

Research Updates in Parkinson's Disease

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University of Nebraska
Medical CenterSM

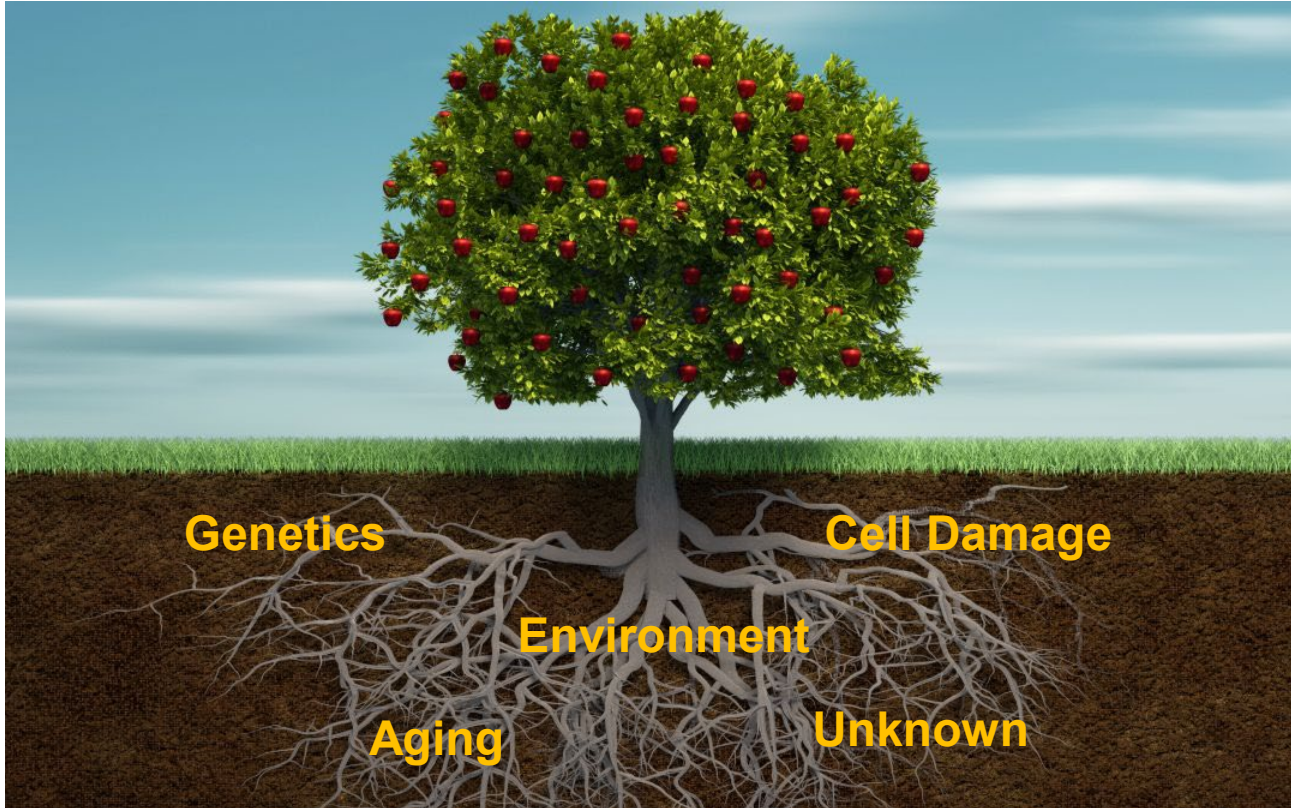
Why is Research Important?

- 2nd most common neurodegenerative disease
 - After Alzheimer's Dementia
- \$14 billion cost of treatment annually
 - Loss of productivity: \$6.3 billion



We still don't have a *cure*

The “cure” isn’t so straightforward





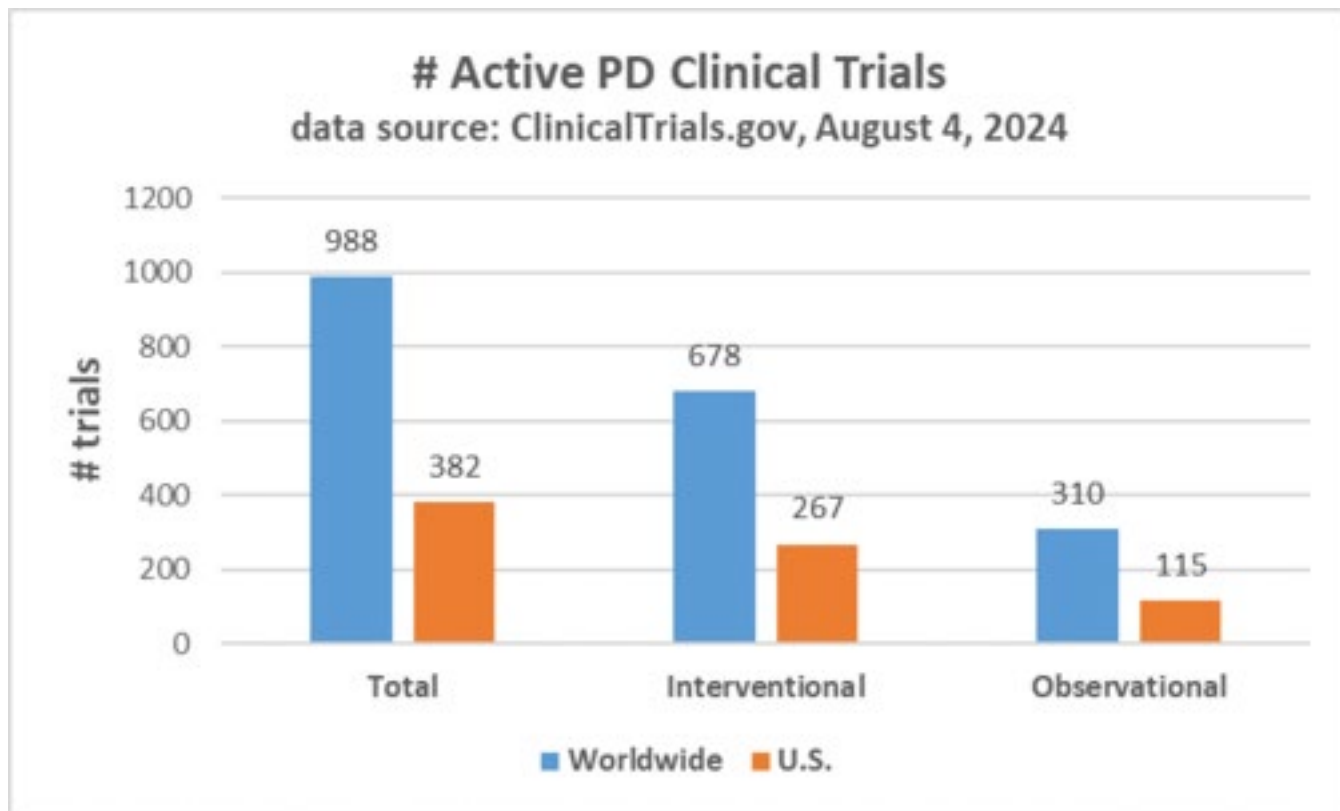
Journal of Parkinson's Disease 14 (2024) 899–912
DOI 10.3233/JPD-240272
IOS Press

