Dear PPMI Participant,

Your continued contributions to the Parkinson’s Progression Markers Initiative (PPMI) are helping us learn more about Parkinson’s and move closer to new ways to measure and treat the disease.

Our seventh volume of this scientific update holds just a few of the many insights that have come from the valuable information you share as a study participant. The impact of your visits is clear in the many peer-reviewed publications that come from PPMI investigators and from researchers who have independently accessed this data.

You know better than anyone that Parkinson’s disease (PD) is different from person to person. We are learning why some groups have different symptoms or progression rates and linking biological changes to genetics and other factors. Understanding these differences could help speed the development of new treatments and enroll the right participants in studies to test their impact.

Thank you for your continued contributions to PPMI and to the pursuit of a cure. Visit the PPMI website (www.michaeljfox.org/ppmi) for information on study activities and contact your site coordinator if you have specific questions about your participation.

We look forward to sharing more PPMI results with you as the study makes even more progress.

Thank you again for your partnership.

Sincerely,

The PPMI Team
About PPMI

Sponsored by The Michael J. Fox Foundation, the landmark Parkinson’s Progression Markers Initiative (PPMI) study launched in 2010 and has built the most robust Parkinson’s data set and biosample library in the field. The study has enrolled over 1,500 participants and plans to expand to more than 4,000 volunteers contributing detailed clinical, imaging and biological data over at least five years. Information from people with Parkinson’s disease (PD) risk factors or early-stage Parkinson’s and control volunteers is allowing scientists to plot the natural history of disease onset and progression to develop treatments for every stage of PD.

In partnership with biotech and pharmaceutical companies, nonprofit organizations, and individual donors, PPMI makes data and biosamples available to the research community. The study’s design and data have enabled discoveries and established standardized methods that allow cross-study comparison and collaboration.

This scientific update holds just a few of the recent insights that have come from the analysis of the valuable information shared by PPMI participants.

Stay up-to-date on PPMI at www.michaeljfox.org/ppmi
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Better Ways to Track and Measure Disease

A biomarker is an objective measure of disease, such as cholesterol level for heart disease. With PPMI data and biological samples, scientists are looking around the body to validate biomarkers of Parkinson’s. This work could develop tests to measure Parkinson’s onset and progression.

Neurofilament Light Chain as a Biomarker of Parkinson’s Progression


Lead Author: Brit Mollenhauer, MD, University Medical Center of Goettingen, Germany

Objective: This project explored neurofilament light chain (NfL) — a protein released when brain cells are damaged — to measure progression in Parkinson’s. NfL levels show cell damage in other brain diseases such as multiple sclerosis.

Methods: PPMI investigators looked at NfL in cerebrospinal (spinal) fluid and blood samples from participants in PPMI and in the single-center De Novo Parkinson’s Disease (DeNoPa) Parkinson’s study.

Results: NfL levels in blood samples were significantly higher in people with Parkinson’s than in those without PD. NfL levels also increased over time with PD and correlated with measures of motor and cognitive symptoms.

Conclusion: NfL changes do not only happen in Parkinson’s, so this likely cannot be a way to diagnose the disease. But these results suggest that a blood test for NfL levels may have the potential to measure progression in Parkinson’s.
**Evolution of Alzheimer’s Disease**

**Biomarkers in Early Parkinson’s Disease**


**Lead Author:** David J. Irwin, MD, University of Pennsylvania

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**Objective:** Some people with Parkinson’s show brain changes like those in Alzheimer’s disease. These researchers analyzed protein levels that are usually changed in Alzheimer’s disease in samples from people with early Parkinson’s disease.

**Methods:** Scientists measured three proteins — amyloid-beta, total tau, and phosphorylated tau — in spinal fluid samples collected over three years from participants with PD and control volunteers.

**Results:** People with PD had lower protein levels than control volunteers at baseline (their first study visit). And people with PD had greater decline in amyloid-beta and phosphorylated tau levels at year three.

Baseline amyloid-beta values predicted small but measurable decline on cognitive, motor and autonomic function. (Autonomic functions are the automatic gastrointestinal, urinary, cardiovascular, sexual, etc. functions that our body undertakes involuntarily.)

