CLINICAL STUDY PROTOCOL

Title:	Black and African Americans Connections to Parkinson's Disease (BLAAC PD) A Project of the Global Parkinson's Genetics Program (GP2)
Acronym:	BLAAC PD
Version Number:	V 5.0
Clinical Phase:	Observational
Funder:	Aligning Science Across Parkinson's; The Michael J. Fox Foundation for Parkinson's Research
Scientific Leadership:	Lana Chahine, MD Department of Neurology 3471 5th Avenue, Suite 810, Pittsburgh, PA, 15213, USA
Coordination Center:	Melissa Kostrzebski, MBA, MS Clinical Trials Coordination Center (CTCC) Center for Health + Technology (CHeT) University of Rochester 265 Crittenden Boulevard CU420694 Rochester, New York 14642

PROTOCOL APPROVAL

Title:	Black and African Americans Connections to Parkinson's Disease (BLAAC PD) A Project of the Global Parkinson's Genetics Program (GP2)
Acronym:	BLAAC PD

Lana Chahine, MD Date
Principal Investigator (BLAAC PD)

DOCUMENT HISTORY

Document	Date of Issue	Summary of Changes
Version 1.0	01 June 2021	Initial Release
Version 2.0	12 September 2021	Removed all references to "atypical parkinsonism" across all study materials **Section 5.0** Documented the Recruitment Methods for the study **Section 5.0** Section Sites will collect reasons for declining to participate (in the Recruitment Activities Log) **Section 7.2** Increased the amount of isolated DNA required per sample from 1200ng to 6000ng and clarified the quality and concentration **Section 7.1** Removed the group B PHI being collected (exact date of birth, diagnosis and date of therapeutic initiation is now replaced by year) **Section 7.2** Established a range for the amount of blood that will be drawn from 6 mL – 8 mL to accommodate two different collection tube types
Version 3.0		**Synopsis:** Updated Specific Aims to include new analyses **Section 3.0** Replaced CARE with NORC **Section 5.0** Updated Recruitment Methods to include events, in-home visits and care navigation **Section 7.2** Removed DNA Isolation **Section 11.** Updated Reimbursement to include Travel Expenses
Version 4.0	17Jan2024	Update Title Page with new CTCC PI Information Removed Investigator Agreement Page **Synopsis:** Updated number of participant enrolled from 5000 to 2000 **SOA:** Added UPSIT **Section 5:** Changed "will" to "may" with regard to Recruitment activities log collection **Section 7.1**: Added information about the UPSIT Test and procedures **Section 13.** Removed Participant Withdrawals as Reportable Events

		Section 15. Added Specimens may be shared with Psomagen, Inc., **Section 20**. Added information about the UPSIT to the Data Analysis Plan
Version 5.0	07Feb2024	Removal of Dr. Singleton as PI. Addition of Dr. Chahine as PI.Subject changed to participant. Minor grammatical updates throughout Number of sites increased to approximately 12 Modification of sample processing and biorepository language, multiple sections. **Synopsis:** rephrasing of primary objective, addition of secondary synopsis, update to specific aims, updated inclusion/exclusion criteria, updated total number of participants to up to 4000 Extension of study time period to ten (10 years). Updates to inclusion/exclusion criteria. Added a specific aim to develop and systematically test strategies that enable recruitment of Black Americans and African Americans to participate in PD research **Recruitment**: NORC removed **SOA:** updated to reflect new questionnaires, removal of footnotes Addition of recruitment methods **Section 7.1**: addition of: language on how visits may be conducted, clinical assessments, removal of UPSIT/replaced with SIT **Section 7.2**: addition of Tasso+ as blood collection option, increase in remuneration, companion travel reimbursement language

BLAAC PD PROTOCOL SYNOPSIS

Protocol Title	Black and African Americans Connections to Parkinson's Disease
Acronym/Working Title	BLAAC PD

Sponsor	Aligning Science Across Parkinson's; The Michael J. Fox Foundation for Parkinson's Research
Clinical Phase	Observational
Investigators	Multi-Center Trial
Study Centers	Up to approximately 12 clinical research sites located in the Continental United States.
Study Period	Five (5) Years - Ten (10) Years with a 1-year trial enrollment period to assess sample size feasibility.
Study Objective and Specific Aims	The general aim of this project is to dissect the genetics of Parkinson's disease (PD) among the Black and African American population. Analyses seek to identify similarities and/or differences related to genetic data collected from other populations that may provide evidence for application of therapies in development and may illuminate novel targets for additional investigation. 1.1 Primary Objectives: To dissect the genetics of Parkinson's disease (PD) among the Black and African American population 1.2 The Specific Aims of this study are: 1.) Screening of pathogenic variants present in the NeuroBooster (previously NeuroPlus) Array Genotyping Platform and analysis of their frequencies in the African or African admixed population. 2.) Genome-wide assessment involving cumulative risk score calculation versus disease status and age at onset and comparison with European populations and heritability calculation. 3.) Pilot analysis of trans-ethnic fine-mapping and admixture mapping to establish analysis pipelines for future larger studies. 4.) Conduct genetic-phenotypic correlations to understand the relationship between genetic variation and observable clinical traits (like dementia) in these populations 5.) Develop and systematically test strategies that enable recruitment of Black Americans and African Americans to participate in PD genetics research
Study Population	Black Americans and African Americans with Parkinson's Disease or without a history of parkinsonism (control participants).
Study Design	This is a multi-center observational study.
Number of Participants	Up to 2,000 participants with Parkinson's Disease (PD) and up to 2,000 healthy controls self-identifying as Black and/or African American.
Inclusion Criteria	Inclusion Criteria for Participants with Parkinson's disease: ● Willing and able to provide informed consent or have a legally authorized representative to provide consent ● Willing and able to complete all study activities ● Age 18 years or older ● Self-identify as Black or African American ● Meet the Movement Disorder Society's diagnostic criteria for Parkinson's disease ● English speaking

