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Health Digital Twins in Life Science and Health Care Innovation

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Abstract

Health digital twins (HDTs) are virtual representations of real individuals that can be used to simulate human physiology, disease, and drug effects. HDTs can be used to improve drug discovery and development by providing a data-driven approach to inform target selection, drug delivery, and design of clinical trials. HDTs also offer new applications into precision therapies and clinical decision making. The deployment of HDTs at scale could bring a precision approach to public health monitoring and intervention. Next steps include challenges such as addressing socioeconomic barriers and ensuring the representativeness of the technology based on the training and validation data sets. Governance and regulation of HDT technology are still in the early stages.

1. INTRODUCTION

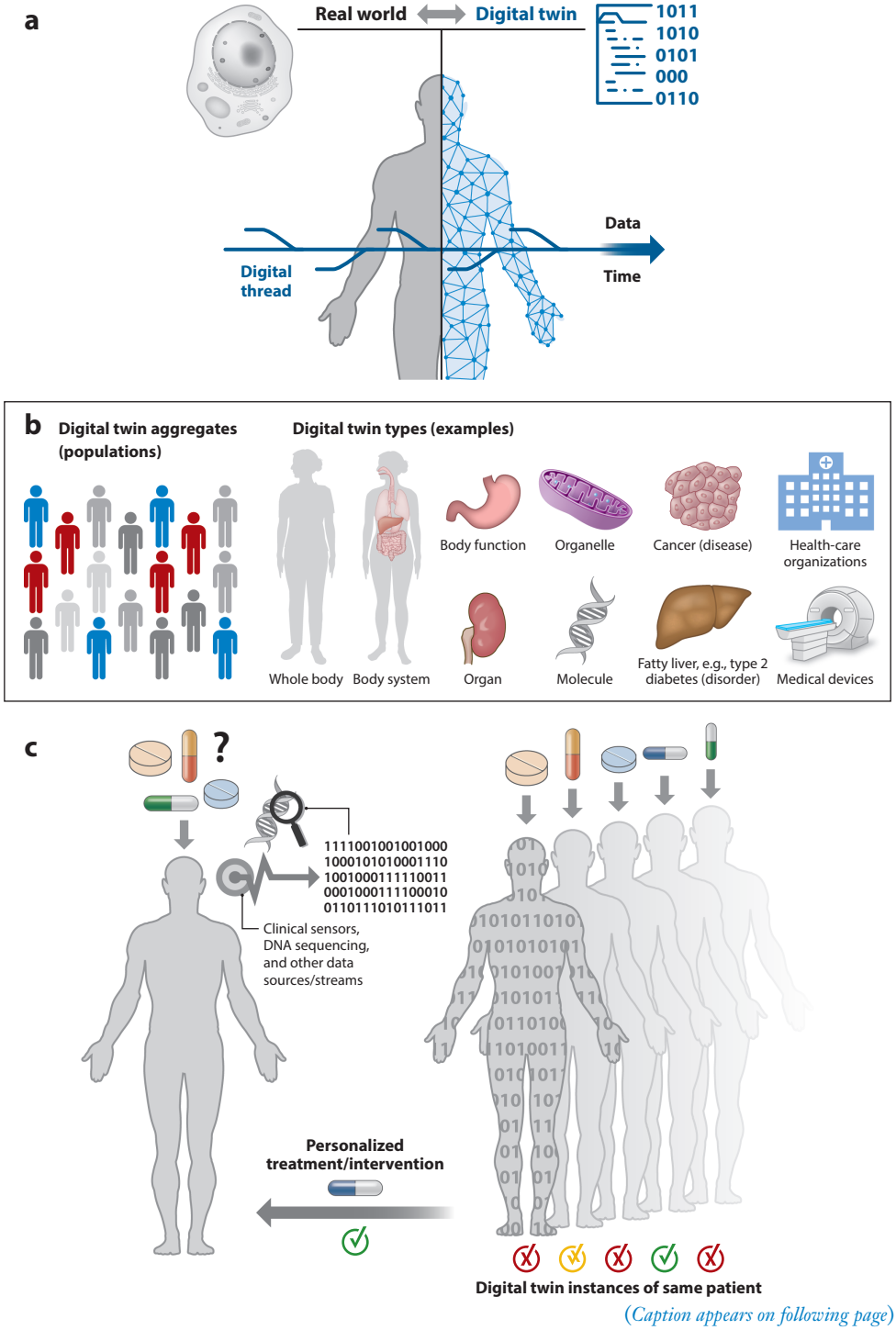
Data analytics has become increasingly important in health care as medicine enters the era of artificial intelligence (AI) and digital health. A cornucopia of health data are available for each patient, including information from electronic health records (EHRs) (1), personal wearables and remote monitoring, and big data analysis such as genome sequencing and imaging (2). Computational capabilities have also evolved to meet the demands of these new data streams, including faster and more powerful computers and analytic algorithms. New technologies such as AI and deep learning have allowed us to harness these new data to improve medical innovation, personalized medicine, and health-care delivery. Internet of Things (IoT) wearables, such as smartwatches, rings, and armbands as well as self-tracking tools that capture data on emotion, calorie consumption, and physical activity, supply a continuous stream of data for real-time updating of digital twins (3). In this context, health digital twins (HDTs) are a new model of analyzing multifactorial patient data to improve patient outcomes and population health.

