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Protocol 4.0

Title:	Parkinson's Foundation PD GENEration Genetic Registry (PDGENE-PF)
Protocol Number:	PDGENE-PF
Sponsor:	Parkinson's Foundation 1359 Broadway, Suite 1509 New York, NY 10018
Funded By:	Parkinson's Foundation
Principal Investigator:	James C. Beck, PhD Parkinson's Foundation 1359 Broadway, Suite 1509 New York, NY 10018
Study Investigator:	Roy Alcalay, MD
Version Number:	Protocol Version 4.0
Version Date:	1March2024
***ClinicalTrials.gov*:**	Clinicaltrials.gov/ct2/show/NCT04994015

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PROTOCOL APPROVAL

STUDY TITLE: Parkinson's Foundation PD GENEration Genetic Registry

STUDY ACRONYM: PDGENE-PF

Protocol V. 4.0
Version Date: 1March2024

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James C. Beck
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James C. Beck, PhD — Date
Parkinson's Foundation
Sponsor, Principal Investigator

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Study Core Facility Locations and Contact Information

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Sponsors and Collaborators

- Parkinson's Foundation
- Indiana University
- CLIA CAP-Certified Laboratory Fulgent Genetics and Psomagen Inc.
- Tasso Inc.
- Global Parkinson's Genetics Program (GP2)
- Aligning Science Across Parkinson's (ASAP)

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Document History

Document	Date of Issue	Summary of Change
Version 2.0	11Mar2021	Original Version
Version 3.0	2Dec2022	Version 3.0-Amendment to Version2.0
Version 4.0	1March2024	Version 4.0-Amendment to Version 3.0

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PDGENE-PF PROTOCOL 4.0 SUMMARY

Protocol Number	PDGENE-PF
Protocol Title	Parkinson's Foundation PD GENEration Genetic Registry
Acronym	PDGENE-PF
Organization	Parkinson's Foundation
Study Centers	Parkinson's Foundation, Parkinson's Foundation Global Care Network, Parkinsons Study Group, Neurology Clinics
Study Objectives	**Primary Objective:** 1. To create a genetic data and sample repository for PD-specific genetic tests for future research use. 2. To provide clinical genetic testing and genetic counseling for people with Parkinson's disease and eligible family members. **Secondary Objectives:** 1. To bank residual deoxyribonucleic acid (DNA) extracted from whole blood samples or saliva or buccal swab for future research use. 2. To bank whole genome sequencing results for future research use. 3. To link existing clinical data with genetic data through other Parkinson's disease studies.
Study Population	People with Parkinson's disease (PWP) People at risk of developing Parkinson's disease (PD)
Study Design	Multi-center, prospective, observational study
Intervention/Treatment	Lab assay for clinically validated genetic variants of Parkinson's disease

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Number of Participants	Up to 500,000 participants over a 15-year enrollment period between December 20, 2020 and December 31, 2035, with estimated enrollment of 15,000 by December 31, 2024. Study Population: Up to 500,000 participants
Inclusion Criteria	**Study Population 1:** People With Parkinson's disease (PWP) 1. Meet Movement Disorder Society (MDS) Clinical Diagnostic Criteria for Parkinson's disease: probable diagnosis based on Investigator discretion. 2. Willingness to undergo genetic testing, and receive genetic test results for at minimum seven Parkinsons-related genes, including: *GBA1*, *LRRK2, SNCA, VPS35, PRKN, PINK1, PARK7*. Participants may choose to also receive additional findings which might be related to their PD diagnosis and/or health-related clinically actionable findings. 3. Based on site clinician's determination, have the capacity to give full informed consent in writing or electronically, or provide consent through a legally authorized representative (LAR)/power of attorney (POA), and have read, understood and completed the informed consent form. 4. Are able to perform, or have a designee who can perform study activities (including completion of either online, in-person or paper surveys). **Study Population 2:** People at risk of developing PD or with a family history of PD 1. Willingness to undergo genetic testing, and may choose to be informed of genetic test results for, at minimum, seven Parkinsons-related genes, including: *GBA1, LRRK2, SNCA, VPS35, PRKN, PINK1, PARK7*. Participants may choose to also receive additional findings which might be related to their PD diagnosis and/or health-related clinically actionable findings. 2. Based on site clinician's determination, have the capacity to give full informed consent in writing or electronically, or provide consent through a legally authorized representative (LAR)/power of attorney (POA), and have read, understood, and completed the informed consent form.. 3. Are able to perform, or have a designee who can perform study activities (including completion of either online, in-person, or paper surveys).
Exclusion Criteria	**Study Population 1:** People With Parkinson's disease (PWP) 1. Probable diagnosis at the time of consent of an atypical parkinsonian disorder (i.e., multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, corticobasal syndrome), including that due to medications, metabolic disorders, encephalitis, cerebrovascular disease, or normal pressure hydrocephalus.

