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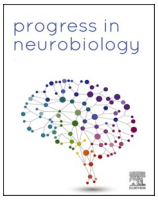

The STRAT-PARK cohort: A personalized initiative to stratify Parkinson's disease

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Abbreviations: PD, Parkinson's disease; TD, tremor dominant; PIGD, postural instability and gait disorder; AR, akinetic rigid; mtDNA, mitochondrial deoxyribonucleic acid; HUS, Haukeland University Hospital; LMDC, London Movement Disorders Centre; MDS, Movement Disorders Society; [^{123}I]FP-SPECT, 123I-Ioflupane single photon emission computed tomography; DAT, dopamine active transporter; ^{18}F-FDOPA, 3,4-dihydroxy-6–18F-fluoro-L-phenylalanine; MDS-UPDRS, International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale; MDS-NMS, International Parkinson and Movement Disorder Society Non-Motor Rating Scale; MoCA, Montreal Cognitive Assessment; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction; OBP, orthostatic blood pressure; GIDS-PD, Gastrointestinal Dysfunction Scale for Parkinson's Disease; RBDSQ, REM Sleep Behavior Disorders Screening Questionnaire; PDSS-2, Parkinsońs Disease Sleeping Scale-2; EQ-5D–5L, 5-level EQ-5D version; B-SIT, Brief Smell Identification Test; VR, virtual reality; PKMAS, ProtoKinetics Movement Analysis Software; qEEG, quantitative electroencephalography; MRI, magnetic resonance imaging; 3 T, 3 Tesla; 7 T, 7 Tesla; FLAIR, fluid attenuated inversion recovery; DTI, diffusion tensor imaging; FA, fractional anisotropy; MTC, magnetization transfer contrast; GRE, gradient echo; STAGE, strategically acquired gradient echo; SWI, susceptibility weighted imaging; DIR, double inversion recovery; QSM, quantitative susceptibility maps; 31P-MRS, ^{31}phosphorous magnetic resonance spectroscopy; NOE, nuclear-Overhauser enhanced; CSI, chemical shift imaging; NAD, nicotinamide adenine dinucleotide; ATP, adenosine triphosphate; USPIO, ultra-small-superparamagnetic-iron-oxide; EDTA, ethylenediaminetetraacetic acid; RNA, ribonucleid acid; PBMC, peripheral blood mononuclear cells; CSF, cerebrospinal fluid; WGS, whole-genome sequencing; Bp, base pair; PCR, polymerase chain reaction; TMT, tandem mass tags; IHC, immunohistochemistry; WB, western blot; FGF21, fibroblast growth factor 21; GDF15, growth/differentiation factor-15; ELISA, enzyme-linked immunosorbent assay; SAA, seed amplification assay; NfL, neurofilament light chain; ECRF, electronic case report form; GDPR, General Data Protection Regulation; PPMI, Parkinson Progression Marker Initiative; UPSIT, University of Pennsylvania Smell Identification Test; OPDC, Oxford Parkinson Disease Center.

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ABSTRACT

The STRAT-PARK initiative aims to provide a platform for stratifying Parkinson's disease (PD) into biological subtypes, using a bottom-up, multidisciplinary biomarker-based and data-driven approach. PD is a heterogeneous entity, exhibiting high interindividual clinicopathological variability. This diversity suggests that PD may encompass multiple distinct biological entities, each driven by different molecular mechanisms. Molecular stratification and identification of disease subtypes is therefore a key priority for understanding and treating PD. STRAT-PARK is a multi-center longitudinal cohort aiming to recruit a total of 2000 individuals with PD and neurologically healthy controls from Norway and Canada, for the purpose of identifying molecular disease subtypes. Clinical assessment is performed annually, whereas biosampling, imaging, and digital and neurophysiological phenotyping occur every second year. The unique feature of STRAT-PARK is the diversity of collected biological material, including muscle biopsies and platelets, tissues particularly useful for mitochondrial biomarker research. Recruitment rate is ~150 participants per year. By March 2023, 252 participants were included, comprising 204 cases and 48 controls. STRAT-PARK is a powerful stratification initiative anticipated to become a global research resource, contributing to personalized care in PD.

Parkinson's disease (PD) is the most rapidly growing neurodegenerative disorder, and a major cause of disability and mortality on a global scale(Bloem et al., 2021). Current treatments for PD are purely symptomatic, and trials of potential disease-modulating therapies have been unsuccessful(Athauda and Foltynie, 2015).

Efforts to understand and treat PD are undermined by its vast clinicopathological heterogeneity. While referred to as a single entity, PD is a heterogeneous syndrome, defined by phenotypical features(Postuma et al., 2015; Postuma and Berg, 2017). Patients exhibit high variability in age of onset, type and severity of clinical features, rate of progression, response to treatment, and underlying neuropathology(Chen-Plotkin et al., 2018; Greenland et al., 2019; Halliday and McCann, 2010). The clinicopathological diversity of PD has led to the hypothesis that distinct biological subtypes of the disease may exist, driven by different molecular mechanisms(Espay et al., 2017b, 2017a). Without stratification, such molecular heterogeneity dilutes the biological signal in observational and interventional studies, limiting both mechanistic and therapeutic breakthroughs. Thus, successful molecular stratification of PD and identification of disease subtypes is a key priority, as this will provide insights into individualized progression and prognosis, and most importantly, enable personalized treatment strategies(Berg et al., 2014; Espay et al., 2017a; Rodríguez-Violante et al., 2017).

Current stratification approaches for PD rely mostly on clinical features, with motor phenotype being the most common(Berg et al., 2021; Campbell et al., 2020; Foltynie et al., 2002; van Rooden et al., 2011). For example, the tremor dominant (TD), postural instability and gait disorder (PIGD), or akinetic rigid (AR) motor subtypes have been extensively used(Erro et al., 2020; Jankovic et al., 1990; Qian and Huang, 2019; Thenganatt and Jankovic, 2014). More recently, non-motor symptoms have gradually gained importance in phenotypical subtyping of PD (Fereshtehnejad et al., 2015). Another approach, using multimodal functional neuroimaging, has led to the hypothesis that two forms of PD can be discerned, depending on whether neurodegeneration starts in the brain or the gut(Horsager et al., 2020). Neurotransmitter-centric disease classifications have also been suggested, correlating motor and/or non-motor symptom constellations with dysfunction and degeneration of specific neuronal populations, such as noradrenergic, cholinergic, or serotonergic(Berg et al., 2021). While the above classification schemes support the view that molecular subclasses of PD may exist, no such subtypes have been established to date. In fact, it has been proposed that a bottom-up strategy may be a more effective approach. Rather than starting from clinical classifications and seeking molecular associations for these, this strategy would stratify PD according to distinctive molecular features, and subsequently characterize the clinical phenotype of the emerging subtypes. This approach may prove more fruitful in defining disease subtypes amenable to specific therapies(Espay et al., 2017b).

A molecular stratification approach for PD may initially focus on known molecular processes associated with the disease. While the molecular pathogenesis of PD remains largely unknown, a number of associated biological processes have been identified; mainly aberrant proteostasis, mitochondrial dysfunction, and neuroinflammation(Bloem et al., 2021; Kalia and Lang, 2015). The aggregation of α-synuclein is at the center of most current pathogenic models for PD. Aberrant proteostasis, in the form of lysosomal and proteasomal dysfunction, is believed to contribute to aggregation of α-synuclein in Lewy pathology, a hallmark feature of PD(Dickson, 2012). This is corroborated by the fact that loss of function variants in the *GBA* gene, encoding the lysosomal enzyme glucocerebrosidase, are associated with increased risk of PD. However, *GBA* risk variants are only found in 7–15% of PD cases(Ren et al., 2022) and there is no robust evidence for impaired proteostasis pathways in the remaining cases.

Mitochondrial dysfunction, mainly in the form of complex I deficiency and aberrant mitochondrial DNA (mtDNA) maintenance, is considered integral to PD(Chen et al., 2019; Flønes and Tzoulis, 2022). Evidence of these mitochondrial defects has been detected in neurons from multiple brain regions(Flønes et al., 2018) and in peripheral tissues, primarily muscle and/or platelets, and to a lesser extent blood cells (Subrahmanian and LaVoie, 2021). However, the results of previous studies have been variable and, in part, contradictory, raising the pertinent question of whether impaired mitochondrial function is a pervasive feature of PD(Flønes and Tzoulis, 2022; Subrahmanian and LaVoie, 2021). Finally, neuroinflammation involving microglial activation and/or dysfunction has been implicated in PD(Hirsch and Hunot, 2009), but its role remains largely obscure.

Importantly, while the aforementioned processes are associated with PD, it remains unknown whether they are pervasively involved in all cases, or only contribute to specific patient subpopulations. Thus, molecular biomarkers targeting these pathways may help us stratify PD and identify molecular subtypes. Moreover, unbiased molecular datasets, such as multi-omics, may enable the discovery of novel molecular pathways, or even allow hypotheses-free, data-driven stratification to take place.

The main goal of the STRAT-PARK initiative is to establish a longitudinal population-based cohort of sufficient size and with appropriately diverse biosampling and measures, to allow resolving the biological heterogeneity of PD and developing biomarkers for patient stratification in clinical practice.

1. Study design

STRAT-PARK is a prospective, longitudinal, multicenter cohort study. A total of 2000 individuals, including individuals with PD (n=1,500) and neurologically healthy, demographically matched

controls (n=500) will be prospectively recruited and followed up at three clinical centers: Haukeland University Hospital (HUS), Bergen, Norway, St. Olav's University Hospital, Trondheim, Norway, and The London Movement Disorders Centre (LMDC), Ontario, Canada. Together, the three sites have an estimated candidate population of at least 4,000 patients at any given time. The current recruitment rate is 150 participants per year. Controls are recruited among the patients' partners, as well as other volunteers, and must have no signs of neurodegenerative or neuropsychiatric disorders. After initial screening and assessment at baseline, participants are followed prospectively with yearly visits until death, drop-out or study discontinuation. The frequency and content of the visits are summarized in Table 1. The study design is illustrated in Fig. 1.

