



# eBRAIN-Health

## Public report

‘Scoping review on digital twins for dementia research’ – Deliverable D2.3.

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### 1. eBRAIN-Health

The Project eBRAIN-Health will deliver a distributed research platform for modeling and simulating complex neurobiological phenomena of human brain function and dysfunction in a data protection compliant environment. It will provide thousands of multilevel virtual brains from patients and healthy human controls for research and innovation. Brain data from multiple sources will be pre-processed. Solving the societal grand challenge of dementia is a big task. Yet it appears feasible in a collective approach. Therefore, we will build an interdisciplinary digital twin for dementia for modelling and simulating complex phenomena at the service of research infrastructure communities. eBRAIN-Health-Cloud will offer end-to-end services for personalized complex brain modelling and simulations in

distributed e-infrastructures with data protection by design and by default and simulation-ready human multiscale brain data that range from molecular (genomics, proteomics, metabolomics) and cellular to electrophysiology and imaging to behavioural, clinical, lifestyle and environmental data as well as data from wearables. Brain data are pre-processed and annotated such that they all relate to a common reference 3D brain space.

eBRAIN-Health-Cloud constitutes a blend of three large-scale research programs: the FET Flagship Human Brain Project with its EBRAINS Research Infrastructure, the EOSC project Virtual Brain Cloud with its Virtual Research Environment for sensitive data and the H2020 project AI-MIND with intelligent tools for dementia risk estimation. The project will have synergies to topics of the Digital Europe Program, such as artificial intelligence, cybersecurity and supercomputing and the European Health Data Space.

eBRAIN-Health-Cloud offers a next-generation clinical research infrastructure and creates an open yet protected space for groundbreaking digital health innovation by the research infrastructure communities comprising academia and the private sector.

## 2. Introduction

### 2.1. Aims of this deliverable

This deliverable consists of a scoping review of peer-reviewed and grey literature providing exploration of the ethical considerations surrounding the development and use of digital brain twins in research, their applications in clinical settings and their wider societal use. This deliverable also lays out some recommendations for policymakers and digital twin researchers as well as avenues for further research on the ethics of digital brain twins. Additionally, the scoping review includes a particular focus on the use and development of digital brain twins in the context of dementia and pre-dementia. In addition to providing an overview of the ethical issues identified in the literature, the findings section of this deliverable offers valuable insights into the points of discussion, policy recommendations and avenues for further research put forward in the literature. The discussion section presents further reflections on the limitations of the present review as well as Alzheimer Europe's perspectives on avenues for further research and consideration of the ethics of digital brain twins.

The ethical value and concerns related to the use and development of digital brain twins in the context of dementia were further discussed through public involvement activities with the eBRAIN-Health Patient and Public Advisory Group. This work fed into the development of ethical guidance on the use of digital brain twins in research and clinical settings. These findings have been integrated into the Initial Legal and Ethical Framework (Deliverable 2.2.).

### 2.2. Background information on digital brain twins

The eBRAIN-Health project platform is focused on building 'digital brain twins'. The term digital brain twins refer to computational models or simulations that aim to replicate and mimic some elements of the complex structure, functionality and dynamics of the human brain. These models seek to capture, for instance, the intricate interplay of neurons, synapses and neural circuits, along with the emergent behaviours and cognitive processes exhibited by the human brain (Braun, 2021) (Ferdousi et al., 2021). Digital brain twins are created through the integration of various disciplines, including neuroscience and computer science and make use of advanced artificial intelligence algorithms. By providing

representations of the neural architecture and activity patterns of the brain, digital brain twins offer a way to deepen our understanding of brain function, explore hypotheses and potentially provide insights into cognitive phenomena and certain brain conditions such as dementia. Digital brain twins are usually updated through AI systems, with new information at regular intervals (e.g. through remote monitoring of certain data). A digital brain twin can serve to better understand the particular brain of an individual person as it offers the possibility of personalisation: this is achieved by inserting personal information about the individual into the brain model with the goal of representing certain features of that person's brain (Braun, 2021) (Ferdousi et al., 2021).

### 3. Partners involved

Alzheimer Europe with feedback from Klaudia Kwiatkowska (University of Vienna) and Manuel Guerrero (Centre for Research Ethics & Bioethics (CRB), Department of Public Health and Caring Sciences, Uppsala University – Sweden).

### 4. Methodology

Based on initial background research into the topic and the aim of the review, the following research questions were developed:

#### Research Questions:

1. What are the ethical and societal implications linked to the design, development and use of digital brain twins in research and in the clinic, particularly in relation to people with concerns about cognitive deterioration or dementia, or who are at higher risk, in a prodromal phase or have dementia?

Although the focus of this review is on cognitive deterioration and dementia, we will also search for literature that pertains to other medical conditions or virtual replicas of other body parts, as this may also be relevant to the dementia context. The scope here thus also covers the use of body or body part-based digital twins in a healthcare context. Some of the ethical questions we will explore will include the following:

- a. What are the ethical benefits and challenges associated with developing body or body-part-based digital twins?
  - b. What are the ethical issues related to the interaction/relationship between a person and their body or body part-based digital twin?
  - c. What are the ethical issues related to communication about digital brain twins to patients (and the public?)
2. What are the gaps in current research into neuro-ethics that pertain to the development and use of digital brain twins? What are the recommended avenues for further research in this area?
  3. What are the current, existing best practices/recommendations for the ethical design, development and use of digital brain twins?

Although this last question will be briefly discussed in this review, the Ethical and Legal Framework Deliverable will provide a more in-depth overview/ list of best practices/recommendations.

Based on the research questions, a number of search strings were tested on different databases. The search strings used for the literature search were selected based on the number of articles they yielded: the searches that yielded more than 5000 results were excluded for practical and time constraints, and the fact that they did not seem to yield articles that were relevant.

The databases that were searched were the following. These were selected based on their relevance to the research question and whether or not they were accessible to the different researchers involved in the process.

- PubMed
- Scopus
- PhilPapers
- PsychInfo

Google and Google Scholar were also searched for additional peer-reviewed or grey literature. Later on, some other articles were included based on the bibliography searches of included literature.

The different search strings that were applied were selected based on the research question and the inclusion of keywords relevant to the research question. A number of different search terms combinations were tested. Some search string results were removed, due to a high number of search results for some key terms (and practical/time constraints) and the fact these searches seem to yield literature that was not directly relevant to the question. The results yielded by the searches are displayed in Annex 1, for each database.

After uploading all searches on the Rayyan database, a number of articles were removed based on keyword exclusion (keywords seemed irrelevant to the research or off-topic). The process of identifying the inappropriate keywords was carried out by Beliz Budak and Daphné Lamirel and the removal of articles was then carried out automatically. The keywords are highlighted in yellow in Annex 2. Duplicates were also removed automatically and manually when needed. The initial screening process was carried out by Daphné Lamirel and based on the title and abstract – when the title and abstract did not clearly meet the exclusion criteria, the articles were kept in the Rayyan database. After the first round of screening, Daphné Lamirel together with Dr Dianne Gove and Dr Angela Bradshaw reviewed the remaining articles' full texts to determine their inclusion in the review. For this last round of reviewing, each full article was screened by at least 2 people and all decisions were made blind to the other reviewers. All reviewers made the same decisions on which articles to include and exclude.

Decisions were based on the following criteria:

**Inclusion criteria:**

- Peer review articles or non-peer-reviewed/ grey literature
- Published in the year 2000 and beyond
- Provides relevant information for answering the scoping review research questions (specified above)

**Exclusion criteria:**

Articles were excluded based on title and/or abstract (if needed) when they met the following criteria:

- The article was published before the year 2000
- Title or abstract mentioned twin studies and animal studies, as well as RCTs, cohort studies, or case-control studies of an intervention that is not linked to digital twin technology

- Title or abstract of the article clearly demonstrated that its focus was not, in any way, linked to any of the following key concepts/terms:  
neuro-ethics, artificial intelligence, digital twins, digital brain, digital brain twins, neuro-twin, virtual replica, virtual representation, simulation, digital embodiment, virtual model, artificial intelligence, algorithm, machine learning, simulation, accurate representation, consent, right to know, risk prediction or assessment, privacy, data sharing, identity, telehealth, telemedicine, e-health.

