

# **Parkinson's Disease and Prevention A Public Health Approach**

Caroline M. Tanner, M.D., PhD.

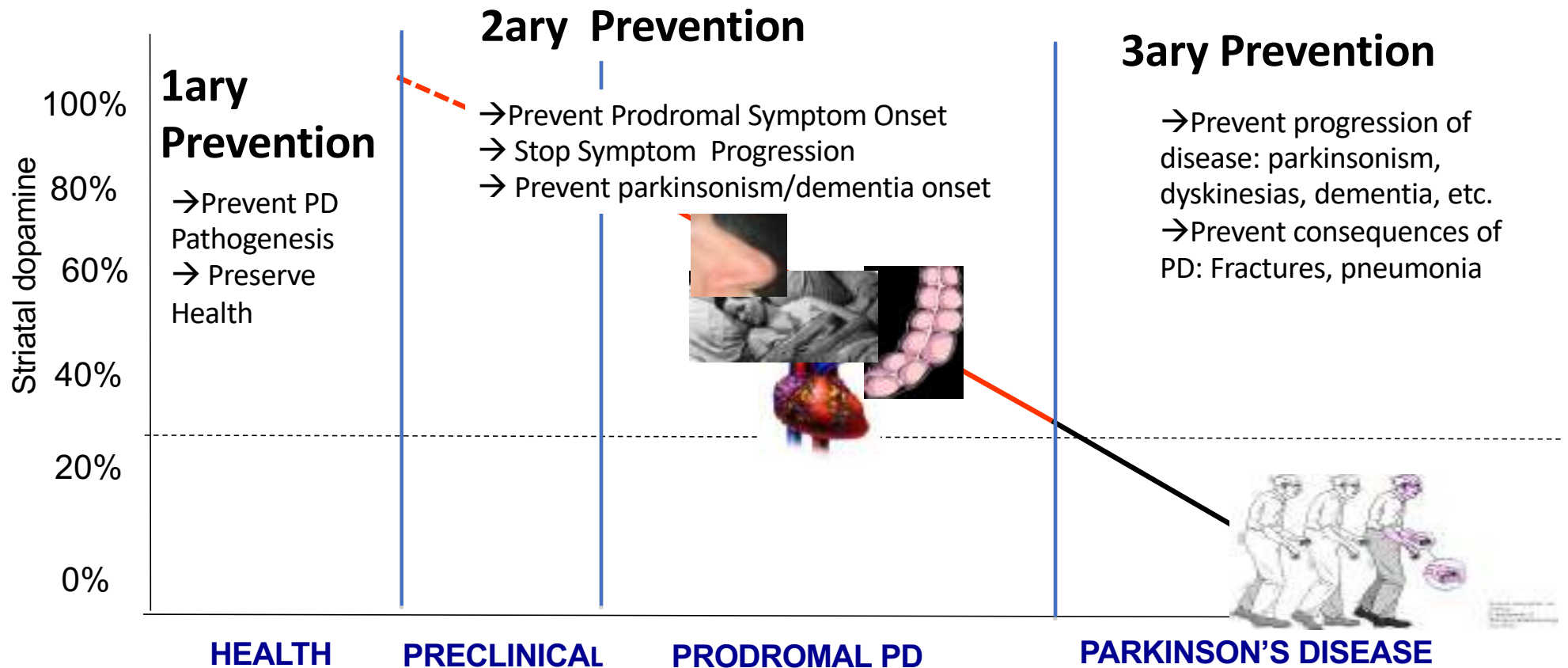
Professor, Neurology, University of San Francisco – California

Associate Director - Research, PADRECC, SFVAHCS

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# Preventing Parkinson's Disease

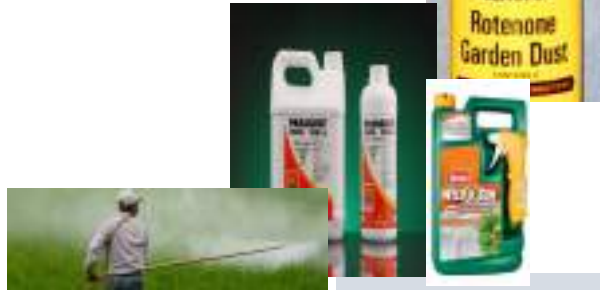


## Primary Prevention

- **Remove or mitigate the cause(s) of Parkinson's disease**
- **The disease process does not occur**