**Conclusion:** The data suggest measuring levels of these proteins may help predict a Parkinson’s diagnosis, but more research needs to be done to understand how reliable these measures are and their role in Parkinson’s.
Clearer Understanding of the Impact of Genetic Changes

Data from participants with LRRK2 or GBA mutations are helping scientists explore different symptoms and types of PD. This information could lead to better research and care.

Clinical and Imaging Characteristics of PD Participants with LRRK2 and GBA Mutations


Lead Author: Tanya Simuni, MD, Northwestern University, Illinois

Objective: This research sought to understand differences in people with different causes of Parkinson’s. They examined characteristics in GBA and LRRK2 mutation carriers with PD compared to participants with sporadic PD (no known cause).

Methods: These researchers compared clinical data from scales and questionnaires and imaging data from a dopamine transporter (DAT) scan.

Results: Participants with a GBA mutation and PD had no difference in any motor, cognitive or autonomic features compared to people with sporadic PD.

PD participants with a LRRK2 mutation had less motor disability and lower scores on a REM sleep behavior disorder (acting out dreams) questionnaire. There was no meaningful difference in cognitive or autonomic features.

Participants with PD and either a LRRK2 or GBA mutation had less dopamine loss via DaTscan when compared with participants with sporadic PD.

Conclusion: The results suggest people with PD and a LRRK2 mutation may experience a milder type of disease. More data on these groups could help participants know what to expect in their disease course and help researchers choose the right participants for studies.
Measures of Glucocerebrosidase Activity in People with Parkinson’s

Journal: Annals of Clinical and Translational Neurology
ncbi.nlm.nih.gov/pmc/articles/PMC7545591

Lead Author: Roy N. Alcalay, MD, Columbia University, New York

Objective: Mutations in the GBA gene can lead to Parkinson’s and cause reduced activity in the glucocerebrosidase (GCase) enzyme — a member of the cell’s cleaning crew that degrades damaged or excess cell parts. This study looked at GCase activity in other PPMI study groups.

Methods: Investigators measured GCase activity in blood from people with PD — with a GBA mutation, a LRRK2 mutation or sporadic PD. Also included were GBA mutation carriers without PD and control volunteers with no genetic connection to Parkinson’s.

Results: People with a GBA mutation (with or without PD) had reduced GCase activity. One type of the mutation caused lower GCase activity in people with PD compared to mutation carriers without PD.

GCase activity was similar between PD without a GBA mutation and control volunteers. But there was still some variability in GCase levels and, in people with PD without a GBA mutation, those with the lowest GCase activity had worse motor function.

Conclusion: GCase activity is lower in people with a GBA mutation. While there is not a significant difference in people with PD without the mutation, there is some variability and connection to worse symptoms.

Drugs against the GCase pathway are already in clinical trials with GBA mutation carriers, so this information could help select people for studies and understand if those drugs would work for non-mutation carriers.
More Information on Non-Motor Symptoms

Non-motor symptoms are extremely common for people with Parkinson’s, but there are few available treatment options. Learning more about the impact of these symptoms from PPMI data could help provide better care and prioritize research needs.

Non-Motor Symptoms and Cognitive Abilities
Five Years into Parkinson’s

Journal: Annals of Clinical and Translational Neurology
ncbi.nlm.nih.gov/pmc/articles/PMC7187707

Lead Author: Daniel Weintraub, MD, University of Pennsylvania

Objective: Parkinson’s science and care has, in the recent past, recognized the non-motor aspects of the disease. But still little is known about how they evolve over time in people with PD or the impact of treatments.

Methods: Investigators looked at data from annual PPMI visits to evaluate prevalence and treatment of non-motor and cognitive symptoms in participants with PD and control volunteers.

Results: People with PD experienced more non-motor symptoms — including depression, insomnia, anxiety and fatigue — after five years in the study. At five years, more than half of participants had three or more non-motor symptoms. Most common were insomnia and REM sleep behavior disorder (acting out dreams). Cognitive impairment also increased slightly.

In control participants, non-motor symptoms remained stable or were less frequent over time.