	Inclusion Criteria for Control Participants: • Willing and able to provide informed consent or have a legally authorized representative to provide consent • Willing and able to complete all study activities • Age 18 years or older • Self-identify as Black or African American • English speaking
Exclusion Criteria	Exclusion Criteria for Participants with Parkinson's disease: • Any condition that, in the investigator's opinion, precludes the individual's ability to carry out study activities Exclusion Criteria for Control Participants: • Diagnosis of the following disorders: Parkinson's disease, Alzheimer's disease, Frontotemporal dementia, Corticobasal syndrome, Dementia with Lewy bodies, Motor neuron disease, Multiple system atrophy, Progressive supranuclear palsy, Spinocerebellar Ataxia (SCA), REM sleep behavior disorder, Any other parkinsonian disorder or dementia NOS • Familial history of any of the following disorders in a 1st degree relative (participant's parent, sibling or child): Parkinson's disease, Alzheimer's disease, Frontotemporal dementia, Corticobasal syndrome, Dementia with Lewy bodies, Motor neuron disease, Multiple system atrophy, Progressive supranuclear palsy, Spinocerebellar Ataxia (SCA), REM sleep behavior disorder, Any other parkinsonian disorder or dementia NOS • Any condition that, in the investigator's opinion, precludes the individual's ability to carry out study activities
Primary Outcome Measures	Novel risk factors and characterization of known genetic risk factors contributing to PD risk in the Black or African American population.
Sample Size Considerations	The study aims to recruit up to 2000 participants with PD and up to 2,000 controls. Power calculations were performed using the GAS power calculation tool by Abecasis et al. Our power to detect an association between common genetic variation (minor allele frequency < 5%) and PD risk was estimated to be 99.8% considering a general disease prevalence = 0.1% (Tysnes et al 2017) and a genotype relative risk effect = 1.5 when including 2,000 cases and 2,000 controls at a significance p-value < 5×10-8 assuming the limitation that the genetic architecture in the Black and/or African American ancestry is unknown.

BLAAC PD SCHEDULE OF ACTIVITIES

Activity	Cases	Controls
Informed Consent	**X**	**X**
Participant ID Number	**X**	**X**
Demographics	**X**	**X**
Inclusion/Exclusion	**X**	**X**

Activity	Cases	Controls
Recruitment source questionnaire	**X**	**X**
Family history questionnaire	**X**	**X**
PD Features	**X**	
CISI-PD	**X**	
REM sleep behavior disorder question	**X**	**X**
MDS UPDRS item 1.12	**X**	**X**
Environmental exposure questionnaire	**X**	**X**
Montreal Cognitive Assessment	**X**	**X**
Reportable Events	**X**	**X**
Biosample Collection	**X**	**X**
Smell Identification Test (SIT)	**X**	**X**

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1. BACKGROUND AND RATIONALE

A major limitation in Parkinson's disease (PD) genomics research is lack of diversity, specifically lack of inclusion of data from the Black and African American population. Enhanced genetics research with this population may enable the identification of a broad range of genetic variation that could elucidate disease mechanisms and inform genetic tests and drug development, specifically for members of this community. Additionally, fine-mapping across Black and African Americans could be extremely useful given the allelic diversity and linkage disequilibrium patterns to identify putative functional variants that can provide insights applicable to a broader disease landscape.

The general aim of this project is to dissect the genetics of PD in the Black and African American population. Deciphering causal and genetic risk factors will help researchers understand if the potential targets for a disease-modifying treatment or prevention strategies that are under investigation in populations of European ancestry are relevant to Black and African Americans, filling a gap of knowledge existing in PD genetics in a valuable and underserved population. This pioneering initiative will give rise to the generation of valuable data for future projects within the Global Parkinson's Genetics Program (GP2) and beyond.

2. PURPOSE OF STUDY

The general aim of this project is to dissect the genetics of Parkinson's disease (PD) among the Black and African American population. Analysis seeks to identify similarities and/or differences related to genetic data collected from other populations that may provide evidence for application of therapies in development and may illuminate novel targets for additional investigation.