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	2. Individuals who have received a blood transfusion within the past 3 months. 3. Individuals who have active hematologic malignancies such as lymphoma or leukemia. 4. Individuals who have had a bone marrow transplant within the past 5 years. 5. Individuals under the age of 18 or age of majority in applicable states at the time of consenting. **Study Population 2:** People at risk of developing PD or with a family history of PD 1. Individuals who have received a blood transfusion within the past 3 months. 2. Individuals who have active hematologic malignancies such as lymphoma or leukemia. 3. Individuals who have had a bone marrow transplant within the past 5 years. 4. Individuals under the age of 18 or age of majority in applicable states at the time of consenting
Study Timeline	Study duration – 15 years Study start date: December 20, 2020 Estimated primary completion date: December 31, 2035
Primary Outcome Measures	The number of participants who deposit their genetic testing data to the Parkinson's Foundation's data repository.
Genetic Testing and Assay Methodologies	Coded whole blood or saliva or buccal samples will be collected either at clinical sites or remotely and sent to a Clinical Laboratory Improvements Amendment (CLIA)-certified genetic testing laboratory to extract DNA and identify the presence of genetic variants in genes such as *LRRK2, GBA1, PRKN, PINK1, PARK7, SNCA* and *VPS35* through whole genome sequencing.
Returning Results Methodology	Participants will receive results by the site clinician or by a centralized genetic counseling service. All participants will undergo genetic counseling services post-genetic testing (locally or through central services).
Sample Size Considerations & Statistical Analysis Plan	Statistical analyses will include the total number of participants who undergo genetic testing and receive results for [1] at minimum seven Parkinsons-related genes, including: *GBA1, LRRK2, SNCA, VPS35, PRKN, PINK1, PARK7* and deposit their genetic testing data and DNA samples to the Parkinson's Foundation as the primary outcome.

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Table 1. List of Acronyms and Definition of Terms

Acronym	Definition
DNA	Deoxyribonucleic Acid
CLIA	Clinical Laboratory Improvement Amendments
CFR	Code of Federal Regulations
iCRF	Integrated Electronic Case Report Form
EDC	Electronic Data Capture
FDA	Food and Drug Administration
GBA1	Glucocerebrosidase 1
GCP	Good Clinical Practice
GP2	Global Parkinson's Genetics Program
ICF	Informed Consent Form
ICH	International Conference on Harmonization
ID	Identification
IRB	Institutional Review Board
LRRK2	Leucine Rich Repeat Kinase 2
NGS	Next Generation Sequencing
MOP	Manual of Procedures
PARK7	Parkinsonism Associated Deglycase
PD	Parkinson's Disease
PI	Principal Investigator
PINK1	PTEN Induced Kinase 1
POP	Parkinson's Outcomes Project
PRKN	Parkin RBR E3 Ubiquitin Protein Ligase
PWP	People With Parkinson's disease
PSG	Parkinson Study Group
SNCA	Alpha-synuclein
VPS35	Vacuolar Protein Sorting 35

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PD GENEration STUDY OVERVIEW

Background

Parkinson's disease (PD) is a chronic neurodegenerative disease characterized by progressive motor disability and includes motor symptoms (such as resting tremor, bradykinesia, and gait disturbance) and non-motor symptoms (such as cognitive decline, sleep impairment, autonomic dysfunction, depression, and fatigue). PD currently affects nearly one million Americans, and its prevalence is expected to double over the next generation.[1]

Although numerous genes have been linked to PD, only a fraction of people with Parkinson's Disease (PWP) receive clinical genetic testing, usually reserved for people with early onset PD. There are many ways to access genetic testing for PD, including clinical genetic testing laboratories, as well as direct-to-consumer or consumer-initiated tests. The associated data are kept separately by each genetic testing company and/or the individual who received the test. Knowledge of one's genetic status may have significant implications for clinical care, potential treatment options, and may provide insight on the rate of disease progression and PD prognosis. More importantly, carrying a mutation may confer eligibility for ongoing genetic-focused clinical trials.

A major barrier to the success of PD-focused clinical trials tailored to target a specific genetic pathway, is that PWP who are mutation carriers often do not know their genotype. Moreover, the site clinicians who may refer PWP to these clinical trials are also unaware of their participants' genetic status.

The purpose of this study is to expand clinical genetic testing and genetic counseling to the PD community. The study aims to develop a central repository for PD-related genomic data by individuals who consent to deposit their data and bank their residual DNA obtained through clinical genetic testing for future research use, including sharing data and biosamples with the Global Parkinson's Genetics Program (GP2). GP2 is a global research study aimed to further understand the genetic contributions to PD through genotyping and sequencing diverse patient groups and studying rare familial forms of PD: (https://gp2.org/). The rationale for this study is explained by the need for a centralized repository of PD-specific genomic data to advance research efforts, accelerate clinical trial timelines, and empower PWP and their clinicians to make more informed decisions for clinical care.

This study is sponsored by the Parkinson's Foundation and funded with the support of the Parkinson's community and their families. Participation in the study is entirely voluntary, and participants will receive no payments for their participation in the study.

STUDY OBJECTIVES

Primary Objectives

1. To create a genetic data and sample repository for PD-specific genetic tests for future research use.
2. To provide clinical genetic testing and genetic counseling for people with Parkinson's disease and eligible family members.

