

# Research Updates in Parkinson's Disease

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**“When will we find a cure?”**





# Foundations of Current Research

## **Disease-Modifying** Treatments (DMTs)

- Targeting the Pathology of Parkinson's
- Accumulation of alpha-synuclein protein in the brain

## Targeting **Genetic** Types of Parkinson's

## Finding Ways to **Detect** Parkinson's Even Before it Starts

## Treating Symptoms to **Improve Long-Term Outcomes**



# Today's Topics

1. Developing Therapeutics
2. Genetic Discoveries
3. Advancing Biomarkers
4. Databases
5. UNMC Studies
6. How to Get Involved





# News-Worthy Breakthroughs

**Breaking News:**  
Parkinson's Disease  
Biomarker Found

► COURTESY OF APPLE



**POTENTIAL BREAKTHROUGH IN PARKINSON'S TREATMENT**

AMERICA'S NEWSROOM

**BREAKTHROUGH PARKINSON'S "VIBRATION" THERAPY**

TODAY

NEW THIS MORNING

**EDGING CLOSER TO A CURE**

Discovery opens the door to further insights into the disease

WATCH MORE VIDEOS | [sunrise.com.au](http://sunrise.com.au)



# Other Areas (Not Covered Today)

- Surgical and advanced therapy updates
    - Deep Brain Stimulation (DBS)
    - Focused Ultrasound
    - Levodopa Infusions (Intestinal & Subcutaneous Pumps)
  - Symptom-specific treatments
    - Cognitive Decline
    - Freezing of Gait
    - Sleep
  - Nutrition and the Gut Biome
  - Quality improvement & outcomes-based projects
    - Hospitalization metrics
    - Fall prevention
  - Therapy comparisons
    - Exercise
- ...and more!**



# Developing Therapeutics



# Types of Therapeutics

## Disease Modifying Therapies

- **Slow** or **halt** the progression of neuron dysfunction / neuron death (i.e. therapies that prevent further neurons from being impacted by the disease)

## Symptomatic Therapies

- **Improve** / **restore function** for the patient (i.e. therapies that improve motor function, cognitive function, etc)





Journal of Parkinson's Disease 13 (2023) 427–439  
DOI 10.3233/JPD-239901  
IOS Press

