PROTOCOL

Title: The Parkinson's Progression Markers Initiative (PPMI) Clinical - Establishing a Deeply Phenotyped PD Cohort

Sponsor: The Michael J. Fox Foundation for Parkinson's Research

Principal Investigator: Kenneth Marek, MD

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The Parkinson's Progression Markers Initiative (PPMI) Clinical

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1 PURPOSE OF STUDY

The Parkinson Progression Marker Initiative (PPMI) is a longitudinal, observational, multi-center natural history study to assess progression of clinical features, digital outcomes, and imaging, biologic and genetic markers of Parkinson's disease (PD) progression in study participants with manifest PD, prodromal PD, and healthy controls. The overall goal of PPMI is to identify markers of disease progression for use in clinical trials of therapies to reduce progression of PD disability.

PPMI is a broad program, expanding the goals of the original PPMI study, that includes this PPMI Clinical protocol, as well as other program initiatives to screen for eligible Clinical study participants, and digital and online studies, to enrich the PPMI database with self-reported participant information, which when combined with the clinical information will enable researchers to better understand and identify early signs of individuals who may be at risk for developing PD and PD progression. Participants in PPMI may be asked to be enrolled in multiple PPMI program protocols and depending on their method of recruitment, participants may be enrolled in varying order, as appropriate. PPMI participants may also be asked to participate in additional PPMI program initiatives (as they are developed), which may only involve a subset of PPMI participants based on information including their cohort designation, and/or site location.

1.1 Primary Objectives of PPMI Clinical

The primary objectives include to:

a. Establish standardized protocols for acquisition, transfer and analysis of clinical, digital, imaging, biologic and genetic data that can be used by the PD research community. This protocol will build on the existing PPMI infrastructure.
b. Develop a comprehensive and uniformly acquired clinical, digital and imaging dataset and repository of biological and genetic samples that would be available to the PD research community to test hypotheses of the underlying molecular pathobiology of PD, enable modeling of PD progression to identify clinical and/or data driven PD progression sub-sets, and inform studies testing PD therapeutics (for examples, clinical trials targeting synuclein, LRRK2, GBA as well as other targets)
c. Use clinical and biological data to estimate the mean rates of change and the variability around the mean of clinical, digital, imaging, biological and genetic outcomes in study participants with PD diagnosis (including patients with a LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and individuals with prodromal Parkinson's disease (including individuals with REM sleep behavior disorder (RBD)), olfactory loss, LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and/or other risk factors for PD with and without dopamine transporter (DAT) deficit and in healthy participants.
d. Confirm existing and identify novel clinical, digital, imaging, biologic and genetic PD progression markers to identify quantitative individual measures or combinations of measures that demonstrate optimum interval change in study participants with PD diagnosis (including patients with a LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1)) and individuals with prodromal Parkinson's disease (including individuals with RBD, olfactory loss, a LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and/or other risk

factors for PD with and without DAT deficit in comparison to healthy controls or in sub-sets of study participants with PD diagnosis or prodromal PD defined by baseline assessments, progression milestones and/or rate of clinical, digital, imaging, biologic and genetic change, or other measures.

e. Evaluate the probability of phenoconversion to clinical characteristics of PD for individuals with prodromal PD enrolled in the prodromal cohorts (including individuals with RBD, olfactory loss, a LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and/ or other risk factors for PD with and without DAT deficit).

1.2 Secondary Objectives

The secondary objectives include the following:

a. Conduct preliminary clinical, digital, imaging, biologic and genetic markers verification studies on promising biological markers in study subsets and/or using stored collected samples.
b. Compare biomarker signatures for study participants with PD diagnosis without known genetic variant to those with known genetic variant (including LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1)).
c. Compare biomarker signatures in study participants with PD diagnosis to individuals with prodromal PD enrolled in the prodromal cohorts (including individuals with RBD, olfactory loss, LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and/or other risk factors for PD with and without DAT deficit).
d. Compare biomarker signature between prodromal PD subsets including individuals with RBD, olfactory loss, LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and/or other risk factors for PD with and without DAT deficit.
e. Develop and test risk paradigms to establish the sequence of early prodromal events (clinical, imaging, biologic changes) in individuals with prodromal PD enrolled in the prodromal cohorts (including individuals with RBD, olfactory loss, LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1) and/or other risk factors for PD with and without DAT deficit) including testing early signal of risk in the associated PPMI program studies.

2 STUDY OUTCOMES

Key PPMI outcomes will be longitudinal change in clinical (motor and non-motor) scales (e.g., MDS-UPDRS, MoCA), Patient Reported Outcomes (PROs) and digital outcomes, quantitative imaging (DAT, SBR, and MRI midbrain melanin), and biologic measures of synuclein, lysosomal function, and analytes related to neurodegeneration (e.g., neurofilament light chain inflammation). Detailed demographic, clinical and biological data will be collected to test specific hypotheses in subsequent analyses and other associated protocols. In addition, data quality metrics including compliance with study procedures, quality metrics related to biosamples, and completeness of data collection will be monitored on an ongoing basis.

3 BACKGROUND AND RATIONALE

3.1 Background for PPMI Clinical

The defining motor features of Parkinson's disease (PD) are characterized by their insidious onset and inexorable but heterogenous progression. Reliable and well-validated biomarkers to monitor PD progression would dramatically accelerate research into both PD etiology and therapeutics. Much progress has been made in identifying and assessing PD biomarkers, and yet no fully validated biomarker or set of biomarkers for PD are currently available. Nonetheless there is increasing evidence that assessment of clinical, digital, imaging outcomes and measurement of analytes from blood, cerebral spinal fluid (CSF), urine, and tissue has already begun to provide crucial tools for PD drug development and for understanding the pathobiology of PD (1-3).

Since 2010, the PPMI study has established a longitudinal clinical and biomarker data resource on approximately 3,175 participants including cohorts with idiopathic PD, PD with genetic variants, prodromal participants and healthy controls. PPMI is an observational, international, multi-center study designed to establish biomarker defined cohorts and to identify PD progression biomarkers to improve understanding of disease etiology and course and to provide critical tools to enhance the likelihood of success of PD therapeutic trials (ClinicalTrials.gov NCT01141023). PPMI is a collaborative effort of PD researchers with expertise in biomarker development, PD clinical study design and implementation, bioinformatics, statistics, and data management. The study is a public-private partnership of academic researchers, the Michael J Fox Foundation (MJFF) and pharmaceutical, biotech, government and foundation partners.

The overall goal of PPMI is to examine clinical, imaging, genetic and biospecimen PD progression markers that individually or in combination will rapidly demonstrate interval change in PD patients in comparison to Healthy Controls (HC) or in sub-sets of PD patients defined by baseline assessments, genetic variants, progression milestones and/or rate of clinical, imaging or biospecimen change. PPMI has established standardized protocols for acquisition, transfer, and analysis of clinical, imaging, genetic and biospecimen data that can be used by the PD research community. PPMI is committed to data and biospecimen sharing. PPMI data are available to the research community on the PPMI website as it is collected and there have been more than eighteen million downloads of PPMI data (as of May 2024). PPMI biospecimens are available by application to the PPMI Biospecimen Review Committee with more than four hundred requests, as of May 2024. All PPMI standardized protocols and PPMI data are available at http://www.ppmi-info.org (4, 5).

PPMI is the most comprehensive natural history dataset of PD participants and serves, according to its original purpose, as a key resource for drug development and understanding of the clinical and biological features of PD progression. The study has demonstrated the enormous value of comprehensive, longitudinal within subject biomarker assessment. PPMI has developed a robust study infrastructure with well-developed study leadership and governance, committed enrolling sites, and expert study cores (data, imaging, biorepositories, bioinformatics, genetics) to ensure the ongoing collection and analysis of study data. The study has developed and expanded methods to enroll biomarker defined

cohorts requiring dopamine imaging deficit for inclusion in the PD cohort, piloted methods to establish prodromal cohorts of hyposmic and RBD participants and has established a novel centralized strategy to enroll participants with PD genetic mutations (6-8). PPMI has also demonstrated the feasibility and safety of multicenter longitudinal collection of CSF (9).

PPMI longitudinal data has and continues to be acquired and reported to inform clinical trials for PD. PPMI data has detailed the progression of the MDS-UPDRS (both off and on PD meds) and cognitive and behavioral outcomes enabling sample size estimation to detect changes in progression due to therapeutic intervention (10-12), Predictors of key PPMI outcomes and of need for PD therapy have also been evaluated (13, 14). Progression of dopamine transporter (DAT) imaging has demonstrated a robust reduction in PD participants and PPMI DAT eligibility data has contributed to its qualification by the EMA as an enrichment biomarker (11, 15, 16). Longitudinal analysis of synuclein, amyloid and tau from CSF has demonstrated a persistent reduction in synuclein and tau in PD participants compared to healthy controls but without significant progression (17-19). The alpha synuclein seed amplification (asyn SAA) assay has been validated in PPMI participants leading to a biologic definition of disease and an integrated biologic and clinical staging platform called the NSD-ISS (37, 38). Several other analytes/pathways have also been assessed including neurofilament light chain, catecholamines, and the lysosomal pathway providing additional data (PPMI website) showing modest changes with progression with reports in press.

A key strength of PPMI is the within participant design so that multiple biomarkers are assessed in each participant. This strategy has enabled studies identifying PD subsets based on several biomarkers and has allowed various multi-modal biomarkers to be compared. There have been several efforts to develop biomarker derived subsets of PD to define risk and/or disease progression to further understand the heterogeneity of PD. Combining genetics with clinical and imaging biomarkers has resulted in a genetic risk score that may be helpful in predicting PD and has led to additional studies combining whole genome sequencing, RNA transcriptomics and clinical and imaging markers (20). DAT and MRI imaging have been combined with clinical outcomes to explore PD subsets and PD pathobiology (21-23). Combining clinical motor outcomes with behavioral and cognitive outcomes has provided insight to the timing of non-motor PD disability and utility of current non-motor scales to track early disease (24-27). Examining biomarkers in genetic cohorts has further identified specific imaging and biologic markers that may distinguish those cohorts (28, 29). PPMI offers the opportunity to examine multiple biomarker data streams and analysis strategies for these data including unbiased data analysis approaches have identified possible PD subsets and predictors of progression (30).