# **What Causes Parkinson's Disease?**

**Pesticides**



**Polychlorinated Biphenyls**



**Head Injury**



**Chlorinated Solvents**



**Some Factors Associated with a Higher Risk of Parkinson's Disease**

**Military Service**



**Age**



**Welding \ Metals?**



**Physical Inactivity**



**Air Pollution**



**Male Sex**

# **PRIMARY PREVENTION OF PARKINSON'S DISEASE**

## **PROOF OF PRINCIPLE**



# Parkinson's Disease in Pesticide Applicators

- Population:
  - 84,740 Farmers & Spouses in Iowa or N Carolina
  - Obtaining pesticide applicator licenses 1993-1997
  - Enrolled in Agricultural Health Study
- Methods:
  - Prospective follow-up for PD
  - In-home neurologist assessment of 1 PD: 3 matched controls; DNA, blood pesticides; expert consensus diagnosis
  - Detailed histories of pesticide application, PPE use, farm & other occupational toxicant exposures, diet & lifestyle, family history





# Parkinson's Disease in Pesticide Applicators

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- Results:

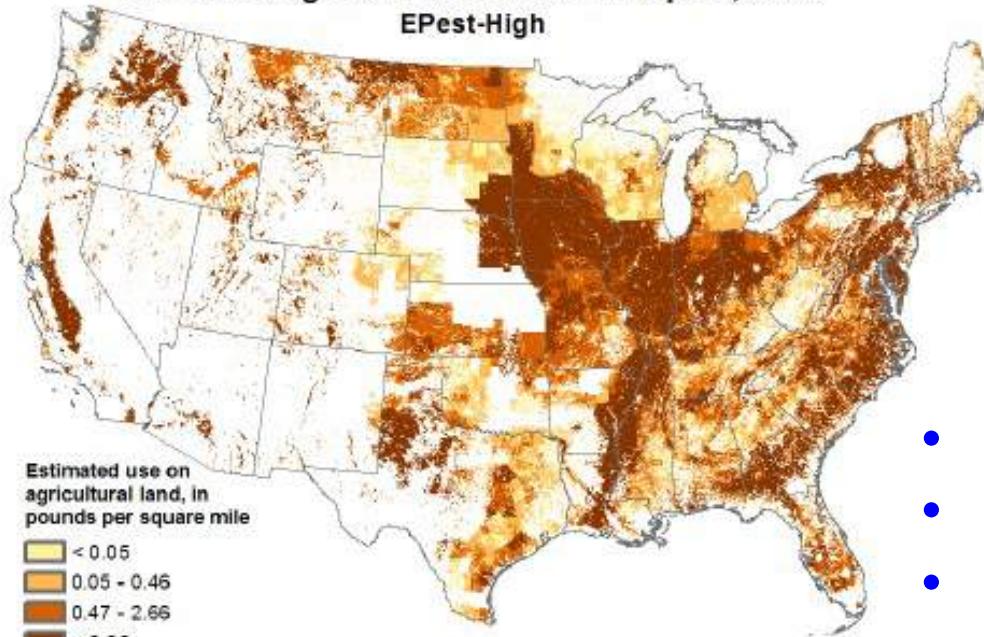
Pesticide	Functional Class	PD Risk (OR)	95%CI	p-value
Paraquat	Herbicide	2.5	1.3-4.7	0.004



# Paraquat

1,1'-Dimethyl-4,4'-bipyridinium dichloride

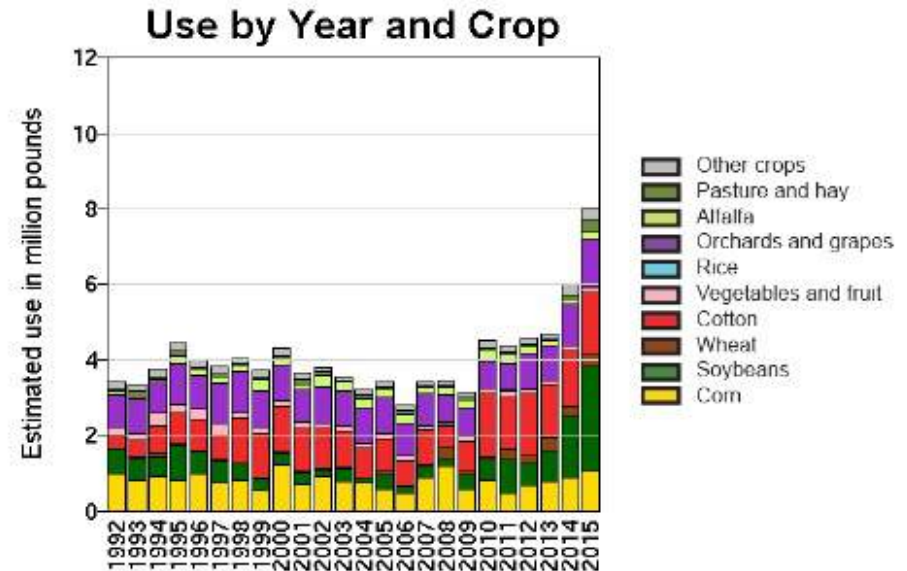
Estimated Agricultural Use for Paraquat , 2010  
EPest-High