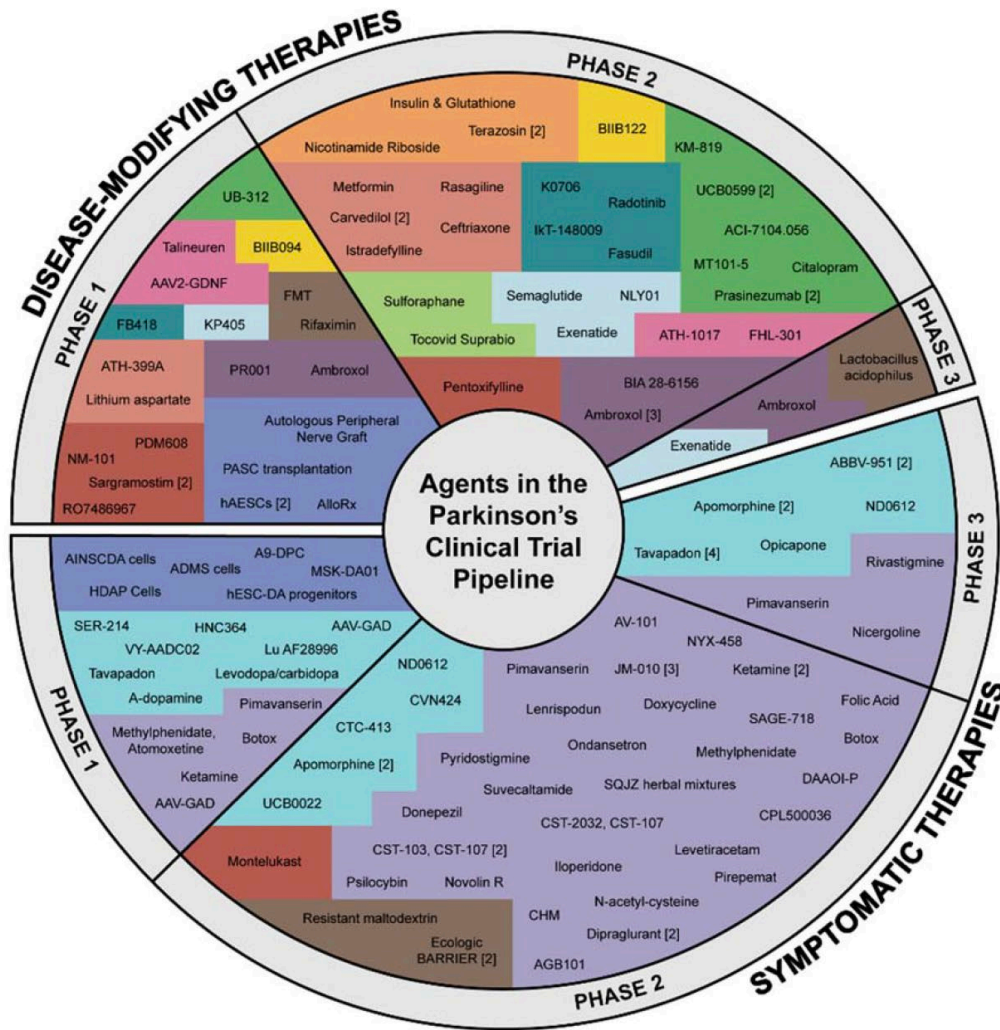
899

Clinical Trial Highlights

Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2024 Update

PDTrialTracker.info





Therapy Targets

- Anti-inflammatory
- Antioxidant
- Cell Therapy
- DMT Other
- Dopaminergic Symptom Relief
- Energy and Mitochondria
- GBA
- GLP-1R Agonist
- Kinase Inhibitor
- LRRK2
- Microbiome/GIT
- Neurotrophic Factors
- Non-dopaminergic Symptom Relief
- Targeting aSN



Today's Topics

1. Finding A **Cure**
 1. Disease Modifying Therapies
2. Symptom-**Specific** Treatments
 1. Improving Quality of Life
3. Emerging **Biomarkers**
 1. Diagnosing PD Earlier
4. Future **Directions**
5. How You Can **Get Involved**





The Quest for A Cure: Disease-Modifying Therapies (DMTs)

What Does Disease-Modifying Mean?



Disease Modifying (DMT)

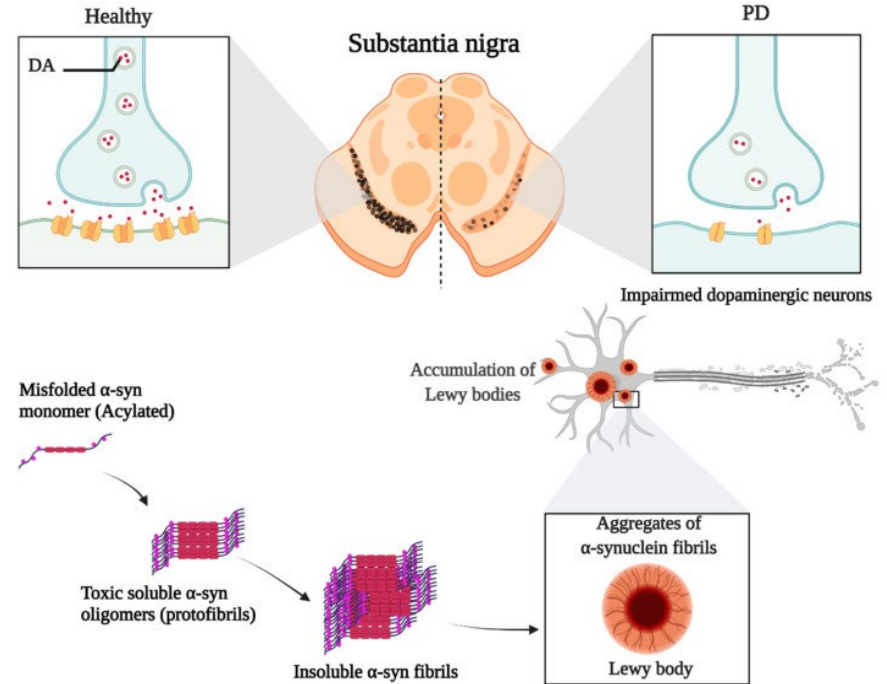
Slows or stops the progression and neuronal cell death

Symptomatic Therapy (ST)

Improves or restores function for the patient

How A Cure Might Work

- Alpha synuclein targets
- Glucagon-like peptide (GLP-1) agonists
- Antioxidants
- Anti-inflammatories
- Gut/Microbiome
- Gene-specific
 - GBA
 - LRRK2