PPMI has also developed prodromal cohorts defined by olfaction, RBD or genetic variant to pilot longitudinal assessment of biomarker prodromal PD and establish biomarkers that predict the development of motor parkinsonism. Overwhelming scientific data have demonstrated that the molecular pathology of Parkinson's disease begins long in advance of clinical symptoms. Longitudinal, densely phenotyped follow-up of individuals at high risk to develop PD enables both understanding of the progression of disease during the prodromal period and could ultimately lead to the testing of therapies that might prevent the onset of

manifest motor PD. The Movement Disorder Society proposed criteria to define prodromal PD for research (31, 32). Prior studies including the Parkinson Associated Risk Syndrome (PARS) study and long-term RBD studies have further demonstrated that prodromal PD participants with hyposmia or RBD with abnormal imaging have high risk of the onset of motor PD within 3-5 years (33, 34). Pilot prodromal data from the ongoing PPMI study has shown that about 35% of hyposmic and RBD participants with abnormal DAT converted to motor PD within four years. Data from the unaffected LRRK2 and GBA mutation carriers shows less than 10 % of participants with abnormal DAT, but mild increase in motor and non-motor features compared to healthy subjects (35). The asyn SAA assay has enabled the identification of individuals prior to the onset of symptoms and enables the investigation of individuals who may ultimately develop motor, non-motor and cognitive manifestations of disease.

PPMI has been committed to open-source data with rapid sharing of all PPMI data to the PD community (36). This data resource now includes clinical (motor and non-motor), digital, imaging, and genetic data plus a robust biorepository including blood, CSF, urine and induced pluripotent stem (IPS) cells.

3.2 Rationale for PPMI Clinical

While the PPMI study has made substantial progress as outlined above, the program offers the opportunity to expand and transform the use of biomarkers to test hypotheses of the underlying molecular pathobiology of PD, enable modeling of PD progression to identify clinical and/or biologic data driven PD progression sub-sets and inform studies testing PD therapeutics including clinical trials targeting synuclein, LRRK2, GBA and other targets. There is a consensus that a PPMI cohort defined by key biomarkers (asyn SAA and DAT) would further elucidate the pathobiology and enable studies of PD progression to accelerate therapeutic development. Further advances in molecular genetics, neurobiology, imaging technology, wearable sensor and remote assessment technology and radiochemistry have provided new tools that may be useful in identification of additional biomarkers for further studies of therapies that may slow or prevent PD disability. PPMI has evolved to expand the consortium of academic centers, PD foundations, pharmaceutical and biotech companies. government agencies, and active study participants, to establish and validate markers of PD progression across the spectrum of disease from prodromal PD to more advanced disease.

In PPMI Clinical, established tools will also be further validated and new technologies including neuroimaging modalities, digital biomarkers, biochemical markers in the CSF and plasma, genetic markers, and early clinical disease markers will be investigated. We will continue to standardize biomarker acquisition and assessment and to establish well-defined quantitative biomarker outcomes that are consistent among many research sites and laboratories. Core laboratories for biomarker analysis will be used for uniformity of analyses and quality control. A major focus of this biomarker consortium will be to extend PPMI infrastructure to new biomarkers and new cohorts, particularly those with prodromal PD. Longitudinal data will include Participant Reported Outcomes with an emphasis on outcomes that reflect participant function throughout the course of PD.

This approach to biomarker development is ambitious and requires collaboration among

many in academics, industry, government, and the public sector. However, PPMI has demonstrated that such an approach is feasible. PPMI has been successful in providing open-source data and fostering effective collaboration. The unmet need for therapeutics that slow or prevent the disability of PD coupled with the enormous value of biomarkers to enable and accelerate clinical studies highlights the need for this strategy to identify and validate biomarkers of PD progression throughout the course of disease.

4 STUDY DESIGN

PPMI Clinical is a longitudinal, observational, multi-center natural history study to assess progression of clinical features, digital outcomes, imaging, biologic and genetic markers of PD progression in study participants with PD diagnosis (including patients with LRRK2, GBA, SNCA or rare genetic variants and individuals with prodromal Parkinson's disease (including individuals with RBD, olfactory deficit, LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1)) enriched for PD biomarkers including a positive asyn SAA and DAT deficit and healthy controls.

We plan to comprehensively assess study participants for a minimum of 5 years. Participants will undergo clinical (motor, neuropsychiatric and cognitive) and imaging assessments, and will donate biosamples including blood, urine, and cerebral spinal fluid (CSF) and skin biopsy. Participants will also be asked to respond to targeted online questionnaires and provide additional digital data as part of other PPMI program protocols (under separate consent).

5 STUDY COHORTS

In PPMI Clinical up to 4775 participants will be enrolled and followed longitudinally from approximately 50-55 international clinical sites across a variety of cohorts as described below (note that the cohorts enrolled might vary across sites).

PPMI has enrolled approximately 3175 participants since 2010 into the following cohorts and is planning to continue to enroll participants as below:

1. Healthy controls (approximately 225 enrolled and up to 100 additional planned; n = up to 325)

2. Parkinson's disease (PD) (approximately 1200 enrolled and up to 500 additional planned; n = up to 1700)

3. Prodromal (at risk for PD) (approximately 1750 enrolled and up to 1000 additional planned; n = up to 2750)

6 RECRUITMENT METHODS

Participants may be identified to participate in PPMI Clinical through targeted recruitment campaigns, directly from a clinical site, myPPMI, or based on participation in other PPMI related recruitment efforts. These other recruitment efforts obtain information from online questionnaires assessing general health and risk of PD, information from additional remote testing including olfactory testing such as the University of Pennsylvania Smell

Identification Test (UPSIT), information based on known PD risk, such as possible REM sleep behavior disorder (RBD) or known genetic variants associated with increased PD risk. Individuals identified through centralized PPMI study recruitment methods, completed under separate consent as applicable, will be referred to PPMI clinical sites to consent to participation in PPMI Clinical and undergo the Screening Visit.

Individuals with a genetic variant will be largely identified through a centralized recruitment process but can be identified by clinical sites. Individuals being considered for participation in PPMI Clinical at clinical sites who may have these genetic variants, but have not previously undergone genetic testing, will undergo evaluation including genetic testing and genetic counseling (under separate consent from the PPMI Clinical study). Existing documentation of lab results will be provided to the PPMI Screening Core for further review and confirmation of eligibility for inclusion in PPMI Clinical. The outcome of this review will be provided to the clinical site, and if approved, these participants would not require additional genetic testing for enrollment. Individuals with identified LRRK2, GBA, SNCA, or rare genetic variants that meet genetic criteria would be further assessed by the referring site team for eligibility to enroll in PPMI Clinical.

7 PARTICIPANT ELIGIBLITY

The predictive eligibility criteria for all participants to be considered eligible for the Screening visit, as well as to advance to the Baseline visit, will be iteratively optimized based on data collected from activities conducted during the recruitment processes outlined above, as well as activities completed at the Screening visit.

Participants who consented to the Screening visit under Clinical protocol amendment 3.2 (Version 2.2 dated January 30, 2023), will complete the Screening and Baseline visit per the amendment 3.2 schedule of assessments and be assessed under the eligibility criteria outlined in Appendix 1.

7.1 Healthy Controls (HC)

7.1.1 Inclusion Criteria (HC)

a) Male or female age 30 years or older at Screening visit.
b) Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before SPECT imaging.
c) Confirmation that participant is eligible based on centrally determined criteria for the University of Pennsylvania Smell Identification Test (UPSIT) completed through other recruitment efforts.
d) Confirmation that participant is eligible to proceed to Baseline based on Screening SAA status (as determined by CSF, blood, skin, or other validated measure).
e) Able to provide informed consent.
f) Either is male, or is female and meets additional criteria below, as applicable:
   - Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Baseline SPECT imaging test prior to injection of DaTscan™.

7.1.2 Exclusion Criteria (HC)

a) First degree relative with PD (i.e., biologic parent, sibling, child).
b) Current or active clinically significant neurological disorder (in the opinion of the Investigator).
c) Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).
d) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening visit.
e) Current treatment with anticoagulants (e.g., coumadin, heparin, oral thrombin inhibitors) that might preclude safe completion of the lumbar puncture.
f) Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
g) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
h) Any other reason that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.

7.2 Parkinson's Disease (PD)

7.2.1 Inclusion Criteria All PD Participants

a) Male or female age 30 years or older at Screening Visit.
b) Has a clinical diagnosis of Parkinson's disease at Screening Visit.
c) Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia.
d) Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before SPECT imaging.
e) Able to provide informed consent.
f) Confirmation that participant is eligible based on centrally determined criteria for the University of Pennsylvania Smell Identification Test (UPSIT) completed through other recruitment efforts.
g) Either is male, or is female and meets additional criteria below, as applicable:
   - Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Baseline SPECT imaging test prior to injection of DaTscan™.

7.2.2 Exclusion Criteria All PD Participants

a) Atypical PD syndromes due to either drugs (e.g., metoclopramide, flunarizine, neuroleptics) or metabolic disorders (e.g., Wilson's disease), encephalitis, or degenerative diseases (e.g., progressive supranuclear palsy).
b) A clinical diagnosis of dementia as determined by the investigator.
c) Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).

d) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening visit.
e) Current treatment with anticoagulants (e.g., coumadin, heparin, oral thrombin inhibitors) that might preclude safe completion of the lumbar puncture.
f) Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
g) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
h) Any other reason that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.