2. OVERVIEW OF HEALTH DIGITAL TWINS

Digital twins are virtual models of physical objects, that is, the digital twin is a virtual representation of a physical twin. The original physical twins were manufacturing equipment; digital twins were introduced in 2002 as a concept in the manufacturing industry for product life-cycle management (4). In theory, the virtual model of manufacturing equipment could be created by analyzing product factors collected by personnel and sensors. These models could be used to iteratively model, test, and optimize the manufacturing products in the virtual space, which could then be applied to maintenance scheduling, inventory management, engineering innovation, and so on. This technology has since percolated manufacturing, supply chain management, plant operations, civil engineering, and transportation via rail, road, and shipping (5). In 2010, the concept took form under the more official name of digital twin during the US National Aeronautics and Space Administration venture to create digital simulations of spacecrafts for testing (6).

This technology has only recently been applied to health care under the umbrella field of precision medicine, with the coined term of health digital twins. In HDTs, the digital twin is a virtual representation of the patient, the physical twin, and is generated using multimodal individual patient data, population data, and real-time input of patient and environmental variables (7) (**Figure 1**).

An HDT is a tool for personalized medicine, which seeks to combine generalizable epidemiological data with real-time patient-specific data. Continuous streams of patient physiological and environmental data are now available with the widespread adoption of IoT devices, such as wearables and environmental sensors as well as smartphone-based applications that track physical activity, calorie intake, and mental health status. These real-time, continuous measurements, in combination with EHR data such as laboratory results, exams, imaging, and genomics data, can be processed into clinical markers. This information can then be used in predictive models to generate actionable information to inform treatment plans. Finally, the efficacy of the chosen plan of action can be quantified and fed back into the model to improve future predictions. This closed-loop system ensures that the digital twin becomes an increasingly accurate representation of the physical twin (8). These HDT models can be utilized to model patient factors, optimize treatment, and predict outcomes. HDTs can also be used for a variety of applications in public health and health-care operations (**Table 1**).



(Caption appears on following page)

Figure 1 (*Figure appears on preceding page*)