Quick Review: What's Happening in the Parkinson's Brain

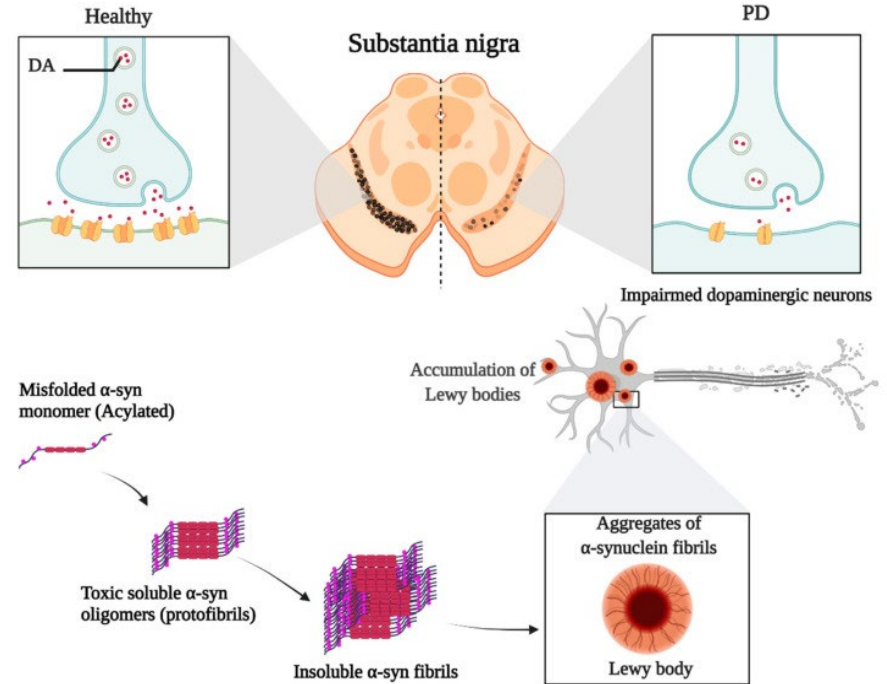


The brain makes a protein called **alpha-synuclein**

Protein misfolds while being made

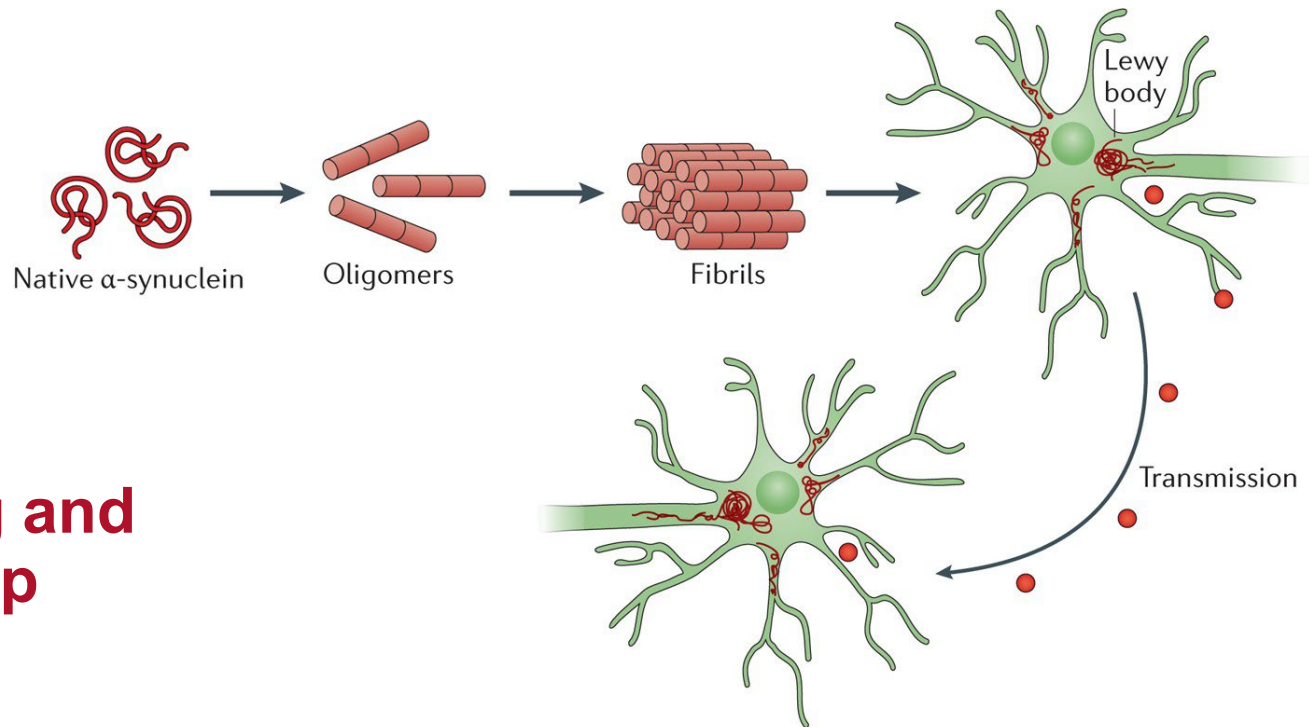
→ Builds up in the brain and becomes **toxic**

→ Kills off **dopamine cells** and causes Parkinson's Disease





Alpha Synuclein Therapies



Goal:

**Stop misfolding and
toxic build-up**

Alpha Synuclein Therapies

- Give or create **antibodies against** α -synuclein
 - Through IV
 - As a vaccine
- Block α -synuclein
- Break down misfolded α -synuclein

Caveat: Not every PD has an alpha-synuclein problem





PASADENA Trial: Prasinezumab

- Antibody = a natural “fighter” in the body
- Binds to abnormal alpha-synuclein protein
- Cleans out the bad protein

October 2024:

Phase II PASADENA Trial

“Less progression of motor symptoms by **up to 40%**”

Next Steps:

*Phase II Trial (PADOVA)
on-going*



Can a Cough Medicine Cure PD?

Ambroxol

- Cough medicine used on 50+ countries
 - **NOT** FDA approved in the US
- Enzyme tied to specific genetic mutation (GBA)
 - **Clears alpha-synuclein**



Mullin S, Smith L, Lee K, et al. Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucocerebrosidase Gene Mutations: A Nonrandomized, Noncontrolled Trial. *JAMA Neurol.* 2020;77(4):427–434. doi:10.1001/jamaneurol.2019.4611



Can a Cough Medicine Cure PD?

Ambroxol

ASPro-PD Trial

- Ambroxol vs Placebo
- Patients **with and without** the GBA genetic mutation

Next Steps:

**Now recruiting in the UK
2023-2027**



Mullin S, Smith L, Lee K, et al. Ambroxol for the Treatment of Patients With Parkinson Disease With and Without Glucocerebrosidase Gene Mutations: A Nonrandomized, Noncontrolled Trial. *JAMA Neurol.* 2020;77(4):427–434. doi:10.1001/jamaneurol.2019.4611



Hot Topic: GLP-1 Agonists

Ozempic-like drug may help slow the progression of Parkinson's symptoms

Written by [Finn Cohen](#) on April 9, 2024 — Fact checked by [Hannah Flynn](#)



April 19, 2024

Are GLP-1 Diabetes Drugs Like Ozempic Coming For Parkinson's Disease?

By Michael S. Okun





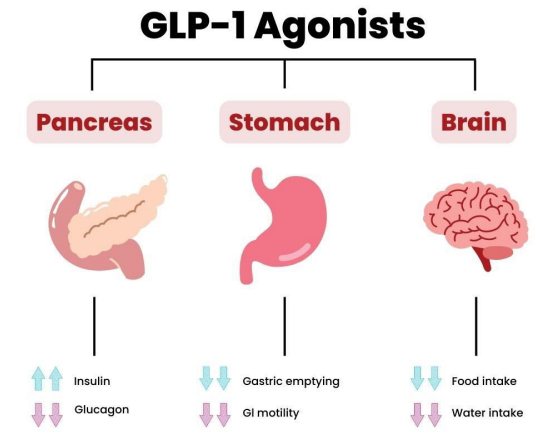
Diabetes Medications: GLP-1 Agonists

- Trigger insulin release
 - Used for diabetes and weight loss
 - Receptors also in the brain



GLP-1 agonists may block brain's "inflammatory response"

NOTE: Ozempic, Mounjaro, Wegovy do NOT cross into the brain!