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Secondary Objectives

1 To bank residual deoxyribonucleic acid (DNA) extracted from whole blood or saliva or buccal swab samples for future research use.
2 To bank whole genome sequencing results for future research use.
3 To link existing clinical data with genetic data through other Parkinson's disease studies.

STUDY DESIGN

Study Overview

The Parkinson's Foundation PD GENEration Genetic Registry study is an observational prospective registry study whose primary aim is to develop a central repository for PD-related genomic data for future research.

The study cohort is comprised of up to 500,000 individuals, 18 years of age or older who are clinically diagnosed with PD, or are at-risk for developing PD (i.e, have a family history or carry a known PD-related genetic mutation). This is an internationally-based study with potential for expansion across multiple countries.

The study intervention involves a lab assay for at minimum seven genetic variants for Parkinson's disease. Participants may choose to receive additional genetic findings which might be related to their Parkinson's disease diagnosis and/or health-related clinically actionable findings.

Study Population: Up to 500,000 participants

STUDY POPULATION

Inclusion Criteria

Up to 500,000 individuals aged 18 or older who have a confirmed clinical diagnosis of PD (Study Population 1), or those who are at risk of developing PD or with a family history of PD (Study Population 2), based on Investigator discretion and sponsor approval, are eligible to participate in this study.

There are no restrictions for study participation based on gender, race or ethnic origin for either of the two study groups. Participants in both study groups must meet specified criteria for participation. Individuals who have received genetic testing in the past, other than through this study, are eligible to enroll.

Participants must also meet the following criteria in order to enroll in the study:
Study Population 1: People With Parkinson's disease (PWP)

1. Meet Movement Disorder Society (MDS) Clinical Diagnostic Criteria for Parkinson's disease: probable diagnosis based on Investigator discretion.
2. Willingness to undergo genetic testing, and may choose to be informed of genetic test results for, at minimum, seven Parkinsons-related genes, including: *GBA1, LRRK2, SNCA, VPS35, PRKN, PINK1, PARK7*. Participants may choose to also receive additional

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findings which might be related to their PD diagnosis and/or health-related clinically actionable findings.
3. Based on site clinician's determination, have the capacity to give full informed consent in writing or electronically, or provide consent through a legally authorized representative (LAR)/power of attorney (POA), and have read, understood and completed the informed consent form.
4. Are able to perform, or have a designee who can perform study activities (including completion of either online, in-person, or paper surveys).

Study Population 2: People at risk of developing PD or with a family history of PD
1. Willingness to undergo genetic testing, and may choose to be informed of genetic test results for, at minimum, seven Parkinsons-related genes, including: *GBA1, LRRK2, SNCA, VPS35, PRKN, PINK1, PARK7*. Participants may choose to also receive additional findings which might be related to their PD diagnosis and/or health-related clinically actionable findings.
2. Based on site clinician's determination, have the capacity to give full informed consent in writing or electronically, or provide consent through a legally authorized representative (LAR)/power of attorney (POA), and have read, understood, and completed the informed consent form.
3. Are able to perform, or have a designee who can perform study activities (including completion of either online, in-person, or paper surveys).

Exclusion Criteria

Study exclusion criteria include:
Study Population 1: People With Parkinson's disease (PWP)
1. Probable diagnosis at the time of consent of an atypical parkinsonian disorder (i.e., multiple system atrophy, progressive supranuclear palsy, dementia with Lewy bodies, corticobasal syndrome), including that due to medications, metabolic disorders, encephalitis, cerebrovascular disease, or normal pressure hydrocephalus
2. Individuals who have received a blood transfusion within the past 3 months.
3. Individuals who have active hematologic malignancies such as lymphoma or leukemia.
4. Individuals who have had a bone marrow transplant within the past 5 years.
5. Individuals under the age of 18 or age of majority in applicable states at the time of consenting

Study Population 2: People at risk of developing PD or with a family history of PD
1. Individuals who have received a blood transfusion within the past 3 months.
2. Individuals who have active hematologic malignancies such as lymphoma or leukemia.
3. Individuals who have had a bone marrow transplant within the past 5 years.
4. Individuals under the age of 18 or age of majority in applicable states at the time of consenting

STUDY PROCEDURES

Recruitment

Targeted recruitment for the study will include people among the global PD community with a confirmed or probable diagnosis of PD. All recruitment materials will be reviewed and approved by the Institutional Review Board (IRB) prior to implementation. Recruitment materials include digital and print flyers, email communications, informational videos, and word-of-mouth advertising.

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Recruitment methods will include direct advertising to the PD community through the Parkinson's Foundation's outreach network and their clinicians, as well as self-referral from public sources. Clinicians at Parkinson's Foundation-approved participating centers will invite their patients to participate by informing patients of the study during regularly scheduled patient visits. Study recruitment will also involve efforts to recruit participants from underrepresented and minority populations.

Secondary populations of people at risk for developing PD (Study Population 2) will be evaluated and invited to enroll in the study on a case-by-case basis per Investigator determination and sponsor approval.

