressure (PAP) due to narrowing of pre-capillary arterioles which places an increased workload on the right ventricle. It is a clinical diagnosis based on criteria that distinguish PAH patients from other presentations of pulmonary hypertension, such as those with predominant heart or lung disease and patients with chronic thromboembolism. Nonetheless, PAH comprises a heterogeneous group of conditions, subclassified as idiopathic, heritable, drug-induced, and PAH associated with other medical conditions such as connective tissue diseases and congenital lung disease. The risk of death increases as mean PAP rises above 15 mmHg and resistance to blood flow through the lungs rises above 2 Wood Units (WU)[37]; a mean PAP > 20 mmHg and PVR > 2 WU with a pulmonary capillary wedge pressure ≤ 15 mmHg is now the accepted definition of PAH.[38] Right heart function is a key contributing factor in survival of patients with PAH.[39,40] Following diagnosis, 5-year survival is poor, ranging from 23% to 69% across different presentations, even in the most experienced treatment centers.[41]

Recent years have seen significant therapeutic advances. Currently, 4 classes of drugs have been approved that improve function and wellbeing in patients with PAH. However, optimal drug selection and dosing remain a challenge. Moreover, management decisions are based on the patient's current state, often recorded in a clinical setting, and use multiple risk assessment tools, including those recommended by the ESC guidelines, to estimate their expected disease or therapy response trajectory.[38,42]

Specifically, patients are assigned a risk category (high, high-intermediate, low-intermediate, low) according to assessments of 6-minute walk distance, physician-assessed World Health Organization (WHO) functional class and plasma levels of N-terminal pro-brain natriuretic peptide (NT-proBNP) or BNP[38,42] on clinic visits, supplemented during clinical reviews by imaging techniques, such as echocardiography and cardiac magnetic resonance, which are typically scheduled at guideline recommended and expert option-based intervals (eg, every 3 to 6 months). Clinicians, often in multidisciplinary teams, synthesize this information into a conceptual model of the patient to make critical decisions, informed by discussions with the patient, and based on their collective perspective. The opportunity to integrate high-frequency data collected remotely using implanted sensors to measure PAP and cardiac output, mobile apps to measure patient-reported quality of life and remote field walk tests, and home measurement of NT-proBNP could extend the value of existing risk scores (Figure 2). As such, PAH as an ideal candidate to explore the clinical utility of a digital twin.

An overview of a digital twin for a patient with PAH

A patient digital twin for PAH would be composed of 3 important components. First, is the knowledge, data-based or hybrid representation of the patient condition (the patient condition twin), produced by inputting initial data from the patient into a "nominal" model. The second is the time-evolving patient and clinician "journey" through the healthcare system during which the patient

