

# Looking Forward: The Future of Treatment in Parkinson's Disease

Erin L. Smith, MD  
Assistant Professor  
Department of Neurological Sciences  
Movement Disorders Division

University of Nebraska  
Medical Center

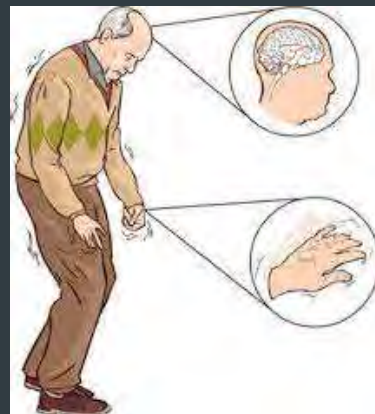


Nebraska  
Medicine

1

## Why is This Important?

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



2

**PD is also complex!**

- Motor Symptoms
- Non-motor Symptoms
- Complications of Therapy
- Disability & Social Impact

**THE PARKINSON'S ICEBERG**

WHAT PEOPLE SEE	
Tremor	Akinesia/bradykinesia
Rigidity	Postural disturbance
Lack of facial expression	

WHAT PEOPLE DON'T SEE	
Constipation	Sleep difficulties
Soft speech	Bladder dysfunction
Panic attacks	Depression
Loss of smell	Anxiety
Hypotension	Hallucinations
Impulse control disorder and delusional behavior	Sweating
	Dementia
	Erectile difficulties

TEMPLE HEALTH

3

**Most importantly:**

**We still don't have any disease-modifying therapies**

*i.e., there is no cure*

4

# Foundations of Current Research

## Disease-Modifying Treatments *Slowing Down the Disease*

- Targeting **Pathology**
- Targeting **Genetics**

## Detecting Parkinson's *Earlier Intervention*

- Pre-Parkinson's (**Prodromal**) Symptoms
- **Biomarkers** in the blood, spinal fluid (CSF), skin

## Improving Therapies *Better Quality of Life*

- New Medications
- Wearable Devices
- Surgical Options



5

# Disease-Modifying Research Advances **Slowing Down the Disease**



6

# What Does Disease-Modifying Mean?

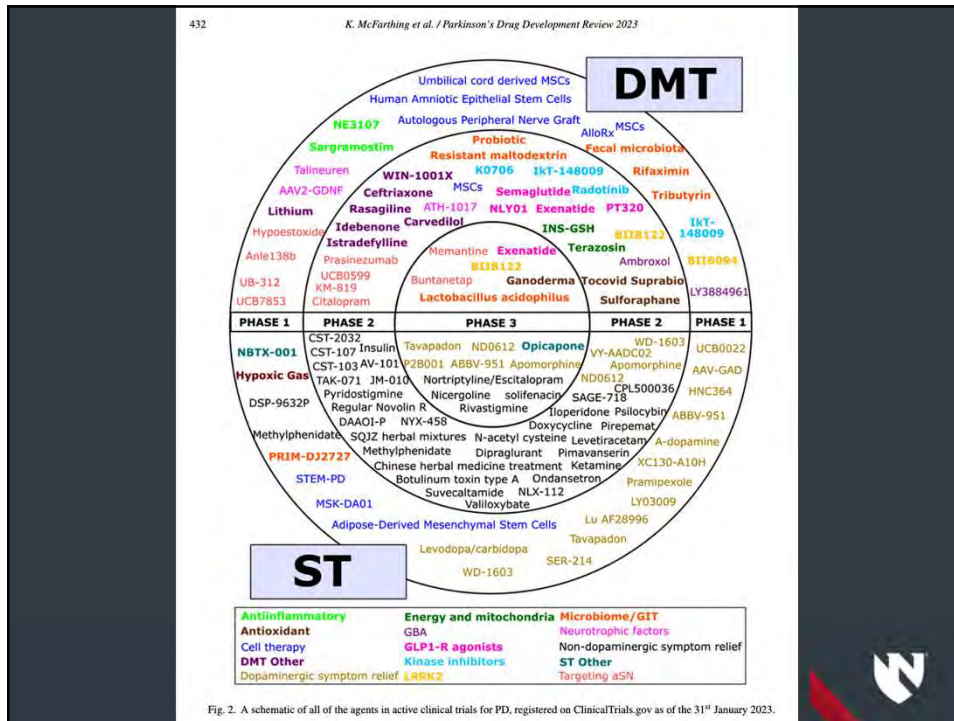
## Disease Modifying (DMT)