1.1. Inclusion and exclusion criteria

To be eligible for participation, patients must have a diagnosis of clinically established or probable PD according to the Movement Disorders Society (MDS) diagnostic criteria for PD(Postuma et al., 2015), and be able to consent and participate in the study. Participants recruited in Norway must in addition have 123I-Ioflupane single photon emission computed tomography [^{123}I]FP-SPECT (e.g., dopamine active transporter (DAT) scan), or 3,4-dihydroxy-6–18F--fluoro-L-phenylalanine (^{18}F-FDOPA) PET scan confirming nigrostriatal degeneration. Controls are eligible for participation if they are able to consent and participate in the study, and lack signs of parkinsonism, or other neurodegenerative disorder at screening/baseline. A detailed list of participation criteria is given in the study protocol.

1.2. Recruitment procedure and centers

STRAT-PARK aims to recruit a disease population which is as unselected as possible and, therefore, representative of the general disease population. Subjects are recruited from the outpatient departments of the study centers "as they present" for first referral or follow-up. In the Norwegian health care system, all individuals suspected to have PD are referred to neurological evaluation and follow up by a public neurology clinic. The Norwegian sites involved in the study are primary referral centers for PD for their respective regions and, therefore, see virtually all newly diagnosed cases in the population. LMDC is a tertiary referral center serving a large population of southwestern Ontario. Patients are referred by family doctors directly, while community neurologists tend to refer patients in need of advanced treatment. Thus, the patient group recruited there is more selected and less representative of the general population. Healthy controls are recruited among the partners or close relatives of the patients and other volunteers.

1.3. Procedures

STRAT-PARK participants undergo comprehensive clinical assessment annually with biosampling and imaging every second year. Examinations and biosampling take place in the "ON" dopaminergic state to minimize patient discomfort, except from motor assessment and qEEG at the London site, which is conducted both in the "OFF" and "ON" states. The frequency and content of the visits is summarized in Table 1.

1.3.1. Clinical assessments and questionnaires

Medical history including comorbidities, family history, and current medication is recorded. Environmental and occupational exposures such as smoking and alcohol intake, pesticide exposure and others are documented. Vital signs and body metrics are recorded.

Motor functions are assessed using the International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale (MDS-UPDRS)(Goetz et al., 2008), part III. At the Norwegian sites, motor assessment is conducted in the "ON" state. At LMDC, motor assessment is performed in both "ON" and "OFF" state.

Non-motor symptoms are assessed using the relevant items in the MDS-UPDRS and specific scales, including the International Parkinson and Movement Disorder Society Non-Motor Rating Scale (MDS-NMS) (Chaudhuri et al., 2020) and the Montreal Cognitive Assessment (MoCA) (Nasreddine et al., 2005). Autonomic dysfunction is assessed with the Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction (SCOPA-AUT) questionnaire(Visser et al., 2004) and measurement of orthostatic blood pressure (OBP)(Gibbons et al., 2017). Gastrointestinal function is assessed using the Gastrointestinal Dysfunction Scale for Parkinson's Disease (GIDS-PD)(Camacho et al., 2021). Sleep changes are assessed with the REM Sleep Behavior Disorders Screening Questionnaire (RBDSQ)(Stiasny-Kolster et al., 2007) and Parkinsońs Disease Sleeping Scale (PDSS-2)(Trenkwalder et al., 2011). Quality of life is assessed using the 5-level EQ-5D version (EQ-5D-5L)(Herdman et al., 2011). Olfactory function is measured with the Brief Smell Identification Test (B-SIT)(Doty et al., 1996). Administration and rating of non-motor scales and testing for cognition is done in the dopaminergic "ON" state at all sites.

1.3.2. Digital and neurophysiological biomarkers

The LMDC site performs objective motor assessment. They use full body wearable wireless inertial sensing-based motion capture system using Xsens MVN suit to quantify the cardinal motor symptoms of bradykinesia and tremor. The KINARM Endpoint robot, which comprises a robotic manipulandum (robot handle) coupled with a Virtual Reality (VR) display, is used to extract the upper-limb kinematic data which in turn characterizes the PD-related upper limb motor impairments. Finally, gait assessment is done using the Zeno walkway (Zenometrics LLC, Peekskill, NY) in conjunction with the ProtoKinetics Movement Analysis Software (PKMAS). These data are captured and collated via the PKMAS software, resulting in numerous spatial, temporal and pressure-related gait parameters. These parameters are compared with the gait variables derived from the inertial sensing-based motion capture system. The Norwegian sites will implement wearable sensors during 2024, with an emphasis on remote monitoring of physical activity and motor symptoms.

Speech and eye movement are examined at LMDC. Speech is recorded using a head-mounted microphone (AKG-c520, AKG Acoustics, USA) and a digital recording device (Zoom H4nPro, Zoom Corporation, USA) as described(Boutsen et al., 2023). Eye movement examination is done using a screen-based eye tracking device (Tobii Pro fusion, Tobii, Stockholm) as described(De Kloe et al., 2022). During the test, the participant's eye movements, including pursuits and saccades in both horizontal and vertical direction and opto-kinetic nystagmus, are recorded using a visual stimulus. Quantitative cortical (surface) electroencephalography (qEEG) is performed at LMDC in the resting condition with eyes-closed using a standard 32-channels wireless biosignal acquisition system that is recorded with a 256 Hz frequency sampling rate. The qEEG parameters is recorded both in the dopaminergic "ON" and "OFF" state.

1.3.3. Imaging

Imaging is performed every second year throughout the study. Magnetic resonance imaging (MRI) is conducted on a 3 Tesla (3 T) MR-PET scanner at HUS (Biograph mMR, Siemens Healthineers, Erlangen, Germany) and LMDC (3 T Discovery MR750; GE Medical Systems, Milwaukee, Wisconsin using a 32-channel head coil), and a 7 Tesla (7 T) scanner at St. Olavs University Hospital (SIEMENS MAGNETOM Terra scanner). High-resolution 3D T1- and 2D T2-weighted and T2-fluid attenuated inversion recovery (T2-FLAIR) sequences are performed for global and regional cerebral volume measurements. Diffusion tensor imaging (DTI), acquired with 60 directions spread across two b-value shells (1000 and 2500 s/mm^2) and opposite phase images for distortion correction, is used for mapping brain water diffusion and assessing changes in cellularity using fractional anisotropy (FA) and structural connectivity (tractography). Neuromelanin imaging using magnetization transfer contrast

Table 1
Currently performed examinations and biosampling.

Event	Sites where the event is currently performed	Screening	Visit-0	Visit-1	Visit-even[a]	Visit-odd[b]
Time			**Baseline**	**Year-1**	**y**	**x**
Informed consent	All sites	X				
Informed consent biobank	All sites	X				
Inclusion/exclusion evaluation	All sites	X				
Medical history	All sites	X	X	X	X	X
Record of concomitant medication	All sites	X	X	X	X	X
Vital signs - BP and pulse with the participant sitting on a chair.	All sites		X	X	X	X
Orthostatic blood pressure - BP and pulse in the supine position after 5 min rest. - BP and pulse after 1 min standing. - BP and pulse after 3 min standing.	All sites		X	X	X	X
Body metrics: height	All sites		X			
Body metrics: weight & BMI	All sites		X	X	X	X
General neurological examination	All sites	X	X	X	X	X
Clinical scales - MDS-UPDRS I-IV o Part III includes H&Y staging. - MDS-NMS - PDSS-2 - RBDSQ - SCOPA-AUT - GIDS-PD - EQ-5D-5L - MoCA - B-SIT	All sites	X	X	X	X	X
Objective motor assessment - Full body wearable wireless intertial sensing-based motion capture system using Xsens MVN to quantify bradykinesia and tremor. - KINARM Endpoint robot coupled with VR-display to extract upper-limb kinematic data. - Zeno walkway to assess gait.	LMDC		X	X	X	X
Speech examination	LMDC		X		X	
Eye movement examination	LMDC		X		X	
EEG (32-channels)	LMDC		X		X	
DAT-scan - Patients that have not undergone a DAT-scan previously is referred at screening/baseline.	HUS, St. Olav's.	X				
Routine blood tests - Blood counts, liver and kidney function tests and electrolytes (see Study Protocol for complete list).	All sites		X		X	
Blood collection for biobanking - Whole blood EDTA: All sites - Whole blood EDTA-snap-frozen: HUS, St. Olav's - Serum: All sites - PAXgene blood for RNA: All sites - Fullblood for PBMCs: HUS - Platelet isolation and cryopreservation: HUS	All sites		X		X	
Cerebrospinal fluid collection - Routine analyses for cells, protein and glucose. - β-amyloid, total tau protein, and phosphorylated tau protein. - Cell-free CSF for biobanking.	All sites		X		X	
Muscle biopsy - Needle biopsy of vastus lateralis.	All sites		X		X	
MRI of the brain - 3 T MRI: HUS, LMDC - 7 T MRI: St. Olav's	All sites		X		X	
Postmortem examination	HUS, St. Olav's					

[a] Visit repeats every even year (e.g., 2, 4, 6, 8, 10, 12, etc.) until death or dropout.
[b] Visit repeats every odd year (e.g., 1, 3, 5, 7, 9, 11, 13, etc.) until death or dropout. Abbreviations: BP, Blood Pressure; BMI, Body Mass Index; MDS-UPDRS, International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale; MDS-NMS, International Parkinson and Movement Disorder Society Non-Motor Rating Scale; PDSS-2, Parkinsońs Disease Sleeping Scale-2; RBDSQ, REM Sleep Behavior Disorders Screening Questionnaire; SCOPA-AUT, Scales for Outcomes in Parkinson's Disease – Autonomic Dysfunction; GIDS-PD, Gastrointestinal Dysfunction Scale for Parkinson's Disease; 5Q–5D-5 L, 5-level EQ-5D version; MoCA, Montreal Cognitive Assessment; B-SIT, Brief Smell Identification Test; KINARM; Kinesiological Instrument for Normal and Altered Reaching Movements; VR, Virtual Reality; EEG; Electroencephalogram, DAT, dopamine transporter; EDTA, Ethylenediaminetetraacetic Acid; HUS, Haukeland University Hospital; RNA, ribonucleic acid; PBMC, Peripheral Blood Mononuclear Cells; CSF, Cerebrospinal Fluid; MRI, Magnetic Resonance Imaging; 3 T, 3 Tesla; 7 T, 7 Tesla; LMDC, London Movement Disorders Center.