427

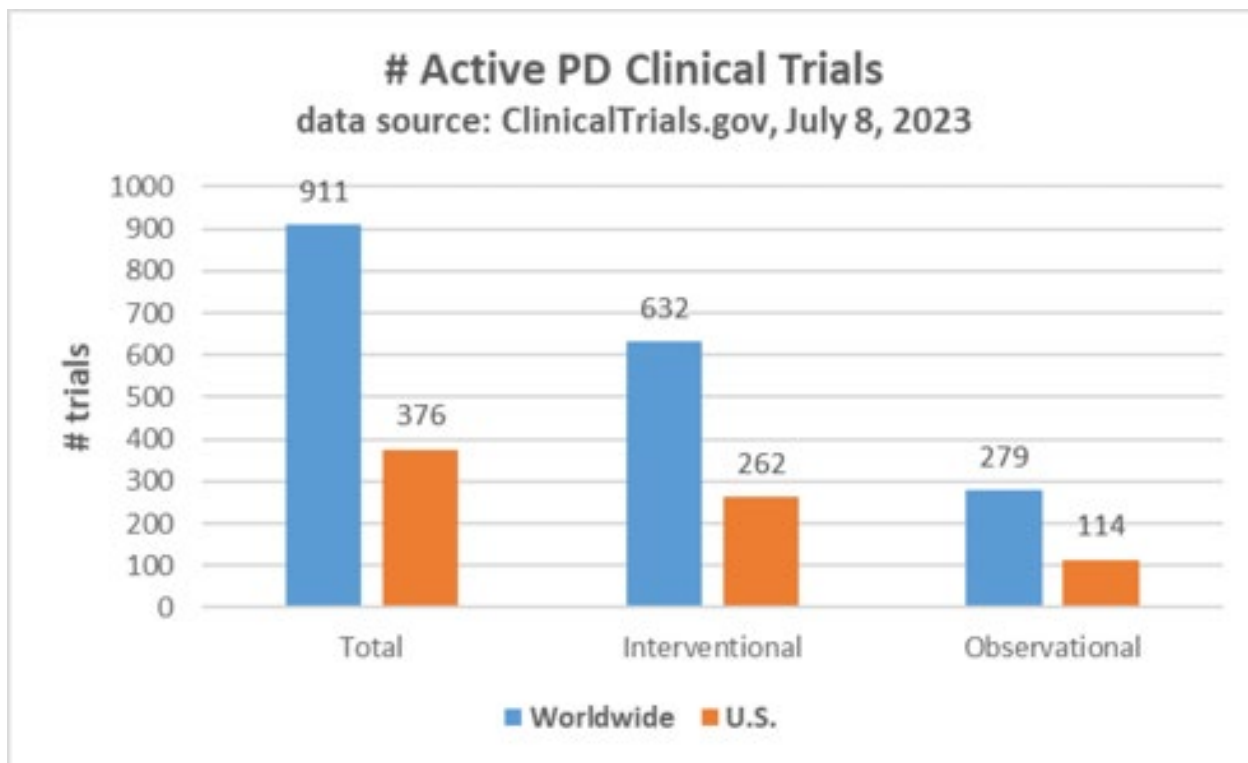
## Clinical Trial Highlights

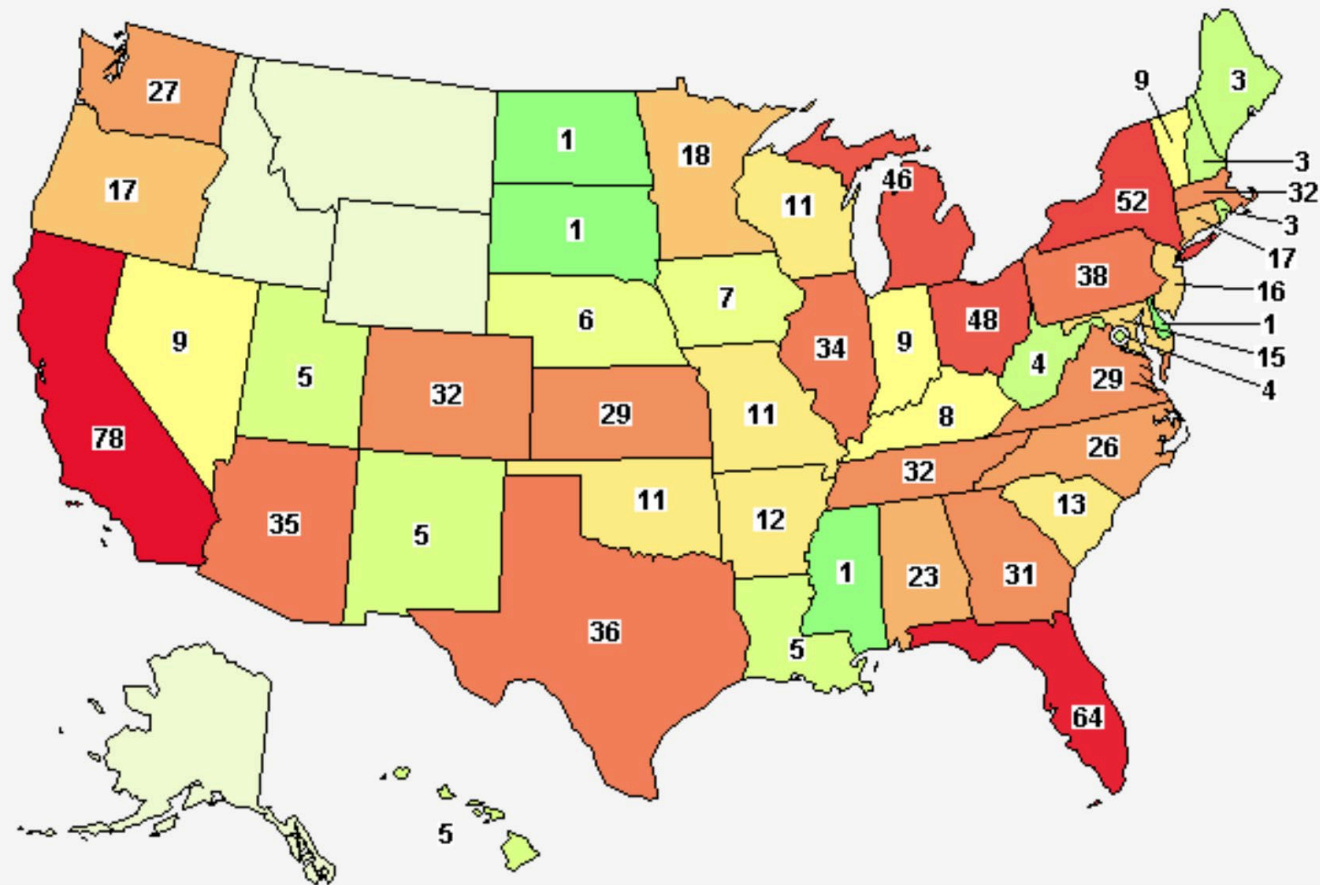
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# Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2023 Update



# PDTrialTracker.info





Colors indicate the number of studies with locations in that region.

Least  Most

Labels give the exact number of studies.

