



Parkinson's
Progression
Markers
Initiative

PPMI Scientific Update

**Volume 8 | New Tests for Parkinson's Disease
and Scientific Discoveries Fueled by PPMI**

Dear PPMI Participant,

Volunteers like you are PPMI's most valued partners. You are helping scientists and doctors learn how best to measure and treat Parkinson's disease, and the impact of your participation cannot be overstated.

Here we share our latest PPMI scientific update. We highlight only a handful of the insights uncovered from the information you share as a study volunteer. Your impact can be felt in the many peer-reviewed publications, penned by both PPMI scientists and independent researchers who access this data. With your data, we are learning more about symptoms, progression and disease risk.

To stay up to date on all PPMI findings, log into myPPMI (myppmi.org). This hub for all things PPMI shows new information from the study and more opportunities to add to Parkinson's research. (If you have any issues logging into myPPMI, please email support@myppmi.org.)

Your ongoing contributions to PPMI are appreciated.

We look forward to sharing even more results with you as we continue to make progress, together.

Thank you 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. Since then, PPMI has built the most robust Parkinson's data set and biosample library in the field.

PPMI has enrolled over 1,800 participants at medical centers across the globe. People recently diagnosed with Parkinson's disease (PD), individuals with Parkinson's risk factors (e.g., loss of smell, REM sleep behavior disorder) and control volunteers join at a study site. Over at least five years, these participants have clinical exams and imaging scans and share biological samples at a study site.

In parallel, more than 36,000 volunteers are participating online. These partners — people with and without PD — share data on health and wellness over time. Together, data from these groups allows scientists to plot the natural history of disease onset and progression to develop treatments for every stage of PD.

PPMI makes its data and biosamples available to the research community. The study's design and data have made it a cornerstone of Parkinson's research. Scientists have downloaded PPMI data more than 13 million times.

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

Learn more at michaeljfox.org/ppmi

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Better Ways to Track and Measure Disease

A biological marker is an objective measure of disease, such as cholesterol level for heart disease. With spinal fluid contributed by PPMI participants, PPMI has validated a biomarker for Parkinson's disease. And with PPMI data and samples, scientists are looking around the body for other biomarkers.

Tool to Predict Impulse Control Disorders in Parkinson's Disease

Journal: *Annals of Clinical and Translational Neurology* doi.org/10.1002/acn3.51569

Lead Author: Daniel Weintraub, MD, University of Pennsylvania

Objective: A class of medications for Parkinson's disease (dopamine agonists) may cause impulse control disorders (ICDs). These can include compulsive gambling, shopping, eating or sexual activity. This side effect can greatly impact quality of life. In this study, researchers looked for predictors of developing an impulse control disorder with these medications.

Methods: Investigators searched genetic data of people with PD in PPMI and other studies for predictors of ICDs. They also looked at clinical factors. They then created a formula for calculating the risk of ICDs.

Results: The scientists found four new gene variants linked to risk of ICDs. They also linked ICD risk to some clinical factors. These included age, duration of PD, medication use, ethnicity and sex. With these findings they created a formula to predict risk of an ICD. They divided participants into four groups based on presence of risk factors. In the highest risk group, nearly 40 percent had an ICD. In the lowest risk group, only seven percent had an ICD.

Conclusion: Doctors could use this formula before prescribing a dopamine agonist. If someone is in the highest risk group, they may opt for another type of medicine. This could help lower the risk of ICDs and protect individuals from their harmful effects.

Test for Parkinson's Protein to Aid Detection of Parkinson's Disease

Journal: *Acta Neuropathologica Communications* doi.org/10.1186/s40478-021-01282-8

Lead Author: Marco J. Russo, MD, New York University

Objective: Alpha-synuclein is a protein that clumps in the brains of people with Parkinson's. In its early stages, Parkinson's disease may be difficult to diagnose. A new test may aid in accurate early diagnosis. In this study, investigators compared the performance of this test when done by three different laboratories.