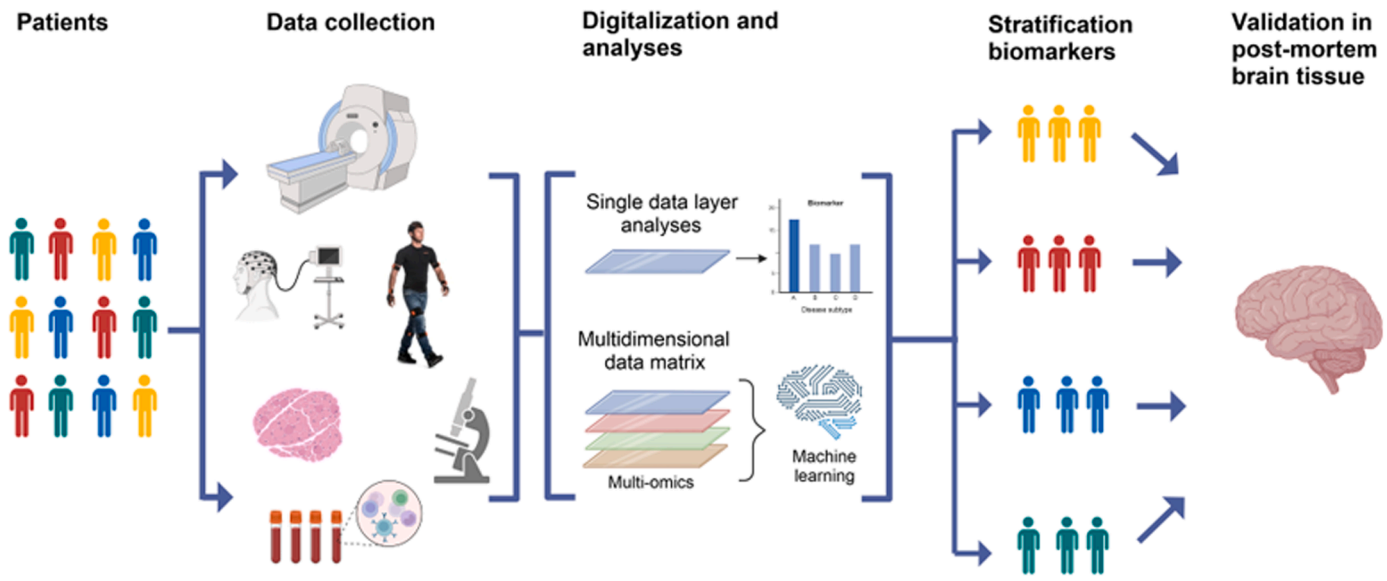

Fig. 1. Overview figure of the STRAT-PARK initiative. Data from clinical assessment and questionnaires, imaging, neurophysiological examinations, biosampling and postmortem examinations will ultimately be used to employ multidimensional data integration and data-driven analyses to identify and validate stratification biomarkers for PD. Created with BioRender.com.

(MTC) imaging is performed using a 3D multi-echo gradient echo (GRE) sequence with an MTC pulse to detect and quantify neuromelanin in the substantia nigra and locus coeruleus(He et al., 2023, 2021). Strategically acquired gradient echo, (STAGE) multi-echo, multi-flip-angle susceptibility weighted imaging (SWI), is used to provide the following quantitative data: proton-density, T1- and T2*-maps and simulated double inversion recovery (DIR) as well as SWI minimum-intensity projections and quantitative susceptibility maps (QSM) to quantify the iron in various deep gray matter nuclei(Chen et al., 2018; Liu et al., 2020; Wang et al., 2018). ^{31}phosphorous magnetic resonance spectroscopy (31P-MRS), using a proton-decoupled, nuclear-Overhauser enhanced (NOE) chemical shift imaging (CSI) sequence to assess the intracerebral concentration of phosphorylated metabolites, including nicotinamide adenine dinucleotide (NAD) and adenosine triphosphate (ATP), as previously described (Brakedal et al., 2022). Microvascular imaging is based on modified susceptibility weighted imaging (SWI) sequences, using the ultra-small-superparamagnetic-iron-oxide (USPIO) contrast agent "ferumoxytol"(Buch et al., 2020; Liu et al., 2018). Not all sequences are acquired at all sites and field strengths.

1.3.4. Biosampling

Blood sampling is performed every second year and includes routine clinical tests (see study protocol for complete list) and biobanking of whole ethylenediaminetetraacetic acid (EDTA) blood, serum, PAXgene blood for ribonucleic acid (RNA) analyses, peripheral blood mononuclear cells (PBMCs), platelet isolation for mitochondrial assays, and flash-frozen whole blood samples. The latter is ideal for metabolomic analyses, including the assessment of volatile metabolites, such as ATP and the NAD-metabolome. Cerebrospinal fluid (CSF) sampling is performed every second year. The CSF undergoes routine analyses for cells, protein and glucose, as well as measurement of β-amyloid, total tau protein, and phosphorylated tau protein. Cell-free CSF is biobanked for future analyses. Needle muscle biopsy of the vastus lateralis is performed every second year. Biological samples are stored at the dedicated STRAT-PARK biobank at Haukeland University Hospital. Detailed operating procedures for obtaining and processing each sample type are given in the study protocol and lab manual (supplementary material).

1.3.5. Postmortem examination

Postmortem examination and tissue collection is performed on participants who have consented to this. Autopsy is performed within 48 hours after death. The left cerebrum, cerebellum and brain stem are divided into anatomical regions, snap-frozen in liquid nitrogen and stored at −80 C. The right cerebrum, cerebellum and brain stem are fixed in formalin, divided into anatomical areas and embedded in paraffin blocks. In addition, samples are collected for formalin fixation and freezing from the heart, muscle, liver, kidney, and each anatomical segment of the intestine. Postmortem tissue samples are stored at the dedicated STRAT-PARK biobank at Haukeland University Hospital.

1.4. Dataset generation

While STRAT-PARK is collecting material for a broad spectrum of future biomarker-related analyses, the following analyses are already planned and will generate data in parallel with cohort recruitment.

1.4.1. Genomics

The genome of all participants will be mapped in DNA extracted from muscle biopsy (or blood where muscle is not available), using whole-genome sequencing (WGS) at mean coverage 30X per base pair (bp) and 150 bp paired-end reads. Muscle DNA is chosen as this tissue is superior to blood for assessing somatic/heteroplasmic mtDNA changes. Cases of monogenic parkinsonism will be identified, and the data stored for future analyses. *GBA* status will be assessed by targeted sequencing of a preamplified region to ensure specificity, as described(Zampieri et al., 2017). mtDNA will be assessed from the WGS data including heteroplasmic changes at levels as low as 1 %. mtDNA total copy number and proportion of major arc deletion are characterized by quantitative real-time PCR as described(Dölle et al., 2016; Flønes et al., 2018).

1.4.2. Transcriptomics & proteomics

The transcriptome will be assessed by RNA-sequencing in PaxGene whole blood, following ribosomal and globin depletion protocols. The proteome will be assessed in the same blood samples by quantitative proteomics using Tandem Mass Tags (TMT) labeling and mass spectrometry.

1.4.3. Mitochondrial function

The mitochondrial respiratory chain is assessed in PBMCs, muscle,

and platelets using a combination of immunohistochemistry (IHC), Western blot (WB), and specific enzyme activities as previously described(Fløtnes et al., 2018). Serological markers of mitochondrial dysfunction, including fibroblast Growth Factor 21 (FGF21) and Growth/Differentiation Factor-15 (GDF15), are measured in serum and/or CSF using established ELISA assays. FGF21 is a marker of mitochondrial myopathy and is elevated in patients and animals with mitochondrial dysfunction(Lehtonen et al., 2016). Serum GDF15 levels are elevated in patients with mitochondrial disease and respiratory chain deficiencies(Yatsuga et al., 2015). Moreover, increased serum and/or CSF levels of GDF15 in PD have been reported by several studies (Yao et al., 2017).

1.4.4. Markers of proteinopathy and neuronal injury

CSF is undergoing analyses for levels of tau, phosphorylated tau, and amyloid β, as well as α-synuclein seed amplification assays (SAA), to determine the presence of misfolded α-synuclein. SAA was recently reported to show high accuracy in differentiating PD patients from controls. Intriguingly, approximately 7% of the individuals with idiopathic PD were negative for α-synuclein SAA in a large recent study, raising the possibility for stratification(Siderowf et al., 2023). Finally, as a general marker of neuronal injury, neurofilament light chain (NfL) is measured in serum using the Simoa NF-light® assay.