Targeted overall recruitment for this study is up to 500,000 enrolled participants. The Study Team will keep an active log of all potential participants from both study populations.

Informed Consent

This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50.

In accordance with relevant regulations, an informed consent agreement explaining the procedures and requirements of the study, together with any potential hazards/risks will be provided to each participant. Each participant will provide a signed informed consent form electronically or in-person.

The participant must be assured of the freedom to withdraw from participation in the study at any time.

If there are changes made to the protocol, also requiring changes to the informed consent that affect the participants directly during their enrollment period of the study, participants will be contacted by email to notify them of said changes. Re-consent may be required at the discretion of the sponsor and IRB.

The consent process for each participant who signs informed consent will be documented in the study files and will include the title of the study, that the consent allows for discussion with a research coordinator or clinician for the opportunity to address questions and answers, how the participant demonstrated comprehension (if consent was discussed), that the consent was signed prior to the study procedure, and that the participant received a signed copy of the consent.

Non-English Speaking Participants

Participants must be able to read and understand the informed consent form in a language that is Study-translated, and IRB approved.

In the event a non-English speaking participant wishes to participate and there is no informed consent form available in their native language, then they may be consented through a site appointed and approved translator or translation service, based on study sponsor discretion. The site responsible for consent must request approval for the use of a translator or translation service from sponsor prior to participant enrollment.

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ENROLLMENT PROCEDURES

Once participant informed consent has been obtained and documented, study enrollment may begin. Participation in the study can occur in three ways:

1- **Participant may self-refer into the study**
2- **In-Person Enrollment**
3- **Online Enrollment**

The three enrollment options are outlined below:

Self-Referral Enrollment

- Clinician contacts participant and informs them of study, or participant self-refers to the study through the Parkinson's Foundation directly
- Before consenting, all participants will view an informational video about PD and the study
- Participant consents and submits clinical information (including but not limited to, taken from participant's electronic medical record, basic demographics, contact information, family history, age at onset, year of diagnosis, deep brain stimulation status, referral source)
- Centralized site coordinator connects with participant remotely to confirm eligibility and survey information
- Sample collection kit (i.e. primarily whole blood or, secondarily, saliva or buccal swab) is mailed to participant. Participant completes collection and mails sample to genetic testing laboratory
- Genetic testing laboratory releases report to Parkinson's Foundation and the referring provider
- Genetic counseling and disclosure of results will be provided either through centralized genetic counselors or site-based genetic counseling if available

In-person Enrollment

- Site recruits participant and refers them to on-site coordinator
- Before consenting, all participants will view an informational video about PD and the study
- On-site coordinator consents participant
- Needed clinical information (including but not limited to, taken from participant's electronic medical record, basic demographics, contact information, family history, age at onset, year of diagnosis, deep brain stimulation status, referral source) is gathered by self-reported online form or by on-site coordinator
- Site collects primarily whole blood or, secondarily, saliva or buccal swab and ships samples to genetic testing laboratory
- Genetic testing laboratory releases report to Parkinson's Foundation and the referring provider
- Genetic counseling and disclosure of results will be provided either through centralized genetic counselors or site-based genetic counseling if available
- Through this pathway participants may also be dual-recruited into center specific bio-bank studies as per local IRB approval

Online Enrollment

- Referring clinician contacts participant to sign HIPAA release of information, if applicable, by site
- Referring clinician sends participant name and contact information to Parkinson's Foundation or to centralized site
- Before consenting, all participants will view an informational video about PD and the study

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- Parkinson's Foundation or centralized site coordinator connects with participant remotely to consent them and gather clinical information (including but not limited to, taken from participant's electronic medical record, basic demographics, contact information, family history, age at onset, year of diagnosis, deep brain stimulation status, referral source)
- Sample collection kit (i.e. primarily whole blood or, secondarily, saliva or buccal swab) mailed to participant. Participant completes kit and mails sample to genetic testing laboratory
- Genetic testing laboratory releases report to Parkinson's Foundation and to referring provider if they chose to receive their results
- Genetic counseling and disclosure of results will be provided either through centralized genetic counselors or site-based genetic counseling if available

Site Visits

The study will consist of two mandatory participant visits, which include an initial baseline visit, followed by a genetic counseling visit. Both mandatory visits can be conducted either in person or remotely.

In the event that the initial sample collected at baseline does not meet quality standards, participants will be asked to come in for an additional (or multiple) Quality Not Sufficient (QNS) visit. Each of the study visits are described below:

Baseline Visit

The Baseline Visit will be performed either by site staff or remotely through a centralized process. During the baseline visit, the study team will review informed consent and HIPAA permission to use Protected Health Information (PHI), if applicable.

The study team will gather relevant clinical information (including but not limited to, taken from participant's electronic medical record, basic demographics, participant contact information, family history, age at onset, year of diagnosis, deep brain stimulation status, referral source) and input the data directly in the electronic data capture (EDC) system.

The study team will collect primarily whole blood or secondarily a saliva, or buccal swab sample from the participant during the in-person baseline visit, or ship a sample collection kit (i.e. primarily whole blood or, secondarily, saliva or buccal swab) to the participant's home if the baseline visit is performed remotely.