Key concepts of health digital twins. (*a*) Bidirectional mapping. Digital twins are not a mere unidirectional map, digital shadow, or simulation model of a physical, real-world entity in the digital domain. Digital twins can effectively become a dynamic (closed loop) virtual representation or mirror of their physical twins; that is, they can influence, and be influenced by, the physical entities they represent. In a digital thread, a digital twin's data create a pipeline over time, for example, from a person's or cell's birth to death, or from 2010 to 2030 for a given population, enabling tracing and tracking, asking of questions, and the discovery of useful relations between various data over time. (*b*) Digital twin types include the whole human body, a body system or body function, a single organ, a cellular or subcellular organelle, a molecule, a specific disease or disorder (represented under one of the previous types), or other organisms such as a virus (interacting with one of the previous types). Health-care organizations can also have corresponding digital twins of organizations to better monitor and optimize their running. Similarly, we can have digital twins of medical devices, for example, an MRI scanner. Digital twin aggregates are collections of digital twin instances belonging to different individuals, for example, data sets covering one family, population group, or whole population. (*c*) Identical copies of a digital twin, all belonging to the same individual, can be used for in silico testing and comparisons of various treatment options to answer individual-specific questions such as which treatment or intervention will be most successful in a given condition. Figure adapted from Reference 46.

3. APPLICATIONS OF HEALTH DIGITAL TWINS

3.1. Drug Discovery and Development

HDTs can provide significant leaps in the efficiency of drug discovery and development. Current research and development pipelines are resource intensive and face an overall failure rate as high as 96% (9). Even compounds that pass the preclinical phase into clinical trials have a 90% failure rate

Table 1 Key terms related to health digital twins

Term	Definition
Digital twin	A virtual representation of a patient's anatomy, physiology, and health, including details on lifestyle, family history, and medical conditions
Data sources	Electronic health records, wearables, imaging, genomics, and other sources used to generate the data to create a digital twin
Data analytics	Algorithms and statistical techniques used to recognize trends, forecast outcomes, and guide clinical judgment
Simulation	The use of digital twins to predict how the patient's body will respond to available interventions in order to optimize care and avoid negative outcomes
Machine learning	Algorithms that can learn from data and predict health outcomes, including disease risk, illness progression, and treatment response
Personalization	The capability to give customized treatment and support by tailoring the digital twin to each patient, taking into account their specific health history and circumstances
Interoperability	The ability of the digital twin to communicate and exchange data with other health systems and technologies, such as electronic health records, wearables, and remote monitoring systems, to ensure a complete and accurate representation of the patient's health
Privacy and security	The use of secure systems and protocols to safeguard the confidentiality and privacy of patient data, including precautions to prevent unauthorized access, alteration, or disclosure
User experience	The design of user-friendly interfaces and tools to support the use and interpretation of the digital twin by healthcare providers, patients, and researchers
Integration with clinical workflow	The implementation of digital twin technology into electronic health records, clinical decision support systems, and care pathways
Evaluation and validation	The use of rigorous methods to evaluate and validate the accuracy, reliability, and effectiveness of the digital twin model, including comparisons to real-world outcomes and ongoing monitoring and refinement of the digital twin based on new data and insights

(10). Two primary factors in US Food and Drug Administration (FDA) approval are drug efficacy and safety, which account for 57% and 17% of failed trials, respectively (11). The application of HDT technology to virtually represent organs, organ systems, and whole patients can inform the drug discovery process, including target selection, drug delivery, and design of clinical trials.

Target discovery can be improved through the granular modeling of biological processes of specified organ systems. For example, Subramanian (12) created an HDT of the liver in homeostasis, where pathological conditions can be accurately modeled through customization of parameters. As an example, progressive familial intrahepatic cholestasis type 2 is due to mutations of the bile salt export pump (BSEP). A virtual knockout of BSEP was created and a similar phenotype of increased total bile acids in plasma was observed in both the model and in real diseased patients. The liver HDT was able to accurately identify ileal bile acid transporter inhibitors to show improved phenotypes comparable to clinical trials. More broadly, organ HDTs allow for the exploration of multiple targets for specific disease states, decreasing the cost associated with obtaining preliminary drug or target data.

Drug delivery is highly dependent on the formulation of the capsule for solid-dosage oral drugs. All solid capsule drugs in the United States need to undergo a drug performance analysis via the US Pharmacopeia dissolution apparatus (13). Results provide key insights into the bioavailability and therapeutic effectiveness of the drug. In the context of a colon-targeted solid-dosage drug, HDTs can be used to replicate in vivo peristalsis and other aspects of the human gastrointestinal tract that affect dissolution of solid-dosage drugs. HDTs were created for both the proximal colon and the solid tablet, allowing for real-time optimization of solid drug parameters through parallel simulations (14). This iterative digital workflow can be leveraged to decrease costs and increase the manufacturing speed of capsule formulation.