Methods: The investigators randomly selected spinal fluid samples from PPMI participants, with and without PD, for testing. Three independent laboratories performed the test in parallel. In the seed amplification assay, normal alpha-synuclein molecules are mixed together with a specimen that could have abnormal alpha-synuclein (such as the spinal fluid obtained from lumbar puncture). If abnormal alpha-synuclein is present in the specimen, it will lead to the normal molecules changing shape and clumping up.

Results: The results of the test were very similar across laboratories. All displayed high accuracy (identifying 86 to 96 percent of people with PD). In people with PD, the seeded alpha-synuclein clumped together.

Conclusion: The test for seeding alpha-synuclein is an emerging, reliable diagnostic tool for early-stage PD.

Biomarker Breakthrough in Testing for Alpha-synuclein Activity

Journal: *The Lancet Neurology* [doi.org/10.1016/S1474-4422\(23\)00109-6](https://doi.org/10.1016/S1474-4422(23)00109-6)

Lead Author: Andrew Siderowf, MD, University of Pennsylvania

Objective: As described above, alpha-synuclein seeding amplification assays (SAAs) may help diagnose Parkinson's disease from control participants. PPMI researchers then looked at whether the test relates to the different “types” of PD. They also reviewed results in groups at risk for developing Parkinson's disease.

Methods: Researchers looked at SAA results across PPMI cohorts. The participants were from 33 centers in Austria, Canada, France, Germany, Greece, Israel, Italy, the Netherlands, Norway, Spain, the United Kingdom and the United States. This analysis included 1,123 PPMI volunteers who enrolled between July 2010 and July 2019.

Results: The ability of the test to identify sporadic (cause unknown) PD in people with smell loss was 98.6 percent. It was positive (showing disease) only in 67.5 percent of people with LRRK2 PD and in 78.3 percent of people with sporadic PD without smell loss. People with LRRK2 PD and normal smell function had an even lower positivity rate: 34.7 percent.

Among at-risk groups, 44 (86 percent) of 51 participants with REM sleep behavior disorder (RBD) or hyposmia (smell loss) had positive alpha-synuclein SAA. Twenty-five (8%) of 310 people with a LRRK2 or GBA mutation without PD were positive.

Conclusion: These results show that the test identifies, provides information about the differences in PD, and detects disease in people before a clinical diagnosis. These findings suggest a crucial role for the alpha-synuclein SAA in therapeutic development.

Editor's Note: PPMI leadership has shared more on these results and their impact in webinars, blog posts and other media. Visit the myPPMI portal for a special webinar for PPMI volunteers or michaelfox.org to read more.

Marker of Cell Death Predicts Worsening of Movement Symptoms

Journal: *Frontiers in Neuroscience* doi.org/10.3389/fnins.2022.959261

Lead Author: Yumei Liu, Qingdao University, China

Objective: Neurofilament light chain (NfL) is a protein released when brain cells are damaged. Scientists looked at whether NfL levels could predict worsening of motor symptoms in people with PD.

Methods: Investigators used blood serum and spinal fluid samples donated by people with and without PD in PPMI. They examined the relationship between NfL levels and movement symptoms at baseline and over a three-year period of time.

Results: People with PD had more NfL in both blood and spinal fluid than people without PD. Higher NfL levels at baseline (study enrollment) were linked to more severe movement symptoms time. And more rapidly increasing levels of NfL were also linked to worsening movement symptoms.

Conclusion: NfL in the blood and spinal fluid may be used to predict worsening of motor function in PD. This tool could help select people for studies to ease movement symptoms or test the impact of new treatments. It could also help doctors offer patients a more accurate prognosis and tailor treatment choices to meet individual needs.

More Data on Symptoms and Progression

People experience Parkinson's disease in different ways. Learning more about subtypes, symptoms and progression could help improve care and prioritize research needs.