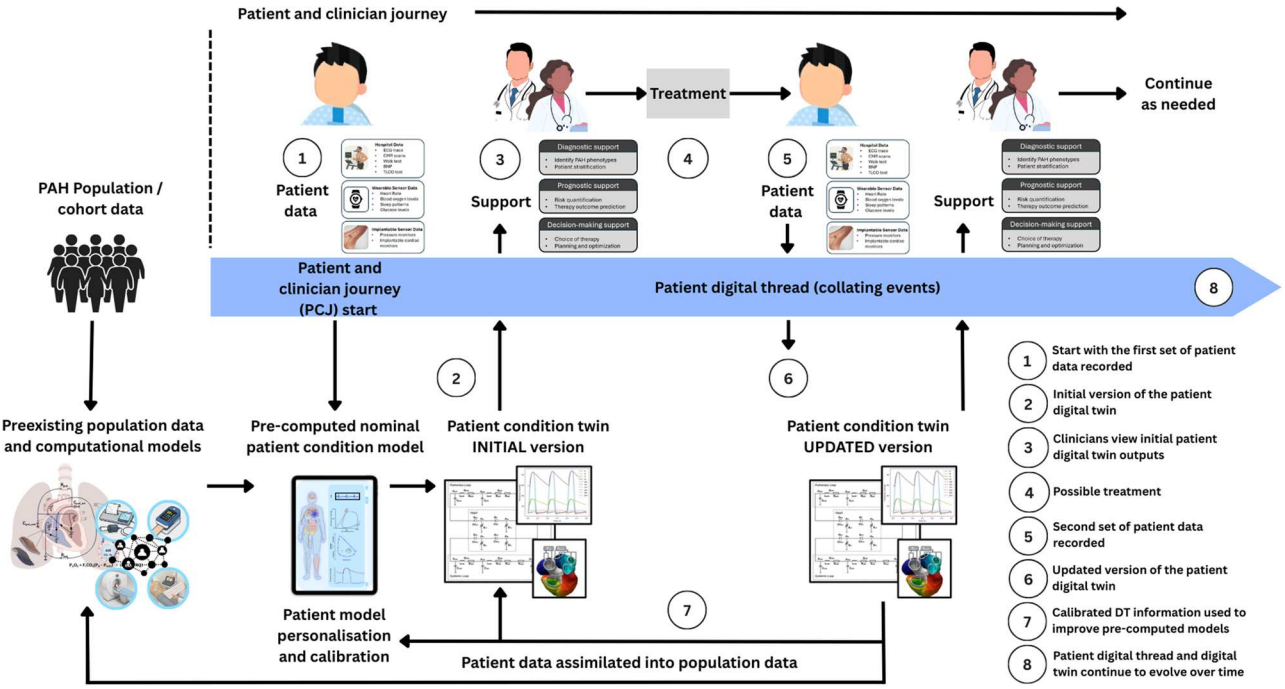

Figure 2 A schematic representation of the patient and clinician journey. Initially, a set of pre-computed "nominal" PAH models (e.g., a set of hybrid knowledge and data-based models by age, gender, etc) is available based on and informed by data from the PAH patient population—left-hand side of the figure. The step-by-step process of working with a new individual patient is described in steps ① through to ⑧. Arrows indicate patient-specific data flows iteratively informing and updating the models as new measurements become available and model outputs for supporting clinical decision-making and treatments.

condition twin is updated. Third is the broader population of patients with PAH, which can be used to provide comparative data. As patient condition twins and patient journeys are created for increasing numbers of patients, there will be a corresponding population of historical patient digital twins.

A schematic presentation of the interplay of these components is given in Figure 2. On the left-hand side of Figure 2 is a set of pre-computed "nominal" PAH models (eg, a set of hybrid knowledge and data-based models for representative age, gender, etc). These are based on and informed by data from the PAH patient population. When a specific individual patient first presents to the healthcare system ① the best available nominal model is selected and personalized to that patient in order to create the first version of the patient condition twin ②. This information can then be used to make initial clinical decisions ③ regarding possible treatments ④. Following this, additional patient data ⑤ are used to update the patient condition twin ⑥. Calibration processes can be built into the patient condition twin throughout the patient and clinician journey and the nominal models regularly updated ⑦. In addition, the data from the patient can be used to create a "digital thread" consisting of all the events during the patient and clinician journey⑧.

The pre-computed nominal patient condition twin is calibrated using mechanistic model parameters (for example, pressure, flow, PaO_2, imaging data) or learning to predict outcomes (for example, a clinical worsening event) from patient data but will often require combining the two approaches. Once a digital representation of the patient is developed, simulation-based and/or data-based forecasts can be performed. Growth and remodeling models, for instance, can be used to predict changes in cardiac anatomy and function in response to alterations in pressure or volume loading.[43,44] If sufficient data are available, then statistical or ML models (eg, neural networks or random forests), operating directly on learned, expert-selected, or model parameters or simulation outputs, can be used to predict patient outcomes.[20] In the case of patients with PAH, some outcomes are intrinsically hard to simulate directly. For example, the 6-minute walk test is an emergent phenomenon, meaning its outcome arises from the coordinated interaction of multiple systems (cardiovascular, pulmonary, muscular, autonomic) along with psychological and environmental factors, rather than being determined by any single physiological variable. Likewise, a clinical worsening event (eg, hospitalization due to PAH or initiation of new PAH-specific therapy) may be due to a combination of compounding factors. In these cases, where there is not a clear system to simulate, predictions could be provided by ML models trained on both clinical and model-based biomarkers. Furthermore, if this approach is successful, the same models could be used to identify model parameters or patient attributes that improve the forecasted 6-minute walk performance or avert hospitalization, and which could be used to inform therapy selection.

Engineering solution and road map to digital twins for PAH

Building a nominal model

Given the known anatomy, physiology, and physics of the underlying cardiovascular system, we propose starting with a knowledge-based model of the cardiopulmonary circulation, based on patients with PAH, augmented with a data-based approach to forecast patient outcomes and map physiological simulations to emergent outputs, such as the 6-minute walk test.