Quality Not Sufficient Sample Re-collection Visit(s)

In the event the laboratory issues a Quality Not Sufficient (QNS) report for a participant, a QNS Sample Re-collection visit must be initiated. The following activities will be performed:

- Inform participant of QNS report and confirm they agree to provide another sample
- If the participant agrees, collect a new sample from participant or ship a new sample collection kit to participant if QNS Sample Re-collection Visit is performed remotely
- If participant does not agree to another collection, or multiple attempts of testing are unsuccessful, they should be considered an early termination

Genetic Counseling Visit

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Following the baseline visit to collect the biospecimen sample, (and if applicable, the QNS visit or visits), the Genetic Counseling Visit will be performed by the site appointed genetic counselor or site clinician, or centrally through the centralized genetic counseling center.

During the genetic counseling visit, the counselor will review genetic test results with the participant via phone or video call, and answer any questions.

At the conclusion of the counseling session, participants will be sent their genetic test results, a genetic counseling letter, and informational materials.

If a translator is needed to perform the genetic counseling visit for participants, sites must request approval for the use of a translator or translation service from the sponsor and the genetic counseling core (if applicable) prior to participant consent.

Optional Additional Health Findings

The study may request that the CLIA-certified laboratory analyze the original sequence data to identify additional genetic findings that are deemed important to participants' PD diagnosis or health. The choice of the genes to evaluate would be determined by the PD GENEration steering committee and would include PD-related genes as well as health-related clinically actionable genes informed by American College of Medical Genetics and Genomics (ACMG) current recommendations. The PD GENEration steering committee would determine which additional genes would be important to report to participants. This list could change over time as new knowledge is gained about these genes and their impact on disease. Participants will be required to provide informed consent at enrollment to indicate their willingness to receive these additional findings. If consent is not obtained, then additional findings will not be reported or disclosed. [7] [8] Participants who opt out of additional findings may still participate in the primary study. Documentation of informed consent status will be stored electronically for future reference.

These reported additional findings may include PD-related conditions that are rare, atypical, or overlapping. Additional findings could also include non-PD related genes that may be associated with a high risk of developing specific health conditions such as cancer, heart disease, [10] [CLP11] or other conditions that can cause sudden death or have serious effects on participant's health. Depending on symptom onset, many of these conditions may be prevented or effectively treated with evidence-based interventions. An example is one of the inherited breast cancer syndromes caused by BRCA1. Approximately 2-4% percent of our population will be expected to have an additional finding based on published literature.

Genetic counseling for Additional Health-Related Findings

Participants may contact the study team at any time to change their mind about receipt of additional findings. Participants who consent to be informed of positive (e.g. abnormal) additional health-related findings will be notified via email, phone call, or posted letter that an additional health-related findings is identified. At this step, participants will have the opportunity to continue with or decline disclosure of an additional finding from the sequence data of their prior sample. Documentation of this decision will be electronically stored.

Participants who agree to receive information about a positive additional finding will receive results disclosure by their site clinician or a centralized genetic counselor. Participants may also request to speak to a genetic counselor prior to disclosure, to help decide about the risks and benefits of possibly receiving genetic results. Following the genetic counseling session about additional genetic findings, the participant will receive the test report and summary letter.

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Participants who change their mind about receiving additional findings may have an opportunity to change their decision by contacting the Parkinson's Foundation.

Risk/Benefit Assessment

Since PD GENE-PF is an observational study, most participants will not likely undergo major risks or benefits by participating. However, potential anticipated risks and benefits for some participants are listed below.

Possible risks for participation in this study include loss of confidentiality (the unintentional release of personally identifiable information). The mitigation for such loss is that the Parkinson's Foundation's data repository will assume responsibility for maintaining the confidentiality of all patient data, and will adhere to the principles outlined in the patient informed consent, confidentiality, data collection and storage protocols, and safety practices outlined in this study protocol.

Participants who undergo clinical genetic testing as part of this study will receive the clinical report for clinically actionable PD relevant genes including: *GBA1, LRRK2, SNCA, VPS35, PRKN, PINK1, PARK7*. This report may lead to additional information regarding the possible roles of their genes in their PD diagnosis.

From genetic testing as part of this study, participants may receive additional information that informs their PD diagnosis such as the possibility of dementia or severe progression which may cause psychological sequelae. In addition, it may predict that other relatives are at risk for PD which could cause emotional effects to the participant. Some results related to PD may predict other health conditions, such as the metabolic disorder Gaucher disease. Genetic test results may result in other unexpected findings like discovering unknown biological relationships in the family. It is possible that genetic test results could result in genetic discrimination or loss of privacy about information about health issues. Sometimes genetic test results can result in changes to insurance or result in additional medical costs to the patient.

Benefits from participation in the study include that participants will receive information that may be important to them and their family about their PD diagnosis. This information could be useful for life planning and knowing familial risks. Genetic test results could inform their medical care such as helping them determine if they are eligible for a clinical trial. Participants may also receive additional helpful information in the event that additional genetic variants are detected or classifications changed.

