

# Digital Twins for Developing Parkinson's Disease Medications: Opportunities and Challenges on the Road Towards Brain Digital Twins

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## Abstract

Think about the existence of your digital double—your body modelled in computers which would be able to test drugs' efficacy before they will be applied to you. This is the reality of digital twin technology—a complex set of digitalized measurements constantly updated as more information becomes available. In case of Parkinson's disease, the disease of many millions of people across the world, the dream of having individual disease digital twin mapping brain activity and predicting an individual reaction to a treatment is not yet a reality. However, surprisingly enough, much of the infrastructure required to create such brain digital twins has been developed. First of all, there are validated measurements using smart devices such as a smartwatch or a smartphone. Second, there are complicated computer algorithms modelling the processes of gene expression at cellular and tissue levels which affect brain networks functionality. Finally, there is an opportunity to run digital trials using artificial intelligence and regulators' expertise based on analogous trials in Alzheimer's disease. This review discusses the present status of the digital twin technology in developing medications for Parkinson's disease. It provides the analysis of evidence coming from wearables, computational brain science, pharmaceuticals modelling, and regulatory policy changes. It evaluates the current situation, pinpoints some difficulties related to the integration of various data types, individualization of diseases, and aligning digital twin results with patients' needs and regulations. And finally, it presents the way to overcome these difficulties in order to develop digital twins that would become acceptable for regulators in future. The practice of developing digital twins in Alzheimer's disease encourages our thoughts. Already here, the usage of AI-generated digital twins allowed reducing the

number of trial participants from 9 to 26 percent and receiving positive opinion from regulatory agencies. The efforts in critical path initiatives aimed to achieve regulatory approval are well visible. Although complete brain digital twins for Parkinson's disease development are still several years away, a fast converging progress in collecting multidimensional patient data, modelling the disease at molecular and brain network level, and using artificial intelligence technologies brings the goal ever nearer.

**Keywords:** Digital twins, Parkinson's disease, drug development, digital health technologies, in-silico trials, computational neuroscience, quantitative systems pharmacology, regulatory science.

## I. Introduction

Approximately 10 million people suffer from Parkinson's disease (PD), and the number of people affected by this illness is expected to increase because of population aging. Specifically, the estimated number of PD patients in 2040 may reach 17 million people. For several decades, scientists have been pursuing the goal of finding a drug that will cure PD and change its course; however, current drugs can only relieve symptoms. No significant regulatory agency has yet approved a disease-modifying treatment for Parkinson's. Developing a new treatment for this condition requires overcoming several difficulties, such as significant individual variability in disease progression, lack of sensitivity or objectivity of selected endpoints, high rates of placebo effects, high costs, and large cohorts needed for prolonged clinical trials.

Digital twins (DTs) are virtual counterparts of their real-world analogs that constantly evolve

along with updates of additional information. As of today, digital twins are used in virtually all areas of science and engineering, while biomedical applications allow DTs to simulate various biological structures and processes from a single cell through an organ or a whole organism to an individual person. The concept of DT is becoming increasingly popular in neurodegenerative diseases due to possible ability to predict disease progression and improve clinical trials. This paper aims at describing existing advances in using digital twins and similar technology in the development of new drugs for PD, as well as identifying challenges and suggesting ways to overcome them and build regulatory-compliant brain DTs for Parkinson's patients.

## 2.2 The Concept of Digital Twins in Parkinson's Disease

### 2.2.1 Conceptual Framework

Healthcare digital twins range in complexity and integration from simple sensors, which capture physiological variables in real time but cannot predict them, through individualized patient profiles based on multimodal datasets (digital patients) to whole-population models that simulate the effects of treatments (in silico trials). True digital twins incorporate all of these features: they are personalized, continuously updated, biophysically informed, and have the ability to simulate counterfactual scenarios [6,9,10].

The digital twin paradigm for PD drug development is defined hierarchically, following the framework developed by Barricelli et al. [1] and Niederer et al. [7] as:

Level 1: Digital Biomarker	Sensor-derived measure associated with clinical condition	Tremor measurement using smartwatch [24,33]	Regulated
Level 2: Digital Outcome	Clinically validated sensor measure used as trial outcome	Wearable device-derived gait speed [36,38]	Developmental
Level 3: Prognostic Digital Twin	Artificial intelligence tool predicting individual disease course	CNODE prediction of brain morphometry evolution [59]	Experimental
Level 4: Mechanistic Digital Twin	Biophysical model connecting mechanism to phenotype	Spiking whole-brain network models [49,50,51,52]	Emerging
Level 5: Digital Patient Twin	Multi-scale model optimizing therapy	Not applicable for PD	Future

## 2.2 Differentiation from Other Concepts

The term digital twin is frequently confused with other concepts that are similar yet different from one another. Artificial intelligence (AI) algorithms for progression prediction [59,60,63,64] make forecasts but do not have two-way updating capabilities and do not incorporate mechanism-based reasoning. Control arms [72,73,74,75] use historical data to improve trial design but cannot be considered personalized digital twins. Quantitative systems pharmacology (QSP) modeling algorithms can connect molecular mechanisms to patient outcomes, but they are usually not personalized but average-based [39,40,41,42,43,44,45,46].

## III. Foundation for Parkinson's Disease Brain Digital Twins

### 3.1 Digital Health Technologies for Phenotyping

Phenotypic data is at the core of every patient digital twin. PD has become one of the primary use cases for DHTs within neurology [21,22,23,24,25,26]. Assessment based on smartphones and wearables allows objective, non-contact, remote measurements of motor function features [27,28,29,30]. In the PASADENA phase 2 trial of prasinezumab, a monoclonal anti-alpha-synuclein antibody, two years of testing included both active assessments (speeded tapping) and passive monitoring (hand movement power, gait metrics) in 316 early-stage PD patients [33,34,35]. It was shown that digital markers indicated progressive changes in the absence of therapy, as well as numerical differences between the treatment groups, proving their feasibility as exploratory outcome measurements [33,34,35].

Some key digital measures in the context of PD include:

- Gait speed, measured using wearable accelerometer data and shown to be a progression marker [36,37,38]
- Tapping variability and hand turning, measured using touchscreen test data of smartphone apps [31,32,33]
- Passive monitoring measures: u-turn speed, hand movement power [33,34]
- Composite scores: derived using multiple streams of sensor data [31,32,33]

A specific initiative aimed at increasing regulatory maturity of DHTs is called the **Critical Path** for

Parkinson's (CPP) 3DT\*\*. This is a global pre-competitive effort that focuses on advancing the regulatory landscape regarding DHTs [36,37,91,95]. As part of its efforts, CPP engages FDA early on in 2024 and EMA in 2025 to set the path for qualification of digital monitoring biomarkers for disease-modifying therapy trials [36,37,91,95].

### 3.2 Mechanistic brain models

The mechanistic underpinning is what differentiates the digital twin from the traditional statistical machine learning approach in AI. Various methods are pertinent to the construction of the brain twin in patients with Parkinson's disease.