In a simplified model, blood flow through the heart's 4 chambers and the pulmonary and systemic circulation is captured by the cardiovascular component while gas concentrations in air and blood across the lung and tissue compartments are tracked by the pulmonary component. The model can encode cardiovascular system attributes such as electrical signals (heart rate), anatomical features (eg, atrial and ventricular volumes), biomechanical measurements (eg, strain and volume changes), and hemodynamic data (eg, pressure transients) as well as pulmonary system attributes, including ventilation rate and lung volumes. The model predicts the changes in pressure and volume throughout the cardiovascular system based on the material properties (resistance, compliance, and contractility) and the system state (heart rate), and predicts air flow, breathing rate, and gas partial pressures dynamics in the pulmonary system.

Data sources for the twin

Cardiovascular function (right heart catheter, blood pressure, ECG, ejection fraction, blood flows) and anatomy (arterial and heart dimensions) can be measured in hospital visits. This can provide detailed measurements to inform an initial baseline hospital model that can be updated with sensor data or regular lower fidelity measurements. Tracking the cardiopulmonary system over time requires continuous monitoring. This can take the form of wearables (motion, heart rate, ECG), implanted cardiac monitors (heart rate, heart rate variability, rhythm, and physical activity), or implanted PAP sensors (pulmonary artery pressure and cardiac output), increasingly used in research if not clinical practice. Population databases or patient registries will be required to train statistical/ML models to provide estimates, with uncertainty, of unknown attributes. For example, estimating myocardial stiffness based on disease type, age, body mass index, and sex. Similarly, observed physiological responses to therapeutic interventions, as tracked through remote monitoring devices, can be used to facilitate model predictions.[4,45,46]

In PAH, genomic and transcriptomic information provides additional insight into disease susceptibility, vascular remodeling pathways, and treatment response. Pathogenic variants in genes such as BMPR2, SOX17, EIF2AK4, and other pathways, together with somatic and epigenetic changes, influence pulmonary vascular cell proliferation, vascular stiffness, and right ventricular adaptation. Integration of these molecular signatures into digital twins can support the estimation of model parameters, refine mechanistic models of vascular signaling and remodeling, and enable hybrid models linking molecular drivers to hemodynamic and structural disease trajectories.[28,47]

Calibration and prediction

Model personalization relies on a combination of forward and inverse modeling approaches. In forward modeling, parameters are directly extracted from data—such as using MRI or gated CT to estimate anatomical features (eg, right ventricle end diastolic volume). Inverse modeling involves adjusting model parameters so that the simulated outputs match observed data, a process known as calibration.[48] Model calibration strategies vary in complexity and cost. They can include brute-force grid search, local (eg, gradient descent, Newton's method, Levenberg-Marquardt) or global (eg, Bayesian optimization, swarm-based algorithms)[49,50] optimization approaches, or sampling approaches (eg, Markov chain Monte Carlo methods to perform Bayesian inference). Calibration efforts can be focused by first identifying which model parameters are practically estimable from available data.[51,52]

Once initially calibrated, the digital twin can be continuously refined and validated using new data as part of the patient and clinician journey. This can be achieved with Bayesian approaches where our prior uncertainty about parameter values (represented by a statistical distribution) is updated with data to generate new parameter estimates (ie, a posterior distribution). By representing model parameters by distributions, uncertainty in clinical observations due to noise, observation errors, uncertainty due to imputation or extrapolation of missing data, or estimation of properties from registries can be accounted for and propagated forward as a single predictive uncertainty.[24,53]

The processes of calibration and prediction will require a significant number of simulations to test different sets of material parameters or explore how uncertainty in parameters impacts model forecasts. One strategy to reduce time, computational, and energy costs is to leverage surrogate modeling or emulation. This involves building computationally cheaper models that approximate the behavior of the more complex, high-fidelity simulations. These surrogates can then be used for rapid exploration of parameter space, uncertainty quantification, and real-time predictions, significantly reducing the computational burden. Additionally, making use of historical simulations can further mitigate these costs. While all patients are unique, they invariably share common anatomy, physiology, and pathology, allowing insights from past simulations to inform and accelerate new model developments.