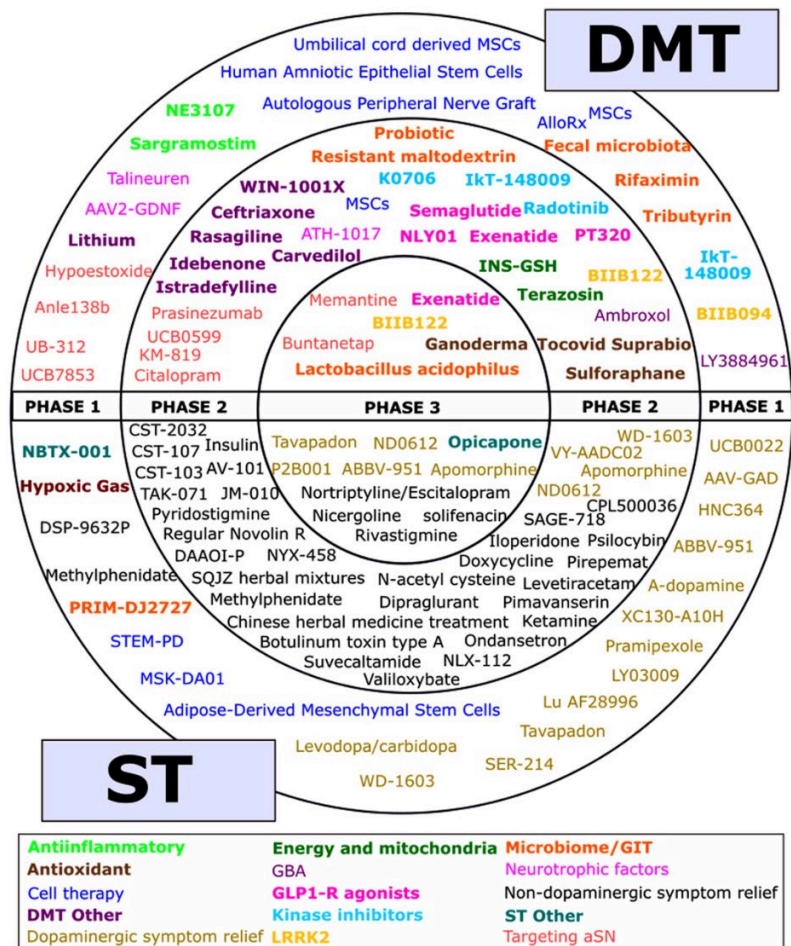
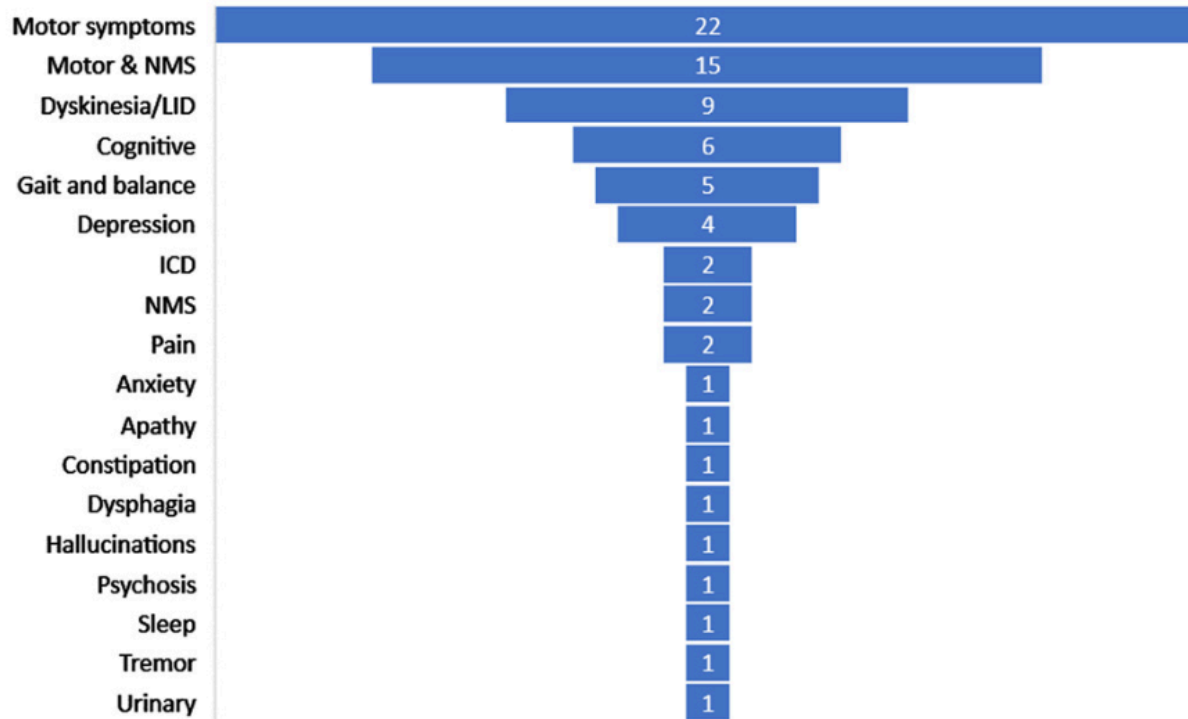


Fig. 2. A schematic of all of the agents in active clinical trials for PD, registered on ClinicalTrials.gov as of the 31<sup>st</sup> January 2023.