Clinical trials are the last stage of drug development, take 12–15 years on average, and enroll thousands of patients (15, 16). HDTs may be used to partially virtualize the control arm of clinical trials, decreasing the number of physical patients needed. Unlearn.AI, a Series B start-up developing machine learning–powered HDT clinical trials, has shown promising results. They used existing longitudinal data in cognitive exams and labs from patients with Alzheimer's disease to create HDTs. These HDTs were used to generate synthetic patient data at different time points simulating natural disease progression, that is, the control data. The synthetic data were statistically indiscernible from real collected data (17). HDTs have the potential to save significant costs and accelerate trial timelines by decreasing the number of necessary real-life subjects to recruit, compensate, and administrate.

3.2. Treatment Decision Support

HDTs can aid in the customization of care for patients for whom standard therapy is ineffective. Clinical guidelines dictate therapy specifics such as dosage, timing, and duration. They often take a one-size-fits-all approach abstracted from clinical trials (18). Complex diseases such as hypersensitivities, hypertension, cancer, and autoimmune disease are associated with thousands of genes across multiple cell types, all of which change with disease progression, patient environment, drug regimens, and physiology. As a result, patient response rate to treatments ranges widely (25–80%), with an estimated 2.2 million adverse drug reactions per year (19).

HDTs allow for a unique opportunity to personalize care by providing targeted therapies. A recent HDT framework using single-cell RNA sequencing was used to create multicellular network models to analyze these complex diseases. The model was applied to seasonal allergic rhinitis where patient-specific HDTs were used to identify high-risk genes (20). While relatively resource intensive, finding ways to easily scale such personalized tracking and prediction is a prime potential of HDT technologies.

Lung cancer is another disease that has shown promise with HDT-informed therapy. Chemotherapy for advanced lung cancer accrues a survival benefit of two months alongside adverse effects from toxicity (21). There are major challenges in the dosage and delivery of chemotherapy due to variability in tumor location and patient lung parameters, resulting in poor drug delivery to tumor sites and off-target toxicity. Existent pulmonary delivery devices have efficiencies of less than 25% (22). HDTs for lungs were developed using high-resolution CT and MRI. These models were used to simulate different delivery methods and dosages to generate a bronchial map of predicted drug concentrations (23). Such models allow for a more accurate targeting of tumor sites, resulting in increased therapeutic efficacy and decreased adverse effects.

HDTs can also be useful in guiding decision making in novel circumstances with no real-world evidence. For example, therapies are often complicated by multiple comorbid or superimposed diseases—HDTs can be used to model the complex interactions of these diseases and potential drugs to inform therapy.

3.3. Applications to Health-Care Delivery and Operations

HDTs offer new ways to monitor individual patients within a population to inform the delivery of care. Through real-time monitoring of patients' digital twins, physicians can make remote decisions regarding their care, offering potential cost savings and better outcomes. For example, let us consider the typical case of patients with diabetes who are worried about acute illnesses such as kidney failure or diabetic ketoacidosis. These patients can be triaged to the emergency department or an outpatient visit (depending on severity and likelihood of acute complications) based on real-time data input regarding blood sugar levels, patient symptoms, and vitals that is integrated into the patient's existing digital twin to stratify probability of diseases and complications in real time.

Remote monitoring also enables new modes to track the health of isolated and elderly individuals, including monitoring and taking timely action in case of physical inactivity as well as more dangerous acute events such as fall and crash detection. Wearables, such as smartphones and smartwatches, can provide data from built-in sensors (e.g., gyroscope, accelerometer, heart rate, and pulse oximetry), which are then processed by advanced algorithms to estimate gait stability and physical exertion. HDTs combining real-time data with other risk factors such as preexisting conditions, previous falls and fractures, and gait patterns during previous falls can be used to warn patients of potential risk when similar patterns are detected (24–30).

