Review

Advancing Early Identification of Clinical Trials in Neurosurgical Interventions for Parkinson's Disease: The Critical Role of AI-Driven Platforms and Technological Innovation

José E. Valerio , Guillermo de Jesús Aguirre Vera , Maria P. Fernandez Gomez , Jorge Zumaeta , Andrés M. Alvarez-Pinzon *

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Advancing Early Identification of Clinical Trials in Neurosurgical Interventions for Parkinson's Disease: The Critical Role of AI-Driven Platforms and Technological Innovation

José E. Valerio [1,2,3,4], Guillermo de Jesus Aguirre Vera [1,5], Maria P. Fernandez Gomez [1], Jorge Zumaeta [1] and Andrés M. Alvarez-Pinzon [1,6,7,8,*]

[1] Neurosurgery Oncology, Latinoamerica Valerio Foundation, Weston, Florida, USA
[2] Department of Neurological Surgery, Palmetto General Hospital, Miami, Florida, USA
[3] Neurosurgery Oncology Center of Excellence; Department of Neurosurgery, Miami Neuroscience Center at Larkin, South Miami, Florida, USA
[4] GW School of Business; The George Washington University, Washington, DC, USA
[5] Tecnológico de Monterrey School of Medicine, Monterrey, Mexico
[6] The Institute of Neuroscience of Castilla y León (INCYL), Cancer Neuroscience, University of Salamanca (USAL), Salamanca, Spain
[7] Cellular Theraphy Program, Universidad de Granada, Hospital Real de Granada, Granada, Spain
[8] Institute for Human Health and Disease Intervention (I-HEALTH), Florida Atlantic University, Jupiter, Florida, USA
* Correspondence: andresmauricioalvarez07@gmail.com

Abstract: Parkinson's disease (PD) is a progressive neurodegenerative disorder characterized by motor and non-motor dysfunctions that significantly impact patients' quality of life. While pharmacological treatments provide symptom relief in early stages, advanced cases often necessitate neurosurgical interventions such as deep brain stimulation (DBS) and focused ultrasound (FUS) for symptom control. However, the early identification and recruitment of eligible candidates for clinical trials remain critical challenges that hinder the advancement of these therapeutic strategies. This review explores the current opportunities and future directions in leveraging artificial intelligence (AI) and cutting-edge technological innovations to enhance neurosurgical and neuroscience interventions for PD. AI-driven platforms are revolutionizing clinical trials by improving patient selection, optimizing trial design, and refining treatment personalization. Machine learning algorithms and big data analytics facilitate more precise patient stratification, risk assessment, and outcome prediction, ultimately accelerating the development of novel therapeutic approaches. These advancements not only improve trial efficiency but also expand the range of available treatment options, enhancing patient outcomes and quality of life. Despite these advancements, challenges remain in integrating AI into clinical trial frameworks, including data standardization, regulatory considerations, and the need for extensive validation studies. Multidisciplinary collaboration among neurosurgeons, neuroscientists, AI specialists, and regulatory bodies is essential to address these barriers and establish guidelines for the ethical and effective implementation of AI-driven technologies in neurosurgical research. By harnessing AI and technological innovation, this paper highlights the transformative potential of these advancements in shaping the future of neurosurgical interventions for PD, ultimately improving therapeutic outcomes and patient care.

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Introduction and Epidemiology

Parkinson's disease is one of the most common neurological conditions worldwide, and the fastest growing in terms of prevalence, deaths according to the Global Burden of Disease (GBD) 2015, and the leading cause of disability among neurological disorders [1,2]. It is a progressive and deteriorating disease that presents with both motor and non-motor symptoms. The global incidence of Parkinson's disease was estimated over 8.5 million people in 2019 by the World Health Organization (WHO), with 5.8 million disability-adjusted life years (DALYs), increasing 81% since 2000, 329 000 deaths, increasing 100% since 2000 [3]. The global burden of Parkinson's disease has increased from 2.5 to 6.1 million in the last three decades. [4]. While dopaminergic therapies are effective in managing symptoms like bradykinesia, they are not as effective for symptoms like postural inability and gait difficulties, which commonly appear in patients 10-15 years after symptom onset. [5]. This highlights the need for new treatment approaches that improve patients' quality of life.

Surgery, particularly deep brain stimulation, has effectively treated medication-refractory tremors, especially in patients without motor fluctuations. Even after optimization with levodopa, patients with tremors can benefit from deep brain stimulation. [6]. Common targets for this therapy are the subthalamic nucleus (STN) or the globus pallidus internus (GPi), and it significantly improves motor symptoms in the short and long term. A common consensus among professionals is that deep brain stimulation significantly enhances the quality of life for patients with movement disorders [7]. However, patients may experience stimulation-induced side effects such as dysarthria, imbalance, and dyskinesia, which may require adjustments in stimulation [8], particularly in the initial stage following surgery [9]. This proves the necessity of ever-evolving treatment refining, which uses rising technologies to improve patients' health.

The current trend is cutting-edge technologies that use Artificial Intelligence, this technology can help to address critical challenges that healthcare providers face. AI's ability to learn and analyze patterns from large data sets, identifying patterns that may otherwise go unnoticed [10]AI is a powerful tool that can complement humans. When used under human supervision, AI has been shown to improve patient outcomes and reduce errors in clinical settings [11].

This review aims to describe the current advancements in diagnosing Parkinson's disease, particularly in the early stages of the disease. Currently, there are no biomarkers for the early stages of Parkinson's disease or for tracking its progression [12]. Artificial intelligence has the potential to significantly enhance symptom monitoring and potentially define molecular subtypes through global datasets [13]. This review also aims to critically evaluate how early-phase trials are conducted and to establish alternatives to refine the design and execution of neurosurgical studies in Parkinson's disease.

Methods:

A systematic and comprehensive literature search was conducted using PubMed, employing Boolean operators and the following search terms: *Parkinson AND Artificial Intelligence*, and *Parkinson AND Machine Learning*. The selection process was guided by well-defined inclusion criteria, focusing on studies that utilized AI-driven methodologies to enhance diagnostic accuracy, early screening, patient stratification, and therapeutic optimization in Parkinson's disease (PD). Additionally, only studies that incorporated AI and machine learning (ML) algorithms to refine neurological imaging, biomarker identification, predictive modeling, and neurosurgical interventions were included.

The screening process prioritized machine learning-enhanced patient sampling, emphasizing datasets from PD patients where AI technologies facilitated pattern recognition, neuroimaging analysis (e.g., MRI, PET, and functional imaging), and real-time neurophysiological monitoring. Particular emphasis was placed on studies demonstrating the role of AI in preoperative planning for deep brain stimulation (DBS), precision targeting for focused ultrasound (FUS), and optimization of closed-loop neuromodulation systems.

Pathomechanisms Leading to Parkinson's Disease: An AI-Driven Perspective

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The pathogenesis of PD is driven by a complex interplay of genetic, molecular, and environmental factors, leading to progressive neurodegeneration. Central to PD pathology is the degeneration of dopaminergic neurons in the substantia nigra and the accumulation of alpha-synuclein aggregates, both of which have been linked to immune dysfunction and neuroinflammatory pathways.