For each patient digital twin, we will have a catalog of data, decisions, parameter sets, forecasts, and simulations which together constitute the digital thread. This digital thread provides a comprehensive, historical record of the twin's evolution and all associated information.[18]

By collating these individual digital threads of patient digital twins into a "digital tapestry," a collective representation or network that integrates data and histories across multiple individuals, we can identify historical conditions where a current digital twin is in a similar state to a past networked twin. In these conditions, simulations and data can conceivably be efficiently shared between twins, reducing the computational cost of calibration and predictions. The digital tapestry can be understood as a dynamic, interconnected graph database of digital threads, enabling cross-patient analysis and leveraging collective historical data to inform individual predictions.

Creating retrospective virtual cohorts from large registry data allows us to generate databases of model parameters and predictions alongside events (drug regimens, surgical interventions), clinical outcomes (6-minute walk test, NTproBNP), and adverse events (hospitalizations or death). We can then combine digital twin features, clinical data, and patient demographics with these events and outputs of interest to train ML models, for example, neural networks, support vector machine, logistic regression, or random forests.[17,54] We can then test whether the addition of digital twin features improves predictions, if applying the ML model of drug response can facilitate therapy selection and using SHapley Additive exPlanations (SHAP[55]) or feature importance analysis we can identify which patient data or model attribute most informs each prediction.[15]

Clinical evaluation

In silico tools are relatively new, and there remains uncertainty on the best approach to clinically evaluation. For a PAH digital twin care pathway, a 3-stage process can facilitate this. First, while building the digital twin, we can host a multidisciplinary panel to familiarize clinicians with the technology and engineers with clinical expectations and provide reference estimates of the expected value of digital twins. We can present potential outputs from a digital twin to the panel to test what predictions, what magnitudes, and what confidence would be needed to inform or change a diagnosis and so inform the power calculations for subsequent studies. Second, we can run a prospective parallel multidisciplinary decision panel to test if digital twin predictions for actual patients would change the recommended therapy, although this recommendation will not be applied to the actual patient.[56] Third, we can compare digital twin forecasts against actual patient outcomes and evaluate whether the course of clinical treatment aligns or deviates from the digital twin prediction, or the decision of the research multidisciplinary decision panel given the digital twin prediction.[56] This would demonstrate the feasibility, accuracy, and impact of a digital twin care pathway, providing the evidence base to support prospective trials. Such trials would be likely to take the form of stepped-wedge cluster randomized studies in which different hospitals (rather than individual patients) are randomized to using or not using the digital twin.

Limitations

Digital twins offer significant promise but have limitations (Table 1). They remain an observational, model-based decision-support approach, and should not be considered a substitute, but rather complementary to, randomized clinical trials. While they can propose and refine causal evidence, this will need to be confirmed in clinical studies. The use of digital twins will require clear awareness of their methodological and practical constraints.

Digital twins beyond pulmonary hypertension

Beyond PAH, digital twins are being applied in other clinical domains. In diabetes, a randomized trial showed that cloud-based digital twins used to tune automated insulin delivery improved glucose control in people with type 1 diabetes.[57] In oncology, MRI-calibrated digital twins have been used to predict chemotherapy response and optimize treatment in breast cancer.[58] In heart failure, patient digital twins have been used to guide pacemaker therapy.[59]

The digital twin approach can be applied across respiratory diseases.[60] However, in contrast to pulmonary hypertension, which is characterized by right ventricle dysfunction and can leverage extensive developments in cardiac modeling and digital twins, other respiratory digital twins, including chronic obstructive pulmonary disease (COPD), acute respiratory distress syndrome (ARDS), and asthma, will require detailed mathematical models of the lungs. Currently, many lung models focus on simulating a representative case and are still in the early stages of developing personalization strategies.[60,61] Examples of digital twin, or patient-specific models, include personalizing a lumped parameter respiration model to intensive care unit data for ARDS cases[62]; in asthma, CT-based patient-specific airway models link small-airway narrowing to worse control/quality of life and predict partial reversal with type-2 biologics[63]; in COPD, patient-specific models have been developed for diagnosis and monitoring.[64] These frameworks provide the mathematical foundations needed to create respiratory digital twins, and their use is expected to expand with greater availability of home monitoring, enabling transition of patient-specific models into dynamic digital twins.[65]

The future of cardiopulmonary digital twins

Cardiopulmonary digital twins have significant potential to impact and personalize patient care (Figure 3). We have outlined a

Table 1 Limitations of digital twin approaches in medicine.

