Characterizing the Frequency of Clinically Reportable Variants in Major Genes Established in Parkinson's Disease in a Large American Cohort

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PD GENEration: Mapping the Future of Parkinson's Disease

Introduction

PD GENEration, launched in partnership with the Parkinson Study Group (PSG) in September 2019, is a multi-center, observational study in North America, designed to offer genetic counseling, in English and Spanish, and Clinical Laboratory Improvement Amendments (CLIA)-certified genetic testing to people with Parkinson's disease (PWP). The PD GENEration test panel, performed by Fulgent Genetics, includes next generation sequencing (NGS) of 7 genes: *LRRK2, GBA1, SNCA, PRKN, PINK1, PARK7, VPS35*. The broad objectives of the study are to facilitate access to clinical genetic testing to PWP, and their clinicians, and offer educational materials to clinicians on PD genetics, in order to help accelerate clinical trials in PD, improve PD care and research, and empower PWP and their care teams.

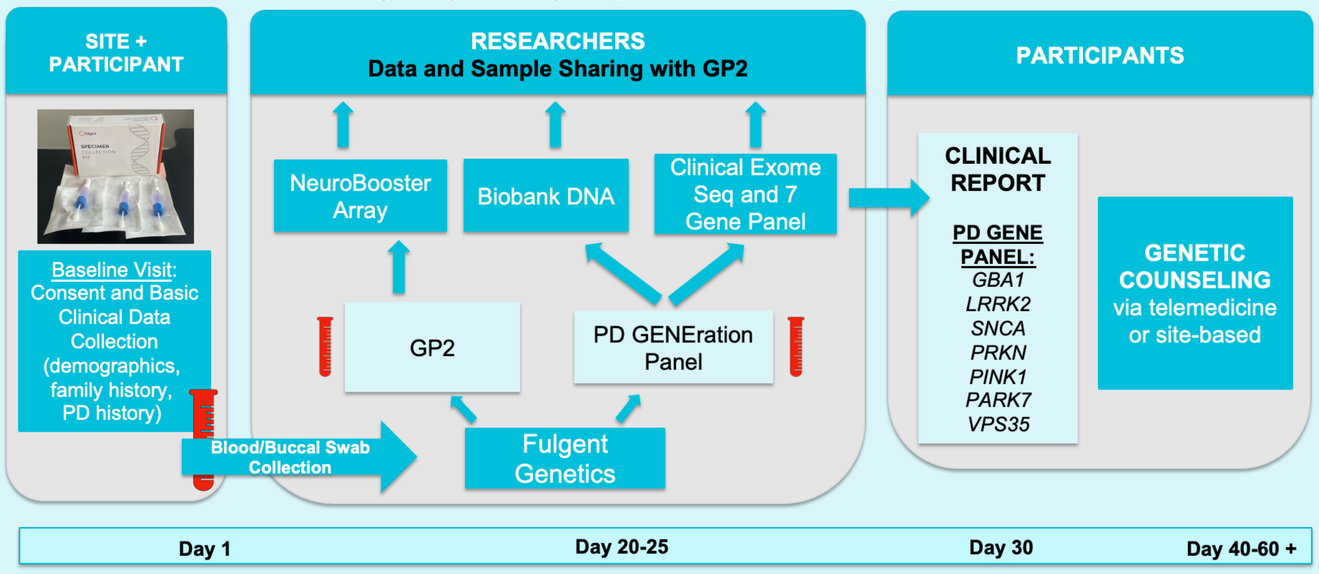
Methodology

Participants receive genetic test results of variants classified as pathogenic or likely pathogenic based on the American College of Medical Genetics (ACMG) criteria. In addition, the E365K *GBA1* risk allele is returned as it was considered actionable, i.e. eligible for clinical trial enrollment. Variants of unknown significance (VUS) are not reported but are catalogued for research use and shared among a global consortium of PD geneticists and clinicians to centralize discussions of VUS identified across multiple cohorts (ClinGen Parkinson's Gene Curation Expert Panel: https://clinicalgenome.org/affiliation/40079). De-identified data is shared with researchers who are advancing the PD genetics field, such as the Global Parkinson's Genetics Program (GP2). Curated gene variants will be deposited in the National Institute of Health (NIH) ClinGen and ClinVar repositories.