Moreover, HDTs may also give patients more autonomy over health-care decisions, including how to respond to health predictions and changing factors, when to seek care, what types of treatments may best uphold their values, and so on. By offering more easily understandable predictions of health outcomes, HDTs can be leveraged to increase patient engagement with their own treatments and shift the duty of interpretation from physician alone to HDT outputs and patient interpretations (24).

3.4. Applications to Public Health

HDT applications in public health are largely focused on interpersonal and community-wide health monitoring and intervention, particularly in the wake of the COVID-19 pandemic. One study created HDTs of smartphone users, capturing COVID-19 infection status and symptoms for contact tracing. With real-time data on patient location, comorbidities, and disease severity, the authors were then able to integrate the COVID-19 HDTs with HDTs of local hospitals in order to inform patient flow in real time (31). Another study by Deren et al. (32) presented a model of a virtual system for tracking and managing disease outbreaks; this model integrated spatiotemporal

data with cloud computing platforms and AI location technology to provide disease traceability through proximity analysis. In this way, HDTs can offer new degrees of granularity into the health of populations, particularly as it relates to infectious disease. Such systems could be applied similarly to other public health measures; for example, HDTs capturing cardiovascular health behaviors such as exercise could be combined with geospatial data to identify new geographic areas for public parks or outdoor gyms and such data could also be used to identify populations at higher risk of inactivity for intervention at the public school system or outpatient clinic level (33).

The popularity of the IoT may also allow for additional measurements, such as home-based ambient sensors to measure temperature, air quality, and light. Gathering such data can be used to not only inform individual patient HDT models for personalized care but also address population-level interventions regarding factors such as environmental racism and geographic locations (2). In such ways, applying individual patient models to aggregated high-granularity data offers new opportunities for evidence-based, highly dynamic public health intervention.

4. ISSUES WITH HEALTH DIGITAL TWINS

4.1. Adoption

HDTs are still in the early diffusion phase of adoption. A recent mapping review of 88 papers related to HDTs found growing momentum in the field, including 18 patent applications (8). The impact of HDT technology in medicine will ultimately depend on its adoption among pharmaceutical innovators, clinicians, payers, and health systems. With the surplus of digital health technologies and AI modeling applications available, the question remains which of these technologies will be useful for decreasing the costs and increasing the value of innovation and clinical care.

Meanwhile, new frameworks for the ethical development and utilization of HDTs are important for sustainable and safe innovation. Recent progress in developing ethical guidelines for autonomous AI can be cross-applied to the case of HDTs (34). Incorporating biomedical ethics such as nonmaleficence, justice, accountability, and respect for autonomy (including privacy) into the development of HDTs will be crucial for driving adoption (35).

Adoption also largely relies on how HDTs are paid for, with a variety of options mirroring those of new AI systems coming to market. HDTs, like other AI technologies, present the unique situation of existing somewhere between fixed equipment such as EHRs and variable services such as screenings. One option would be to reimburse HDTs under a fee-for-service model based on the estimated value delivered. For example, IDx-DR, the first FDA-approved autonomous AI for diabetic retinopathy screening, is currently reimbursed for every patient visit at a set rate (36). However, HDTs present a unique circumstance; once purchased by a provider, HDTs represent a fixed base cost (the subscription/purchase) and near-zero marginal costs (for each new patient's HDT). A per-patient model may not accurately capture the actual cost of the HDT services from the provider side.