When the articles did not meet the criteria for exclusion based on title and abstract, the full text was sought. The articles were excluded based on full text when they met the following criteria:

- Full text not available in English
- Full text does not specifically refer to the term digital twins or other terms used to describe such technology (namely: DIGITAL REPLICA, SIMULATION/COMPUTATIONAL SIMULATION, VIRTUAL REPRESENTATION, COMPUTATIONAL REPRESENTATION)
- The full text does not refer to digital twins in a healthcare context or linked to a specific body part or health condition
- The article mentions digital twins but is of technical nature and does not refer to any ethical questions or societal benefits and challenges of digital twins
- The article discusses examples of digital twins applications in healthcare but does not specifically mention ethics or other societal benefits/challenges of digital twins
- The article refers to digital twins but is not specifically related to healthcare (e.g. related to another context such as manufacturing/industry)
- The article discusses the ethics of AI but does not mention digital twins.

### **Search results:**

The number of articles resulting from the initial search was 4614 in total, after automatic deduplication and removal of articles containing irrelevant search terms. After the screening of titles and abstracts as well as full-text screening and manual deduplication when needed, 32 articles were selected including 3 grey literature articles. More information about these articles is available in Annex 3.

## **5. Scoping review findings**

### **5.1. Impact on societal wellbeing**

The use of digital twins is deemed by many as carrying the potential to revolutionise healthcare by bringing about large-scale improvement in health outcomes and driving healthcare costs down. More particularly, the use of digital twins in a clinical setting would translate into the use of precision medicine on a large scale. Personalised or precision medicine is an approach to medicine that takes into account individual variability in genes, environment and lifestyle for each person to select the treatment and medical care that works best for them (Ahmadi-Assalemi, et al., 2020). In principle, a digital twin would use a patient's individual data (e.g. about a body part, such as the brain) to make predictions, decisions, evaluations and representations that are tailored to the individual's unique traits (genetic, environmental and, lifestyle). This would subsequently allow clinicians to tailor treatment according to individual-specific characteristics, thus enabling a more precise and personal approach to healthcare (Ahmadi-Assalemi, et al., 2020) (Bogaardt, et al., 2021) (Braun, 2021) (Corral-Acero, et al., 2020) (Evers & Salles, 2021) (Ferdousi, et al., 2021) (Huang, et al., 2022) (Jeske, 2020) (Kamel Boulos, et al., 2021) (Khan et al., 2022) (Leo, et al., 2022) (Schwartz et al., 2021) (Voigt, et al.,

2021). Access to personalised data that is updated regularly can allow clinicians to detect medical abnormalities earlier, diagnose asymptomatic conditions that are often left untreated and better track signs of disease progression (Bogaardt, et al., 2021) (Jeske, 2020) (Kamel Boulos, et al. 2021) (Schwartz et al., 2020). Digital twins of the body or certain body parts would also be used to simulate and predict the responses to different treatment options, such as the side effects of medication, and thereby optimise a person's treatment trajectory and promote less invasive treatments (Ahmadi-Assalemi, et al., 2020) (Bogaardt, et al., 2021) (Corral-Acero, et al., 2020) (Evers & Salles, 2021) (Kamel Boulos, et al., 2021) (Khan et al., 2022) (Pigni, et al., 2021) (Rahman, et al., 2022) (Voigt, et al., 2021). It is emphasised, however, that the human aspect of clinical evaluation and decision-making, is still needed, and that digital twins should serve to enhance clinical care rather than replace clinicians. (Bogaardt, et al., 2021) (Evers & Salles, 2021) (Rahman, et al., 2022). Digital twins could also enable the assessment of one's risk of developing health conditions in the future and empower citizens to make disease-preventative choices, for instance, linked to their lifestyle (Coorey et al., 2021) (Corral-Acero, et al., 2020) (Kamel Boulos et al., 2021). The use of precision medicine is deemed particularly beneficial in the current context of rising chronic health conditions and non-communicable diseases, which are characterised by high complexity and interaction between many genetic, environmental and lifestyle factors that affect disease progression. Precision medicine and digital twins can help with simplifying the complex picture of a condition by narrowing down the picture to the individual's personal patterns of the disease (Kamel Boulos, 2021) (Khan et al., 2022) (Voigt, et al., 2021). For instance, in the case of Multiple Sclerosis, there are multiple high-risk factors for the progression of the disease, and management of the condition can strongly benefit from identifying individual specific factors that are more closely associated with disease progression (Kamel Boulos, 2021) (Voigt, et al., 2021).

The introduction of digital twins in the healthcare system also promises to improve health outcomes by encouraging a stronger involvement of patients in the management of their own health. According to Ahmadi-Assalemi (2020) an important challenge faced by healthcare systems is the absence of active participation of its beneficiaries. A digital twin can enable individuals to better understand their current health statuses and lead them to take a more active role in decisions that concern their health (Huang, et al., 2022) (Schwartz et al., 2021). Stronger engagement of patients with their own health has been shown to lead to improved health outcomes, as it leads patients to be more engaged with the healthcare system in general and more compliant with treatment and other lifestyle-related recommendations (Ahmadi-Assalemi, et al., 2020) (Bogaardt, et al., 2021) (Corral-Acero, et al., 2020) (Leo, et al., 2022) (Voigt, et al., 2021).

Digital twins also carry the promise of bringing about strong improvement in health research. The use of digital twins in the context of healthcare and medical research would contribute to an advance in the understanding of current diseases as well as contribute to the discovery of new treatments. The possibility of building a virtual representation of an organ, such as that of the brain would allow researchers to use these models as a way to conduct studies including in-silico experimentation, advance understanding of different biological mechanisms and perform testing for new treatments (Ahmadi-Assalemi, et al., 2020) (Bogaardt, et al., 2021) (Coorey et al., 2021) (Corral-Acero, et al., 2020) (Ferdousi et al., 2021) (Leo, et al., 2022) (Lim, 2014). A digital twin provides the possibility to bring together all existing data about an existing body or system in an interoperable way (Ferdousi et al., 2021) (Kamel Boulos, et al., 2021). This is particularly relevant as a current key obstacle in the health research field is data fragmentation. For instance, in the field of neuroscience, many researchers and proponents of large projects such as the Human Brain Project argue that improvement in our understanding of the brain is currently being halted by the fact that there is insufficient cohesion

among different brain data (Lim, 2014). Mapping existing knowledge on a unifying platform, such as a digital brain twin, is needed to make better sense of complex organs such as the brain (Lim, 2014).

The benefits of introducing digital twins in healthcare and research also include a reduction in healthcare costs. A higher and more accurate generation of data can contribute to a better quantification and understanding of health and disease (Ferdousi et al., 2021). This can bring about social value by ensuring a better allocation of healthcare resources (Leo et al., 2022). Better quality and efficiency in disease diagnosis, treatment and prediction, can help drive healthcare and treatment costs down (Ahmadi-Assalemi, et al., 2020) (Bogaardt, et al., 2021) (Braun, 2021) (Evers & Salles, 2021) Digital twins can save time for healthcare professionals and help them to make fewer errors. The use of digital twins can also enable healthcare systems to manage less urgent cases more efficiently. In particular, the opportunity for patients to engage with their own health data can encourage self-diagnosis and self-treatment, and therefore translate into fewer interactions with the healthcare system. Digital twins can also reduce the time and costs for the pre-clinical and clinical testing of pharmaceutical interventions (Ferdousi et al., 2021). Treatment testing can benefit from more efficiency, due to the potential for less animal and human testing (Ferdousi et al., 2021) (Rahman, et al., 2022). The reduction of medicine time to market can also drive the cost of drugs down (Leo et al., 2022).

Although digital twins show promising ways of reducing costs for healthcare, digital twins may not bring about an immediate reduction in healthcare spending. Indeed, the development of digital twins requires a considerable investment of resources to develop the required technology. Pigni and colleagues (2021) note that the initial development of a digital twin would require a large investment, but that subsequent development and distribution of digital twin services would be at a very low cost. Another issue regarding cost concerns the rapidly evolving pace of technology: there could be pressure to purchase the newest versions of digital twins, and this may result in failure to allocate healthcare resources in the most efficient way (Leo, et al., 2022). Leo and colleagues recommend making comparisons and using evidence, to correctly estimate the cost-effectiveness of adopting the newest technological releases.

Another societal benefit arising from the use of digital twins in medical research is a reduction in animal suffering. Currently, animal testing is widespread in research and pharmaceutical research. Many are calling for new ways of testing and validating treatments. Virtual models such as digital brain twins provide a promising alternative (Rahman, et al., 2022).