- Slows or stops the progression and neuronal cell death

## Symptomatic Therapy (ST)

- Improves or restores function for the patient

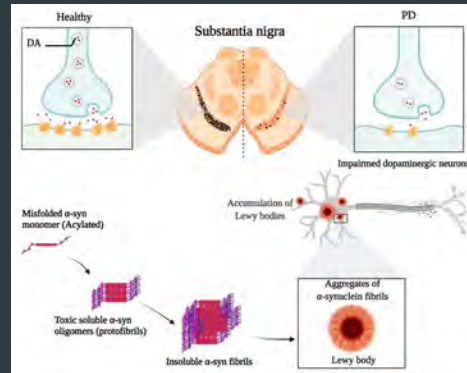
7



8

## Mechanisms of DMTs

- Alpha synuclein targets
- Antioxidants
- Anti-inflammatories
- Gene-specific or “gene-modifying” (more on that later)



9

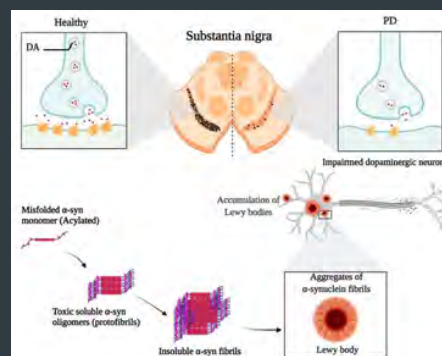
## Quick Review: Pathological Processes in PD

### Hypothesis of alpha-synuclein protein

Misfolds while being made

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

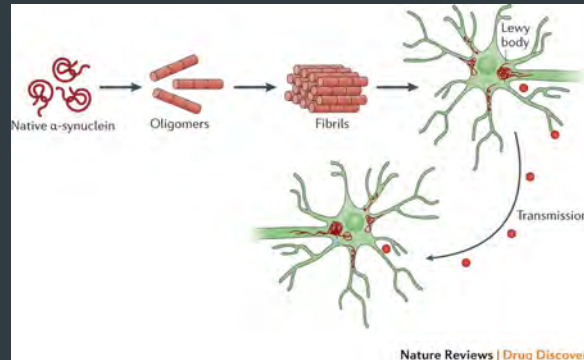
→ This causes **dopamine cell death** and Parkinson's Disease



*These misfolded protein bunches are called **Lewy Bodies***

10

## Alpha Synuclein Therapies



Goals:

1. Stop the misfolding before it starts
2. Clean out already misfolded proteins

Sheila M. Fleming, Ashley Davis, Emily Simons, Targeting alpha-synuclein via the immune system in Parkinson's disease. *Current vaccine therapies, Neuropharmacology, Volume 202, 2022, 108870,*

11

## Alpha Synuclein Therapies

- Give or create antibodies against  $\alpha$ -synuclein
  - Given through IV
  - Given as vaccine
- Give a medication that disrupts the protein misfolding or gets rid of it after

Studies ongoing  
Seem well-tolerated so far



Front. Mol. Neurosci., 05 December 2019  
Sec. Brain Disease Mechanisms  
Volume 12 - 2019 | <https://doi.org/10.3389/fnmol.2019.00299>

12

## 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 called 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

13

## Can a Cough Medicine Cure PD?

### Ambroxol

- JAMA (2020)
- 18 patients
  - Safe and well-tolerated
- ASPro-PD (2023)
- Enrolling in the UK
  - Patients with and without the GBA 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