ADDITIONAL INCLUSION / EXCLUSION CRITERIA FOR PD SUBGROUPS

7.3 Parkinson's Disease (PD Sporadic)

7.3.1 Inclusion Criteria

a) A diagnosis of Parkinson's disease for 2 years or less at Screening Visit.
b) Hoehn and Yahr stage I or II at Baseline.
c) Not expected to require PD medication within at least 6 months from Baseline.
d) Confirmation that participant is eligible to proceed to Baseline based on Screening SAA status (as determined by CSF, blood, skin, or other validated measure).

7.3.2 Exclusion Criteria

a) Receiving treatment for PD, including levodopa, dopamine agonists, MAO-B inhibitors, amantadine or another PD medication, except for low-dose treatment of restless leg syndrome (with permission of medical monitor), or Deep Brain Stimulation (DBS).
b) Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of Baseline visit, except for low-dose treatment of restless leg syndrome (with permission of medical monitor).
c) Has taken levodopa or dopamine agonists prior to Baseline visit for more than a total of 90 days.

7.4 Parkinson's Disease (PD LRRK2 or GBA variant)

7.4.1 Inclusion Criteria

a) A diagnosis of Parkinson's disease for 2 years or less at Screening Visit.
b) Hoehn and Yahr stage I or II at Baseline
c) Confirmation of causative LRRK2 or GBA from the PPMI Screening Core.
d) Confirmation that participant is eligible to proceed to Baseline based on Screening SAA status (as determined by CSF, blood, skin, or other validated measure).

7.5 Parkinson's Disease (PD SNCA or rare genetic variant such as Parkin or Pink1)

7.5.1 Inclusion Criteria

a) Confirmation of causative SNCA or rare genetic variant (such as Parkin or Pink1) from the PPMI Screening Core.
b) Hoehn and Yahr stage I, II, or III at Baseline
c) Confirmation that participant is eligible to proceed to Baseline based on Screening SAA status (as determined by CSF, blood, skin, or other validated measure).

7.6 Parkinson' Disease (PD Normosmic)

7.6.1 Inclusion Criteria

a) A diagnosis of Parkinson's disease for 7 years or less at Screening Visit.
b) Hoehn and Yahr stage I, II, or III at Baseline.

7.7 Parkinson' Disease (PD Normosmic LRRK2)

7.7.1 Inclusion Criteria

a) A diagnosis of Parkinson's disease for 7 years or less at Screening Visit.
b) Hoehn and Yahr stage I, II, or III at Baseline.
c) Confirmation of causative LRRK2 from the PPMI Screening Core.

7.8 Prodromal

7.8.1 Inclusion criteria (Prodromal)

a) Confirmation that participant is eligible based on centrally determined criteria for the University of Pennsylvania Smell Identification Test (UPSIT) completed through other recruitment efforts.
b) Male or female age 40 years or older (except age 30 years or older for SNCA, or rare genetic variants (such as Parkin or Pink1) participants).
c) Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before SPECT imaging.
d) Able to provide informed consent.
e) Either is male, or is female and meets additional criteria below, as applicable:
   - Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Baseline SPECT imaging test prior to injection of DaTscan™.
f) Confirmation that participant is eligible based on asyn SAA status (as determined by CSF, blood, skin, or other validated measure).

7.5.2 Exclusion Criteria (Prodromal)

a) Clinical diagnosis of PD, other parkinsonism, or dementia at screening.
b) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Baseline Visit.
c) Current treatment with anticoagulants (e.g. coumadin, heparin) that might preclude

safe completion of the lumbar puncture.

d) Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
e) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
f) Currently taking levodopa, dopamine agonists, MAO-B inhibitors, amantadine or another PD medication, except for low-dose treatment of restless leg syndrome (with permission of medical monitor).
g) Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of Baseline visit, except for low-dose treatment of restless leg syndrome (with permission of medical monitor).
h) Any other reason that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.

8 OBTAINING INFORMED CONSENT

8.1 Consent Process

The procedures and requirements of the study, together with any potential hazards/risks, and the freedom to withdraw from participation in the study at any time, will be explained to each potential participant as part of the consent process. The consent process will take place in a space that allows for privacy and confidentiality and should allow for enough time for the individual to consider participation and ask any questions. Consent will be obtained by the study Investigator or delegated study staff, as applicable. Sites may obtain informed consent remotely (e.g., by telephone, videoconference, or e-Consent) after the consent form has been provided to the potential participant (e.g., mail, email, e-sign document), as deemed appropriate by the Investigator. All signatures will be obtained before any Clinical study procedures begin. Each participant will sign such an informed consent to document agreement to participate in the study, as well as to document HIPAA authorization and compliance with GDPR regulation, as applicable. The signed informed consent may be uploaded to a secure portal for remote monitoring.

It is the responsibility of the Investigator (or as delegated to the person obtaining consent) to make sure that the participant understands what she/he is agreeing to and that informed consent is obtained before the participant is involved in any protocol-defined procedures, including screening procedures. Each participant will be provided with a copy of the consent form. In addition to obtaining initial consent to participate, Investigators must ensure ongoing consent as part of this longitudinal study (for example, documentation at an annual study visit that the participant continues to understand the procedures and requirements of the study).

8.2 Identification of Research Proxy

There is the potential for development of cognitive impairment in participants over the course of study participation. Therefore, in accordance with good clinical practices in ensuring each participant's ability to give ongoing informed consent, identification of a research proxy will enable continued participation for participants whose ability to consent becomes

compromised. Identification of a research proxy through use of the Advance Directive for Clinical Research Participation form, enables participants to clarify their preferences, thus guiding the substitute decision maker and the Investigator. It is noted that the accepted term and/or required directive for a designated substitute decision maker (also known as a Legally Authorized Representative/LAR) may vary on a country/state/provincial basis.

During the initial consent process, or at any time during assessment of ongoing consent as applicable, a participant may identify a substitute decision maker who will be permitted to carry out the participant's wishes regarding continued participation (or not) in PPMI Clinical should the participant lose the ability to make his or her own decision. The site Investigator will exercise clinical judgment and ascertain a participant's ability to continue giving informed consent. This ascertainment may include a discussion including review of the study purpose, differences between research and clinical assessments, and the risks of study participation. If deemed necessary by the Investigator, the participant will be approached about contacting the person(s) named in the advance directive while the participant is still capable of discussing the need to invoke the research proxy. Should the Investigator deem it necessary to invoke the LAR, the designated individual will be contacted by telephone, if not already present at the study visit, to discuss the next steps for determining the participant's continuing participation.

Designation of a LAR is voluntary; thus, identification of a substitute decision maker is not required to participate in PPMI. However, if in the absence of a substitute decision maker the Investigator deems a participant no longer able to provide ongoing consent, the participant will be withdrawn from the study.

Documentation is required for completion of the Advance Directive, routine review of the participant's continuing ability to give informed consent at each visit, any discussion with the participant's substitute decision maker, as well as documentation of informed consent (and assent of the participant) should a LAR be invoked.

9 PPMI Program Initiatives

9.1 myPPMI

The PPMI Program created the myPPMI web portal (myppmi.org) for all PPMI participants. This website is a central dashboard for PPMI participants to have visibility to information such as their journey through the PPMI Program, status in participating studies, general news about PPMI, additional resources, or new research opportunities that may be available to them under the PPMI Program. Materials for any new research activities will be submitted to the respective IRB/Ethics Committees for review and approval prior to implementation. Sites will need to provide participants' personally identifiable information (PII) centrally, such as contact information, for PPMI participants to be eligible to register an account with myPPMI.

9.2 Permission to be Contacted for Follow Up of Persons with Neurologic Disease

The Follow Up of Persons with Neurologic Disease (FOUND) study (Caroline Tanner MD, PhD, Principal Investigator, University of California-San Francisco (UCSF)) provides a

parallel, centralized system to prospectively collect vital status and disease progression information from persons with parkinsonism, related disorders and healthy controls who are participating in clinical research studies. Participation in FOUND complements in-person and remote study assessments, enables continuity of follow up of individuals who complete or withdraw from the study and may also aid in PPMI study retention. Participation in FOUND will enable centralized contact both during and after completion of PPMI, using convenient methods for systematic data collection (e.g., regular mail, telephone, internet contacts).

During the initial consent process for PPMI Clinical, and as needed at subsequent follow up visits, participants may be asked if their contact information can be shared with the FOUND study team at UCSF. The participant's decision will be documented in the PPMI informed consent and PPMI database. If a participant agrees to be contacted, UCSF will be notified. Individuals who do not indicate interest in FOUND at clinical visits can also indicate interest later using the myPPMI portal. UCSF will contact interested participants and invite them to participate in FOUND. UCSF is responsible for obtaining consent to participate in FOUND. UCSF will share their participants' status in FOUND with PPMI sites at regular intervals. Sites will be asked to talk with PPMI participants who have not enrolled in FOUND to identify any issues impeding enrollment and when possible, to address these issues. The data collected from the FOUND study will be uploaded into the PPMI data repository at the Laboratory of Neuro Imaging (LONI), The Institute for Neuroimaging and Informatics in Los Angeles, California, at regular intervals.

9.3 Permission to be Contacted from Pathology Core

Post-mortem analysis of brain tissue is pivotal to Parkinson's disease research, allowing researchers to examine changes noted in the post-mortem brain tissue and correlate it with changes in neuropsychological, imaging, and biomic data collected throughout the PPMI Clinical study. However, there is limited availability to this type of tissue, leading to organized efforts to facilitate brain donation planning through the PPMI Pathology Core.