Limitation	Implication	Mitigation strategy
Observational rather than experimental system	Cannot currently replace randomized control trials	Use alongside trial evidence
Data quality, missingness, and heterogeneity	Noise, bias, and drift can degrade digital twin accuracy	Uncertainty quantification, robust calibration, sensor validation, and data wrangling more generally.
Computational burden	High cost for large-scale deployment	Surrogate modeling, reusable priors, pre-computed template twins
Limited mechanistic understanding for some pathways	Partial physiological representation	Hybrid models incorporating physics + ML/ data science
Privacy and regulation	Data sharing and compliance challenges	Trusted research environments, federated learning, encryption
Generalizability concerns	Risk of bias if trained on unrepresentative cohorts	Diverse training datasets, fairness monitoring, staged clinical evaluation
Dynamic updating and model drift	Risk of performance decline over time	Continual learning, model updating, frameworks, monitoring, and version control
Clinical workflow integration	Burden on clinicians; adoption barriers	Human-centered design, multidisciplinary evaluation, step-wedge implementation

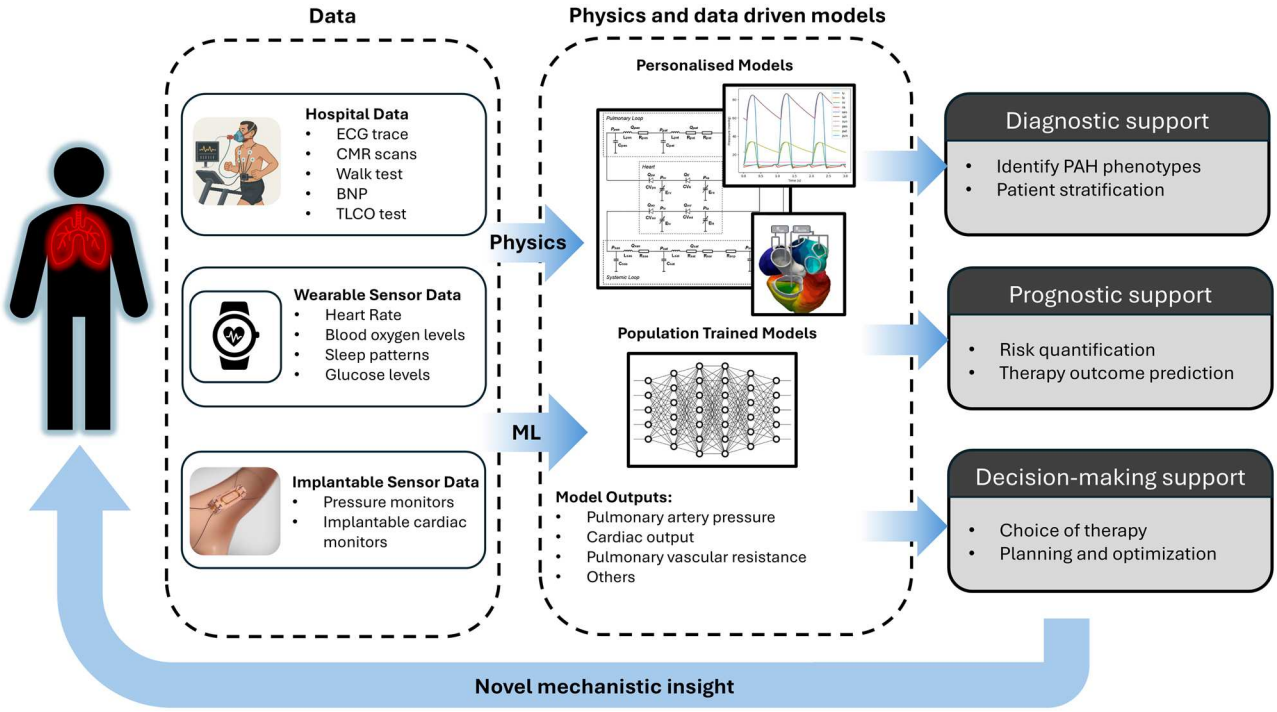

Figure 3 Implementation of PAH digital twin: patient-specific data, gathered from implantable devices, wearables, and scans feeds into 2 modeling streams: physics-based approaches generating personalized models, and machine learning (ML) techniques developing population-trained models. The integration of these "physics and data driven models" aims to provide comprehensive diagnostic, prognostic, and therapeutic support, while also fostering novel mechanistic insights that can refine patient understanding and care.

set of technical challenges and a roadmap to move from patient-specific models to a point where digital twins can be evaluated prospectively.

