Pre-motor Parkinson's Disease Can be Diagnosed – **Not Yet**

Web Ross

VA Pacific Islands Health Care System

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Ground Rules

- **Focus of pre-motor diagnostic strategies will be on sporadic PD**
- **The setting for discussions of pre-motor PD diagnosis will be the general population as opposed to special populations such as those with family history.**

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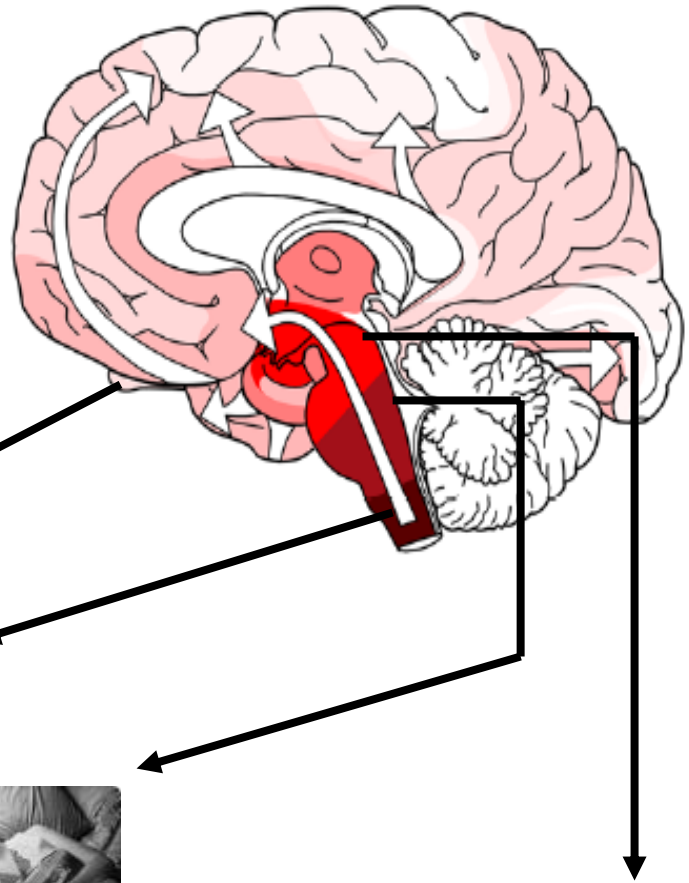
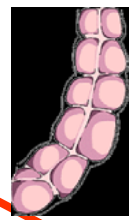
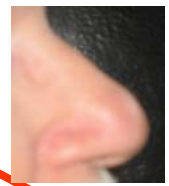
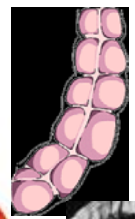
Does a pre-motor phase of PD exist?

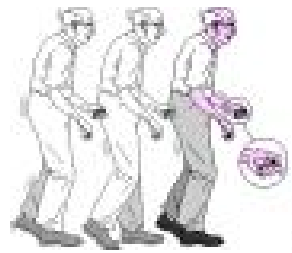


Synuclein pathology in gut









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4 to ≥ 13 Years

What are the pre-motor symptoms

- Impaired olfaction
- Disorders of sleep
  - REM sleep behavior disorder
  - Excessive daytime sleepiness
- Slow reaction time
- Autonomic abnormalities
  - Constipation
  - ~~Prolonged QT interval~~
- ~~Depression / Cognitive impairment~~

