MASSACHUSETTS GENERAL HOSPITAL
PSYCHIATRY ACADEMY

Symptoms and Diagnosis of Parkinson's Disease 2021

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No Conflicts of Interest

Financial Disclosures:

- Steering committee for PD GENEration (Parkinson's Foundation)
- Medical Advisor for Accordant, a CVS/Caremark Disease Management Company
- Participated in clinical research sponsored by Schering-Plough/Merck, Pfizer, Acorda, Bristol-Myers Squibb, Biogen, Sanofi/Genzyme, Abbvie, Roche
- Consultant for Mitsubishi Tanabe Pharma

Outline

- Symptoms of Parkinson's Disease
- Diagnosis of Parkinson's Disease
  - Diagnostic Tests for PD
- Symptoms of Wearing off

Symptoms of PD

Common Presenting Complaints:

- Fatigue
- Weakness
- Tremor
- Reduced dexterity
- Impaired Handwriting (“micrographia”)
- Decreased arm swing when walking
- Stiffness, muscle cramps, shoulder pain
- Scuffing or tripping with a slower gait
- Falls
- Anxiety
- Depression

Signs of PD

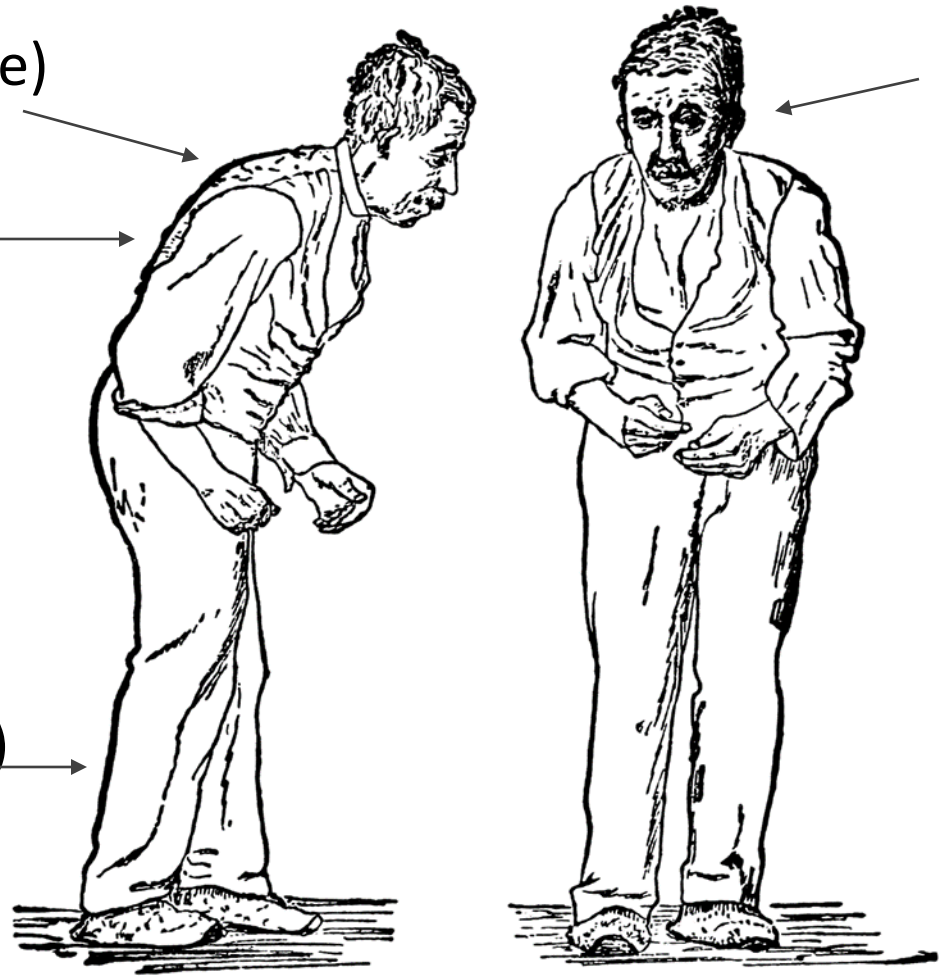
- Hypomimia (decreased facial expression, “masked facies”)
- Decreased eye blink rate
- Hypophonia (softness of voice)
- Dysarthria (slurred speech)
- Bradykinesia (slowness of fine motor testing)
- Extrapyramidal rigidity (to passive movement)
- 4-6 Hz rest tremor
- Difficulty arising from a chair
- Abnormal gait: scuffing, shuffling, “en bloc” turns
- Postural instability (impaired balance on pull test)

