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Review of Digital Twin Projects in Medical Research and their ELSI Programs

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Introduction

The incorporation of digital twin technology in medical research for personalized medicine is witnessing incredible growth all over the world in recent years.¹ In addition to advancement of new technologies, ethical concerns and efficacy issues of animal models in drug development and testing, as well as the changing legal landscape that gives more leeway for non-animal-based alternative drug testing, also have stimulated widespread scientific and industry interests in digital twins in medical research.²

However, regardless of the burgeoning research projects in digital twins in medical research, there is a lack of consensus on the meaning of the term, digital twin, in the field of medical research, and ambiguities permeate attempted definitions of digital twin-related consortium and projects. This note takes the position that a uniform definition of digital twin in medical research might not be necessary at least at the current stage, as long as a sufficiently fine-grained concept of digital twin is available to enable effective comparison and avoid misleading references.

Part I of this note deals with the lack of consensus and ambiguities in the term of digital twins in literature and academic or institutional attempts to define digital twins, debunks the inconsistencies, and thereby provides a framework of conceptualizing digital twins with diverse meanings. Part II summarizes undergoing digital twin projects, which are selected in consideration of the scope maps in Part I. Part III reviews the ELSI (ethical, legal and social issues) programs of digital twin projects, highlights the relative inactivity and introduces relevant programs in similar fields that can serve as references for digital twin projects.

1. Diverse Meanings of Digital Twins

1.1. Digital Twin VS Virtual Human

1.1.1. digital twin

The term “digital twin” comes from the world of industrial applications, and originally a digital twin is defined as³: 1) A data structure for the real-world system; 2) Some process that links data together to form dynamic; and 3) Some link to the real world that feeds back data into the data-propagation/generation process.

¹ Sun T, He X, Li Z. Digital twin in healthcare: Recent updates and challenges. *Digit Health*. 2023 Jan 3;9:20552076221149651. doi: 10.1177/20552076221149651. PMID: 36636729; PMCID: PMC9830576.

² Zushin PH, Mukherjee S, Wu JC. FDA Modernization Act 2.0: transitioning beyond animal models with human cells, organoids, and AI/ML-based approaches. *J Clin Invest*. 2023 Nov 1;133(21):e175824. doi: 10.1172/JCI175824. PMID: 37909337; PMCID: PMC10617761; see also De Los Angeles A, Hyun I, Latham SR, Elsworth JD, Redmond DE Jr. Human-Monkey Chimeras for Modeling Human Disease: Opportunities and Challenges. *Stem Cells Dev*. 2018 Dec 1;27(23):1599-1604. doi: 10.1089/scd.2018.0162. PMID: 30319057; PMCID: PMC7366261.

³ Grieves, M. W. *Virtually Intelligent Product Systems: Digital and Physical Twins*. Complex Systems Engineering, Theory and Practice. Reston, VA: American Institute of Aeronautics and Astronautics, 2019, 175-200.

In healthcare and medical research, consortiums, research institutes and business entities make their own definition of digital twins when incorporating the terms into the projects. The following descriptive definition of digital twins has been offered.

Definitions of digital twins in healthcare and medical research:

- Health digital twins are defined as virtual representations (“digital twin”) of patients (“physical twin”) that are generated from multimodal patient data, population data, and real-time updates on patient and environmental variables.⁴
- Digital Human Twin (DHT) consists of virtual replicas of an individual which encompasses all the morphological (anatomical), physiological, and ideally cognitive properties, to establish an all-round digital representation of the human body. A key feature of the DHT is the bi-directional data flow between the physical entity and its virtual replica, allowing for real-time continuous updating of the virtual model and, conversely, targeted interventions on the physical systems based on predictive simulations performed on DHTs.⁵
- Digital twin which we define here as a living replica of a physical system (human or non-human).⁶
- A digital twin for personalized health care service is a data-driven, interactive computerized model that aims to offer health-related information that properly simulates or predicts the health conditions of a particular person.⁷
- A digital representation of a target entity with data connections that enable convergence between the physical and digital states at an appropriate rate of synchronization.⁸ although it is not, strictly speaking, a bio-digital twin definition, it is relevant to the definition of digital twin.

⁴ Venkatesh, K.P., Raza, M.M. & Kvedar, J.C. Health digital twins as tools for precision medicine: Considerations for computation, implementation, and regulation. *npj Digit. Med.* 5, 150 (2022). <https://doi.org/10.1038/s41746-022-00694-7>

⁵ Cellina, M.; Cè, M.; Ali, M.; Irmici, G.; Ibba, S.; Caloro, E.; Fazzini, D.; Oliva, G.; Papa, S. Digital Twins: The New Frontier for Personalized Medicine? *Appl. Sci.* **2023**, *13*, 7940. <https://doi.org/10.3390/app13137940>.

⁶ Popa, E.O., van Hilten, M., Oosterkamp, E. *et al.* The use of digital twins in healthcare: socio-ethical benefits and socio-ethical risks. *Life Sci Soc Policy* 17, 6 (2021). <https://doi.org/10.1186/s40504-021-00113-x>.

⁷ Huang PH, Kim KH, Schermer M, Ethical Issues of Digital Twins for Personalized Health Care Service: Preliminary Mapping Study, *J Med Internet Res* 2022;24(1):e33081 doi: 10.2196/33081.

⁸ ISO/IEC 30173: 2023 “Digital Twin – Concepts and Terminology”

Digital Twin can also be defined by setting out a specific method. In explaining the construction of an immune digital twin, the following 4 stages are explained in detail in place of a formal definition of digital twin.⁹

- Stage 1: Define a specific application and construct an appropriate generic template model.
- Stage 2: Personalize the template model to an individual patient.
- Stage 3: Final immune digital twin testing and uncertainty quantification.
- Stage 4: Continue to collect individual patient data for ongoing improvement of the immune digital twin to improve generic models and reflect changes.

Further, although the definition of digital twins varies, as highlighted in bold, all definitions consider the dynamic relation between the virtual and the real, which can be measured as the level of control between the two¹⁰. While some definitions describe the level of control vaguely as “interactive”, some definitions strictly require “real-time” or “bi-directional data flow.” This idea of level of control is key to the definition of digital, which will be discussed in more detail in section 2.3.3.

1.1.2. virtual human

In research of digital-twin-driven projects, some use the term virtual human in place of or in combination with “twins”. For instance, EDITH, a European Commission-funded initiative to create a digital twin of the human body, known as the European Virtual Human Twin, defines the virtual human twin (VHT) “as a distributed and collaborative infrastructure, a collection of technologies and resources (data, models) that enable it, and a collection of Standard Operating Procedures (SOP) that regulate its use. The virtual human twin can be imagined as an n-dimensional data space, which digital twins in healthcare models constantly crawl. The associated knowledge space could be represented by knowledge graphs linking data and models.”¹¹ The Virtual Physiological Human (VPH) is defined as a “methodological and technological framework that, once established, will enable collaborative investigation of the human body as a single complex system.”¹²

Unlike digital twin’s emphasis on the dynamics of the virtual and the real, the existing definitions of virtual human twins seem to be used to refer to the higher level “infrastructure” or “space” that encompasses personalized digital twin models. It is also worth noting that virtual humans

⁹ Laubenbacher, R., Niarakis, A., Helikar, T. *et al.* Building digital twins of the human immune system: toward a roadmap. *npj Digit. Med.* 5, 64 (2022). <https://doi.org/10.1038/s41746-022-00610-z>.

¹⁰ For detailed explanation of the level of control, see Part 1.3.3.

¹¹ M. Viceconti, M. De Vos, S. Mellone and L. Geris, “Position Paper From the Digital Twins in Healthcare to the Virtual Human Twin: A Moon-Shot Project for Digital Health Research,” in *IEEE Journal of Biomedical and Health Informatics*, vol. 28, no. 1, pp. 491-501, Jan. 2024, doi: 10.1109/JBHI.2023.3323688.