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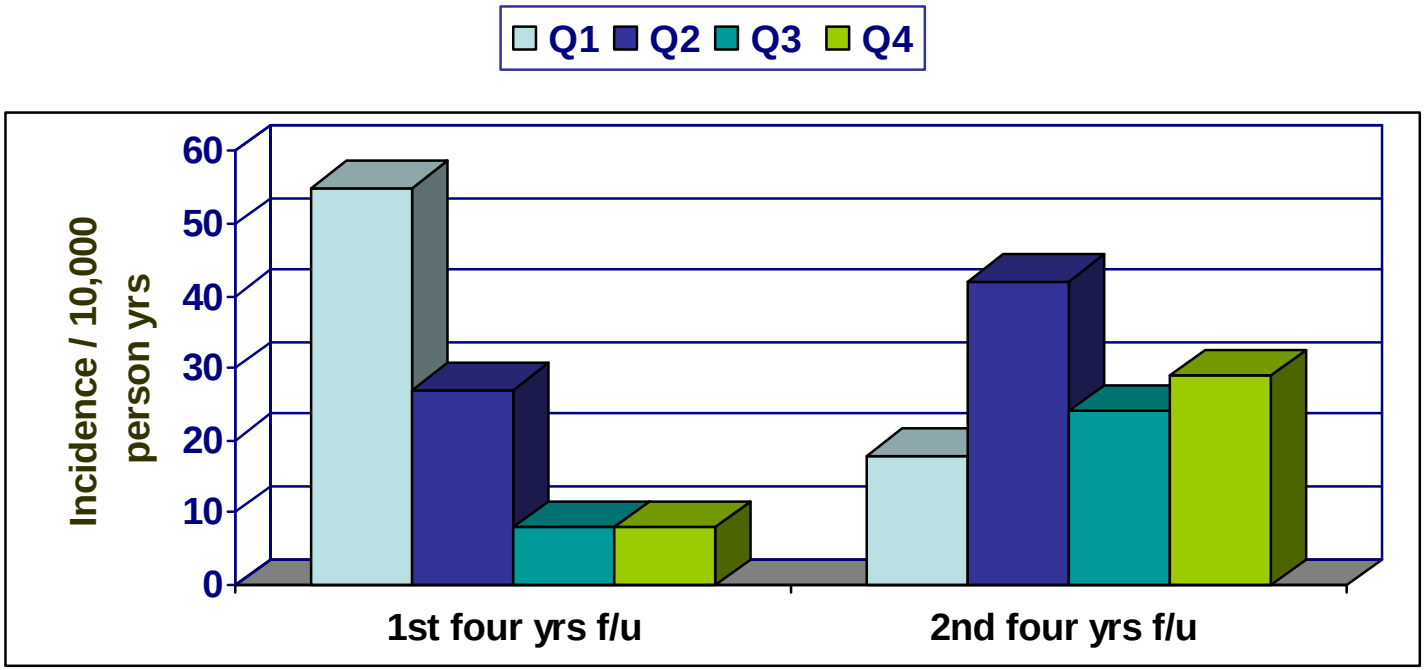
Olfactory dysfunction in the HAAS

Age adjusted PD incidence/10,000 p-ys by quartile of odor identification among 2263 men at risk