The PPMI Pathology Core is overseen by Indiana University. Indiana University is responsible for coordinating all logistics up-to death, including obtaining consent, identifying a removal specialist, coordinating with clinical sites, and interfacing with the decedent's family. Indiana University also ensures the removal specialist follows outlined removal and shipping guidelines to transfer the whole brain to a neuropathological team, while a small tissue sample is shipped to Indiana University for DNA extraction. The neuropathological team is responsible for post-mortem activities including receiving specimens, specimen dissection and preparation for embedding and processing, performing neuropathological evaluation of tissue, coordinating clinicopathological case conferences (CPCs), and coordinating long-term storage location of brain tissue samples.

For clinical sites based in the United States, site coordinators will discuss the PPMI Pathology Core with participants and provide them with more information at initial consent to PPMI, or subsequent study visits as applicable. Individuals who do not indicate interest in Pathology Core at clinical visits can also indicate interest later using the myPPMI portal. Participants will be asked to provide permission to allow their contact information to be

transferred to the Pathology Core team at Indiana University. PPMI participants may also be presented with opportunities to learn more about brain donation outside of their PPMI site visits and elect to either be contacted by, or directly contact, the Pathology Core team. The Pathology Core team will discuss tissue donation further with participants and answer questions. The Pathology Core team is responsible for obtaining consent for participants interested in donation planning.

The Pathology Core team will also provide support to international PPMI sites that are interested in contributing to PPMI brain tissue donation activities. The team will work with neuropathologists at local sites to ensure the harmonization of brain tissue collection and processing, help establish workflows from consent to donation, and ensure regulatory considerations are met for participant inclusion in the PPMI Pathology Core.

The data and images collected across the Pathology Core will be collated by the team at Indiana University and transferred to the PPMI data repository at the Laboratory for Neuro Imaging (LONI), The Institute for Neuroimaging and Informatics in Los Angeles, California, at regular intervals. It is possible that collected tissues may be distributed to approved researchers for future analysis.

10 PARTICIPANT INFORMATION AND STUDY ID

10.1 Participant Profile Information

When a participant provides consent to participate, the following participant identifiers may be collected in the electronic database capture (EDC) system: full name (first name, middle name, last name), home address, phone number, email address, date of birth, sex, city/municipality of birth and country of birth.

10.2 Participant ID Number

A Participant ID number will be assigned to all PPMI Clinical participants, if not previously assigned under another PPMI Program protocol. Newly enrolled participants will be assigned a unique ID number, generated automatically. The PPMI Participant ID number will be used to identify a participant on all study related documentation (e.g., clinical database, biological specimens).

11 STUDY VISIT PROCEDURES

Participants may complete assessments prior to consent to PPMI Clinical to be deemed eligible for the Screening visit (e.g., the UPSIT). These pre-screening activities are conducted outside the PPMI Clinical study, and under separate consent, as applicable to the respective activity.

Screening, Baseline and Annual study visits may occur over the period of more than one day due to the complexity of the visits and resources required at the site. The date each assessment was completed will be captured within the EDC system and will therefore reflect whether a visit requires a duration of more than one day to complete.

The Baseline visit should be completed within 60 days after the Screening visit. Follow-up

6 month and annual visits should be completed with ±45 days of the target visit date. Out of window visits will not be considered a protocol deviation but will be monitored throughout the study for each site.

It is the goal of the study that the clinical assessments be conducted by the same individual throughout the study. Assessments that require completion by the Site Investigator (or trained designee) include the following.

- Informed Consent
- Research proxy designation
- Review Inclusion/Exclusion criteria
- Neurological Examination
- MDS-UPDRS Parts Ia, III, IV, MDS-UPDRS Repeat Part III, Hoehn & Yahr
- Modified Schwab & England ADL
- Features of Parkinsonism
- Other Clinical Features
- Primary Research Diagnosis
- Cognitive Categorization
- Clinical Global Impression (CGI)

11.1 Out of Clinic Annual Visits

To enable continued involvement of participants in the PPMI Clinical study and enhance study retention, participants who are unable to attend annual visits in person due to reasons such as participant burden, advanced disease, and/or participant safety (e.g., such as COVID-19), are eligible for assessment out of the clinic. Options for Out of Clinic visits include virtual visits by video link (i.e., telemedicine), enhanced telephone, phone/audio only, or in-home assessments in which PPMI site staff travel to the participant's home. Sites should complete as many assessments indicated on the Out of Clinic Schedule of Activities for the scheduled annual visit as is feasible, based on the type of out of clinic visit conducted and ability to do an assessment (i.e., videoconference versus in-home or audio only). Sites will record visit status, indicating if the visit was OOC, in the EDC.

11.2 Healthy Control and PD Cohort Visits

11.2.1 HC and PD Screening Visit

Refer to the PPMI Schedule of Activities for the applicable cohort to determine the activities to be conducted at the Screening visit.

All newly enrolled participants in these cohorts will undergo a screening evaluation prior to the Baseline visit. The Screening visit will take about 8 hours to complete (could occur over more than one day).

During the informed consent process the following activities will also be described, as applicable:

- Discuss start of or ongoing participation in other relevant PPMI Program initiatives including myPPMI.

- An explanation of FOUND in PPMI will be given and participants will be asked permission to have their contact information sent to the FOUND coordinating site at UCSF so that UCSF study team can contact them about their interest in participation. Participants may take time to review and complete consent at a subsequent visit.
- An explanation of the PPMI Pathology Core will be given and participants will be asked permission to have their contact information sent to the Pathology Core study team. Alternatively, participants may take time to review and complete this information at a subsequent visit.
- An explanation of the purpose and procedures for identification of a substitute decision maker (or research proxy) will be given. Participants may take time to review and complete research proxy at a subsequent visit.

11.2.2 HC and PD Baseline Visit

Refer to the PPMI Schedule of Activities for the applicable cohort to determine the activities to be conducted at the Baseline visit.

Once all study procedures are completed, the Investigator (or designee) must ensure that the participant meets eligibility for the relevant cohort in order to continue with longitudinal follow up visits. This Baseline visit is anticipated to take 8 hours (could occur over more than one day).

11.2.3 HC and PD Follow up Visits

Refer to the PPMI Schedule of Activities for the applicable cohort to determine the activities to be conducted at follow up visits.

After the Baseline visit is completed, participants will be evaluated in clinic every 6 months for the first two years. Annual visits are anticipated to take about 6-8 hours (could occur over more than one day), while the 6-month in clinic visits will take about 2-4 hours. After two years, all participants will continue to be evaluated every 6 months remotely and annually in the clinic, for a minimum of 5 years of longitudinal follow up visits. Options for Remote 6-month visits include virtual visits by video link or telemedicine, or phone/audio only. The remote 6-month visits will take about 1-2 hours. Sites should complete as many assessments at the Remote ("R") visit as is feasible, based on how the visit is conducted (i.e., videoconference versus in-home or audio only) and ability to do an assessment.

11.3 Prodromal Cohort Visits

11.3.1 Screening Visit

Refer to the PPMI Schedule of Activities to determine the activities to be conducted at the Screening visit.

All newly enrolled participants will undergo a screening evaluation prior to the Baseline visit. The Screening visit will take about 8 hours to complete (could occur over more than one day).

During the informed consent process the following activities will also be described, as applicable:

- Discuss start of or ongoing participation in other relevant PPMI Program initiatives including myPPMI.
- An explanation of FOUND in PPMI will be given and participants will be asked permission to have their contact information sent to the FOUND coordinating site at UCSF so that UCSF study team can contact them about their interest in participation. Participants may take time to review and complete at a subsequent visit.
- An explanation of the PPMI Pathology Core will be given and participants will be asked permission to have their contact information sent to the Pathology Core study team. Alternatively, participants may take time to review and complete this information at a subsequent visit.
- An explanation of the purpose and procedures for identification of a substitute decision maker (or research proxy) will be given. Participants may take time to review and complete at a subsequent visit.

11.3.2 Baseline Visit

Refer to the PPMI Schedule of Activities to determine the activities to be conducted at the Baseline visit.

Once all Baseline study procedures are completed, the Investigator (or designee) must ensure that the participant meets eligibility in order to continue with longitudinal follow up visits. This Baseline visit is anticipated to take about 6-8 hours (could occur over more than one day).

11.3.3 Follow Up Visits

Refer to the PPMI Schedule of Activities to determine the activities to be conducted at the follow up visits.

After the Baseline visit is completed, participants will be evaluated in clinic annually and remotely every 6 months, for a minimum of 5 years of longitudinal follow up visits. Annual visits are anticipated to take about 6-8 hours (could occur over more than one day). Options for Remote 6-month visits include virtual visits by video link or telemedicine, or phone/audio only. The remote 6-month visits will take about 1-2 hours. Sites should complete as many assessments at the Remote ("R") visit as is feasible, based on how the visit is conducted (i.e., videoconference versus in-home or audio only) and ability to do an assessment.

12 EVENT DRIVEN MODIFICATION OF SCHEDULED VISITS

12.1 New Clinical Diagnosis

If, after enrollment (i.e., Baseline visit), a PD or Prodromal participant receives a new clinical diagnosis of PD or other neurodegenerative disorder (meaning the clinical diagnosis occurred outside the context of the PPMI research assessments), attempt to schedule an in person PPMI visit as soon as possible after the site is made aware of the new clinical diagnosis.

A participant may be seen up to 3 months in advance of the next scheduled target visit date. If the next scheduled visit is a 'R' visit, then the 'R' visit should be modified to an in person visit.

a) Participant assessed at an annual visit – follow schedule of activities for the respective annual visit.
   - If Year 3, annual visit SPECT imaging and MRI should be conducted.

b) Participant is assessed in person at an 'R' visit
   - In addition to the activities already conducted at an 'R' visit, the following other assessments should be administered, including:
     - *Note: Imaging, skin biopsy and lumbar puncture not required*
     - Research biosamples (blood and urine) collection
     - Vital signs
     - All Neurological/Motor Assessments, including a full UPDRS
     - All Non-Motor Assessments *(Note: UPSIT not required for Prodromal participant)*
     - All Cognitive Assessments
     - All Neuropsychological Assessments
     - Safety and General Health assessments, as applicable.