14

## How About an Asthma Treatment?

### Montelukast (Singular)

Anti-inflammation

MONTPARK  
Phase 2

- Oral film
- Coming 2024
- Sweden



15

## 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"

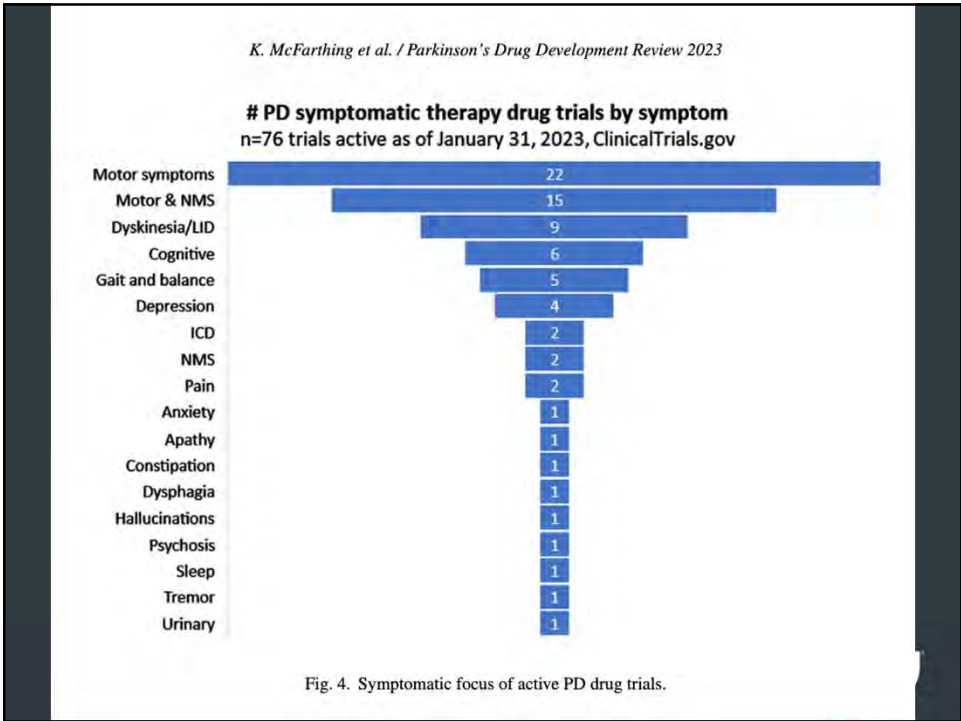


16



# Symptomatic Therapies Improving Quality of Life

17



18

## Symptom-Targeted Treatments

- Motor Symptoms
  - Tremor, stiffness, slowness
- Dyskinesias
- Cognitive Changes
- Gait & Balance
- Depression
- Others:
  - Pain, Impulse-Control Disorders, Apathy, Constipation, Hallucinations

Goals:  
Symptomatic Only  
NOT disease-modifying



19

## What about those gloves??

Featured on Good Morning America  
(December 2022)

Stanford Medicine  
Peter Tass Labs



20

## The Parkinson's Gloves

- 2021 Study (Tass)
  - 6 participants said it 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:  
NOW ENROLLING

Tass PA. Vibrotactile coordinated reset stimulation for the treatment of Parkinson's disease. *Neural Regen Res.* 2022 Jul;17(7):1495-1497. doi: 10.4103/1673-5374.329001. PMID: 34916431. PMCID: PMC8771098.

21

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

E. C. Klaver<sup>1,2</sup> · J. P. P. van Vugt<sup>1</sup> · B. R. Bloem<sup>3</sup> · R. J. A. van Wezel<sup>2,5</sup> · J. Nonnekes<sup>4,6</sup> · M. C. Tjepkema-Cloostermans<sup>1,7</sup>

### 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)

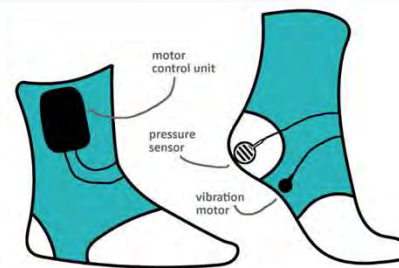


Fig. 1 Schematic overview of the vibrating socks, including the motor control unit, pressure sensor (FlexiForce A401 pressure sensor) and vibration motor (Adafruit Mini Motor Disc 1201)

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

22

nature medicine

Article <https://doi.org/10.1038/s41591-023-02584-1>

## A spinal cord neuroprosthesis for locomotor deficits due to Parkinson's disease

- Electrical Stimulation (EES) of lumbosacral spinal cord
- Tested in rhesus monkeys
  - Plan to expand to larger human group