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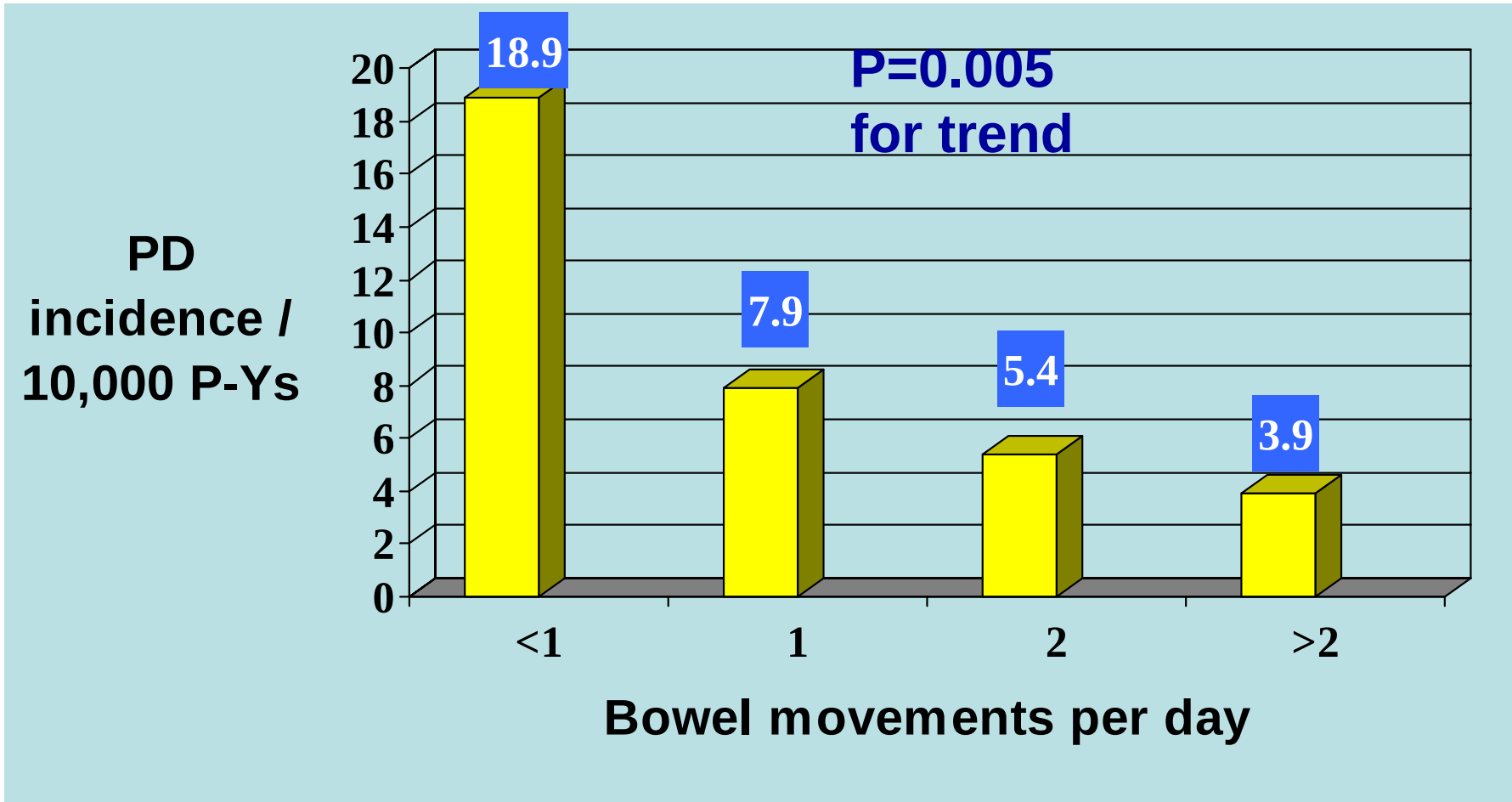
Age adjusted PD incidence / 10,000 p-ys by bowel movement frequency



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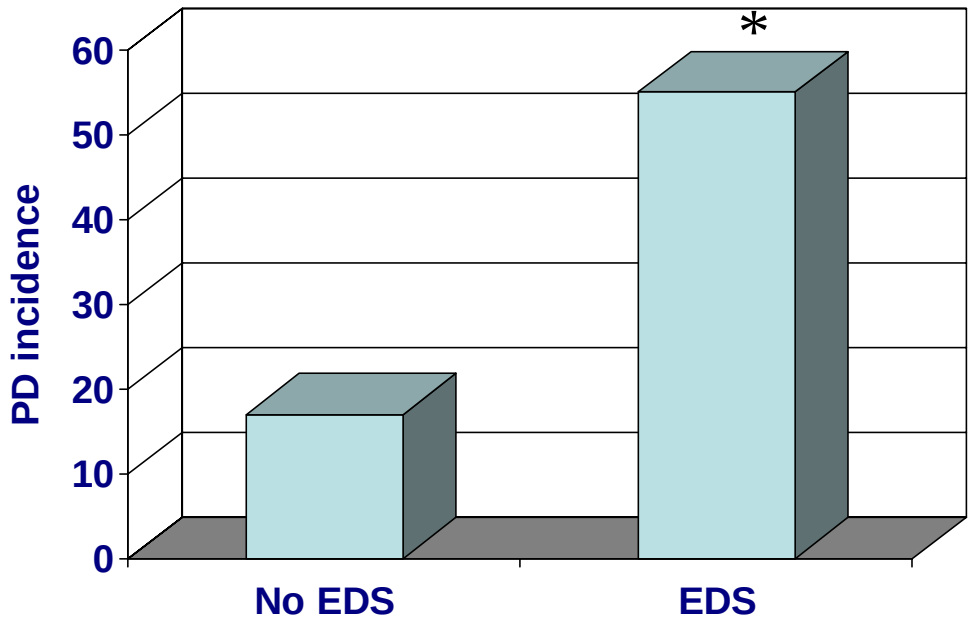
Excessive daytime sleepiness (EDS)