Estimated use on agricultural land, in pounds per square mile

- < 0.05
- 0.05 - 0.46
- 0.47 - 2.66
- > 2.66
- No estimated use

**Toxicity:**  
**Redox activity →**  
**superoxide anions**



- Commonly used herbicide
- > 100 crops
- Agricultural, landscaping uses
- Banned in EU 2007
- Use in the US, worldwide has been increasing

# Can Parkinson's Disease Be Prevented?

Example 1: Diet

## Risk of Parkinson's disease associated with the herbicide paraquat is attenuated by high dietary intake of polyunsaturated fatty acids

Kamel et al, 2012



- PD cases and matched controls in AHS PD study
- Diet **before** PD diagnosis from a food frequency questionnaire

### RESULTS:

- Parkinson's disease inversely associated with high dietary polyunsaturated fatty acids, notably  $\alpha$ -linolenic acid: "Healthy diet"

(OR 0.4, 95% CI 0.2-0.8)

- Association of Parkinson's disease with paraquat attenuated with healthy diet, stronger in those with low intake of  $\alpha$ -linolenic acid

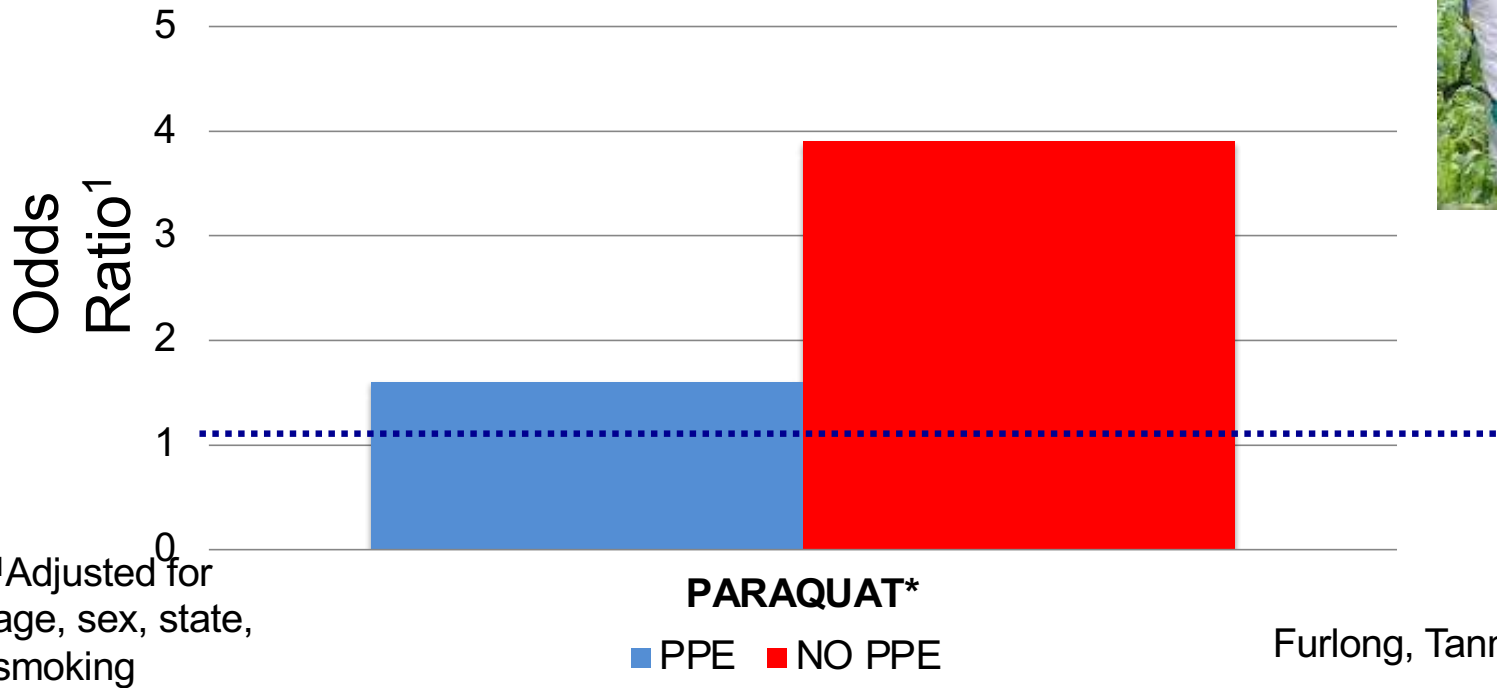
Healthy diet, No paraquat	1.0 (referent)
Unhealthy diet, No paraquat	1.4 (0.5-3.9)
<b>Healthy diet, Used paraquat</b>	<b>1.3 (0.7-2.5)</b>
<b>Unhealthy diet, Used paraquat</b>	<b>4.5 (1.7-12)</b>

# Can Parkinson's Disease Be Prevented?

Example 2:  
Protective Behaviors

Applicators were asked if they used Personal Protective Equipment (PPE) (masks, gloves, respirators) and washed off immediately after a spill.