1.5. Standardization of data and material collection, storage and management

STRAT-PARK has implemented standard operating procedures across all sites for the collection of data and biological samples. These are described in detail in the study protocol and lab manual (supplementary material). Study personnel receive training in study procedures, including carrying out clinical scale assessment, electronic case report form (eCRF) data registration, and the collection, management, and storage of biospecimens.

Clinical, imaging and molecular data from all centers are registered and stored in a centralized infrastructure, including an eCRF (Viedoc - The New Standard in eClinical Data Management, Viedoc WWW Document (n.d.)), imaging data server (SECTRA PACS for research), and other research servers at Haukeland University Hospital and the University of Bergen). All biological material is stored in the centralized STRAT-PARK biobank organized under The Research Biobank for Aging, Dementia and Neurology at Haukeland University Hospital.

1.6. Statistics

Having no indication of the potential number and size of PD biological subtypes, an informative power calculation cannot be performed. Given the clinical heterogeneity and complexity of PD, it is likely that a large population will be required. STRAT-PARK will dynamically adjust the size of the cohort based on results from the first analyses. Descriptive statistics and data analyses for the cohort demographics presented herein were performed using R version 4.2.2 and RStudio 2022.12.0 Build 353.

1.7. Ethics

The study is conducted in full accordance with the ICH E6 guideline for Good Clinical Practice and the principle of the Declaration of Helsinki, and the laws and regulations of Norway, including the General Data Protection Regulation (GDPR), and Canada. Ethics committees have approved the study in Norway (REK 74985) and Canada (HSREB 115770 and HSREB 114092). All participants must provide informed consent to be included.

1.8. Data sharing

The datasets and code required to reproduce the cohort demographics can be made available upon request to the corresponding author. STRAT-PARK data will be deposited in the European Genome-Phenome Archive (http://ega-archive.org/), a service for permanent archiving and sharing of genetic, phenotypic, and clinical data generated for the purposes of biomedical research. The data will be accessible following an application to the Data Access Committee (DAC). A detailed Data Access Plan is currently being developed and is expected to become available during 2024.

2. Cohort demographics

We present the preliminary and baseline demographics of the participants. As of March 9th, 2023, 252 participants were included in the STRAT-PARK cohort, comprising 204 individuals with PD and 48 healthy controls. Participation percentage for the different examinations is presented in Fig. 2A. The male to female ratio was 1.8:1 for PD patients and 0.5:1 for controls (Fig. 2B). At baseline, the mean age was 66.2 ± 7.9 and 63.1 ± 10.2 for patients and controls respectively (Fig. 2C). The mean age at diagnosis was 61.9 ± 8.8, while the mean age of onset of motor symptoms was approximately 3.5 years earlier, at 58.6 ± 9.1 years (Fig. 2D). PD patients had a mean disease duration of 7.7 ± 5.4 years (Fig. 3A). At baseline, motor phenotypes were defined according to the TD/PIGD classification. Most patients were classified as either postural instability and gait disorder (N = 91) or tremor-dominant (N = 83), while 20 of the patients were characterized as indeterminate (Fig. 3B). The mean MDS-UPDRS III score was 25.4 ± 12.1, and mean Hoehn & Yahr stage was 2.1 ± 0.6 (Fig. 3C and Table 2).

3. Discussion

There is an urgent need for identifying biological subtypes of PD to enable precision medicine and care. The aim of the STRAT-PARK initiative is to establish a cohort database and biobank which can be used to conduct bottom-up, biomarker-based classifications of PD, as well as an in-depth characterization of clinicopathological correlates and environmental factors associated with emerging disease subtypes. To this end, STRAT-PARK aligns with recent recommendations on use of molecular biomarkers, deep phenotyping methods, and data-driven analyses(Dorsey et al., 2020; Fereshtehnejad and Postuma, 2017; Hipp et al., 2018; Mestre et al., 2021; Schalkamp et al., 2022), and has several additional advantages, as outlined below.

The biological samples collected, and molecular data generated in STRAT-PARK have been specifically tailored to allow the assessment of biomarkers reflecting principal processes currently associated with the pathogenesis of PD, such as aberrant proteostasis and mitochondrial dysfunction. At the same time, sample and data collection is broad enough to allow new emerging mechanisms and pathways to be explored.

A unique feature of STRAT-PARK is the inclusion of comprehensive biomarkers of mitochondrial integrity, which will be assessed cross-sectionally and longitudinally, in successive biospecimens of muscle biopsy and platelets, as well as in the patient brain, using 31P-MRS to assess the levels of phosphorylated energy intermediates and metabolites. Furthermore, micro-vascular imaging with ferumoxytol will detect and quantify micro-angiogenic changes which may be associated with mitochondrial dysfunction, similar to that seen in mitochondrial disorders(Reichard and Asosingh, 2019), and/or neuroinflammation(Desai Bradaric et al., 2012). *In vivo* assessment of proteinopathy markers will allow the cohort to be stratified based on the composition of proteinopathy, and its longitudinal change in time. This will also allow us to further explore proposed associations between mitochondrial impairment, neuroinflammation and proteinopathy(Fløtnes et al., 2022; Fløtnes and Tzoulis, 2022). Post-mortem neuropathological examination will

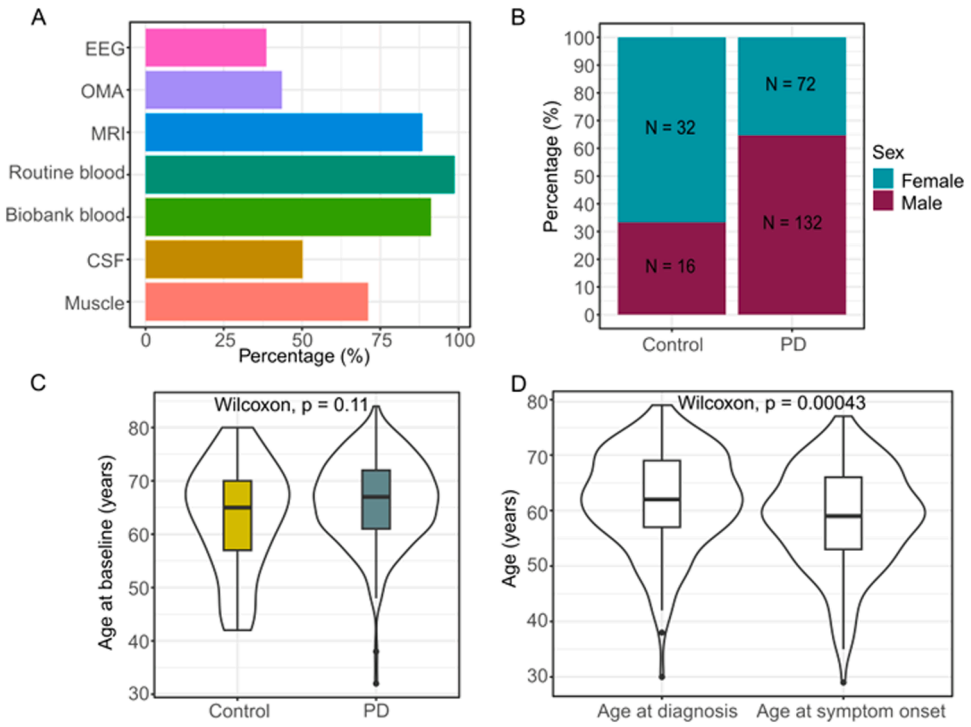

Fig. 2. Demographic data extracted from the baseline visit of the participants in the STRAT-PARK cohort. (A) Bar plot of percentage of participants who have successfully undergone the different examinations. The examinations listed (except for EEG and OMA) are currently being performed at all three sites. "Routine blood" is routine blood samples, and "Biobank blood" is blood samples collected for the biobank. Abbreviations: EEG, Electroencephalogram; OMA, Objective Motor Assessment; MRI, Magnetic Resonance Imaging; CSF, Cerebrospinal Fluid. (B) Bar plot of sex-distribution of the participants. (C) Violin plot of age at baseline (years) for patients and controls. (D) Violin plot of age at diagnosis and age at symptom onset (i.e., age at onset of motor symptoms).

provide the ground truth against which mitochondrial and proteinopathy biomarkers will be validated.

Finally, wearable sensor technology will provide quantitative measures of bradykinesia, tremor, mobility, dyskinesia, gait and axial motor impairments in PD, that are objective and may be more sensitive than clinical scale-based motor assessment(Memar et al., 2018). These assessments will provide multiple high-resolution measures of motor function, which are ideal for data-driven stratification. Moreover, wearable sensors will enable monitoring of physical activity and exercise, which may play an important role in influencing clinical and molecular measures, as well as disease progression(Tsukita et al., 2022).

An additional advantage of the STRAT-PARK initiative is that, thanks to the diverse clinical and molecular measures it provides, it can support recently proposed frameworks for biological classification of PD, including NSD-ISS and SynNeurGe(Höglinger et al., 2024; Simuni et al., 2024).

So far, the STRAT-PARK project has shown satisfactory progress and is well underway to becoming a large international PD cohort. With the current recruitment rate, we expect the cohort to be fully included by 2035. However, data are being continuously curated and the dataset from the first 300 participants is expected to be analysis-ready in June 2024. As expected, healthy controls are more challenging to recruit than patients, and are currently in a ratio of 1:4, rather that the desired 1:3. The sex balance of the cohort is similar to that reported from other cohorts(Marek et al., 2018; Mollenhauer et al., 2013). The cohort is heterogenous in terms of severity of both motor and non-motor symptoms, illustrated, for instance, by substantial variation in the MDS-UPDRS III and MDS-NMS total scores.