Age adjusted PD incidence / 10,000 P-Ys among 3078 men aged 71 to 91 years in the HAAS free of PD at baseline (1991)



*** P = 0.004**

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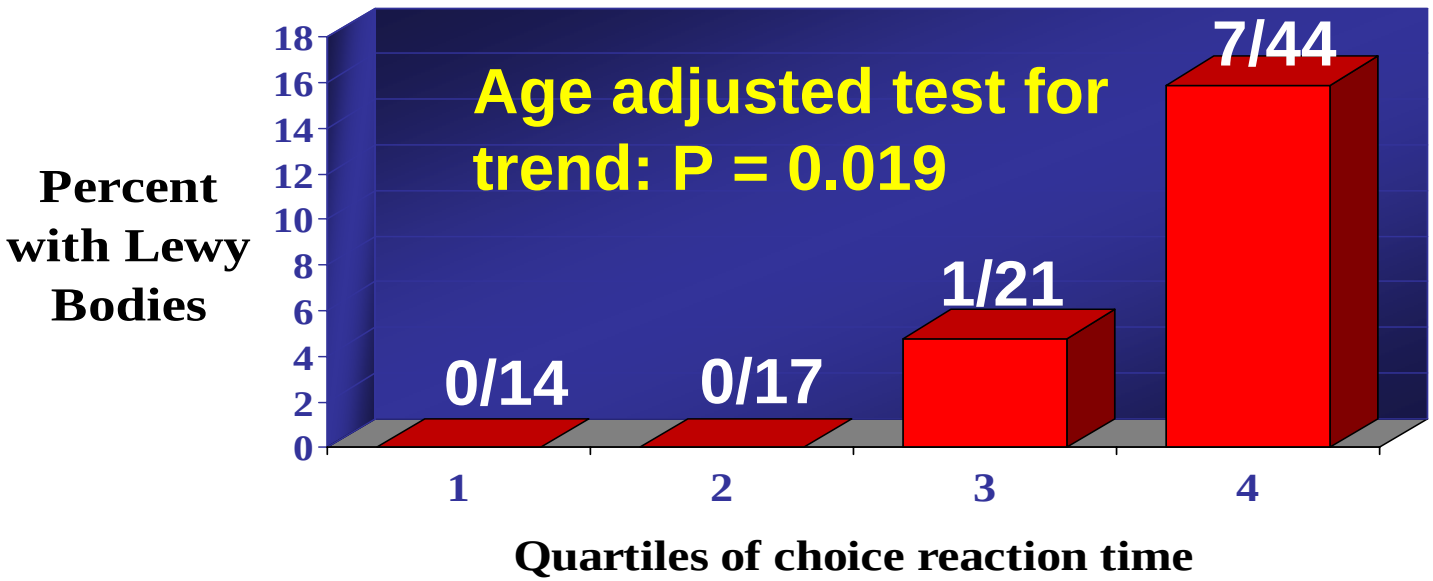
Reaction time testing