**# PD symptomatic therapy drug trials by symptom**  
n=76 trials active as of January 31, 2023, ClinicalTrials.gov

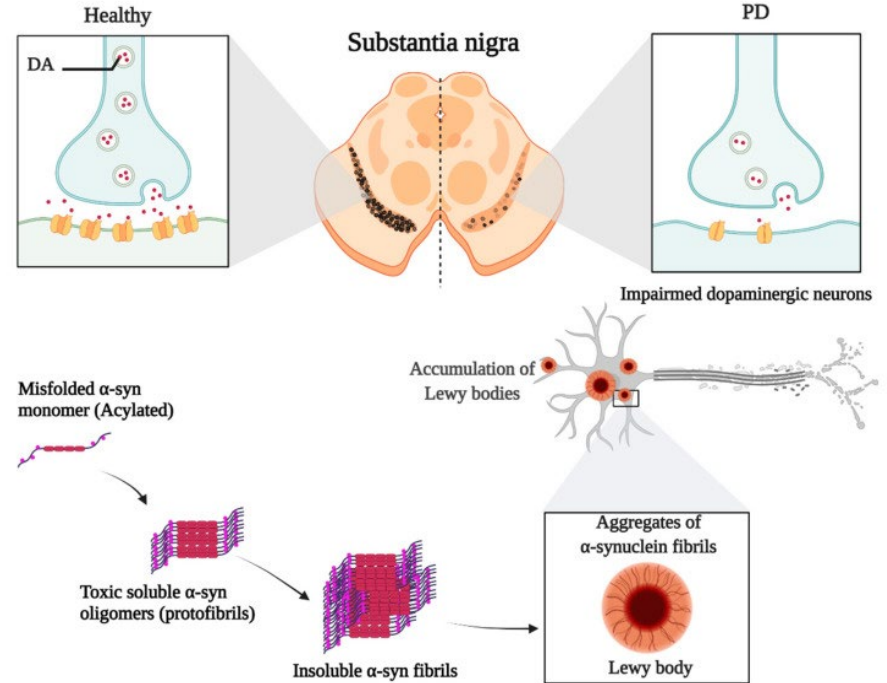


Motor symptoms  
Dyskinesias  
Cognitive  
Gait & balance  
Depression  
Apathy  
Pain  
Constipation  
Bladder

Fig. 4. Symptomatic focus of active PD drug trials.