AI-powered systems are increasingly being deployed to model the molecular and cellular pathways underlying PD, offering advanced insights into:

- Neuroinflammation Modeling: AI-driven simulations analyze the activation of microglia and astrocytes, which respond to alpha-synuclein aggregates and other neuronal signals by secreting pro-inflammatory cytokines and reactive oxygen species. These models help predict neurodegenerative progression by assessing inflammasome pathway activation (NLRP3) and caspase-1-mediated cytokine production.
- Genetic and Environmental Risk Mapping: Deep learning frameworks integrate genomic, transcriptomic, and exposomic data to elucidate interactions between environmental neurotoxins (e.g., MPTP, rotenone) and immune-mediated neurodegeneration. These computational approaches refine risk stratification models, identifying high-risk patients before clinical manifestation.
- Neuropeptide Dysregulation and Sleep-Wake Cycle Prediction: AI-based neuroimaging and cerebrospinal fluid (CSF) analysis have revealed the dysregulation of orexin neurons, which are implicated in sleep disturbances, autonomic dysfunction, and neurodegeneration. Predictive models assess orexin-A deficiency and its impact on oxidative stress and brain-derived neurotrophic factor (BDNF) expression, offering potential therapeutic targets.

By leveraging AI and machine learning, this review aims to explore cutting-edge applications in neurosurgical and neuroscience interventions, optimizing clinical trial design, patient selection, and treatment personalization for PD.

Anatomical and Structural Changes

Identifying the specific morphological structure implicated in the pathogenesis of Parkinson's Disease in each patient is an important clinical feature. Due to variations in disease progression, the pace of cognitive deficit, neuropsychiatric symptomatology, and responses to different treatment modalities may vary. Clinical decision-support systems could be a helpful alternative to assist clinicians in decision-making for patients [14–16].

A study utilized a wide range of morphological features alongside clinical test scores to develop a machine-driven method for differentiating Parkinson's Disease and progressive supranuclear palsy (Richardson’s syndrome), which is considered the most common phenotype of progressive supranuclear palsy [17]. Early stage and accurate differentiation diagnosis of both conditions is difficult for clinicians due to overlapping symptoms [18]. The classification method utilized by the study involved a feature selection method followed by a classification algorithm. After the ranking, a support vector machine (SVM) with a linear kernel was implemented to manage the balance, reducing misclassification and minimizing errors. The result was a combination of subcortical morphological properties, including regional brain volumes, brain surface area, and the ratio of brain surface area to volume, which can distinguish between Parkinson's Disease and progressive supranuclear palsy [19].

The thalamus plays a crucial role in the pathogenic process and clinical disease onset of symptoms. A systematic review aimed to elucidate the morphological changes in the subthalamic nuclei in Parkinson's disease patients. Using support vector machines, a type of machine learning, researchers developed an algorithm that could predict the UPDRS III score for limb bradykinesia, axial akinetic score, and UPDRS III improvement. Applying pattern analyzing techniques to MRI revealed morphological changes, including increased volumes of bilateral thalami enlargement and atrophy of the left thalamic subnuclei [20].

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Utilization of Plasma Proteomics on Predicting Parkinson's Onset

The clinical heterogeneity of Parkinson's presents a significant challenge for developing neuroprotective strategies that prevent disease progression. One of the main difficulties is the lack of measurable biomarker indicators [21]. This has led to calls for markers that can impartially assess Parkinson's disease phenotypes and potential therapeutic pathways and identify biomarkers associated with the disease's clinical pathophysiology [22].

Recent evidence suggests that cerebrospinal fluid (CSF) and blood biomarkers may have diagnostic and prognostic value by accurately reflecting the underlying mechanisms of Parkinson's disease. For example, specific biomarkers such as α-synuclein, lysosomal enzymes, amyloid and tau pathology indicators, and neurofilament light chain show promise for early diagnosis of Parkinson's disease [23].

A study used mass spectrometry-based proteomic phenotyping to identify a panel of blood biomarkers in Parkinson's disease. The study characterized a group of De novo Parkinson's disease patients and healthy controls through collection protocols, and a machine learning model was trained with this information. Utilizing a regression pattern, the model identified a panel of proteins that could distinguish between De novo Parkinson's disease and control samples with 100% accuracy based on the expression of eight proteins (GRN, MASP2, HSPA5, PTGDS, ICAM1, C3, DKK3, and SERPING1). This biomarker selection revealed a distinctive signature of protective and detrimental mechanisms, shedding light on the pathways that trigger oxidative stress and neuroinflammatory responses, key factors leading to α-synuclein aggregation and Lewy body formation. This underscores the importance of machine learning in early identification and diagnosis of neurodegenerative diseases, as the model was able to identify this signature in the prodromal non-motor phase (stage 2 NSD), occurring up to 7 years before the onset of motor or cognitive symptoms (stage 3) [24].

The current diagnosis of Parkinson's Disease heavily relies on clinical and motor symptoms. Cognitive impairment is particularly prevalent, and in the early stages of the disease, it could arise in an insidious form such as mild cognitive impairment in up to 25% of newly diagnosed patients [25,26]. Cognitive decline tends to worsen, leading to significant disability. Parkinson's Disease patients with mild cognitive impairment are six times more likely to develop dementia than matched controls, with a prevalence of 80% after 15 to 20 years of living with the disease [27]. A dual syndrome hypothesis was established regarding two different structural and neurotransmission components involved in cognitive decline [28]. The first correlated to the reduction of dopamine levels in the basal ganglia, ultimately causing a disturbance in the cortico-basal ganglia-thalamus-cortical (CBGTC) loops [29,30].

Event-related potentials depict neural activity obtained from scalp-recorded EEG. These are commonly calculated by averaging EEG activity specific to a time-bound episode of an observable event, such as a sensory stimulus or a motor reaction. It is thought that event-related potentials mirror the aggregation of postsynaptic potentials of large groups of synchronously active pyramidal neurons from the cerebral cortex [31]. Current trials have recently described the effectiveness of the clinical diagnostic value and status of Parkinson's disease in patients with DBS. This method is considered a promising alternative due to its noninvasiveness for the patients [32].

A recently developed study used high-resolution EEG recording to analyze brain activity during Go/No-Go (VGNG) and auditory Oddball (AOB) cognitive task performance in patients with early and advanced-stage Parkinson's Disease. Event-related potentials were analyzed through Brain Network Analytics technology to produce portrayals of brain activity [33]. The study identified potential markers for early-stage Parkinson's disease using a machine-learning algorithm. The analysis resulted in 15 distinct features that can distinguish early-onset Parkinson's disease from healthy controls. Five of these features are related to three specific cognitive functions: early sensory processing (P50 amplitude, latency), information filtering (amplitude and topographic similarity), and response-locked activity. These findings are promising and could be an important tool for early

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diagnosis. Further research with larger patient samples and testing on premotor phase patients can help fully understand its potential as an auxiliary early diagnostic tool [34].

Cerebrospinal fluid (CSF) is a commonly tested biomarker collected from patients with neurological symptoms. Researchers have suggested that CSF closely reflects the changes in Parkinson's Disease patients. For example, there are significant increases in ion densities like iron, while ferritin levels decrease over time. CSF has the potential to be an important biomarker for tracking neurodegeneration over time [35]. This becomes relevant when considering the genetic factors of Parkinson's disease. While most cases of Parkinson's are idiopathic, there is evidence of a genetic pattern linked to the illness [36].

Mutations in the leucine-rich repeat kinase 2 (LRRK2) gene are the most common cause of autosomal dominant Parkinson's disease. Understanding the pathophysiological mechanisms could lead to therapeutic targets for genetically triggered Parkinson's disease. Understanding the pathophysiological mechanisms could lead to therapeutic targets for genetically triggered Parkinson's disease. Identifying this biomarker could facilitate its potential inhibition [37–39].