Instead, there also exist several alternative and complementary methods to reimburse AI-based technologies such as HDTs (37). First, HDTs could simply be a cost of business for health systems and innovators, where HDTs streamline care to save costs as well as improve outcomes related to performance metrics. However, while some larger health systems and medical innovators may be able to pay for HDTs as a cost of business, this model could exclude smaller systems and innovation firms from using this promising technology. This model of paying for HDTs will likely have a place in the private innovation and pharmaceutical space but may not be as applicable to the clinical care sector. Second, HDTs could also be paid for in a bundled or global payment system for clinical services. For example, if an HDT of a patient's cardiac health is created for the management of their atrial fibrillation, the HDT technology cost would be bundled into the reimbursement for

atrial fibrillation management. Third, many new AI technologies are currently being reimbursed under a provisional new technology add-on payment in the United States (38). Such models could also be cross-applied to HDT technologies to facilitate adoption on a temporary basis before including the technology in global or bundled payments.

HDTs are an ecosystem that is directly dependent on developments in closely related fields of medicine and health care, for example, in silico medicine, health data technologies, and high-performance computing. The adoption of new technologies in these fields will in turn facilitate the innovation and adoption of HDTs. For example, the expansion of free and accessible cloud-based repositories for health data would stimulate new HDT technologies by removing a large barrier to innovation—access to and storage of data. New in silico models and AI algorithms could in turn generate new iterations of HDTs as well. In fact, this intersectional HDT ecosystem is an area being emphasized by the newly launched HDT consortium in Europe: Ecosystem for Digital Twins in Healthcare (EDITH) (39).

4.2. Equity

The development of HDTs can be affected by a variety of socioeconomic factors, which may ultimately threaten the representativeness of the technology depending on selection bias for the training and validation cohorts. Differences in the external validity of HDT technologies among underrepresented populations could further exacerbate health disparities (40).

Moreover, the costly nature of many data sources that feed into HDTs could pose barriers to accessibility. Multimodal data streams that can inform HDT models are contingent on the specific sensors and logistical factors relevant to each patient. For example, an HDT of a patient's heart could utilize data from personal wearables. While the model may still function without the data from this wearable, if the lack of data from these devices affects the validity of the HDT predictions, it raises concerns about the potential for further barriers in access to this technology. Without a clear business model and regulations for how HDTs will be translated into patient care, some patients may be left unable to access the highest-quality HDT technology (41).

On the other hand, HDTs could offer new opportunities to bolster equity. Health systems could use HDT data at the population level to pinpoint high-risk populations and deploy preventative measures. And at a more granular level, analysis could further pinpoint which particular factors are more predictive of disparities in health. For example, the Media and Innovation Lab at the University of Miami is sending MILBox, a remote health-monitoring package, into underserved Black and Latinx rural and urban settings to evaluate contributing factors to Alzheimer's disease and cardiovascular disease. The project hopes to transform disease prevention and enable equitable treatment by identifying the environmental and behavioral factors driving disparities, for example, air pollution, exercise time, and geographic location (42).

Moreover, HDTs could be used to supplement underserved and underrepresented populations in clinical trials data, potentially adjusting trial results to be more representative of the populations that the trial's technology is meant to serve. Some studies have already shown that HDTs are promising for recovering higher statistical power affected by low enrollment, high dropout rates, and small-*N* trials (43).

4.3. Governance and Regulation

HDT technology is still quite new to the regulatory landscape, though other forms of AI-enabled medical devices have already been evaluated and approved by the FDA. HDTs currently fit under the FDA's framework of Software as a Medical Device (SaMD), which also covers AI/machine learning algorithms (44). The SaMDs are currently classified based on the severity of the disease

addressed and the level of clinical decision making for which the SaMD is responsible; class I is low risk and class IV is highest risk (45). While such granularity is a commendable first step, further details are needed to specify regulations for the various types of AI models currently available. In the future, AI models that continue to learn from new data may require ongoing reapproval, a process that must be triggered at a regular interval or benchmark and that has yet to be determined by regulators such as the FDA. HDTs, most of which incorporate some method of AI, will be similarly diverse in their presentations and will necessitate their own regulatory considerations.