¹² Ibid.

evolved from a representation of human figures using computer graphics called Boingman for ergonomic analysis for airplane chairs.¹³ As such, instead of being considered a living model, the implication of a static but accurate spatial representation is emphasized. This spatial and non-temporal focus is congenial to the existing themes of virtual humans.

Despite the more abstract connotation of virtual humans compared to digital twins, according to a survey of clinical physicians all over the world, clinical physicians are more aware of the term “Virtual Physiological Human” than the more widely used term “Digital Twin.”¹⁴ This implies the use and significance of different terms largely affected by fields of professions.

1.1.3. “Digital twins” as methods

As discussed above, if digital twins can be defined as a set of methods, it is possible to consider digital twins as long as they utilize specific methods regardless of their naming. This broad definition of digital twin is significant in order to prevent overlooking the importance of research projects that focus on the substructure of the human body. Current digital-twin-driven research can be conceived at different levels from substructure (molecular, cells, issues), organ, and body (inter-organ/system). Regarding digital twins at the substructure-level, due to their amorphous nature, instead of being referred to as digital twins, it is usually described as a systematic map of the substructure. One of the prominent examples is the Human Atlas Project, which aims to create “cellular reference maps with the position, function and characteristics of every cell type in the human body.” As such, in the summary table of digital twin projects in medical research, we include both expressively named digital twins as well as those projects that integrate computational and mathematical sciences and biomedical sciences to construct virtual models in medical research.

1.2. Medicine VS Healthcare- fields of applications

The field that digital twins operate in also significantly affects the descriptive definitions of digital twins, as it controls the scope of application of bio-digital twins and determines the subjection of the real, which the virtual replicates. Here, we focus on the two most frequently used fields, healthcare and medicine.

The word “medicine” comes from the Latin word “medeor” and “medicor”, verbs meaning to heal or cure, and therefore presuming diseases.¹⁵ Moreover, the origin of personalized medicine, which closely relates to many bio-digital twin projects, comes from the study of diseases that uses human variations and/or human differences in certain respects (such as genetics and metabolism) to explain overt phenotypic differences such varying susceptibilities to and

¹³ One of the earliest Virtual Humans used for ergonomic analysis for airplanes was William Fetter’s Landing Signal Officer, developed for Boeing in 1959. W.A. Fetter. See A Progression of Human Figures Simulated by Computer Graphics, IEEE Computer Graphics and Applications, Vol.2, No9, 1982, pp.9-13.

¹⁴ Lesage R, Van Oudheusden M, Schievano S, Van Hoyweghen I, Geris L and Capelli C (2023) Mapping the use of computational modelling and simulation in clinics: A survey. *Front. Med. Technol.* 5:1125524. doi: 10.3389/fmedt.2023.1125524.

¹⁵ Online Etymology Dictionary, <https://www.etymonline.com/word/medicine>.

manifestations of diseases.¹⁶ Therefore, “disease” is an indispensable element when applying digital twins in the field of medicine. In contrast, healthcare does not necessarily presume diseases and encompasses all matters concerning health.

Moreover, this centrality of disease in “medicine” is demonstrated by analyzing the use of medicine in academic papers on digital twins. Although some articles using the two terms interchangeable, articles focus on medicine tend to only include applications in dealing with diseases, while applications for healthcare go beyond merely diseases-related research. For instance, “Digital Twin Application Areas in Medicine”¹⁷ states that “In medicine, the most ambitious application of digital twins aims to improve the prevention, diagnosis, and treatment of diseases.”¹⁸ In categorizing different applications of digital twins, the note structures the usage according to disease life cycle as shown below.

Meanwhile, the discussion of digital twins in healthcare extends to areas other than disease such as general health management and hospital management. For instance, one of the papers mentions that “the evolution of digital twins will concern the simulation of healthcare institutions or processes, aimed at improving organizations’ workflow and resource management.”¹⁹ Another article argues “current work being conducted in the (healthcare) field showcases its promises in assisting precision healthcare, hospital/clinic management, and pandemic response, and the operation of machine learning and modeling.”²⁰

In terms of practice, GE Healthcare, an US medical technology company has invented an AI-powered healthcare management system, the Command Center Software.²¹ There, digital twin is used to visualize the hospital in a safe environment to test changes in system performances in order to empower strategic decisions from bed allocation, level of care configuration, surgical block schedule optimization to staffing design.

However, it is noteworthy that although a perceivable distinction exists between medicine and healthcare and their respective implications for digital twins, a strict distinction can be regarded as insignificant for two reasons. Firstly, because healthcare defines a field broader than medicine, sometimes healthcare can be used to replace medicine. Secondly, the term disease can also be defined broadly to include diseases related issues, which basically refers to conditions in the absence of health. For instance, one article identifies applications of digital in precise medicine to include both disease focused applications (such as person-centric

¹⁶ Goetz LH, Schork NJ. Personalized medicine: motivation, challenges, and progress. *Fertil Steril*. 2018 Jun;109(6):952-963. doi: 10.1016/j.fertnstert.2018.05.006. PMID: 29935653; PMCID: PMC6366451.

¹⁷ Iqbal JD, Krauthammer M, Biller-Andorno N. The Use and Ethics of Digital Twins in Medicine. *Journal of Law, Medicine & Ethics*. 2022;50(3):583-596. doi:10.1017/jme.2022.97.

¹⁸ Cellina, M.; Cè, M.; Ali, M.; Irmici, G.; Ibba, S.; Caloro, E.; Fazzini, D.; Oliva, G.; Papa, S. Digital Twins: The New Frontier for Personalized Medicine? *Appl. Sci.* **2023**, *13*, 7940. <https://doi.org/10.3390/app13137940>.

¹⁹ Armeni, P.; Polat, I.; De Rossi, L.M.; Diaferia, L.; Meregalli, S.; Gatti, A. Digital Twins in Healthcare: Is It the Beginning of a New Era of Evidence-Based Medicine? A Critical Review. *J. Pers. Med.* **2022**.

²⁰ Ghatti, S., Yurish, L.A., Shen, H., Rheuban, K., B. Enfield, K., Facticeau, N.R., Engel, G., & Dowdell, K. (2023). Digital Twins in Healthcare: A Survey of Current Methods. *Archives of Clinical and Biomedical Research*.

²¹ GE Healthcare, Digital Twin, <https://www.gehccommandcenter.com/digital-twin>.

prevention and risk stratification, disease modeling), as well as merely disease related applications (like surgical planning, organizations and medical training).²²

1.3. Refining the Definition of Digital Twins for Human

As shown in Section 1.1, the origin of the term digital twins come from industrial applications, where the utility of digital twins for engineered objects relies on the fact that there exists a formal specification for the “twinning” real counterpart. Several preconditions are necessary to enable the twinning process in the case of industrial application. (1) there must be a common formal specification that is shared by and links different individual examples within a type/class of the real entities; (2) the common formal specification must not only include a list of the formal component of the real entities, but also how those components interact in order to faithfully simulate and predict the behaviors of the real entities.²³ However, these two requirements pose questions when it comes to twinning of a living human being: namely the issue of heterogeneity and the issue of multidimensional representation of functions.

1.3.1. heterogeneity

However, as human beings are not engineered machines and the diversity of human beings invariably implicate the issue of heterogeneity, meaning the biological property that leads to intrinsic variability in an organism, too often in building the digital twin, an experimental or clinical data set can be seen as a widely scattered series of points and a statistical analysis generates a line drawn through the cluster of points, and this approach could explicitly ignore differences in individuals.²⁴ Therefore, the means of constructing the common formal specification of digital twins in healthcare and medical science shall be fundamentally different from the conventional mechanistic approach, and shall encompass as much varied trajectories as possible.²⁵

1.3.2. multi-dimensional function

Another limitation of the conventional mechanistic approach of digital twins is derived from the conventional “data-centric” approach in the mechanistic field, where some of the data, which might be essential to explain the functions of the human body, is not available.²⁶ Unlike digital twins for car crash dummy tests, the digital twins for medicine discovery and new pathology are only attainable by expounding on elements beyond the formal components of human physiology, but how those components function and interact within human bodies. As such, digital twins should place emphasis on the characterization and representation of functions in

²² Cellina, M.; Cè, M.; Ali, M.; Irmici, G.; Ibba, S.; Caloro, E.; Fazzini, D.; Oliva, G.; Papa, S. Digital Twins: The New Frontier for Personalized Medicine? *Appl. Sci.* **2023**, *13*, 7940. <https://doi.org/10.3390/app13137940>.