## 5.2. Inequalities, discrimination and injustice

Despite their promise of improved health outcomes for all, digital twins used for healthcare also carry the risk of exacerbating societal inequalities. As observed with many digitalised health products or services, digital twins may face inequality in access. The services might not be accessible to everyone, such as those from lower socio-economic status or living in rural areas, or not be covered by healthcare insurance (Ahmadi-Assalemi et al., 2021) (Braun, 2021) (Coorey et al., 2021) (Corral-Acero et al., 2020) (Huang et al., 2022) (Kamel Boulos et al., 2021) (Schwartz et al., 2021). Inequality in access may also result from the disproportionate use of digital twins in Western countries, which have more available facilities for technological development. This would contribute to widening the global health rich-poor divide (Corral-Acero et al., 2020) (Schwartz et al., 2021). Digital twins may also exclude individuals with disabilities or cognitive issues due to lack of accessibility (e.g. if a digital twin contains complex language or is not adapted to those with visual, speech or hearing impairments). It is therefore best practice for digital twin design to be made accessible to their user, particularly by conducting research



on the need of those who may be at risk of experiencing limitations in technology usage, such as elderly people, people with cognitive problems and/or with disabilities (Schwartz et al., 2021). Universal healthcare approaches are suggested to limit issues of unequal access (Huang et al., 2022). Universal healthcare refers to a healthcare approach in which all individuals in a particular country or region are provided with access to essential healthcare services without facing financial constraints. It aims to ensure that everyone, regardless of their socioeconomic status or other factors, can receive necessary medical care when needed. The funding for universal healthcare typically comes from various sources, such as government taxes or mandatory insurance contributions, and the services may be delivered through public or private providers.

Schwartz and colleagues (2021) suggest offering different options for data collection, for instance, including web-based self-report options in addition to monitoring devices, as the former might be easier to use and less costly. The design of digital twins should also be adapted to different levels of technological access: for instance, by incorporating interfaces that require minimal data downloads for people who have limited WiFi availability (Schwartz et al., 2021).

Bias and discrimination also constitute major ethical concerns for the use of any digital health technology that employs Artificial intelligence (AI). Due to a lack of access of some population groups to measuring devices and testing, such as MRI/pet, and metrics not being culturally appropriate or sensitive, some population groups may not be accurately represented in the input data used by certain big data-based tools. Digital twins that use and are trained on non-representative datasets may therefore lack accuracy or relevance for certain gender, sexual, ethnic or socioeconomic groups, resulting in poorer treatment for disadvantaged groups (Braun, 2021) (Corral-Acero et al., 2020) (Ferdousi et al., 2021) (Huang et al., 2022) (Kamel Boulos et al., 2021) (Khan et al., 2022) (Voigt et al., 2021). Of related concern is the very nature of algorithmic functioning which may be biased and fail to take into account key information to guarantee that digital twins are non-discriminatory (Huang et al., 2022). For example, a healthcare algorithm designed to identify groups with a higher need for healthcare examined individuals' healthcare expenditures but failed to take into consideration the fact that healthcare expenses were lower for black communities due to their existing lack of access to healthcare (Huang et al., 2022). To minimise the bias and discrimination brought about by digital twins, data used to train the digital twin algorithms should be more representative of the population group for which it is making predictions and assessments (Huang et al., 2022) (Kamel Boulos et al., 2022) (Khan et al., 2022). To monitor bias in digital twins, Braun (2021) recommends more transparency: providing accurate information on the type of data being used and their sources, and on the background presumptions of the algorithms.

Injustice may also take place if the digital twin reveals information that is harmful to the individual. Individuals may not always want to know about all their health data: for instance, a person might be reluctant to know about their likelihood of developing a certain condition in the future if they are not able to access treatment for it (Kruzinna, 2021). Additionally, more detailed information about individuals' health status, may also lead to arbitrary decisions made about healthcare or treatment, instead of a case-by-case, deliberated approach. This could occur, for instance, if an individual falls on one side of a cut-off point by only a few data points designed to determine their access to treatment or insurance coverage (Bogaardt et al., 2021).

To limit injustice and discrimination, there is a need for Public Involvement (PI) in the development and deployment of digital twins. Currently, many digital twins are developed by private-sector companies and this limits opportunities for PI. Reflection on the ethics of digital twins is needed but this should be embedded into the technological development of the services (Braun, 2021) (Rainey, 2022). We should be wary of technological solutionism and avoid conceptualising digital twins as a

remedy to all societal problems (Krutzinna, 2021). The implementation of robust governance mechanisms is recommended to protect the rights of individuals who have digital twins. These should also ensure fair use of their health data and promote transparency about all derived benefits and harms of digital twin usage at both individual and societal levels (Karmel-Boulos et al., 2021).

### 5.3. Autonomy and empowerment for patients and clinicians

The use of digital twins implies access to higher quantities and more personalised information about an individual's health – this increases their autonomy as they are better able to manage their health and optimise decisions about lifestyle (Bogaardt, et al., 2021) (Braun, 2021) (Schwartz et al., 2020) (Tretter, 2021) (Voigt, et al., 2021). Increased information and a better understanding of health, can also enable patients to be more involved in healthcare decisions about treatment and diagnostic procedures (Corral-Acero, et al., 2020) (Voigt, et al., 2021). A specific feature of digital twins is their capacity to reduce the distance between the data and the individual, particularly as data may often be inputted by the patient into an app or cloud system, or may be directly or indirectly accessible by the individual (Bogaardt, et al., 2021) (Schwartz et al., 2021) (Voigt, et al., 2021). Citizens who share their data with a digital twin may therefore become 'self-scientists' and learn to evaluate their own health patterns (Schwartz et al., 2021). Yet, the use of digital twins in a clinical setting can also be detrimental to an individual's autonomy. An individual may be harmed if a digital twin-derived health recommendation turns out to be inaccurate (Ferdousi et al., 2021). Moreover, personalised medicine often focuses more on the individual determinants of health as opposed to social or environmental factors, such as economic difficulties or pollution (Huang, et al., 2022). Digital twins may, therefore, shift responsibility for health onto individual actions, instead of addressing the social and environmental determinants and their structures (Huang, et al., 2022). Victim blaming, for instance, of individuals with chronic health conditions may also occur, whereby individuals are accused of not taking action to solve their health conditions. Emphasising individual factors in health can also lead to powerlessness and guilt for individuals who do not follow personalised health recommendations (Huang, et al., 2022) (Krutzinna, 2021). To avoid promoting a neoliberal approach to health, it is crucial to include socio-economic and environmental variables in data used in health-related digital twin services (Krutzinna, 2021). A neoliberal approach to health refers to a perspective that emphasises market-oriented principles and individual responsibility in the organisation and delivery of healthcare services. It involves a belief in the efficiency and effectiveness of free markets and limited government intervention in healthcare. In a neoliberal framework, healthcare is often seen as a commodity rather than a social right, and market forces are relied upon to allocate healthcare resources and determine access. A neoliberal approach to health often implies less investment in welfare state interventions and public healthcare services.

In addition to impacting an individual's autonomy in various ways, the introduction of the digital twin in a clinical setting also carries implications regarding clinicians' autonomy and the patient-clinician relationship. Clinicians may benefit from increased autonomy from digital twins; access to more precise information about their patients can enable them to make more informed and accurate decisions (Corral-Acero, et al., 2020). This is particularly relevant in a context where there is a constant and large expansion of knowledge in the healthcare industry which may be difficult to keep up with (Corral-Acero et al., 2020). Yet, technology-derived health information also runs the risk of being treated as a source of more objective information and too much power may subsequently be given to the digital twin. This can threaten the position of clinicians as main experts, and reduce their autonomy in the patient-clinician relationship context (Corral-Acero, et al., 2020) (Huang, et al., 2022) (Mittelstadt, 2021). Beyond the societal perception of digital twins, we should note that it is well possible that one day, technology (e.g. a digital twin) becomes as or more accurate than human decision-making (Corral-Acero et al., 2020) – this is a moral implication that must be considered and

reflected upon. Clinicians may also have less autonomy due to having to dedicate a new portion of their time to understanding and explaining the technology to their patients (Leo, et al., 2022). The use of the digital twin in a clinical setting also raises questions linked to responsibility in clinical decisions. If a digital twin assessment is wrong, it can be difficult to retrace the error made by the algorithm, due to black box issues. Questions thus arise as to how much responsibility should be borne by the clinician, who ultimately might have been the one making the final decision (Bogaardt et al., 2021). Explainability and transparency are therefore essential elements for patients and clinicians to make informed decisions and enhance the trustworthiness of digital twins (Ferdousi et al., 2021) (Braun, 2021) (Schwartz et al., 2021). Schwartz (2021) recommends plain language explanations, especially for the use of digital twins with limited clinician support. It is worth noting that the use of digital brain twins with limited clinician support raises specific ethical issues which are elaborated on in the discussion section of the deliverable. Findings also highlighted that education about digital twins to citizens and healthcare professionals is also key to enhancing their explainability and trustworthiness. Training in AI and digital twins could be embedded early on in the medical university curriculum and engineering students could receive basic education about biology (Corral-Acero et al., 2020). It is important to note, however, that the explainability and precision of a digital twin model may impact its level of precision and complexity and careful reflection about this trade-off is needed (Corral-Acero et al., 2020).