Specific aims:

1. Screening of pathogenic variants present in the NeuroBooster (previously NeuroPlus) Array Genotyping Platform and analysis of their frequencies in African or African admixed populations
2. Genome-wide assessment involving cumulative risk score calculation versus disease status, age at onset and SIT scores, and comparison with other populations and heritability calculation.
3. Pilot analysis of trans-ethnic fine-mapping and admixture mapping to establish analysis pipelines for future larger studies. By using ~5K ancestry informative markers on the NeuroBooster array that tag regions that are highly variable between European and African populations, local ancestry methods can be utilized to increase our statistical power exponentially with regard to association signals possibly harbored within these regions based on differential linkage disequilibrium signatures. We and others have successfully employed admixture methods for localization of association signals and fine mapping of loci including in sample sizes similar to that proposed here. If summary data are available for other continental ancestries, these data can also be leveraged in terms of trans-ethnic fine mapping to possibly identify novel loci as well as refine credible intervals around known loci.
4. Conduct genetic-phenotypic correlations to understand the relationship between genetic variation and observable clinical traits (like dementia) in these populations.
5. Develop and systematically test strategies that enable recruitment of Black Americans and African Americans to participate in PD genetics research

3. STUDY DESIGN

The study is a project of the Global Parkinson's Genetics Program (GP2, https://parkinsonsroadmap.org/gp2/), which is part of the Aligning Science Across Parkinson's initiative (ASAP, https://parkinsonsroadmap.org/), and is Implemented by the Michael J. Fox Foundation for Parkinson's Research. GP2 is an international effort aimed at generating significant insight into the genetic basis of PD and democratizing access to results and data. GP2 is funded by ASAP and is part of the core ASAP strategic objectives which include: support collaboration, generation of resources and democratize data. The GP2 initiative is funded through 2030.

The Michael J. Fox Foundation for Parkinson's Research (MJFF) is the ASAP implementation partner and is supporting its various efforts including GP2 and BLAAC PD.

BLAAC PD aims to generate phenotypic and genetic data on a cohort of at least 1000 and up to 2,000 PD (including familial/sporadic PD cases) and at least 1000 and up to 2,000 control Black and African American participants. While this sample size is modest compared to similar studies of PD risk in White populations, it will constitute the largest sample ever aggregated of Black and African American Parkinson's participants and will therefore be a foundation for future collection efforts to generate even greater sample sizes.

Recruitment, engagement and retention materials will be provided by MJFF. A biorepository and/or gene sequencing center contracted with MJFF, on behalf of GP2, will be providing biosample storage and management along with performing testing and analyses. Database creation and management will take place through a management center contracted with MJFF, on behalf of GP2. The Clinical Trials Coordination Center (CTCC) department in Center for Health and Technology (CHeT) at the University of Rochester Medical Center (URMC) will be providing site management and data monitoring.

4. INCLUSION AND EXCLUSION CRITERIA

Inclusion Criteria for Participants with Parkinson's disease:

- Able and willing to provide informed consent or have a legally authorized representative to provide consent
- Age 18 or older
- English speaking
- Self-identify as Black or African American
- Meet the Movement Disorder Society's diagnostic criteria for Parkinson's disease

Exclusion Criteria for Participants with Parkinson's disease:

- Any condition that, in the investigator's opinion, precludes the individual's ability to carry out study activities

Inclusion Criteria for Control Participants:

- Able and willing to provide informed consent or have a legally authorized representative to provide consent

- Willing and able to complete all study activities
- Age 18 years or older
- English speaking
- Self-identify as Black or African American

Exclusion Criteria for Control Participants:

- Diagnosis of Parkinson's disease and/or any of the following disorders: Alzheimer's disease, Frontotemporal dementia, Corticobasal syndrome, Dementia with Lewy bodies, Motor neuron disease, Multiple system atrophy, Progressive supranuclear palsy, Spinocerebellar Ataxia, REM sleep behavior disorder, or any other parkinsonian disorder or dementia NOS
- Familial history of PD and/or any of the following disorders: Alzheimer's disease, Frontotemporal dementia, Corticobasal syndrome, Dementia with Lewy bodies, Motor neuron disease, Multiple system atrophy, Progressive supranuclear palsy, Spinocerebellar Ataxia, REM sleep behavior disorder, or any other parkinsonian disorder or dementia NOS
- Any other condition that, in the investigator's opinion, precludes the individual's ability to carry out study activities

5. RECRUITMENT METHODS

Potential Black and African American participants with and without PD will be ascertained from all of the following:

- Site coordination such as invitation from review of electronic medical records in health systems/Clinical Data Research Networks (CDRNs) and/or databases, and contact with participants of prior research studies who consented to be re-contacted;
- Outreach to community groups, foundations and organizations led by sites and study leadership;
- Self-referrals from public registries such as BLAACPD.org, Fox Trial Finder and clinicaltrials.gov;
- In-person events such as those organized by community groups, foundations, medical centers, and specialty societies;
- In-home visits for interested potential participants who have difficulty with transportation or reside a significant distance away from study sites (Site Permitting)
- Flyers/Bulletins;
- Radio ads;
- Newsletters;
- Social Media posts;
- Through the care-navigation process; and,
- Other tactics to be determined

Basic information about the study eligibility criteria (age, diagnosis of Parkinson's disease, absence of exclusionary criteria) may be determined by the study staff prior to contact with potential participants or by providing potential participants with recruitment materials; site-based contact with potential participants may be during a clinical visit or remotely by telephone. Recruitment materials will be reviewed and approved by the Institutional Review Board (IRB) prior to implementation.