**c**

Magnetic resonance imaging   Anatomical model   Computational model

Vertebrae   Spinal levels

Hotspots

Dorsal roots

L1 L2 L3 L4 L5 S1

23

nature medicine

Article <https://doi.org/10.1038/s41591-023-02584-1>

## A spinal cord neuroprosthesis for locomotor deficits due to Parkinson's disease

One human with PD (Called P1)

- Deep Brain Stimulator (DBS) resistant gait freezing
  - Improved with and without DBS on
- Benefit lasting after 2 years

**f**

Individual with Parkinson's disease (P1)

24

# Marijuana

- 2023 Parkinsonism & Related Disorders
  - 152 patients
    - Medical Cannabis
    - Control Group
  - Followed over a long period: 2008-2022

## LONG-TERM SAFETY OF MEDICAL CANNABIS IN PARKINSON'S DISEASE:



A RETROSPECTIVE CASE-CONTROL STUDY

Goldberg T, Redlich Y, Yogev D, Fay-Karmon T, Hassin-Baer S, Anis S. Long-term safety of medical cannabis in Parkinson's disease: A retrospective case-control study. *Parkinsonism Relat Disord.* 2023 Jul;112:105406. doi: 10.1016/j.parkreidis.2023.105406. Epub 2023 May 5. PMID: 37211456.



25

# 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

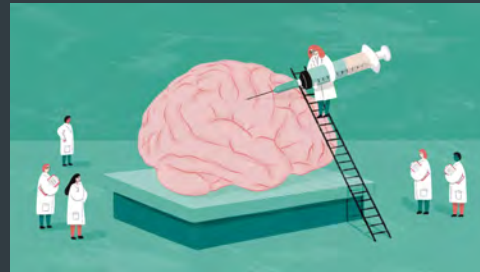


26

## Stem Cells & PD

July 2023 meta-analysis:

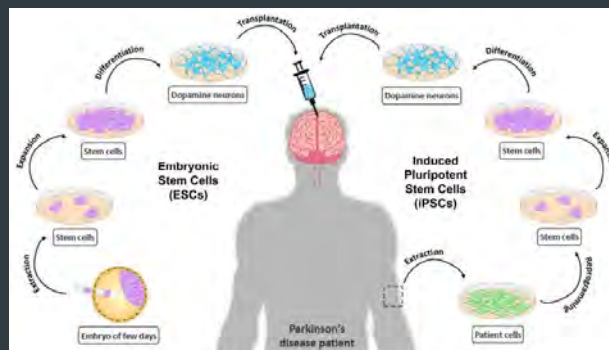
- Beneficial after 36 months
  - Improved ADLs in OFF state
- Allografts (not autografts) gave best benefit
- Transplantation in basal ganglia or other sites seemed successful



27

## Stem Cells & PD

- Adverse events related to surgery
- One confirmed and four possible cases of **graft-induced dyskinesia**



Wang, F., Sun, Z., Peng, D. et al. Cell-therapy for Parkinson's disease: a systematic review and meta-analysis. *J Transl Med* 21, 601 (2023). <https://doi.org/10.1186/s12967-023-04484-x>

28

## Focused Ultrasound

- MRI machine
- Ultrasound waves “burn” Parkinson’s centers
  - “Like a magnifying glass and a light”
- Treats tremor & dyskinesias
- Same targets as DBS
  - Subthalamic Nucleus
  - Globus Pallidus Interna



29

## Focused Ultrasound

- Unilateral procedure
  - (ie, treats only one side of the body)
- Reason: Side effects
  - Slurred speech
  - Numbness/tingling
- Bilateral procedures being studied
  - California, Canada



30

## Focused Ultrasound

- Performing States:
  - CHI (Nebraska)
  - Chicago
  - Missouri
  - Kansas
  - Colorado

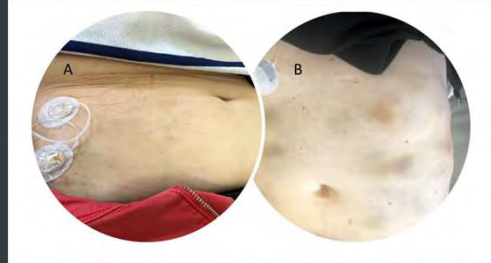


31

## Subcutaneous Pump (AbbVie)

- Shown to be safe and well-tolerated
  - Fewer complications than intestinal pump (DUOPA)
- FDA rejected application
  - Early 2023
  - Issues with pump design itself

abbvie



Mid 2024 Launch ??