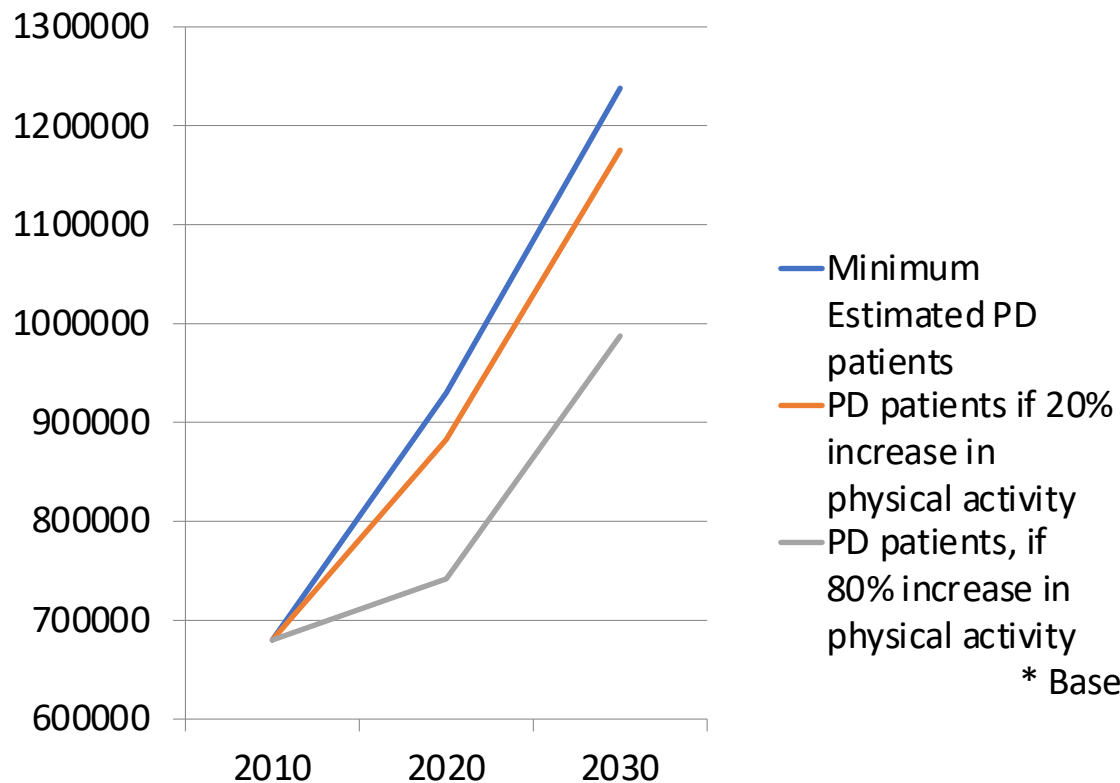
Increased Risk of PD Was Not Observed in Farmers Using PPE During Pesticide Application



Furlong, Tanner, Goldman, et al, 2015

# What If Adults Just Exercised More ?

**Estimated Number of People with PD in the U.S.\* & the Projected Reduction in PD If Physical Activity in Adults Increases**