# Mechanisms of DMTs

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

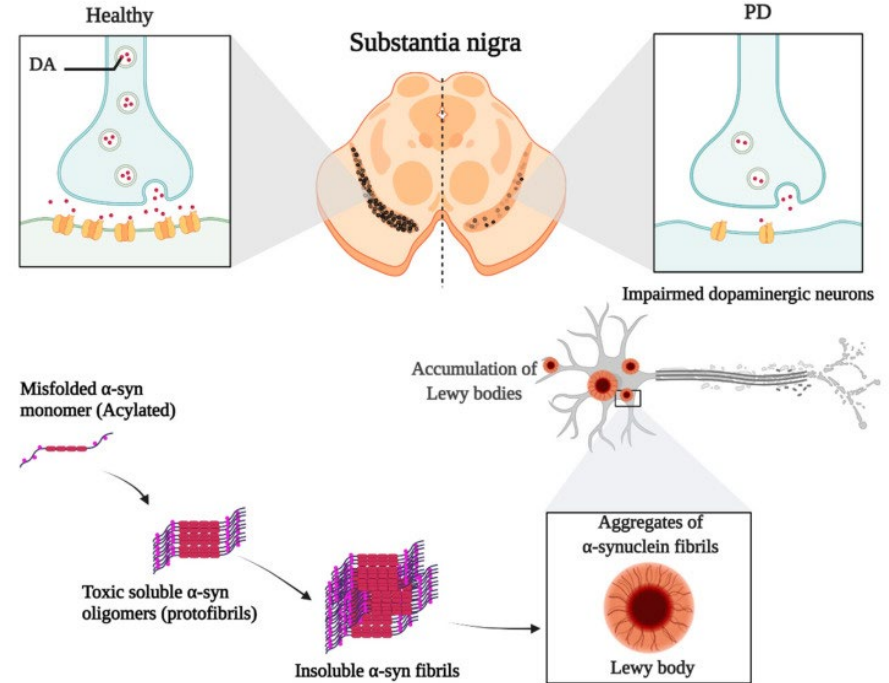


# Quick Review: Pathological Processes in PD



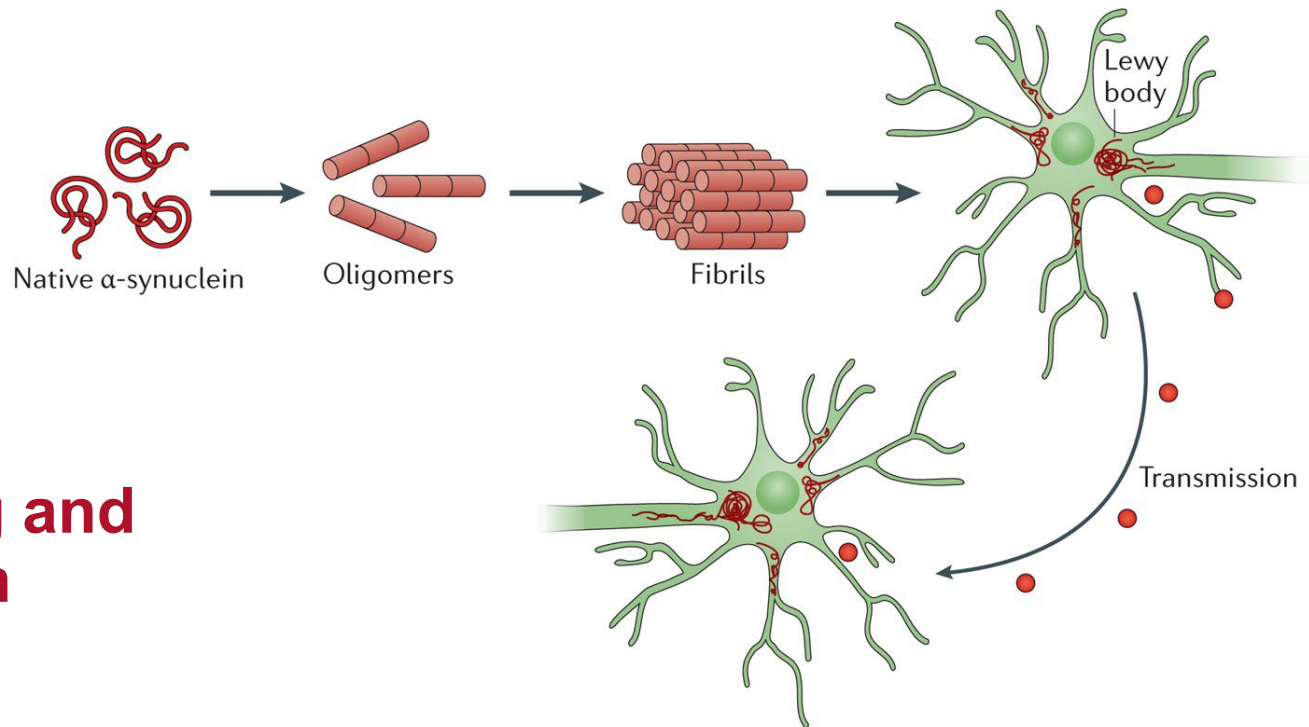
## Hypothesis of **alpha-synuclein protein**

Misfolds while being made  
→ Builds up in the brain and becomes **toxic**  
→ Leading to **dopamine cell death** and Parkinson's Disease





# Alpha Synuclein Therapies



**Goal:**  
**Stop misfolding and aggregation**





# Alpha Synuclein Therapies

- Give or create **antibodies against**  $\alpha$ -synuclein
  - Through IV
  - As a vaccine
- Block  $\alpha$ -synuclein
- Break misfolded  $\alpha$ -synuclein

**Studies ongoing**

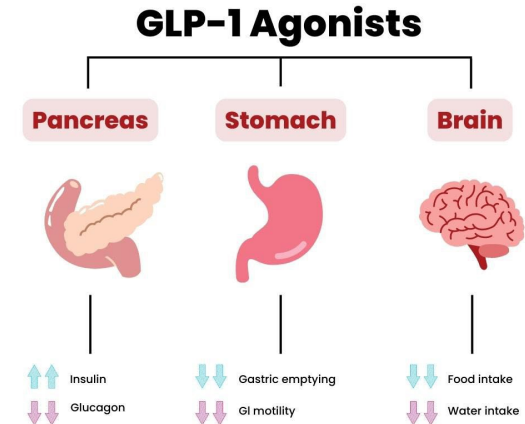
**Seem well-tolerated so far**  
*Caveat: Not every PD has an alpha-synuclein problem*



# Diabetes Medications: GLP-1 Agonists

- Study suggested 30% risk of PD in pts with type 2 diabetes
- GLP-1 agonists = used to trigger insulin release
  - Used for diabetes and weight loss
  - Receptors also present in the brain