Increased reliance on digital twin-derived health information may also diminish the value accorded to the experiential recounts and personal opinions of patients, negatively impacting person-centred and shared decision-making approaches to care (Huang et al., 2022) (Mittelstadt, 2021). One should also note that digital twins may not necessarily ensure objective assessments in the clinical setting over subjective ones – in reality, their predictions and use would be still employed by clinicians and therefore subject to human assessment. Their functioning and design may also be laden with biases, and therefore not be considered objective in their assessments (Ferdousi et al., 2021) (Huang et al., 2022).

#### 5.4. Privacy and data protection

Digital twins of body parts (e.g. the brain) or the entire body make use of an individual's personal and highly sensitive health information. Collecting such data can impede citizens' ability to control their personal information and conflict with their right to privacy, autonomy, freedom and non-maleficence. (Ahmadi-Assalemi, et al., 2020) (Ferdousi et al., 2021) (Voigt et al., 2021). It is therefore essential for a digital twin service provider to be transparent about how an individual's data is being used. Informed consent about data usage should be sought unless there are valid ethical and legal reasons for which this is not viable. The commitment to the right to privacy and data protection as well as to transparency should be upheld and managed by appropriate governance mechanisms (Ferdousi et al., 2021) (Karmel Boulos et al., 2021).

In practice, in the field of health-related AI, informed consent often fails to be upheld due to several ongoing practices. According to Huang and colleagues (2022), the issue of hyper-collection is pervasive and can strongly undermine people's right to privacy. Hypercollection takes place when AI-based digital health tools (such as a digital brain twin) may collect a large amount of data to help inform the health status of the individual and also resort to more information than what is necessary for the scope of their services. Algorithms may extend data collection to so-called 'health-related' data, which does not immediately fall under the direct remit of 'health-related' such as information about social media usage. Additionally, even when the data falls under the remit of health, non-necessary data may still be processed without adequate justification. Huang and colleagues (2022) recommend that appropriate justification for the use of data type be provided in addition to the informed consent process. Sharing such large quantities of information can also put individuals at increased risk of

inference attack, a mining technique by which a large quantity of authorised data is used to infer other information about an individual, which the latter may not want to share/disclose. Using data that is not required for the development of the digital brain twin service, simply for the sake of 'better performing personalised health services' may not justify this risk (Huang et al., 2022).

Of additional concern are practices of data repurposing. An individual might provide consent for their data to be used in one algorithmic process for one specific purpose but such data or algorithm may then be used to perform another function to which the individual might not have agreed (Ferdousi et al., 2021) (Khan et al., 2022). The dynamic consent process for data sharing can help with this concern; dynamic consent enables individuals to modify their preferences of data usage depending on how their data is being used and opt out of their data being used altogether. Dynamic consent enables two-way, ongoing communication between researchers and research participants. For instance, research participants are able to upload additional health data, or researchers may inform participants about new research opportunities (Ahmadi-Assalemi, et al., 2020) (Leo et al., 2022).

A digital twin service may rely on data sharing 'in real time' or at regular intervals. Individuals may therefore be at risk of being monitored on a variety of parameters in a non-transparent manner, by a third party (the digital twin service providers). Tracking an individual's health-related behaviours by a third party may significantly alter the trust that the patient has in their clinician. Surveillance may occur, a process by which a third party such as a digital health company, tracks individuals on a range of parameters and uses these to influence the same individuals' behaviours without them knowing (Jeske, 2020). For instance, digital brain twins may generate real-time brain data that may be re-used for neuromarketing purposes (Rainey, 2019).

Sharing information with a digital twin service company may also open the road to individual data sharing for profit-making purposes, a process also known as data brokerage. According to a study by Hockvale and colleagues, 29 of the 36 most commonly used applications used for depression and smoking cessation, sold data to Google and Facebook for advertising and analytical services, and only 12 of them disclosed to the users that they did so (Huang, et al., 2022). The commodification of data without compensation also poses serious ethical concerns (Jeske, 2020). Digital obsolescence may also affect users' ability to control their data. Digital obsolescence takes place when a digital resource is no longer readable or accessible because the physical media, the reader required to read the media, the hardware or the software that runs on it, is no longer available. Shutdowns of digital twin service providers or developers, which is common practice in the field of start-ups and new technology, can make it difficult for individuals (who have shared their info) to access or reuse their shared data if a proper management system has not been adequately implemented beforehand (Huang et al., 2022).

Additionally, data sharing increases the risk of information being used against individual interests and the likelihood of discrimination. In particular, security breaches or unorthodox practices can take place, for instance, data can be sought to inform screening for insurance or employment, without an individual's knowledge or consent (Coorey et al., 2021) (Huang et al., 2022) (Karmel Boulos et al. 2021). These dangers are exacerbated by the fact that anonymisation alone does not ensure that people remain unidentifiable. According to Pola and colleagues, 99.98% of Americans would be correctly identified in any data set using 15 demographic attributes (Leo, et al., 2022). The availability of genetic information also opens the door to inferences about an individual's general disposition to health and survival. This can lead to possible malefic usages such as the classification of some population groups as genetically superior, or using genetic data in a cybercrime context (for example, when an individual's DNA is placed on a scene as a crime to frame them) (Ahmadi-Assalemi, et al., 2020) (Kamel Boulos et al., 2021).

Safeguarding individuals against unorthodox data usage is therefore essential to uphold non-maleficence and ensure public trust towards digital twins (Corral-Acero et al., 2020). Individuals may find it difficult to make informed decisions about data sharing due to the high complexity of AI-based services and black box issues (Ahmadi-Assalemi, et al., 2020) (Ferdousi et al., 2021) (Leo et al., 2022). Rather than providing an exhaustive explanation of the algorithmic functioning which can create overwhelm, it is recommended that people are made aware of the content, type of data used and potential harms of sharing their data with a digital twin. It can also be helpful to include comic or pictorial explanations in consent forms to facilitate explainability during the informed consent process.

One should note that too strong of a focus on data protection may impede research development, to which data sharing is key (Khan et al., 2022). Leo and colleagues (2022) highlight the ethical dilemma between balancing the public interests of improved health outcomes versus individual interests linked to privacy (Leo et al., 2022). Bogaart and colleagues (2021) describe the right to privacy as operating as a golden middle. Individuals might also have different attitudes to privacy depending on the context and purpose of data sharing (e.g. an individual who has a terminal illness compared to a healthy individual) (Sun et al., 2022).

### 5.5. Representation, control and freedom(s)

The concept of the digital twin, or in other words creating a virtual representation of a person's body part or entire body, also carries important implications regarding personhood (Braun, 2021). If a digital brain becomes advanced to the point where it is considered identical to that of a person's brain, one could argue that such a model constitutes a real, separate person. This scenario can raise important moral concerns, for instance, related to experimenting with and shutting down the digital twin (Lim, 2014). It could also grant powers for digital twins to act on behalf of represented persons and thereby threaten individuals' autonomy. Certain qualities of personhood have been put forward and these can be used to assess a digital twin model; these include: consciousness, reasoning, self-motivated activity, communication and self-awareness (Lim, 2014).

Even if a digital twin is not deemed to constitute a fully-fledged 'person', it is ethically relevant to reflect on how a virtual brain or other body part simulations should relate to the person that they are representing, and how an individual can maintain adequate control over their digital twin without experiencing threats to their autonomy. Braun argues that digital twins, even if identical to a person or person's body part, remain separate from the represented person. Yet, they also require substantial interaction with the person. Conceiving a digital twin as a 'surrogate' rather than a 'person' maintains the existing link between the represented person and representing body, while still accounting for some degree of separation. Similarly, digital twins can be conceptualised as further extensions of a body part or person's body, similar to prosthetics (Nyholm, 2021). Rather than constituting bodies that replace the body part and threaten an individual's bodily integrity, digital twins open up new freedoms for individuals such as more information on health status (Braun, 2021). Nyholm (2021) explains that to determine if a digital twin constitutes an extension of a person's body, one must be able to positively answer questions such as 'Would the removal of the digital twin mean a significant drop in the patient's capacities?', and about whether the information provided by the digital twin is sufficiently accurate. Such conceptualisations of digital twins can also open the opportunity for digital twins to be used to act on behalf of the represented person when the latter is not able to have their interests heard, for instance in the case of a person who is affected by a stroke or at a late stage of dementia, or for vulnerable children (Braun, 2021; Braun and Krutzinna, 2022). The concept of a digital twin as a surrogate, as opposed to a real person, also encapsulates the idea that digital twins remain substitutes and therefore, even when truly identical, may not always adequately promote the interests of the represented person and should not substitute them (Braun, 2021).