\* Based on Marras, 2018

# The Dilemma

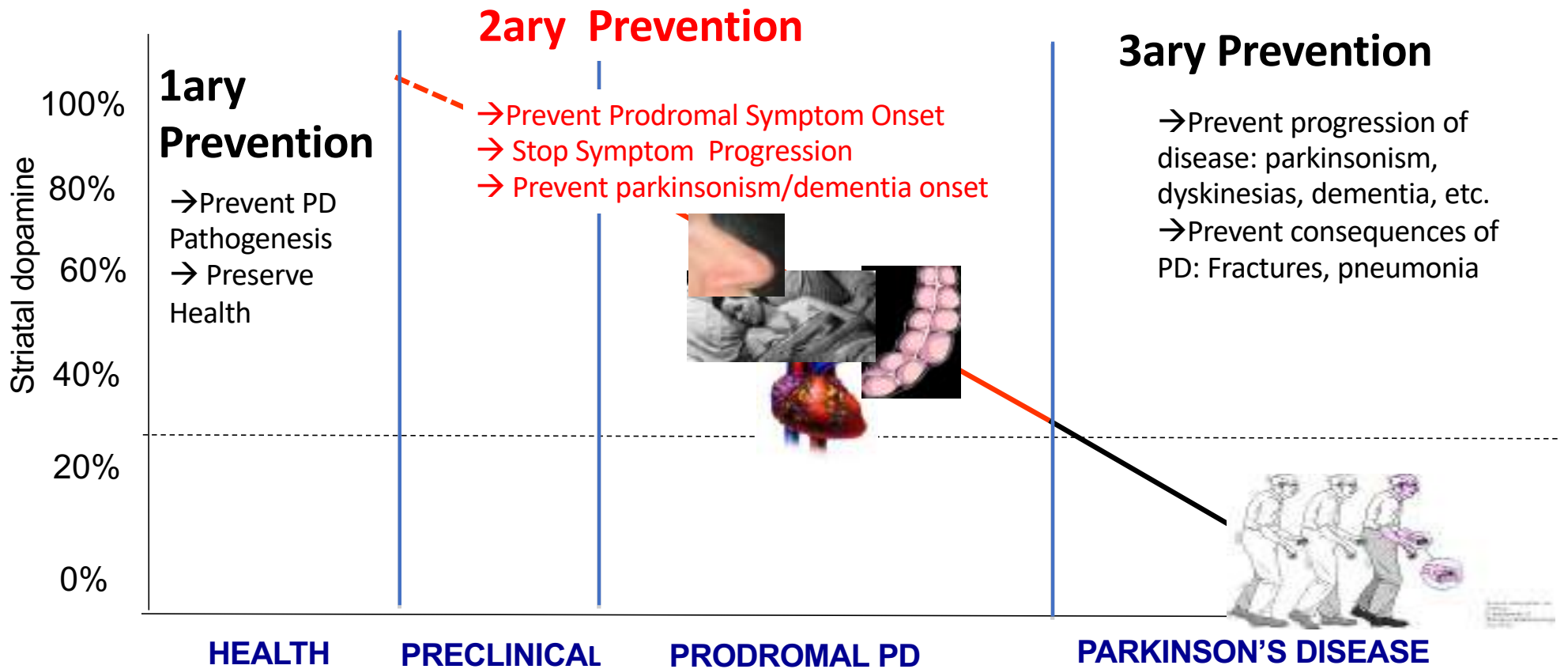
- Environment may not be cleaned up
- People may not follow health recommendations

**Secondary prevention:** aim is to correct departures from a state of health.

→ Target people with prodromal Parkinson's disease



# Preventing Parkinson's Disease



The challenge:

Efficiently Identifying Prodromal PD

# Genes & Parkinson's Disease

- Total < 20 % PD
- Penetrance reduced:  
Other genes & environmental factors also important

- **Autosomal Dominant. ~ 5% PD**

PARK-*SNCA*, PARK-*LRRK2*, PARK-*VPS35*

- **Autosomal Recessive < 5% PD**

PARK-*Parkin*, PARK-*PINK1*, PARK-*DJ1*, PARK-*DNAJC6*

### ***Complex phenotypes < 1% PD***

PARK-*ATP13A2*, PARK-*PLA2G6*, PARK-*FBXO7*, PARK-*DNAJC6*, PARK-*SYNJ1*

- **Glucocerebrosidase 5 – 8 % PD**

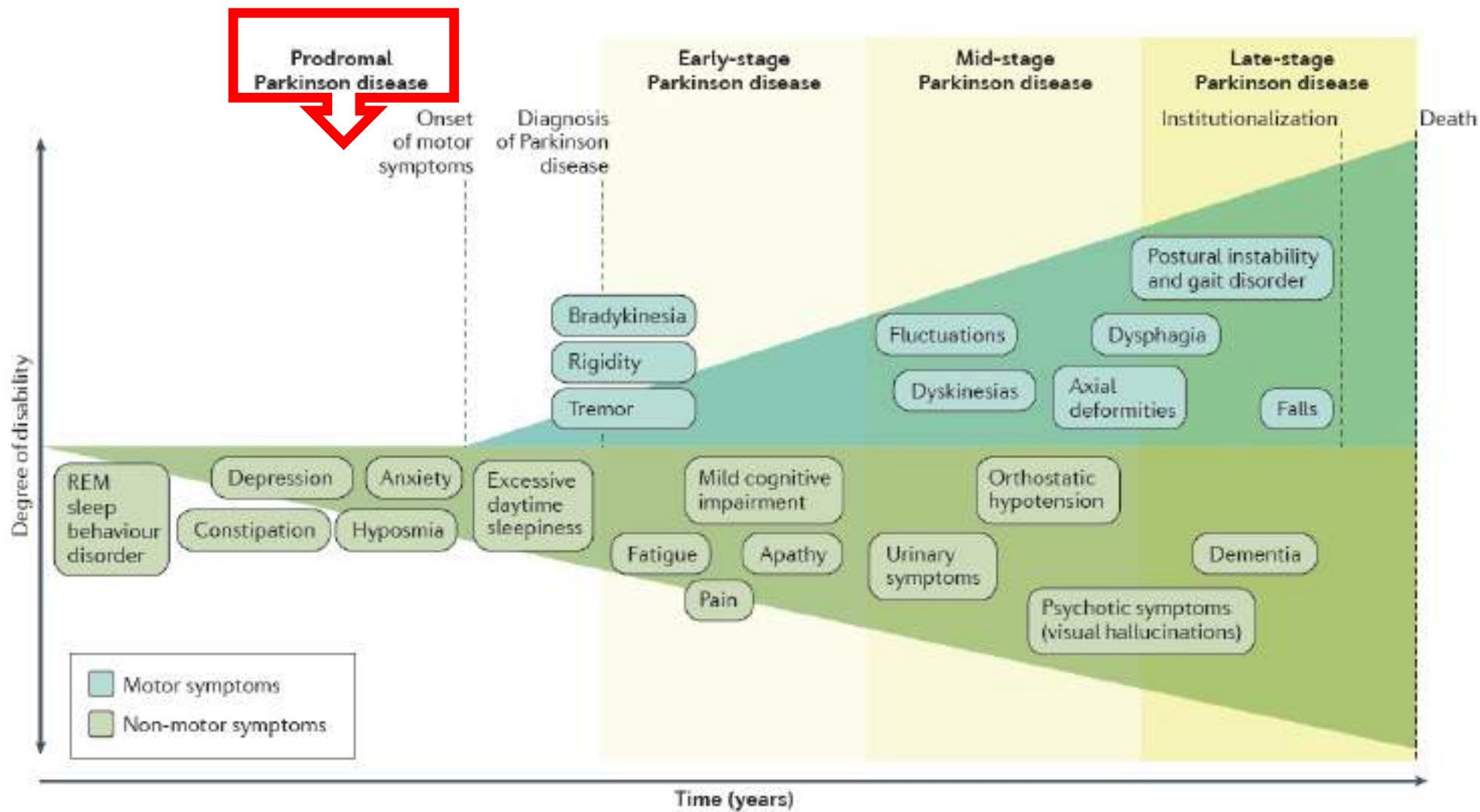
# Preventing Genetic Causes of Parkinson's Disease