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

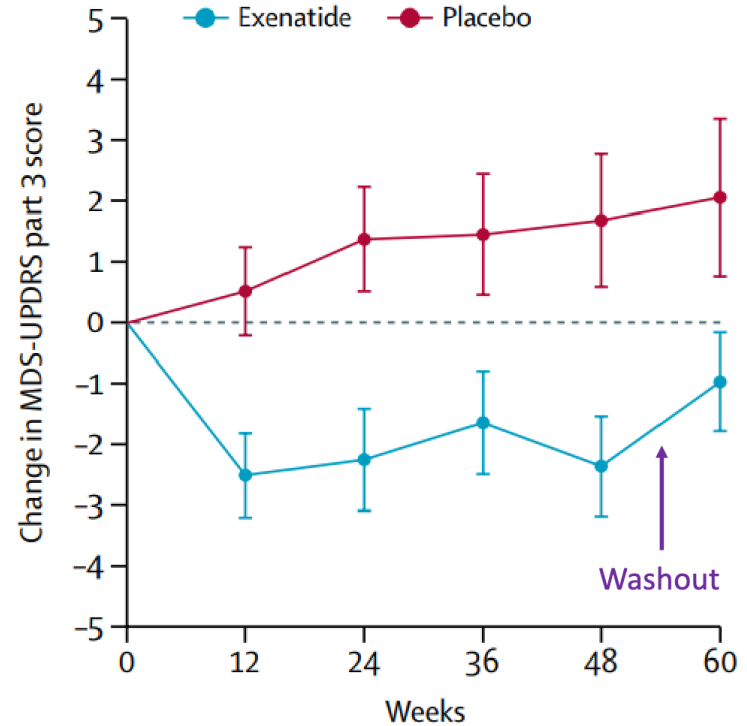


# Diabetes Medications: GLP-1 Agonists



## Exenatide

- 2017 Phase 2 Trial
- Hopeful results for slowing PD down
- More studies ongoing in Norway and South Korea



# What about those Parkinson's Gloves ???



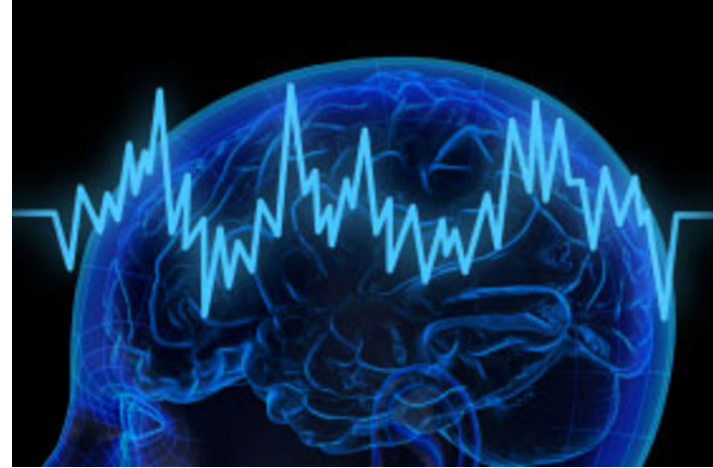
Featured on Good  
Morning America  
(December 2022)

Stanford Medicine  
Peter Tass Labs



# The Parkinson's Gloves

- 2021 Study (Tass)
  - 6 participants helped tremors, stiffness
- Vibration in fingertips
  - “Resets” abhorrent electrical activity in the brain
  - Similar tools tested for swallowing and freezing of gait
- FDA approval may not be for a few years



## Status:

NOT currently recruiting.  
Website survey to sign up  
for future studies.

Similar glove study  
recruiting in  
Eugene, Oregon



# 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

JAMA (2020)

- 18 patients
- Safe and well-tolerated

ASPro-PD

- 2023 Phase III Clinical Trial Enrolling in the UK
- Patients with and without the GBA genetic mutation



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

# Fibroblast Growth Factor 1 (FGF1)



## Hypothesis:

Disrupting small blood vessels in the brain causes damage to dopamine-producing cells that are dying off in Parkinson's

FGF-1 aims to **stimulate new blood vessel growth** to slow down PD or even reverse it

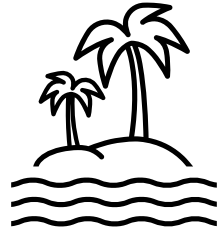




# Fibroblast Growth Factor 1 (FGF1)



- 2022 study in Bahamas
- Gave FGF-1 through nasal route



December 2022 Update:  
Drug was safe and well-tolerated

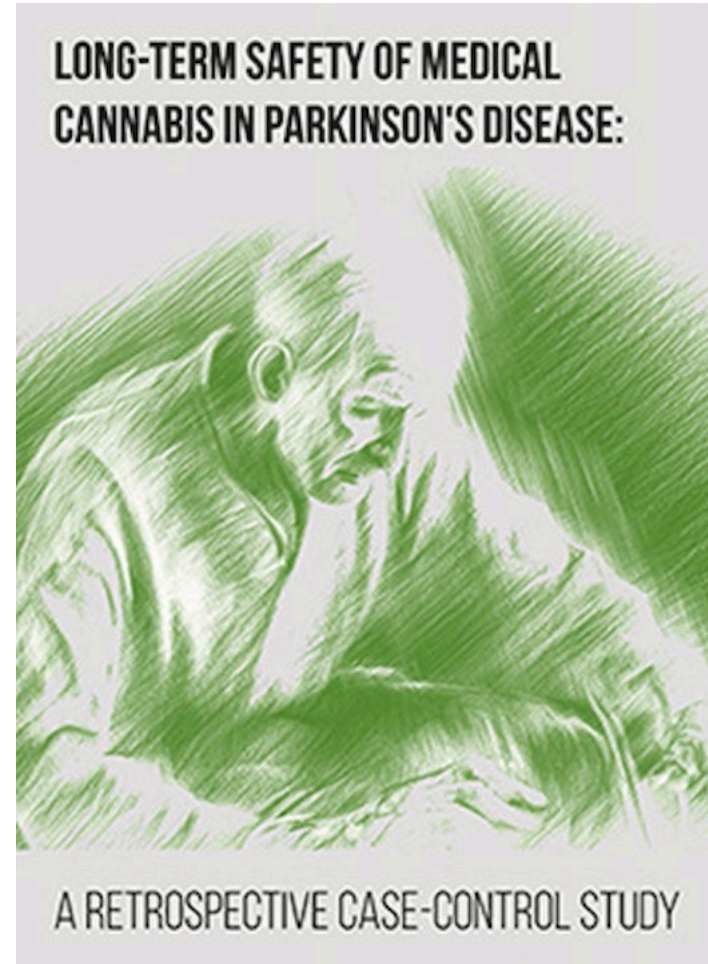


ZHITTYA GENESIS MEDICINE INC.