Risks from receiving additional secondary health related findings results about serious health risks include anxiety or emotional distress.

Study Methodology

This study will be conducted under the supervision and direction of the Parkinson's Foundation. The study will involve whole genome sequencing with clinical reporting of at minimum seven PD genes, and the option for return of additional findings and raw genetic data generation. Analysis and interpretation for PD genes and additional targeted genes will be performed within CLIA/CAP regulations. Analysis and interpretation of additional targeted genes beyond genes returned via this study will be conducted under a research protocol (non-CLIA/CAP). DNA will be stored in a CLIA-approved facility for future analyses. Genetic testing results will be returned to the referring

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clinician and will be provided to participants. All participants will undergo genetic counseling for the return of results.

Participant Identification (ID)- PDGENE ID

A unique PDGENE ID number will be auto-generated and assigned in sequential order to identify study participants on all study forms and research specimens.

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A Table outlining the study visits can be found below.

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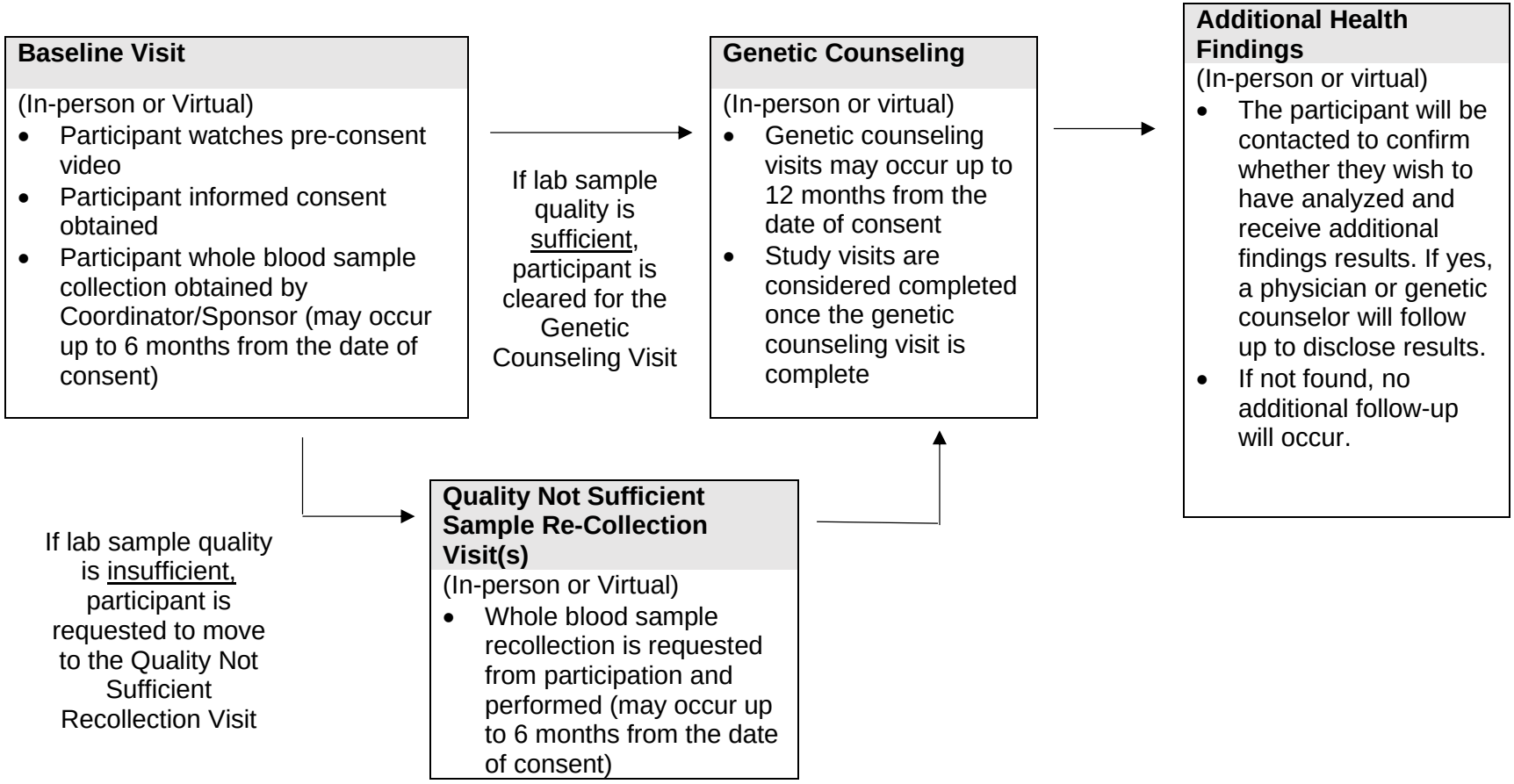
Table 2: Study Site Visits



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DATA COLLECTION AND MANAGEMENT

The Parkinson's Foundation's data repository group will be responsible for all data collection and management.

An integrated electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used to capture primary source data for this study. The paper CRF will constitute the source document when data is first recorded on paper, then entered into the EDC. The paper CRF is for back–up only and should only be used in the event of EDC application technical issues.