Control from the represented person over the surrogate is needed to ensure that a represented person's decision-making capacities are safeguarded and that digital twins do not threaten an embodied person. One could argue that a person's simulation must be owned by the represented person. Yet, data used for research cannot fall under the ownership of a person, according to GDPR legislation (Braun, 2021). Braun argues that a person can exert control over their simulation (e.g. decide how it is being used and for which circumstances it should act on their behalf), as long as dynamic consent is enforced. A person should be able to choose their preferred forms of digital twins and how such twins are being used for current treatment decisions and future predictions and should be able to modify and opt out of the service. This should be complemented by the possibility of interacting with and receiving updates from the digital twin service (Braun 2021; Tigard 2021). Digital twin users should be able to understand the twin's usages and make deliberations based on informed conversations with healthcare professionals (Tigard, 2021). Transparency of the digital twin (Tigard, 2021) is essential and Braun (2021) recommends further reflection on methods to ensure interoperable interfaces between a person and their simulation. Considering dynamic consent as a necessary condition for legitimate representation by a digital twin may, however, run the risk of excluding certain groups of individuals, such as people with less cognitive resources who may not be in a position to give dynamic consent (Krutzinna, 2021). It is therefore important to develop methods to include such groups, for instance, using proxies, whilst still considering their increased vulnerabilities to such tools (Krutzinna, 2021).

Tretter (2021) notes that an individual's ability to control their digital twin may not be as straightforward as it seems. A digital twin might significantly alter an individual's relationship to the world and this may not be reversible in the long run. Digital twins have an ambivalent and two-way impact on someone's relationship with the external world, also referred to as a person's hermeneutic freedom. On the one hand, the digital twin opens up possibilities: individuals have access to more information about their health status and can achieve better outcomes. Yet, on the other, a digital twin can change how one perceives the world, also referred to as hermeneutic relations, and this may infringe on one's freedom. As an illustration, a digital twin might provide new information about how different behaviours impact our health e.g. the impact of the nutrient and calories of an ingested food item might be recorded and quantified in terms of its impact on future health status, and such information may strongly impact how an individual perceives any food they ingest for the rest of their life. This can become the dominant way of seeing the outside world, and disable the person from experiencing the world directly, which may lead to restrictions in daily life. Bogaardt and colleagues (2021) explain that digital twins may profoundly transform personal identity, for example, if all 'healthy' behaviours become quantifiable.

According to Braun (2021), the impact of the digital twin on hermeneutic relations or personal identity can be prevented by the preselection of certain functions and dynamic consent. The digital twin could for instance only provide information about certain situations that are deemed necessary, such as serious health-threatening situations, so that the majority of the time, the digital twin is not changing an individual's perception of his external world. Yet, according to Tretter (2021), this is not a convincing solution. In practice, it might be that only after one sees and experiences the long-term effects of the digital twin prediction that one decides or is able to inhibit certain functions, and this may not always be technologically possible. And even if such pre-emptive disabling of function is feasible, the digital twin can still impact hermeneutic relations. For instance, the silence of the digital twin could be interpreted in different ways by the user: it could either signify that a certain function has been switched off or that one's eating behaviour is acceptable. This could lead to questioning or suspicion and still transform an individual's relationship to eating habits (Tretter, 2021). Of further concern is the issue of lack of alternatives (Leo et al., 2022): if digital twins become commonplace and

one of the only ways to access certain life-saving treatments, individuals may be forced to use digital twins and accept permanent, long-term restrictions in their hermeneutic freedom.

Currently, much remains to be reflected upon regarding how digital twins affect individual freedoms and effective ways for individuals to control a digital twin according to their preferred interests (Tigard, 2021). Other types of consent such as broad, open or meta-consent have also been suggested as possible alternatives to dynamic consent and this requires further exploration (Tigard, 2021). Furthermore, and in practice, the control of digital twins will most likely be shared by the individual and organisation involved in developing or using the twin – this prompts the need for robust governance mechanisms to guarantee the ethical management of digital brain twins (Karmel Boulos et al., 2021).

### 5.6. Conceptual issues

The language used to describe digital twins also carries ethical concerns. Lupton (2021) explains that language is of high ethical importance due to its strong influence on public debate, policy and healthcare resource allocation and research funding. At present, the anthropomorphisation of many digital or AI-based services is prevalent. In other words, many digital tools are defined with human qualities, with terms such as ‘twin’ or ‘intelligence’, or the idea that they are able to ‘learn by themselves’ and make decisions. Against this background, the concept of a ‘digital twin’ is often interpreted as a virtual representation that is (almost) identical to that of the organ, brain or person that is simulated. Furthermore, digital twins are often associated with the concepts of ‘personalised medicine’ or ‘precision medicine’, which promote the idea that digital twins possess high levels of accuracy (Lupton, 2021).

Yet, in practice, science is still at the very early stages of digital twin development. Currently used models of digital twins often lack accuracy and mistakes made by digital twins are commonplace, for instance, due to incorrect information or labelling of data (Ferdousi et al., 2021) (Huang et al., 2022) (Lupton, 2021). Problems related to inaccuracy are compounded by the fact that digital twins might use a large amount of low-quality data but this may be forgotten amongst its non-transparent and poorly understood algorithmic functioning (Bogaardt et al., 2021). Patients also routinely lie or fail to reveal all relevant information about their health and behaviours (Mittelstadt et al., 2021) which further impacts data quality. Some sceptics in the digital twin field argue that the level of error and inaccuracy in the data would be so high and anchored within the digital twin system that the latter should be deemed ‘highly unreliable’ (Mittelstadt et al., 2021). Very few models of digital twins have reached clinical translation and many algorithmic models remain obscure and inaccurate. Even if current models were to be validated in a clinical setting, a process of strict assessment and quality control from regulatory bodies would be required before any of these tools could be used in practice (Corral-Acero et al., 2020). Potential sceptical attitudes towards new technologies may also make some healthcare systems or healthcare professionals more reluctant to adopt such tools (Bogaardt et al., 2021).

Developing a digital twin for the brain is considered by many a complicated, and even irrational, endeavour. The adequacy of a digital twin can be conceptualised as dependent on both the complexity and the current understanding of the simulated body part (Evers and Salles, 2022). The brain is the most structurally and functionally complex organ in the human body, and we still lack a lot of understanding about its processes. Additionally, the brain is part of a system that is strongly interrelated to other body parts and environmental experiences – this may fail to be fully accounted for by a digital twin (Evers and Salles, 2021). Another key challenge in digital twin development is to find methods to ensure interoperability between different data sources (Khan et al., 2022). Current conceptualisations of digital twins are therefore misleading and potentially harmful as they may lead

the public and policymakers to wrongly assume that digital twins constitute precise effigies of human body parts (Lupton, 2021). Lupton recommends avoiding ‘techno-utopian’ terms and using terms such as ‘simulation’ or ‘computerised model’ instead (Khan et al., 2022) (Lupton, 2021). Salles and Evers (2021) call for ‘scientific modesty’ when specifying the goals of digital twins and interpreting study conclusions. The idea that we are close to creating an identical representation of a human brain may also cause unnecessary public fear of such tools due to unwarranted worries about the outperformance of humans by machines (Corral-Acero et al., 2020) and may detract from focusing on the benefits of digital brain twins. Coorey and colleagues recommend that advocates of digital twin technology should avoid too much ‘hype’ around the technology, and provide an accurate and balanced picture of individual and collective benefits (2021). It is important for researchers and other professionals working in the digital twin field to highlight that any model is a simplified representation of reality and is based on a number of assumptions. Different claims about, for instance, the potential impact or generalisability of a digital twin model should be, whenever possible based on substantive evidence (Corral-Acero et al., 2020). It is also argued ethical discussions about digital brain twins may be taking place too early as the technology of digital brain twins is in the early stages of development (Braun, 2021) (Khan et al., 2022).