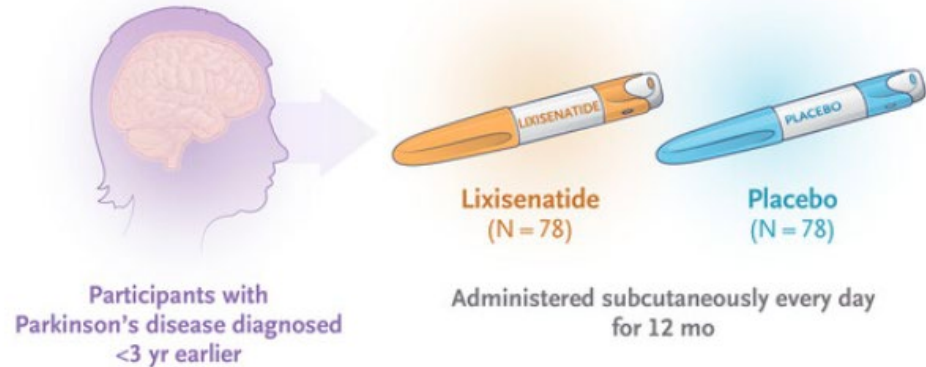


Diabetes Medications: GLP-1 Agonists

LIXIPARK Phase 2 Trial

Drug: *Lixisenatide*

- Early PD patients
 - Compared patients getting drug vs placebo group
- Followed 1 year
- Less progression of “motor disability” than placebo



Authors: Wassilios G. Meissner, M.D., Ph.D., Philippe Remy, M.D., Ph.D., Caroline Giordana, M.D., David Maltête, M.D., Pascal Derkinderen, M.D., Ph.D., Jean-Luc Houéto, M.D., Mathieu Anheim, M.D., Ph.D., ⁴³⁷, for the LIXIPARK Study Group* [Author Info & Affiliations](#)

Published April 3, 2024 | N Engl J Med 2024;390:1176-1185 | DOI: 10.1056/NEJMoa2312323
VOL. 390 NO. 13 | Copyright © 2024

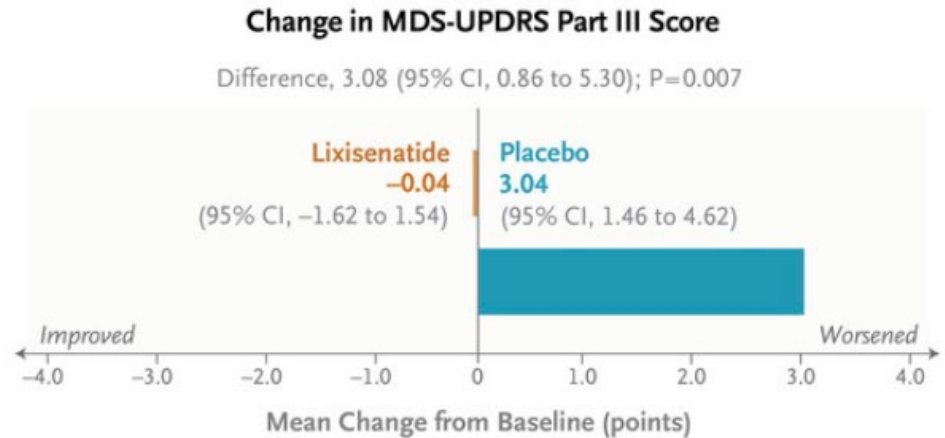


Diabetes Medications: GLP-1 Agonists

- Medication group stayed stable
- Placebo group worsened

Major side effects:

- *Nausea*
- *Vomiting*
- *Acid reflux*



Next Steps:
Phase 2 & 3 Trials
Testing on Larger Groups for a
Longer Time



Hot Topic: Stem Cells



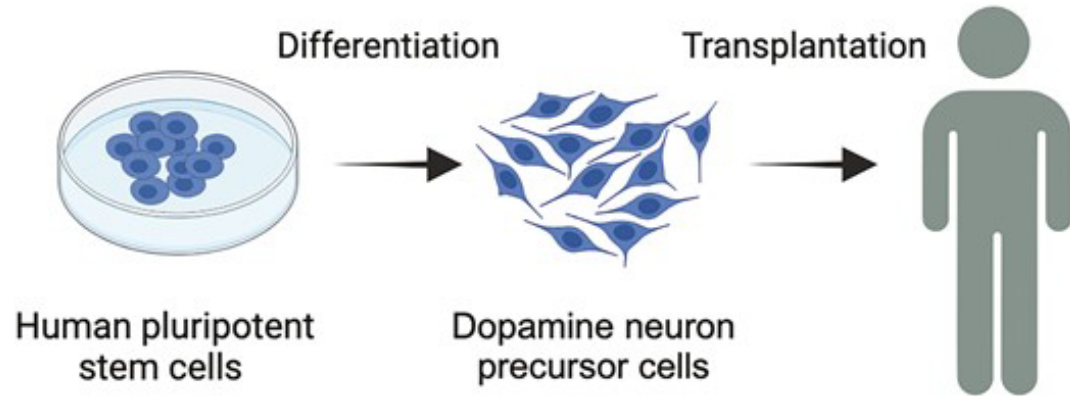


Stem Cells and PD

“New” cells that can be turned into any type of body cell
→ Make new brain cells (neuron)

How They Work:

1. *Reduce inflammation*
2. *Regulate immune system*
3. *Restore normal brain cell function*
4. *Promote making new cells*



Stem Cells and PD



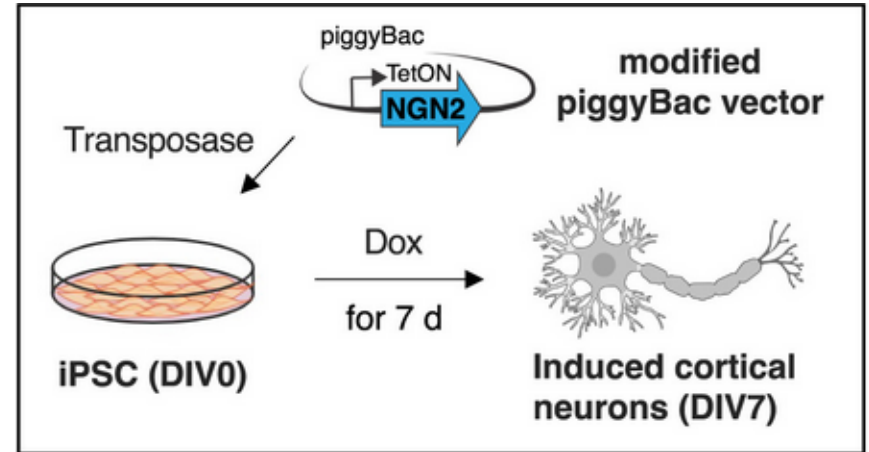
Uses:

1. “Model” Parkinson’s for research use

1. (ie) “Parkinson’s in a petri dish”
2. Study new treatments without risking harm to real patients

2. Treatment

1. Make new dopamine brain cells
2. Give them to PD patients





Stem Cell Clinical Trials

Sponsor	Type	Cells	Trial stage	Clinical progress
Kyoto University/ CiRA/Sumitomo	Allogeneic	One iPSC line (HLA matched and unmatched to recipients). Requires immunosuppression	PMMA clearance 2018	Phase I initiated
Sloan Kettering/ BlueRock Therapeutics/Bayer	Allogeneic	Embryonic stem cell line (WA09/ H9). Requires immunosuppression	FDA clearance January, 2021	Phase I safety trial completed August 2023. Phase II proposed for 2024
Lund University/ StemPD/Novo Nordisk	Allogeneic	Embryonic stem cell line (RC17). Requires immunosuppression	Swedish Medical Products Agency November, 2022	Phase I initiated
Scripps Research/ Aspen Neuroscience	Autologous	Patient-specific iPSCs. Does not require immunosuppression	FDA clearance August, 2023	Phase I initiated

Branden J Clark, Mariah J Lelos, Jeanne F Loring, Advancing Parkinson's disease treatment: cell replacement therapy with neurons derived from pluripotent stem cells, Stem Cells, Volume 42, Issue 9, September 2024, Pages 781–790, <https://doi.org/10.1093/stmcls/sxae042>



Stem Cells & PD

Limitations & Barriers

- Finding a high enough dose that works **without** causing side effects
- Transplant “matching”
- Graft-induced dyskinesias