Three phases of PD GENEration:

1) Pilot study- launched in Sept. 2019 and aimed at feasibility
2) Clinical study- launched in Nov. 2020- continuation of the Pilot study at a larger scale, aimed at frequency and characterization of clinical phenotypes
3) Registry study- launched in Jan. 2021 and aims to make genetic counseling and testing accessible to 15,000 participants

PD GENEration Registry Study Pipeline For Participants and Researchers



	Enrollment Goals Cumulative	CLIA Approved, CAP Certified Testing	NGS of 7 Genes (del/dup)	Bank DNA for Future Research Use	Post-Test Genetic Counseling	Data Collection: Family History	Demographics	MDS-UPDRS	MOCA	Patient and Provider Surveys
Pilot Study	600	✓	✓	✓	✓	✓	✓	✓	✓	✓
Clinical Study	2000	✓	✓	✓	✓	✓	✓	✓	✓	✓
Registry Study	15000	✓	✓	✓	✓	✓	✓			

Results

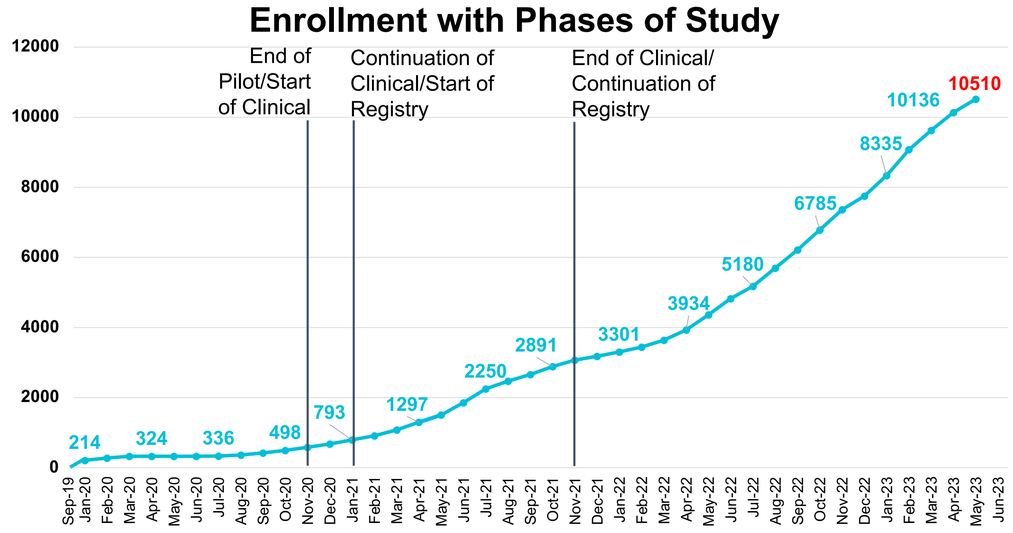
Enrollment

The PD GENEration study has, as of June 1, 2023, enrolled 10,510 participants, showing a 7x increase in recruitment since the start of the Registry study.

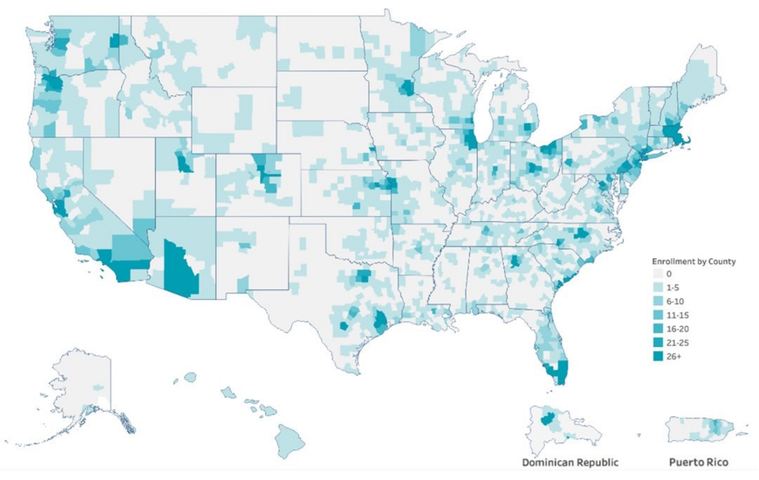
Study Enrollment Per Country

United States (US): **10,117**
Puerto Rico (PR): **33**
Dominican Republic (DR): **305**
Canada: **60**