Currently, the STRAT-PARK cohort has an overrepresentation of Hoehn & Yahr stage 2, although the range is 0 – 4. As the study progress, we anticipate the distribution of severity stages to become more even, as more newly diagnosed patients are being recruited, and included patients progress. To encourage participation across disease stages, the protocol offers some flexibility, such as declining or withdrawing from certain procedures (i.e. muscle biopsy, lumbar puncture, and MRI). Furthermore, at the Norwegian sites all clinical assessment is conducted in the "ON" state, which may be of benefit to patients with advanced disease. The study has an active patient and public involvement (PPI) component and collaborated closely with patient associations and family physicians' networks to reach patients of all disease stages.

The STRAT-PARK study has several limitations. Cognitive function is only tested using MoCA, which makes it difficult to thoroughly characterize the cognitive impairment of the participants. Olfaction is evaluated using B-SIT, which is currently not used in any of the largest PD cohorts (e.g. Parkinson Progression Marker Initiative (PPMI) uses UPSIT(Marek et al., 2011) and Oxford Parkinson Disease Center (OPDC) discovery cohort uses Sniffin' Sticks(Szewczyk-Krolikowski et al., 2014)). Additionally, the sensitivity to diagnose olfactory dysfunction is lower for B-SIT than UPSIT(Doty et al., 1996). However, it has the advantage of being easy and quick to administer, valid in cross-cultural settings and it is possible to convert UPSIT scores to B-SIT scores(Lawton et al., 2016). The fact that patients are primarily tested in the "ON" state minimize discomfort, but also presents challenges in assessing the impact of dopaminergic treatment on the MDS-UPDRS III score. Nonetheless, evaluating motor function in the "ON" state is likely to provide a more accurate reflection of how patients are typically monitored in real-world scenarios. This may be of value when translating our findings to clinical practice.

In conclusion, currently, there is no consensus on how to subtype PD (Albrecht et al., 2022) and most existing classification systems rely on clinical features alone, which provide no insight into molecular pathogenesis and therapeutic targets. Achieving molecular stratification of PD could change our understanding of the disease, from that of a highly heterogeneous clinically defined syndrome of obscure etiopathogenesis, to specific disease subtypes, each driven by defined molecular processes. Accounting for such subtypes would decrease the complexity and

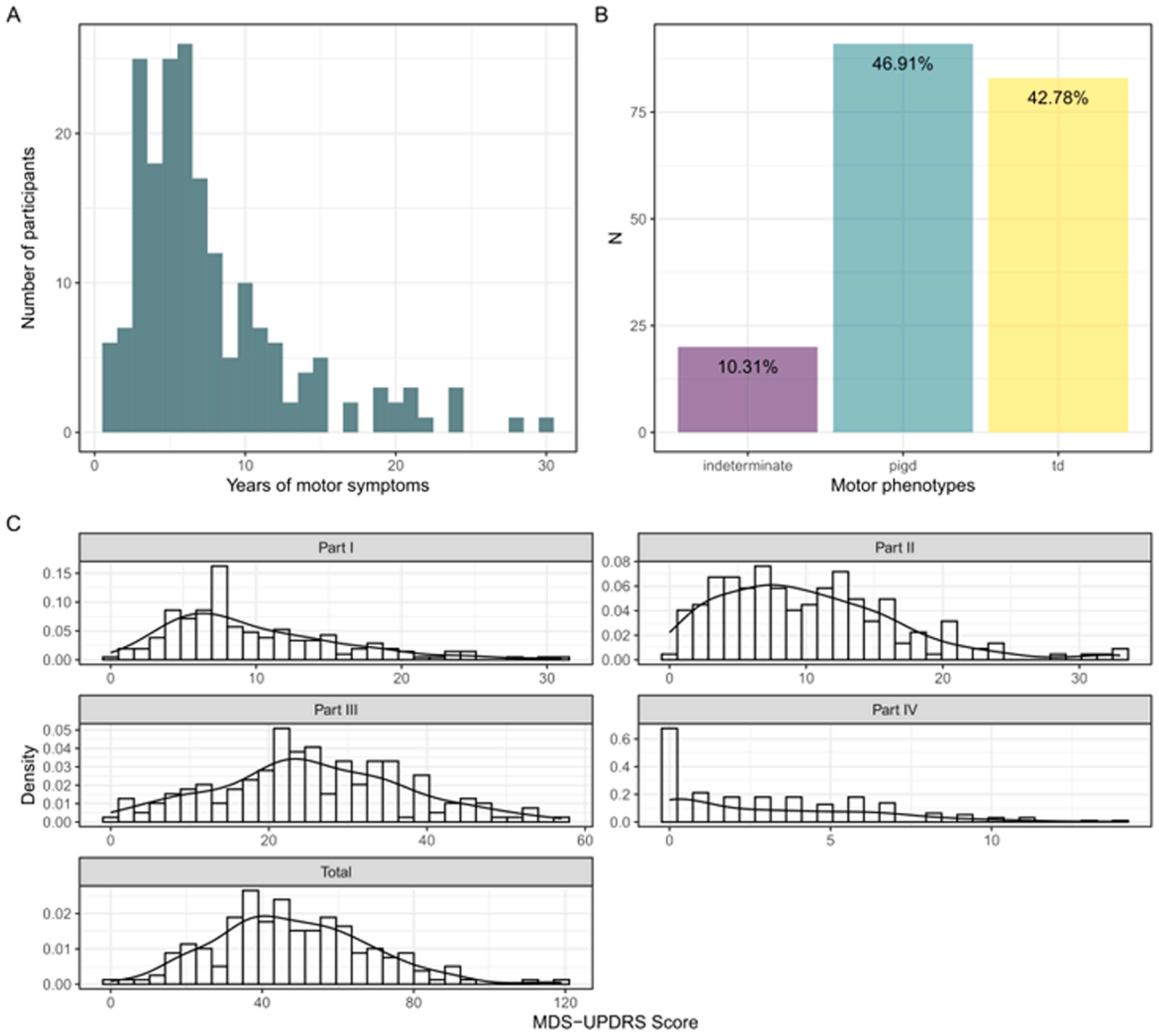

Fig. 3. Duration of motor symptoms, motor phenotype distribution and MDS-UPDRS I-IV results from the STRAT-PARK cohort at baseline. (A) Histogram of duration of motor symptoms (years). (B) Bar plot of distribution of motor phenotype using the TD/PIGD classification. Abbreviations: TD, Tremor Dominant; PIGD, postural instability and gait disorder. (C) Histograms of the MDS-UPDRS scores for part I, II, III, IV and total score. Abbreviations: MDS-UPDRS, International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale.

heterogeneity of the PD spectrum and allow research to focus on pathophysiologically more homogeneous samples and/or cohorts, thereby increasing the signal-to-noise ratio in both mechanistic and treatment studies. Biomarkers of mechanistically defined PD subtypes would allow for selecting patients for trials of targeted therapy, ultimately increasing the likelihood of positive outcome.

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Table 2
Cohort characteristics.

Variable	Group	Mean	Standard deviation	Range
Age at onset of diagnosis	patient	61.94	8.76	30–79
Age at onset of motor symptoms	patient	58.57	9.13	29–77
B-SIT	control	9.51	2.13	0–11
B-SIT	patient	6.29	2.44	0–12
Hoehn & Yahr stage (taken as part of the MDS-UPDRS)	patient	2.07	0.59	0–4
MDS-NMS non-motor fluctuation score	patient	2.1	7.3	0–66
MDS-NMS total score	patient	68.49	68.09	2–410
MDS-UPDRS I	patient	9.79	6	0–31
MDS-UPDRS II	patient	10.06	6.59	0–33
MDS-UPDRS III	patient	25.38	12.09	0–57
MDS-UPDRS IV	patient	3.11	3.19	0–14
MDS-UPDRS total score	patient	48.32	19.97	4–119
MoCA	control	26.3	2.09	21–30
MoCA	patient	24.76	3.52	13–31
Years of motor symptoms	patient	7.68	5.41	1–30

Abbreviations: B-SIT, Brief Smell Identification Test; MDS-UPDRS, International Parkinson and Movement Disorder Society Unified Parkinson's Disease Rating Scale; MDS-NMS, International Parkinson and Movement Disorder Society Non-Motor Rating Scale; MoCA, Montreal Cognitive Assessment.

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Declaration of Competing Interest

none

Data availability

Data will be made available on request.

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Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.pneurobio.2024.102603.

References

Albrecht, F., Poulakis, K., Freidle, M., Johansson, H., Ekman, U., Volpe, G., Westman, E., Pereira, J.B., Franzén, E., 2022. Unraveling Parkinson's disease heterogeneity using subtypes based on multimodal data. Park. Relat. Disord. 102, 19–29. https://doi.org/10.1016/j.parkreldis.2022.07.014.

Athauda, D., Foltynie, T., 2015. The ongoing pursuit of neuroprotective therapies in Parkinson disease. Nat. Rev. Neurol. 11, 25–40. https://doi.org/10.1038/nrneurol.2014.226.

Berg, D., Borghammer, P., Fereshtehnejad, S.-M., Heinzel, S., Horsager, J., Schaeffer, E., Postuma, R.B., 2021. Prodromal Parkinson disease subtypes — key to understanding heterogeneity. Nat. Rev. Neurol. 17, 349–361. https://doi.org/10.1038/s41582-021-00486-9.

Berg, D., Postuma, R.B., Bloem, B., Chan, P., Dubois, B., Gasser, T., Goetz, C.G., Halliday, G.M., Hardy, J., Lang, A.E., Litvan, I., Marek, K., Obeso, J., Oertel, W., Olanow, C.W., Poewe, W., Stern, M., Deuschl, G., 2014. Time to redefine PD? Introductory statement of the MDS task force on the definition of Parkinson's disease: time to redefine PD. Mov. Disord. 29, 454–462. https://doi.org/10.1002/mds.25844.