²³ An G (2022) Specialty Grand Challenge: What it Will Take to Cross the Valley of Death: Translational Systems Biology, “True” Precision Medicine, Medical Digital Twins, Artificial Intelligence and *In Silico* Clinical Trials. *Front. Syst. Biol.* 2:901159. doi: 10.3389/fsysb.2022.901159.

²⁴ Ibid.

²⁵ Grieves, M. W. (2019). *Virtually Intelligent Product Systems: Digital and Physical Twins*. Reston, VA: American Institute of Aeronautics and Astronautics.

²⁶ Wright, L., Davidson, S. How to tell the difference between a model and a digital twin. *Adv. Model. and Simul. in Eng. Sci.* 7, 13 (2020). <https://doi.org/10.1186/s40323-020-00147-4>

multiple dimensions, not just the descriptions of components.²⁷ This principle is also a reflection of the famous quote from Richard Feynman: “What I cannot create, I cannot understand.” If the goal of digital twins in the medical world is to understand disease in order to achieve better health, what must be done is re-creation of the process of disease within the human body to fully understand the disease, which is technologically and economically impractical.

In conclusion, the successful translation of digital twins from the mechanistic world to the medical field requires additional attention to multi-dimensional analysis of function, which usually requires understanding of heterogeneity of human beings (non-linear modeling).²⁸

1.3.3. level of control

Another important aspect of digital twins that has not been clearly defined is the meaning of the term, “twin”. As seen in section 1.1, the variety of the definitions of digital twins partly contributes to the ambiguity of the term. However, there are still several ways to specifically define twinning and to carefully distinguish it from computational modeling so that a standardization of technology can be established to avoid misunderstanding and failure of reasonable expectations.

The interactions between the twin/model and the real entity can be sorted into three categories: (a) a digital representation without a data flow (digital models); (b) a digital representation with a unidirectional data flow (digital shadows); and (c) a digital representation with a bi-directional data flow (digital twins).²⁹ Only the last case is considered as digital twins.

Many ongoing digital twin projects focus on model development and have not yet enabled (or not intended) real-virtual interaction technology at all. One example of the one-directional model between a real patient and the virtual space is the foundation models developed by Helmholtz Munich. The foundational models are large-language models that collect a large amount of individuals’ health data from medical data such as medical images, biomarkers, and genetics, to environmental and lifestyle data to enable personalized treatment and prediction of disease progression.³⁰ These models can be used to develop personal health dataspace including the undergoing “European Health Dataspace (EHDS)” by the European Union.³¹

Additionally, there are also different types of interactions between the real and the virtual: one way is to have scientists or researchers to interact with the virtual models during the

²⁷ See footnote 24, An G (2022).

²⁸ Although not discussed in this paper, organoid medical research, which has gained a lot of attention in recent years, provides a means to tackle these two difficulties. A key advantage of organoids is that they can be used to create models that reflect patient-specific disease-causing features (heterogeneity). In addition, genetic and/or environmental perturbations can be introduced and manipulated, and the response they elicit can be continuously monitored, allowing analysis of human diseases in multiple dimensions. 2023 PRIME Progress Report. https://www.jsps.go.jp/file/storage/e-toplevel/08_followup/FY2023/FY2024_PRIME_E.pdf

²⁹ Mohsen Attaran, Bilge Gokhan Celik, Digital Twin: Benefits, use cases, challenges, and opportunities, Decision Analytics Journal, Volume 6, 2023, 100165, ISSN 2772-6622, <https://doi.org/10.1016/j.dajour.2023.100165>.

³⁰ Interview, Foundation Models in Medical Research, Helmholtz Munich. <https://www.helmholtz-munich.de/en/newsroom/interviews/interview-with-fabian-theis-and-bjoern-eskofier-on-foundation-models>.

³¹ European Commission, European Health Data Space Regulation (EHDS), https://health.ec.europa.eu/ehealth-digital-health-and-care/european-health-data-space_en#more-information.

development stage. Another way is to make patients interact directly with virtual models, enabling patient-centric bidirectional methods in the application of digital twins.³²

The Digital Twin Consortium, in its definition of digital twin published in December 2020, takes a broader view of digital twins in terms of the level of synchronization by including both unidirectional and bidirectional mechanisms. Under that definition, “to *synchronize* is to cause the virtual representation to match more-closely the real-world, and/or cause the real-world to match the virtual representation of a desired state more closely.”³³ The term “synchronization” is chosen instead of “twined” because “twined” is too circular, and compromises the intent and flexibility desired in the general definition. As such, both unidirectional and bidirectional data flow can adequately be referred to as digital twins depending on the desirable level of synchronization.

1.3.4. Predictability

From the reliability of prediction and confidence on application of digital twin technology, the Heads of Science for Data Science and of Digital Metrology in UK’s National Physical Laboratory (part of the National Measurement System) suggest in a paper that digital twins shall fulfill several requirements. The paper considers digital twins as composed of three important parts: (a) a model of the object, (b) an evolving set of data relating to the object, and (c) a means of dynamically updating or adjusting the model in accordance with the data.³⁴

As for part (a), not all models are appropriate for constructing digital twins. In general, a model for a digital twin should be: 1) sufficiently physics-based that updating parameters within the model based on measurement data is a meaningful thing to do; 2) sufficiently accurate that the updated parameter values will be useful for the application of interest, and 3) sufficiently quick to run that decisions about the application can be made within the required timescale.³⁵

As for part (b), the model within the digital twins should extend the use of that model beyond a snapshot at a specific moment, and extend the use of the model to timescales over which the object and its behavior will change significantly. Furthermore, one of the challenges with the data sets in digital twins is to identify which measurements have the most effect on the parameters to be updated within the twin.

Regarding part (c), it requires the creation of a physical twin, which is identical with the human body at the time of creation, and continues to be identical and similar over time. This implies that a digital twin is only meaningful when it reaches the stage of creation of prototype, which can be used to compare with the model to determine similarity and update the parameters in the model. Additionally, prototypes are usually generated in small numbers, and when the models and

³² Schwartz SM, Wildenhaus K, Bucher A and Byrd B (2020) Digital Twins and the Emerging Science of Self: Implications for Digital Health Experience Design and “Small” Data. *Front. Comput. Sci.* 2:31. doi: 10.3389/fcomp.2020.00031.

³³ A glossary of digital twins and digital twin technology from the Digital Twin Consortium.

<https://www.digitaltwinconsortium.org/glossary/glossary/#synchronization>

³⁴ Wright, L., Davidson, S. How to tell the difference between a model and a digital twin. *Adv. Model. and Simul. in Eng. Sci.* 7, 13 (2020). <https://doi.org/10.1186/s40323-020-00147-4>.

³⁵ Ibid.

prototypes are insufficiently similar, the prediction of the models will be less reliable, thereby limiting the impact of digital twin application, and simultaneously bringing about new knowledge that updates the model. In summary, in order to trust the predictions of the digital twin, there must be trust in the data, trust in the model, and trust in the updating procedure.

The approach above distinguishes a digital twin from a model by defining a digital twin as a type of model that reaches a certain level of predictability. In contrast, in differentiating the two, instead of focusing on the level of predictability, one can also look at the interaction between the twin/model and the actual entity.

1.4. Scope of Digital Twins in this Note

Regarding section 1.1, the scope of this note includes both digital twins and virtual humans as both are important technologies to realize digital twins in the medical field.

In terms of section 1.2, given the expansive application and the unpredictable potential of digital twins in healthcare, this note does not explore digital twins in healthcare in its full breath, but rather focuses on digital twins in medical research.