Enrollment with Phases of Study



Distribution of Enrollment in US, DR, PR



Demographics

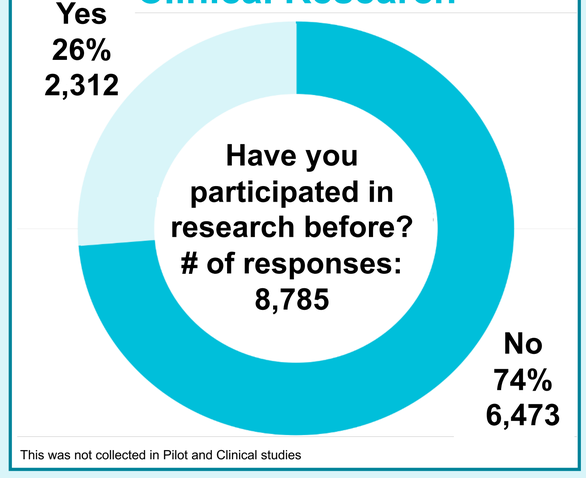
58%:42% genetic sex of Male:Female

69 years average age at enrollment

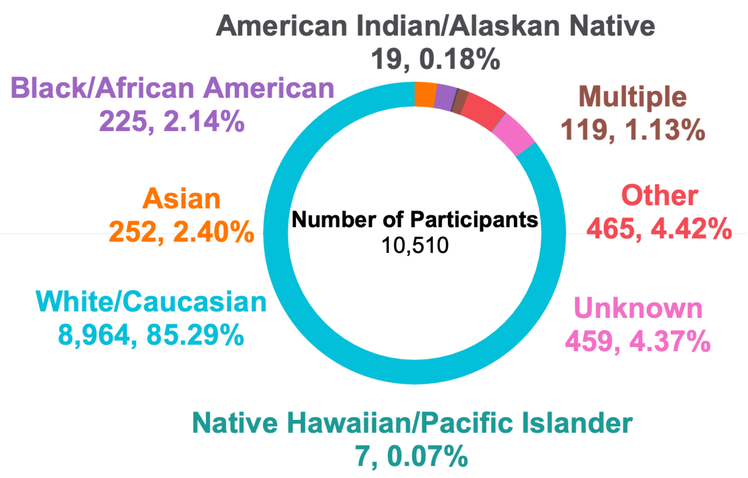
62 years average age at diagnosis

58% diagnosed in the last 5 years

74% New to Clinical Research



This was not collected in Pilot and Clinical studies



14.7% Racially Diverse

Significantly higher than the average US Clinical Trial Racial Diversity of =<2%

Hispanic Participants

1,009 Participants

10.1% Overall

Black and African American Participants

225 Participants

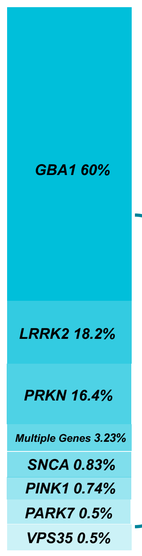
2.1% Overall

15 Seminars, webinars, and in-person educational events have taken place in one year.

Genetics

Positive Genetic Makeup in Cohort (n=8,506 completed testing)

Gene	Heterozygotes	Homozygotes/ compound heterozygotes	Key pathogenic variants
GBA1	622 (7.3%)	23 (0.3%)	E365K *(E326K)* N409S *(N370S)* L483P *(L444P)*
LRRK2	196 (2.3%)	2 (0.02%)	G2019S R1441C/H N1437H
PRKN	120 (1.4%)	57 (0.7%)	Exon del, R275W
SNCA	9 (0.1%)	0	Duplications, A53T
VPS35	5 (0.06%)	0	D620N
PINK1	4 (0.05%)	4 (0.05%)	L347P
PARK7	3 (0.04%)	2 (0.02%)	P158 del
Multiple Genes	35 (0.4%)		GBA/LRRK2/PRKN



12% 1. PD-Related High-Risk Ancestry (Ashkenazi Jewish, Berber, or Basque Ancestry)

30% 2. Positive First-Degree Family History

22% 3. Age of onset <50

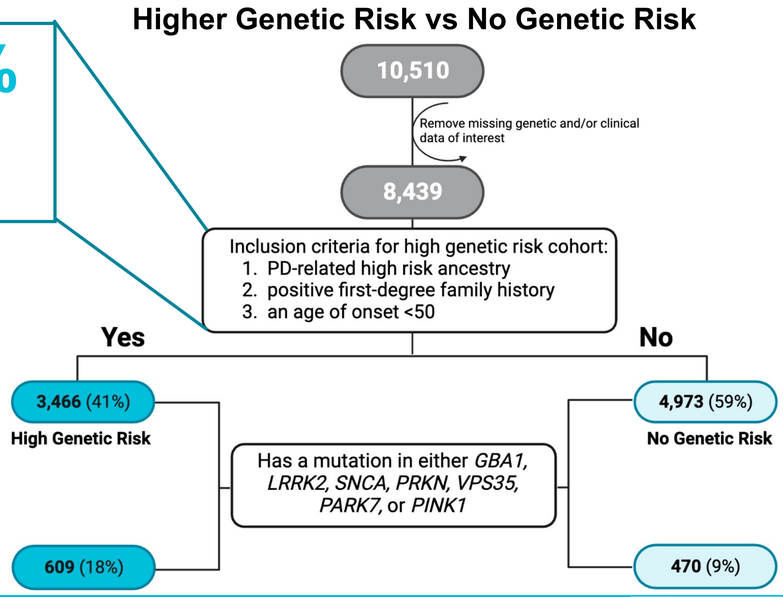
1,082 (12.7%) have a positive reportable variant. The breakdown of positive genetic carriers is shown on the left.