Bloem, B.R., Okun, M.S., Klein, C., 2021. Parkinson's disease. Lancet 397, 2284–2303. https://doi.org/10.1016/S0140-6736(21)00218-X.

Boutsen, F.R., Park, E., Dvorak, J.D., 2023. An efficacy study of voice quality using cepstral analyses of phonation in Parkinson's disease before and after SPEAK-OUT! ®. Folia Phoniatr. Et. Logop. 75, 35–42. https://doi.org/10.1159/000525884.

Brakedal, B., Dölle, C., Riemer, F., Ma, Y., Nido, G.S., Skeie, G.O., Craven, A.R., Schwarzlmüller, T., Brekke, N., Diab, J., Sverkeli, L., Skjeie, V., Varhaug, K., Tysnes, O.-B., Peng, S., Haugarvoll, K., Ziegler, M., Grüner, R., Eidelberg, D., Tzoulis, C., 2022. The NADPARK study: a randomized phase I trial of nicotinamide riboside supplementation in Parkinson's disease. e6 Cell Metab. 34, 396–407. https://doi.org/10.1016/j.cmet.2022.02.001.

Buch, S., Wang, Y., Park, M.-G., Jella, P.K., Hu, J., Chen, Y., Shah, K., Ge, Y., Haacke, E. M., 2020. Subvoxel vascular imaging of the midbrain using USPIO-Enhanced MRI. Neuroimage 220, 117106. https://doi.org/10.1016/j.neuroimage.2020.117106.

Camacho, M., Greenland, J.C., Williams-Gray, C.H., 2021. The gastrointestinal dysfunction scale for Parkinson's disease. Mov. Disord. 36, 2358–2366. https://doi.org/10.1002/mds.28675.

Campbell, M.C., Myers, P.S., Weigand, A.J., Foster, E.R., Cairns, N.J., Jackson, J.J., Lessov-Schlaggar, C.N., Perlmutter, J.S., 2020. Parkinson disease clinical subtypes: key features & clinical milestones. Ann. Clin. Transl. Neurol. 7, 1272–1283. https://doi.org/10.1002/acn3.51102.

Chaudhuri, K.R., Schrag, A., Weintraub, D., Rizos, A., Rodriguez-Blazquez, C., Mamikonyan, E., Martinez-Martin, P., 2020. The movement disorder society nonmotor rating scale: initial validation study. Mov. Disord. 35, 116–133. https://doi.org/10.1002/mds.27862.

Chen, Y., Liu, S., Wang, Y., Kang, Y., Haacke, E.M., 2018. STrategically Acquired gradient echo (STAGE) imaging, part I: creating enhanced T1 contrast and standardized susceptibility weighted imaging and quantitative susceptibility mapping. Magn. Reson Imaging 46, 130–139. https://doi.org/10.1016/j.mri.2017.10.005.

Chen, C., Turnbull, D.M., Reeve, A.K., 2019. Mitochondrial dysfunction in Parkinson's disease—cause or consequence? Biology 8, 38. https://doi.org/10.3390/biology8020038.

Chen-Plotkin, A.S., Albin, R., Alcalay, R., Babcock, D., Bajaj, V., Bowman, D., Buko, A., Cedarbaum, J., Chelsky, D., Cookson, M.R., Dawson, T.M., Dewey, R., Foroud, T., Frasier, M., German, D., Gwinn, K., Huang, X., Kopil, C., Kremer, T., Lasch, S., Marek, K., Marto, J.A., Merchant, K., Mollenhauer, B., Naito, A., Potashkin, J., Reimer, A., Rosenthal, L.S., Saunders-Pullman, R., Scherzer, C.R., Sherer, T., Singleton, A., Sutherland, M., Thiele, I., van der Brug, M., Van Keuren-Jensen, K., Vaillancourt, D., Walt, D., West, A., Zhang, J., 2018. Finding useful biomarkers for Parkinson's disease. Sci. Transl. Med. 10, eaam6003 https://doi.org/10.1126/scitranslmed.aam6003.

De Kloe, Y.J.R., Hooge, I.T.C., Kemner, C., Niehorster, D.C., Nyström, M., Hessels, R.S., 2022. Replacing eye trackers in ongoing studies: a comparison of eye-tracking data quality between the Tobii Pro TX300 and the Tobii Pro spectrum. Infancy 27, 25–45. https://doi.org/10.1111/infa.12441.

Desai Bradaric, B., Patel, A., Schneider, J.A., Carvey, P.M., Hendey, B., 2012. Evidence for angiogenesis in Parkinson's disease, incidental Lewy body disease, and