Control participants may also be recruited through above methods (e.g., partners of the participants visiting a clinical neurology department).

Information about recruitment activities may be collected for this study, including but not limited to: the status of potential participants, such as if they have been contacted, if they are undecided about participating, and reasons for declining to participate. Recruitment information will be shared on a regular basis with MJFF.
Recruitment activities, namely primary reason for exclusion, may be tracked to identify primary barriers negatively affecting site recruitment milestones. Recruitment related variables will be collected from Control or PD excluded participants that decline to participate and analyzed to improve study performance by implementing engagement and recruitment strategies.

6. CONSENT PROCESS

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

Informed Consent:
The process of informed consent will be obtained by the participant and/or legally authorized representative (LAR) and will take place at the beginning of the visit by the site investigator or a delegated study staff member, prior to any study procedures. Options for obtaining informed consent must be approved by the individual institution's IRB and may be conducted in-person, remotely via a HIPAA-compliant audio and/or video call, or electronically (eConsent) using a HIPAA and 21 CFR Part 11 compliant methodology, and will be performed prior to the first study-related procedure. Participants will sign the informed consent form (ICF) remotely in writing and will return it to the site (included with the recruitment materials). Once received, study personnel will send a copy of the final signed consent and the remote participant materials to the participant.

It is the Investigator's responsibility to make sure that the participant understands what they are agreeing to and that informed consent is obtained before the participant is involved in any protocol-defined procedures. It is also the Investigator's responsibility to retain the original signed informed consent form and provide each participant with a copy or electronic version of the signed consent form.

Participant Eligibility:
Participant eligibility will be determined in-person or remotely via HIPAA-compliant audio and/or video call as part of the study procedures.

7. STUDY PROCEDURES

7.1. Clinical Assessments

All study procedures would ideally be completed in a single day but may be completed over separate days when necessary, preferably within 30 days.

Following consent, the following (comprised of GP2 Minimum Plus Common Data Elements) will be collected: demographics (sex, age, race, ethnicity), recruitment category, family history of PD and other specified neurodegenerative disorders, diagnostic checklist, clinical diagnosis, PD history, and general status evaluation (CISI-PD). Information pertaining to the Movement Disorder Society's (MDS) Clinical Diagnostic Criteria for PD, as well as year of diagnosis, first motor symptom, and motor symptoms onset, PD treatment, family history, and other relevant PD phenotypic manifestations, will be collected via interview/examination of the participant and/or from the participant's medical record where available. In addition, a cognitive test (Montreal Cognitive Assessment (MoCA)) and questions on sleep, orthostasis, and environmental exposures will be administered. All study staff conducting the MoCA must have a current (not expired) certificate from MoCA Cognition/MoCA Test, Inc. In-person collection of all data is preferred but remote collection (site permitting) and in hybrid format (remote plus in person) may occur where necessary; however, the MoCA can only be conducted in-person.

Smell Identification Test (SIT):

The Smell Identification Test (SIT; a revision of the UPSIT) is a 40-item, multiple choice, scratch and sniff test used to evaluate odor identification. It is a forced-choice test in which participants must identify an odor among four response alternatives. There are four booklets containing ten odorants each. The instructions will be explained to the participants by the coordinator at the clinical site.

SIT is collected via self-administration either in-person or remotely. Participants may complete the SIT independently. It will be reviewed for completion prior to the end of the visit. Coordinators may assist participants with scratching the SIT card and may hold SIT card to the participant's nose if assistance is required secondary to participant shaking or tremors. Tests obtained remotely will be returned to the site and verified for completeness. The SIT will be scored by member of the study team reflecting the number of correct responses out of 40 items.

SIT	
Number of Cards per participant	4
SITs must be obtained following specific instructions. All site staff delegated the authority to obtain smell test must be listed on the Delegation Log.	

Sites may follow their local institutional policy regarding the length of time required to save the SIT tests. This documentation is part of the participant's source information for the study.

7.2. Sample collection

Blood collection by phlebotomy:

Blood (up to 18mL) will be drawn through a needle in participant's arm. Blood samples should be gently mixed by inverting the tube 8-10 times following collection, labeled, and stored in a freezer at -80 ℃ until shipped.

Blood Sample Collection

Collection Tube Type	Whole Blood Collection K2EDTA tubes
Collection Tube Volume	6mL-8mL
Number of Tubes per participant	2-3 (12mL -18 mL total)
Blood must be drawn following site-specific standard lab protocols/processes. All site staff delegated the authority to draw blood must be listed on the Delegation Log.	