12% Male

Genetic Positivity Rate by Genetic Sex

17% Female

Higher Genetic Risk vs No Genetic Risk



Conclusion

PD GENEration makes genetic testing and counseling accessible for PWP and their clinicians. The Parkinson's Foundation plans to continue to recruit beyond 15,000 participants based on the needs of the patient and research community. By "opening the door" for genetic testing to all those interested and from all backgrounds, the study helps inform care, diversify the data, engage people in research, and qualify more for enrollment in precision medicine clinical trials for PD. Data generated from this study will be openly accessible to the research community.

For more information on the PD GENEration study, please scan the QR Code.

More about PD GENEration

Curation of Parkinson's Disease Genes Performed by an International Expert Panel: A ClinGen Initiative

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Introduction

There has been a great emphasis on the importance genetics plays in PD, with genetic testing for PD becoming more widely used because of observational studies such as PD GENEration and ROPAD (ClinicalTrials.gov Identifiers: NCT04994015 and NCT03866603, respectively). In addition, precision medicine clinical trials for PD require genetic testing prior to enrollment. However, we and others have shown that the definition of PD-related genes and the content of PD panels in the diagnostic setting vary in the number of genes targeted and in variant interpretations. Based on the National Institutes of Health (NIH) Genetic Testing Registry (GTR), there are 502 unique commercially available clinical genetic tests for PD, from 28 Clinical Laboratory Improvement Amendments (CLIA)-approved clinical laboratories (reported as of December 2020). Importantly, the size of these panels range anywhere from 5 to 62 genes. Given these differences, and the start of precision medicine trials being offered for PD, we collaborated with the ongoing gene and variant curation efforts lead by MDSGene (www.mdsgene.org), to develop a Parkinson's disease Gene Curation Expert Panel (PD-GCEP) under ClinGen, a centralized resource across diseases that applies defined criteria to establish gene-disease validity, and whose findings are recognized by the FDA. The overall objective of this work is to enable variant curation based on ClinGen gene curation to generate consensus for the interpretation of variants for inclusion in precision medicine clinical trials for PD.

Methodology

To close this gap in the field, we formed the **Parkinson´s Disease Gene Curation Expert Panel (PD-GCEP)**, recognized by ClinGen, with the mission of defining the clinical validity of gene-disease relationships for PD and atypical parkinsonism.

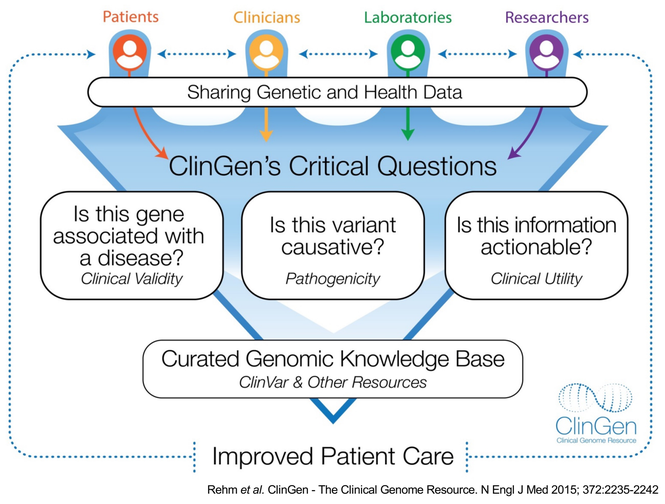
We first targeted the curation of seven well-established PD genes following the ClinGen protocol and using its curation interface.

ClinGen provides a framework in which there are 5 clinical validity classifications (no known disease relationship, limited, moderate, strong, and definitive).

Figure 1 shows the purpose PD-GCEP will have in bettering PD patient care and **Figure 2** shows a screenshot of the PD GCEP website landing page that describes the overview and goals of gene curation.