Given the diverse array of potential HDT models that are currently available and in the pipeline, there is a need for a base level of standardization and interoperability. Industry, government, academia, and health systems must develop a standardized set of HDT methods and best practices, likely enforced by approval and safety agencies such as the FDA. Examples of already-existing HDT consortiums include the Swedish Digital Twin Consortium, DigiTwins Consortium, and Digital Twin Consortium (46). Such intersectional conversations involving clinicians, experimentalists, and modelers are necessary to develop mutually agreeable best practices in the developing field of HDTs (47).

Interoperability is also a crucial but often-overlooked aspect of novel digital health models such as HDTs. HDT models should have the capability of sharing their virtual patient representations with other HDT models, potentially offering synergistic applications to modeling different aspects of a patient. Similarly, biobanks that supply data to models such as HDTs should be standardized in terms of data coding, storage, and handling. Interoperability is also key in the current EHR-driven health-care ecosystem. HDTs should be created with the intent of seamless integration into the clinical workflow; technologic compatibility with EHRs should allow for real-time analysis and EHR alerts as well as manipulation of the data inputs and HDT outputs. For medical innovators, the interoperability of an HDT model is needed to allow interaction with other commonly used modeling or analysis software as well as with the variety of clinical trial database software systems. Such steps can be facilitated by regulators and academia alike and would greatly assist the rapid and safe innovation and dissemination of HDT technologies.

In evaluating the highly nuanced and technical aspects of such decisions, the FDA and similar regulators globally should be sure to use advisory committees or similar avenues to consult expert data scientists. Expert input is necessary to inform these regulatory frameworks as well as to evaluate specific HDT models and their respective data sets.

4.4. Data Privacy and Ownership

Given the highly sensitive and detailed information entailed in HDTs, patient rights such as privacy and informed consent are of utmost importance. Knowing real-time, multifactorial health details about patients could be exploited by insurers or employers without the right safeguards. HDT data could also easily be commercialized via a secondary data economy, which presents ethical concerns even when the data are deidentified. Whether patients are able to control the dissemination and utilization of their HDTs has yet to be clarified by data rights and health-care regulators (46, 48).

Additionally, the cybersecurity of HDT data is also important (48). Data breaches and losses can violate clear ethical and legal principles. The details of liability are complicated and will likely be determined through trial and error in the courts and among regulators as HDTs are adopted.

4.5. Health Digital Twin Banks and Big Data Infrastructures

Having digital banks of well-cataloged, discoverable, reusable, and repurposable instances of various HDTs, including live ones that are continuously updated with real-time or near-real-time

data, can prove very useful for clinical trial matching and large-scale population studies. An HDT bank would offer controlled access to an organized repository of HDT instances (representing individuals) and instance aggregates (representing populations). Exchange and interoperability with similar banks should also be possible but will require achieving adequate levels of HDT data and software standardization. These banks could one day become critical for highly successful clinical trial matching and for the execution of large-scale and longitudinal population studies, among other uses (46).

Suitable big data research infrastructures, for example, trusted research environments, personal health trains (PHTs), and federated data platforms, already exist and could help realize this vision of HDT banks, all while preserving individuals' data privacy and security (see Section 4.4). These infrastructures also support working with distributed multicenter data (banks). Private data can remain under the full control of HDT instance owners, that is, the patients represented by the HDTs. With emerging concepts and technologies such as PHTs and Web3/blockchain protocols, we should soon see the development of decentralized Web applications that enable users to control their own digital twin instances, identity, content, and data, that is, control access to their individual health-connected sensor data and models held in small, personal data lockers in the hosting bank in a decentralized, peer-to-peer trust model (49).

5. CONCLUSION

HDTs are a form of personalized medicine that offer a new way of monitoring and treating patients by combining general population data and real-time patient-specific data. HDTs have the potential to improve decision making, optimize treatment, and predict outcomes for patients with complex diseases. HDTs can also be used in drug discovery and development and to monitor health at the community and population levels. However, HDTs are in the early phase of adoption, and their impact will depend on various factors such as cost, advancements in related fields, and socioeconomic factors. HDTs have the potential to improve equity in health care, but clear regulations and business models are needed to ensure equal access to high-quality technology.

DISCLOSURE STATEMENT

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