Motor signs/symptoms

Kyphosis (stooped posture)

Decreased armswing
+/- tremor

Festinating gait (shuffling)



Hypomimia

-Gowers, 1886

Rest tremor & Bradykinesia

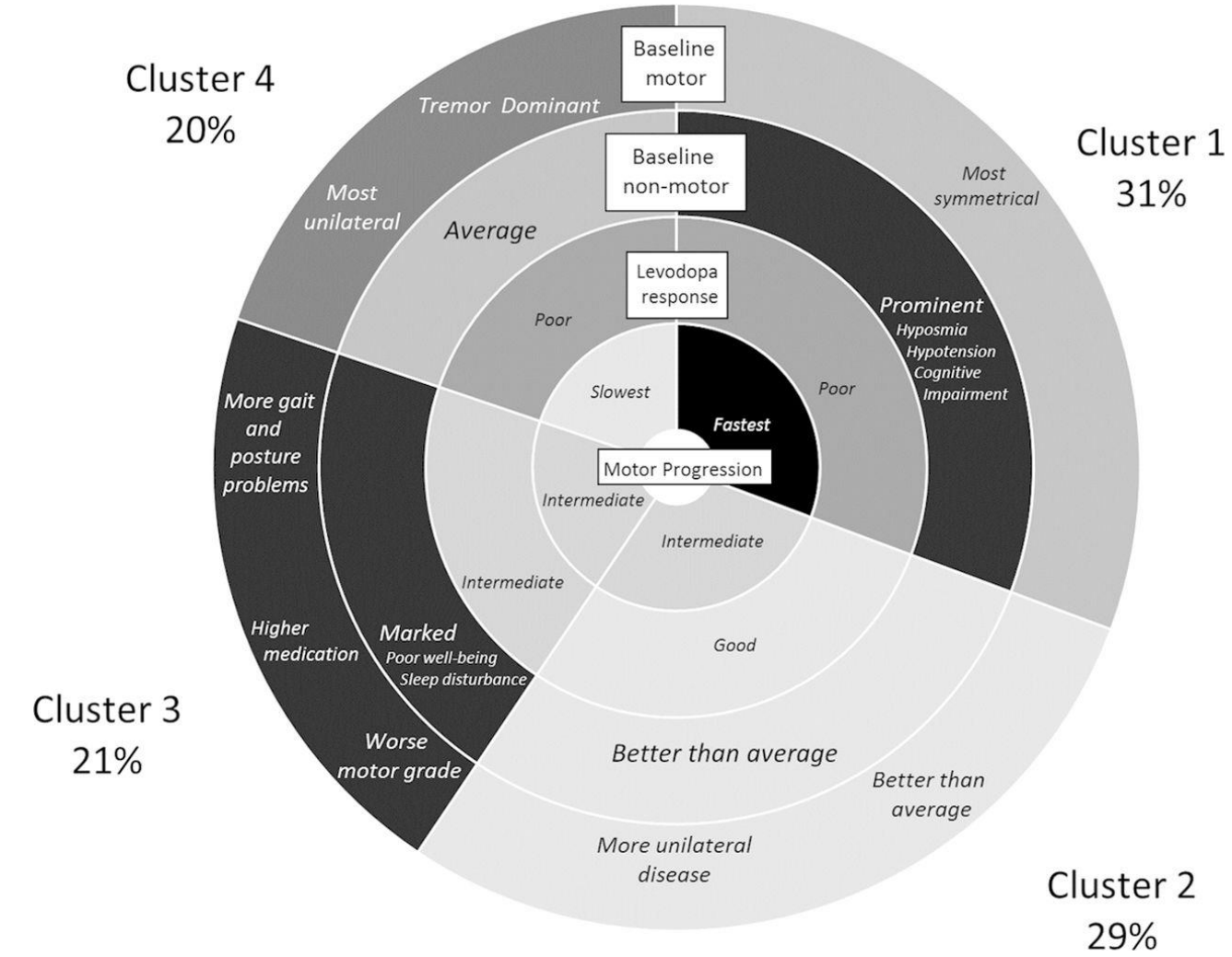
- Right upper extremity rest tremor: mild (2/4, between 1-3 cm on MDS-UPDRS)
- Bradykinesia of rapid succession movements:
  - 3/4 on the MDS-UPDRS: Any of the following:
    - a) more than 5 interruptions during tapping or at least one longer arrest (freeze) in ongoing movement;
    - b) moderate slowing;
    - c) the amplitude decrements starting after the 1st tap