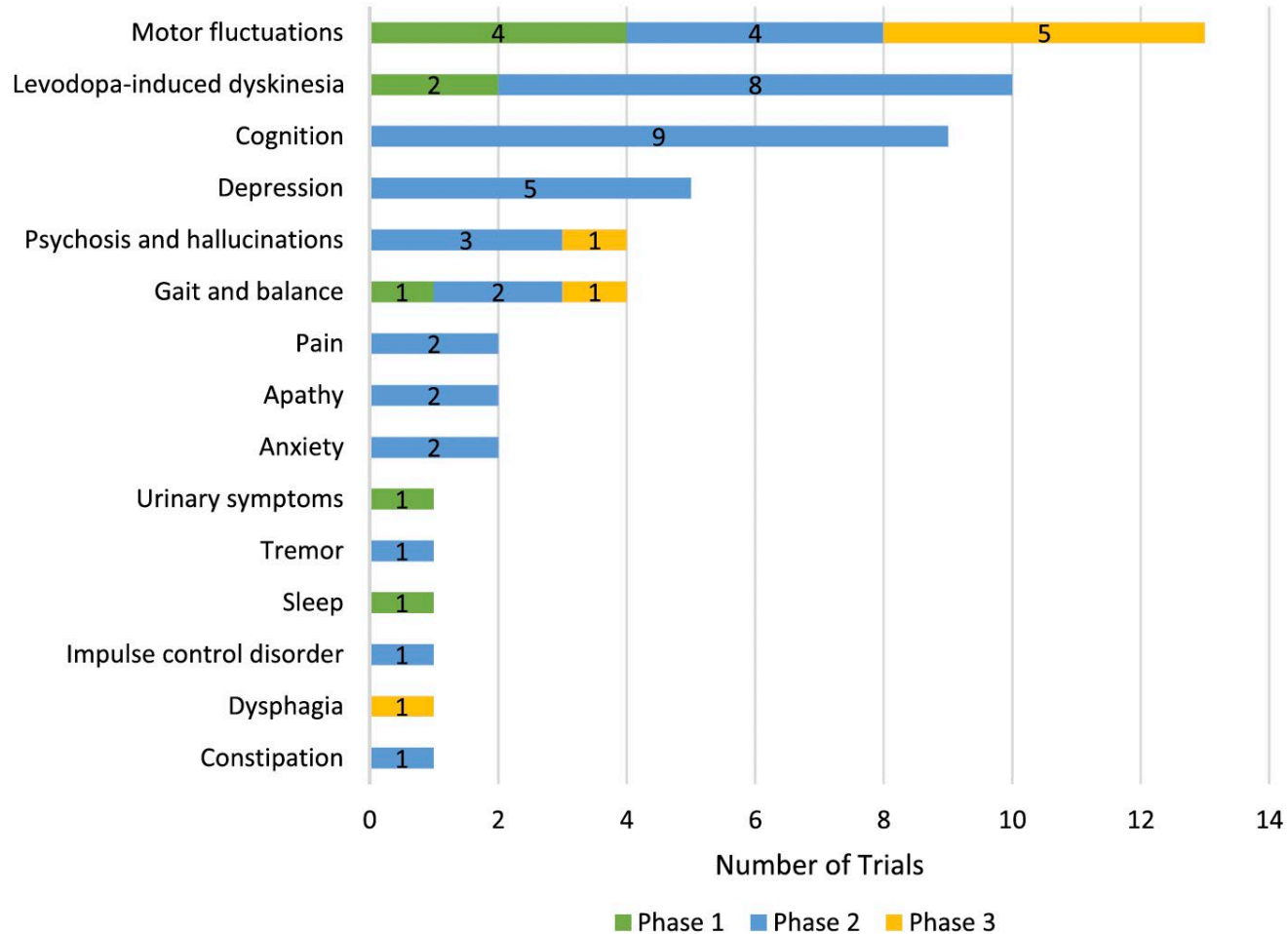
Next Steps:

*Many more studies needed
Likely will be years ahead*

***Stem Cell Therapy is NOT
an FDA approved therapy
for Parkinson’s Disease***



Improving Quality of Life: Symptom-Specific Therapies





Hot Topic: The Parkinson's Gloves



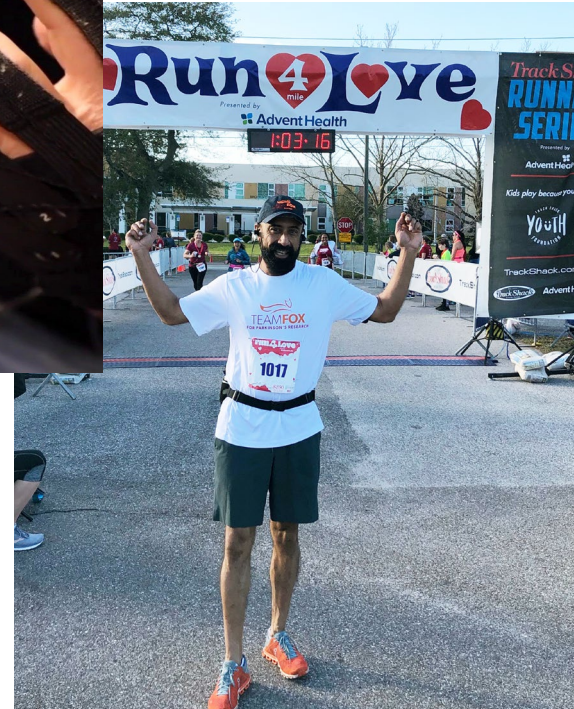


The Parkinson's Gloves

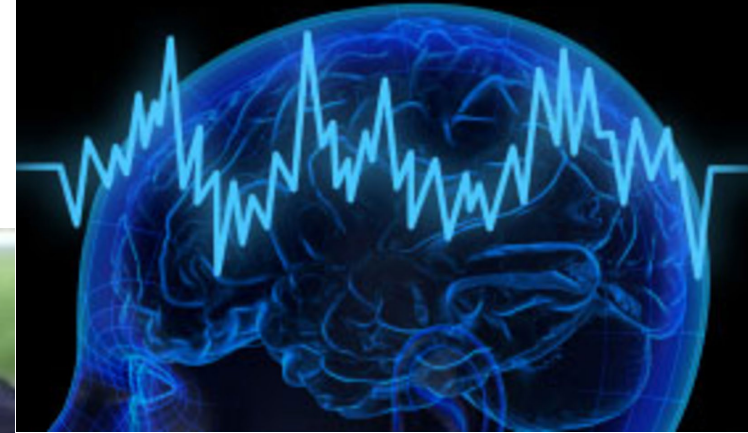
- Featured on Good Morning America
 - (December 2022)
- Stanford Medicine
 - Peter Tass Labs

Vibration in fingertips

- “**Resets**” electrical activity in the brain
- Tested for:
 - Swallowing
 - Tremor
 - Freezing of gait



The Parkinson's Gloves



***Next Steps:
Not yet recruiting.
Website survey to sign
up for future studies.***

***Similar glove study
recruiting in
Portland, Oregon***

Good vibrations: tactile cueing for freezing of gait in Parkinson's disease



E. C. Klaver^{1,2}  · J. P. P. van Vugt¹ · B. R. Bloem³ · R. J. A. van Wezel^{2,5} · J. Nonnekes^{4,6} · M. C. Tjepkema-Cloostermans^{1,7}

Why not Parkinson's socks?