A research study conducted proteomics analysis of CSF from healthy controls, Parkinson's disease (PD) patients with and without the LRRK2 G2019S mutation, and individuals with non-manifesting LRRK2 G2019S. This analysis used mass spectrometry (MS) to identify necessary biomarkers. This was done through a predictive machine learning model developed to assist in classifying Parkinson's disease based on bioelement abundance. Machine learning-based proteomics is a powerful technology for identifying differences in protein abundance. However, CSF generally has low protein concentrations and an expanded dynamic range of disturbances [40–42] By applying co-variate (ANCOVA) analysis and machine learning, the last one benefits from large subsets of samples. The tool used was OmicLearn, which assisted in executing the data analysis, model execution, and producing the plots and charts [43]. Researchers identified specific proteins correlated with clinical scores and enhanced neuroinflammation, once again demonstrating the critical role of machine learning in pattern elucidation [44].

The first multicenter trial has been conducted to test for significant elemental signatures in CSF compared to control patients. This trial focused on the density of bio elements rather than the concentrations of biomolecules. Chemical elements do not degrade and remain stable at low and moderate temperatures. A predictive machine learning model was trained to classify Parkinson's Disease Patients and matched controls based on predictions of the density of bio elements in CSF. The model used a radial kernel Support Vector Machine (SVM) algorithm, which was trained on preprocessed CSF levels of As, Fe, Mg, Ni, Se, and Sr from a recently discovered cohort. The study showed that the model had an area under the receiver operating characteristic curve of 0.76 for the differentiation of Parkinson's Disease and Age-matched controls based purely on calculations made identifying the bio elements. Supporting the hypothesis of bio elements having the potential to distinguish among disease cohorts. However, further advancements are needed to understand factors contributing to a center bias, as presented in the study. Nonetheless, this study serves as a precedent for the potential of machine learning in discovering patterns of information [45].

Other mutations related to PD pathogenesis

The pathogenesis of Parkinson’s disease (PD) is influenced by a complex interplay between genetic predisposition and environmental factors. Recent advancements in artificial intelligence (AI) and computational genomics have facilitated the identification of novel gene variants implicated in PD, significantly enhancing our understanding of disease mechanisms. Machine learning algorithms and big-data approaches have enabled large-scale genome-wide association studies (GWAS) and deep-learning-driven mutation analyses, uncovering both established and newly emerging genetic risk factors.

Recent studies have identified several putative or confirmed PD-associated genes, including ANK2, DNAH1, STAB1, NOTCH2NLC, UQCRC1, ATP10B, TFG, CHMP1A, GIPC1, KIF21B, KIF24, SLC25A39, SPTBN1, and TOMM22. However, due to the novelty of these findings, the specific

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molecular mechanisms linking these mutations to PD remain inconclusive, necessitating further investigation through AI-assisted proteomic and transcriptomic modeling.

One notable genetic variant, TMEM175, has been linked to dysfunctional lysosomal K+ channels and has shown a significant association with PD in Italian population studies. AI-driven functional studies suggest that TMEM175 variants impact autophagic-lysosomal proteolytic flux, leading to impaired protein degradation pathways and increased unfolded protein response activation—both crucial contributors to PD pathogenesis.

Additionally, mutations in the RAB32 gene have recently been associated with familial PD, specifically influencing LRRK2 kinase hyperactivity, a well-established pathogenic driver in PD. The variant c.213C > G/p.S71R has been identified as a high-risk mutation, strongly correlated with familial PD cases, exhibiting an odds ratio of 65.5. AI-powered structural modeling and pathway analysis have further validated its role in exacerbating neuronal degeneration via aberrant kinase signaling. While the LRRK2 p.Gly2019Ser mutation remains the most well-characterized PD-related mutation, emerging evidence suggests that other rare variants, including p.Arg1441Cys and p.Asn1437His, contribute to PD with varying degrees of pathogenicity in specific populations.

By integrating AI-driven genomic analytics, network-based mutation prediction, and deep-learning models, researchers can refine the classification of genetic risk factors, predict individual susceptibility, and uncover novel therapeutic targets. This approach holds immense potential for personalized medicine strategies, enabling earlier intervention and more tailored neurosurgical and pharmacological treatments for PD.[46]

Disease Progression Patterns

Parkinson's disease can be classified primarily based on the age of onset of the disease. Models have described distinct needs and characteristics of patients with young onset age [47]. Changes in speaking patterns and handwriting strokes are potential parameters to consider when attempting to diagnose this disorder early [48]. Efforts to classify Parkinson's disease subtypes have focused on tremor-dominant subtypes, as well as characteristics of postural instability and gait-dominant subtypes [49].

Research in this field has led to new ways of predicting the development of Parkinson's disease. Baseline clinical characteristics, cerebrospinal fluid samples, and imaging techniques have been used to predict changes in MDS-UPDRS and dopamine-transporter binding. While not highly effective on their own, accuracy increased when short-term changes were added to the prediction model [50]. This has raised the question of whether weather patterns could have a significant correlation with Parkinson's disease progression. If this were the case, they could be standardized to aid machine learning models in predicting patterns through large data clusters.

Current Treatment

The management of Parkinson's disease (PD) requires a multimodal approach aimed at symptom control, disease progression mitigation, and quality of life enhancement. Pharmacological interventions remain the first-line treatment, with levodopa being the most effective therapy for alleviating motor symptoms such as bradykinesia, rigidity, and tremor. However, long-term levodopa use is associated with motor fluctuations and dyskinesias, necessitating adjunctive therapies such as dopamine agonists and monoamine oxidase B (MAO-B) inhibitors to extend dopaminergic therapy efficacy, particularly in early-stage PD. Additional therapeutic options, including amantadine, clozapine, beta-blockers, benzodiazepines, anticholinergics, cannabinoids, and botulinum toxin, have been explored, though with varying degrees of clinical evidence supporting their efficacy.

The Role of AI in Personalized PD Treatment

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The integration of AI-driven analytics and machine learning models is revolutionizing PD management by enabling personalized treatment regimens tailored to individual patient profiles. These technologies enhance therapeutic decision-making by:

- Predictive Modeling for Medication Response: AI algorithms analyze longitudinal patient data to predict levodopa response patterns, risk of motor fluctuations, and dyskinesia onset, allowing for dynamic treatment adjustments.
- Neuroimaging and Biomarker-Based Treatment Optimization: Machine learning models assist in processing MRI, PET, and molecular biomarker data to stratify patients based on disease progression and therapeutic response, ensuring optimized pharmacological and neurosurgical interventions.
- Digital Health and Wearable Technologies: AI-powered wearable sensors and mobile applications enable real-time monitoring of motor and non-motor symptoms, facilitating remote disease management and adaptive treatment adjustments in response to daily symptom fluctuations.
- Closed-Loop Neuromodulation: AI-driven systems are being integrated into deep brain stimulation (DBS) and focused ultrasound (FUS) technologies, allowing for adaptive, real-time modulation of neural circuits based on continuous symptom feedback, significantly enhancing treatment efficacy while reducing side effects.