As for section 1.3, although the note identifies the problems and ambiguities in the terms of digital twin, it does not suggest a formal uniform definition is necessary for the current stage. On the contrary, this note includes “digital twins” projects of all types with various levels of relations between the virtual and the real except those that do not reflect a connection at all (i.e. merely digital models). Moreover, because an accurate evaluation of the level of control requires analyzing more detailed information than those published online, it is not practical to categorize projects based on level of control and other issues identified in section 1.3. As such, projects in Part 2 can encompass those that might be considered inappropriate under the more restrictive definitions of “digital twins” and “twinning”

At the current stage, a static and singular definition of digital twin imposed through a top-down system either by regulations or by industry practices does not exist. The stance of the author in this note is that digital twin is still a technology in progress, and the definition shall be formed through continual negotiations among different stakeholders from researchers, medical practitioners, to corporate actors, and last but not least, patients who represent the interests of a diverse range of individuals from the public.

1.5. Digital Twin as a Metaphor

It is also important to consider the use of the term digital twins as a language metaphor and ³⁶“sociomaterial imaginaries.” The symbolic effects of the term digital twins can affect political

³⁶ Braun M. Represent me: please! Towards an ethics of digital twins in medicine. J Med Ethics. 2021 Mar 15;medethics-2020-106134. doi: 10.1136/medethics-2020-106134. Epub ahead of print. PMID: 33722986.

and policy debate and thereby influence research and health funding decisions.³⁷ Further, it has direct impacts on the decision-making process of patients because the choice of the words can have an impact on what patients give priority to.

Additionally, the term “twin” suggests a very strong resemblance to humans, particularly if it brings to mind human identical rather than fraternal twins. As explained in the previous two sections, the term, digital twin, implies an extremely high-level of accuracy and certainty in terms of predictability, which obscures the heterogeneity and multidimensionality in human bodies, which are fundamentally different from industrial and mechanical applications. In health and medical care, where uncertainty, anxiety, fear and a feeling of loss of control are understandably central affective states, the use of descriptive language for such novel technologies offer the promise of better control, efficacy and certainty that is hard to resist.³⁸ Meanwhile, the use of mechanical metaphors for human bodies are common in the postindustrial world: we use pumps for hearts, bellows for lungs. In a reciprocal rhetorical move, digital machines are often anthropomorphized: described as possessing ‘intelligence’, ‘making decisions’ or able to ‘learn’ by being ‘trained’ on datasets.³⁹ While it is criticized that such technological metaphors of the human body can convey misleading concepts of health and disease, the similarity between the human body and machine does function as useful metaphors. Eventually, it has to do with how the stakeholders from patients, doctors to researchers and medicine companies reach an equitable understanding of its usage and implications to minimize misleading techno-utopia promises.

2. Digital-Twin-Driven Research and Development Projects

2.1. Summary of project review results

The ongoing digital twin projects demonstrate a diverse range of possibilities in terms of its names, themes, objectives and focuses.

In terms of naming, as shown in section 1.1, in addition to “digital twin” and “virtual human”, projects are also named with “in silico Patient” and “atlas.” As discussed in section 1.5, the term digital twin is not completely neutral, and can carry with it specific cultural and social images, which will affect perceptions of individual body and health. Regardless of the project awareness and intention of appropriating such cultural and social images, by including digital twin in the project name, unless clearly articulated in the description of the project, it inadvertently conveys

³⁷ Jasanoff S. Future imperfect: science, technology, and the imaginations of modernity. In: Jasanoff S, Kim S-H, eds. *Dreamscapes of Modernity: Sociotechnical Imaginaries and the Fabrication of Power*. Chicago: University of Chicago Press, 2015: 1–33

³⁸ Lupton D. *Medicine as Culture: Illness, Disease and the Body*. 3rd edn. London: Sage, 2012.

³⁹ Lupton D. Language matters: the ‘digital twin’ metaphor in health and medicine. *Journal of Medical Ethics* 2021;47:409, <https://jme.bmj.com/content/47/6/409.full>, see also footnote 24, An G (2022) Specialty Grand Challenge: What it Will Take to Cross the Valley of Death: Translational Systems Biology (suggesting impossibility of BDT).

a promise to build a digital equivalent of an individual patient, despite of the absence of a clear standard regarding what can be considered as appropriately “equivalent”.

Compared to the diversity in project names, the overall themes are relatively unified, because almost all the projects listed below share the similar goal of creating models, simulations, representations or merely twins of the target aspect of human beings. Additionally, some projects shift their perspectives from model-building to theoretical framework, virtual space, or research infrastructure. In those cases, the themes are described as constructing general “platform,” “reference map,” “consortium,” and “metaverse.” In some projects, construction of specific digital twins can be a necessary components of the abstract framework such as in the case of 3D-BrAI_n and PRIME, while in other projects, researches are not necessarily conducted based on individual patients, nor necessarily linked to specific characteristics or genetic markers, and the “digital twin” is relevant here mainly as a research method.

The objectives of digital twins projects can be divided into the pre-application stage, which aims at enhancing and expanding scientific knowledge and the application stage, and the application stage can be further divided into disease monitoring, diagnosis, and treatment (See Figure 1). Further, digital twins for clinical decision-making serve as examples for monitoring and diagnoses. Examples of digital twins treatment can include development of precise medicine and drug testing. As clearly shown in the tables below, most of the projects claim more than one objective. While some projects focus on a single objective, others such as European Virtual Human Twins (VHT) Initiatives cover almost all the objectives from the pre-application stage to the application stage.

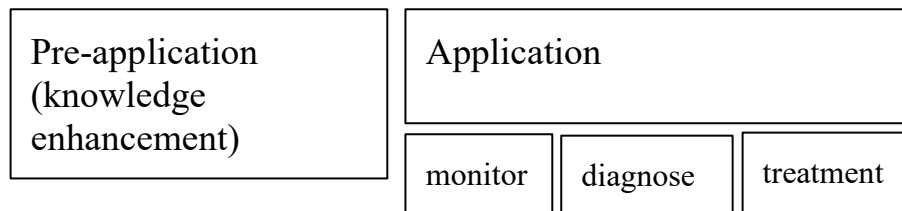


Figure 1. Stages of Digital Twins Projects

Last but not least, digital twin projects can be organized in terms of the focus or target of research (See Figure 2). Given the daunting task of making a complete digital twin, it is usually more practical to start with a single type of cell or organ, and build up the whole digital twin step by step, although sometimes cell-focused researches are too elemental to be named as digital twins. Organ-focused digital twins projects are more prevalent. While some projects target a specific disease of an organ, others try to build a comprehensive model for the whole organ. Between organ and body, there are also projects that analyze the working of multiple organs in order to tackle a particular disease or to better understand a particular physiological system such as the Immune Digital Twin.

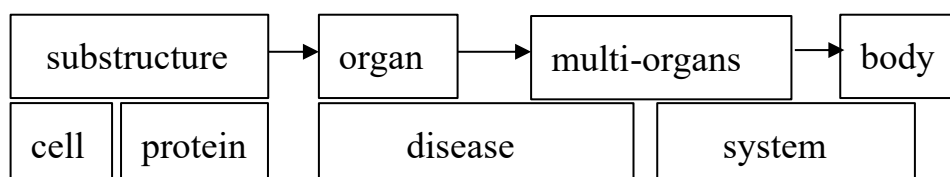


Figure 2. Focus/Targets of Digital Twins Projects

2.2. Digital-Twin-Driven Projects

The following tables summarize large-scale research projects related to digital twins in medical research. The first column describes the official project name. The second column shows the project time span. The third column provides a brief summary of what the project tries to build or achieve. The fourth column lists the major objectives. The fifth column shows the level of the bio-digital twin and the focus of the level in the project. The sixth column shows what kinds of ELSI programs are conducted along with the project.