Quantitative systems pharmacology (QSP) modeling links the effects of molecules to cell and network-level functions. Recent research by Ivanova and Karelina (2024) described a mechanistic QSP model of the  $\alpha$ -synuclein pathway in mice resembling humans with Parkinson's disease, which included  $\alpha$ -syn production, aggregation, degradation, and redistribution within neurons, secretion to interstitial fluid, endocytosis, and clearance by neurons and microglia [39]. The model accurately replicated the pre-clinical findings and predicted that the immunotherapy efficacy is dependent upon several factors such as the decrease in the amount of aggregated  $\alpha$ -synuclein protein and reduced inflammatory activity of microglia [39]. Such multifaceted systems offer blueprints for further PD-specific application [40,41,42,43,44,45,46]. Other researchers have developed a humanized, clinically calibrated QSP model for hypokinetic movement disorders in PD [45,46].

Whole-brain network models for simulation of spiking neural activity have been successfully employed in neurological conditions [49,50,51,52,53,54]. Scientists have introduced whole-brain computational models to create virtual brain twins of individual patients based on neuroimaging data (primarily MRI imaging) and mathematical equations [52,53,54,55,56,57,58]. Such models allow investigating the brain dynamics as a whole, rather than being limited to particular brain areas, and enable testing of how the brain of a person responds to certain changes or stimuli in controlled environments [49,50,51,52,53,54]. Virtual Brain software created by Jirsa et al. Offers an open-source computational framework for personalized brain network modeling, which has already been successfully applied to epilepsy and

may be transferred to Parkinson's disease [56,57,58].

Digital Brain Twins (DBT) stands for an advanced method that allows simulating individual brain activity in healthy and diseased subjects [49,50,51,52]. The method uses MRI-derived metrics to evaluate pathological changes in the microstructural parameters (neurite density and orientation, myelin, iron, and brain metabolite levels) and creates subject-specific brain avatars [50,51]. Pathological mean-field models can be developed based on specific changes observed on the mesoscopic level of organization, which results in personalized DBTs with simulated brain activity reflecting pathological processes [49,50,51,52].

Neuromorphic computing platforms provide an efficient brain-like simulation solution that may enable real-time, high-fidelity modeling of the pathological condition [79,80,81,82,83,84,85]. As reported by Raikar et al. (2024), neuromorphic computing provides a promising hardware-based platform for modeling diseases in drug discovery based on the brain's architecture [79]. Neuromorphic hardware is highly energy-efficient compared to traditional computers because it mimics biological principles of functioning, and thus may be used at the large scale in modeling PD pathophysiology [79,80,81,82]. In particular, recent work by Chatzipaschalis et al. (2023) demonstrated bio-inspired neuromorphic circuits based on CBRAM technology for PD emulation and therapy [84].

### 3.3 Artificial intelligence for Progression Forecasting and Personalization

With recent advances in machine learning, there are ever-increasing opportunities for the forecasting of individual PD progression.

CNODE (Conditional Neural ODE) stands among state-of-the-art frameworks enabling accurate forecasting of individual PD progression [59]. Specifically, CNODE was demonstrated on the Parkinson's Progression Markers Initiative (PPMI) dataset, modelling morphological brain changes through continuous time as a neural ordinary differential equation [59]. Crucially, this method jointly estimates the patient-specific initial time and the rate of progression to align trajectories onto a progression curve [59]. Such an estimate allows to overcome heterogeneity in PD onset, progression rate and the severity of symptoms [59,92,93].

Generative artificial intelligence models like MultiNODEs (Multiple Neural Ordinary

Differential Equations) are currently developed for the application in the context of digital twins of patients with PD [60,61]. In particular, the AIPD (Artificial Intelligence for Parkinson's Disease) initiative at Fraunhofer SCAI uses the generative artificial intelligence to perform personalized forecasts of PD outcome trajectories, e.g., UPDRS sub-items, based on NCER-PD/LuxPARK, PPMI and ICEBERG datasets [60,96]. Importantly, this approach enables conducting simulations that take into account counterfactual scenarios like "What if the treatment was altered at baseline?" by changing defined covariates [60,61]. Collaborations with pharmaceutical companies are expected to provide clinical trial design tools [60,96].

Proteostasis Activity Score of  $\alpha$ -Synuclein constitutes another crucial development. In Lim and Vendruscolo (2025), the authors constructed the network of proteins mediating the proteostasis of  $\alpha$ -synuclein in the substantia nigra both at the proteomic and transcriptomic level. They also proposed a score – proteostasis activity score (PAS) estimating the activity of the proteostasis network regulating  $\alpha$ -synuclein [62]. Then, a digital twin of the  $\alpha$ -synuclein proteostasis network in substantia nigra cells was designed through the use of single-cell data [62]. Its further utilization includes target identification for PD treatment and drug repurposing [62].

### 3.4 Digital Twins Methods for In-silico Trials

The most developed regulatory use case of digital twins today is optimizing clinical trials, with applications from AD giving direction for PD.

AI-generated digital twins based on ML techniques can predict individual placebo outcomes [68]. In the AWARE phase 2 trial, AI-generated DTs predicted individual placebo outcomes with Pearson correlations between the predicted and the observed outcome of 0.30-0.46 [68]. Incorporating such DTs as covariates into ANCOVA reduced the total variance by 9-15%, while at the same time reducing the number of patients in the control arm by 17-26%

[68]. Importantly, the methodology was endorsed by FDA and EMA [68,69,70,76,77].

Conceptually, such an approach can be translated to PD although there are issues of increased phenotypic heterogeneity and historical control database immaturity compared to AD [63,64,65]. A synthetic control arm methodology is under active development for PD as part of the AIPD project, with defined goals to combine patient trajectories synthetically across multiple studies and select synthetic control cases based on predefined user criteria [60,61,96].

As far as regulatory approval, the new FDA guidance on real-world evidence and AI-based methods for clinical trials as of 2026 advances towards digital twin validation in pivotal trials [69,70,77]. The FDA and the EMA released joint guidelines on good AI practices in drug development as of January 2026 (transatlantic agreement on AI validation) [69,70]. For rare diseases, aggressive cancers, and neurodegenerative disorders, a counterfactual patient simulation using an external control arm based on real-world evidence is possible without needing placebo patients [71,72,73,74,75].