progressive supranuclear palsy. J. Neural Transm. 119, 59–71. https://doi.org/10.1007/s00702-011-0684-8.
Dickson, D.W., 2012. Parkinson's Disease and parkinsonism: neuropathology. a009258–a009258 Cold Spring Harb. Perspect. Med. 2. https://doi.org/10.1101/cshperspect.a009258.
Dölle, C., Flønes, I., Nido, G.S., Miletic, H., Osuagwu, N., Kristoffersen, S., Lilleng, P.K., Larsen, J.P., Tysnes, O.-B., Haugarvoll, K., Bindoff, L.A., Tzoulis, C., 2016. Defective mitochondrial DNA homeostasis in the substantia nigra in Parkinson disease. Nat. Commun. 7, 13548 https://doi.org/10.1038/ncomms13548.
Dorsey, E.R., Omberg, L., Waddell, E., Adams, J.L., Adams, R., Ali, M.R., Amodeo, K., Arky, A., Augustine, E.F., Dinesh, K., Hoque, M.E., Glidden, A.M., Jensen-Roberts, S., Kabelac, Z., Katabi, D., Kieburtz, K., Kinel, D.R., Little, M.A., Lizarraga, K.J., Myers, T., Riggare, S., Rosero, S.Z., Saria, S., Schifitto, G., Schneider, R.B., Sharma, G., Shoulson, I., Stevenson, E.A., Tarolli, C.G., Luo, J., McDermott, M.P., 2020. Deep phenotyping of Parkinson's disease. JPD 10, 855–873. https://doi.org/10.3233/JPD-202006.
Doty, R.L., Marcus, A., William Lee, W., 1996. Development of the 12-Item cross-cultural smell identification test(CC-SIT). Laryngoscope 106, 353–356. https://doi.org/10.1097/00005537-199603000-00021.
Erro, R., Picillo, M., Scannapieco, S., Cuoco, S., Pellecchia, M.T., Barone, P., 2020. The role of disease duration and severity on novel clinical subtypes of Parkinson disease. Park. Relat. Disord. 73, 31–34. https://doi.org/10.1016/j.parkreldis.2020.03.013.
Espay, A.J., Brundin, P., Lang, A.E., 2017a. Precision medicine for disease modification in Parkinson disease. Nat. Rev. Neurol. 13, 119–126. https://doi.org/10.1038/nrneurol.2016.196.
Espay, A.J., Schwarzschild, M.A., Tanner, C.M., Fernandez, H.H., Simon, D.K., Leverenz, J.B., Merola, A., Chen-Plotkin, A., Brundin, P., Kauffman, M.A., Erro, R., Kieburtz, K., Woo, D., Macklin, E.A., Standaert, D.G., Lang, A.E., 2017b. Biomarker-driven phenotyping in Parkinson disease: a translational missing link in disease-modifying clinical trials. Mov. Disord. 32, 319–324. https://doi.org/10.1002/mds.26913.
Fereshtehnejad, S.-M., Postuma, R.B., 2017. Subtypes of Parkinson's disease: what do they tell us about disease progression? Curr. Neurol. Neurosci. Rep. 17, 34. https://doi.org/10.1007/s11910-017-0738-x.
Fereshtehnejad, S.M., Romenets, S.R., Anang, J.B., Latreille, V., Gagnon, J.F., Postuma, R.B., 2015. New clinical subtypes of Parkinson disease and their longitudinal progression: a prospective cohort comparison with other phenotypes. JAMA Neurol. 72, 863–873. https://doi.org/10.1001/jamaneurol.2015.0703.
Flønes, I.H., Fernandez-Vizarra, E., Lykouri, M., Brakedal, B., Skeie, G.O., Miletic, H., Lilleng, P.K., Alves, G., Tysnes, O.-B., Haugarvoll, K., Dölle, C., Zeviani, M., Tzoulis, C., 2018. Neuronal complex I deficiency occurs throughout the Parkinson's disease brain, but is not associated with neurodegeneration or mitochondrial DNA damage. Acta Neuropathol. 135, 409–425. https://doi.org/10.1007/s00401-017-1794-7.
Flønes, I.H., Nyland, H., Sandnes, D.-A., Alves, G.W., Tysnes, O.-B., Tzoulis, C., 2022. Early forms of α-synuclein pathology are associated with neuronal complex i deficiency in the substantia nigra of individuals with Parkinson's disease. Biomolecules 12, 747. https://doi.org/10.3390/biom12060747.
Flønes, I.H., Tzoulis, C., 2022. Mitochondrial respiratory chain dysfunction—a hallmark pathology of idiopathic Parkinson's disease?, 874596 Front. Cell Dev. Biol. 10. https://doi.org/10.3389/fcell.2022.874596.
Foltynie, T., Brayne, C., Barker, R.A., 2002. The heterogeneity of idiopathic Parkinson's disease. J. Neurol. 249, 138–145. https://doi.org/10.1007/PL00007856.
Gibbons, C.H., Schmidt, P., Biaggioni, I., Frazier-Mills, C., Freeman, R., Isaacson, S., Karabin, B., Kuritzky, L., Lew, M., Low, P., Mehdirad, A., Raj, S.R., Vernino, S., Kaufmann, H., 2017. The recommendations of a consensus panel for the screening, diagnosis, and treatment of neurogenic orthostatic hypotension and associated supine hypertension. J. Neurol. 264, 1567–1582. https://doi.org/10.1007/s00415-016-8375-x.
Goetz, C.G., Tilley, B.C., Shaftman, S.R., Stebbins, G.T., Fahn, S., Martinez-Martin, P., Poewe, W., Sampaio, C., Stern, M.B., Dodel, R., Dubois, B., Holloway, R., Jankovic, J., Kulisevsky, J., Lang, A.E., Lees, A., Leurgans, S., LeWitt, P.A., Nyenhuis, D., Olanow, C.W., Rascol, O., Schrag, A., Teresi, J.A., van Hilten, J.J., LaPelle, N., 2008. Movement disorder society-sponsored revision of the unified Parkinson's disease rating scale (MDS-UPDRS): scale presentation and clinimetric testing results: MDS-UPDRS: clinimetric assessment. Mov. Disord. 23, 2129–2170. https://doi.org/10.1002/mds.22340.
Greenland, J.C., Williams-Gray, C.H., Barker, R.A., 2019. The clinical heterogeneity of Parkinson's disease and its therapeutic implications. Eur. J. Neurosci. 49, 328–338. https://doi.org/10.1111/ejn.14094.
Halliday, G.M., McCann, H., 2010. The progression of pathology in Parkinson's disease. Ann. N. Y. Acad. Sci. 1184, 188–195. https://doi.org/10.1111/j.1749-6632.2009.05118.x.
He, N., Chen, Y., LeWitt, P.A., Yan, F., Haacke, E.M., 2023. Application of Neuromelanin MR imaging in Parkinson disease. J. Magn. Reson Imaging 57, 337–352. https://doi.org/10.1002/jmri.28414.
He, N., Ghassaban, K., Huang, P., Jokar, M., Wang, Y., Cheng, Z., Jin, Z., Li, Y., Sethi, S. K., He, Y., Chen, Y., Gharabaghi, S., Chen, S., Yan, F., Haacke, E.M., 2021. Imaging iron and neuromelanin simultaneously using a single 3D gradient echo magnetization transfer sequence: combining neuromelanin, iron and the nigrosome-1 sign as complementary imaging biomarkers in early stage Parkinson's disease. Neuroimage 230, 117810. https://doi.org/10.1016/j.neuroimage.2021.117810.
Herdman, M., Gudex, C., Lloyd, A., Janssen, Mf, Kind, P., Parkin, D., Bonsel, G., Badia, X., 2011. Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D–5L). Qual. Life Res. 20, 1727–1736. https://doi.org/10.1007/s11136-011-9903-x.
Hipp, G., Vaillant, M., Diederich, N.J., Roomp, K., Satagopam, V.P., Banda, P., Sandt, E., Mommaerts, K., Schmitz, S.K., Longhino, L., Schweicher, A., Hanff, A.-M., Nicolai, B., Kolber, P., Reiter, D., Pavelka, L., Binck, S., Pauly, C., Geffers, L., Betsou, F., Gantenbein, M., Klucken, J., Gasser, T., Hu, M.T., Balling, R., Krüger, R., 2018. The luxembourg parkinson's study: a comprehensive approach for stratification and early diagnosis. Front. Aging Neurosci. 10, 326. https://doi.org/10.3389/fnagi.2018.00326.
Hirsch, E.C., Hunot, S., 2009. Neuroinflammation in Parkinson's disease: a target for neuroprotection? Lancet Neurol. 8, 382–397. https://doi.org/10.1016/S1474-4422(09)70062-6.
Höglinger, G.U., Adler, C.H., Berg, D., Klein, C., Outeiro, T.F., Poewe, W., Postuma, R., Stoessl, A.J., Lang, A.E., 2024. A biological classification of Parkinson's disease: the SynNeurGe research diagnostic criteria. Lancet Neurol. 23, 191–204. https://doi.org/10.1016/S1474-4422(23)00404-0.
Horsager, J., Andersen, K.B., Knudsen, K., Skjærbæk, C., Fedorova, T.D., Okkels, N., Schaeffer, E., Bonkat, S.K., Geday, J., Otto, M., Sommerauer, M., Danielsen, E.H., Bech, E., Kraft, J., Munk, O.L., Hansen, S.D., Pavese, N., Göder, R., Brooks, D.J., Berg, D., Borghammer, P., 2020. Brain-first versus body-first Parkinson's disease: a multimodal imaging case-control study. Brain 143, 3077–3088. https://doi.org/10.1093/brain/awaa238.
Jankovic, J., McDermott, M., Carter, J., Gauthier, S., Goetz, C., Golbe, L., Huber, S., Koller, W., Olanow, C., Shoulson, I., et al., 1990. Variable expression of Parkinson's disease: a base-line analysis of the DATATOP cohort. The Parkinson study group. Neurology 40, 1529–1534.
Kalia, L.V., Lang, A.E., 2015. Parkinson's disease. Lancet 386, 896–912. https://doi.org/10.1016/S0140-6736(14)61393-3.
Lawton, M., Hu, M.T.M., Baig, F., Ruffmann, C., Barron, E., Swallow, D.M.A., Malek, N., Grosset, K.A., Bajaj, N., Barker, R.A., Williams, N., Burn, D.J., Foltynie, T., Morris, H. R., Wood, N.W., May, M.T., Grosset, D.G., Ben-Shlomo, Y., 2016. Equating scores of the university of pennsylvania smell identification test and sniffin' sticks test in patients with Parkinson's disease. Park. Relat. Disord. 33, 96–101. https://doi.org/10.1016/j.parkreldis.2016.09.023.
Lehtonen, J.M., Forsström, S., Bottani, E., Viscomi, C., Baris, O.R., Isoniemi, H., Höckerstedt, K., Österlund, P., Hurme, M., Jylhävä, J., Leppä, S., Markkula, R., Heliö, T., Mombelli, G., Uusimaa, J., Laaksonen, R., Laaksovirta, H., Auranen, M., Zeviani, M., Smeitink, J., Wiesner, R.J., Nakada, K., Isohanni, P., Suomalainen, A., 2016. FGF21 is a biomarker for mitochondrial translation and mtDNA maintenance disorders. Neurology 87, 2290–2299. https://doi.org/10.1212/WNL.0000000000003374.
Liu, S., Brisset, J.C., Hu, J., Haacke, E.M., Ge, Y., 2018. Susceptibility weighted imaging and quantitative susceptibility mapping of the cerebral vasculature using ferumoxytol. J. Magn. Reson Imaging 47, 621–633. https://doi.org/10.1002/jmri.25809.
Liu, Y., Li, J., He, N., Chen, Y., Jin, Z., Yan, F., Haacke, E.M., 2020. Optimizing neuromelanin contrast in the substantia nigra and locus coeruleus using a magnetization transfer contrast prepared 3D gradient recalled echo sequence. Neuroimage 218, 116935. https://doi.org/10.1016/j.neuroimage.2020.116935.
Marek, K., Chowdhury, S., Siderowf, A., Lasch, S., Coffey, C.S., Caspell-Garcia, C., Simuni, T., Jennings, D., Tanner, C.M., Trojanowski, J.Q., Shaw, L.M., Seibyl, J., Schuff, N., Singleton, A., Kieburtz, K., Toga, A.W., Mollenhauer, B., Galasko, D., Chahine, L.M., Weintraub, D., Foroud, T., Tosun-Turgut, D., Poston, K., Arnedo, V., Frasier, M., Sherer, T., 2018. The Parkinson's progression markers initiative (PPMI) - establishing a PD biomarker cohort. Parkinson's Progression Markers Initiative Ann. Clin. Transl. Neurol. 5, 1460–1477. https://doi.org/10.1002/acn3.644.
Marek, K., Jennings, D., Lasch, S., Siderowf, A., Tanner, C., Simuni, T., Coffey, C., Kieburtz, K., Flagg, E., Chowdhury, S., Poewe, W., Mollenhauer, B., Klinik, P.-E., Sherer, T., Frasier, M., Meunier, C., Rudolph, A., Casaceli, C., Seibyl, J., Mendick, S., Schuff, N., Zhang, Y., Toga, A., Crawford, K., Ansbach, A., De Blasio, P., Piovella, M., Trojanowski, J., Shaw, L., Singleton, A., Hawkins, K., Eberling, J., Brooks, Deborah, Russell, D., Leary, L., Factor, S., Sommerfeld, B., Hogarth, P., Pighetti, E., Williams, K., Standaert, D., Guthrie, S., Hauser, R., Delgado, H., Jankovic, J., Hunter, C., Stern, M., Tran, B., Leverenz, J., Baca, M., Frank, S., Thomas, C.-A., Richard, I., Deeley, C., Rees, L., Sprenger, F., Lang, E., Shill, H., Obradov, S., Fernandez, H., Winters, A., Berg, D., Gauss, K., Galasko, D., Fontaine, D., Mari, Z., Gerstenhaber, M., Brooks, David, Malloy, S., Barone, P., Longo, K., Comery, T., Ravina, B., Grachev, I., Gallagher, K., Collins, M., Widnell, K.L., Ostrowizki, S., Fontoura, P., Ho, T., Luthman, J., Brug, M. van der, Reith, A.D., Taylor, P., 2011. The Parkinson progression marker initiative (PPMI). Progress in neurobiology. Biol. Markers Neurodegener. Dis. 95, 629–635. https://doi.org/10.1016/j.pneurobio.2011.09.005.
Memar, S., Delrobaei, M., Pieterman, M., McIsaac, K., Jog, M., 2018. Quantification of whole-body bradykinesia in Parkinson's disease participants using multiple inertial sensors. J. Neurol. Sci. 387, 157–165. https://doi.org/10.1016/j.jns.2018.02.001.
Mestre, T.A., Fereshtehnejad, S.-M., Berg, D., Bohnen, N.I., Dujardin, K., Erro, R., Espay, A.J., Halliday, G., van Hilten, J.J., Hu, M.T., Jeon, B., Klein, C., Leentjens, A. F.G., Marinus, J., Mollenhauer, B., Postuma, R., Rajalingam, R., Rodríguez-Violante, M., Simuni, T., Surmeier, D.J., Weintraub, D., McDermott, M.P., Lawton, M., Marras, C., 2021. Parkinson's disease subtypes: critical appraisal and recommendations. JPD 11, 395–404. https://doi.org/10.3233/JPD-202472.
Mollenhauer, B., Trautmann, E., Sixel-Döring, F., Wicke, T., Ebentheuer, J., Schaumburg, M., Lang, E., Focke, N.K., Kumar, K.R., Lohmann, K., Klein, C., Schlossmacher, M.G., Kohnen, R., Friede, T., Trenkwalder, C., 2013. Nonmotor and diagnostic findings in subjects with de novo Parkinson disease of the DeNoPa cohort (DeNoPa Study Group). Neurology 81, 1226–1234. https://doi.org/10.1212/WNL.0b013e3182a6cbd5.