Table 1a: Projects Supported by European Commission (Ongoing Funding)

1. Project Name	2. Time Span and funding resource	3. Theme	4. Objective	5. Focus/Target	6. ELSI-related programs
3D-BrAI (Revolutionary high-resolution human 3D brain organoid platform integrating AI-based analytics)	• April 2023- March 2028 • Horizon Europe⁴⁰ https://3dbrain-project.eu/	- a bio-digital twin model of the human brain	- personalised precision medicine for central nervous system disorders	Organ (brain)	NA
CERTAINTY(A CELLulaR limmunoTherapy virtuAl twin for personallised cancer treatmeNT)	• Dec 2023- May 2028 • Horizon Europe⁴¹ https://www.certainty-virtualtwin.eu/	- a multi-scale patient-specific human virtual twin	- cancer treatment	multi-organ	Yes
European Virtual Human Twins (VHT) Initiatives	• Since 2023 • Horizon Europe⁴² https://www.virtualhumantwins.eu/	- integrated, validated digital representations of the human body	- a deeper understanding of human physiology, pathology, and disease etiology, as	body	Yes

⁴⁰ <https://cordis.europa.eu/project/id/101098791>.

⁴¹ <https://cordis.europa.eu/project/id/101136379>

⁴² <https://digital-strategy.ec.europa.eu/en/policies/virtual-human-twins>; Horizon Europe (80 million EUR), Digital Europe Programme (24 million EUR), pan-European federated infrastructure for Intensive Care Units' (ICU) (5 million EUR) and Innovative Health Initiative (20 million EUR).

			well as facilitating personalized, patient-centric medicine		
EDITH (Ecosystem Digital Twins in Health) ⁴³ as part of the European Virtual Human Twin, focusing on integration and ecosystem	• Since 2023 • funded as part of VHT https://www.edith-csa.eu/	- an integrated multiscale, multi-time, and multi-discipline representation of quantitative human physiology and pathology	- to accelerate the development, integration, and adoption of patient-specific predictive computer models	body	Yes
Virtual Humans by ELEM Biotech ⁴⁴	• Since 2018 • European Innovation Council Fund https://www.elem.bio/	- Predictive modeling and simulation for Virtual Humans based on supercomputers in the Cloud	- to be used as surrogates in virtual patient trials, in clinician support, and in treatment innovation and development	body	NA
GEMINI (Generation of Multi-scale Digital Twins of Ischaemic and Haemorrhagic Stroke Patients)	• Dec 2023-Nov 2029 • Horizon Europe⁴⁵ https://dth-gemini.eu/	- multi-organ and multi-scale computational models	- for treatment decision support and improved fundamental understanding of acute strokes	Disease (ischaemic and haemorrhagic stroke)	NA

⁴³ <https://www.digitaleurope.org/news/the-ecosystem-digital-twins-in-health-edith-project-kicks-off/>

⁴⁴ Founded in 2018, ELEM Biotech is a biomedical software technology company that creates virtual humans using mathematical modelling on high performance computing in the cloud.

⁴⁵ <https://cordis.europa.eu/project/id/101136438>.

OPTOMICS (Combining optoacoustic imaging phenotypes and multi-omics to advance diabetes healthcare) ⁴⁶	• Jan 2021 - Dec 2026 • Horizon Europe https://optomics.munichimaging.eu/	- develop digital twin	- for type 2 diabetes healthcare	Disease (diabetes)	NA
SMASH-HCM (Stratification, Management, and Guidance of Hypertrophic Cardiomyopathy Patients using Hybrid Digital Twin Solutions)	• Jan 2024 - Dec 2027 • Horizon Europe⁴⁷ https://smash-hcm.eu/	- a digital-twin platform	- to dramatically improve HCM stratification and disease management both for clinicians and patients	Disease (Hypertrophic cardiomyopathy)	NA
Swedish Digital Twin Consortium	• Sept 2022 - Aug 2029 • Horizon Europe⁴⁸ https://www.sdtc.se/	- a multi-disciplinary consortium with partners from health care, medical and technical faculties and industry (EU)	- to increase efficiency of medicine (personalized medicine) and cure human disease by testing the best-performance drug	body	NA
Health virtual twins for the personalised management of stroke related to atrial fibrillation ⁴⁹	• Jan 2024- Dec 2028 • Horizon Europe https://cordis.europa.eu/project/id/101137115	- personalised, integrated, multi-scale computational models (virtual twins)	- personalised management of stroke related to atrial fibrillation	Disease (Atrial Fibrillation-Related Stroke)	NA

⁴⁶ <https://optomics.munichimaging.eu/>

⁴⁷ <https://cordis.europa.eu/project/id/101137115>.

⁴⁸ <https://cordis.europa.eu/project/id/101057619>; <https://link.springer.com/article/10.1186/s13073-025-01435-7>

⁴⁹ <https://cordis.europa.eu/project/id/101136244>; <https://pubmed.ncbi.nlm.nih.gov/39401519/>

	36244				
Virtual Physiological Human Institute (VPH Institute)	• since 2007 • Involving several European Commission-funded project https://www.vph-institute.org/	- the use of individualized physiology based computer simulations	- in prevention, diagnosis, prognostic assessment, and treatment of a disease and development of a biomedical product.	body	NA

Table1b: Projects Supported by European Commission (Funding Ended)

1. Project Name	2. Time Span and funding	3. Theme	4. Objective	5. Scale	6. ELSI programs
Virtual Human in the CompBioMed project (A Centre of Excellence in Computational Biomedicine)	• Oct 2019 - March 2024 • Horizon Europe⁵⁰ https://www.compbiomed.eu/	- the creation of virtual physiological humans	- personalized medicine	body (the use and development of computational methods for biomedical applications)	NA
DIGIPREDICT project (AI-deployed DIGItal Twins for PREDICTing disease progression and need for early intervention in infectious and cardiovascular diseases)	• Jan 2021- March 2025 • Horizon Europe⁵¹ https://www.digipredict.eu/	- a digital representation of a patient and disease process	- predict the progression of disease and the need for early intervention in infectious and cardiovascular diseases to be used at hospitals	body	Yes

⁵⁰ <https://cordis.europa.eu/project/id/675451>

⁵¹ <https://cordis.europa.eu/project/id/101017915>

beyond COVID-19)					
EBRAINS (European Brain ReseArch INfrastructureS) ⁵²	• Sept 2022 - Feb 2025 • Horizon Europe⁵³ programme https://humanbrainproject.eu/en/	- infrastructure for personalised brain models	- a deeper understanding of the complex structure and function of the human brain	Organ (Brain)	Yes
MeDiTATe (Medical Digital Twin for Aneurysm Prevention and Treatment)	• Jan 2020- Dec 2024 • Horizon Europe⁵⁴ https://meditate-project.eu/	- an image based medical Digital Twins of cardiovascular districts	- for a patient specific prevention and treatment of aneurysms and to make it available as "a service" for all in academia, hospital and industry	Organ (heart, aneurysm prevention)	NA
Neurotwin	• Jan 2021- June 2025 • Horizon Europe⁵⁵ https://www.neurotwin.eu/	- brain models that characterize individual pathology and predict the physiological effects of transcranial electromagnetic stimulation	- for optimal brain stimulation protocols in Alzheimer's disease	Organ (brain)	NA
PerMedCoE (Exascale Centre of Excellence in Personalised	• Oct 2020 - Dec 2023 • Horizon Europe⁵⁶	- a sustainable roadmap	- to scale-up the essential software for the cell-level simulation	organ	Yes

⁵² <https://roadmap2021.esfri.eu/projects-and-landmarks/browse-the-catalogue/ebrains/>

⁵³ <https://cordis.europa.eu/project/id/101079717>

⁵⁴ <https://cordis.europa.eu/project/id/859836>

⁵⁵ <https://cordis.europa.eu/project/id/101017716>

⁵⁶ <https://cordis.europa.eu/project/id/951773>

Medicine)	https://perme.dcoe.eu/				
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Table 1c: Projects by Countries