Predicting Speed of Progression Using Machine Learning

Journal: *npj Parkinson's Disease* doi.org/10.1038/s41531-022-00439-z

Lead Author: Anant Dadu, PhD, University of Illinois at Urbana-Champaign

Objective: Parkinson's disease presents in many different ways. Scientists aimed to create a model to identify different disease subtypes and to predict disease progression.

Methods: Researchers analyzed PPMI data using machine learning. Computers can group and predict activity by learning from data. It used demographics, biospecimen results, vital signs, genetics, and motor symptom score to predict progression type.

Results: This study revealed three disease subtypes: slow, moderate and fast progressors on measures of movement, sleep and cognition. Clinical, demographic, biological, and genetic characteristics associated with each subtype were identified. Machine learning also predicted disease severity five years after diagnosis.

Conclusion: Predicting disease course can inform patient counseling, clinical care, and treatment planning. Within PD, this would allow symptom-specific care (for example, earlier intervention to reduce risk of falls and address cognitive decline). Prediction tools may also speed the research of complex disease and facilitate more efficient clinical trial design. Future studies could be shorter, smaller, and more cost effective, speeding the rate of new treatment development.

Brain Changes in People with REM Sleep Behavior Disorder and with Thinking Problems

Journal: *npj Parkinson's Disease* doi.org/10.1038/s41531-022-00326-7

Lead Author: Javier Oltre, PhD, University of Barcelona and Institute of Biomedical Research August Pi i Sunyer (IDIBAPS), Spain

Objective: Rapid eye movement sleep behavior disorder (RBD) is often a sign of brain changes. In this disorder a person acts out their dreams: kicking, hitting or yelling while asleep. Some people with RBD are later diagnosed with Parkinson's disease. This disorder is also linked to thinking and memory issues. This study looked at brain changes and cognitive impairment in people with PD and RBD.

Methods: Scientists used PPMI data shared by people with Parkinson's and RBD, people with PD without RBD, and control participants. They compared cognitive ability, thickness of the outer part of the brain (which is responsible for cognition), and brain volume.

Results: People with both Parkinson's and RBD had changes in several parts of the brain. These changes were not seen as much in control participants and people with PD without RBD. Worsening of cognitive ability of people with PD and RBD was linked to changes in certain parts of the brain.

Conclusion: Researchers linked worsening of cognitive ability and specific brain changes in people with Parkinson's and RBD. Understanding more about these biological changes can teach scientists about how they may better treat and prevent memory and thinking issues, in both people with PD with RBD and without the sleep disorder.

Long-term Physical Activity and Exercise May Slow Disease Progression

Journal: *Neurology* doi.org/10.1212/WNL.00000000000013218

Lead Author: Kazuto Tsukita, MD, PhD, Kyoto University, Japan

Objective: The value of physical activity and exercise to people with PD is well known. Most studies, however, have only examined the short-term benefits of active exercise. This study looked at the effects of exercise and regular physical activity on Parkinson's disease in the longer term.

Methods: The researchers analyzed PPMI data to determine how vigorous exercise influences the severity of PD symptoms over five years.

Results: When maintained over time, higher levels of regular physical activity (e.g., walking, swimming) helped slow symptom progression. The scientists also found that moderate to vigorous exercise (especially ones that helped with balance such as dancing) helped slow decline in postural and gait function. Work-related activities (paid work or volunteer activities that require at least some physical activity such as walking) were linked to slower decline of brain processing speed.

Conclusion: Maintaining a high level of physical activity over the course of PD may slow disease progression. Work or volunteer-related physical activity may help sustain the brain's ability to quickly process information and inputs.

Association of Early Weight Change with Cognitive Decline in Parkinson's Disease

Journal: *Neurology* doi.org/10.1212/WNL.0000000000201404

Lead Author: Ryul Kim, MD, Inha University, South Korea

Objective: Weight loss can be part of Parkinson's disease. Weight gain can be a medication side effect. Scientists studied the link between weight change in early PD and changes in cognition over the eight-year period.