Following completion of an in person visit as described above, resume participant's regular visit schedule.

12.2 Need for PD Therapy

Note: The site should document any new or changed PD medication dose and start date on the LEDD Medication Log.

If the site becomes aware that a PD or Prodromal participant is planning to or has already started PD medication, attempt to schedule an in person PPMI visit as soon as possible after the site is made aware. It is preferable to have the participant seen prior to starting medication. If a participant is not assessed in person prior to starting PD medication, conduct the next study visit per the regular visit schedule (participant should hold medication prior to conducting the visit).

A participant may be seen up to 3 months in advance of the next scheduled target visit date of either an annual visit or remote 'R' visit.

a) Participant assessed at an annual visit – follow schedule of activities for the annual visit; no additional activities are required.

b) Participant is assessed in person at an 'R' visit – In addition to the activities already conducted at 'R' visit, the following other assessments should be administered, including:
   - *Note: Imaging, skin biopsy and lumbar puncture not required*
   - Research biosamples (blood and urine) collection

- Vital signs
- All Neurological/Motor Assessments, including a full UPDRS
- All Non-Motor Assessments *(Note: UPSIT not required)*
- All Cognitive Assessments
- All Neuropsychological Assessments
- Safety and General Health assessments, as applicable.

12.3 Withdrawal from the Study

If a participant withdraws from the study and does not want to be seen for any more assessments, complete the Conclusion of Participation assessment under the last completed visit.

12.3.1 Withdrawal During Scheduled Visit

If a participant withdraws from the study during a scheduled annual visit, proceed with the visit as outlined in the schedule of activities and complete the Conclusion of Participation assessment.

12.3.2 Withdrawal Outside Scheduled Visit

If a participant withdraws from the study outside of a scheduled visit, determine whether the participant agrees to be seen for one more in-person visit, or prefers to conduct a remote 'R' visit. Complete the Conclusion of Participation assessment once the visit is completed.

a) Withdrawal at remote 'R' visit:
   - Conduct study procedures for that visit schedule of activities

b) Withdrawal at in person annual visit – conduct study procedures for that annual visit schedule of activities, with the following exceptions, as feasible:
   - Research biosamples (blood and urine) collection – only if not done in the last 3 months
   - Lumbar puncture for collection of CSF – only if not done in the last 3 months
   - Skin biopsy – only if not done in the last 6 months, up to Year 4
   - MRI (Prodromal and PD cohorts only)– only if not done in the last 6 months, up to Year 4.
   - SPECT Imaging (Prodromal and PD cohorts only) – only if not done in the last 6 months, up to Year 4.

13 CLINICAL ASSESSMENTS

Refer to the PPMI Assessments and eCRF Completion Manual for a detailed description of the clinical assessments and instructions for administration.

14 SAFETY ASSESSMENTS

14.1 Medical Conditions Review, Physical and Neurological Examination

Medical and family history, as well as a complete physical and neurological exam will be captured on all participants according to the schedule of activities. A neurological exam will also be conducted annually, as well as at the last completed visit if possible.

14.2 Vital Signs/Weight/Height

Pulse rate (supine and standing), blood pressure (supine and standing), and temperature will be determined at every in person visit. The supine blood pressure and pulse rate will be determined after 1-3 minutes of quiet rest and the standing pressure and rate will be determined after 1-3 minutes in the standing position. Weight and height will also be collected at baseline and annually.

14.3 Clinical Laboratory Tests

Routine clinical safety laboratory tests indicated in the table below will be performed at the Screening visit. A central laboratory will be implemented to conduct identical analysis methods and utilize consistent normal ranges and thus common interpretation of laboratory changes. If not stated otherwise, venous whole blood will be collected in blood collection tubes (vacutainers). All samples for laboratory analysis must be collected, prepared, labelled, and shipped according to the laboratory's requirement as detailed in the lab manual. The total amount of blood needed for the clinical safety lab tests will be no more than 5 ml. No more than 60 ml will be drawn at the Screening visit, including both safety and research blood samples. Abnormal clinical laboratory values that are unexpected or not explained by the participant's clinical condition may, at the discretion of the investigator, be repeated as soon as possible until confirmed, explained, or resolved.

The coagulation panel (PT/PTT) will be collected and sent to a local lab for analysis prior to completion of the Screening lumbar puncture. Sites have the option, per clinical practice, to collect an additional blood sample to evaluate coagulation results prior to the conduct of post Screening visit lumbar puncture assessments. If completed, this sample should also be sent to a local lab facility for analysis. Results will be evaluated to determine, in the opinion of the Investigator, whether there are any issues that may preclude conduct of the follow up lumbar puncture. Results from any follow up coagulation panel should be maintained as part of the participant's study documents; however, will not be included in the study database.

CENTRAL LAB TESTS	
METABOLIC PANEL	**COMPLETE BLOOD COUNT**
Sodium (Na) Potassium (K) Chloride (Cl) Carbon Dioxide (CO2) Blood Urea Nitrogen (BUN) Glucose Calcium (Ca) Creatinine (Crn) Bilirubin Total Albumin Total Protein Aspartate aminotransferase (AST) Alanine aminotransferase (ALT) Alkaline Phosphatase (ALKP) Uric Acid	White Blood Cell Count (WBC) Red Blood Cell Count (RBC) Hemoglobin (Hb) Hematocrit (HCT) Platelet Count (PLT)

15 BIOLOGIC RESEARCH SAMPLING

Refer to the PPMI Biologics Manual for the detailed description of the biologic samples collected and processing instructions.

15.1 Research Blood Samples

Whole blood (about 10 ml), serum (about 30 ml) and plasma (about 10 ml) will be collected to conduct proteomic, metabolomic, genetic and other research analyses. Approximately 60 ml will be drawn at any visit, including both clinical safety labs and research blood samples.

It is strongly advised that the research blood samples are collected in a fasted state (i.e., minimum of 8 hours since last meal/food intake) to ensure the quality of samples for future analyses. If fasting is not possible, then participants should be advised to eat a low lipid diet. All research samples will be sent to a central biorepository to be stored indefinitely for research purposes. Samples will be made available to researchers to conduct analyses related to PD and other disorders.

15.2 Urine

Urine (about 10-15 ml) will be collected to conduct analyte analyses.

15.3 Lumbar Puncture / Cerebral Spinal Fluid (CSF)

The lumbar puncture (LP) is performed by the site investigator, or another qualified clinician appointed by the investigator. A lumbar puncture for the collection of 15-20 ml of CSF will be conducted for all participants per the visit schedule unless there is evidence of clinically significant coagulopathy or thrombocytopenia that would interfere with the safe conduct of the procedure. In addition, an LP may be conducted under fluoroscopy as deemed necessary by the site investigator or as per site's standard practice. The first 2 ml of CSF will be processed for cell count, protein, and glucose levels. Participants will be closely monitored on the day of the procedure for adverse events. Participants will also be contacted by phone 2 to 3 [business/working] days following an LP to assess for any adverse events. The CSF samples will be sent to a central biorepository to be stored indefinitely for research purposes. The CSF samples will be made available to researchers to conduct analyses related to PD and other disorders.

15.4 Skin Biopsy

The skin biopsy is performed by the site investigator, or another qualified clinician appointed by the investigator. Skin punch biopsy will be performed under local anesthesia (lidocaine) in the posterior neck according to the Schedule of Activities. Up to two punches will be completed and the skin samples will be processed as described in the PPMI Biologics Manual and shipped to the central biorepository for storage and analysis. Remaining samples may be used to evaluate other proteins, analytes or potential biomarkers. Participants will be monitored on the day of the procedure for adverse events. Participants will also be contacted by phone 2 to 3 [business/working] days following a skin biopsy to assess for any adverse events.

16 IMAGING

16.1 Dopamine Transporter SPECT Imaging

Refer to the PPMI SPECT Technical Operations manual for a detailed description of the SPECT imaging procedures.

Participants will undergo dopamine transporter imaging to measure dopamine transporter binding using single photon emission computed tomography (SPECT). All new and transitioning participants will also undergo follow up SPECT imaging as indicated in their cohort visit schedule.

To lessen participant burden, a participant's previously acquired SPECT imaging may be used in place of a newly acquired scan if the previous scan was acquired within 6 months of the study scheduled SPECT, it meets protocol acquisition standards, and passes QC requirements for the research study analysis. Participants may require a repeat DaT scan if the previously acquired DaT is older than 6 months at the point of a Baseline visit.

The SPECT imaging procedure will be performed at the study sites using DaTscan™ to target the dopamine transporter and all imaging data will be submitted for analysis to the Imaging core. SPECT imaging eligibility was determined using pre-specified imaging cut-offs.

Women of childbearing potential must have a urine (or serum if required by the site) pregnancy test prior to injection of DaTscan™. The result must be confirmed as negative prior to proceeding with the injection. Before the DaTscan™ injection, participants will be pre-treated with stable iodine (10 drops of a saturated solution of potassium iodide) to reduce the uptake of DaTscan™ by the thyroid. If the participant is allergic to iodine, then potassium perchlorate 400 mg) can be substituted for potassium iodide. Participants will be injected with up to 5 mCi of DaTscan™. Within a 4-hour (+/- 30 minute) window following the injection, participants will undergo SPECT imaging for approximately 30 minutes (or up to an hour if the participant moved during scanning).

Participants will be monitored by study personnel for adverse events on the day that a dopamine transporter SPECT scan is obtained. Participants will also be contacted by phone 2 to 3 [business/working] days following the injection/scan to assess adverse events.

The product used to complete the dopamine transporter SPECT scans is being used "off-label" in the PPMI Clinical study. The imaging result obtained from the scan is not intended to provide information about a clinical diagnosis.