Gait & Balance signs/symptoms

- Decreased armswing
- Scuffing gait
- >2 steps on pull test= slight postural instability
- H&Y Stage 2.5

Heterogeneity of Parkinson's Disease Phenotypes

- Tremor-Predominant
- Postural-Instability Gait Disorder
- Predictors of worse prognosis:
  - older age at diagnosis
  - non-levodopa-responsive motor symptoms
  - deficits on cognitive testing

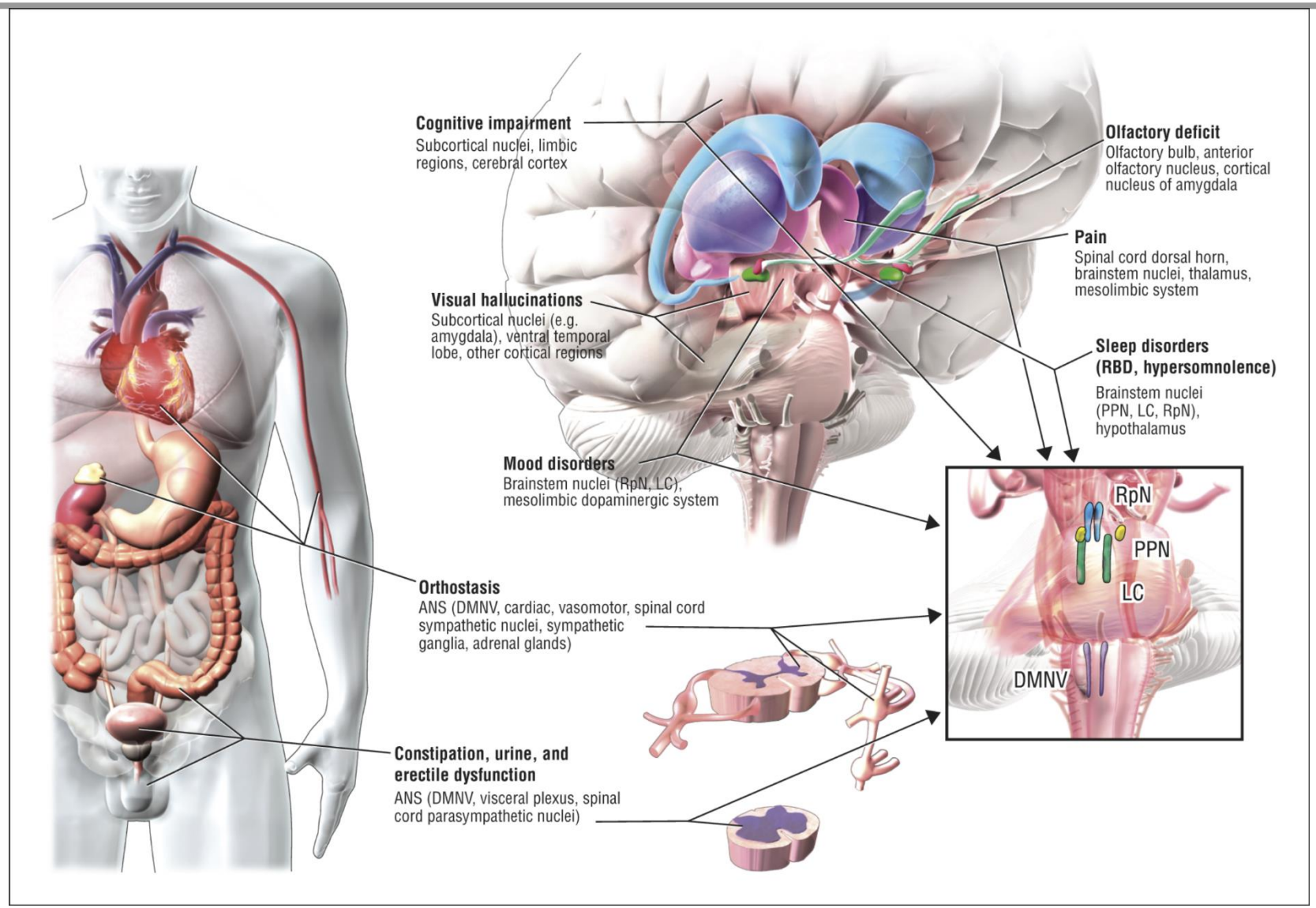


Michael Lawton et al. J Neurol Neurosurg Psychiatry 2018;89:1279-1287