Figure 1: Purpose of a PD GCEP and VCEP

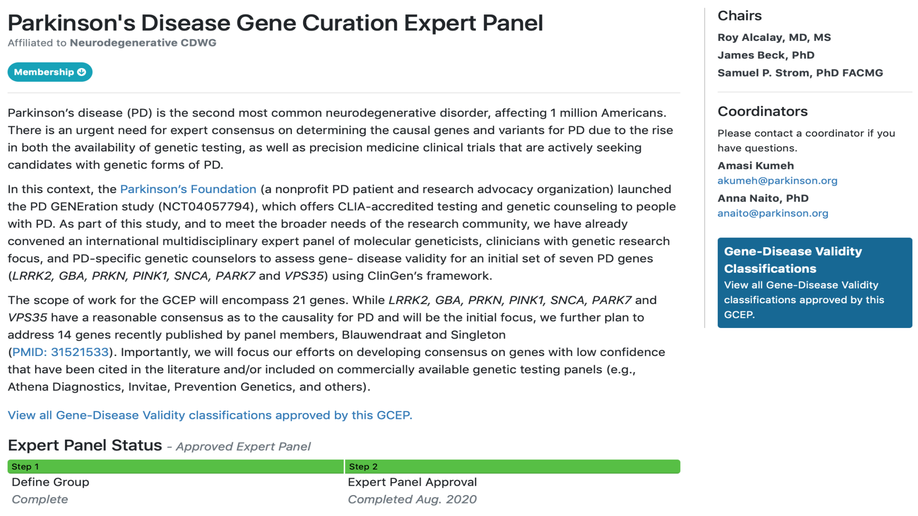
Create authoritative central resource that defines the clinical relevance of genes and variants for use in PD precision medicine and research.



Rehm *et al.* ClinGen - The Clinical Genome Resource. N Engl J Med 2015; 372:2235-2242

Figure 2. PD GCEP Overview and Goals

Website: https://clinicalgenome.org/affiliation/40079



Parkinson's Disease Gene Curation Expert Panel

Affiliated to **Neurodegenerative CDWG**

Membership

Parkinson's disease (PD) is the second most common neurodegenerative disorder, affecting 1 million Americans. There is an urgent need for expert consensus on determining the causal genes and variants for PD due to the rise in both the availability of genetic testing, as well as precision medicine clinical trials that are actively seeking candidates with genetic forms of PD.

In this context, the Parkinson's Foundation (a nonprofit PD patient and research advocacy organization) launched the PD GENEration study (NCT04057794), which offers CLIA-accredited testing and genetic counseling to people with PD. As part of this study, and to meet the broader needs of the research community, we have already convened an international multidisciplinary expert panel of molecular geneticists, clinicians with genetic research focus, and PD-specific genetic counselors to assess gene- disease validity for an initial set of seven PD genes (*LRRK2, GBA, PRKN, PINK1, SNCA, PARK7* and *VPS35*) using ClinGen's framework.

The scope of work for the GCEP will encompass 21 genes. While *LRRK2, GBA, PRKN, PINK1, SNCA, PARK7* and *VPS35* have a reasonable consensus as to the causality for PD and will be the initial focus, we further plan to address 14 genes recently published by panel members, Blauwendraat and Singleton (PMID: 31521533). Importantly, we will focus our efforts on developing consensus on genes with low confidence that have been cited in the literature and/or included on commercially available genetic testing panels (e.g., Athena Diagnostics, Invitae, Prevention Genetics, and others).

View all Gene-Disease Validity classifications approved by this GCEP.

Expert Panel Status – *Approved Expert Panel*

Step 1	Step 2
Define Group	Expert Panel Approval
Complete	*Completed Aug. 2020*

Chairs

Roy Alcalay, MD, MS
James Beck, PhD
Samuel P. Strom, PhD FACMG

Coordinators

Please contact a coordinator if you have questions.

Amasi Kumeh
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Anna Naito, PhD
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Gene-Disease Validity Classifications
View all Gene-Disease Validity classifications approved by this GCEP.

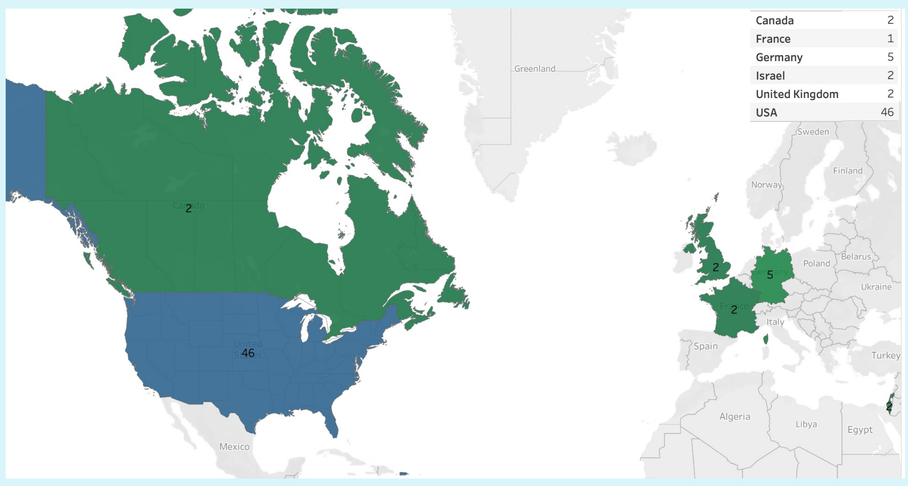
Results

The PD GCEP panel was formally approved in August 2020 consisting of 62 leaders worldwide representing different disciplines such as clinical neurology, genetics, and molecular genomics. **Figure 3** depicts the global representation of PD-GCEP members.