16.2 Magnetic Resonance Imaging (MRI)

Refer to the PPMI MRI Technical Operations manual for a detailed description of the MRI imaging procedures.

Participants will undergo an MRI brain scan at the screening or baseline visit and will also undergo follow up MRI scans as indicated in the visit schedule. At the discretion of the Investigator and Imaging staff, participants who have presence of pacemakers, aneurysm clips, artificial heart valves, ear implants, metal fragments or foreign objects in the eyes, skin or body or any other known contra-indication to MRI may be advised not to complete a Baseline (or follow-up) MRI scan, but these participants may still participate in the study.

17 RISKS TO PARTICIPANTS

17.1 Blood Sampling

Risks associated with venous blood draw include pain and bruising at the site where the blood is taken. Sometimes people can feel lightheaded or even faint after having blood drawn.

17.2 MRI

Participants should notify the study doctor if they suffer from claustrophobia because they may become anxious while in the magnetic resonance scanner. The investigator may treat the participant for anxiety if indicated. There may be loud noises such as knocking or hammering that occur while the MRI is being conducted. Participants should also inform the study doctor if they have a pacemaker or metal implants (screws, plates or clips) because this may preclude MR evaluation.

17.3 SPECT Imaging Using DaTscan™

Risks of DaTscan™: DaTscan™ is administered at radiotracer doses and is not expected to have any pharmacological or toxicological effects. DaTscan™ binds to the dopamine and serotonin transporter. At pharmacologic doses DaTscan™ might be expected to have stimulant-like effects and affect cardiovascular responses. However, in the proposed study the estimated mass dose of DaTscan™ is very low (<30/pmol kg). More than 500,000 doses of the radiotracer have been administered to human participants.

Iodine: Prior to each injection, participants will be pretreated with Lugol's (or similar) solution, 10 drops of a saturated solution of potassium iodide, to reduce thyroid uptake of the radioactive agent. Participants may experience a metallic or bitter taste in their mouths from the iodine. Participants with allergies to iodine might get itching, a rash, bloating, severe blood pressure changes (shock), and death if given iodine. Participants who are allergic to iodine may be imaged without Lugol's or if available may be administered potassium perchlorate rather than Lugol's.

In addition to the known risks listed above, these imaging procedures may cause unknown risks to the participant, or a developing embryo or fetus or possible risks to the future offspring of male participants. Female participants of childbearing potential will be asked to have a pregnancy test. Female participants and male participants whose partners become pregnant within 30 days of DaTscan™ injection should report the pregnancy on the Report of Pregnancy data form in EDC within 24 hours of notification of the pregnancy.

17.4 Lumbar Puncture

The most common risks of a lumbar puncture are pain at the site and a temporary headache usually due to a small amount of CSF leakage around the needle insertion site. Lying down for 30 -60 minutes after the test may make a headache less likely to occur. There is a slight risk of infection because the needle breaks the skin's surface, providing a possible portal of entry for bacteria. A temporary numbness to the legs or lower back pain may be experienced. There is a small risk of bleeding in the spinal canal. Participants will have blood drawn at the Screening or Baseline visit to test for coagulopathies.

17.5 Skin Biopsy

Risks associated with performing punch biopsies of the skin include pain and bruising at the site where the biopsy is taken. There is a small risk that the biopsy site may change color. The skin biopsy may leave a scar. There is also a small possibility of infection or bleeding at the biopsy site. Although very rare, it is possible to have an allergic reaction to the local anesthetic (lidocaine) or betadine.

17.6 Disclosure of Genetic Information

All genetic information will be maintained in a confidential research file. While every effort will be made to maintain confidentiality there is a small risk that information will be disclosed.

18 REFERRALS IN THE CASE OF CLINICALLY RELEVANT FINDINGS

If an assessment, lab, or MRI reveals a clinically significant abnormality (e.g., MRI structural lesion, indication of suicidality, depression, or renal impairment on metabolic profile), the participant will be informed of this result and instructed to follow up with his or her primary care physician. Should there be a safety concern warranting a referral for medical or psychiatric follow-up, the Investigator should provide the participant with the appropriate referral as necessary. The sites will follow their standard procedures for clinically urgent and non-urgent medical situations identified during study visits.

19 RETURN OF RESEARCH INFORMATION

In addition to the standard of care/clinically relevant results described above, information collected may result in obtaining research findings that could impact a participant's clinical care choices or decisions due to the extensive clinical and biomarker characterization that participants undergo in PPMI to achieve the goals of this study (for example, genetic results from non-CLIA certified testing, change in research diagnosis). The Investigator will use his/her judgment in determining whether to discuss these findings with the participant.

Participants may be able to receive some other personal information from their research tests. PPMI is making some personal research information available through the myPPMI. Learning personal research information is a choice. The participant's choice will not impact their participation in PPMI or this study. If the participant chooses to view their research information, they will be asked to sign a separate consent form.

20 POTENTIAL BENEFITS TO PARTICIPANTS

There are no direct anticipated benefits to study participants in this study. However, new

information may be generated by the study that will support development of better treatments for Parkinson's disease.

21 CONCOMITANT MEDICATIONS

21.1 Use of Concomitant Medications

Concomitant medications, including over-the-counter (OTC), dietary supplements (e.g., herbal remedies) or prescriptions, are permitted during the study period, except for the following medications that might interfere with dopamine transporter SPECT imaging which are restricted for 5 half-lives prior to a DaTscan™ injection: alpha methyldopa, methylphenidate, modafinil, amphetamine derivatives and other CNS stimulants. Medications known to be associated with drug induced parkinsonism will not be allowed for 6 months prior to screening and for the duration of the study, dopamine receptor blockers (neuroleptics), metoclopramide and reserpine. All concomitant medications reported at the time of the Screening visit and for the duration of participation are recorded on the study medication logs.

21.2 Initiation of PD Medication

It is anticipated that PD participants will not require PD medications for at least 6 months after Baseline. However, PD medications may be initiated at any time after enrollment at the discretion of the participant or treating physician (see Section 11.2). The medication used is at the discretion of the treating physician. The Investigator will document any new medications or changes in medication at each study visit on the study medication logs.

22 PARTICIPATION IN CLINICAL TRIALS

It is understood that individuals may want to participate in therapeutic clinical trials. It is preferred, but not required, that participants who choose to participate in clinical trials of investigational therapeutics, begin their clinical trial following 12 months of participation in PPMI. All participants who do enroll in a clinical trial may remain in the PPMI Clinical study. PPMI will work collaboratively with the clinical trial sponsor to share PPMI study data and encourage clinical trial participants to remain in PPMI Clinical in whatever capacity possible. Contact the Site Management Core for further instruction and to determine whether an in-person PPMI visit may be needed before the participant begins a therapeutic clinical trial. For those studies testing a drug, the Investigator will document on the medication log the study drug dosage, if applicable and known, and, if unknown, will report on the identity of the study drug and dosage after it is unmasked. Other information pertaining to participation in other clinical trials or observational studies may be documented in the PPMI study database.

23 COSTS FOR PARTICIPATION

All research travel, assessments and tests will be provided with no cost to the study participant.

24 PAYMENT AND REIMBURSEMENT FOR PARTICIPATION

Participants will be paid for completed study visits based on the visit type. Participants who require travel to the clinical site, or incur other costs associated with a study visit, will be reimbursed according to the study reimbursement guidelines. Participants will have the option to receive funds using either a pre-paid card, or direct deposit to a personal account.

25 PARTICIPANT WITHDRAWALS

Study participants will be informed during the consent process that they have the right to withdraw from the study at any time without prejudice and may be withdrawn at the Investigator's or Sponsor's discretion at any time. Any information that has already been collected prior to the study participant's withdrawal will not be removed. Participants who withdraw from the PPMI Clinical study might no longer be able to participate in some studies under the PPMI program.

26 ADVERSE EVENTS

26.1 Adverse Event Reporting Requirements

Site investigators and coordinators will be instructed to assess for adverse events at the study visit when SPECT imaging, lumbar puncture, or skin biopsy is conducted, as well as by telephone 2 to 3 [business/working] days following such activity. Adverse experiences, whether observed by the investigator, or elicited from or volunteered by the participant, should be recorded on the Adverse Event Log. Events occurring outside of the study procedure adverse event reporting period defined above do not require documentation for study purposes (i.e., will not be listed on the Adverse Event Log).

Any adverse event ongoing at the 2 to 3 [business/working] day reporting telephone visit, should be followed until resolution or stabilization. Adverse events reported following a premature withdrawal or conclusion of participation visit should be followed not more than 30 days from last study procedure (i.e., SPECT imaging, lumbar puncture, skin biopsy).

Adverse events will be reported by the site as required by the site's Institutional Review/Ethics Board and to the Radiation Safety Committee, as applicable.

26.2 Serious Adverse Event Reporting Requirements

Serious adverse events pertaining to SPECT imaging using DaTscan™, lumbar puncture, or skin biopsy will be reported as follows (see Operations Manual for detailed SAE reporting instructions):

a) Any serious adverse event occurring within 24 hours following the DaTscan™ injection will be documented on the Adverse Event Log and reported to GE Healthcare using PPMI GE Healthcare SAE Form, whether assessed as related to administration of DaTscan™ or not.

b) Any serious adverse event occurring more than 24 hours following the DaTscan™ injection that is assessed as being related to the DaTscan™ injection will

be documented on the Adverse Event Log and reported to GE Healthcare using PPMI GE Healthcare SAE Form.

c) Any serious adverse event occurring up to 3 days following a lumbar puncture or skin biopsy will be documented on the Adverse Event Log and may result in additional follow up with the site.

d) The Investigator will comply with his/her local Institutional Review Board (IRB)/Ethics Board, and Radiation Safety Committee (as applicable), regarding the reporting of adverse experiences.