Given the ambiguity associated with a digital twin’s level of representativeness, it is important to reflect on the standards required to be able to qualify a digital twin as *precise enough* to justify its use in a clinical setting (Mittelstadt et al., 2021). The setting of such standards raises important ethical implications regarding epistemic responsibility for clinicians, data scientists, and model developers (Lim 2014; Braun, 2021). According to Braun (2021), the level of representativeness of a digital twin depends on the level of accuracy of the model and the accuracy and transparency of data. Yet reflection is also needed regarding context: standards of precision may be dependent on the situation in which the digital twin is being used. Society may demand higher degrees of digital twin precision in matters that have more stakes such as using a digital twin to determine whether one should get a mastectomy to avoid cancer as opposed to using it for cognitive enhancement purposes (Braun, 2021). Corral-Acero and colleagues (2020) assert that as a new field, gold standards and clear guidelines should be developed to determine the level of accuracy needed for the use of digital twins in different contexts. There is a need to build on existing work in this area of existing guidelines in computational modelling and for different stakeholders to collaborate and reflect on new standards and how this will impact regulation (Corral-Acero et al., 2020). An implication of healthcare-related digital twin development is the generation of highly detailed information about individuals’ health and thus a greater gradation of healthy states. This may lead to important transformations in conceptions and societal perceptions of what constitutes normal or healthy. The normal may become individualised: citizens will, for instance, be able to know where they stand with regard to their health status compared to people with similar demographic, socio-economic and lifestyle variables, as opposed to just gender and age today. Despite having been previously deemed healthy, some individuals may be classed as abnormal or unhealthy when compared to a new reference group (Bruynseels et al., 2018). Digital twins may also create new groups of ‘healthy ill’ people, who are currently symptomless but are predicted to develop diseases in the future based on the digital twin information. Ethical questions as to whether such groups of healthy ill should deserve therapy, ‘enhancing treatment’ or daily care can also have important moral implications and affect healthcare resource allocation (Bruynseels et al., 2018). Individuals may run the risk of being compared, tracked and placed into different performance categories and what was seen as normal before may become subject to enhancement. Detailed gradation in health also opens the door to the desire for continuous enhancement practices, for instance, to reach certain brain states and promote professional success (Rainey, 2022; Bruynseels et al., 2018). In this case, wealthy individuals may be unequally advantaged due to their access to health-promoting tools such as new technologies (Rainey, 2022).



## 6. Discussion and next steps

The use of digital brain twins in dementia research and clinical practice carries wide-ranging, and oftentimes interrelated socio-ethical implications. The ethical benefits and concerns of digital twins, include but are not limited to well-being, improved healthcare, cost-benefit, autonomy, freedom, control, discrimination and stigma, bias, justice, non-maleficence, beneficence, personhood, representation, patient-clinician relationship, understandability, explainability, transparency and animal suffering.

### 6.1. Limitations of this scoping review

This scoping review was limited in its capacity to answer the proposed research question as no literature on the ethics of digital brain twins specifically used for dementia-related conditions was found. For this reason, the review inclusion criteria were broader in scope and included literature on the general use of digital twins in healthcare. This undoubtedly highlights the pressing need for more research on the ethical implications of using digital brain twins for dementia, pre-dementia stages, dementia risk reductions and other neurodegenerative disease areas. Furthermore, the topic of AI in healthcare and dementia has already been widely explored in previous ethics literature and is also relevant to digital brain twins (references?). The present review, however, focused specifically on digital twins and therefore did not touch upon all such issues, including, for instance, the ethics of risk disclosure and communication or other issues of bias and stigma related to Big Data and AI use. Yet these issues are relevant to the ethics of digital brain twins and should be taken into account for discussions about this topic and developing recommendations. There may also be additional or novel ethical issues specifically linked to digital brain twins which may be less relevant in relation to dementia-related conditions.

Another limitation is that the review's inclusion criteria may have excluded otherwise relevant peer-reviewed articles on the ethics of digital twins. It is also possible that this may have excluded articles focused on issues of the Global South and AI (e.g. linked to inequality in access), which are not always translated into English (e.g. from Hispanic or African literature).

### 6.2. Discussion, recommendations and avenues for further research

The current literature on digital twins in healthcare indicates that these tools can be highly beneficial from a societal perspective. Data-driven virtual representations of the brain represent a promising avenue for research in the dementia field, tackling the data fragmentation problem, enabling a better understanding of brain mechanisms and opening the door to *in silico* experimentation. In a clinical context, digital brain twins could transform healthcare for patients with dementia: therapies and their side-effects could be evaluated in an individualised manner and symptomless individuals could obtain information about their future risk of developing dementia.

Nonetheless, science is still in the early stages of digital brain twin development. Careful assessment of the benefits and costs associated with digital brain twin use in healthcare research and practice is needed before large-scale deployment and adoption by healthcare practices and research institutions take place. Once digital brain twins become common practice in research and the clinic, continuous evidence-based assessment of their effectiveness, benefits and costs will be required. Currently, there is a dearth of research on the use of digital brain twins in a clinical context. Introducing a digital twin in the patient-clinician relationship would have major consequences, and current literature highlights the importance of ensuring the explainability, interpretability and transparency of such technologies. Ethicists and other relevant experts, together with the public, clinicians and people with dementia, should reflect on ways to uphold these principles and safeguard the shared decision-making process.

In the case of people with dementia, it is recommended to implement measures to guarantee that people have the ability to engage in a supported or shared decision-making process as long as possible (Alzheimer Europe, 2019). Methods for ensuring transparency, explainability and clear communication of digital brain twins need to be reflected upon. In particular, future research should look at how to make sure a digital brain twin is understandable and accessible to populations who experience cognitive problems such as people with MCI or with dementia. Moreover, literature on the use of AI in the medical field highlights that the process of trust is an embodied experience that may not always respond to ‘rational explanations’ and also depends on larger the social and institutional context (Goisau Durnova, 2018; Quinn et al., 2021). This needs to be taken into consideration when investigating the perceived trustworthiness of digital brain twins.

The literature findings also indicate that ethicists should broaden their understanding of how to publicly communicate about digital brain twins. Language, therefore, needs to accurately reflect the level of precision and accuracy provided by a digital twin. Some ethicists argue that researchers should change their terminology, and only refer to ‘computational models of the brain’ in place of ‘digital brain twins’. One could consider, however, that these terms may carry the risk of further obscuring the conceptualisation of digital twin models and their main goals. More research on terminology is needed as only two peer-reviewed journal articles covered this area. This should be complemented by consultations with key stakeholders to understand how language affects perceptions and healthcare-related decision-making.

The findings of this scoping review demonstrate that digital brain twins may be empowering for the public but may also be the source of powerlessness, discrimination, harm, inequality and injustice. It is therefore crucial for robust governance mechanisms to be implemented to ensure that digital brain twins are developed and used in an ethical manner, on an individual and societal level. And such governance mechanisms should make sure to include the views of all relevant stakeholders including the public and vulnerable groups. Healthcare providers, policymakers and technology developers need to be cautious about the potential implications of digital twins on individual responsibility in health (e.g. on how potential insight into relevant lifestyle and risk factors are reported in relation to brain health). Jones et al. (1984) identified six factors which may increase the likelihood of a particular attribute becoming a stigma. One of these (the origin of the attribute) is linked to the extent to which it is considered controllable (i.e. and therefore could or could not have been prevented). This may lead to some people being considered personally responsible for their condition and hence blamed, thereby contributing towards and perpetuating stigma (Corrigan et al. 2001). Similarly, Weiner et al. (1988) explored ten different health conditions in terms of their controllability and concluded that those ascribed to controllable factors were considered more stigmatising than those that were not. Efforts should therefore be directed towards empowering individuals, promoting health and digital literacy and ensuring equitable access to resources and interventions that address both individual behaviours and the structural determinants of health.

Access to digital brain twins should not be dictated or influenced by financial status or other socio-demographic attributes. Future inquiries should also look at how to make sure people with cognitive problems have adequate access to and understanding of digital brain twins, and explore concerns related to digital exclusion, which may be more prevalent amongst older adults (Mubarak et al, 2022). Upholding people’s right to justice implies exploring effective methods for anticipating structural bias in datasets and analysing the potential societal implications of using a digital brain twin system before it is implemented. According to Owens and Walker (2020), failure to anticipate bias in AI systems and address it should be classified as a form of ‘scientific misconduct’. Moreover, current attempts to correct the bias created by AI are mainly focused on increasing data representativeness. Yet, research indicates that this is not sufficient to eradicate all forms of bias from AI tools (Li et al., 2022). It is

therefore recommended for future research on bias in digital twins to also delve into the broader origins of bias and its social structures.