As patient digital twins move from being a research topic to a clinical tool, this will raise questions on both their regulation and how they are used in regulatory processes, and how they are integrated into learning-health system infrastructures.[66] Currently, the U.S. Food and Drug Administration (FDA) has published research and regulatory science tools outlining the process for establishing the verification (demonstrating the model is correctly implemented) and validation (demonstrating the model replicates the system of interest) of patient-specific models.[20,67,68] Many of these approaches can be applied to digital twins. Additional tests may be required to account for twin operational robustness, automated twin updating, and predictions and, if digital twins are networked in a digital tapestry, novel and unforeseen risks of such interconnectedness. For example, there is a risk of error propagation where inaccurate data or faulty predictions from one twin could spread and adversely affect the accuracy and reliability of other twins within the network.

The FDA has also published research on the use of models for in silico trials conducted on cohorts of virtual patients.[20,67] At the point where large cohorts of PAH digital twins become available and there is confidence in their accuracy, then it becomes possible to perform 3 types of virtual studies. As noted earlier, digital twins can be used in simulation studies, to assess drugs, devices, and diagnostics in a virtual cohort or individual patient and can create a virtual control population for a clinical trial. Moreover, recruiting patients for clinical trials is often challenging and time-consuming, particularly when trying to assemble a diverse and balanced patient group based on various patient or regional demographics. In this context, using patient digital twins of under-represented groups could be a pragmatic initial application, allowing estimation of whether these groups would be expected to have a different response, especially in terms of physiological changes, prior to needing full predictions of complex biological effects. While not a substitute for randomization, digital twins offer a scalable, ethically safe, and efficient approach to inform trial design and address key recruitment challenges.

The digital twin would also provide a clearer picture of patient outcomes. In medicine, autopsies can be performed, but these can be resource-intensive, provide only a snapshot of the patient, and can sometimes be inconclusive. Patient digital twins, however, could facilitate digital autopsies, identifying missed opportunities or common factors that lead to death or adverse outcomes. By replaying the digital thread, alternate care decisions could be identified, and through thorough prediction, various care options could be evaluated to review decisions and look for ways to improve care.

Finally, knowledge-based digital twins provide a physics and physiological-informed representation of a patient. As this model reflects the actual patient, it is scalable to account for new and novel datasets. We have described a model based on physiological measurements, but the framework can be extended to account for omics measurements of protein expression levels. At the same time this representation of physiology provides a platform for virtual experimentation and testing, allowing patient physiology, pathology, and therapies to be extensively studied across multiple scales and using measurements taken while the patient is in hospital but crucially also from when they are in the community, sleeping, exercising, and living their lives, providing a framework that can then be applied to other forms of pulmonary hypertension and cardiovascular disease.

An Example Digital Twin (Inset Box)

To provide an example of a physics-based and physiology-based model that could be used to create a digital twin, we will consider a model for simulating an individual patient's right ventricle.[50] This could be considered as a minimal viable product that captures the essential features of the right heart and pulmonary circulation. In this example, we first build a model of blood flow. We model 3 pressures: in the right atria (P_{RA}), the right ventricle (P_{RV}), and in the pulmonary artery (P_{PA}). We also model flow across the tricuspid (F_{TV}) and pulmonary (F_{PV}) valves. We can estimate the flow across each valve, using a simple model, by dividing the pressure difference across the valve by a measure of tricuspid (R_{TV}) and pulmonary valvular (R_{PV}) resistance:

$$F_{TV} = \frac{P_{RA} - P_{RV}}{R_{TV}}$$

$$F_{PV} = \frac{P_{RV} - P_{PA}}{R_{PV}} \frac{P_{RV} - P_{PA}}{R_{PV}}$$

We can now write the rate of change of volume in the right ventricle (V_{RV}) as a derivative in terms of the flow in and out of the right ventricle and then in terms of the pressure in these 3 chambers.

$$\frac{dV_{RV}}{dt} = F_{TV} - F_{PV} = \frac{P_{RA} - P_{RV}}{R_{TV}} - \frac{P_{RV} - P_{PA}}{R_{PV}} \frac{P_{RV} - P_{PA}}{R_{PV}}$$

In this simple model, we can use a data-based phenomenological model to set the pulmonary artery, right ventricular, and right atrial pressures as cyclical contraction relaxation patterns.