Neurosurgical Interventions and AI-Enhanced Clinical Trial Matching

For advanced PD cases that are refractory to pharmacological treatments, neurosurgical interventions such as Deep Brain Stimulation (DBS) and Focused Ultrasound (FUS) have emerged as highly effective strategies for symptom relief and motor function improvement. These interventions rely on precise patient selection, optimal targeting, and personalized neuromodulation strategies, where AI plays a pivotal role in enhancing surgical outcomes and trial efficiency.

AI-driven platforms are transforming clinical trial matching and patient recruitment, addressing one of the major challenges in advancing neurosurgical treatments for PD. These technologies improve trial identification, streamline coordination among scientific teams, clinicians, and researchers, and integrate seamlessly with electronic medical record (EMR) systems to enhance efficiency. Key innovations include:

- AI-Enhanced EMR Integration for Early Diagnosis and Trial Matching: Machine learning algorithms analyze structured and unstructured EMR data—including clinical notes, imaging results, genetic markers, and wearable device outputs—to identify patients who may benefit from early surgical intervention or experimental therapies.
- Automated NLP-Driven Eligibility Screening: Natural Language Processing (NLP) algorithms scan medical records and physician notes to identify eligible candidates for clinical trials, reducing the time required for manual screening and increasing recruitment efficiency.
- Dynamic Risk Assessment and Personalized Trial Selection: AI models assess disease progression, comorbidities, and potential surgical risks, enabling clinicians to match patients with the most appropriate trial based on their unique clinical and genetic profiles.
- Real-Time Coordination with Research Teams and Clinicians: AI-powered platforms enable seamless communication between neurosurgeons, neurologists, and trial coordinators, ensuring efficient recruitment, monitoring, and treatment adaptation throughout the study.
- Wearable and Digital Biomarker Integration: AI-powered wearable devices collect continuous symptom data, allowing researchers to assess real-world disease progression and adapt trial eligibility criteria dynamically, ensuring that patients are enrolled at the optimal stage for intervention.
- AI-Guided Surgical Planning and Precision Targeting: Deep learning models analyze patient-specific neuroimaging data to assist neurosurgeons in determining optimal electrode placement in DBS or lesioning targets in FUS, improving accuracy and reducing complications.

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By leveraging AI-driven clinical trial matching, EMR-integrated patient selection, and real-time coordination with multidisciplinary teams, PD research is moving toward a data-driven, precision medicine approach that accelerates the development of neurosurgical innovations and enhances patient outcomes. Future research should continue refining AI-assisted trial recruitment, predictive analytics for surgical outcomes, and adaptive neuromodulation technologies, ensuring that patients receive the most effective and personalized neurosurgical treatments.[51].

Neurosurgical interventions and their significance in the context of PD subtypes

The management of medication-resistant tremors in Parkinson's Disease (PD) has evolved significantly, offering several surgical and ablative approaches tailored to individual patient needs. Patients who experience intolerable side effects from pharmacological treatments or continue to have tremors despite optimized medication regimens are prime candidates for surgical intervention[51]. Focused ultrasound thalamotomy has emerged as a viable alternative to deep brain stimulation (DBS) and traditional lesional surgery, thus expanding the eligibility for such interventions, particularly among elderly patients and those with significant comorbidities. Bilateral subthalamic nucleus (STN) stimulation has demonstrated robust efficacy in alleviating motor symptoms and enhancing quality of life[51,52], showing an impressive 82% reduction in resting tremor during "off" medication periods, as evidenced by both randomized controlled studies and long-term follow-ups. Additionally, STN stimulation has proven effective in patients with fluctuating conditions and dyskinesias, sustaining its therapeutic benefit for over five years[51,53,54].

DBS is specifically indicated to certain subtypes of PD, especially in patients with motor fluctuations refractory to pharmacological therapy. DBS has shown a high effectivity in Tremor-Dominant Type (TDT) assessment, with studies showing that patients with DBS experience significant improvement in tremor control, despite there being studies which suggest that GPi DBS offers better gait results for this specific subtype [55,56] Akinetic-Rigid Type (ART) has also been shown to benefit from DBS, with evidence showing this when subthalamic nucleus (STN) is targeted. This is true when compared to GPi DBS, providing significant improvements in rigidity, akinesia, and posture and gait disorders [57]. Mixed type PD treated through DBS has been established to generally lead to a significant motor symptoms improvement, specifically in tremor, rigidity, and bradykinesia, this is particularly true when there is an “off” medication state [58]

The globus pallidus internus (GPi) has also been described as an alternative target for those with medication-refractory motor complications, exhibiting comparable outcomes to STN stimulation over one and ten-year follow-ups, though with generally lesser motor effects and insufficient reduction of PD medications[51,59,60]. Thalamic ventral intermediate nucleus (VIM) stimulation has been shown to provide sustained relief from unilateral limb tremors, demonstrating a greater than 60% improvement over ten years. While VIM stimulation cannot address other motor symptoms of PD, it remains a suitable option, especially for elderly patients due to its favorable safety profile [51,61,62].

Historically, lesional surgery, including radiofrequency thalamotomy, provided an initial strategy for treating refractory tremors from the 1960s to the 1980s. However, advancements have favored the use of DBS, particularly with VIM stimulation, which offers superior functional outcomes and a lower rate of adverse events. Gamma knife thalamotomy and magnetic resonance-guided focused ultrasound (FUS) thalamotomy present newer modalities, the latter distinguished by its non-invasive nature and real-time monitoring capabilities[51,63].

In conclusion, the selection of surgical intervention for PD tremor must consider the patient's overall health, specific symptoms, and treatment goals. The advancements in surgical techniques and technology have not only enhanced the efficacy of treatment options but also improved the risk-benefit profile, paving the way for individualized patient care in managing PD tremors.

DBS in Comparison with FUS and GK Therapy for Parkinson’s Disease

Deep Brain Stimulation (DBS), Focused Ultrasound (FUS), and Gamma Knife Radiosurgery (GKRS) each offer unique advantages and limitations in the neurosurgical management of

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Parkinson's disease (PD). The choice of therapy depends on factors such as patient age, cognitive status, comorbidities, and symptom severity, along with the need for reversibility, adjustability, and long-term efficacy.

Deep Brain Stimulation (DBS)

DBS is a well-established and adjustable neurosurgical intervention that involves the implantation of electrodes into target brain regions, such as the subthalamic nucleus (STN) or globus pallidus internus (GPi). The key advantages of DBS include:

- Reversibility and Adjustability: Unlike lesion-based therapies, DBS allows for dynamic adjustments in stimulation parameters, ensuring personalized symptom control over time.
- Long-Term Efficacy: DBS has demonstrated sustained benefits in motor symptom reduction, with patients experiencing significant improvements in tremor, bradykinesia, and rigidity.
- Reduced Medication Dependence: Many patients undergoing DBS experience a reduction in levodopa-equivalent doses, mitigating long-term medication-related complications.

However, DBS is associated with surgical risks, including intracranial hemorrhage, infection, and hardware-related complications. It is particularly recommended for younger patients with intact cognitive function and minimal comorbidities.

MRI-Guided Focused Ultrasound (MRgFUS)

MRgFUS is a non-invasive, incision-free procedure that uses high-intensity ultrasound waves to create precise thermal lesions in target brain areas, such as the thalamus or subthalamic nucleus. Its primary advantages include:

- No Need for Implantation: Unlike DBS, FUS does not require permanent hardware, eliminating risks related to device infections or lead displacement.
- Effective Symptom Relief: Studies show significant tremor reduction and motor symptom improvement following FUS, particularly in patients with tremor-dominant PD.