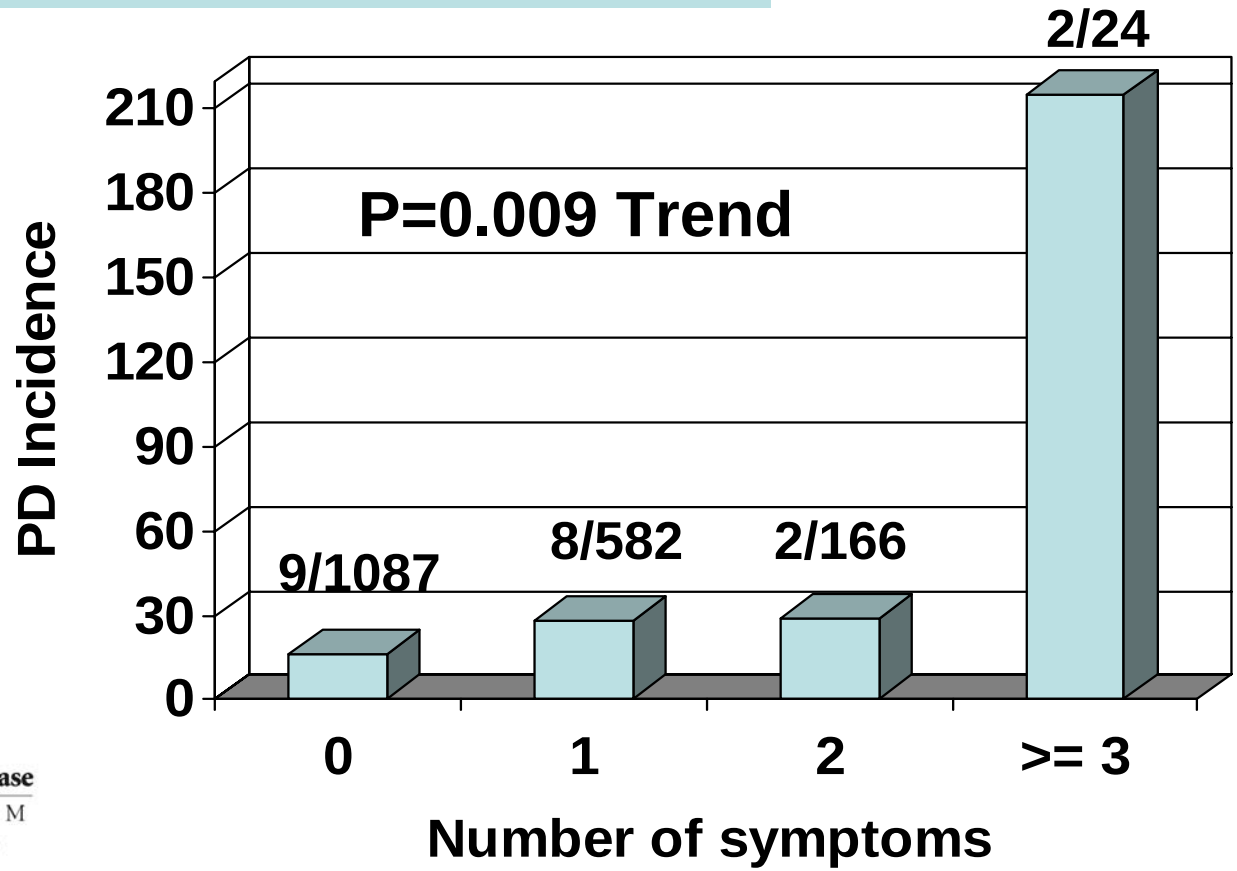
- There is significant prolongation of both simple and choice reaction times in Parkinson's disease. This may reflect slowness in motor readiness as well as execution.
- Prolongation of reaction time may be associated with pathology in the gain setting nuclei in the brainstem (Braak stage 2)

% with Lewy bodies by quartiles of Choice reaction time measured approximately 2.2 years prior to death