Blood collection by TASSO+ kit:

In exceptional cases, blood may be collected using the Tasso+ kit, which allows for collection of microliter capillary whole blood samples. This kit may be used only in situations where phlebotomy is not feasible (i.e. off-site) or when a participant is unwilling to undergo a venipuncture. Tasso+ kit may also be administered remotely through two kits that are mailed to the participant's home. Remote Tasso+ kit blood collection will be observed by site staff by way of a HIPAA-compliant video/web conferencing platform. Blood samples should be collected and packaged according to the manual of procedures. Blood samples collected via self-administration remotely will be returned to the study site via a provided shipping kit.

Tasso+ Kit Blood Sample Collection	
Collection Tube Type	Tasso+ Kit with EDTA tube
Collection Tube Volume	2 x 0.5 mL
Number of Tubes per participant	2

Saliva:

A saliva sample (2 mL) may be collected if the participant is unable or unwilling to donate a blood sample. The saliva sample can only be collected after the patient has taken nothing by mouth (food, drink, gum, tobacco or smoking) for 30 minutes prior to sample collection.

Individuals that participate remotely and who are unable/unwilling to provide blood with the Tasso+ kit will provide saliva using a kit that is mailed to their home. Saliva collection will be observed by site study staff by way of a HIPAA-compliant video/web conferencing platform; however, a support person can assist the participant. Saliva samples should be collected and mixed according to package instructions. Saliva samples collected via self-administration remotely will be returned to the study site via provided shipping kit. Saliva will only be obtained at in-person visits if the participants is unable/unwilling to provide blood.

Saliva Sample Collection	
Collection Tube Type	ORAGENE OG500 SALIVA KITS for DNA Extraction
Number of Tubes per participant	1
Participants (or with assistance from caregiver) will collect saliva samples with the vial included in the kit provided and will return to the clinical site for batch shipment.	

Sample Identification:

The sample will be labeled with a code or unique identifier and collection date.

Sample Storage and Shipments:

Blood and saliva samples will be stored on site and shipped in batches to Psomagen, Inc. in Rockville, MD, a gene sequencing center contracted with MJFF for sample analysis.

8. RISKS TO PARTICIPANTS

Questionnaires and cognitive tests may cause boredom, frustration, or fatigue. Participants will be encouraged to take breaks between tasks if needed.

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.

There is a potential for invasion of privacy or breach in confidentiality. The study will use a HIPAA-compliant video/web conferencing platform for all study-related activities completed remotely. All remote activities will be completed in a private setting and will not be recorded. The study site investigators will assume full responsibility for maintaining the confidentiality of all data. See also Data Management (Section 17) and Data/Sample Storage for Future Use (Section 19) for further details.

9. POTENTIAL BENEFITS TO PARTICIPANTS

There are no direct benefits to participants for participation in the study.

10. COSTS FOR PARTICIPATION

Participants will not be charged for participation in this research.

11. PAYMENT FOR PARTICIPATION

Participants will be paid $100.00 for taking part in this study.

Reimbursement for reasonable travel expenses for the minimum visit required to complete study activities may be provided upon request. If a participant requires a companion to accompany them to their visit, some reimbursement costs will be paid for a companion using the same guidelines as participant. Original receipts must be provided to site personnel for reimbursement.

12. PARTICIPANT WITHDRAWALS

Participants have the right to withdraw their consent at any time, for any reason, without prejudice. In the event the participant requests the destruction of their stored DNA samples, the biorepository storing the DNA samples will be notified of the request. The biorepository is responsible for the destruction of samples at a participant's request or at the end of the storage period. Since the samples are coded, the biorepository is required to provide documentation confirming that said stored DNA samples have been destroyed. Participant genomic or phenotype data will be removed from the data platform; however, it may not be possible to retrieve data already distributed for research use.

13. REPORTABLE EVENTS

Based on the nature of the study, routine adverse events will not be collected. In this study, the following pre-specified events that are thought to be relevant to the safety and feasibility of the study population will be considered Reportable Events (RE). Sites are required to communicate all REs to

the CTCC within 24 hours of the event, or the Site Investigator's knowledge of the event.

- Compromise of confidentiality
- Unanticipated problem

Site Investigators will comply with their local Institutional Review Board (IRB/IEC) regulations regarding the reporting of reportable events.

14. REGULATORY/ETHICS

14.1. 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, 56, 312 and 314, as applicable.

All procedures not described in this protocol will be performed according to the study Manual of Procedures unless otherwise stated. Laboratory tests/evaluations described in this protocol will be conducted in accordance with quality laboratory standards as described in the laboratory process unless otherwise stated.

14.2. Institutional Review Board/Independent Ethics Committee

The Principal Investigator, MJFF, and the CTCC will supply all necessary information to the Investigator for submission of the protocol, consent form, and recruitment materials to the site's IRB/IEC for review and approval. The Investigator agrees to provide the IRB/IEC all appropriate material. The study will not begin and/or protocol amendments will not be instituted until the Investigator has obtained appropriate IRB/IEC approval. A copy of the approval letter listing all documents and versions that were approved and approved consent form must be submitted to the Sponsor and CTCC.