- 2023 Dutch Study
- 31 patients
 - 60-65% felt that wearing vibrating socks helped
 - Most used with an audio cue (eg, counting or metronome)

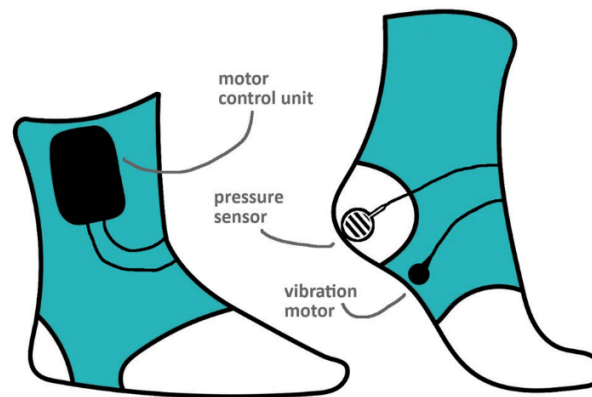


Fig.1 Schematic overview of the vibrating socks, including the motor control unit, pressure sensor (FlexiForce A401 pressure sensor) and vibration motor (Adafruit Mini Motor Disc 1201)

Journal of Neurology (2023) 270:3424–3432
<https://doi.org/10.1007/s00415-023-11663-9>



Hot Topic: Marijuana, CBD, and Parkinson's Disease



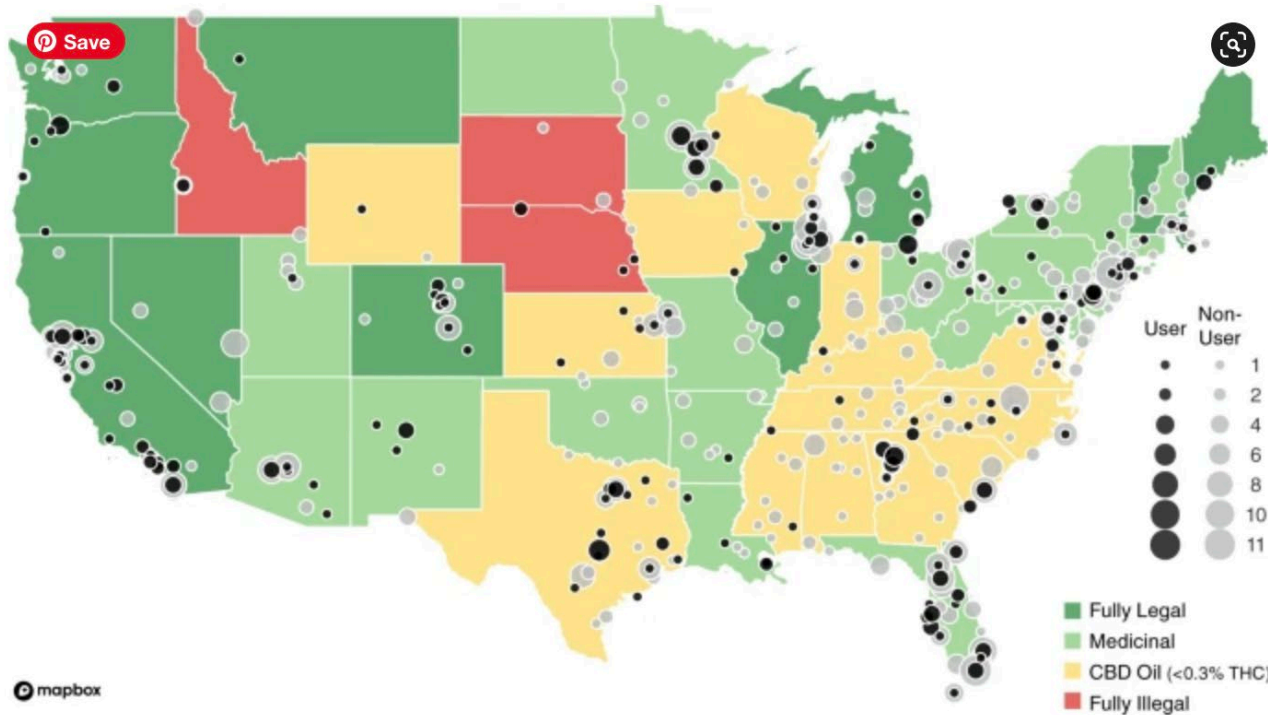
Expert Briefing Webinar

Marijuana & Parkinson's Disease:
What do we Really Know?





Fig. 1: A Geographic representation of survey participants.



Feeney, M.P., Bega, D., Kluger, B.M. et al. Weeding through the haze: a survey on cannabis use among people living with Parkinson's disease in the US. *npj Parkinsons Dis.* 7, 21 (2021). <https://doi.org/10.1038/s41531-021-00165-y>



Marijuana & PD

A few small studies (< 30 people)

- May help with:
 - Sleep
 - Tremor
 - Dyskinesias

Barriers:

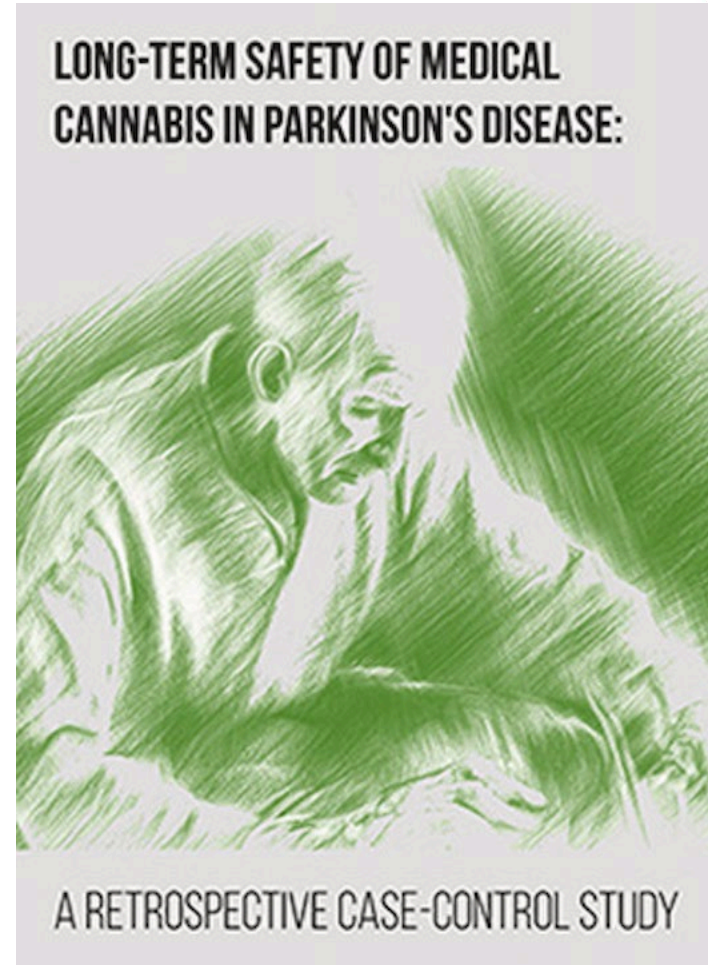
- Hard to use same form
- Hard to use same doses
- Hard to "measure" improvement

**Bottom Line:
Not Enough Data**



Marijuana & PD

- 2023 Parkinsonism & Related Disorders
 - 152 patients
 1. Treatment Group (Medical Cannabis)
 2. Control Group
 - Followed from 2008-2022



Marijuana & PD



RESULTS

MOTOR OUTCOMES

LEDD H&Y



There were no significant differences between the MC and the control groups for LEDD or H&Y stage progression ($p=0.90, 0.77$, respectively).

NON-MOTOR OUTCOMES



Based on self-reports by patients to their treating physicians, a Kaplan-Meier analysis revealed no evidence of relative worsening in psychotic, depressive, or cognitive symptoms over time in the MC-treated group ($p=0.16-0.50$).