1. Project Name	2. Country, Time Span	3. Theme	4. Objective	5. Scale	6. ELSI-related programs
Immune Digital Twin (IDT) ⁵⁷	• US • Since 2022 (7 year plan)	- a medical digital twin (MDT) focusing on immune system⁵⁸ - a blueprint for immune system	- for clinical decision-making	multi-organ	NA
Foundational Models in health research	• Germany • Since 2023 • by Helmholtz Munich which is funded by Helmholtz Association https://www.helmholtz-munich.de/en/computation-al-health-center/foundation-models-in-medicine	- large-language models trained by large health dataset	- personalized treatment and disease prediction	body	NA

Table 1d: Projects by Multiple Trans-Continental Groups

1. Project Name	2. Time Span and funding	3. Theme	4. Objective	5. Scale	6. ELSI-related programs
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⁵⁷ <https://www.nature.com/articles/s41746-022-00610-z>

⁵⁸ <https://arxiv.org/pdf/2310.18374>

Human Cell Atlas (HCA)	• Since Oct 2016⁵⁹ • Funding from multiple sources⁶⁰ https://www.humancellatlas.org/	- a comprehensive reference map for human cells	- for understanding human health and diagnosing, monitoring and treating disease.	cell	Yes
Human Heart Atlas	As part of the project of HCA	- a spatial mapping of individual cells	- to resolve the identity of the cardiac cell types by illumination of cells' organization into cellular communities that form distinct cardiac structures	cell	NA
IBI (International Brain Initiative)	• Since 2017 • funded by Fonds de recherche du Québec and Canadian Institutes of Health Research⁶¹ https://www.internationalbraininitiative.org/about	- a global platform brain research - circuitry and molecular multiscale brain mapping	- understanding mental illness trajectories and building mental health strategies	organ	Yes

⁵⁹ <https://www.humancellatlas.org/learn-more/#event-launch-of-the-human-cell-atlas>

⁶⁰ <https://www.humancellatlas.org/funders-supporting-hca/>

⁶¹ <https://www.internationalbraininitiative.org/about>

	tive.org/				
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Table 1e: Projects by Private Companies

1. Project Name	2. Country,	3. Theme	4. Objective	5. Scale	6. ELSI-related programs
Nova Heart ⁶²	• UK • project of AIBODY	- a dynamic, 3D digital twin of a patient's heart using 2D transthoracic echocardiogram data	- to improve clinical workflow and personalized medicine	Organ (heart)	NA
Silico Patient for Rheumatoid Arthritis ⁶³	• US • project by GNS Healthcare and Scipher Medicine⁶⁴	- in silico patient models	- improved clinical trial design and maximize the impact of drugs	Disease (Rheumatoid Arthritis)	NA

Table 1f: Projects in Japan

1. Project Name	2. Time Span and funding	3. Theme	4. Objective	5. Scale	6. ELSI-related programs
PRIME (The University of Osaka Premium Research Institute for Human Metaverse Medicine)	• 2022 Dec- • As part of the World Premier International Research Center Initiative (WPI) funded by the Ministry of Education,	- a bio-digital patient twin	- to combine biological sciences with mathematical computer sciences to combat multi-factor diseases and realized personalized medicine.	body	PRIME ELSI Team was founded along with the launch of PRIME in 2022

⁶² <https://aibody.io/nova-heart>

⁶³ <https://www.aitiabio.com/gns-to-develop-the-worlds-first-in-silico-patient-for-prostate-cancer/>; <https://www.aitiabio.com/gns-healthcare-and-scipher-medicine-collaborate-to-develop-worlds-first-in-silico-patient-for-rheumatoid-arthritis/>

⁶⁴ <https://www.sciphermedicine.com/gns-healthcare-and-scipher-medicine-collaborate-to-develop-worlds-first-in-silico-patient-for-rheumatoid-arthritis/>

	Culture, Sports, Science and Technology (MEXT). https://prime.osaka-u.ac.jp/about/				
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3. ELSI-related Programs of Digital Twin Projects

3.1. Ethics Guidelines

Among twenty-one digital-twin-related projects listed in Table 1 discovered through online research, it is found that at least eight incorporate ELSI-related programs in its current research. Moreover, the majority of the approaches to deal with ELSI are non-binding guidelines, self-assessment, templates, and training materials for researchers to observe ethical rules. Not all of the projects publish the details of their ELSI-related program online, and the following charts provide some examples where the organizations disclose the materials and documents for their ELSI-related programs.

Table 2a: Materials and Documents for Ethics Guidelines

Human Cell Atlas	Ethics Submission Guidance Document ⁶⁵ Ethics and Data Governance Document ⁶⁶
EDITH	VHT roadmap –chapter on Standards, regulations, legal, ethical and social aspects of the Virtual Human Twin ⁶⁷
PerMedCoE ⁶⁸	Ethics and legal assessment of use cases (not yet available)

3.1.1.Ethics Guideline of Human Cell Atlas

Human Cell Atlas (HCA) aims to create a reference map for all human cells that can be used by all researchers. It is committed to creating open access reference maps of tissue and biological systems that will be useful to scientific researchers, and host individual datasets in a public

⁶⁵ <https://drive.google.com/file/d/1hRh8CPnYV7AtmvB2AAgLuF5CdIdsb3Lu/view>.

⁶⁶ <https://drive.google.com/file/d/1112-L6LTSAlsDCcqEZRIEy43TebUVCGB/view>.

⁶⁷ <https://zenodo.org/records/8200955>.

⁶⁸ <https://permedcoe.eu/summary/>.

database for further use by scientific researchers. Currently, only data that can be publicly shared can be currently submitted to HCA.⁶⁹ In order for members of the HCA community to understand the ethical framework, and for researchers to adapt their own regulations, laws and local requirements to the HCA standard, the Ethics Working Group of HCA has created the Ethics Toolkit to help facilitate adaptability and compliance.

Ethics and Data Governance Document provides an overview of HCA ethical principles, rules and procedures. It incorporates all fundamental principles suggested by the Global Alliance for Genomics and Health Framework for Responsible Sharing of Health Related Data as the following:⁷⁰

- Respect Individuals, Families and Communities
- Advance Research and Scientific Knowledge
- Promote Health, Wellbeing and the Fair Distribution of Benefits
- Foster Trust, Integrity and Reciprocity

In order to promote these principles and help those who are involved in data sharing to implement the values in practice, the following core elements of responsible data sharing are promulgated:

- Transparency;
- Accountability;
- Data quality and security;
- Privacy, data protection and confidentiality;
- Risk-benefit analysis;
- Sustainability;
- Education and training;
- Accessibility and dissemination.

One element that is provided in the Alliance publication but missed in the HCA Document is “recognition and attribution,” which usually requires a “design systems of data sharing with a view towards recognition and attribution that are meaningful and appropriate to the medium or discipline concerned and which provide due credit and acknowledgement of all who contributed to the results” and “extend recognition and attribution both to primary purposes and, as appropriate, to secondary or downstream uses and applications.”⁷¹ Although HCA values the importance of completely open data, and freedom of nonprofit and commercial utilization of data⁷², the element of recognition and attribution of researchers with different means and levels of attribution is not affirmed anywhere in the Document.

⁶⁹ but a registered access tier may also become available in the next development phases of the HCA Data Coordination Platform (DCP). See Human Cell Atlas Ethics Submission Guidance Document, 2020 Jan 27, <https://drive.google.com/file/d/1hRh8CPnYV7AtnvB2AAGLuF5CdFdsb3Lu/view>

⁷⁰ Knoppers BM. Framework for responsible sharing of genomic and health-related data. Hugo J. 2014 Dec;8(1):3. doi: 10.1186/s11568-014-0003-1. Epub 2014 Oct 17. PMID: 27090251; PMCID: PMC4685158.

⁷¹ Framework for responsible sharing of genomic and health-related data, 4.7 Recognition and Attribution, <https://www.ga4gh.org/framework/>

⁷² HCA does not prohibit commercial use of data, but its Data Release Policy and ethics guidelines pose certain restrictions on the data use. <https://www.humancellatlas.org/data-release-policy/>; <https://data.humancellatlas.org/about/data-use-agreement>; <https://www.nature.com/articles/s41467-024-54306-x>

Further, the Ethics Submission Guidance Document of HCA (which is used for researchers and institutes who plan to contribute their data to HCA) explains the Core Consent Elements, which are items that shall be informed when obtaining consent in research consent forms, including but not limited to “international sharing of data” and “a risk that the participant could be re-identified in the future, including through linkage with external databases.”