The signed informed consent, withdrawal of consent form (if applicable), and genetic results will be uploaded into the EDC with access restrictions. The EDC system is designed to ensure timeliness and accuracy of data, as well as the prompt reporting of data from the study on an ongoing basis to the study sponsor. Data submitted to the EDC system are immediately stored in the secure central study database and are accessible for review by study management staff. Data review and query processing will be done through interaction with the genetic testing laboratory and the data repository team.

Data quality is monitored via data queries generated in real time as the data are entered. Any changes to the data will be fully captured in an electronic audit trail. The cycle of electronic data entry, review, query identification/resolution, and correction occurs over the course of the study period until all participants have completed the study. The system is compliant with relevant FDA regulatory requirements per 21 CFR Part 11.

Maintenance and Retention of Records

The Parkinson's Foundation will retain all study records required by federal regulations in a secure and safe facility with limited access. Regulations require retention for a period of at least three years after the investigation is completed or discontinued.

Data Transfer

The Parkinson's Foundation will receive data cuts of all genetic/genomic data on a routine basis from the genetic testing laboratory of all consented participants via secure File Transfer Protocol server. Participants' clinical data will be gathered either by a centralized site coordinator through virtual visit, by site coordinator who consents participants OR self-furnished by the participant through a secure link to EDC survey. If clarification of clinical data is required, the Parkinson's Foundation may reach out to the attending clinician at the participating center.

Use of Specimens for Research Purposes

Requests for participant samples for research purposes must be made to the Parkinson's Foundation to gain access to the biorepository. A researcher wishing to obtain specimens should contact the Parkinson's Foundation with a research proposal outlining the purpose and intended use of the specimens. If deemed appropriate by the Parkinson's Foundation, a request to the biorepository will be made which includes a unique study identifier, the requested specimen, and the requested volume/amount. To reduce damaging materials by recurrent freeze-thaw cycles, biorepository recommends that the study limit the return of banked specimens to well-characterized requests with specific scientific or research-related goals. The specimen will be shipped directly to the researcher.

PARTICIPANT STATUS

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Lost To Follow-Up

Participants will be considered lost to follow-up (LFTU) once all of the following have been met over the span of one year:

- The participant has not completed their Genetic Counseling visit within approximately 6 months of results being made available, or they have not submitted a sample for testing within one year of consent to participate.
- Site or centralized coordinator or the Parkinson's Foundation has contacted the participant regarding their results disclosure three times via email or telephone without receiving a response from the participant, before or within six months of results being made available.
- The site or centralized coordinator or the Parkinson's Foundation has sent the Participation Notice Letter (see Appendix A), regarding their results disclosure to the participant via certified, return receipt mail or email without any response from the participant.

Participants who are considered LTFU remain eligible to receive their genetic testing results within approximately 10 years of results being made available if they contact the study sponsor or site, prior to study closure and as is feasible per study staff availability.

Study Withdrawal

Participants will be advised in the electronic informed consent form that they have the right to withdraw from the study at any time without prejudice or compromising regular clinical care and may be withdrawn at their clinician's discretion at any time.

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There are multiple permissions given by participants for this study in the informed consent process. For this reason, participants wishing to withdraw from the study must submit their request in writing to the study's Principal Investigator to confirm which portion of the study from which they wish to withdraw. This email or letter will be sent to the Parkinson's Foundation and will confirm the participants' withdrawal from all or a portion of the study. This email/letter will be retained electronically, by the Parkinson's Foundation. In the event the participant requests the destruction of their stored DNA samples, the biospecimen bank will be notified of the request and documentation will be generated confirming that said stored DNA samples have been destroyed.

A participant may withdraw or be withdrawn from the study for the following reasons:

- Withdrawal of consent, desire not to have results disclosed, or refusal to share information as part of the registry
- Request from clinician based on the best interest of the study participants
- Early termination of study
- Refusal to submit a second or subsequent sample if first sample is deemed as a QNS
- Changes in health status, such as cognitive decline or death

GOOD CLINICAL PRACTICE/ADMINISTRATION

REGULATORY/ETHICS

Compliance Statement

This study will be conducted in accordance with the Good Clinical Practice (GCP) guidelines promulgated by the International Conference on Harmonization (ICH) and the Food and Drug Administration (FDA), and any applicable national and local regulations, including FDA regulations under 21 CFR Parts 11, 50, 54, and 56.

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Manual of Operations
Procedures not described in this protocol will be performed according to the study Manual of Operations (MOP), unless otherwise stated.

Institutional Review Board/Independent Ethics Committee
This study will be conducted in accordance with the provisions of 21 Code of Federal Regulations (CFR) Part 50.

The Parkinson's Foundation will utilize a central Institutional Review Board (IRB), however, participating sites may elect to utilize their local IRB for study oversight.

Protocol Amendments
Changes to the protocol may only be implemented via an approved protocol amendment process. Protocol amendments must be approved by the Parkinson's Foundation and the central IRB of record prior to implementation, except when necessary to eliminate hazards and/or to protect the safety, rights or welfare of participants. All study team members will receive training on the protocol and subsequent amendments. Protocol deviations, if applicable, will be recorded and submitted to the IRB, and the study team will prioritize resolving the deviations.