32



# Specific Populations


Earlier Intervention & Precision Medicine

Biomarkers  
Genetics



33

# Biomarkers



34

## What is a Biomarker?

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



35

## How Can We Use Biomarkers?

*Clinical diagnosis still only 80-90% accurate*

Biomarkers can be used to:

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



36

## News-Worthy Biomarkers

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

**Omaha  
World-Herald**

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

Julie Anderson May 30, 2023 Updated May 31, 2023

37

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

Andrew Siderow\*, Luis Concha-Marambaio\*, David-Erick Lafontant, Carly M Farris, Yihua Ma, Paula A Ukena, 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 Videncovic, Seung Ho Choi, Ryan Kurth, Chelsea Cospell-Garcia, Christopher S Coffey, Mark Frasier, Luis M A Oliveira, Samantha J Hutten, Todd Shera, 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
  - Symptomatic, Pre-PD, Genetic Carriers, Healthy Controls
  - Consented to a **spinal tap**

**W**

38

## CSF Alpha Synuclein Assay Results

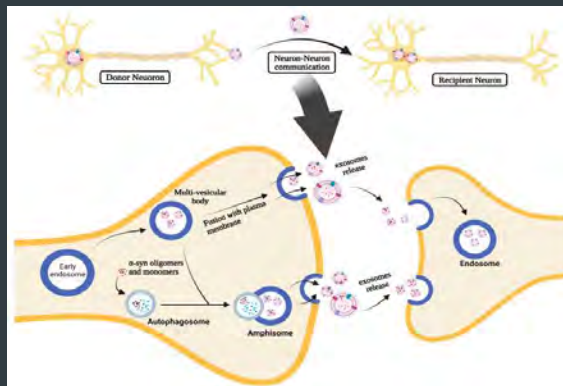
	Specificity	Sensitivity
Healthy Controls	96.3	--
PD Sx with Negative DAT	90.7	--
All Symptomatic PD		87.7
PD + Normal Smell		63
PD + Hyposmia		97.2
Sporadic (no gene)		93.3
LRRK2 PD		67.5
GBA PD		95.9

39

## 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



40

## Genetics & PD

- **Age** is still our greatest known PD risk factor
- **Genetic** links to PD are rapidly expanding
  - 10-15% of PD pts have a genetic variant
- We've identified many **environmental risks (or protectors)**
  - Head injuries
  - Smoking
  - Coffee
  - Medications
- Genetic variants may contribute to 25% PD risk
  - (+) FHx = 3-4x risk of developing PD

41

## 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

42

## 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 for respiratory illnesses, improves the function of GBA in neurons



43

## What about 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.

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

PMCID: PMC8385515

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](#),<sup>a,\*</sup> [Suchi Sarin](#),<sup>b,c,d</sup> and [Alberto J. Espay](#).<sup>e,\*</sup>

44

# AI to Measure Disease Progression

250 patients (PD & controls)

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

Compared:

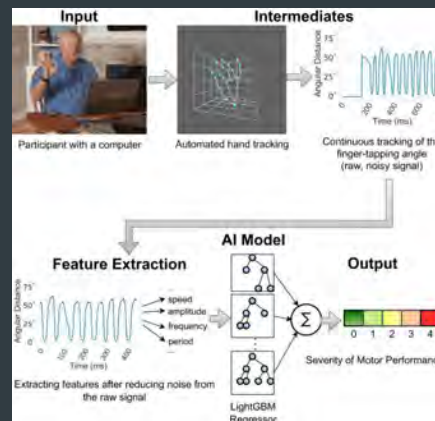
- Expert neurologists
- MDS-UPDRS certified “non-experts”
- Computer generated score



45

# AI to Measure Disease Progression

- Neurologists were still the most accurate
- AI outperformed MDS-UPDRS certified non-neurologists



Islam, M.S., Rahman, W., Abdelkader, A. et al. Using AI to measure Parkinson's disease severity at home. *npj Digit. Med.* 6, 156 (2023). <https://doi.org/10.1038/s41746-023-00905-9>