As of 2022, the PD GCEP is now affiliated with the recently formed Neurodegenerative Clinical Domain Working Group (CDWG) within the ClinGen infrastructure. The PD-GCEP has curated and published the clinical validity of *LRRK2, GBA1, PRKN, PINK1, SNCA, VPS35,* and *PARK7,* as there is reasonable consensus in the field as to them playing a role in the causality of PD. The PD-GCEP found that all these genes are classified as "definitive", elucidating that certain variants in these genes are causative for PD as shown in **Table 1.**

We provided a QR code to the PD-GCEP ClinGen website where the evidence criteria applied to confirm definitive gene-disease relationship according to ClinGen's Gene Validity Evaluation Criteria (SOP8, SOP9) and the full curation conducted by the PD-GCEP is listed and accessible.

Figure 3: PD-GCEP Panel Members' Locations



PD-GCEP Curations

Table 1: PD-GCEP Gene Curations

Gene	Mode of Inheritance	Classification	Last Evaluated
GBA1	Autosomal Dominant	Definitive	May 2022
LRRK2	Autosomal Dominant	Definitive	May 2021
PRKN	Autosomal Recessive	Definitive	January 2023
SNCA	Autosomal Dominant	Definitive	May 2022
VPS35	Autosomal Dominant	Definitive	November 2021
PINK1	Autosomal Recessive	Definitive	January 2023
PARK7	Autosomal Recessive	Definitive	June 2022

Conclusion

We have demonstrated the feasibility of establishing consensus by a leadership curation team using the ClinGen framework. Next, we plan to curate more controversial PD genes that are not necessarily included in all commercial PD panels, e.g., *GCH1,* as well as genes linked to atypical parkinsonism. Our expert panel curations via the ClinGen pathogenicity framework will help guide precision medicine efforts in PD and enable informed FDA decision-making in future therapeutic trials.

In parallel with gene curation efforts, plans to develop a Variant Curation Expert Panel (VCEP) to begin curation of variants among *GBA*, *LRRK2* and *PRKN* are underway to address the fieldwide needs of generating consensus on the variants that have clinical implications. Variant interpretation is not black and white because of two main reasons: lack of sharing a standard protocol to interpret the variants, and lack of communication between experts and laboratories, creating multiple interpretations. There are four application parts and we currently are awaiting approval for Part I. For more information about VCEPs and joining please use the following QR code.

Acknowledgements

We would like to acknowledge the commitment and work done by our fellow PD-GCEP members. We also would like to acknowledge the ClinGen group and funding: U24HG009650

Parkinson's Foundation

Parkinson.org

MOREHOUSE SCHOOL OF MEDICINE

POSTER #1437

Building a Coalition to Advance Engagement of Black and African American Communities in Parkinson's Disease Research Using Best Practices in Diversity, Equity and Inclusion and Patient Engagement

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[1] Parkinson's Foundation Research Advocate/Volunteer, [2] Parkinson's Foundation [3] Emory University, [4] Morehouse School of Medicine, [5] Atrium Health, [6] Adena Medical Center and Kettering Medical Center, [7] John Hopkins Medicine, [8] Stanford University School of Medicine, [9] Columbia University, [10] Northwestern University, [11] Jefferson Health

Background

- Black and African American communities are underrepresented in Parkinson's research.[1,2]
- Not considering the lived experiences of Black and African American communities hinders drug development and improved understanding of Parkinson's, leading to health inequities with these communities excluded from the benefits of research participation.
- ***The Parkinson's Foundation Learning Institute*** has the potential to mitigate these health inequities through targeted and tailored training in research advocacy for Black and African American people with Parkinson's and care partners and improve enrollment in research studies, such as **PD GENEration**.

The Parkinson's Foundation Learning Institute was established in 2008 and has trained over 400 volunteers in research advocacy to date. We have created a national network of research advocates around the U.S. that are actively changing the face of Parkinson's disease research.

PD GENEration is the Parkinson's Foundation's largest study and a national initiative that offers genetic testing for clinically relevant Parkinson's-related genes and genetic counseling at no cost. To date, more than 10,000 participants enrolled in the study, 2% identify as Black or African American.

Methods: Building a Coalition

Guided by best practices in diversity, equity and inclusion (DEI) and patient engagement [3,4]

- The Parkinson's Foundation built a coalition in 2020 led by Black and African American people with Parkinson's and their care partners. The coalition is a special interest group (SIG) in Black Diaspora.
- Black and African American clinicians, social workers, nurses and researchers were invited to join the coalition as key partners to driving systemic change among organizations and communities.