In the event of approved protocol changes throughout any period of study participation, changes to the informed consent process will be updated accordingly, and all participants will be contacted via email to notify them of said changes.

Participant Confidentiality
The Parkinson's Foundation and the genetic testing laboratory will ensure that the privacy of participants, including their personal identity and personal medical information, will be maintained at all times.

After a participant signs an informed consent, it is required that the Parkinson's Foundation permit any study monitor, independent auditor or regulatory agency personnel to review the signed informed consent(s) and the portion of the participant's medical record that is directly related to the study. This review shall include all study relevant documentation, including participant medical history to verify eligibility, laboratory test result reports, as applicable, admission/discharge summaries for hospital admissions occurring while the participant is in the study, and adverse events reports, reports of deaths occurring during the study, and unanticipated events occurring during the study.

The participant's authorization allows the Sponsor to receive and review the participants' protected health information that may be re-disclosed to any authorized representative of the Sponsor or other central services (e.g., genetic counseling core) facility for review of participant medical records in the context of the study.

Participants' medical records may be accessed to confirm medical history. Participation in the study may be documented in the participants' medical record.

Quality Assurance (QA) Audits/Site Visits
In accordance with ICH Guidelines for Good Clinical Practice 5.18, the study will be remotely monitored to verify that:

- The rights and well-being of human participants are protected.
- The reported study data are accurate, complete, and verifiable from source documents.

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- The conduct of the study is in compliance with the currently approved protocol/amendment(s), with GCP, and with the applicable regulatory requirement(s).

The Parkinson's Foundation has the responsibility and expertise to monitor all procedures for safety and for GCP and regulatory compliance, and to hold meetings to review GCP and regulatory compliance. Monitoring activities will include:

- Verifying participant consent was obtained.
- Communicating deviations from the protocol, good clinical practice (GCP), and the applicable regulatory requirements to the investigator and taking appropriate action designed to prevent recurrence of the detected deviations.
- Federal regulations 21 CFR §56.109(f) and 45 CFR §46.109(e) state that an IRB shall conduct continuing review of research covered by these regulations at intervals appropriate to the degree of risk, but not less than once per year, and shall have authority to observe or have a third party observe the consent process and the research. Continuing review by the IRB routinely includes interim progress reports, as directed by the Board, review of proposed changes to research, adverse event reports, review of any protocol deviations, visits to the research site, and annual review of the research.

During the course of the study, central monitoring (remote evaluation) will be carried out by the Parkinson's Foundation's data repository group to ensure compliance.

STUDY CONCLUSION

Publication of Research Findings

Publication of the results of this study will be governed by the policies and procedures developed by the Parkinson's Foundation and in accordance with the International Committee of Medical Journal Editors (ICJME) Uniform Requirements for Manuscripts Submitted to Biomedical Journals.

Data Sharing

The Parkinson's Foundation is committed to public access to data sharing for future related and unspecified research. Any data shared for future use (i.e., beyond the purposes of this study) will be done so in a manner consistent with the principle of safeguarding participant privacy and consistency with participant informed consent.

All data shared outside the study and their authorized agents will be aggregated using a Global Unique Identificaton Number (GUID), with event dates and times as unique identifiers (no names or other unique personal identifiers will be shared). The GUID tool performs a one-way encryption to create a participant "fingerprint," that allows anonymized identification and analysis of participant data. The fingerprint cannot be used to recreate original participant data or participant protected health information. Participants may have already been assigned a GUID as part of their participation in another clinical study. For those participants who do not have a GUID, a study team member will create a GUID for them.

Study Closeout

A comprehensive communication plan will be developed and disseminated to ensure timely reporting of study results to study participants and sites following study completion.

ClinicalTrials.gov

A description of this study, including a summary of the study protocol and results, is available on *http://www.ClinicalTrials.gov*, as required by federal mandates for open access.

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REFERENCES

[i] Marras, C., Beck, J. C., Bower, J. H., Roberts, E., Ritz, B., Ross, G. W., et al. (2018). Prevalence of Parkinson's disease across North America. *Npj Parkinson's Disease*, *4*(1), 1–7. http://doi.org/10.1038/s41531-018-0058-0.

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APPENDIX A:
Participant Notice Letter

Date [Month, Day, Year]

[Participant Name]
[Participant Address]

Subject: Participant Notice

Dear [Participant Name],

You are being contacted regarding your participation in the PD GENEration Genetic Registry Study by the Parkinson's Foundation through [site name]. We have attempted to reach you regarding your genetic test results through the email and phone number that was provided at the time of your consent to participate in this study and have not been successful.

If you are still interested in receiving your results for the study, please feel free to contact us to schedule a genetic counseling appointment:

[site email]

Or

[site number].

If we do not hear from you, we will assume you are no longer interested in receiving your results and you will not be contacted further.

Thank you.

Sincerely,
[Senders name]

[Senders contact]