Nasreddine, Z.S., Phillips, N.A., Bédirian, V., Charbonneau, S., Whitehead, V., Collin, I., Cummings, J.L., Chertkow, H., 2005. The montreal cognitive assessment, MoCA: a brief screening tool for mild cognitive impairment. J. Am. Geriatr. Soc. 53, 695–699. https://doi.org/10.1111/j.1532-5415.2005.53221.x.

Postuma, R.B., Berg, D., Stern, M., Poewe, W., Olanow, C.W., Oertel, W., Obeso, J., Marek, K., Litvan, I., Lang, A.E., Halliday, G., Goetz, C.G., Gasser, T., Dubois, B., Chan, P., Bloem, B.R., Adler, C.H., Deuschl, G., 2015. MDS clinical diagnostic criteria for Parkinson's disease. Mov. Disord. Off. J. Mov. Disord. Soc. 30, 1591–1601. https://doi.org/10.1002/mds.26424.

Postuma, R.B., Berg, D., 2017. The new diagnostic criteria for Parkinson's disease. Int Rev. Neurobiol. 132 55–78. https://doi.org/10.1016/bs.irn.2017.01.008.

Qian, E., Huang, Y., 2019. Subtyping of Parkinson's disease - where are we up to? Aging Dis. 10, 1130–1139. https://doi.org/10.14336/AD.2019.0112.

Reichard, A., Asosingh, K., 2019. The role of mitochondria in angiogenesis. Mol. Biol. Rep. 46, 1393–1400. https://doi.org/10.1007/s11033-018-4488-x.

Ren, J., Zhang, R., Pan, C., Xu, J., Sun, H., Hua, P., Zhang, L., Zhang, W., Xu, P., Ma, C., Liu, W., 2022. Prevalence and genotype–phenotype correlations of GBA-related Parkinson disease in a large Chinese cohort. Eur. J. Neurol. 29, 1017–1024. https://doi.org/10.1111/ene.15230.

Rodríguez-Violante, M., Cervantes-Arriaga, A., Fahn, S., Tolosa, E., 2017. Two-hundred years later: Is Parkinson's disease a single defined entity? RIC 69, 129. https://doi.org/10.24875/RIC.17002291.

van Rooden, S.M., Colas, F., Martínez-Martín, P., Visser, M., Verbaan, D., Marinus, J., Chaudhuri, R.K., Kok, J.N., van Hilten, J.J., 2011. Clinical subtypes of Parkinson's disease. Mov. Disord. 26, 51–58. https://doi.org/10.1002/mds.23346.

Schalkamp, A.-K., Rahman, N., Monzón-Sandoval, J., Sandor, C., 2022. Deep phenotyping for precision medicine in Parkinson's disease. Dis. Models Mech. 15, dmm049376 https://doi.org/10.1242/dmm.049376.

Siderowf, A., Concha-Marambio, L., Lafontant, D.-E., Farris, C.M., Ma, Y., Urenia, P.A., Nguyen, H., Alcalay, R.N., Chahine, L.M., Foroud, T., Galasko, D., Kieburtz, K., Merchant, K., Mollenhauer, B., Poston, K.L., Seibyl, J., Simuni, T., Tanner, C.M., Weintraub, D., Videnovic, A., Choi, S.H., Kurth, R., Caspell-Garcia, C., Coffey, C.S., Frasier, M., Oliveira, L.M.A., Hutten, S.J., Sherer, T., Marek, K., Soto, C., 2023. Assessment of heterogeneity among participants in the Parkinson's progression markers initiative cohort using α-synuclein seed amplification: a cross-sectional study. Lancet Neurol. 22, 407–417. https://doi.org/10.1016/S1474-4422(23)00109-6.

Simuni, T., Chahine, L.M., Poston, K., Brumm, M., Buracchio, T., Campbell, M., Chowdhury, S., Coffey, C., Concha-Marambio, L., Dam, T., DiBiaso, P., Foroud, T., Frasier, M., Gochanour, C., Jennings, D., Kieburtz, K., Kopil, C.M., Merchant, K., Mollenhauer, B., Montine, T., Nudelman, K., Pagano, G., Seibyl, J., Sherer, T., Singleton, A., Stephenson, D., Stern, M., Soto, C., Tanner, C.M., Tolosa, E., Weintraub, D., Xiao, Y., Siderowf, A., Dunn, B., Marek, K., 2024. A biological definition of neuronal α-synuclein disease: towards an integrated staging system for research. Lancet Neurol. 23, 178–190. https://doi.org/10.1016/S1474-4422(23)00405-2.

Stiasny-Kolster, K., Mayer, G., Schäfer, S., Möller, J.C., Heinzel-Gutenbrunner, M., Oertel, W.H., 2007. The REM sleep behavior disorder screening questionnaire–a new diagnostic instrument. Mov. Disord. 22, 2386–2393. https://doi.org/10.1002/mds.21740.

Subrahmanian, N., LaVoie, M.J., 2021. Is there a special relationship between complex I activity and nigral neuronal loss in Parkinson's disease? A critical reappraisal. Brain Res., 147434 https://doi.org/10.1016/j.brainres.2021.147434.

Szewczyk-Krolikowski, K., Tomlinson, P., Nithi, K., Wade-Martins, R., Talbot, K., Ben-Shlomo, Y., Hu, M.T.M., 2014. The influence of age and gender on motor and non-motor features of early Parkinson's disease: initial findings from the Oxford Parkinson disease center (OPDC) discovery cohort. Park. Relat. Disord. 20, 99–105. https://doi.org/10.1016/j.parkreldis.2013.09.025.

Thenganatt, M.A., Jankovic, J., 2014. Parkinson disease subtypes. JAMA Neurol. 71, 499–504. https://doi.org/10.1001/jamaneurol.2013.6233.

Trenkwalder, C., Kohnen, R., Högl, B., Metta, V., Sixel-Döring, F., Frauscher, B., Hülsmann, J., Martinez-Martin, P., Chaudhuri, K.R., 2011. Parkinson's disease sleep scale–validation of the revised version PDSS-2. Mov. Disord. 26, 644–652. https://doi.org/10.1002/mds.23476.

Tsukita, K., Sakamaki-Tsukita, H., Takahashi, R., 2022. Long-term effect of regular physical activity and exercise habits in patients with early Parkinson disease. Neurology 98. https://doi.org/10.1212/WNL.0000000000013218.

Viedoc - The New Standard in eClinical Data Management | Viedoc [WWW Document], n.d. URL ⟨https://www.viedoc.com/⟩ (accessed 6.28.23).

Visser, M., Marinus, J., Stiggelbout, A.M., Van Hilten, J.J., 2004. Assessment of autonomic dysfunction in Parkinson's disease: the SCOPA-AUT. Mov. Disord. 19, 1306–1312. https://doi.org/10.1002/mds.20153.

Wang, Yu, Chen, Y., Wu, D., Wang, Ying, Sethi, S.K., Yang, G., Xie, H., Xia, S., Haacke, E. M., 2018. STrategically acquired gradient echo (STAGE) imaging, part II: correcting for RF inhomogeneities in estimating T1 and proton density. Magn. Reson Imaging 46, 140–150. https://doi.org/10.1016/j.mri.2017.10.006.

Yao, X., Wang, D., Zhang, L., Wang, L., Zhao, Z., Chen, S., Wang, X., Yue, T., Liu, Y., 2017. Serum growth differentiation factor 15 in Parkinson disease. Neurodegener. Dis. 17, 251–260. https://doi.org/10.1159/000477349.

Yatsuga, S., Fujita, Y., Ishii, A., Fukumoto, Y., Arahata, H., Kakuma, T., Kojima, T., Ito, M., Tanaka, M., Saiki, R., Koga, Y., 2015. Growth differentiation factor 15 as a useful biomarker for mitochondrial disorders. Ann. Neurol. 78, 814–823. https://doi.org/10.1002/ana.24506.

Zampieri, S., Cattarossi, S., Bembi, B., Dardis, A., 2017. GBA analysis in next-generation era: pitfalls, challenges, and possible solutions. J. Mol. Diagn. 19, 733–741. https://doi.org/10.1016/j.jmoldx.2017.05.005.