26.3 Adverse Event Definitions

Adverse Events (AE)
An AE is any undesirable experience occurring to a participant during study participation, whether or not considered related to the study procedure.

Serious Adverse Event (SAE)
An SAE is an AE that is fatal or life-threatening, or results in hospitalization, prolongation of hospitalization, persistent or significant disability/incapacity, or a congenital anomaly/birth defect. A life-threatening AE is an AE that, in the view of the investigator, places the participant at immediate risk of death from the reaction, as it occurred. Important medical events that may not result in death, be life-threatening, or require hospitalization may be considered an SAE when, based upon appropriate medical judgment, they may jeopardize the participant and may require medical or surgical intervention to prevent one of the outcomes listed in this definition.

Inpatient admission in the absence of a precipitating, treatment-emergent, clinical adverse event is not participant to immediate reporting. For example:

- Admission for treatment of a pre-existing condition not associated with the development of a new adverse event.
- Social admission (e.g., participant has no place to sleep).
- Protocol-specific admission during a clinical study (e.g., for a procedure required by another study protocol).
- Optional admission not associated with a precipitating clinical adverse event (e.g., for elective cosmetic surgery).

Inpatient admission does not include the following:

- Emergency Room/Accident and Emergency/Casualty Department visits
- Outpatient/same-day/ambulatory procedures
- Observation/short-stay units
- Rehabilitation facilities
- Hospice facilities
- Respite care (e.g., caregiver relief)
- Skilled nursing facilities
- Nursing homes

- Custodial care facilities

26.4 Assessing Relationship of Adverse Events

The assessment of the relationship of an AE to the imaging procedure, lumbar puncture, or skin biopsy is a clinical decision based on all available information at the time the event is being documented. The following definitions of the relationship between the AE (including SAEs) and the study procedure should be considered:

- Unrelated - No possible relationship
  The temporal relationship between study procedure and the adverse event onset/course is unreasonable or incompatible, or a causal relationship to study procedure is implausible.

- Unlikely - Not reasonably related, although a causal relationship cannot be ruled out.
  While the temporal relationship between study procedure and the adverse event onset/course does not preclude causality, there is a clear alternate cause that is more likely to have caused the adverse event than the study procedure.

- Possible - Causal relationship is uncertain
  The temporal relationship between study procedure and the adverse event onset/course is reasonable or unknown, and while other potential causes may not exist, a causal relationship to the study procedure does not appear probable.

- Probable - High degree of certainty for causal relationship
  The temporal relationship between study procedure and the adverse event onset/course is reasonable and other causes have been eliminated or are unlikely.

- Definite - Causal relationship is certain
  The temporal relationship between study procedure and the adverse event onset/course is reasonable and other causes have been eliminated.

26.5 Assessing Intensity/Severity of Adverse Event

In addition to assessing the relationship of the adverse event to the study procedure, an assessment is required of the intensity (severity) of the event. The following classifications should be used:

- *Mild:*
  A mild AE is an AE, usually transient in nature and generally not interfering with normal activities.
- *Moderate*:
  A moderate AE is an AE that is sufficiently discomforting to interfere with normal activities.
- *Severe:*
  A severe AE is an AE that incapacitates the participant and prevents normal activities. Note that a severe event is not necessarily a serious event. Nor must a serious event necessarily be severe.

27 SIGNIFICANT STUDY EVENTS

There are important events that might occur during a participant's follow up in the study, such as initiation of PD medication, new clinical diagnosis, an SAE, pregnancy, or death. This information will be captured within the study database and may result in additional follow-up with the site. These events are fully described in the Operations Manual.

28 STUDY MONITORING AND SITE MANAGEMENT

The PPMI Steering Committee has the responsibility to monitor all procedures for safety, GCP, and regulatory compliance. The study sites will be managed and overseen in an ongoing manner to verify:

(a) The rights and well-being of human participants are protected.
(b) The reported study data are accurate, complete, and attributable.
(c) The conduct of the study follows the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

29 PRIVACY AND CONFIDENTIALITY

Privacy of participants will be protected in that each person will have the option to voluntarily choose whether to participate in this study. It is the responsibility of the site Investigator to consider the participant's privacy and confidentiality when completing study visits and related protocol activities.

The Site Investigator must assure that the confidentiality of participants, including their personal identity and personal medical information, will be maintained at all times. U.S. sites have additional confidentiality obligations to study participants under the Health Insurance Portability and Accountability Act (HIPAA), while European sites have additional obligations under the EU General Data Protection Regulation (GDPR). Participants will be identified by participant ID numbers on data forms and other study materials submitted to the Site Management Core (SMC), the central laboratory, and central biorepository.

The Site Investigator will permit the study monitor or designated SMC representative to review signed informed consent(s) and that portion of the participant's medical record that is directly related to the study (or provide certified copies of source documentation upon request). This shall include all study relevant documentation including participant medical history to verify eligibility, laboratory test result reports, admission/discharge summaries for hospital admissions occurring while the participant is in the study, and autopsy reports for deaths occurring during the study (when available). In addition, electronic document storage will be maintained within the Florence electronic trial master file. Identifiable participant information may be stored within this system, which has been validated and deemed compatible with 21 CFR Part 11 requirements. Only study staff requiring access to related study documentation will have permission to view identifiable information.

30 DATA AND SAMPLE SHARING AND STORAGE FOR FUTURE USE

Additional data collected for this study will be maintained and stored indefinitely at the study Cores on secure, password protected systems. All study information (data and samples) will be accessed only by those who require access as pertains to the individual's role in the study. All organizations responsible for data storage and review will observe the highest precautions

to ensure data integrity and security.

Data collected for this study may be transferred and shared across participating PPMI Cores including the Clinical Trials Statistical and Data Management Center (CTSDMC) at the University of Iowa, Indiana University PPMI Cores (Indianapolis, IN), the Site Management Core at the Institute for Neurodegenerative Disorders (New Haven, CT), and the Statistical Core at the University of Iowa (Iowa City, IA) for conducting analyses as pertains to the study including, but not limited to, enrollment, compliance, study outcomes and, in combination from the data received from other PPMI Program studies, to enable modifications to the predictive prodromal eligibility criteria. All PPMI data will be incorporated into a fully harmonized PPMI database.

All data obtained during the conduct of PPMI Clinical will be sent to the Laboratory of Neuro Imaging (LONI) in Los Angeles, California to be stored indefinitely for research purposes. Research data will be made available to researchers to conduct analyses related to PD and other disorders. Researchers will be required to comply with the PPMI data agreement to receive data. All personally identifiable information will be removed before it is shared outside the study.

Research biosamples will be shipped and stored indefinitely for research purposes at the Biorepository Cores at Indiana University School of Medicine, BioRep in Milan, Italy and Tel Aviv Sourasky Medical Center in Tel Aviv, Israel. Research specimens will be made available to researchers to conduct analyses related to PD and other disorders through an application process to the Biospecimen Review Committee (BRC). All personally identifiable information will be removed before it is shared outside the study.

31 ANALYSIS PLAN

The overall goal of PPMI is to identify markers of disease progression to inform clinical trials of therapies to reduce progression of PD disability. Correspondingly, all primary and secondary analyses of the PPMI data will focus on this goal. However, due to the rich nature of data collected as part of this study, many additional exploratory analyses will be examined throughout the study – both within and outside of the primary study steering committee.

Throughout the course of the study, analyses will be periodically updated to examine and compare baseline characteristics among the various subsets enrolled into the study. Continuous variables will be examined using a t-test and dichotomous variables will be examined using a chi-square test. Appropriate assumptions will be assessed for each comparison and necessary adjustments (i.e., transformations) will be made prior to analysis.

31.1 Primary Objectives

31.1.1 Comparison of progression biomarkers among cohorts/subsets

Use clinical and biological data to estimate the mean rates of change and variability around the mean of clinical, digital, imaging, biological, and genetic outcomes in study participants with PD diagnosis [including patients with a LRRK2, GBA, SNCA, or rare genetic variants (such as Parkin or Pink1)] and individuals with prodromal Parkinson's

disease [including individuals with RBD, olfactory loss, LRRK2, GBA, SNCA, or rare genetic variants (such as Parkin or Pink1)] and/or other risk factors for PD with and without DAT deficit and in healthy participants.

Due to the large number of progression endpoints possible for consideration, a substantial number of analyses will be conducted to examine the change and variability over time. These analyses will include standard logistic, linear, and longitudinal models, and many other proposed approaches for assessing these data. Primary interest will focus on well-known and accepted measures of disease progression (such as the MDS-UPDRS). But, an examination and potential development of novel progression endpoints to better characterize disease progression over time in this heterogeneous cohort will be considered.

Given the development of asyn SAA assay and the neuronal synuclein disease integrated staging system (NSD-ISS), both prodromal and PD participants who are SAA will be compared.

Comparison of clinical, digital, imaging, biological, and genetic outcomes in asyn SAA positive and asyn SAA negative study participants with PD diagnosis and Prodromal. The asyn SAA positive NSD Stage 1-6 will be evaluated to examine baseline stage dependent progression of clinical, digital, imaging, biological, and genetic outcomes.

31.1.2 NSD Subgroups

Analyses will also be conducted to assess whether there are subgroup differences observed with respect to disease progression. Analyses will confirm existing and identify novel clinical, digital, imaging, biologic, and genetic PD progression markers to identify quantitative individual measures or combinations of measures that demonstrate optimum interval change in study participants with PD diagnosis [including patients with a LRRK2, GBA, SNCA or rare genetic variants (such as Parkin or Pink1)] and individuals with prodromal Parkinson's disease [including individuals with RBD, olfactory loss, LRRK2, GBA, or rare genetic variants (such as Parkin or Pink1)] and/or other risk factors for PD with and without DAT deficit in comparison to healthy controls or in subsets of study participants with PD diagnosis or prodromal PD defined by baseline assessments, progression milestones and/or rate of clinical, digital, imaging, biologic, and genetic change, or other measures.