However, key limitations of FUS include:

- Irreversibility: Unlike DBS, lesions created by FUS cannot be adjusted or reversed, making long-term management challenging.
- Potential Side Effects: Speech and gait disturbances, limb weakness, and imbalance can occur, especially if lesions extend beyond the target region.

Gamma Knife Radiosurgery (GKRS)

GKRS is another non-invasive technique that utilizes focused radiation to create targeted brain lesions, primarily in the ventral intermediate nucleus of the thalamus. While it is less commonly used for general PD treatment, it has shown efficacy in tremor control, with:

- Studies reporting a 54.2% reduction in upper limb tremor scores and up to 93.9% improvement in tremor-related symptoms.
- Significant improvements in activities of daily living (up to 72.2%), particularly in patients who are not candidates for DBS or FUS.

However, GKRS carries risks such as:

- Delayed Onset of Effect: Unlike DBS and FUS, symptom relief from GKRS takes weeks to months to manifest due to the gradual radiation-induced lesioning process.
- Radiation Side Effects: Transient hemiparesis, mild contralateral numbness, and, in rare cases, dysphagia and persistent sensory deficits have been reported.

AI-Driven Patient Selection and Personalized Neurosurgical Decision-Making

Advances in AI and machine learning are playing a crucial role in optimizing patient selection for these interventions by:

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- AI-Enhanced EMR Integration: Algorithms analyze clinical, imaging, and genetic data to stratify patients based on disease progression and suitability for DBS, FUS, or GKRS.
- Predictive Outcome Modeling: Machine learning models assess potential benefits and risks of each intervention based on individual patient characteristics.
- Personalized Trial Matching: AI-driven platforms identify eligible patients for experimental neurosurgical trials, ensuring early intervention opportunities.

The Role of Machine Learning in Novel Genes Identification

Genome-wide association studies have been conducted to identify gene variants associated with complex traits. For Parkinson's disease, approximately 90 independent risk variants are associated with 78 genomic loci [64]. Despite significant advancements, there are limitations in further functional analyses of Genome-wide association studies. More than 90% of all significant SNPs identified in GWAS are in non-coding regions [65], and the causal gene of the single-nucleotide polymorphisms is still unclear in most GWAS loci [66].

In a study, a gradient-boosting model was developed that utilized transcriptomic, epigenomic, and other relevant datasets for Parkinson's disease. The machine learning model went through two steps. First, it conducted feature selection to detect and reduce redundant variables from the datasets. Followed by transforming the dataset into a subset containing the selected features by training a model on the complete dataset and retaining the features present in the resulting subset. The second step involved creating the terminal training model using the features chosen in the first step. Then, it transformed the dataset into a subset containing the selected features by training a model on the complete dataset and retaining the features present in the resulting subset. The second step involved creating the terminal training model using the features chosen in the first step. This model helped identify genes that may be differently expressed in Parkinson's disease-relevant models, leading to the discovery of new genes associated with the inositol phosphate biosynthetic pathway. These advancements using Artificial Intelligence will help harness larger datasets to discover and describe the biological mechanisms of Parkinson's disease onset, improving the precision of predictions [67].

Role of Artificial Intelligence in Data Pattern Analysis and Collection

Artificial intelligence (AI) is transforming the way data is analyzed, structured, and interpreted in neurosurgical research and clinical practice. By leveraging machine learning (ML), deep learning, and natural language processing (NLP), AI can extract meaningful insights from large-scale patient datasets, medical records, imaging studies, and clinical trial data, enabling faster, more precise decision-making.

AI-Driven Data Collection and Pattern Recognition

AI algorithms can analyze multimodal data sources, including:

- Electronic Medical Records (EMR): AI-enhanced EMR systems automate data extraction, helping identify disease progression trends and personalized treatment responses.
- Neuroimaging Data: Machine learning models detect subtle changes in MRI, PET, and functional imaging scans, aiding in early diagnosis and surgical planning.
- Wearable and Sensor Data: AI-powered remote monitoring devices continuously collect motor function metrics, allowing real-time adjustments to therapy.
- Genetic and Biomarker Analysis: AI can correlate genomic profiles with disease phenotypes, identifying potential therapeutic targets for Parkinson's disease (PD).

AI in Patient Symptom Assessment and Trial Matching

A study demonstrated the capability of generative AI models (e.g., ChatGPT) in analyzing patient-reported pain experiences, classifying responses from open-ended questionnaires, and

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identifying key correlations among age, education level, mobility needs, and independence. Such advancements enable:

- Automated Patient Stratification: AI can cluster patients into risk groups based on disease severity and potential clinical trial eligibility.
- Predictive Modeling for Surgical Outcomes: AI models assess individual patient responses to DBS, FUS, and other interventions, optimizing treatment recommendations.
- Early Diagnosis and Personalized Interventions: AI-powered diagnostic tools detect subtle disease markers, expediting earlier intervention and patient enrollment in research trials.

Challenges and Future Directions

Despite its potential, AI integration in neurosurgical and neuroscience research faces key challenges, including:

- Bias and Model Reliability: AI models must be trained on diverse, high-quality datasets to ensure accuracy and generalizability.
- Clinical Validation: AI-driven recommendations require rigorous validation through multicenter trials before routine clinical implementation.
- Data Privacy and Security: Handling sensitive patient information demands robust ethical and regulatory safeguards.

By addressing these challenges, AI has the potential to revolutionize neurosurgical decision-making, optimize clinical trial recruitment, and enhance personalized treatment strategies, ultimately improving patient outcomes in Parkinson's disease management.

Application of Deep Learning Technologies to Connectome Patterns

The brain's pathological disturbances often spread through axonal pathways to various cortical and subcortical regions, instead of being confined to a single locus, making the connectome's organization complex and influential in shaping brain disease [68]. Diffusion MRI is a technique that characterizes brain injuries, providing crucial information about the physical environment within tissues and examining physiological, architectural, and microstructural characteristics [69]. Artificial Intelligence has been utilized in analyzing image studies across various organ systems [70–72].

Deep learning techniques are showing promise in discerning imaging pattern characteristics [73]. Approaches like Convolutional Neural Networks (CNN) have demonstrated exceptional performance in tasks related to image recognition. [74]. One study analyzed the possible differences between Parkinson's disease patients and healthy controls using deep learning to analyze the connectome matrix. The study concluded that deep learning effectively improved diagnostic accuracy when trained with the DKI-weighted connectome matrix [75].

The Role of AI in Improving Deep Brain Stimulation

Recent literature has shown that deep learning and other artificial intelligence (AI) technologies have increasingly played a key role as a predictor for optimal deep brain stimulation parameters for Parkinson Disease[76]. This section will review current clinical trials incorporating AI and assess the most important findings from each, detailing insights on the improvements of diagnostics and treatment through Artificial Intelligence Technologies.

One significant area of advancement is clinical decision-making supported by AI. Recent developments have led to the initial FDA approvals for AI-based deep brain stimulation (DBS) systems, allowing decision-aid models to be approved to play a clinical role. The techniques associated with AI have modernized significantly, evolving into three main categories: analysis and segmentation, image reconstruction, and, more recently, methods for artifact correction and noise reduction. These advancements stem from progress in deep learning algorithms, enhancements in localized processing capabilities, and an increasing recognition of deep learning's potential in medical imaging [77].