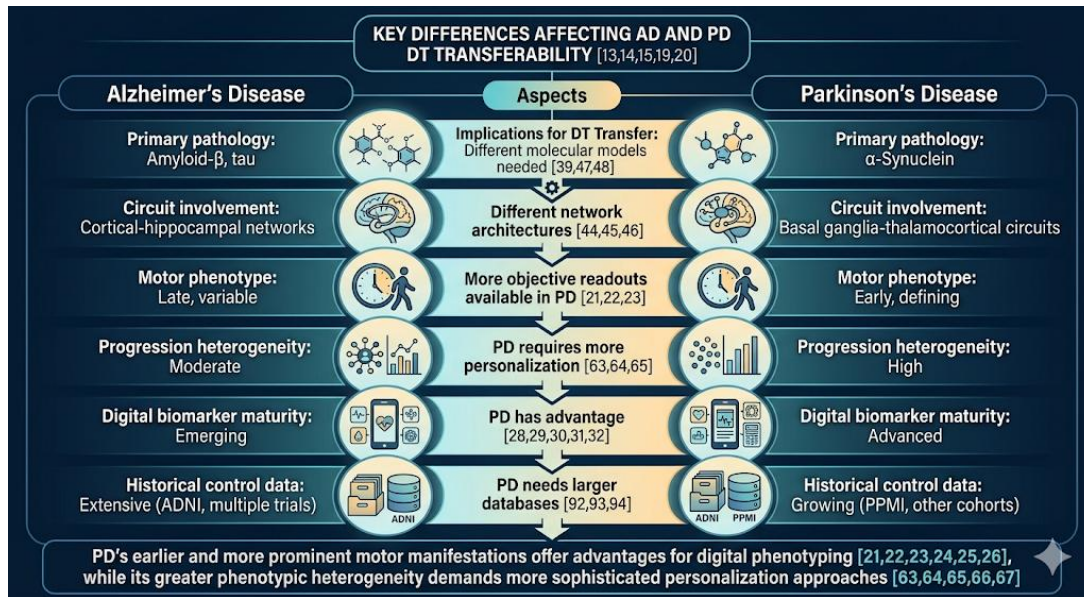
## IV. Lessons From Alzheimer's Disease

Alzheimer's disease has been an important testbed for digital twin technology application in neurodegeneration and has important lessons for PD.

### 4.1 Figure 1. Key differences affecting AD and PD DT transferability

#### 4.1 AD Digital Twin Platforms

AD whole-brain digital twin platforms use structural and functional imaging, along with amyloid and tau biomarkers, and cognitive tests to model personalized disease progression and test virtual interventions [49,50,51,52,53,54]. In AD single-cell digital twins, snRNA-seq and snATAC-seq is used for identifying cell-type specific targets and repurposable drugs [62]. For PD, substantia nigra dopamine neurons and striatal projection neurons can be targeted through a similar mechanism [62].



#### 4.2 Regulatory Precedents

The regulatory framework established for AD digital twins can be taken as a precedent for PD. The FDA and EMA have:

1. Supported the PROCOVA approach based on use of AI-generated DTs as covariates in AD trials [68,69,70]
2. Issued joint principles for good AI practice (January 2026) to ensure harmonized standards for AI validation in drug development [69,70]
3. Allowed the use of external control arms based on real-world data for counterfactual simulation at the patient level [71,72,73,74,75,77]

#### 4.3 Transferability to PD

Key differences between AD and PD affect transferability [13,14,15,19,20]:

### V. Current Status of Digital Twins for PD Research

#### 5.1 R&D Programs and Initiatives

Some of the prominent programs dedicated to improving PD digital twin technologies include the following:

CPP 3DT (Critical Path for Parkinson's): Global pre-competitive consortium consisting of FDA, EMA, industry partners, and academic organizations aiming at qualification of digital biomarkers for monitoring purposes [36,37,91,95]. Formal feedback provided by EMA in 2025 and informal one by FDA in 2024 in favor of using gait speed as a marker of disease progression in early PD

[36,37,91]. Underlined the importance of standardization, relevance, and longitudinal follow-up [36,37,95].

AIPD Doctoral Training Network: Training program in EU funded by Marie Skłodowska-Curie Actions, which includes multiple AI-based research projects related to PD [60,96]. In particular, project DC13 focuses on "Generative AI for Simulating a Digital Parkinson's Disease Twin" based on MultiNODE frameworks [60]. Objectives include artificial creation of synthetic control arms and conducting counterfactual medicine experiments [60,61]. Collaboration with pharmaceutical companies to conduct clinical trials [60,96].

PPMI and WATCH-PD: Longitudinal studies used for model training and validation [92,93,94]. WATCH-PD study focused on the early stages of PD, with follow-ups conducted during 12 months and presented to regulators [94]. Since 2010, PPMI dataset contains more than 1,500 participants making it one of the largest longitudinal datasets for training AI-based models [92,93].

EBRAINS 2.0 and VBT Projects: European initiatives that provide infrastructures for building multi-scale models of brain function and digital twins [97,98].

#### 5.2 Organoid and Experimental Platforms

Human midbrain organoids (hMOs)\*\* generated using induced pluripotent stem cells provide a valuable alternative model system for Parkinson's

disease (PD) [86,87,88,89,90]. In a recent study carried out by Raji et al. (2025), a differentiation protocol involving tri-phasic manipulation of WNT signaling and bioreactor-based culture conditions was proposed to improve the production efficiency, maturation, and functional capabilities of dopamine neurons in hMOs [86]. The current platform provides an effective means of studying PD

pathogenesis as well as for screening potential therapies [86,87,88]. Several other studies have also created PD-specific dopamine neuronal 3D cultures for phenotypic characterization and therapeutic screening purposes [90]. Digital twin platforms incorporating organoid information are a novel approach to personalized medicine [86,87,88,89,90].