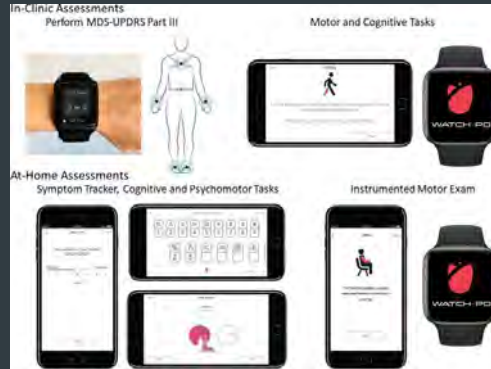


46

## Other Uses of AI

### Smartwatch & other wearable devices

- Track symptoms
- Cognitive exercises
- Remote motor exams



Adams, J.L., Kangaroo, T., Tracey, B. et al. Using a smartwatch and smartphone to assess early Parkinson's disease in the WATCH-PD study. *npg Parkinsons Dis.* 9, 64 (2023). <https://doi.org/10.1038/s41531-023-00497-x>

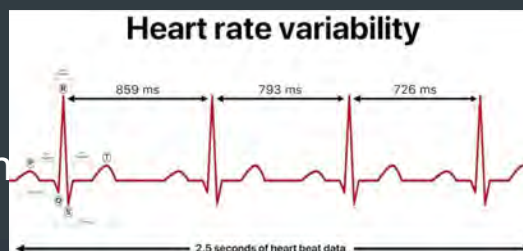
47

## Can an EKG Detect Prodromal PD?

### Heart Rate Variability (HRV)

- Reduced in PD and RBD
- Autonomic dysfunction
- Correlates with dopamine depletion

Low HRV associated with **2-3x increased PD risk**



Karabayir, I., Gunturkun, F., Butler, L. et al. Externally validated deep learning model to identify prodromal Parkinson's disease from electrocardiogram. *Sci Rep* 13, 12290 (2023). <https://doi.org/10.1038/s41598-023-38782-7>

48

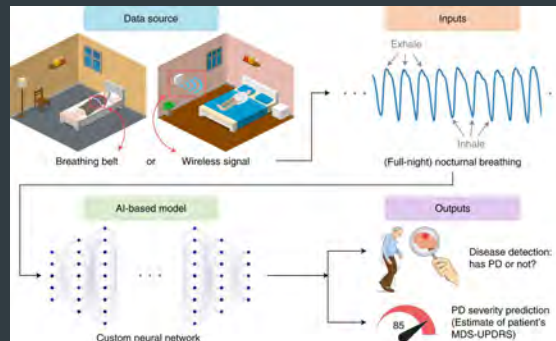


## “Nocturnal Breathing” can predict PD

Looked at over  
7,000 sleep studies

AI could predict:

- PD vs non-PD
- Disease severity
- Disease progression



Yang, Y., Yuan, Y., Zhang, G. et al. Artificial intelligence-enabled detection and assessment of Parkinson's disease using nocturnal breathing signals. *Nat Med* 28, 2207–2215 (2022).  
<https://doi.org/10.1038/s41591-022-01932-x>

49

## “How Do I Get Involved?”



Visit [clinicaltrials.gov](https://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)