## Theoretical Approach:

- Identify gene mutation carriers
- Intervene to block or correct effect of mutation before pathologic process begins

- New treatments at the research stage
- Genetic testing for people with PD available





Prodromal Diagnosis	Cases/Controls 2,717/13,585	OR (95%CI)
Constipation	477/953	2.8 (2.5,3.1)
REM Sleep BD	22/37	3 (1.8,5.1)
Seborrheic dermatitis	110/346	1.6 (1.3,2.0)
Anosmia	24/64	1.9 (1.2,3.0)
Neurogenic bladder	45/138	1.6 (1.2,2.3)
Anxiety	578/1837	1.8 (1.9,2.3)
Depression	789/2271	2.1 (1.9,2.3)

## Screening for Prodromal PD in the Electronic Medical Record

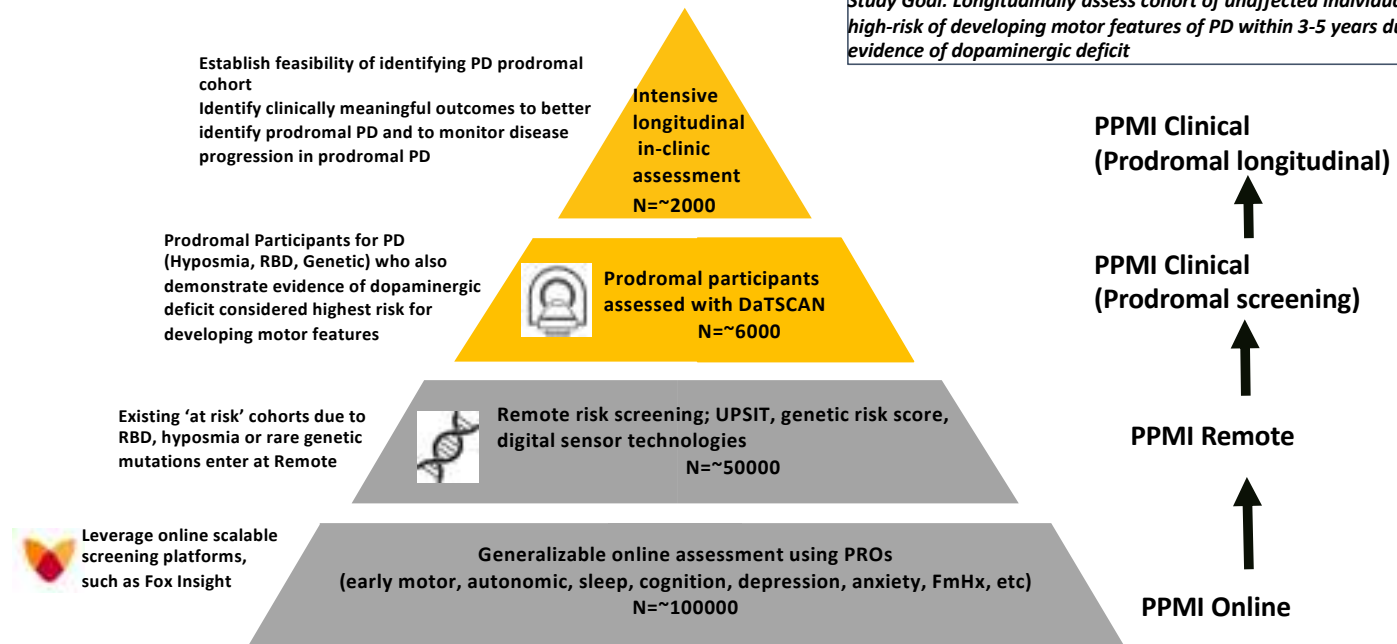
Newly diagnosed PD 2004 – 2010 & Matched Controls