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Deep brain stimulation (DBS) is an effective treatment for Parkinson's disease (PD), and its clinical outcomes have been further refined by the evolving role of artificial intelligence (AI). Recent applications of AI in this context focus on advancing neuroimaging technologies and predicting optimal stimulation parameters[78].

One study used AI with functional magnetic resonance imaging (fMRI) to predict the best DBS parameters for patients with PD. Researchers trained a machine learning model to determine optimal stimulation settings based on fMRI patterns, achieving a precision of 88%. This approach could potentially reduce the need for outpatient visits to adjust DBS and provide an objective biomarker for treatment response [76].

Another study found that AI algorithms applied to reconstructed, postprocessed MRI images significantly improved image quality and diagnostic usefulness when assessing neuropsychiatric functions in PD patients undergoing DBS. With MRI images, the incorporation of AI-driven noise reduction strategies allowed better visualization and monitoring of brain changes related to DBS treatment. could effectively observe clinical changes in both motor and cognitive functions, potentially aiding clinical decision-making [79].

Algorithms for Reviewing MRI

Deep brain stimulation offers a significant opportunity for clinicians to improve a patient's quality of life. However, it also presents many challenges, particularly in determining each patient's proper settings and parameters. Setting up deep brain stimulation often requires multiple clinical visits to review numerous potential parameters to find the optimal setting for symptom relief and to minimize side effects [80]. This process puts significant financial strain on patients and healthcare systems and prolongs the time before patients can benefit from this treatment option [81]. Neuroimaging techniques have played a crucial role in enhancing surgical outcomes, especially in movement disorders like Parkinson's disease. Diffusion tensor imaging allows for the anatomical segmentation of cortical areas and functional subregions within the deep target area [82].

Studies have used AI-based magnetic resonance imaging volumetry to compare possible structural differences between essential tremor and tremor-dominant Parkinson's disease patients. This approach has helped to identify important anatomical and structural changes between the subtypes, showing variations in the occipital lobes, hippocampus, putamen, pallidum, and mesencephalon. Essential tremor patients showed decreased caudate nucleus and thalamic volumes. Despite the limitations of the study, this approach highlights the importance of Artificial Intelligence as a valuable tool for understanding clinical phenotypes and their underlying pathology, aiding in describing the benefits of targeting different areas when using therapeutic measures such as neurosurgical interventions [83].

Prospective fMRI data has been used with optimal standards to identify brain activity patterns with clinical benefits in Parkinson's disease patients as an indicator of deep brain stimulation efficacy. The prediction of optimal deep brain stimulation settings was achieved through machine learning, which analyzed brain responsiveness patterns [84]. Another study explored the potential of achieving personalized deep brain stimulation through whole brain radiomics using machine learning techniques like regularized binary logistic regression (LR), Gaussian naïve Bayes (NB), K-nearest neighbors (KNN), highlighting the effectiveness of Artificial Intelligence as a tool for clinical decision support and providing personalized recommendations for Parkinson's disease patients [85].

Tools for radiologic assessment have been developed. Imaging patterns of regional glucose metabolism have allowed for reliable differentiation between Parkinson's disease (PD) and atypical Parkinsonian syndromes [86]. A meta-analysis of 24 studies analyzed the use of this tool, with 12 of the trials relying on Artificial Intelligence for automated identification. The analysis concluded that AI-mediated diagnostics had an accuracy comparable to that of a specialist radiologist, further supporting its role as an important adjunct tool for future diagnostics [84].

Patient Voice Assessment of Patients with Parkinson's Disease with Machine Learning and Deep Learning

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Recent studies have highlighted the significance of speech changes in the early detection of Parkinson's Disease. Speech alterations are particularly important as they can manifest up to 10 years before cardinal motor impairment [87]. Speech disorders affect up to 89% of Parkinson's Disease patients, but only 3% to 4% receive treatment, which may include medication, speech therapy, surgical procedures, deep brain stimulation, and vocal fold enhancement [88]. Speech production changes in Parkinson's Disease include increased noise levels due to incomplete vocal fold closure and voicing leakage from difficulties in fine motor movements for starting and finishing speech. Evaluating speech disability typically involves expensive and laborious examinations such as laryngoscopes and video-stroboscopic approaches [89].

Several studies have explored the use of machine learning techniques to assist in addressing speech impairments and deficits in Parkinson's disease patients. Feature-based machine learning and deep learning techniques have shown comparable results in classification. The machine learning approach was made through three models, *k*-nearest neighbors (kNN), naïve Bayes (NB), and support vector machine (SVM)demonstrated their effectiveness in voice analysis [90]. The results highlighted the relevance of machine learning in analyzing voice characteristics with low cardinality data sets, improving diagnostic accuracy when the correct features are provided. However, some limitations need to be addressed, such as using a single speech task for evaluation, which may lead to suboptimal results. Further exploration of convolutional neural network (CNN) methods and architectures could enhance deep learning model training [91].

A summary of the main current evidence, detailing the description of the articles, key insights, and recommendations found in the reviewed manuscripts, can be found in **Table 1**.

Table 1. Summary of current evidence.

Article	Article description	Conclusion	Recommendations
Johnson, KA et. Al.[77]	This article provides an overview of the key findings from the Deep Brain Stimulation Think Tank XI. The focus is on the latest technologies in neuromodulation and new hypotheses regarding the integrative networks that support DBS treatment. The discussions also covered cutting-edge advances in other areas including physiology, translational neuromodulation, neuroethical dilemmas, algorithmic modeling, and artificial intelligence.	The meeting highlighted significant advancements in neuromodulation, particularly in understanding the mechanisms of Deep Brain Stimulation through animal models and human studies. It emphasized the importance of utilizing AI and large data-driven approaches to advance DBS as a widely used therapy.	The article recommends a continued emphasis on translational neuromodulation to gain a deeper understanding of this approach. It also suggests leveraging neurophysiological markers and machine learning algorithms to develop individualized treatments tailored to each patient, considering factors such as physiological changes, circadian rhythms, and sleep.

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Purrer, V et. Al. [83]	The article discusses the issue of misdiagnosing patients with Parkinson's disease and Essential tremor due to overlapping tremor features. The study examines if different tremor types have distinct brain characteristics. The researchers reviewed MRI scans of 61 patients with essential tremor and 29 with tremor-dominant Parkinson's disease. They used Artificial Intelligence brain volumetry to compare various cortical and subcortical regions.	The study results indicate that essential tremor and tremor-dominant Parkinson's disease share structural changes and show neurodegenerative mechanisms, particularly in the basal ganglia-thalamocortical. The study also found possible specific involvement of the thalamus in essential tremors.	The study suggests that AI-powered brain volumetry is a quick, reliable, and independent method to analyze brain volume. It helps understand specific patterns of brain atrophy in both discussed pathologies. The study underscores the need for further research to comprehend disease progression and to develop new treatment strategies.
Haliasos N et Al. [85]	was to develop a machine learning-based predictive model for selecting patients for deep brain stimulation (DBS) using whole-brain white matter quantitative data from medical imaging and clinical variables. The study utilized machine learning methods such as logistic regression, support vector machine, naive Bayes, k-nearest neighbors, and random forest.	The study concluded that machine learning models can effectively predict the extent and progression of deterioration tailored to individual patients. It demonstrated high accuracy, particularly with the state-of-the-art Random Forest model, achieving up to 95% accuracy.	The article suggests further research into the potential of machine learning algorithms as auxiliary tools for clinicians in diagnostics and, importantly, for accurately predicting the progression of each patient's illness and potential treatment responses, thus enabling personalized medicine.
Zhao, T et. Al. [84]	The study aimed to assess the effectiveness of 18F-FDG PET imaging in	The study found that 18F-FDG PET is highly accurate in differentiating PD	The article acknowledges the potential impact of this differentiation in