Methods: The researchers analyzed PPMI data shared by people with PD. They reviewed scores on tests of processing speed, global cognitive function, attention and executive function (such as multitasking or problem solving). The researchers divided participants into three groups: weight loss, weight maintenance and weight gain. The loss and gain groups were defined as a change of more than three percent of body weight in the first year.

Results: People who lost weight shortly after being diagnosed with PD experienced decline in global cognitive and executive functions sooner than those in the weight maintenance group. The weight gain group was slower to experience worsening of processing speed — how quickly the brain handles information — and attention.

Conclusion: Weight change early in the course of PD may affect how quickly cognition worsens. While there is more to learn about this relationship, these findings show the importance of maintaining a healthy weight. People recently diagnosed with PD should work with doctors on weight maintenance.

Greater Understanding of Risk

We know about risk factors linked to Parkinson's disease. PPMI data is offering insights on who gets Parkinson's, who doesn't and why. This could point to ways to prevent disease.

Characteristics of LRRK2 Mutation Carriers without Parkinson's Disease

Journal: *npj Parkinson's Disease* doi.org/10.1038/s41531-022-00404-w

Lead Author: Tanya Simuni, MD, Northwestern University

Objective: LRRK2 genetic mutations increase one's risk of Parkinson's disease. In this study, researchers evaluated how test results of people in PPMI with a specific LRRK2 mutation (LRRK2 G2019S) without Parkinson's change over time. They then compared these data to data collected from control volunteers without a LRRK2 mutation. Their other aim was to find any predictors of future PD in non-manifesting LRRK2 carriers.

Methods: The researchers looked at test results captured over two years. These included tests around motor and non-motor symptoms. They also reviewed dopamine transporter (DAT) scan results and analysis of biological samples including blood and spinal fluid.

Results: People with the LRRK2 mutation scored worse on many tests early in their study participation compared to control volunteers. But their scores did not worsen over time and very few developed PD during the two years.

Conclusion: More data is needed to better understand LRRK2 and to identify reliable predictors of PD. Longer studies will help researchers address this critical need.

Autonomic Symptoms as Risk Markers for Parkinson's Disease

Journal: *Clinical Autonomic Research* doi.org/10.1007/s10286-022-00889-8

Lead Author: Cameron Miller-Patterson, MD, University of Pennsylvania

Objective: Scientists look for factors that may predict development of Parkinson's disease. Identifying these early signs may help researchers study the disease in its earliest stages. This study looked at autonomic issues — including problems with breathing, digestion and heartbeat — in people who have other risk factors of PD.

Methods: Scientists used PPMI data from people who don't have a PD diagnosis but are at increased risk. These people have REM sleep behavior disorder (RBD), hyposmia (smell loss), or a mutation in the LRRK2 or GBA gene. They looked at data over an average of 30 months to study associations between autonomic issues, a PD diagnosis and decline in independence and functional abilities.

Results: The investigators linked two autonomic issues — gastrointestinal dysfunction and female sexual dysfunction — with an increased risk of PD. (Gastrointestinal dysfunction includes constipation, nausea and vomiting. Female sexual dysfunction includes decreased sex drive and pain with intercourse.) People who had these features were more likely to be diagnosed with Parkinson's during the study period than people who did not have these issues. Cardiovascular issues — low blood pressure and changes in heart function — predicted decline in functional ability (e.g., bathing, eating, getting dressed, etc.).

Conclusion: This study showed that gastrointestinal and female sexual dysfunction predicted future diagnosis of PD in people at risk for the disease. These symptoms, in presence of other risk factors, may help individuals (and their doctors) more closely monitor for development of Parkinson's movement symptoms. The findings around heart health may encourage people to adopt healthy lifestyle choices.