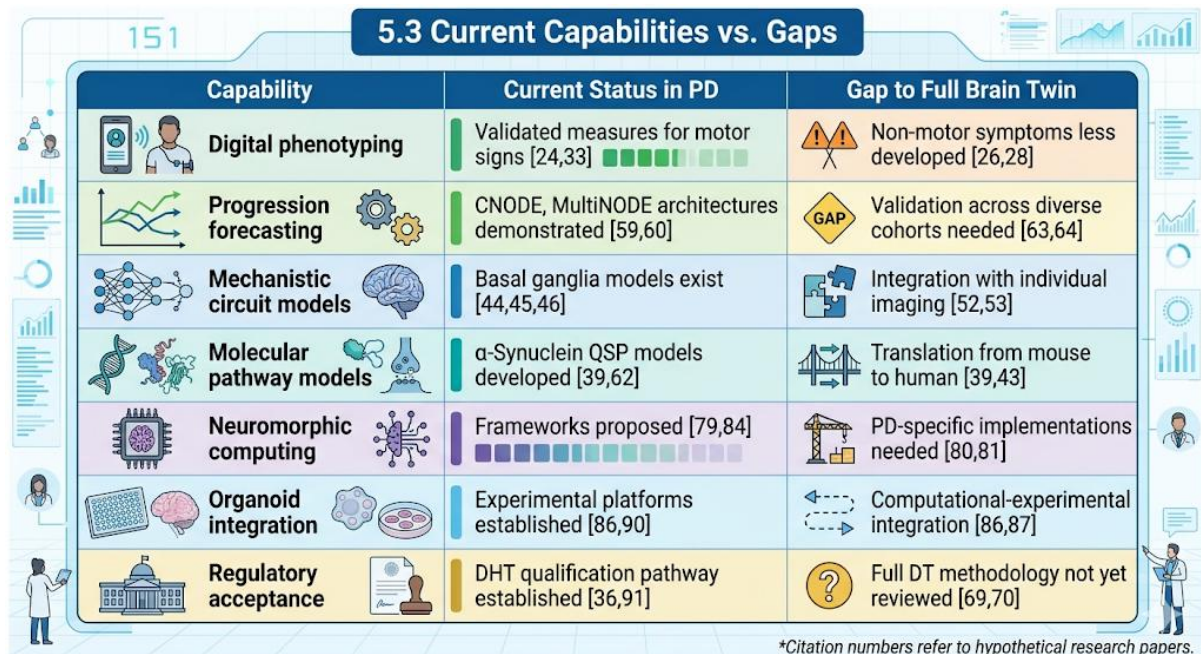


Figure 1. Current Capabilities vs. Gaps

## VI. Challenges and Barriers

### 6.1 Technical Challenges

Data integration continues to be one of the key challenges [64,65,66]. For PD brain twins, the integration of multi-modal longitudinal data such as clinical assessments, brain imaging (structure, function, molecules), wearables, genetics, and novel biomarkers needs to occur [28,29,30]. While current data sets are generally limited in scope, being isolated from one another and collected at varying timepoints with missing data, even the comprehensive PPMI data set is coarsely sampled compared to wearable data streams (typically every 6-12 months) [92,93,94].

The modeling of heterogeneity poses particular difficulties in the case of PD [63,64,65,66,67]. In contrast to the relatively homogeneous pathophysiology seen in specific subgroups of AD, the variability in PD is substantial in terms of onset age (from 40 up to 80 years and more), type of first symptoms (tremor vs. Postural Instability/Gait Difficulty vs. Non-Motor

Symptoms), speed of progression and responsiveness to treatments [13,14,15,16]. This variability has to be accounted for within the same architecture [59,60,61].

Computationally, the scalability to run brain-wide simulations is highly challenging [52,53,54]. Simulations of 86 billion neurons, considering proper connectivity among neurons, are not possible using current computational hardware resources, although new methods, such as neuromorphic computing and model simplification, can help achieve this goal [79,80,81,82,83,84,85].

Validation of digital twins is yet another issue for which there is no standardized protocol [68,71,78]. Validation of a counterfactual is difficult because standard metrics of validation do not apply in situations when ground truth (for example, an outcome that was never observed due to treatment intervention) is impossible to ascertain [68,71].

### 6.2 Regulatory Challenges

Pathways for qualification as a drug development tool for digital twins are still evolving for PD [69,70,76,77]. Though the FDA and EMA have qualified the PROCOVA approach for covariate adjustment in AD, this is only a limited application (covariate adjustment), not broader use of the digital twins themselves [68,69,70]. More advanced uses, such as replacing control groups or using as an endpoint in trials, will need further investigation.

Harmonization including across multiple device platforms, data collection formats, and processing pipelines, is critical for regulatory approval [36,37,91,95]. The CPP 3DT project has highlighted interoperability standards as a top priority, but there is still work to be done harmonizing among the many different device and software vendors in the PD digital health landscape [36,37,91].

The issues of patient privacy and data ownership need to be addressed [2,8]. Digital twins use sensitive longitudinal data. Standards for data governance and anonymization, as well as informed patient consent to build the twins, need to be established [2,8,9].

### 6.3 Challenges in Implementation and Practice

Relevance to clinical practice must be established [16,17,18]. Digital assessments and twin forecasts should be validated against clinically relevant outcomes such as quality of life, functional autonomy, and caregiver stress [16,17,18,100]. Patient participation in measure selection has been encouraged in the CPP project, but more work is needed in this area [36,37,91].

Implementation challenges for global studies include logistical problems [21,22,23]. All study locations may not have access to standardized hardware, stable internet connection, or technical support for digital phenotyping tasks [21,22]. Equitable access is vital for obtaining generalizable data [21,22,100].

Development of digital twins can be costly and infrastructurally demanding [6,7,8]. Development and validation of brain twins for PD will take years of investment in computational facilities and expertise [6,7,8,9].

## VII. Future Directions and Roadmap

### 7.1 Short-term Goals (1-3 Years)

Achieve regulatory qualification of digital monitoring biomarkers for early PD via the CPP 3DT initiative [36,37,91,95]. This will be made possible by the completion of the 12-month trial period for WATCH-PD, which has shown gait speed to be a promising marker [94,95].

Create methodology for PD synthetic controls following AD successes [60,61,68]. The work done at AIPD on synthetic trajectory generation for PD using MultiNODE needs to be tested against completed PD trials [60,61,96].

Create a historical control database specific to PD along the lines of ADNI for AD cases [92,93,94]. Creation of such a database, with contributions from PPMI, WATCH-PD, and industry clinical trials, would significantly enhance model development and validation efforts [92,93,94].

Retrospective validation of progression forecasting models (CNODE and MultiNODE) [59,60,61]. Retrospective validations have been performed thus far; it will be necessary to validate these algorithms prospectively as well [59,60].

Link  $\alpha$ -synuclein proteostasis digital twins with clinical data [62]. Creation of a single-cell digital twin of the  $\alpha$ -synuclein proteostasis network provides an avenue to personalized molecular modeling [62].

### 7.2 Medium-Term Goals (3-5 Years)

Combine mechanistic models of circuits with personalized imaging information [49,50,51,52,53,54]. Basal ganglia-thalamocortical network modeling based on personalized structural and functional connectivity would enable prediction of treatment effects at a circuit level by dopaminergic and non-dopaminergic drugs [44,45,46,52].

Design and validate a novel method of PROCOVA specifically tailored for PD patients using historical control databases [68,69,70]. Size reduction calculations in PD clinical studies should be performed and communicated to regulatory agencies [68,69,70].

Create and validate PD digital twin in a prospective clinical study as an exploratory approach to identify stratification criteria or optimal endpoints [60,61,68].

Validate the applicability of neuromorphic computing systems for PD-specific purposes [79,80,81,82,83,84,85]. The advantages of utilizing neuromorphic models in simulating and comprehending neurological diseases make it possible to develop effective treatment strategies.

### 7.3 Long-Term Vision (5-10 Years)

Complete digital twins of patients which encompass all the aspects of molecular pathology ( $\alpha$ -synuclein, inflammation, mitochondrial physiology), circuit dynamics, digital phenotyping, and clinical

endpoints that would allow for true personalization of interventions [5,6,7,8,9,10].