31.1.3 Analysis of progression of participants through the NSD-ISS

Evaluate the probability of progression through the NSD-ISS for NSD participants [including individuals with RBD, olfactory loss, LRRK2, GBA, SNCA, or rare genetic variants (such as Parkin or Pink1)] and/or other risk factors for PD with and without DAT deficit and for participants with clinical manifestations causing functional impairment. This analysis will involve estimating the number and percentage of participants that progress to subsequent stages. For each period of time, the percentage and a 95% confidence interval will be reported.

31.2 Secondary Objectives

31.2.1 Ancillary biomarker studies

Conduct preliminary clinical, digital, imaging, biologic, and genetic markers verification studies on promising biological markers in study subsets using stored collected samples. A series of ancillary analyses will be conducted to verify known and novel proposed PD biomarkers. These studies will vary substantially depending on the type of marker. But, as much as possible, the methods and analysis plans for all verification studies will be reviewed centrally by the PPMI steering committee in advance of implementation.

31.2.2 Compare genetic and idiopathic PD

Compare biomarker signatures for study participants with PD diagnosis without known genetic variants to those with known genetic variant [including LRRK2, GBA, SNCA, or rare genetic variants (such as Parkin or Pink1)]. These analyses will initially involve a high-level comparison of whether PD progression over time differs among those with and without a known genetic variant. Subsequent analyses will be implemented in much the same way as above, with the exception that models will implicitly assume and examine potential interactions between presence or absence of a known genetic variant and each of the potential progression markers considered in the various models.

31.2.3 Compare NSD-ISS stage biomarker signatures

Compare biomarker signatures for study participants with NSD [including individuals with RBD, olfactory loss, LRRK2, GBA, SNCA, or rare genetic variants (such as Parkin or Pink1)] and/or other risk factors for PD with and without DAT deficit with and without functional impairment.

31.2.4 Model predictors of NSD progression

Develop and test risk paradigms to establish the sequence of early biomarker and clinical events (clinical, imaging, biologic changes) in individuals with NSD stages 1-3 [including individuals with RBD, olfactory loss, LRRK2, GBA, SNCA, or rare genetic variants (such as Parkin or Pink1) and/or other risk factors for PD with and without DAT deficit] including testing early signal of risk in the associated PPMI online studies.

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33 APPENDIX 1

Eligibility Criteria for Participants consented under Clinical Protocol Amendment 3.2 (Version 2.2 dated January 30, 2023) for Screening and Baseline

Healthy Controls (HC)

Inclusion Criteria (HC)

a) Male or female age 30 years or older at Screening visit.
b) Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before SPECT imaging.
c) Confirmation that participant is eligible based on Screening SPECT imaging.
d) Able to provide informed consent.
e) Either is male, or is female and meets additional criteria below, as applicable:
    - Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Screening SPECT imaging test prior to injection of DaTscan™.

Exclusion Criteria (HC)

a) First degree relative with PD (i.e., biologic parent, sibling, child).
b) Current or active clinically significant neurological disorder (in the opinion of the Investigator).
c) Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).
d) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening visit.
e) Current treatment with anticoagulants (e.g., coumadin, heparin, oral thrombin inhibitors) that might preclude safe completion of the lumbar puncture.
f) Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
g) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
h) Any other reason that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.

Parkinson's Disease (PD)

Inclusion Criteria (PD)

a) Male or female age 30 years or older at Screening Visit.
b) A diagnosis of Parkinson's disease for 2 years or less at Screening Visit.
c) Not expected to require PD medication within at least 6 months from Baseline.
d) Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia.
e) Hoehn and Yahr stage I or II at Baseline.
f) Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before SPECT imaging.
g) Confirmation that participant is eligible based on Screening SPECT imaging.
h) Able to provide informed consent.
i) Either is male, or is female and meets additional criteria below, as applicable:
    - Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Screening SPECT imaging test prior to injection of DaTscan™.

Exclusion Criteria (PD)

a) Currently taking levodopa, dopamine agonists, MAO-B inhibitors, amantadine or another PD medication, except for low-dose treatment of restless leg syndrome (with permission of medical monitor).
b) Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of Baseline visit, except for low-dose treatment of restless leg syndrome (with permission of medical monitor).
c) Has taken levodopa or dopamine agonists prior to Baseline visit for more than a total of 90 days.
d) Atypical PD syndromes due to either drugs (e.g., metoclopramide, flunarizine, neuroleptics) or metabolic disorders (e.g., Wilson's disease), encephalitis, or degenerative diseases (e.g., progressive supranuclear palsy).
e) A clinical diagnosis of dementia as determined by the investigator.
f) Previously obtained MRI scan with evidence of clinically significant neurological disorder (in the opinion of the Investigator).
g) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening visit.
h) Current treatment with anticoagulants (e.g., coumadin, heparin, oral thrombin inhibitors) that might preclude safe completion of the lumbar puncture.
i) Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
j) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
k) Any other reason that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.

Parkinson's Disease (PD) with LRRK2 or GBA variant

Inclusion Criteria (PD - LRRK2 or GBA)

a) Male or female age 30 years or older at Screening Visit.
b) A diagnosis of Parkinson's disease for 2 years or less at Screening Visit.
c) Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia.
d) Hoehn and Yahr stage I or II at Baseline.
e) Confirmation of causative LRRK2 or GBA (willingness to undergo genetic testing as part of genetic screening and be informed of genetic testing results, or approved documentation of prior genetic testing results).
f) Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before SPECT imaging.
g) Confirmation that participant is eligible based on Screening SPECT imaging.
h) Able to provide informed consent.
i) Either is male, or is female and meets additional criteria below, as applicable:
    - Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Screening SPECT imaging test prior to injection of DaTscan™.

Exclusion Criteria (PD - LRRK2 or GBA)

a) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening visit.
b) Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture.
c) Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
d) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.

e) Any other reason that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.

Parkinson's Disease (PD) with SNCA or rare genetic variant

Inclusion Criteria (PD - SNCA or rare genetic variant (such as Parkin or Pink1))

a) Male or female age 30 years or older at Screening Visit.
b) Parkinson's disease diagnosis at Screening Visit.
c) Patients must have at least two of the following: resting tremor, bradykinesia, rigidity (must have either resting tremor or bradykinesia); OR either asymmetric resting tremor or asymmetric bradykinesia.
d) Hoehn and Yahr stage I, II, or III at Baseline.
e) Confirmation of causative SNCA or rare genetic variant (such as Parkin or Pink1) (willingness to undergo genetic testing as part of genetic screening and be informed of genetic testing results, or approved documentation of prior genetic testing results).
f) Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before SPECT imaging.
g) Confirmation that participant is eligible based on Screening SPECT imaging.
h) Able to provide informed consent.
i) Either is male, or is female and meets additional criteria below, as applicable:
    - Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Screening SPECT imaging test prior to injection of DaTscan™.

Exclusion Criteria (PD - SNCA or rare genetic variant (such as Parkin or Pink1))

a) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Screening visit.
b) Current treatment with anticoagulants (e.g., coumadin, heparin) that might preclude safe completion of the lumbar puncture.
c) Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
d) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
e) Any other reason that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.

Prodromal

The specific predictive eligibility criteria for participants recruited through PPMI Remote to advance to PPMI Clinical will be iteratively optimized based on data collected from these studies.

Inclusion criteria (Prodromal)

For Screening:

a) Confirmation that participant is eligible based on centrally determined predictive criteria including the University of Pennsylvania Smell Identification Test (UPSIT).
    - For participants in PPMI Remote, referral to the clinical site confirms predictive eligibility.
    - For participants identified by the clinical site, predictive criteria are based on generalized risk such as first degree biologic relative, known risk of PD including RBD, or known genetic variants associated with PD risk.
        - Additionally, confirmation of UPSIT eligibility during the Screening visit prior to SPECT Imaging.
b) Male or female age 60 years or older (except age 30 years or older for SNCA, or rare genetic variants (such as Parkin or Pink1) participants).
c) Individuals taking any of the following drugs: alpha methyldopa, methylphenidate, amphetamine derivatives or modafinil, must be willing and medically able to hold the medication for at least 5 half-lives before SPECT imaging.
d) Able to provide informed consent.
e) Either is male, or is female and meets additional criteria below, as applicable:

- Female of childbearing potential who is not pregnant, lactating, or planning pregnancy during the study and has a negative pregnancy test on day of Screening SPECT imaging test prior to injection of DaTscan™.

For continuation to Baseline visit and ongoing follow-up:

f) Confirmation that participant is eligible based on *Screening SPECT imaging.

Exclusion Criteria (Prodromal)

a) Clinical diagnosis of PD at screening, other parkinsonism, or dementia.
b) Received any of the following drugs: dopamine receptor blockers (neuroleptics), metoclopramide and reserpine within 6 months of Baseline Visit.
c) Current treatment with anticoagulants (e.g. coumadin, heparin) that might preclude safe completion of the lumbar puncture.
d) Condition that precludes the safe performance of routine lumbar puncture, such as prohibitive lumbar spinal disease, bleeding diathesis, or clinically significant coagulopathy or thrombocytopenia.
e) Any other medical or psychiatric condition or lab abnormality, which in the opinion of the investigator might preclude participation.
f) Currently taking levodopa, dopamine agonists, MAO-B inhibitors, amantadine or another PD medication, except for low-dose treatment of restless leg syndrome (with permission of medical monitor).
g) Has taken levodopa, dopamine agonists, MAO-B inhibitors or amantadine within 60 days of Baseline visit. except for low-dose treatment of restless leg syndrome (with permission of medical monitor).
h) Any other reason that, in the opinion of the investigator, would render the participant unsuitable for study enrollment.