As a research involves big data, AI and organoid, the document also covers risks that exist for the research donors who contribute their research data to the HCA databases such as risks that “there may be new ways of linking data back to tissue donors that cannot be foreseen today” and “revealing information that was previously unforeseen” as technology advances; “a risk that information revealed through projects using HCA data be used to make certain statements or conclusions related to individuals, families, groups or communities, which could lead to discrimination or stigmatization”; and “metadata being made available could reveal the donor’s age, geographic location, limited clinical information, cause of death, ethnicity, etc.” Additionally, the document explains what obligations the researchers agree to by contributing data to the HCA database.

HCA’s ethics-related practices are complemented by the Equity Working Group (EqWG), whose goal is to promote and support progress for equity in the HCA through publications and statements.

3.1.2.Data diversity of HCA

As part of the ethics-related program, HCA’s Diversity Task Force (DTF) examines issues related to the tracking and sampling of diversity in HCA data. Further, an open statement published by the Human Cell Atlas Equity Working Group (EqWG) and of the Human Cell Atlas Ethics Working Group (EWG) states in its very beginning that “human life is diverse,” which shows the very foundation of the research of HCA envisions diversity and heterogeneity.

3.1.3.Ethical guidelines of Horizon Europe Program

Unlike the non-compulsory guidelines provided by HCA, projects funded by Horizon Europe are subject to binding ethical rules, although those rules are not project-specific. The projects funded by Horizon Europe are bound by compulsory ethical rules. All the Horizon Europe projects that receive European Research Council grants must follow the Ethics Appraisal Procedure, which includes grants reviews and checks from the pre-research to the post-research stages.⁷³ Although the guidelines and roadmap provided by European Commission are not digital twin-specific⁷⁴, its publication Ethics By Design and Ethics of Use Approaches for Artificial Intelligence summarizes six key principles and non-binding ethical requirements when applying artificial intelligence in science and innovations: 1) respect for human agency; 2)

⁷³ European Research Council, Ethics Guidelines, <https://erc.europa.eu/manage-your-project/ethics-guidance>; see also legally binding principles in the Regulation of the European Parliament and of the Council, <https://eur-lex.europa.eu/legal-content/EN/TXT/?uri=CELEX%3A52018PC0435/>

⁷⁴ European Commission, 2021 July 5, Identifying serious and complex ethics issues in EU-funded research, https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/guidelines-on-serious-and-complex-cases_he_en.pdf; Ethics and Data Protection Decision Tree, <https://ec.europa.eu/assets/rtd/ethics-data-protection-decision-tree/index.html>.

privacy, personal data protection and data governance; 3) fairness; 4) individual, social, and environmental well-being; 5) transparency; and 6) accountability and oversight. Further the document recommends practical steps and ethical deployment in applying these principles.⁷⁵

3.2. Data Protection

Research organizations offer different types and levels of requirements and guidelines regarding handling and protection of data. For example, while EBRAINS asks all the data providers to include comprehensive information about the handling of incidental findings, and recognized certain rights in data control (such as erasure and modification),⁷⁶ HCA publishes more comprehensive and detailed requirements on informed consent, data ownership and data use. As such, this section will focus on the analysis of data protection of HCA.

Table 2b: Materials and Documents for Data Protection

Human Cell Atlas	• Biomedical Research Database Data Protection Impact Assessment Template⁷⁷ • Material/Data Transfer Agreement (MDTA)⁷⁸ • Ethics and Data Governance Document⁷⁹ • HCA Data Release Policy
Human Brain Project (the hosting organization of EBRAINS)	Data Governance Information Page ⁸⁰
PerMedCoE	DPIA (Data Protection Impact Assessment of the Use Cases) ⁸¹

3.2.1. Informed consent: HCA local-focused consent

Currently, HCA research data is made available through open access (public database), and in the future HCA plans to have managed and controlled data, which can only be made available upon application and approval of the Data Access Compliance Office.

One feature of HCA is its effort to empower local communities through efforts of data protection. At HCA the nature of information to be generated, stored, analyzed and shared with the community, and the modalities of conduct of these activities are also determined in consultation with local scientists, members of the community, ethics committees and other similar groups of

⁷⁵ European Commission, Ethics By Design and Ethics of Use Approaches for Artificial Intelligence, 2021 Nov. 25, https://ec.europa.eu/info/funding-tenders/opportunities/docs/2021-2027/horizon/guidance/ethics-by-design-and-ethics-of-use-approaches-for-artificial-intelligence_he_en.pdf.

⁷⁶ https://strapi-prod.sos-ch-dk-2.exo.io/EBRAINS_Data_Provision_Protocol_dfe0dcb104.pdf

⁷⁷ <https://www.humancellatlas.org/ethics-working-group/>

⁷⁸ <https://docs.google.com/document/d/1MpUXC7ayY7RAYeZrEMbEdoYn2l-rIBDR/edit#heading=h.gidgxs>

⁷⁹ <https://drive.google.com/file/d/1112-L6LTSAIsDCcqEZRIEy43TebUVCGB/view>

⁸⁰ <https://ebrainsethicsandsociety.tekno.dk/tools/data-governance/>

⁸¹ <https://permedcoe.eu/deliverables/>

the community. Moreover, HCA obtains written consent to participate from each participant, but only after the participant is completely satisfied with their explanations and with their answers to the community's questions about the study. During its data handling process, it is stated that the HCA is committed to making sure that information is collected and shared in an appropriate manner with participating individuals and/or the groups that comprise their identity.⁸² In other words, the value of diversity and value of community autonomy converge during the process of data handling. Instead of imposing top-down uniform data protection rules and procedures, HCA data handling allows flexibility and diversity according to the needs and backgrounds of different communities.

3.2.2.HCA's data ownership

In the HCA template for Material/Data Transfer Agreement (MDTA), the ownership of the data belongs to either the Providing Institute or the Receiving Institute, who will "retain ownership of the Research Materials and shall have the unrestricted right to use, assign, or distribute the Research Materials to any third parties for any other purposes."⁸³ The ownership of data determined by the negotiations between parties and the nature of the collaboration.

Meanwhile, parties have the option to contribute the data to HCA, meaning that party "will enter into a data contribution agreement with the HCA, and appropriately acknowledge all members of the Research Team"⁸⁴ as detailed in the agreement. Parties (original data for the providing party and derived data for the receiving party) who enter into a data contribution agreement with HCA will follow the HCA Data Release Policy⁸⁵, as may be amended from time to time by the HCA, which imposes certain restrictions and obligations on the data owner given the strong public interests in using the data according to the Fort Lauderdale Principles, which was agreed among biomedicine experts at the meeting held in Fort Lauderdale in 2003..

3.2.3.HCA's data use restriction

The HCA Data Release Policy follows the Fort Lauderdale Principles, which provides the broadest and the most unrestricted use of data to the extent that it does not infringe on patient and donor consent and legal regulations across different countries, in order to encourage research and development, and to maximize its benefit to society.⁸⁶

Specifically, under the HCA Data Release Policy, the parties shall enter into an data sharing that follows the Fort Lauderdale Principles. Data should be uploaded as soon as possible after generation. Data users may immediately analyze part or all of the data but should refrain from

⁸² Amit, I., Ardlie, K., Arzuaga, F. *et al.* The commitment of the human cell atlas to humanity. *Nat Commun* 15, 10019 (2024). <https://doi.org/10.1038/s41467-024-54306-x>.

⁸³ See section 9.2, Human Cell Atlas - Ethics Toolkit Template: Material/Data Transfer Agreement (MDTA), <https://docs.google.com/document/d/1MpUXC7ayY7RAYeZrEMbEdoYn2l-rIBDR/edit?tab=t.0>.