# Marijuana

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



# Marijuana



## 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

# Stem Cells for PD

Unfortunately, symptomatic only

- *Not* being used as a cure
- Replaces dopamine, does not prevent spread of disease

Logic:

- Dopamine cells are dying, let's replace them

Trials done in 1980s and 1990s with mixed effects

- Some benefited, some had no effect, and some worsened due to uncontrollable dyskinesias

Trying again with argument that we have better quality stem cells and surgical techniques

# Sargramostim (Leukine)



Olson et al. *Translational Neurodegeneration* (2023) 12:26  
<https://doi.org/10.1186/s40035-023-00361-1>

Translational  
Neurodegeneration

RESEARCH

Open Access



An open-label multiyear study of sargramostim-treated Parkinson's disease patients examining drug safety, tolerability, and immune biomarkers from limited case numbers

Katherine E. Olson<sup>1†</sup>, Mai M. Abdelmoaty<sup>1†</sup>, Krista L. Namminga<sup>1</sup>, Yaman Lu<sup>1</sup>, Helen Obaro<sup>2</sup>, Pamela Santamaria<sup>3</sup>, R. Lee Mosley<sup>1</sup> and Howard E. Gendelman<sup>1\*</sup>

Olson, K.E., Abdelmoaty, M.M., Namminga, K.L. et al. An open-label multiyear study of sargramostim-treated Parkinson's disease patients examining drug safety, tolerability, and immune biomarkers from limited case numbers. *Transl Neurodegener* 12, 26 (2023). <https://doi.org/10.1186/s40035-023-00361-1>

## UNMC Study

- Anti-inflammatory medication
- Given as skin injection
- 5 patients over 33 months
- Motor scores remained stable

Could this slow down PD progression?

## Future Directions:

Need a larger number with control group



# Genetic Discoveries



# Genetics & PD

- **Age** is still our greatest known PD risk factor
- We've identified many **environmental risks (or protectors)**
  - Head injuries
  - Smoking
  - Coffee
  - Medications

- **Genetic** links to PD are rapidly expanding

**10-15% of PD pts have a genetic variant**

- Genetic variants may contribute to 25% PD risk

**(+) Family History = 3-4x risk of developing PD**



# Why do genes in PD matter?

*→ It's all treated the same anyway, right??*

Knowing genetic variants in PD can help us:

1. Validate theories for what causes PD
2. Customize predictions for disease progression
3. Guide clinical trial design
4. Individualize treatment for specific patients





# Two Main Genetic Mutations

## Leucine-rich repeat kinase 2 (LRRK2):

- Regulates alpha-synuclein protein
- Role in removing waste from the cell

## Glucocerebrosidase (GBA):

Works in the cell to break down waste

### Example: **Ambroxol**

- Approved in Europe as a cold medicine
- Improves function of GBA in brain cells (neurons)



# Advancing 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**

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

*Andrew Siderowf\*, 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 Kieburtz, 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†*

**Breaking News:**  
**Parkinson's Disease**  
**Biomarker Found**

## Lancet (May 2023)

- 1123 subjects from PD Progression Markers Initiative database (PPMI)
  - Symptomatic, Pre-PD, Genetic Carriers, Healthy Controls
  - Consented to a **spinal tap**