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	distinguishing between Parkinson's Disease (PD) and Atypical Parkinsonian Syndromes (APSs).	from APSs. It also highlighted the significance of AI techniques, particularly deep learning, as powerful tools that can provide diagnostic performance comparable to traditional radiologist assessments.	diagnosing PD from APDs. Additionally, it noted good accuracy for multiple system atrophy and progressive supranuclear palsy, suggesting potential for treatment response and disease monitoring.
Chahine, LM et. Al.[50]	The objective of this study was to investigate the key indicators that predict changes in motor and total MDS-UPDRS and DAT imaging within the first five years after being diagnosed with PD. This large-scale multicenter prospective cohort study was conducted internationally.	The results of the article demonstrate that initial and temporary changes in evaluations of motor disability (MDS-UPRRS) are the strongest predictors of long-term changes in the metrics used in the article. CSF and imaging measures in the early stages of PD indicated changes in MDS-UPDRS and dopamine transporter binding.	The main finding of this study is the potential for applying machine learning to Parkinson's progression markers. This supports future efforts to establish reproducible and replicable models that utilize machine learning techniques applicable in clinical settings.
Talai, AS et. Al. [19]	The study aimed to address the challenge that clinicians encounter in distinguishing between Parkinson's disease (PD) and progressive supranuclear palsy (PSP) due to their similar symptoms. The researchers evaluated the benefit of including additional morphological characteristics, in	The study concluded that incorporating morphological features, along with clinical features, could be valuable for future computer-aided diagnostic protocols to differentiate between PD and PSP-RS patients.	The study also found that Support Vector Machines, a type of machine learning model, effectively achieved its purpose. It suggests that exploring other machine learning models such as random forests or neural networks could provide even better results when

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	addition to clinical features, for the automated classification of PD and PSP-RS patients.		performing the classification process.
Lin, J et. Al.[92]	The article discusses the impact of magnetic resonance-guided focused ultrasound (MRgFUS) thalamotomy on the exploration of brain structure. It investigates the long-term changes in brain networks and identifies genetic changes related.	The study concludes that MRgFUS thalamotomy effectively reduces tremors in PD patients. However, it induces dynamic changes in the network topology of the brain. Making correlations with gene signatures	The authors recommend future studies to focus on the correlation between the structural network changes induced by MRgFUS thalamotomy and dopaminergic pathways. They also emphasize the importance of genetic mechanisms in the alteration of dopaminergic pathways.
Yasaka, K et. Al. [93]	The study aimed to determine if Parkinson's disease can be distinguished from healthy controls by identifying neural circuit disorders using deep learning techniques and parameters.	The study found that PD can be differentiated from healthy controls by using a deep learning technique to analyze parameter-weighted connectome matrices.	It is recommended that further research be conducted on the distribution of dopamine before and after MRgFUS thalamotomy to gain a deeper understanding of the overall changes induced by this therapy. Additionally, the study suggests exploring sex-specific differences and considering variations in morphology between genders to reduce bias.

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Michell, AW et. Al. [21]	This study used mass spectrometry proteomics to identify a panel of blood biomarkers for early Parkinson's Disease. The researchers applied a machine learning model to identify PD patients.	The study concludes that clinicians must detect Parkinson's Disease at early stages. It also highlights the potential of machine learning models to identify the disease up to 7 before motor symptoms arise.	The study advocates for a multivariate approach using state-of-the-art machine learning models and proteomics to validate and potentially apply these findings in future clinical settings.
Hassin-Baer, S et. Al. [34]	The aim of this study is to explore the potential of biomarkers to differentiate between early-stage Parkinson's disease and healthy brain function using electroencephalography, event-related potentials, and Brain Network Analytics, with the help of machine learning for data analysis.	The study found that Brain Network Analytics is an effective tool for distinguishing patients with Parkinson's Disease. The use of machine learning to incorporate event-related potentials was also highlighted.	The article recommends further research with larger and more diverse groups of participants to reduce bias. Additionally, it suggests specific studies focusing on the premotor prodromal phase of Parkinson's disease in patients.
Maass, F et. Al. [45]	The manuscript aims to validate the use of a model that can classify Parkinson's disease patients and age-matched controls based on the levels of specific bio-elements in cerebrospinal fluid. Mass spectrometry and a Support Vector Machine model were used to differentiate between PD and control groups.	The study found that the Support Vector Machine model could successfully distinguish Parkinson's Disease from control patients within a local cohort. However, its performance was lacking when applied to external cohorts, which attributed to center-specific biases. Nevertheless, the study suggests that bioelemental patterns in CSF could serve as potential biomarkers	The study recommends further research that adheres to more rigorous protocols for pre-clinical and clinical analysis standards, in order to reduce variability and enhance the reliability of bioelemental biomarkers. Additionally, it suggests using mimics in future research to strengthen the model predictions.

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		for Parkinson's Disease.	
Yu, E. et. Al. [67]	The aim of this study is to identify potential genes associated with Parkinson's disease through Genome-wide association studies loci. Firstly, all the genes and Single nucleotide polymorphisms are defined. Then, machine learning is used to select genes from different loci.	The study utilized Parkinson's Disease relevant transcriptomics, epigenomics, and other genetic data sets to develop a boosting model. This model nominated causal genes from Parkinson's Disease Genome-wide association studies loci, identifying novel genes potentially involved, such as those in the inositol phosphate biosynthetic pathway.	The study recommends further research that addresses the limitations of this study's development. Specifically, it suggests including a more diverse population, as the study was conducted only in Europeans. It also suggests a broader analysis that includes chromosome X and a wider gene set, not limited to the established Parkinson's Disease genes.
Costantini G et. Al. [91]	This article delves into the use of machine learning (ML) and deep learning (DL) models for evaluating vocal characteristics in individuals with Parkinson's Disease. The study compares both models to determine which approach is the most effective.	The study concluded that both models achieved similar results in classifying Parkinson's Disease patients based on vocal analysis. K-nearest neighbors slightly outperformed the other models.	This study supports the use of AI as a non-invasive, cost-effective tool for early detection and tracking of Parkinson's Disease. It emphasizes the importance of collecting high-quality voice data and suggests further research into models that integrate complex neural network architectures.

Ethical and Regulatory Considerations in AI-Driven Trials

The integration of artificial intelligence (AI) into clinical trials, particularly in neurosurgery and Parkinson's disease (PD) research, introduces a host of ethical and regulatory challenges. While AI

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promises to enhance patient selection, treatment personalization, and outcome prediction, these benefits come with significant concerns related to data privacy, informed consent, and algorithmic bias.

1. Data Privacy and Security

AI systems rely on large datasets containing sensitive patient information, which raises serious concerns about data privacy. Ensuring patient confidentiality is paramount, particularly when integrating data from diverse sources, such as electronic health records (EHRs), genomic data, and neuroimaging. Stringent measures must be implemented to prevent data breaches and protect patient anonymity. Additionally, data sharing between institutions must be secure and regulated to comply with laws like the Health Insurance Portability and Accountability Act (HIPAA) in the U.S. or the General Data Protection Regulation (GDPR) in the EU.