In order to promote the ethical use of digital brain twins for dementia research and clinical practice, it is key for personal data to be adequately protected from dangers to privacy and that people to have sufficient control over how their digital brain is being used. Currently, dynamic consent has been suggested to tackle this issue, but more research is needed on how to make sure dynamic consent grants people sufficient control over their brain data and usage of their digital twin, and how to make sure they are not harmed. It is also important to note that in the context of AI usage, dynamic consent may pose additional ethical concerns as even if a person wishes to revoke their consent, it might be impossible to track all the possible ways in which one's personal data were used and processed by an AI system (Teare et al., 2020). In particular, broad consent is a consent approach that allows the use of data for a wide range of research purposes, beyond the scope of the original study. While broad consent facilitates data sharing and promotes research efficiency, it raises concerns regarding individual control and oversight. The challenge lies in defining the boundaries and limitations of broad consent to ensure that individuals have a reasonable understanding of the potential future uses of their data while still respecting their preferences and right to autonomy and self-determination. Broad consent also provides a useful way for people with diminishing cognitive capacities (e.g. people with dementia) to agree to have their data used for future research and future developments in digital brain twins but who may not be able to provide specific informed consent at a later point in time (Wjertz and Boldt et al., 2022). Current literature also indicates that there is still a lack of research about which types of consent would be best suited for sharing data with a digital twin and that it may be worth exploring alternatives to dynamic and broad consent.

Of crucial importance is also whether a digital brain twin possesses qualities of 'personhood'. This topic was explored only in two articles identified in the literature. Ethical reflection about digital brain twins should include these long-term considerations. Yet ethical and public discourse on digital brain twins should also be adapted to the current context of the early-stage development of the technology, and avoid fear-mongering, promoting false perceptions and detracting from current important ethical issues, such as privacy and bias. Available literature has indicated that a digital brain might be used, in the future, to represent the interests of a person who is unable to voice them, such as someone in a late stage of dementia. Research is needed to explore the appropriate mechanisms to do so and possible ethical risks.

There is an agreement in the literature that a digital twin, including digital brain twins, would impact how our society views the world and how individuals interact with their external worlds and health status. If suddenly, all health information is made available and trackable, the concept of health would be transformed and individuals might feel pressured to continuously improve their brain health. This situation could be psychologically and socially harmful and lead to stigma. More understanding of this aspect in the context of dementia-related conditions is needed. It may be useful to think of the psychological consequences of being able to access one's digital brain twin and explore the ethics of risk disclosure and the 'right to know' in the context of digital brain twins for dementia.

Additionally, open access to data may have specific implications for people with cognitive impairment who are not able to fully comprehend the available information. For instance, a false interpretation that one's dementia has progressed may have important ethical, social and psychological consequences. It may also be that digital brain twins make people at risk of dementia or with cognitive issues overly concerned or preoccupied with their health, without necessarily having the relevant knowledge and skills to make sense of it, which may lead to harm and powerlessness. Furthermore, while some individuals may find the visual representation of or more detailed information about a

brain provided by a digital brain twin helpful and empowering, others might become distressed or confused by the images; this issue, in relation to dementia, has yet to be explored in the research.

As the use of digital brain twins implies access to more detailed information about one's health, it is important to reflect and conduct ethical research on whether and how new categories of healthy ill should deserve therapy, 'enhancing treatment' or daily care and on questions related to healthcare resource allocation (Bruynseels et al., 2018). Becoming part of a healthy ill category could also raise ethical issues linked to beneficence and non-maleficence due to the impact this may have on people's sense of personal identity, relationships with others, employment status and healthcare insurance and psychological well-being.

Over the years, the parameters for healthy versus ill have been changed in several conditions and in both directions, for example with the emergence of the asymptomatic or at-risk group of people based on biomarkers for Alzheimer's disease. Being identified as "at risk" or "preclinical" for a condition like Alzheimer's disease can have significant psychosocial implications for individuals and their families. Anxiety, uncertainty, and psychological distress may arise from knowing about the increased risk of developing a progressive neurodegenerative condition. Ethical considerations include ensuring data protection, access to appropriate support services, psychological counselling and education to help individuals navigate the emotional and cognitive challenges associated with being in the "asymptomatic/at risk" group. It is important for healthcare professionals, researchers, policymakers and ethicists to engage in ongoing dialogue to address these ethical concerns and ensure that changing parameters for health and illness resulting from the use of digital brain twins are navigated thoughtfully, respecting the rights and well-being of individuals involved.

Regarding the use of digital brain twins without clinical support or with limited clinician support mentioned in the literature, further ethical research on this specific topic is necessary. In particular, the use of digital brain twins without clinician support may raise several ethical concerns related to inadequate interpretation and understanding, and misinterpretation or misunderstanding of the data could lead to unnecessary anxiety, incorrect self-diagnosis or inappropriate decision-making regarding their health. Digital brain twins, without clinician support, may focus solely on neuroimaging data or specific aspects of brain health, potentially neglecting other important factors that contribute to an individual's overall well-being. The absence of a clinician's comprehensive assessment and understanding of a patient's medical history, context and individual might hinder the delivery of personalised and holistic care. Relying solely on digital brain twins without clinician support as opposed to with clinical support may also increase the risk of deepening existing health disparities, particularly as access and understandability of digital health technologies can vary among different population groups.

## 7. Conclusion

Overall, this deliverable provides a comprehensive overview of the existing literature on the ethics of digital brain twins, highlights the gaps in current research and suggests directions for future investigations in the field of neuro-ethics and dementia-related conditions. Although the aim of this review was to explore what was known of this topic in relation to dementia and pre-dementia issues, the review also included literature that pertains to other medical conditions or virtual replicas of other body parts, as this may also be relevant to the dementia context and due to lack of literature on the topic.

The review examined the impact of the use and development of digital brain twins on societal wellbeing, the presence of inequalities, discrimination and injustice, the effect on autonomy and empowerment for patients and clinicians, issues of privacy and data protection as well as representation, control and freedom concerns. The review also discussed conceptual issues, including the terminology and language used to describe digital brain twins. It also identified existing recommendations on the ethical use and development of digital brain twins in research, the clinic and within wider society.

The review has highlighted the urgent need for more research on the ethical implications on the use of digital brain twins in the context of dementia, pre-dementia stages, dementia risk assessment and disclosure and other neurodegenerative disease areas. The findings of this scoping review will also serve to inform the eBRAIN-Health Initial and Final Legal and Ethical Frameworks, which provide an overview of the ethical implications of the eBRAIN-Health project and the adherence of the project to ethical principles and values.

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Rainey, S., 2022. Datafied Brains and Digital Twins: Lessons From Industry, Caution for Psychiatry. *Philosophy, Psychiatry and Psychology* , 29(1), pp. 29-42 .

Schwartz, S., et al. 2020. Digital Twins and the Emerging Science of Self: Implications for Digital Health Experience Design and "Small" Data. *Frontiers in Computer Science*, 2(0).

Sun, T. et al., 2022. The Digital Twin in Medicine: A Key to the Future of Healthcare?. *Frontiers*, 9(0).

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## 9. Annexes

### 9.1. Annex 1

#### **Information about search strings (search strings that were removed are highlighted in yellow):**

Philpapers (open access):

Query	Return
(digital) AND (twins) AND (ethics) AND (cognitive)	0
(digital) AND (twins) AND (ethics) AND (brain)	0
(Digital twins) AND (ethics) AND (health)	6
(simulation) AND (brain) AND (ethics) AND (person)	1
(ethics) AND (digital twin)	14
(risks) AND (digital twin)	5
(benefits) AND (digital twin)	5
(challenge) AND (digital twin)	8
Total	39

PubMed:

Query	Return
(digital) AND (twins) AND (ethics) AND (cognitive)	0
(digital) AND (twins) AND (ethics) AND (brain)	0
(Digital twins) AND (ethics) AND (health)	10
(simulation) AND (brain) AND (ethics) AND (person)	96
(ethics) AND (digital twin)	27
(risks) AND (digital twin)	115
(benefits) AND (digital twin)	47
(challenge) AND (digital twin)	113
Total	408

Scopus:

Query	Return
(digital) AND (twins) AND (ethics) AND (cognitive)	52
(digital) AND (twins) AND (ethics) AND (brain)	497
(Digital twins) AND (ethics) AND (health)	1193



(simulation) AND (brain) AND (ethics) AND (person)	2549
(ethics) AND (digital twin)	1901
(risks) AND (digital twin)	12632- Removed due to high volume
(benefits) AND (digital twin)	6889- Removed due to high volume
(challenge) AND (digital twin)	17608-Removed due to high volume