$$P_{PA} = \max\left(\left(P_{PA(sys)} - P_{PA(dia)}\right)\sin(wt) + P_{PA(dia)}, P_{PA(dia)}\right)$$

$$P_{RV} = \max\left(\left(P_{RV(sys)} - P_{RV(dia)}\right)\sin(wt) + P_{RV(dia)}, P_{RV(dia)}\right)$$

$$P_{RA} = \max\left(\left(P_{RA(sys)} - P_{RA(dia)}\right)\sin(wt) + P_{RA(dia)}, P_{RA(dia)}\right)$$

Where w is the period, t is the time, $P_{RA(sys)}$, $P_{RV(sys)}$, and $P_{PA(sys)}$ are the systolic pressure values for the corresponding chamber, and $P_{RA(dia)}$, $P_{RV(dia)}$, and $P_{PA(dia)}$ are the corresponding diastolic pressure values. We can then run our simulator to predict the volume transients and corresponding pressure volume loop in the right ventricle (Figure A).

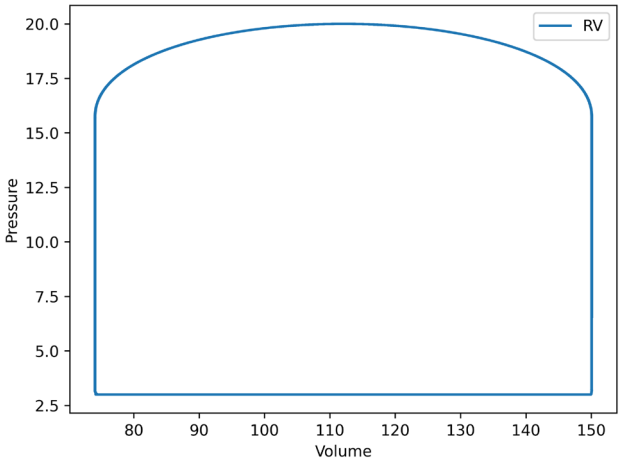

Figure A Simulated right ventricular pressure-volume loop generated using a minimum viable product approach. The simulation is based on the flow, change in volume, and pressure dynamics defined by Equations (1)-(6).

In this simple model, we can use cine MRI or echocardiography to estimate initial and changes in volume. We can use pressure catheters and flow measurements to estimate resistances, and we can use echo measurements to estimate valve opening and closing times. We can then predict how a drug that reduces pulmonary resistance or alters pre-load influences right ventricle function by adjusting the relevant model parameters (eg, pulmonary vascular resistance) and observing the simulated physiological changes. If we have pressure data from an implanted device (eg, a pulmonary artery pressure sensor),[69,70] daily pressure measurements from implanted sensors enable us to continuously recalibrate key parameters (eg, valve resistances and ventricular stiffness), tracking whether a patient is responding to therapy, deteriorating despite treatment, or maintaining stable function over time. We can then input patient demographics, sensor observations, the estimated physiological parameters from the mechanistic model (model properties), and the simulated physiological responses (model outputs) into an ML model that could forecast changes in function or adverse clinical events. We could also train an ML model to map the data, parameters, and simulations to clinical indices, for example, the 6-minute walk test. This then allows for forecasts of changes in function, but also clinical indices.

It is important to recognize that this model greatly simplifies the physiology of the beating heart and pulmonary circulation. There is no Frank-Starling relationship between preload and stroke volume, and neither is there an interaction between the left and right sides of the heart. More detailed models can incorporate these effects and provide a much more comprehensive representation of the cardiovascular response in PAH[71,72] and are a logical next step in complexity.

Conclusion

A case is made for the pursuit of patient digital twins for PAH as an important step toward predictive and personalized cardiovascular medicine. Successfully navigating the technical, validation, and regulatory pathways is essential to adopting digital twins for optimizing individual treatment strategies and enabling in silico clinical trials. Ultimately, the realization of patient digital twins provides a framework for combining patient data, AI, and physics- and physiology-based models to improve patient monitoring, diagnosis, and care.

Author contributions

S.N. and M.R.W. wrote the original draft which was reviewed and edited by all authors. S.-Y.W. produced the figures.

Supplementary material

Supplementary material is available at *American Journal of Respiratory and Critical Care Medicine* online.

Conflicts of interest

Please see the ICMJE disclosure forms, which have been provided as supplementary material.

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