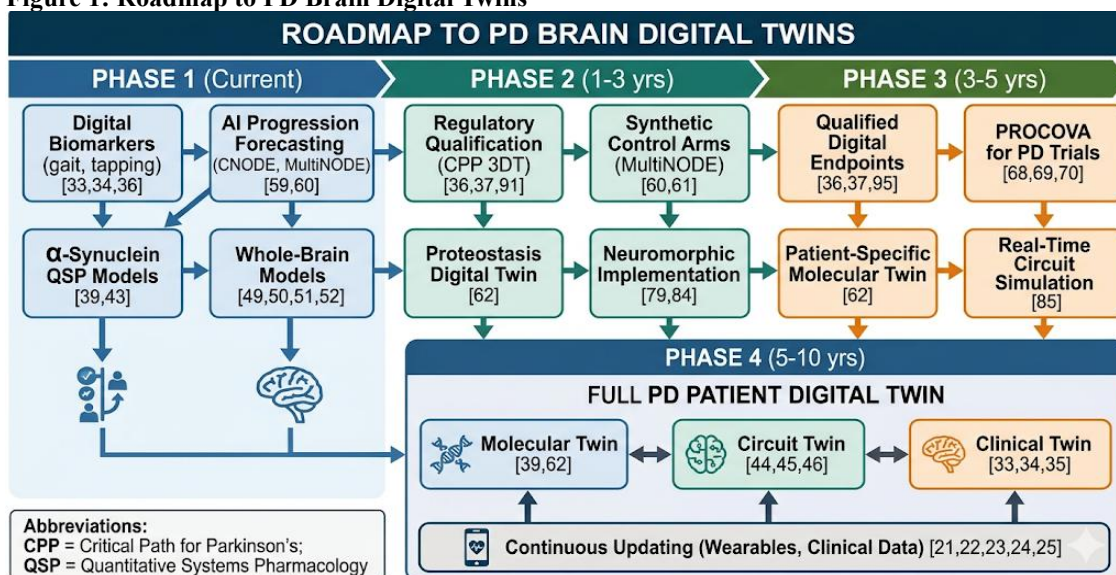
In-silico first-in-human trials in which potential treatments are studied on virtual populations of PD twins before actual trials begin, allowing for fast dose optimization and patient stratification [68,69,70,71].

Updating clinical decision making in support whereby patients' twins are continuously updated

using real-world data (wearables, clinical follow-up visits), allowing clinicians to make informed adjustments to therapy [61,100].

Cooperation framework between humans, artificial intelligence, and robots as envisioned by Hizeh et al. (2025) with multimodal sensing allowing continuous personalized intervention through intelligent agents forming a basis for a dynamic digital twin of PD patients [61].

7.4 Figure 1: Roadmap to PD Brain Digital Twins



Abbreviations: CPP = Critical Path for Parkinson's; QSP = Quantitative Systems Pharmacology

## VIII. Discussion

### 8.1 Synthesis of Current Evidence

The advent of several technological advancements has made it feasible to explore the creation of digital twins in PD. Digital health technology is no longer limited to research applications but has become regulatory engagement measures [36,37,91]. The PASADENA study showed the potential of smartphone-based measures in detecting progression and response to medication in early-stage PD, highlighting the viability of large-scale digital phenotyping [33,34,35]. The CPP 3DT program outlined a regulatory qualification approach, with gait speed identified as the lead candidate digital monitoring biomarker [36,37,95].

Computational science has also advanced significantly. Quantitative systems pharmacology models have been developed and tested on the preclinical α-synuclein pathology model, laying the groundwork for creating disease-specific digital twins [39,43]. The α-synuclein proteostasis network has been comprehensively mapped at a single-cell

level, making digital twins useful for targeting novel therapies and drug repurposing [62]. Modeling frameworks applicable to other neurodegenerative diseases are theoretically transferable to PD cases [49,50,51,52,53,54]. Neuromorphic computing represents an efficient hardware pathway for real-time neural simulations [79,80,81,82,83,84,85].

Regulatory guidelines have also progressed favorably. The FDA and EMA have supported the use of AI-derived digital twins as prognostic covariates in clinical trials for Alzheimer's disease, setting the precedent for similar applications in PD [68,69,70]. The principles of good AI practices outlined jointly by the FDA and EMA provide a transatlantic guideline for validation [69,70]. The MIDD regulatory framework has potential for translation modeling approaches for PD [41,42,43].

### 8.3 Comparison with Other Neurological Diseases

In the progression towards digital twin maturity, PD is located somewhere between other

neurological diseases. In the case of epilepsy, whole-brain digital twins that incorporate patient-specific brain imaging and electrophysiological data have already been employed in clinical practice for surgical procedures [56,57,58]. On the other hand, for AD, AI-generated digital twins have already been approved as prognostic covariates in clinical trials [68]. While digital biomarkers are well-developed in PD, digital twins are still in their infancy [36,37,91].

There are several reasons for this disparity. First, since PD presents distinct motor symptoms, digital phenotyping can generate plentiful data for training purposes [21,22,23,24,25,26]. Nevertheless, the basal ganglia-thalamocortical network is more complicated to simulate than the cortical-hippocampal network mainly impacted by early-stage AD [44,45,46,52]. Second, because of the greater phenotypic variability in PD, digital twins require

#### 8.4 Implications for Drug Development

The success of PD brain digital twins would be highly transformational for drug development [5,6,7,8,9,10]. Clinical trial efficiency through synthetic control arms and prognostic covariates would decrease sample size needs by 20-30%, speeding up the process and saving money [68,71,72,73]. Outcome measures based on continuous digital assessment could more readily identify treatment impacts with reduced sample size or trial duration [33,34,35]. Stratification of trial participants based on the digital twin's predictive power could enrich the trials with fast-progressing patients or molecular subgroups [19,20,62]. In-silico evaluation of new compounds would help in identifying the optimal dosage and target populations prior to first-in-human studies [68,69,70].

#### Conclusion

While there is still no realization of digital twins in drug development for Parkinson's disease, all the pieces of the puzzle are coming into place fast. Smartphone and wearable validated digital biomarkers are already used in phase 2 studies and involving regulators in the process [33,34,35,36,37]. Models for quantifying systems pharmacology have been created and validated for  $\alpha$ -synuclein pathology as well as forming the foundations for PD digital twins [39,43]. Digital twins at the single-cell level are used for finding new targets and repurposing drugs using the  $\alpha$ -synuclein proteostasis network [62]. Frameworks for whole brain modeling

in other neurological disorders are transferable to PD as well [49,50,51,52,53,54]. Neuromorphic computing provides a promising approach for neural simulating [79,80,81,82,83,84,85].

One of such initiatives, Critical Path for Parkinson's 3DT project, represents the type of cooperation that is necessary to succeed. It brings together regulators, industry, academia, and patients in addressing foundational aspects of regulatory maturity [36,37,91,95]. The emerging models of Human-AI-Robot collaboration involve closed-loop sensor-AI-robot systems as the foundation for PD adaptive digital twins [61].

However, substantial gaps remain. Integration of multi-modal longitudinal data across molecular, circuit, and clinical scales is incomplete. Translation of preclinical QSP models to human systems requires further validation. Modeling the remarkable heterogeneity of PD progression remains a fundamental challenge. Validation methodologies for counterfactual predictions are underdeveloped. And regulatory frameworks for full digital twin deployment—beyond covariate adjustment—are still emerging.

The path forward requires sustained investment in data infrastructure, interdisciplinary collaboration, and regulatory science. Near-term priorities include completing qualification of digital monitoring biomarkers, validating proteostasis digital twins, and scaling mechanistic models from preclinical to clinical applications. Medium-term goals focus on integrating mechanistic circuit models, implementing neuromorphic approaches, and demonstrating PD.