The goal of the coalition is to ***redesign and execute the Parkinson's Foundation Learning Institute*** in a culturally responsive way for Black and African American communities and improve enrollment in PD GENEration.

Results: Progress towards Goal

LOGISTICS

- Coalition meets biweekly for planning; the location and date was finalized – Atlanta, GA in Sept 2023
- Refined recruitment process to reduce potential barriers (e.g., modified application)
- Utilized recruitment cohorts for support and sustainability - participants can continue research advocacy with support from Parkinson's Foundation staff, care network and partners

CURRICULUM & EVALUATION

- Redesigned curriculum to align with the unique needs of the Black and African American community (e.g., greater representation among speakers, less content and more discussion, culturally relevant pedagogy[5])
- Expanded metrics to include pre and post measures of self-efficacy, experiences and attitudes towards research, acceptability, feasibility and sustainability

OUTREACH AND SUSTAINABILITY

- Collaboration with Morehouse School of Medicine to advance equitable research
- Added a community day to the Learning Institute to engage community, health and faith-based organizations in partnerships and to provide information and enroll eligible individuals in PD GENEration
- Open House webinar was added before the Learning Institute to promote early rapport and to establish trust

Conclusions: Looking Ahead

- The upcoming Learning Institute will result in 30 people living with Parkinson's and care partners from the Black and African American community trained in research advocacy, including the tools and resources to advocate in their communities about PD GENEration.
- This cohort of Black and African American people living with Parkinson's and care partners will be positioned to drive research agendas and partner with researchers and government agencies on improving quality of life for the Parkinson's community.

1) Bailey M. et al (2020). Parkinson's Disease in African Americans: A Review of the Current Literature. J Parkinsons Dis. 10(3):831-841.; 2) Schneider MG . et al (2009) Minority enrollment in Parkinson's disease clinical trials. *Parkinsonism Relat Disord* 15, 258–262; 3) Vaswani PA, et al (2020). Overcoming Barriers to Parkinson Disease Trial Participation: Increasing Diversity and Novel Designs for Recruitment and Retention. Neurotherapeutics, 17(4):1724-1735. 4) Feeney M, et al (2020). Utilizing patient advocates in Parkinson's disease: A proposed framework for patient engagement and the modern metrics that can determine its success. Health Expect.(4):722-730. 5) Ladson-Billings, G. (1995) Toward a theory of culturally relevant pedagogy. *American Education Research Journal*, 32(3), 465-491

Made possible by support from Robert W. Woodruff Foundation and Genentech, a member of the Roche Group

Outcomes and Impact of Capacity Building for Patient Engagement in Research Through a Patient Advisory Board Model at Academic Research Centers

Gallagher, C., Schroeder, K., Armstrong, M., Carnie, M., Dini, M., Feeney, M., Kluger, B., Seshadri, S., Yarab, N., Wilson, L., Fleisher, J., Davies, P.

Introduction

Involving people with Parkinson's disease (PD) and care partners in research design and execution alongside researchers has gained traction with implementation resources increasing[1]. However, research teams still seek tailored trainings on methods and best practices for this work. A landscape review of the PD community and a survey of staff at academic research centers (Parkinson's Foundation Centers of Excellence- COE) indicated a strong interest in patient engagement opportunities and training. To respond to this, the Parkinson's Foundation initiated a pilot project to create a replicable, sustainable model of patient engagement (PE) in 5 of its COE. Using a patient advisory board (PAB) model, the goal was for participating COE staff, people with PD and care partners to complete the PAB training and work towards developing a comparative effectiveness research (CER) question through ongoing PAB meetings.

Methods

1. A National Collaborative: A national collaborative was established of experts from the Parkinson's Foundation and the COE network to lead the development of this pilot PAB model. People with PD, patient advocates from other disease areas, researchers, clinicians, social workers, and members of the Parkinson's Foundation's patient engagement team came together to help set the priorities and structure of the model and PE training.