Antidepressant use in PD was common at baseline and increased over time. Antipsychotic and cognitive-enhancing medication use was uncommon.
Conclusion: NfL changes do not only happen in Parkinson’s, so this likely cannot be a way to diagnose the disease. But these results suggest that a blood test for NfL levels may have the potential to measure progression in Parkinson’s.

Depression Associated with Worse Cognitive Symptoms in People with Newly Diagnosed Parkinson’s Disease


Lead Author: Jeong Hoon Park, PhD, Kangwon National University Hospital, South Korea

Objective: Although depression is very common in people with PD, only a few studies have investigated the effects of initial depression on cognitive decline. This study looked at the long-term effects of depression early in the disease.

Methods: Investigators reviewed depression scores on scales from baseline. They compared those results to data on if a participant progressed to mild cognitive impairment (memory and thinking problems beyond what is expected with normal aging) during four years of follow-up.

Results: Depression was a risk factor for mild cognitive impairment. In addition, the participants that progressed to mild cognitive impairment were older and had worse motor symptoms during their first year in PPMI.

Conclusion: Depression may influence the overall rate of Parkinson’s progression. Effective depression screening and intervention are critical.
Changes in Autonomic Functions Predict Activities of Daily Living and Depression in Parkinson’s Disease

Journal: Clinical Autonomic Research
link.springer.com/article/10.1007/s10286-020-00672-7

Lead Author: Miriam Sklerov, MD, University of North Carolina

Objective: Changes in autonomic function — the automatic gastrointestinal, urinary, cardiovascular, sexual, etc. functions that our body undertakes involuntarily — can be part of Parkinson’s disease and have a severe impact on daily life. This study compared autonomic function and performance in daily living activities (e.g., eating, bathing, getting dressed, going to the bathroom) in people with Parkinson’s.

Methods: Researchers analyzed PPMI data at baseline, two years after enrollment and five years after enrollment. They also looked at data on depression to see if that related to changes in autonomic function or changes in daily living activities.

Results: Changes in autonomic function impacted the ability to complete daily living activities in people with newly diagnosed PD. The symptoms themselves limited activity and autonomic problems were also linked to greater depression, which in turn impacted daily tasks.

Conclusion: More research is needed to determine how potential treatments could influence these changes in PD. Measures of function are important because regulators like the U.S. Food and Drug Administration want to evaluate therapeutics’ impact not only on biology but also on quality of life.
Greater Definition of Disease Subtypes

Parkinson’s is different from person to person, but there are similarities. Researchers try to identify subtypes of Parkinson’s to help tell patients what to expect, to better study biology and to select the right people for studies.

Parkinson’s Subtypes in Moderate to Advanced PD

**Journal:** Parkinsonism and Related Disorders [ncbi.nlm.nih.gov/pmc/articles/PMC6774826](ncbi.nlm.nih.gov/pmc/articles/PMC6774826)

**Lead Author:** Lan Luo, MD, Beth Israel Deaconess Medical Center, Massachusetts

**Objective:** Scientists have worked to better understand biology and clinical experience in people in three major Parkinson’s motor subtypes: more trouble with balance and gait difficulty, more trouble with tremor, or not able to categorize (indeterminant). This project examined if a patient’s subtype could change with treatment and disease progression.

**Methods:** The scientists gave each participant a tremor score and a balance/gait score. They classified each person’s subtype based on the ratio between the two (i.e., much more tremor, much more balance/gait or similar). With data from another Michael J. Fox Foundation-sponsored study, BioFIND, the team looked at if a person’s subtype changed when their medication was working (“on”) versus not working (“off”). Then with PPMI they looked to see if subtype changed over time as well as with medication effect.

**Results:** As the disease progressed, people in all three motor subtypes saw a less severe difference between symptoms. That is, their originally less dominant symptom (tremor or gait/balance) worsened. Medications to replace dopamine reduced the difference in symptoms only in the worse-tremor subgroup. Medication effect on subtype shift was also more notable with progression.

**Conclusion:** Subtypes are not fixed but change with disease progression and with dopamine treatment. The severity of the subtypes also lessened — people may have had both tremor and gait problems or less severe tremor. The researchers recommend pursuit of a more stable classification system for subtypes based on underlying biological differences.