Members of Northern California Kaiser Permanente

→ **Future PD diagnosis more common in people seeking health care for certain conditions**

# PPMI - PRODROMAL PYRAMID

*Study Goal: Longitudinally assess cohort of unaffected individuals at high-risk of developing motor features of PD within 3-5 years due to evidence of dopaminergic deficit*

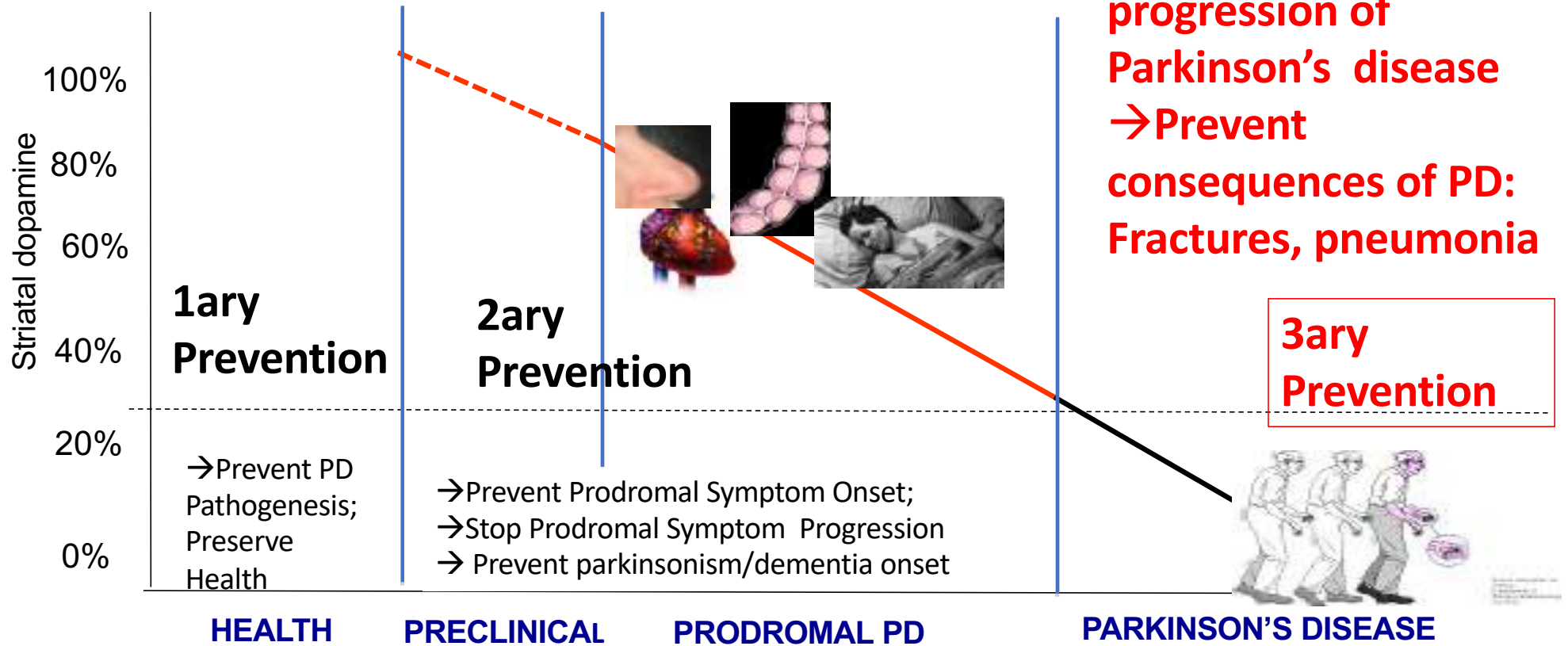


# **What About People Who Have Parkinson's Disease?**

## **Tertiary Prevention**



# Preventing Parkinson's Disease



## Disease Modifying Therapies for PD: Research Approaches



**Goal:** Halt the disease process.

- **Approach:** Prevent aggregation or promote clearance of misfolded alpha-synuclein.