⁸⁴ See section 6.1-2, Human Cell Atlas - Ethics Toolkit Template: Material/Data Transfer Agreement (MDTA).

⁸⁵ Human Cell Atlas, Data Release Policy, <https://www.humancellatlas.org/data-release-policy/>.

⁸⁶ The Wellcome Trust, Sharing Data from Large-scale Biological Research Projects: A System of Tripartite Responsibility, <https://www.genome.gov/Pages/Research/WellcomeReport0303.pdf>.

reporting global analyses until the data producers publish their first paper reporting results of global analyses to allow the data producers the first to present global analyses of their data.

3.3. Organizational Structure and ELSI

The organization structure of research institutes also play an important role in the implementation and generation of guidelines and activities of ELSI. While not all the research institutes differentiated the functions of the ELSI-related committees, and integrated them into the overall organizational structure, HCA's organizational structure illustrates how ELSI-related groups are positioned in the organization to influence its work progress.

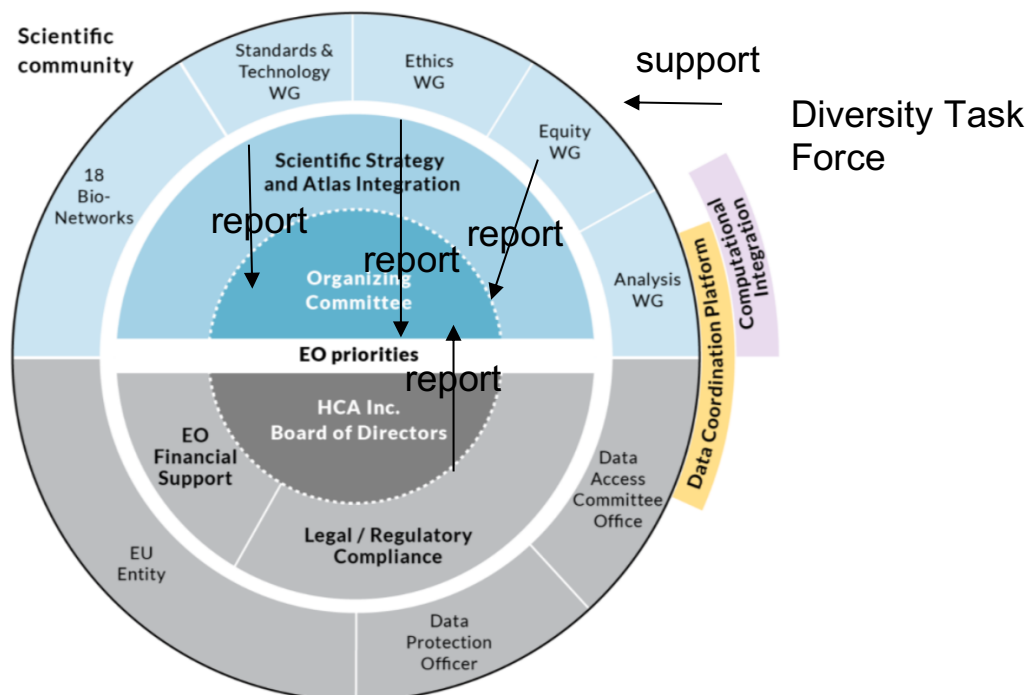


Figure 3: Organizational Structure of HCA⁸⁷

Source: Human Cell Atlas Ethics and Data Governance Document, <https://drive.google.com/file/d/1112-L6LTSAlsDCcqEZRIEy43TebUVCGB/view>.

The HCA is structured through a non-profit legal entity, HCA Incorporated (HCA Inc.), established in the United States. The scientific objectives of the HCA are steered and governed by an Organizing Committee (OC).

The ELSI programs of HCA are constituted by three different internal advisory groups: 1) Ethics Working Group (EWG) and 2) Equity Working Group (EqWG).⁸⁸ However, none of these groups

⁸⁷ <https://drive.google.com/file/d/1112-L6LTSAlsDCcqEZRIEy43TebUVCGB/view>.

⁸⁸ Human Cell Atlas, Working Group, <https://www.humancellatlas.org/learn-more/working-groups/>.

have decision making power or binding authority over the decision-making authority, Organising Committee (OC), and merely affect the directions and progress by reporting to OC.

The Ethics Working Group (EWG) has been set up to examine ethical governance issues related to the HCA. It only has an advisory role, does not provide legal opinions, nor is it responsible for decisions made with respect to the structure or governance of the HCA. The specific role of the EWG includes: discussing ethics-legal issues relevant to the HCA particularly in relation to its global reach; providing input and commenting on ethics governance documents and tools related to the HCA. It shall regularly report to OC any issue it believes should be brought to the attention of, or which requires decision-making by the OC.⁸⁹

The Equity Working Group (EqWG) aims to promote and support progress towards equity in the HCA. The EqWG seeks to engage the global community spanning diverse geographic and ethnic groups to drive inclusive representation and participation, and promote equal benefit from the HCA.

Further, to ensure communication and coordination between the scientific leadership, operational management, and representative funders, HCA also establishes the Joint Coordinating Committee (JCC), which evaluates and reports back to HCA OC on the overall scope and executional success of the HCA operations in achieving the HCA's mission, with special attention to ethical and legal matters. Moreover, in order to bring together groups and centers to compare and disseminate existing methods, it creates the Standards and Technology Working Group (STWG) to smooth the process of technological collaborations of different working groups.

4. End

In summary, Part 1 of this note shows that a unified monolithic definition of digital twin is hard to achieve given the ambiguities and variances in the meanings of digital twins in medical research. However, several key features such as the level of control and predictability of digital twins in medical research can serve as useful factors to differentiate types of digital twins in terms of their functionalities and purposes. Part 2 summarizes major digital twin projects, groups them in terms of regions and categorizes them based on their themes, objectives, and level of focus. Part 3 introduces the ELSI-related programs of the digital twin research institutes to illustrate how institutes integrate ELSI into their activities and organizational structure.

Authors of this Note are members of WPI-PRIME, which is a pilot research institute in Japan aiming at conquering all human diseases using bio-digital twins and human metaverse that integrate biomedical sciences and mathematical and computational sciences. Since the kickoff of PRIME project in 2022, the Ethical, Legal, and Social Issues (ELSI) team has been part of the

⁸⁹ Human Cell Atlas Ethics and Data Governance Document, <https://drive.google.com/file/d/1112-L6LTSAIsDCqEZRIEy43TebUVCGB/view>.

research⁹⁰. The roles of the PRIME ELSI team include policy review regarding ethics and data management, drafting and proposing rules, and designing and implementing Patient and Public Involvement (PPI) programs for PRIME research. Moreover, PRIME established the Equity, Diversity, and Inclusion (EDI) committee in 2024.⁹¹ The EDI Committee consists of researchers from the wet and dry lab, administrative staff as well as researchers from the PRIME ELSI team. So far the EDI Committee has published its Equity Diversity Inclusion and Belonging (EDIB) statement and Terms of Reference, and held the first EDI workshop on “Creating a Workplace to Achieve Diversity: How to Break the Habit of Bias?” in March 2025.⁹² Like other bio-digital twin research projects, much is still needed to be done in order to realize a new technology that would impact the everyday life and future living of all, there is an affirmed and clear intention to develop and enrich ELSI programs at PRIME and many other research projects introduced here.

The utilization of bio-digital twins for predicting prognosis of various chronic diseases lies at the center of PRIME research project. As an ever-changing and ever-evolving technology, this Note might not cover all types of bio-digital twins, but it provides an overview of the past and existing bio-digital twin both as a concept and as an application, which would to some extent help PRIME to navigate its ultimate goal and come up with the most suitable application of bio-digital twins for an unprecedented healthcare technology in the near future.

⁹⁰ <https://elsi.d3c.osaka-u.ac.jp/>

⁹¹ <https://prime.osaka-u.ac.jp/about/edi/>

⁹² <https://prime.osaka-u.ac.jp/about/edi/>

Review of Digital Twin Projects in Medical Research and their ELSI Programs

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