#### References

- [1]. Barricelli, B.R., Casiraghi, E., & Fogli, D. (2019). A survey on digital twin: Definitions, characteristics, applications, and future implications. *\*IEEE Access\**, 7, 167653-167671.
- [2]. Bruynseels, K., Santoni de Sio, F., & van den Hoven, J. (2018). Digital twins in health care: Ethical implications of an emerging engineering paradigm. *\*Frontiers in Genetics\**, 9, 31.
- [3]. Corral-Acero, J., Margara, F., Marciniak, M., et al. (2020). The 'Digital Twin' to enable the vision of precision cardiology. *\*European Heart Journal\**, 41(48), 4556-4564.
- [4]. Erol, T., Mendi, A.F., & Doğan, D. (2020). The digital twin revolution in healthcare. *\*2020 4<sup>th</sup> International Symposium on*

- Multidisciplinary Studies and Innovative Technologies (ISMSIT)\*, 1-7.
- [5]. Kamel Boulos, M.N., & Zhang, P. (2021). Digital twins: From personalised medicine to public health and beyond. *\*Healthcare\**, 9(8), 1046.
- [6]. Liu, Y., Zhang, L., Yang, Y., et al. (2024). A novel digital twin-assisted prediction approach for drug response in cancer patients. *\*Advanced Science\**, 11(15), 2307185.
- [7]. Niederer, S.A., Sacks, M.S., Girolami, M., & Ingham, M. (2021). Scaling digital twins from the artisanal to the industrial. *\*Nature Computational Science\**, 1(5), 313-320.
- [8]. Popa, E.O., van Hilten, M., Oosterkamp, E., & Bogaardt, M.J. (2021). The use of digital twins in healthcare: Socio-ethical benefits and socio-ethical risks. *\*Life Sciences, Society and Policy\**, 17(1), 6.
- [9]. Schwartz, S.M., Wildenhaus, K., Bacher, A., & O'Brien, D. (2020). Digital twins and the emerging science of self: Implications for digital health. *\*Digital Biomarkers\**, 4(3), 87-93.
- [10]. Venkatesh, K.P., Raza, M.M., & Kvedar, J.C. (2022). Health digital twins as tools for precision medicine: Considerations for computation, implementation, and regulation. *\*NPJ Digital Medicine\**, 5(1), 150.
- [11]. Dorsey, E.R., & Bloem, B.R. (2018). The Parkinson pandemic—A call to action. *\*JAMA Neurology\**, 75(1), 9-10.
- [12]. GBD 2019 Parkinson's Disease Collaborators. (2021). Global, regional, and national burden of Parkinson's disease, 1990–2019: A systematic analysis for the Global Burden of Disease Study 2019. *\*The Lancet Neurology\**, 20(11), 895-906.
- [13]. Poewe, W., Seppi, K., Tanner, C.M., et al. (2017). Parkinson disease. *\*Nature Reviews Disease Primers\**, 3, 17013.
- [14]. Kalia, L.V., & Lang, A.E. (2015). Parkinson's disease. *\*The Lancet\**, 386(9996), 896-912.
- [15]. Bloem, B.R., Okun, M.S., & Klein, C. (2021). Parkinson's disease. *\*The Lancet\**, 397(10291), 2284-2303.
- [16]. Lang, A.E., & Espay, A.J. (2018). Disease modification in Parkinson's disease: Current approaches, challenges, and future considerations. *\*Movement Disorders\**, 33(5), 660-677.
- [17]. Athauda, D., & Foltynie, T. (2015). The ongoing pursuit of neuroprotective therapies in Parkinson disease. *\*Nature Reviews Neurology\**, 11(1), 25-40.
- [18]. McFarthing, K., Rafaloff, G., Baptista, M., et al. (2023). Parkinson's disease drug therapies in the clinical trial pipeline: 2023 update. *\*Journal of Parkinson's Disease\**, 13(4), 427-439.
- [19]. Lang, A.E., & Espay, A.J. (2022). A biological classification of Parkinson's disease: The SynNeurGe research diagnostic criteria. *\*The Lancet Neurology\**, 21(12), 1112-1124.
- [20]. Höglinger, G.U., Adler, C.H., Berg, D., et al. (2024). A biological classification of Parkinson's disease: The research criteria for neuronal alpha-synuclein disease. *\*The Lancet Neurology\**, 23(2), 191-204.
- [21]. Espay, A.J., Hausdorff, J.M., Sánchez-Ferro, Á., et al. (2019). A roadmap for implementation of patient-centered digital outcome measures in Parkinson's disease obtained using mobile health technologies. *\*Movement Disorders\**, 34(5), 657-663.
- [22]. Dorsey, E.R., Glidden, A.M., Holloway, M.R., Birbeck, G.L., & Schwamm, L.H. (2022). Teleneurology and mobile technologies: The future of neurological care. *\*Nature Reviews Neurology\**, 18(7), 435-446.
- [23]. Silva de Lima, A.L., Smits, T., Darweesh, S.K.L., et al. (2022). Home-based monitoring of Parkinson's disease using wearable sensors: A systematic review. *\*Journal of Parkinson's Disease\**, 12(1), 81-98.
- [24]. Powers, R., Etezadi-Amoli, M., Arnold, E.M., et al. (2023). Smartwatch inertial sensors continuously monitor real-world motor fluctuations in Parkinson's disease. *\*Science Translational Medicine\**, 15(695), eadd1037.
- [25]. Rovini, E., Maremmani, C., & Cavallo, F. (2017). How wearable sensors can support Parkinson's disease diagnosis and treatment: A systematic review. *\*Frontiers in Neuroscience\**, 11, 555.
- [26]. Artusi, C.A., Mishra, M., Latimer, P., et al. (2022). Integration of technology-based outcome measures in clinical trials for Parkinson's disease. *\*NPJ Parkinson's Disease\**, 8(1), 167.
- [27]. Maetzler, W., Domingos, J., Srulijes, K., Ferreira, J.J., & Bloem, B.R. (2013). Quantitative wearable sensors for objective assessment of Parkinson's disease. *\*Movement Disorders\**, 28(12), 1628-1637.