PD incidence/10,000 person-years by number of early symptoms present

- Excessive Daytime Sleepiness
- Poor olfaction (bottom 20th percentile)
- Slow reaction time (slowest 20th percentile)
- <1 bowel movement/day



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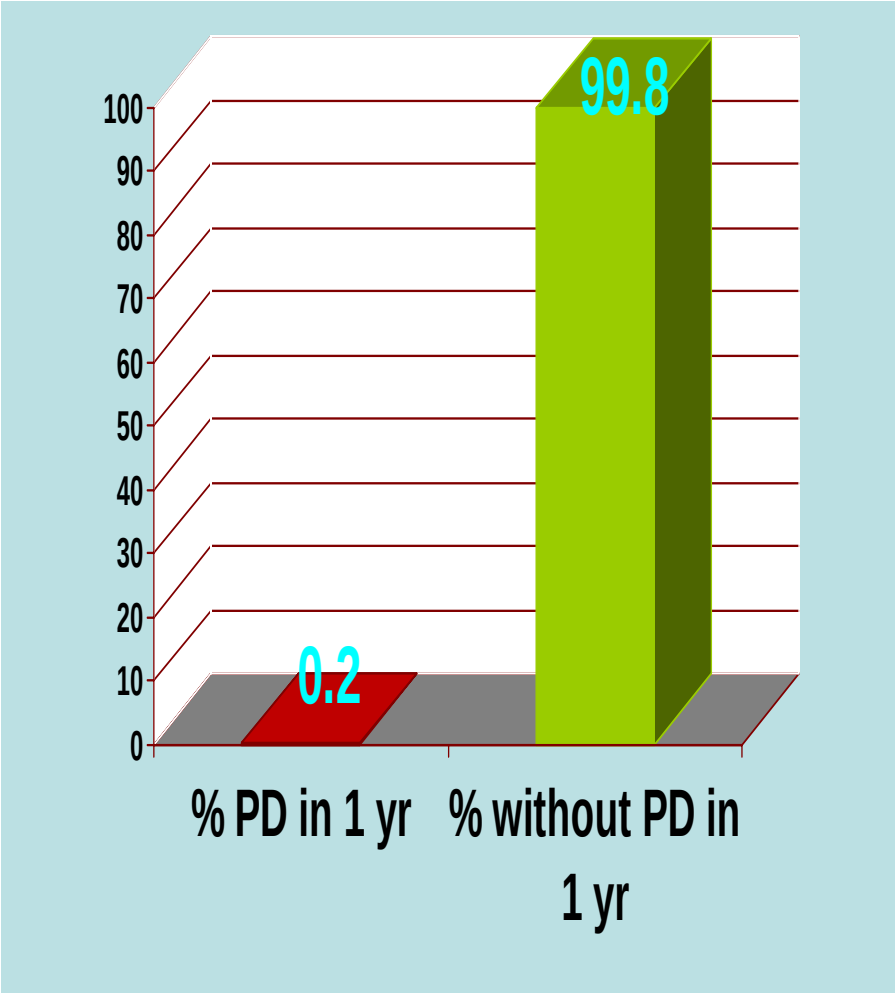
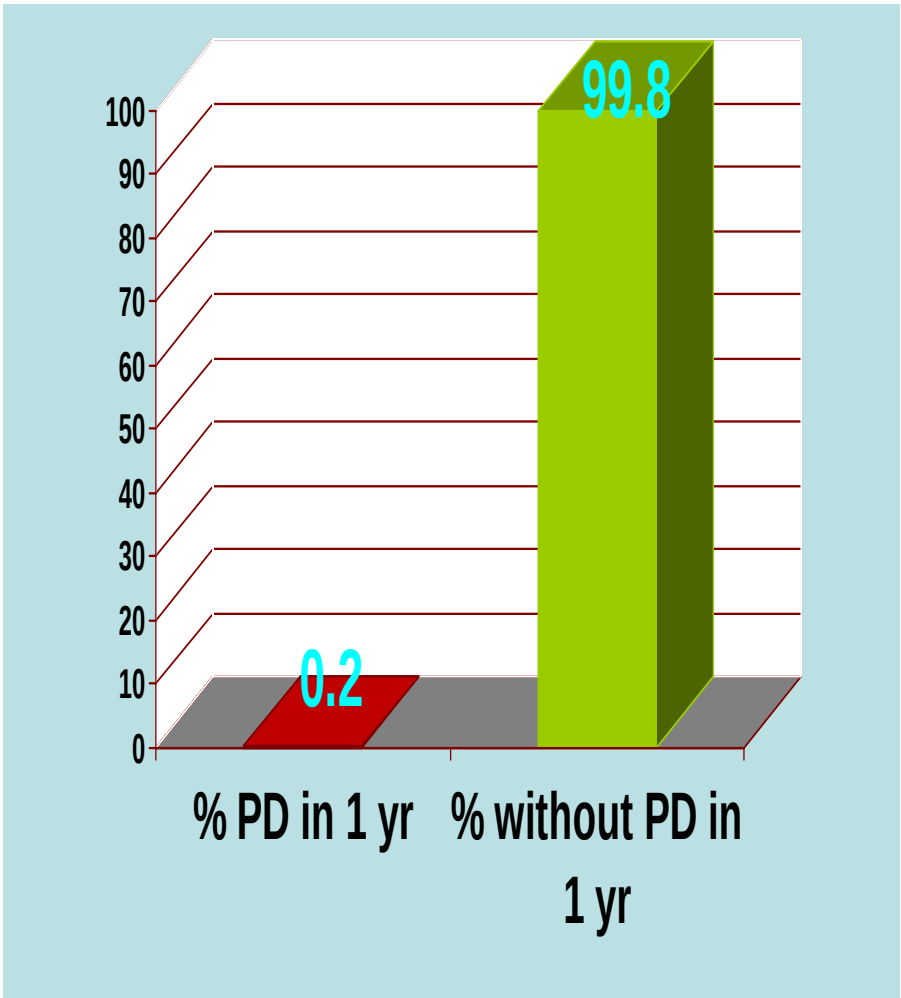
Positive test (≥ 3 pre-motor symptoms) for pre-motor PD