2. Informed Consent

AI's involvement in clinical trials introduces complexity in the informed consent process. Patients must understand how their data will be used by AI systems, what role AI-driven algorithms play in decision-making, and the potential risks and benefits associated with AI-enhanced treatments. Researchers must ensure that AI's decision-making role is clearly explained to patients, emphasizing that these systems are tools rather than final authorities in care. The issue of consent for secondary data use, such as for algorithm training, must also be addressed transparently.

3. Algorithmic Fairness and Bias

AI systems are susceptible to algorithmic bias if they are trained on data that lacks diversity or reflects historical disparities in medical care. These biases may result in inequitable treatment outcomes, particularly for minority populations. Ethical frameworks must evolve to ensure that AI models are fair, unbiased, and inclusive, reflecting the full spectrum of patient demographics. As AI-driven trials become more prevalent, ensuring equitable access to these technologies and minimizing the potential for discrimination is critical.

Morley et al. (2020) emphasize that the ethical considerations in AI must move beyond the technology itself and encompass broader concerns, such as the social implications of its application in healthcare. This includes addressing how AI may inadvertently reinforce existing disparities and ensuring that vulnerable populations are not underserved by technological advancements.

4. Transparency and Accountability

As AI systems become integral to clinical decision-making, ensuring transparency in how algorithms arrive at conclusions is crucial for clinical accountability. Researchers must establish clear protocols for how AI-driven models are developed, validated, and tested before being used in patient care or clinical trials. It is essential that healthcare professionals understand the limitations of AI models and remain actively involved in the decision-making process.

5. Regulatory Oversight

Given the growing role of AI in clinical trials and neurosurgical interventions, regulatory bodies like the FDA, EMA, and other national health authorities must adapt and create specific guidelines for AI-based trials. This includes ensuring that AI technologies undergo rigorous testing to demonstrate safety, efficacy, and clinical relevance. Additionally, regulatory standards should be updated to encompass emerging AI technologies and address the ethical challenges they present.

Future Perspectives in AI-Driven Parkinson's Disease Diagnosis and Treatment

The future of Parkinson's Disease (PD) diagnosis and treatment lies in artificial intelligence (AI), which promises to revolutionize both clinical care and research for neurodegenerative diseases. Currently, PD diagnosis is based largely on motor symptoms, which often only appear after a significant loss of dopaminergic neurons. This late-stage detection limits the effectiveness of early interventions. However, AI has the potential to identify early signs of Parkinson's Disease before motor symptoms are clinically apparent, thus enabling earlier diagnosis and intervention.

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Early Detection and Monitoring

AI tools offer the ability to analyze complex, non-invasive data—such as nocturnal breathing patterns, sleep disturbances, and sensor-based movement data—to identify subtle, pre-symptomatic signs of PD. These early markers could allow for early-stage intervention, improving the long-term quality of life for patients. For individuals who may not have access to specialized clinics—with about 40% of PD patients lacking access to specialists—AI-driven tools can provide remote, continuous monitoring of disease progression and assist in early detection of PD in a cost-effective manner.

One significant development is the AI model that enhances patient monitoring by analyzing nocturnal respiratory data to assess disease progression. This model, validated on large, diverse datasets, has demonstrated high accuracy in diagnosing PD and predicting its severity. The non-invasive nature of the model—using belt-based or contactless radiofrequency (RF) signal analysis to track respiratory patterns—presents an at-home alternative to traditional diagnostic methods, such as the Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS).

The model's continuous, objective data collection can significantly enhance clinical trial efficiency by providing more sensitive progression markers. It offers convenience for at-home monitoring, which could improve patient recruitment and retention in clinical trials by reducing logistical barriers and patient burden.

Impact on Clinical Trials

AI's ability to track subtle changes in disease progression has profound implications for clinical trials. By providing real-time, objective data on disease symptoms, AI can potentially streamline trial processes, making them more efficient and accurate. AI-driven tools could facilitate the use of digital biomarkers to monitor disease progression continuously, improving trial sensitivity and precision. This can ultimately reduce trial durations and costs, allowing for faster evaluation of therapeutic interventions.

Challenges and Future Research Directions

As AI technologies continue to evolve, future research must focus on validating these models in large, heterogeneous populations across diverse clinical environments. This will ensure that the models are robust and reliable for widespread clinical application. AI-based systems must be refined and rigorously tested to ensure they meet the clinical standards for safety, efficacy, and generalizability.

Additionally, multidisciplinary collaborations between AI experts, neurosurgeons, clinicians, and researchers will be essential for optimizing the integration of AI into clinical workflows. This includes addressing challenges related to data privacy, ethical considerations, and regulatory approval, ensuring that AI technologies are used in ways that prioritize patient safety and clinical outcomes.

Conclusion

The application of artificial intelligence (AI) in neuroscience and neurosurgery is revolutionizing the diagnosis, treatment, and management of Parkinson's Disease (PD), marking a significant leap forward in both research and clinical practice. AI's ability to process and analyze complex neuroimaging data, genomic information, and biomarkers is enabling the identification of preclinical signs and the accurate tracking of disease progression. This allows for earlier diagnosis and intervention, critical factors in improving patient outcomes in neurodegenerative diseases like PD. AI models are capable of identifying subtle changes in patients' motor and non-motor symptoms, providing continuous, real-time monitoring through wearable devices, and enabling personalized treatment strategies for patients undergoing neurosurgical interventions.

In neurosurgical interventions, such as deep brain stimulation (DBS) and focused ultrasound (FUS), AI enhances the precision of patient selection and surgical planning. By integrating AI with

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patient-specific data, including neuroimaging and electrophysiological mapping, clinicians can optimize the targeting of affected brain regions, minimizing risks and improving surgical outcomes. Furthermore, AI-driven platforms are streamlining the process of matching patients to clinical trials by analyzing large datasets from electronic medical records (EMRs) and genetic profiles, making it possible to identify the most suitable candidates faster and more accurately. This could dramatically improve the efficiency and effectiveness of clinical trials, reducing both the costs and duration of trial phases.

The integration of AI in clinical trial design further optimizes the process by enabling adaptive trial designs that can adjust based on real-time data. This reduces patient burden, accelerates drug development, and ensures that trials are more patient-centric. AI also plays a critical role in the early diagnosis and early-stage detection of PD, particularly through the analysis of neuroimaging data, speech patterns, and movement disorders. These diagnostic tools help clinicians detect subtle, pre-motor symptoms that were previously difficult to identify, allowing for earlier intervention and more effective neurosurgical treatment.

However, significant challenges remain. To fully integrate AI into neurosurgery and neuroscience research, further validation is required across diverse patient populations, ensuring that AI models are generalizable and clinically effective. Additionally, issues surrounding data privacy, algorithmic transparency, and the ethical implications of AI-driven decisions must be addressed to ensure that AI is used responsibly in clinical settings. The integration of AI into routine clinical workflows also poses challenges in terms of technology adoption and the training of healthcare professionals.

Despite these obstacles, the potential of AI to transform neurosurgery and neuroscience is vast. With precision medicine and tailored treatments on the horizon, AI offers an unprecedented opportunity to improve patient care, reduce surgical risks, and advance clinical research in Parkinson's Disease. As AI technologies continue to evolve, their integration into neurosurgery will lead to more efficient, accurate, and personalized treatment options, ultimately enhancing the quality of life for individuals with PD and accelerating the development of groundbreaking neurosurgical therapies.

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