50

## 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



51

## References & Cited Works

- Adams, J.L., Kangaroo, T., Tracey, B. *et al.* Using a smartwatch and smartphone to assess early Parkinson's disease in the WATCH-PD study. *npj Parkinsons Dis.* 9, 64 (2023). <https://doi.org/10.1038/s41531-023-00497-x>
- Aldred, J., Friero-Alvarez, E., Amalin, A.V. *et al.* Continuous Subcutaneous Foslevodopa/Foscarbidopa in Parkinson's Disease: Safety and Efficacy Results From a 12-Month, Single-Arm, Open-Label, Phase 3 Study. *Neural Ther* 12, 1937–1958 (2023). <https://doi.org/10.1007/s40120-023-00533-1>
- Front. Mol. Neurosci., 05 December 2019 Sec. Brain Disease Mechanisms Volume 12 - 2019 | <https://doi.org/10.3389/fnmol.2019.00299>
- Goldberg T, Redlich Y, Yogeve D, Fay-Karmon T, Hassin-Baer S, Anis S. Long-term safety of medical cannabis in Parkinson's disease: A retrospective case-control study. *Parkinsonism Relat Disord.* 2023 Jul;112:105406. doi: 10.1016/j.parkreidis.2023.105406. Epub 2023 May 5. PMID: 37211456.
- Islam, M.S., Rahman, W., Abdelkader, A. *et al.* Using AI to measure Parkinson's disease severity at home. *npj Digit. Med.* 6, 156 (2023). <https://doi.org/10.1038/s41746-023-00505-9>
- Karabayir, I., Gunturkun, F., Butler, L. *et al.* Externally validated deep learning model to identify prodromal Parkinson's disease from electrocardiogram. *Sci Rep* 13, 12290 (2023). <https://doi.org/10.1038/s41598-023-38782-7>
- Landers M, Seria S, Espay AJ. Will Artificial Intelligence Replace the Movement Disorders Specialist for Diagnosing and Managing Parkinson's Disease? *J Parkinsons Dis.* 2021;11(6):S117-S122. doi: 10.3233/JPD-212545. PMID: 34219671; PMCID: PMC8385515.
- McFarthing, Kevin *et al.* 'Parkinson's Disease Drug Therapies in the Clinical Trial Pipeline: 2023 Update'. 1 Jan. 2023 : 427 – 439.
- Pagano G, Taylor KI, Anzuere-Cabrera J, Marchesi M, Simuni T, Marek K, Postuma RB, Pavese N, Stocchi F, Azulay JP, Mollenhauer B, López-Manzanares L, Russell DS, Boyd JT, Nicholas AP, Luquin MR, Hauser RA, Gasser T, Poewe W, Ricci B, Boulay A, Vogt A, Boess FG, Dukart J, D'Urso G, Finch R, Zanigni S, Monnet A, Pross N, Hahn A, Svoboda H, Britschgi M, Lipsmeier F, Volkova-Volkmar E, Lindemann M, Dzadek S, Holiga S, Rukina D, Kustermann T, Kerchner GA, Fontoura P, Umbricht D, Doody R, Nikolaicheva T, Bonni A, PASADENA Investigators, Prasinezumab Study Group. Trial of Prasinezumab in Early-Stage Parkinson's Disease. *N Engl J Med.* 2022 Aug 4;387(5):421–432. doi: 10.1056/NEJMea2202867. PMID: 35921451.
- Schalkamp, AK., Peal, K.J., Harrison, N.A. *et al.* Wearable movement-tracking data identify Parkinson's disease years before clinical diagnosis. *Nat Med* 29, 2048–2056 (2023). <https://doi.org/10.1038/s41591-023-02440-z>
- Sheila M. Fleming, Ashley Davis, Emily Simons, Targeting alpha-synuclein via the immune system in Parkinson's disease: Current vaccine therapies. *Neuropharmacology*, Volume 202, 2022, 108870.
- Sidorow A, Concha-Marambio L, Lafontant DE, Farris CM, Ma Y, Urenia PA, Nguyen H, Alcalay RN, Chahine LM, Foroud T, Galasko D, Kiebert K, Merchant K, Mollenhauer B, Poston KL, Seibyl J, Simuni T, Tanner CM, Weintraub D, Videnovic A, Choi SH, Kurth R, Caspell-Garcia C, Coffey CS, Frasier M, Oliveira LMA, Hutten SJ, Sherer T, Marek K, Soto C. Parkinson's Progression Markers Initiative: Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using alpha-synuclein seed amplification: a cross-sectional study. *Lancet Neurol.* 2023 May;22(5):407–417. doi: 10.1016/S1474-4422(23)00169-6. PMID: 37059509; PMCID: PMC10327170.
- Yang, Y., Yuan, Y., Zhang, G. *et al.* Artificial intelligence-enabled detection and assessment of Parkinson's disease using nocturnal breathing signals. *Nat Med* 28, 2207–2215 (2022). <https://doi.org/10.1038/s41591-022-01932-x>
- Yang, W., Hamilton, J.L., Kopli, C. *et al.* Current and projected future economic burden of Parkinson's disease in the U.S.. *npj Parkinsons Dis.* 6, 15 (2020). <https://doi.org/10.1038/s41531-020-01112-1>
- Zhang X, Gao F, Wang D, Li C, Fu Y, He W, Zhang J. Tau Pathology in Parkinson's Disease. *Front Neurol.* 2018 Oct 2;9:809. doi: 10.3389/fneur.2018.00809. PMID: 30333786; PMCID: PMC6178019.



52