The Investigator will request from the IRB/IEC a composition of the IRB/IEC members reviewing the protocol and informed consent. Appropriate reports on the progress of this study by the Investigator will be made to the IRB/IEC and Sponsor and the CTCC in accordance with institutional and government regulations. The CTCC will notify the site when the IRB/IEC may be notified of study completion. It is the Investigator's responsibility to notify the IRB/IEC when the study ends. This includes study discontinuation, whether it is permanent or temporary. A copy of the site IRB/IEC's acknowledgement of study completion must be submitted to the CTCC.

14.3. Proposed Changes

The Investigator will discuss any proposed protocol changes with the CTCC Project Manager and no modifications will be made without prior written approval by CTCC and MJFF, except where clinical judgment requires an immediate change for reasons of subject welfare. The IRB/IEC will be informed of any amendments to the protocol or consent form, and approval, where and when appropriate,

will be obtained before implementation.

14.4. Protocol Amendments

Changes to the protocol should only be made via an approved protocol amendment. Protocol amendments must be approved by the Sponsor, the study's Steering Committee and each respective site's IRB/IEC prior to implementation, except when necessary to eliminate hazards and/or to protect the safety, rights or welfare of participants.

15. PRIVACY AND CONFIDENTIALITY OF PARTICIPANTS AND RESEARCH DATA

The site Investigator must assure that the privacy and 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). Participants will be identified by code numbers on case report forms and other study materials submitted to the coordinating center and the testing laboratory.

All trial related documentation is confidential, whether obtained by the Site Investigator or provided by CTCC/the Sponsor. Disclosure of such information is restricted to those involved in the scientific, ethical and clinical trial procedures. While every effort will be made to maintain confidentiality there is a small risk that information will be disclosed. A federal law, called the Genetic Information Nondiscrimination Act (GINA), generally makes it illegal for health insurance companies, group health plans and most employers to discriminate against individuals based on genetic information. However, it does not protect participants against discrimination by companies that sell life insurance, disability insurance or long-term care insurance.

The participant's informed consent process will be carried out in a private setting in-person, by telephone, or using a HIPAA compliant audio/video conferencing platform to ensure confidentiality and privacy. The informed consent will indicate who will have access to the data for the purposes of the study and which personal identifiers these data include. Participants will be informed of sharing of their data for future use and will be asked for consent to future use of information/samples and consent to re-contact for potential participation in future studies. After a participant signs an informed consent (paper or eConsent), it is required that the site Investigator permit the study monitor or regulatory agency personnel to review the signed informed consent(s). Monitors may also request access to limited participant health information related to study activities in order to resolve data discrepancies.

The HIPAA-compliant, web-based database is enforced with security measures to protect this information, which includes access restrictions, assigned user roles, and data encryption. Any Protected Health Information (PHI) that is collected will not be reused or disclosed to any other person or entity except (i) as required by law, (ii) for authorized oversight of the research study, or (iii) for other research for which the use of disclosure of PHI would be permitted by the HIPAA Privacy Rule.

Study identifiers will be assigned to each participant and used in conjunction with case or control and site IDs to label the samples. A master list linking PHI to the study participant ID will be maintained in an electronic document accessible to only necessary site study personnel.

Source documents will be stored in a locked cabinet accessible only to the PI and study personnel. Electronic data will be stored with password protection and will be accessible only by the PI and study personnel.

Specimens will be shared with Psomagen, Inc., a gene sequencing center contracted for sample analysis with MJFF, on behalf of the Global Parkinson's Genetics Program. This study is part of the Global Parkinson's Genetics Program (GP2, https://parkinsonsroadmap.org/gp2/). At the end of the study, leftover specimen will be stored in a freezer for an indefinite time, or if requested, shipped back to the collaborator or destroyed.

16. DOCUMENTATION

16.1. Study File and Site Documents

The Investigator should have the following study documents saved within their Site Investigator Files and sent to the CTCC, upon request, during the study.

- Curriculum vitae for investigator and coordinator
- Signed IRB/IEC form/letter stating IRB/IEC approval of protocol, consent forms, and advertisement notices, notification/approval of protocol amendments, notification of protocol deviations/violations, unanticipated problems, and nonconformance issues reported to the IRB/IEC specific to the study site.
- IRB/IEC approved consent forms (sample) and advertisements as applicable
- Signed protocol (and amendments, where applicable)
- Signed participant consent forms (where applicable, if obtained via written consent)
- Copies of the completed source document worksheets.
- Delegation Log with names, signatures, initials and functional role of all persons completing protocol assessments, providing back-up to the site Investigator and Coordinator, if applicable, as well as staff entering data.
- Certificate for Human Participant Protection Program (HSPP) and Good Clinical Practice (GCP) program for each individual named on the Delegation log who has direct participant contact
- Copy of professional licensure/registration, as applicable, for each individual who has direct participant contact ensuring licensure is in the state/region in which the study will be conducted
- Copies of correspondence to and from contracted gene sequencing center(s), contracted biorepository, MJFF and CTCC
- Record of any Corrective and Preventive Action Plans (CAPA)
- Note to File indicating the assessments that will be considered source documents

The Investigator must also retain all printouts/reports of tests/procedures, as specified in the protocol, for each participant. Sites may follow their local institutional policy regarding the format of these documents, whether electronic or printed/paper.