### **Examples:**

Monoclonal Antibody Infusion against alpha-synuclein

Vaccine development against alpha-synuclein

- **Approach:** Correct abnormal function due to genetic changes; “Personalized medicine”: Patients have identified gene defects

- **Examples:**

LRRK2 inhibitors

Restore glucocerebrosidase enzyme function

Target mitochondrial dysfunction

# Preventing the Consequences of PD: Preventing fractures

- **People with PD have very high risk of fractures**
  - 2- to 4-fold increased risk for fractures
    - ANY fracture: 14 % risk per year (17% in women, 12% in men)
    - HIP fracture: 4% risk per year (4.5% in women, 3.9% in men)
  - Even higher in those > 60
  - These risks far exceed National Osteoporosis Fndn. thresholds for treatment
  - Fractures increase disability, reduce independence, increase mortality
- **Yet, people with PD & other forms of parkinsonism have far lower rates of osteoporosis treatment!**

Join a Parkinson's Study  
without ever leaving  
your home

PARTICIPANTS NEEDED

**TOPAZ**  
TRIAL OF PARKINSON'S AND ZOLEDRONIC ACID



**This study is done from your home!**

- If you are eligible for the study, a nurse will come to your home to give you a short exam.
- You'll receive a one-time dose of the study treatment (either zoledronic acid or a placebo).

**Earn \$100 upon enrollment & \$50 per year during the study.**

Want to learn  
more about joining  
TOPAZ?

Ready to join? Visit  
**[topaz.eurekaplatform.org](https://topaz.eurekaplatform.org)**  
and enter invitation code

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or call:  
**1-800-4PD-INFO**  
(1-800-473-4636)

# Conclusion

## **Prevention is possible!**

A combination of public health and targeted medical interventions has the potential to significantly reduce Parkinson's disease burden.

# Colleagues

## UCSF & SFVAMC

Samuel Goldman  
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Robert Abbott

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Stephen Van Den Eeden  
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## NIEHS

Freya Kamel  
Jane Hoppin  
David Umbach  
Marie Richards  
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Lorene Nelson  
James Tetrud

## NCI

Aaron Blair

## NIA

Andrew Singleton

## Columbia University

Ruth Ottman  
Richard Mayeux  
Karen Marder

## Capital U, Beijing

Bill Piu Chan  
Kitty Gu

## Favaloro U, Buenos Aires

Anabel Chade

## Buddhist Tzu Chi Hosp, Taiwan

Raymond Lo

## University of Michigan

Kelvin Chou

## Cleveland Clinic

Hubert Fernandez

## University of Pittsburg

Franca Cambi

## Rush University

Cindy Comella  
Christopher Goetz  
Kathleen Shannon

## University of Pennsylvania

Jonas Ellenberg

## IND

Kenneth Marek

## University of Rochester

David Oakes

# UCSF Movement Disorders



## Neurology

Jill Ostrem, MD  
Nicholas Galifianakis, MD  
Caroline Tanner, MD, PhD  
Marta San Luciano, MD  
Maya Katz, MD  
Ian Bledsoe, MD,MS  
James Maas, MD, PHD  
Chadwick Christine, MD  
Michael Aminoff, MD  
Robert Edwards, MD  
Ken Nakamura, MD, PhD  
Alexandra Nelson, MD, PhD  
Michael Geschwind, MD  
Amy Viehoveer, MD, PhD  
Nijee Luthra, MD, PhD  
Cameron Dietiker, MD

## Research /Support Staff

Sarah Wang, PhD  
Kristen Dodenhoff, BA  
Farah Kauser  
Joncarmen Mergenthaler  
Janet Allen  
Shatara Blackmon  
Yasmeen Gonzalez  
Jeverly Calaunan  
Kathleen Comyns, MPH  
Samantha Bethel, BA  
Cheryl Meng, MPH  
Danilo Romero  
Kanchi Mehta

## Psychiatry

Andrea Seritan, MD

## Social Work

Monica Eisenhardt, LCSW

## Chaplin

Judith Long

## Physical Therapy

Nancy Byl, PT, PhD  
Heather Bhide, PT

## Neurosurgery

Philip Starr, MD, PhD  
Paul S. Larson, MD  
Edward F. Chang, MD  
Daniel Lim, MD, PhD  
Krzysztof Bankiewicz, MD, PhD  
Coralie De Hemptinne, PhD  
Whitney Chen, PhD  
Doris Wang, MD, PhD

## Neuropsychology

Caroline Racine Belkoura, PhD

## Nursing

Monica Volz, FNP, MS  
Karen Merchant, MSN  
Susan Heath, MS, RN  
Gina Bringas-Cinco, RN  
Annie Li Wong, NP

## Fellows

Jessica Weinstein, MD  
Kyle Mitchell, MD  
Jennifer Choi, MD  
Ethan Brown, MD  
Mitra Afshari, MD  
Melissa Heiry, MD  
Idit Tamir, MD, PhD



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### Sponsors:



Neurotoxin  
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