Negative test: < 3 symptoms

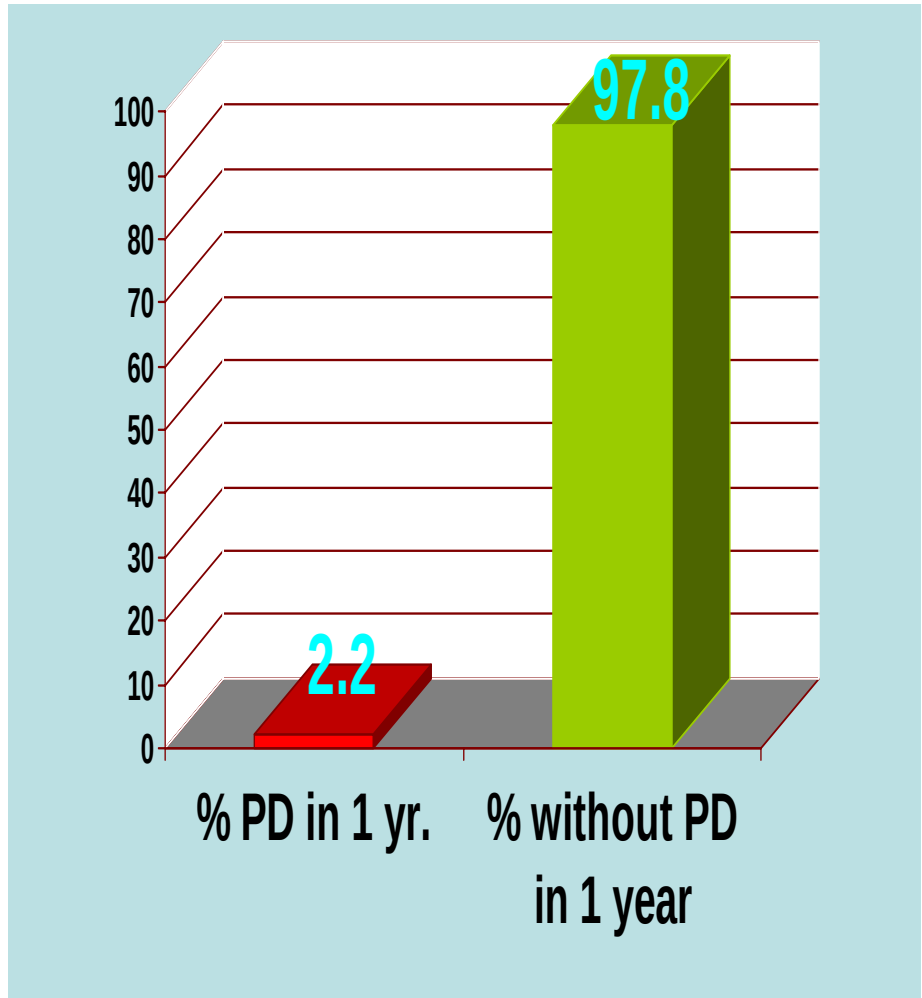


Positive test (≥ 3 pre-motor symptoms) for pre-motor PD

Negative test: < 3 symptoms



Positive test: ≥ 3 symptoms



Radiotracer Imaging for pre-motor PD diagnosis

- Nigral cell loss predates motor manifestations of PD by many years, so radiotracer imaging of the nigrostriatal dopaminergic system should show abnormalities prior to diagnosis
- 10 to 15% of early PD have normal scans –
- There is discordance between imaging and clinical markers in that limit usefulness as a marker of progression
- DAT-SPECT has been used along with hyposmia in relatives of PD
- Abnormal DAT binding in asymptomatic LRRK2 mutation carriers
- Sensitivity, specificity, predictive values are unknown in the general population

Diagnostic accuracy of TRODAT SPECT imaging in <u>early</u> PD (Chou et al, 2004)

Sensitivity = 79%; Specificity = 92%

% PD prevalence	Neg. PV	Pos. PV
50	0.81	0.91
25	0.93	0.77
10	0.98	0.52
5	0.99	0.34
2	0.99	0.17
1	0.99	0.09

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Radiotracer Imaging for pre-motor PD diagnosis

- **Conclusions:**
  - **Clearly worthy of study**
  - **Too early to tell if useful for pre-motor diagnosis**

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Transcranial sonography for pre-motor diagnosis of PD

- Hyperechogenicity in 90% of PD patients
- Pathological correlate unknown
- Adequate bone window is age dependent and absent in 10%
- Sensitivity 91%, specificity 82%, positive predictive value 93% for differentiating PD from atypical parkinsonian in population of early parkinsonian subjects
- Longitudinal studies of pre-motor subjects in general population are lacking
- Conclusions:
  - May assist with differential diagnosis
  - Not a useful tool for pre-motor diagnosis yet.

Pre-motor symptoms (constipation, hyposmia, slow reaction time, EDS) plus imaging assuming 100% sensitivity and specificity for imaging

# symptoms	% of sample	% who get PD	% who do not get PD	# needed to scan for 1 case	Sample screened
0	58.5	0.16	99.84	625	1069
1	31.3	0.28	99.72	354	1131
2	8.9	0.29	99.71	348	3911
≥3	**1.3**	**2.16**	**97.84**	**47**	**3616**

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Conclusions

- There is a pre-motor period associated with symptoms and recognizable neuropathology
- Defining high risk for future PD is possible but identifying pre-motor PD in an individual is not
- A variety of imaging modalities show promise but predictive value is unknown in the general population
- More longitudinal population based studies needed before clinical application is possible