16.2. Maintenance and Retention of Records

It is the responsibility of the Site Investigator to maintain a comprehensive and centralized filing system of all relevant documentation. Site Investigators must retain all study records in a secure and safe facility with limited access.

An electronic case report form (eCRF) utilizing an Electronic Data Capture (EDC) application will be used for this study. In the event of an audit or regulatory authority inspection, the eCRFs can be printed out.

16.3. Primary Source Documents

The investigator must maintain primary source documents supporting data collected for each participant. This includes documentation of Informed consent, when obtained via hand-written signature, and participant-completed assessments.

17. DATA MANAGEMENT

Coded participant information and data will be collected and stored in an electronic case report form (eCRF) in a web-based Electronic Data Capture (EDC) database and may also be recorded on paper forms for entry into the database after it is collected. The eCRFs are used to record study data and are an integral part of the study and subsequent reports. Therefore, the eCRFs must be completed for each participant enrolled according to the participant's source data. Authorized study personnel will each be granted access to the electronic data capture tool via provision of a unique password-protected user ID that will limit access to enter and view data specifically for participants enrolled at their site and based on role assigned in the EDC. The data entered to the eCRF will be securely transmitted to a central database stored on a secure server. Upon completion of a participant's visit or the study, sites have the option to print the completed eCRFs containing the data that were entered. Electronic data will be kept indefinitely.

Query resolution: Once the CTCC, in conjunction with study leaders, MJFF and the principal investigator, agree that all queries have been adequately resolved and the database has been deemed "clean," the database will be officially signed off and deemed locked. All permissions to make changes (append, delete, modify or update) the database are removed at this time.

18. DATA AND SAFETY MONITORING PLAN

In accordance with ICH Guidelines for Good Clinical Practice 5.18 the study will be remotely monitored to verify that:

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

During the course of the study, central monitoring (remote evaluation) is carried out by the CTCC via the web-based electronic data capture (EDC). CTCC will conduct remote monitoring of sites' informed consents, completeness of the EDC questionnaires, and other documents if deemed necessary. The purpose of the review is to determine whether or not the study is being, or has been, conducted and monitored in compliance with the protocol as well as recognized GCP guidelines and regulations. This review will also increase the likelihood that the study data and all other study documentation can withstand a subsequent regulatory authority inspection.

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.

All aspects of the study will be monitored by the site investigator and designees in compliance with Good Clinical Practice (GCP) and applicable regulations. CTCC will be responsible for monitoring site activities to ensure they remain in compliance. There is no clinical monitor or safety monitoring committee for this study. The Study PI, MJFF, and CTCC will review collected reportable events on a routine basis.

19. DATA / SAMPLE STORAGE FOR FUTURE USE

Leftover DNA following genetic analysis derived from this project will be stored with study-specific IDs. The remaining specimen after performing this study will be stored at a biorepository contracted with MJFF on behalf of GP2 indefinitely, shipped back to the collaborator if requested, or destroyed if requested by the participant.

Genetic and clinical information will be stored in the Accelerating Medicines Partnership Parkinson's disease program (AMP PD) data platform or in another third party repository identified by MJFF. Data access is open to qualified researchers worldwide in academia, industry, non-profit organizations and the government. The AMP PD Access and Compliance Team (ACT) reviews data access requests.

De-identified data will be uploaded to secure cloud storage that includes the following safety measures:

- HIPAA certification
- FEDRAMP certification
- FISMA certification
- National Data Protection Legislation (NDPL) compliance where the national provisions adopted pursuant to the Directive 95/46/EC of the European Parliament and of the Council on the Protection of Individuals with Regard to the Processing of Personal Data and on the Free Movement of Such Data, to implement the Directive in the country in which the Customer is established, or the Federal Data Protection Act of 19 June 1992 (Switzerland), as applicable.
- U.S. Department of Commerce Safe Harbor Framework adherence
- ISO/IEC 27001:2005 Certification or a comparable certification
- Regular and recurring security audits
- Immediate reporting of data incidents

Participant-coded genetic information and de-identified personal data will be stored on a management access platform such as the AMP PD data platform and made subject to access controls. Information on this data platform can only be accessed and used by researchers who have been granted formal approval to access data and who have signed access agreements to protect the confidentiality of the information. The access agreements also require researchers to respect the laws

and ethical guidelines for scientific research. Participant information may be combined with information from other people in summary statistics and study analyses. This summary data may be made public (openly accessible) to anyone without restriction.

Data may be moved and stored in different countries, and the platform may be hosted by different servers accessible by the Internet. The data platform may be hosted on commercial cloud servers. The cloud refers to software and services that run on the Internet, instead of on a specific computer. These cloud servers meet international security and safety standards. Data will be stored indefinitely or until it is withdrawn or no longer useful for research.

20. DATA ANALYSIS PLAN

The molecular genetic analysis will be centered on assays of genomic variability including large-scale genotyping or whole genome sequencing of risk variants and disease-linked mutation detection. Psomagen, Inc., a MJFF-contracted gene sequencing center(s) and biorepository will not receive any personal identifiable information that would link the samples back to individual study participants. The outcome of this study is to identify genomic variability that causes or modulates risk for PD.