- **No effect** on motor symptoms or disease progression (good or bad)
- Did not worsen psychiatric or cognitive symptoms

Marijuana & PD

Next Steps:

- *Colorado Studies*
- *Trying different forms and doses*



- *Looking at:*
 - *Tremor*
 - *Sleep*
 - *Dream reenactment*
 - *Hallucinations*
 - *Memory*
 - *Dyskinesias*
 - *Anxiety*



Earlier Detection: Emerging Biomarkers

What is a Biomarker?



“A measurable substance in an organism whose presence is indicative of some phenomenon such as disease, infection, or environmental exposure.”



How Can We Use Biomarkers?

Clinical diagnosis still only has 80-90% accurate

Biomarkers can be used to:

- **Detect** PD before it starts (“Prodromal”)
- **Confirm** or support your diagnosis
- **Guide** disease disease or prognosis
- **Differentiate** between clinically similar diseases
- **Identify** best candidates for clinical trials and specific therapies



News-Worthy Biomarkers



Breaking News:
Parkinson's Disease
Biomarker Found

Omaha
World-Herald

**CHI, Creighton researchers seek marker
for Parkinson's blood test**



Spinal Fluid Testing

Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α -synuclein seed amplification: a cross-sectional study

Andrew Siderow, Luis Concha-Marambio*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Urenia, Hieu Nguyen, Roy N Alcalay, Lana M Chahine, Tatiana Foroud, Douglas Galasko, Karl Kiebertz, Kalpana Merchant, Brit Mollenhauer, Kathleen L Poston, John Seibyl, Tanya Simuni, Caroline M Tanner, Daniel Weintraub, Aleksandar Videnovic, Seung Ho Choi, Ryan Kurth, Chelsea Caspell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Sherer, Kenneth Marek, Claudio Soto, on behalf of the Parkinson's Progression Markers Initiative†*



Lancet (2022)

- Test detects **alpha synuclein in the spinal fluid**
- Requires a **spinal tap** (lumbar puncture)



Spinal Fluid Testing

87.7% of those with PD had a positive test
("Rule In PD")

96.3% of Healthy Controls had a negative test
("Rule Out PD")

Even better for PD patients with change in sense of smell:

Picked up 98.6% of cases

Downside:

Requires an invasive procedure

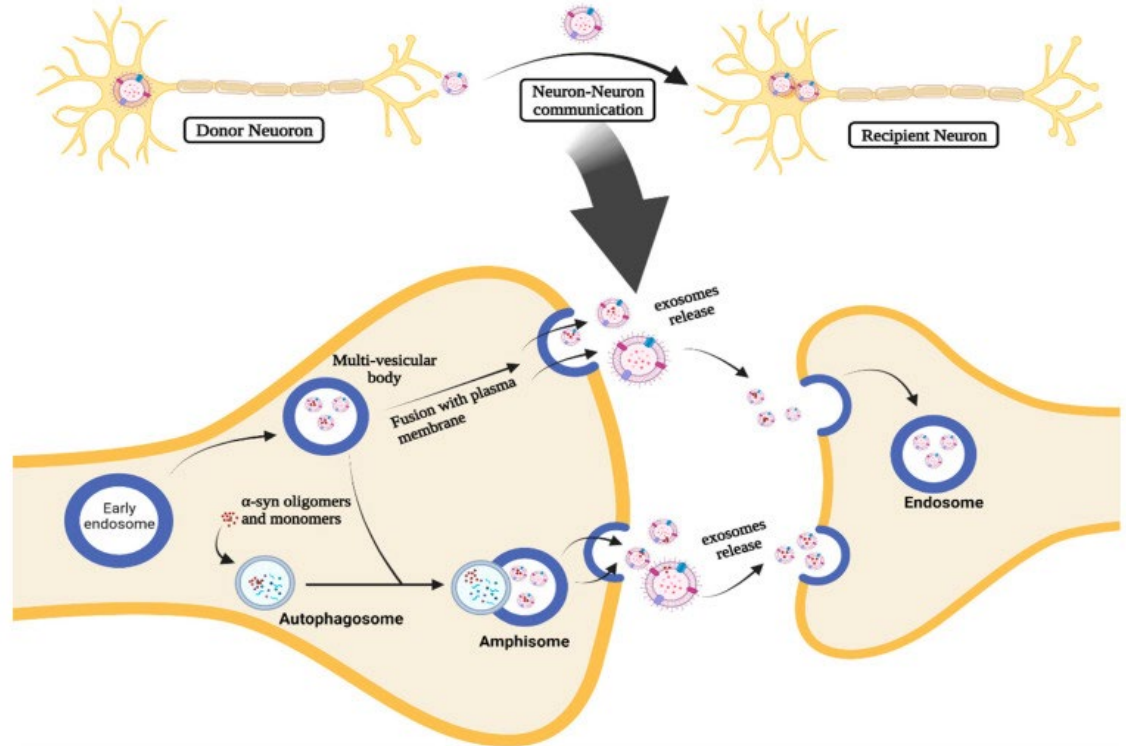


CHI, Creighton researchers seek marker for Parkinson's blood test

Julie Anderson May 30, 2023 Updated May 31, 2023 0



Looking for a “messenger” in the blood that passes on bad alpha synuclein proteins



Plasma proteomics identify biomarkers predicting Parkinson's disease up to 7 years before symptom onset

Compared blood tests from three groups:


1. Parkinson's
2. Healthy Controls
3. REM Behavior Disorder (RBD)

Considered a “precursor” for PD

Received: 6 April 2023

Accepted: 20 May 2024

Published online: 18 June 2024

 Check for updates

Jenny Hällqvist^{1,2,13} ✉, Michael Bartl^{3,4,13} ✉, Mohammed Dakna³, Sebastian Schade⁵, Paolo Garagnani⁶, Maria-Giulia Bacalini⁷, Chiara Pirazzini⁶, Kailash Bhatia⁸, Sebastian Schreglmann⁸, Mary Xylaki³, Sandrina Weber³, Marielle Ernst⁹, Maria-Lucia Muntean⁵, Friederike Sixel-Döring^{5,10}, Claudio Franceschi⁶, Ivan Doykov¹, Justyna Śpiwak¹, Héloïse Vinette^{1,11}, Claudia Trenkwalder^{5,12}, Wendy E. Heywood¹, Kevin Mills^{2,14} & Brit Mollenhauer^{3,5,14}

Computer model could predict who had PD

Blood tests looked similar in most RBD patients

Does this mean we can predict Parkinson's before symptoms start?



Hot Topic: Artificial Intelligence (AI)





AI and PD

Potential Roles:

- Predict early signs and symptoms
- Assess disease progression and/or treatment response
- Close geographical barriers (allowing remote exams)

[J Parkinsons Dis.](#) 2021; 11(Suppl 1): S117–S122.

PMCID: PMC8385515

Published online 2021 Jul 16. Prepublished online 2021 Jun 28. doi: [10.3233/JPD-212545](https://doi.org/10.3233/JPD-212545)

PMID: [34219671](https://pubmed.ncbi.nlm.nih.gov/34219671/)

Will Artificial Intelligence Replace the Movement Disorders Specialist for Diagnosing and Managing Parkinson's Disease?