PsychInfo:

Query	Return
(digital) AND (twins) AND (ethics) AND (cognitive) AND (digital) AND (twins) AND (ethics) AND (brain) AND (Digital twins) AND (ethics) AND (health) AND (simulation) AND (brain) AND (ethics) AND (person) AND (ethics) AND (digital twin) AND (risks) AND (digital twin) AND (benefits) AND (digital twin) AND (challenge) AND (digital twin)	0
(digital) AND (twins) AND (ethics) AND (cognitive)	0
(digital) AND (twins) AND (ethics) AND (brain)	0
(Digital twins) AND (ethics) AND (health)	0
(simulation) AND (brain) AND (ethics) AND (person)	7
(ethics) AND (digital twin)	0
(risks) AND (digital twin)	0
(benefits) AND (digital twin)	1
(challenge) AND (digital twin)	1
Total	9

PsychArticles:

Query	Return
(digital) AND (twins) AND (ethics) AND (cognitive) AND (digital) AND (twins) AND (ethics) AND (brain) AND (Digital twins) AND (ethics) AND (health) AND (simulation) AND (brain) AND (ethics) AND (person) AND (ethics) AND (digital twin)	0

(risks) AND (digital twin)	
(benefits) AND (digital twin)	
(challenge) AND (digital twin)	
(digital) AND (twins) AND (ethics) AND (cognitive)	0
(digital) AND (twins) AND (ethics) AND (brain)	0
(Digital twins) AND (ethics) AND (health)	0
(simulation) AND (brain) AND (ethics) AND (person)	0
(ethics) AND (digital twin)	0
(risks) AND (digital twin)	0
(benefits) AND (digital twin)	0
(challenge) AND (digital twin)	0

### 9.2. Annex 2

**Information about excluded keywords (keywords according to which articles were excluded are highlighted in yellow):**

Keyword exclusion	
survey	396
literature review	336
systematic review	300
cells	118
meta-analysis	106
cohort	106
longitudinal	78
cross-sectional	69
prevalence	64
trials	60
animal	59
observational	45
reviews	42
soil	34
mice	33
in vitro	25

mouse	24
case control	22
case report	22
fish	18
retrospective study	15
animals	15
rats	15
this review	12
retrospective cohort	11
rat	9
randomized controlled trials	8
cadaveric	6
canine	6
equine	6
porcine	5
randomised controlled trials	4
regression analysis	4
retrospectively	4
case reports	4
age-matched	4
cadaver	4
rodent	4
sensitivity and specificity	3
healthy controls	3
transgenic	3
murine	3
regression analyses	2
healthy control	2
cadavers	2
rodents	2

rabbit	2
single arm	1
piglets	1
non-randomised	0
non-randomized	0
nonrandomised	0
nonrandomized	0
broilers	0
purebred	0
beagles	0
broiler	0
rabbits	0
beagle	0

### 9.3. Annex 3

#### **Information about included literature, with grey literature in purple:**

TITLE	YEAR	TYPE OF ARTICLE	AUTHORS
Digital twins for precision healthcare.	2020	Peer-reviewed journal article	Ahmadi-Assalemi, G. and Al-Khateeb, H. and Maple, C. and Epiphaniou, G. and Alhaboby, Z.A. and Alkaabi, S. and Alhaboby, D.
The use of digital twins in healthcare: socio-ethical benefits and socio-ethical risks.	2021	Peer-reviewed journal article	Bogaardt, M-J and Oosterkamp, E. and van Hilten, M. and Popa, E.
Represent me: please! Towards an ethics of digital twins in medicine.	2021	Peer-reviewed journal article	Braun, M.
Ethics of digital twins: four challenges.	2021	Peer-reviewed journal article	Braun, M.
Digital twins and the ethics of health decision-making concerning children.	2022	Peer-reviewed journal article	Braun, M. and Krutzinna, J.
Digital Twins in Health Care: Ethical Implications of an Emerging Engineering Paradigm.	2018	Peer-reviewed journal article	Bruynseels, K. and Santoni de Sio, F. and van den Hoven, J.

The Health Digital Twin: advancing precision cardiovascular medicine.	2021	Peer-reviewed journal article	Coorey, G. and Figtree, G.A. and Redfern, J.
The 'Digital Twin' to enable the vision of precision cardiology.	2020	Peer-reviewed journal article	Corral-Acero, J. And Margara, F. and Marciniak, M. and Rodero, C. and others.
Are Digital Twins Becoming Our Personal (Predictive) Advisors?: Our Digital Mirror of Who We Were, Who We Are and Who We Will Become.	2020	Contribution to conference proceedings	De Maeyer, C. and Markopoulos, P.
Epistemic Challenges of Digital Twins & Virtual Brains: Perspectives from Fundamental Neuroethics.	2021	Peer-reviewed journal article	Evers, K. and Salles, A.
Digital twins for well-being: an overview.	2021	Peer-reviewed journal article	Ferdousi, R. and Laamarti, F. and Hossain, A. and Yang, C. and El Saddik, A.
Digital Twins: Potentials, Limitations and Ethical Issues.	2022	Peer-reviewed journal article	Helbing, D. and Sanchez-Vaquerizo, J.
Ethical Issues of Digital Twins for Personalized Health Care Service: Preliminary Mapping Study.	2022	Peer-reviewed journal article	Huang PH., and Kim, K.H. and Schermer, M.
Mapping the Ethical Issues of Digital Twins for Personalised Healthcare Service.	2022	Peer-reviewed journal article	Huang, P. and Kim, K. and Schermer, M.
Digital Twins in Healthcare: Conceptualisation and Privacy Aspects – Masterthesis.	2020	Master student thesis	Jeske, S.
Digital Twins: From Personalised Medicine to Precision Public Health.	2021	Peer-reviewed journal article	Kamel Boulos, M.N. and Zhang, P.
A Scoping Review of Digital Twins in the Context of the Covid-19 Pandemic.	2022	Peer-reviewed journal article	Khan, A. and Milne-Ives, M. and Meinert, E. and Iyawa, G.E. and Jones, R.B. and Josephraj, A.N.
Simulating (some) individuals in a connected world.	2021	Peer-reviewed journal article	Krutzinna, J.
Health Technology Assessment for In Silico Medicine: Social, Ethical and Legal Aspects.	2022	Peer-reviewed journal article	Leo, C.G. and Tumolo, M.R. and Sabina, S. and Colella, R. and Recchia, V. and Ponzini, G. and Fotiadis, D.I. and Bodini, A. and Minciarone, P.
Brain simulation and personhood: a concern with the Human Brain Project.	2014	Peer-reviewed journal article	Lim, D.
'Represent me: please! Towards an ethics of digital twins in medicine'.	2021	Peer-reviewed journal article	Loh, J.
Language matters: the 'digital twin' metaphor in health and medicine.	2021	Peer-reviewed journal article	Lupton, D.

Near-term ethical challenges of digital twins	2021	Peer-reviewed journal article	Mittelstadt, B.
Should a medical digital twin be viewed as an extension of the patient's body?	2021	Peer-reviewed journal article	Nyholm, S.
Digital Twins: Representing the Future	2021	Non-peer reviewed article	Pigni, F. and Thomas Watson, R. and Piccoli, G.
To explore the pharmacological mechanism of action using digital twin	2022	Peer-reviewed journal article	Rahman, H.U. and Mahmood, M.H.B. and Khan, M.S.A. and Sama, N.U. and Asaruddin, M.R. and Afzal, M.
Datafied Brains and Digital Twins: Lessons From Industry, Caution for Psychiatry	2022	Peer-reviewed journal article	Rainey, S.
Digital Twins and the Emerging Science of Self: Implications for Digital Health Experience Design and "Small" Data.	2020	Peer-reviewed journal article	Schwartz, S.M. and Wildenhaus, K. and Bucher, A. and Byrd, B.
The Digital Twin in Medicine: A Key to the Future of Healthcare?	2022	Peer-reviewed journal article	Sun, T. and He, X. and Song, X. and Shu, L. and Li, Z.
Digital twins running amok? Open questions for the ethics of an emerging medical technology	2021	Peer-reviewed journal article	Tigard, D.W.
Perspectives on digital twins and the (im)possibilities of control	2021	Peer-reviewed journal article	Tretter, M.
Digital Twins for Multiple Sclerosis.	2021	Peer-reviewed journal article	Voigt, I. and Inojosa, H. and Dillenseger, A. and Haase, R. and Akgün, K. and Ziemssen, T.