Control data may be obtained in part from publicly available resources to match PD cases based on genetic background when individual genetic data exists.

To explore genetic risk factors associated with PD in this population, logistic regression, score and fisher exact tests will be used to test each of the imputed variants for an association with disease, adjusting for population substructure, age and gender. From this analysis, PD loci of interest will be extracted to compare with known local risk estimates in other populations. To study the influence of genetic variation on disease onset, linear regression will be applied adjusting by similar covariates. Subsequently, cumulative risk score will be evaluated by selecting the 90 risk loci conferring risk for PD in the European population. SNPs will be weighted by their log odds ratios (as per Nalls et al., 2019), giving greater weight to alleles with higher risk estimates, and a composite genetic risk score will be generated across all risk loci. Genetic risk score will be z-transformed prior to analysis, centered on controls, with a mean of zero and a standard deviation of one in the control participants. Regression models will then be applied to test for association with the risk of developing PD (based on logistic regression) or age at onset, and disease duration (linear regression), adjusting for sex, age, and principal components to account for population stratification. These analyses will be performed using PLINK 1.9 and R.

Additionally, in an effort of studying the proportion of the phenotype attributable to genetic influence, heritability estimates will be calculated. If disease heritability estimates are similar than those in European populations, that could corroborate the lower incidence of PD within this population, probably only explained by health disparities in PD diagnosis. The narrow-sense heritability (h2), a measure of the additive genetic variance, will be calculated using GREML-LDMS to determine how much of the genetic liability for PD is explained by common genetic variants. This analysis will be adjusted for sex, age, and principal components to account for ascertainment bias. To estimate the influence of rare genetic variation on PD etiology, genome-wide gene-based sequence kernel association test - optimized (SKAT-O) analysis of missense and loss-of-function mutations will be performed to determine the difference in the aggregate burden of rare coding variants between

PD cases and controls. This analysis will be performed using RVTESTS. Finally, fast-structure analyses will be performed in order to conduct a pilot trans-ethnic fine-mapping study. Additional analyses may include: runs of homozygosity to further study families with recessive patterns of inheritance, copy number variation and machine learning pipelines.

To evaluate impaired olfactory function in Parkinson's disease patients of African admixed ancestry, we will conduct statistical analyses using SIT scores (Smell Identification Test), a standardized test used to assess a person's ability to identify different odors. The total score is the sum of correct identifications across all odor strips in the test, containing a 40-item scratch and sniff test. When analyzing SIT scores in the context of Parkinson's disease, a lower score on the test may indicate impaired olfactory function. In the case of Parkinson's disease, the loss of smell often occurs before the onset of motor symptoms, making olfactory testing a potential tool for early detection.

From the statistical standpoint, we will explore whether the SIT score is predictive of Parkinson's status in the African admixed population by running a logistic regression analysis, specifying Parkinson's status as the outcome and SIT score as the primary predictive variable of interest. SIT scores will first be normalized to the control mean and standard deviation for the relevant reference population. This helps contextualize the results on to an interpretable scale across populations and place the results in context to understand how an individual's score compares to the general population in terms of standard deviations of change. We will conduct a logistic regression adjusted by gender, age, and principal components to account for population stratification (also on a similar normalized scale). In a stepwise manner, we will prune the initial model to build a more parsimonious model. Finally, we will evaluate the overall fit of the model(s) using metrics like AUC, balanced accuracy and pseudo-R-squared to evaluate the predictive strength of the model(s).

When analyzing SIT scores in the context of PD, a lower score on the test may indicate impaired olfactory function. Olfactory function may be designated as abnormal based on available normative data for age and sex (Brumm, 2023; Doty, 1984}. However, the samples on which normative data were generated lack diversity. Smell test data collected from healthy controls in BLAAC PD will be leveraged to improve generalizability of existing normative data to the Black and African American community. From the statistical standpoint, we explore whether the SIT score is predictive of PD status in the African admixed population by running a logistic regression analysis, specifying PD status as the outcome and SIT score as the primary predictive variable of interest. We will conduct logistic regression adjusted by sex, age, and PCs to account for population stratification (on a normalized scale). In a stepwise manner, we will prune the initial model to build a more parsimonious model. Finally, we evaluate the overall fit of the model(s) using metrics like AUC, balanced accuracy and pseudo-R-squared to evaluate the predictive strength of the model(s).

Finally, study methods and collected phenotypic data may be the basis of additional analysis to report on learnings around engagement of Black and African Americans in genetic Parkinson's research. Potential investigation could focus on, for example, outreach methods, enrollment or declination motivations, and study cohort demographics. These findings may inform future research engagement methods and study design for projects partnering with the Black and African American community.

21. PUBLICATIONS

Publication of results of this study will be governed by the policies and procedures developed by the Global Parkinson's Genetics Program (see publication policy) and in accordance with the International Committee of Medical Journal Editors (ICJME) Uniform Requirements for Manuscripts Submitted to Biomedical Journals. Any presentation, abstract, or manuscript will be made available for review to the Sponsor and GP2 leadership prior to submission.

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