- [28]. Löhle, M., & Reichmann, H. (2023). Digital biomarkers in Parkinson's disease: A review of the current state of development. *Journal of Neural Transmission\**, 130(10), 1267-1280.
- [29]. Adams, J.L., Dinesh, K., Xiong, M., et al. (2020). Multiple wearable sensors in Parkinson's disease: A systematic review and meta-analysis. *Sensors\**, 20(23), 6774.
- [30]. Bot, B.M., Suver, C., Neto, E.C., et al. (2016). The mPower study, Parkinson disease mobile data collected using ResearchKit. *Scientific Data\**, 3, 160011.
- [31]. Lipsmeier, F., Taylor, K.I., Kilchenmann, T., et al. (2018). Evaluation of smartphone-based testing to generate exploratory outcome measures in a phase I Parkinson's disease clinical trial. *Movement Disorders\**, 33(8), 1287-1297.
- [32]. Lipsmeier, F., Taylor, K.I., Postuma, R.B., et al. (2022). Reliability and validity of the Roche PD Mobile Application for remote monitoring of early Parkinson's disease. *Scientific Reports\**, 12, 12081.
- [33]. Taylor, K.I., et al. (2025). Exploratory digital outcome measures of motor sign progression in Parkinson's disease patients treated with prasinezumab. *NPJ Digital Medicine\**, 8(1), 365.
- [34]. Pagano, G., Taylor, K.I., Cabrera, J., et al. (2022). Trial of prasinezumab in early-stage Parkinson's disease. *New England Journal of Medicine\**, 387, 421-432.
- [35]. Pagano, G., et al. (2024). Sustained effect of prasinezumab on Parkinson's disease motor progression in the open-label extension of the PASADENA trial. *Nature Medicine\**, 30, 3669-3675.
- [36]. Stephenson, D., et al. (2025). Advancing the regulatory maturity of digital health technologies with focus on early intervention, Critical Path for Parkinson's 3DT initiative. *Movement Disorders Society Abstracts\**, 40(suppl 1).
- [37]. Critical Path Institute. (2023). Multistakeholder collaborations are vital to advancing technologies in Parkinson's. *Cpath Annual Report\**.
- [38]. Ellis, T., & Rochester, L. (2021). Digital health technology in Parkinson's disease: A review of the current landscape and future directions. *Journal of Parkinson's Disease\**, 11(s1), S15-S24.
- [39]. Ivanova, O., & Karelina, T. (2024). Quantitative systems pharmacology model of  $\alpha$ -synuclein pathology in Parkinson's disease-like mouse for investigation of passive immunotherapy mechanisms. *CPT: Pharmacometrics & Systems Pharmacology\**, 13(10), 1798-1809.
- [40]. Denaro, C., Stephenson, D., Müller, M.L.T.M., Piccoli, B., & Azer, K. (2024). Advancing precision medicine therapeutics for Parkinson's utilizing a shared quantitative systems pharmacology model and framework. *Frontiers in Systems Biology\**, 4, 1351555.
- [41]. Bloomingdale, P., Karelina, T., Cirit, M., et al. (2021). Quantitative systems pharmacology in neuroscience: Novel methodologies and technologies. *CPT: Pharmacometrics & Systems Pharmacology\**, 10, 412-419.
- [42]. Azer, K., Kaddi, C.D., Barrett, J.S., et al. (2021). History and future perspectives on the discipline of quantitative systems pharmacology modeling and its applications. *Frontiers in Physiology\**, 12, 637999.
- [43]. Karelina, T., & Voronova, V. (2022). Quantitative systems pharmacology modeling of neurodegenerative diseases: A critical review. *Frontiers in Pharmacology\**, 13, 908755.
- [44]. Geerts, H., & Spiros, A. (2021). A quantitative systems pharmacology model of the pathophysiology and treatment of Parkinson's disease. *CPT: Pharmacometrics & Systems Pharmacology\**, 10(8), 812-824.
- [45]. Spiros, A., Roberts, P., & Geerts, H. (2014). A quantitative systems pharmacology computer model for schizophrenia and Parkinson's disease. *Current Opinion in Pharmacology\**, 15, 1-7.
- [46]. Roberts, P., Spiros, A., & Geerts, H. (2012). A humanized clinically calibrated quantitative systems pharmacology model for hypokinetic motor symptoms in Parkinson's disease. *Frontiers in Pharmacology\**, 3, 71.
- [47]. Nikolaev, A., & Kuznetsov, A. (2023). Computational models of alpha-synuclein aggregation: A review of the current state and future directions. *Biophysical Reviews\**, 15(4), 871-886.
- [48]. Henderson, M.X., & Trojanowski, J.Q. (2022). Alpha-synuclein pathology and the prion-like hypothesis of Parkinson's disease.

- \*Journal of Neuroscience\*, 42(37), 7105-7112.
- [49]. Palesi, F., Lorenzi, R.M., Casellato, C., et al. (2020). The importance of cerebellar connectivity on simulated brain dynamics. *\*Frontiers in Cellular Neuroscience\**, 14, 1-11.
- [50]. Monteverdi, A., Palesi, F., Costa, A., et al. (2022). Subject-specific features of excitation/inhibition profiles in neurodegenerative diseases. *\*Frontiers in Aging Neuroscience\**, 14, 868342.
- [51]. Monteverdi, A., Palesi, F., Schirner, M., et al. (2023). Virtual brain simulations reveal network-specific parameters in neurodegenerative dementias. *\*Frontiers in Aging Neuroscience\**, 15, 1204134.
- [52]. D'Angelo, E., & Jirsa, V. (2022). The quest for multiscale brain modeling. *\*Trends in Neurosciences\**, 45(10), 777-790.
- [53]. Patow, G., Deco, G., & Kringelbach, M.L. (2024). Whole-brain models for understanding neurological and psychiatric disorders. *\*Nature Reviews Methods Primers\**, 4, 56.
- [54]. Deco, G., & Kringelbach, M.L. (2016). Great expectations: Using whole-brain computational connectomics for understanding neuropsychiatric disorders. *\*Neuron\**, 91(5), 945-947.
- [55]. Schirner, M., McIntosh, A.R., Jirsa, V., Deco, G., & Ritter, P. (2018). Inferring multi-scale neural mechanisms with brain network modelling. *\*eLife\**, 7, e28927.
- [56]. Jirsa, V., Wang, H., Triebkorn, P., et al. (2017). The Virtual Brain: A modeling platform for personalized brain network dynamics. *\*eLife\**, 6, e26775.
- [57]. Sanz-Leon, P., Knock, S.A., Spiegler, A., & Jirsa, V.K. (2015). Mathematical framework for large-scale brain network modeling in The Virtual Brain. *\*NeuroImage\**, 111, 385-430.
- [58]. Ritter, P., Schirner, M., McIntosh, A.R., & Jirsa, V. (2013). The virtual brain integrates computational modeling and multimodal neuroimaging. *\*Brain Connectivity\**, 3(2), 121-137.
- [59]. Wang, X., et al. (2025). Conditional Neural ODE for longitudinal Parkinson's disease progression forecasting. *\*arXiv\**, 2511.04789.
- [60]. AIPD Doctoral Network. (2025). Generative AI for simulating a digital Parkinson's disease twin. Project DC13.
- [61]. Hizeh, H., et al. (2025). Towards Human-AI-Robot collaboration and AI-agent based digital twins for Parkinson's disease management: Review and outlook. *\*arXiv\**, 2511.06036.
- [62]. Lim, C.M., & Vendruscolo, M. (2025). The  $\alpha$ -synuclein proteostasis network and its translational applications in Parkinson's disease. *\*bioRxiv\**, 2025.03.17.643594.
- [63]. Ahamadi, M., Conrado, D.J., Macha, S., et al. (2019). Development of a disease progression model for Leucine-Rich repeat kinase 2 in Parkinson's disease to inform clinical trial designs. *\*Clinical Pharmacology & Therapeutics\**, 107(3), 553-562.
- [64]. Nguyen, P., Tran, T., & Venkatesh, S. (2021). Deep learning for Parkinson's disease diagnosis and progression prediction: A systematic review. *\*Artificial Intelligence in Medicine\**, 117, 102103.
- [65]. Belic, M., Bobic, V., Badza, M., et al. (2023). Artificial intelligence for predicting progression of Parkinson's disease: A systematic review. *\*Journal of Parkinson's Disease\**, 13(2), 191-207.
- [66]. Rizzo, G., & Copetti, M. (2023). Machine learning in Parkinson's disease: From prediction to prevention. *\*Frontiers in Neurology\**, 14, 1128765.
- [67]. Prasuhn, J., & Bruggemann, N. (2022). The potential of artificial intelligence in Parkinson's disease research and clinical care. *\*Journal of Neural Transmission\**, 129(8), 1007-1016.
- [68]. (2025). Using AI-generated digital twins to boost clinical trial efficiency in Alzheimer's disease. *\*Alzheimer's & Dementia: Translational Research & Clinical Interventions\**.
- [69]. (2026). FDA/EMA joint principles for good AI practice in drug development.
- [70]. (2026). FDA guidance on advancing real-world evidence in clinical trials.
- [71]. Wang, H., et al. (2024). Digital twins in clinical trials: A review of current applications and future directions. *\*Clinical Pharmacology & Therapeutics\**, 115(3), 456-468.
- [72]. Liu, R., Rizzo, S., Whipple, S., et al. (2023). Evaluating eligibility criteria of oncology trials using real-world data and AI. *\*Nature\**, 616, 792-798.
- [73]. Thorlund, K., Dron, L., Park, J.J.H., & Mills, E.J. (2020). Synthetic and external controls in