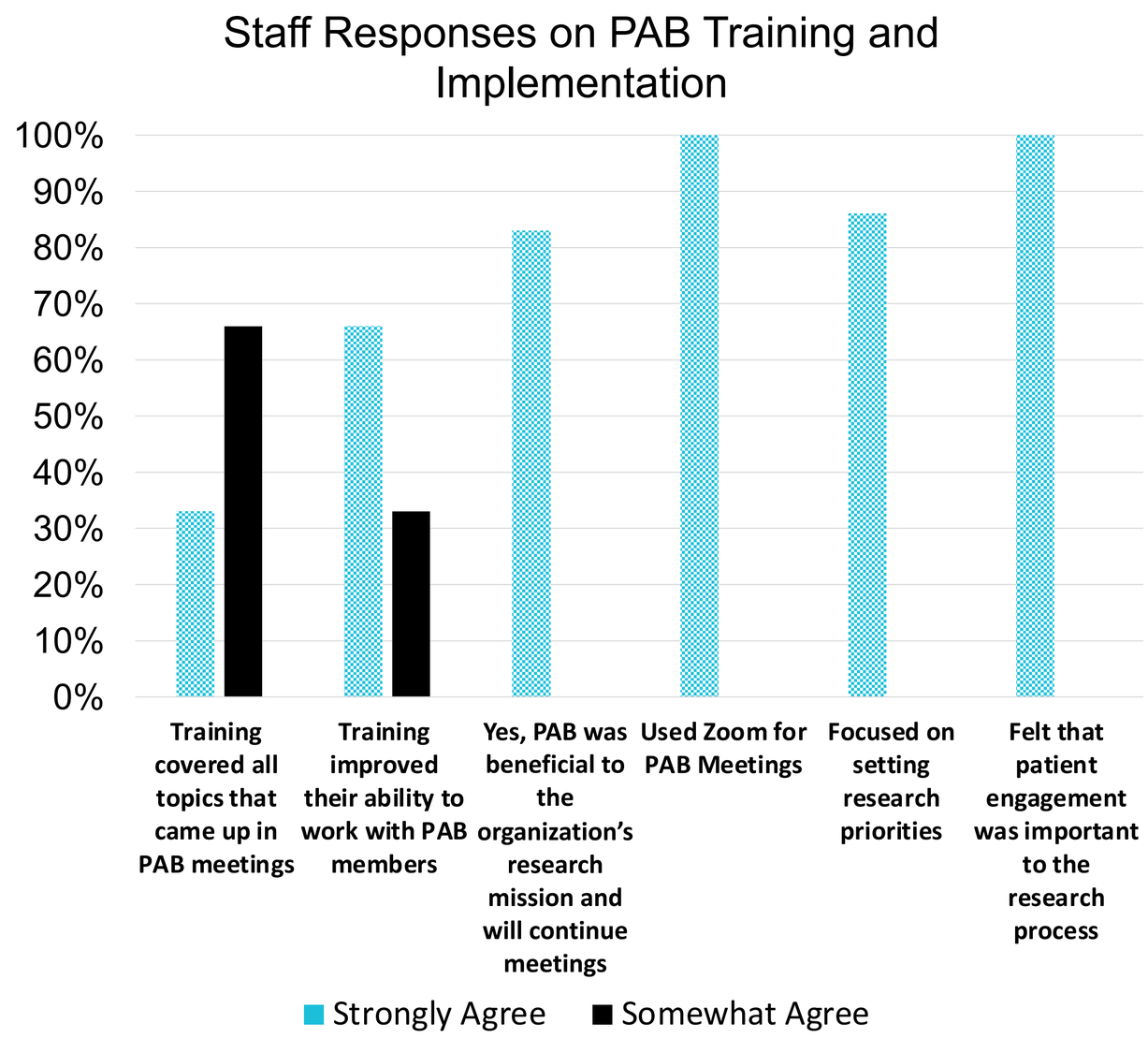
2. Virtual Training: The National Collaborative developed a training for COE staff, people with Parkinson's and care partners. This training was delivered as eight, twice-weekly, hour-long sessions over four weeks and provided online sessions on PE topics, including best practices in PE and community based participatory research, research basics, how to run a PAB and developing a research question.

3. Toolkit and Ongoing Coaching: A toolkit was created to provide templates and resources for planning and running PAB meetings, including example roles and responsibilities, meeting planning checklists and agendas, and meeting facilitation and discussion guides. The Parkinson's Foundation patient engagement staff and patient advisors were available to work with PABs throughout the project. Ad hoc phone calls occurred as needed when PAB challenges arose.

After completing the training and receiving the toolkit, COE conducted PABs with the goal of developing a research question. Baseline and follow-up surveys were administered to measure knowledge, attitudes, intent and behavior towards PE, the training, and PABs.

Results

On average, participating COE held 3.3 PAB meetings over the course of a year. Additional results from COE staff are highlighted below.



Conclusion

This pilot project was effective in engaging and bringing together people with Parkinson's, care partners and COE staff to advance CER. Overall, COE staff found the training to be comprehensive and effective for preparing them to lead PABs at their center. Limitations of this project included COVID-19 and adapting the PAB training to an online format. Ongoing commitment of COE to this work indicates a successful and satisfactory model is in place, and the overall success of this pilot highlights the quality and short-term impact of PABs at academic centers. Future research will explore long term impact, including sustainability of PABs and implementation of CER.

Acknowledgements

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Feeney, M., Evers, C., Agpalo. D., Cone, L., Fleisher, J., Schroeder, K. Utilizing patient advocates in Parkinson's disease: A proposed framework for patient engagement and the modern metrics that can determine its success. *Health Expect. 2020;23(4):722-730.*