[Matt Landers](#),^{a,*} [Suchi Saria](#),^{b,c,d} and [Alberto J. Espay](#)^{e,*}



AI to Measure Disease Progression

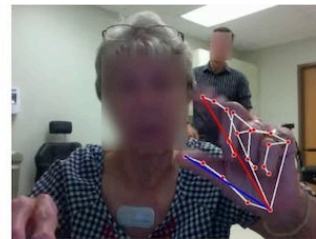
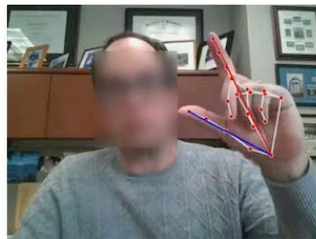
250 patients (PD & controls)

Performed **finger tapping** in front of a webcam

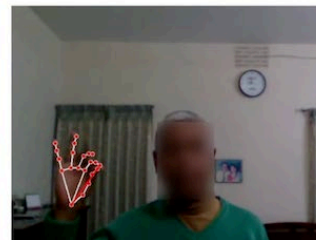
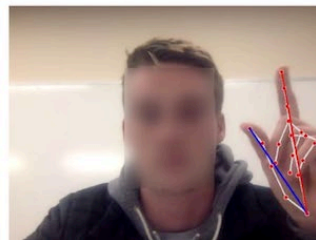
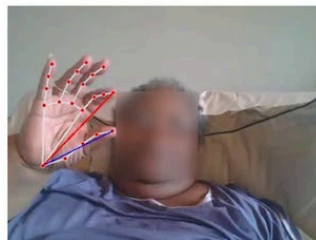
Compared:

- Expert neurologists
- Computer generated score

Individuals with PD



Healthy Control

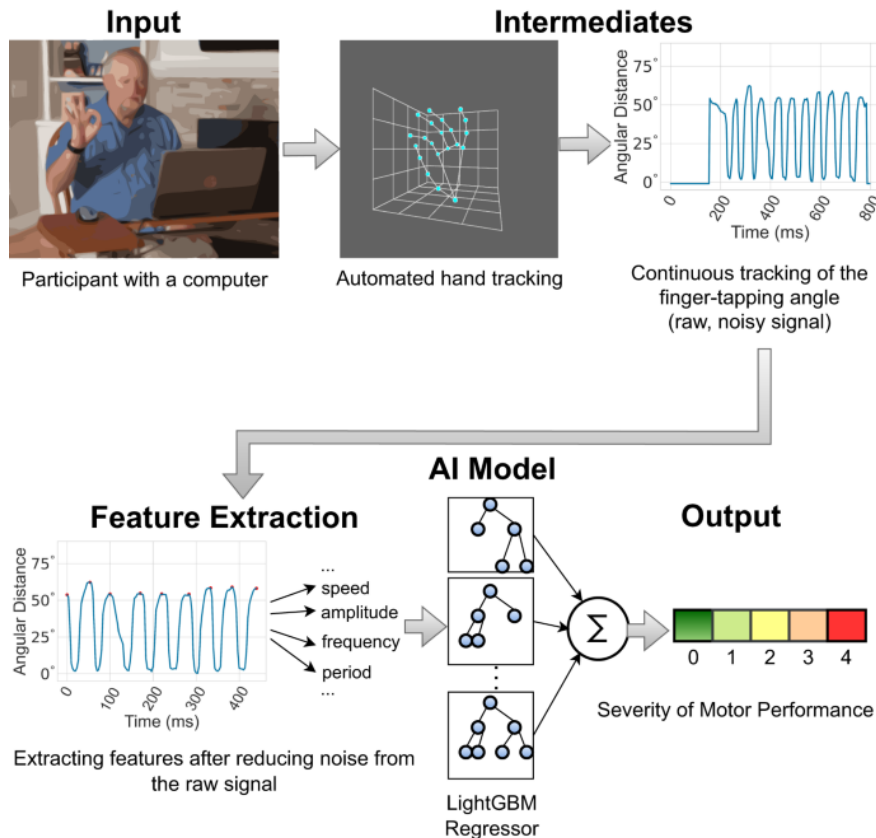




AI to Measure Disease Progression

**Movement Disorder
Neurologists were still
the most accurate !!**

*AI outperformed non-
Movement Disorder
providers*





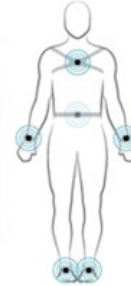
Other Uses of AI

Smartwatch & other wearable devices

- Track symptoms
- Cognitive exercises
- Remote motor exams

In-Clinic Assessments

Perform MDS-UPDRS Part III

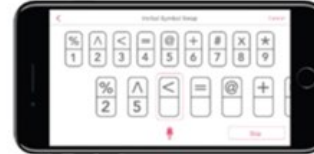


Motor and Cognitive Tasks



At-Home Assessments

Symptom Tracker, Cognitive and Psychomotor Tasks



Instrumented Motor Exam





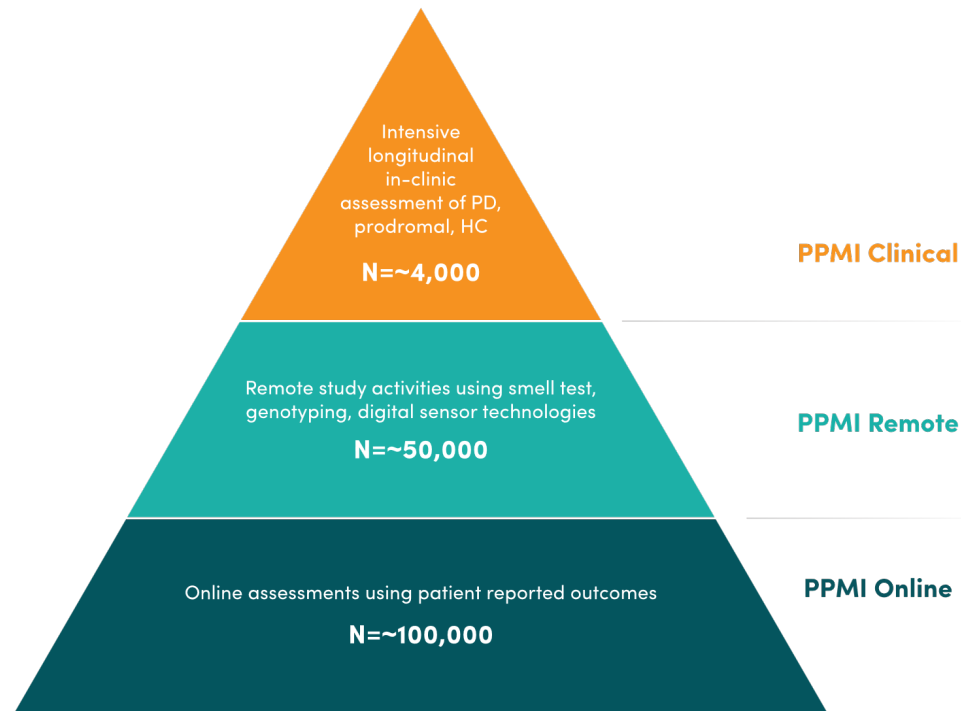
Get Involved

PPMI

- Michael J. Fox Foundation
- No PD diagnosis needed
- Fill out info online
 - Local: KC, Chicago, Denver
- Data accessible upon request



Parkinson's
Progression
Markers
Initiative





PD GENERation

- Michael J. Fox Foundation
- Need PD diagnosis
- In-person or remote options

1. Screening visit (15-30 min)
2. PD GENERation appointment (2 hours)
 1. Clinical assessments and cheek swab
3. Genetic counselor consultation (15-30 min)
 1. Receive and review test results



PD GENERation:

Mapping the Future of
Parkinson's Disease

Help us change the course of Parkinson's



“How Do I Get Involved?”



Visit **clinicaltrials.gov**



Call or email the **UNMC Research Advocate Office**

unmcrsa@unmc.edu

402-559-6941



Reference the **UNMC Clinical Trial Database:**

https://net.unmc.edu/ctsearch/index_unmc.php



Useful Websites

- www.pdtrialtracker.info
- www.clinicaltrials.gov
- www.apdaparkinson.org
- www.michaeljfox.org
- World Health Organization (WHO) Registry



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