# Lancet Article Results



**Breaking News:**  
Parkinson's Disease  
Biomarker Found

**Goal** = Detect Alpha Synuclein in the Spinal Fluid (CSF)

**87.7% of those reporting PD symptoms had a positive test**  
("Rule In PD")

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

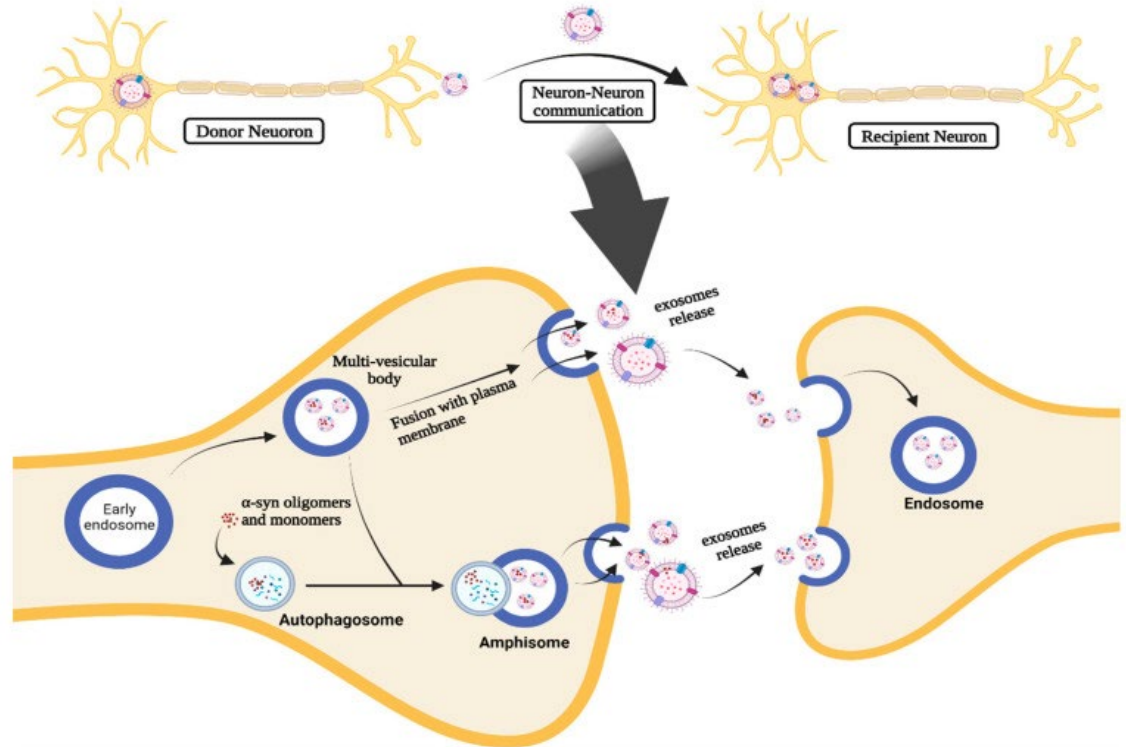
Even better for PD patients with change in sense of smell:  
**Picked up 98.6% of cases**

# 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





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



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

## Currently Enrolling:

- 10 Parkinson's patients already participating
- Seeking at least 25 Parkinson's patients and 50 controls





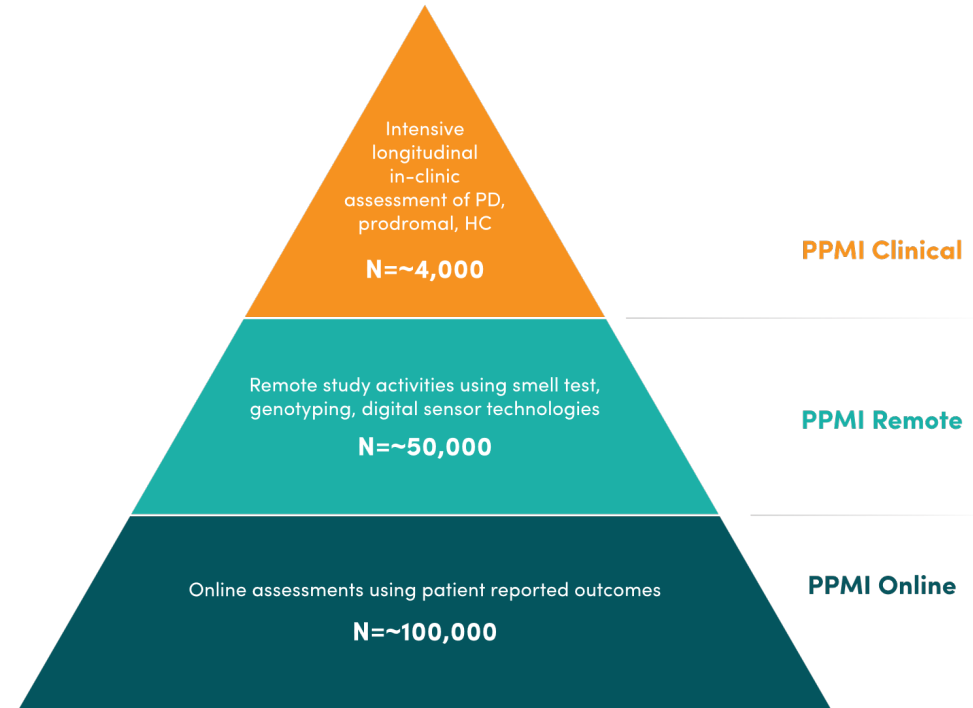
# Databases

# 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](mailto:unmcrsa@unmc.edu)

402-559-6941



Reference the **UNMC Clinical Trial Database:**

[https://net.unmc.edu/ctsearch/index\\_unmc.php](https://net.unmc.edu/ctsearch/index_unmc.php)



# Useful Websites

- [www.pdtrialtracker.info](http://www.pdtrialtracker.info)
- [www.clinicaltrials.gov](http://www.clinicaltrials.gov)
- [www.apdaparkinson.org](http://www.apdaparkinson.org)
- [www.michaeljfox.org](http://www.michaeljfox.org)
- World Health Organization (WHO) Registry



# References

Included in specific slides

Comprehensive list available upon request



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