- clinical trials: A review of methods and opportunities. *Clinical Trials*, 17(5), 479-489.
- [74]. Dron, L., Golchi, S., Hrobjartsson, A., & Thorlund, K. (2022). Synthetic control arms in clinical trials: A systematic review of current applications. *BMJ Open*, 12(4), e058882.
- [75]. Bhatt, A. (2022). Artificial intelligence and machine learning in clinical trial design and execution: A review of recent advances. *Perspectives in Clinical Research*, 13(3), 125-132.
- [76]. EMA. (2024). Reflection paper on the use of artificial intelligence in medicinal product lifecycle.
- [77]. FDA. (2024). Artificial intelligence and machine learning in drug development: Discussion paper.
- [78]. McDermott, M.B.A., Wang, S., Marinsek, N., et al. (2021). Reproducibility in machine learning for health research: A review of the state of the field. *Patterns*, 2(10), 100338.
- [79]. Raikar, A.S., Andrew, J., Dessai, P.P., et al. (2024). Neuromorphic computing for modeling neurological and psychiatric disorders: Implications for drug development. *Artificial Intelligence Review*, 57, 318.
- [80]. Davies, M., Wild, A., Orchard, G., et al. (2021). Advancing neuromorphic computing with Loihi: A survey of results and outlook. *Proceedings of the IEEE*, 109(5), 911-934.
- [81]. Donati, E., & Indiveri, G. (2023). Neuromorphic bioelectronic medicine for nervous system interfaces: From neural computational primitives to medical applications. *Progress in Biomedical Engineering*, 5(1), 013002.
- [82]. Aboumerhi, K., Güemes, A., Liu, H., Tenore, F., & Etienne-Cummings, R. (2023). Neuromorphic applications in medicine. *Journal of Neural Engineering*, 20(4), 041004.
- [83]. Chicca, E., Stefanini, F., Bartolozzi, C., & Indiveri, G. (2014). Neuromorphic electronic circuits for building autonomous cognitive systems. *Proceedings of the IEEE*, 102(9), 1367-1388.
- [84]. Chatzipaschalis, I.K., Tsiapas, E., Fyrigos, I.A., Rubio, A., & Sirakoulis, G.C. (2023). CBRAM-based bio-inspired circuit for the emulation and treatment of Parkinson's disease. *IEEE Transactions on Circuits and Systems II: Express Briefs*, 70(6), 2181-2185.
- [85]. Schuman, C.D., Kulkarni, S.R., Parsa, M., et al. (2022). Opportunities for neuromorphic computing algorithms and applications. *Nature Computational Science*, 2(1), 10-19.
- [86]. Raji, H., Perez, M., Bertoli, F., Lam, A., Volpicelli-Daley, L., & Deleidi, M. (2025). Enhanced generation of functionally mature, midbrain-specific dopaminergic neurons in 3D organoid culture for Parkinson's disease modeling. *bioRxiv*, 2025.07.29.667404.
- [87]. Smits, L.M., & Schwamborn, J.C. (2020). Midbrain organoids: A new tool to investigate Parkinson's disease. *Frontiers in Cell and Developmental Biology*, 8, 359.
- [88]. Kim, H., Park, H.J., & Choi, H. (2021). Human pluripotent stem cell-derived brain organoids as a model for Parkinson's disease. *International Journal of Molecular Sciences*, 22(14), 7453.
- [89]. Chlebanowska, P., Tejchman, A., Sułkowski, M., Skrzypek, K., & Majka, M. (2020). Use of 3D organoids as a model to study idiopathic forms of Parkinson's disease. *International Journal of Molecular Sciences*, 21(3), 971.
- [90]. Bolognin, S., Fossépré, M., Qing, X., et al. (2019). 3D cultures of Parkinson's disease-specific dopaminergic neurons for high content phenotyping and drug testing. *Advanced Science*, 6(3), 1800927.
- [91]. Stephenson, D., et al. (2021). The Critical Path for Parkinson's: A global collaboration to accelerate drug development. *Journal of Parkinson's Disease*, 11(s1), S5-S13.
- [92]. Marek, K., Chowdhury, S., Siderowf, A., et al. (2018). The Parkinson's Progression Markers Initiative (PPMI): Establishing a PD biomarker cohort. *Annals of Neurology*, 84(5), 655-668.
- [93]. Parkinson's Progression Markers Initiative. (2023). PPMI data release notes.
- [94]. WATCH-PD Study Group. (2024). Wearable sensors and digital assessments in early Parkinson's disease: The WATCH-PD study.
- [95]. Critical Path Institute. (2025). 3DT initiative: Digital monitoring biomarkers for Parkinson's disease.
- [96]. European Commission. (2024). AIPD – Artificial Intelligence for Parkinson's Disease: Doctoral Network.
- [97]. EBRAINS 2.0 Project. (2024). EBRAINS Research Infrastructure: Digital brain twins.



- 
- [98]. Virtual Brain Twin (VBT) Project. (2025). Personalized brain models for clinical applications.
- [99]. Hirtz, D., & Stephenson, D. (2024). Regulatory science for Parkinson's disease: Progress and priorities. *Movement Disorders*, 39(5), 789-797.
- [100]. Bloem, B.R., Henderson, E.J., Dorsey, E.R., et al. (2023). Integrated and patient-centered care for Parkinson's disease: The future is now. *The Lancet Neurology*, 22(8), 720-732.