Non-motor symptoms in PD

- Anxiety
- Depression
- Apathy
- Fatigue
- Insomnia
- Sleep disturbance
  - REM Behavior Disorder
  - Restless Legs/PLMS
  - Sleep Apnea
- Pain/Paresthesias
- Sialorrhea (drooling)
- Dysphagia (swallowing)
- GI motility (constipation)
- Bladder instability
- Orthostatic hypotension
- Olfactory loss
- MCI
- Dementia
- Psychosis

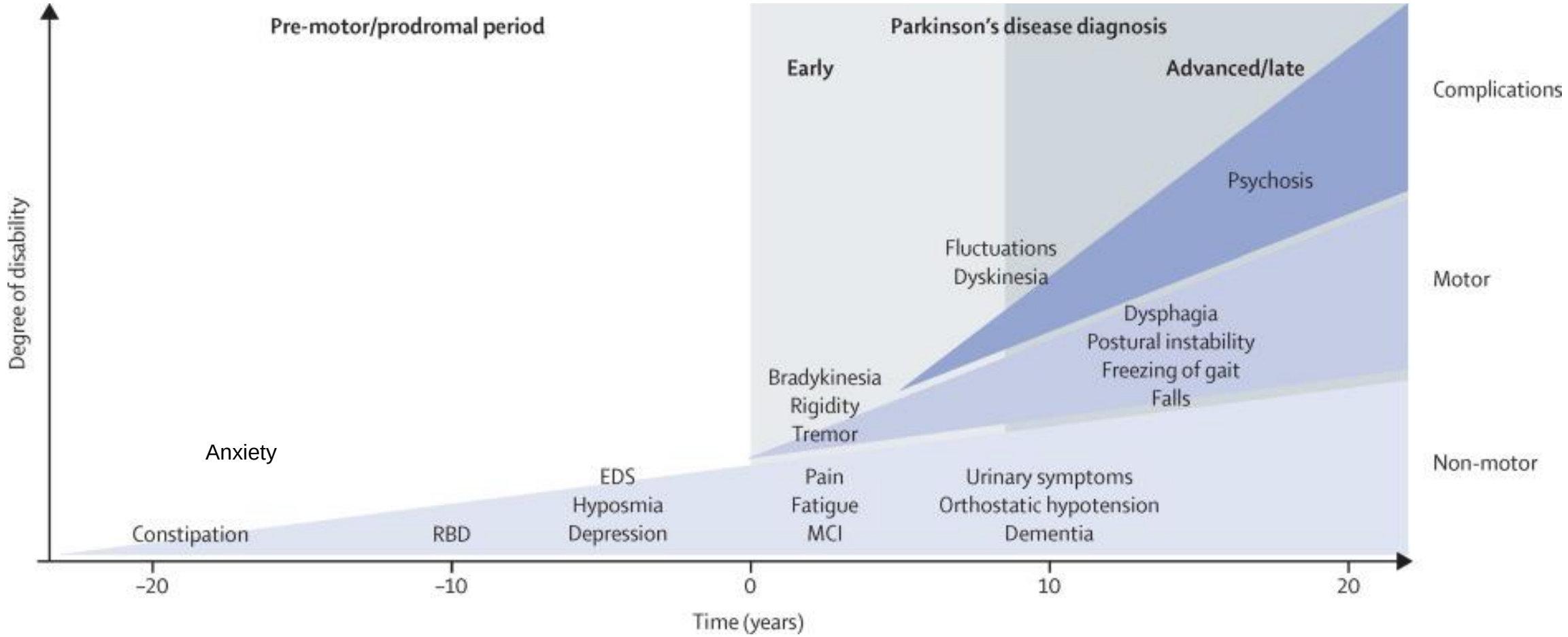
Non-motor symptoms in PD



From: **Overview of the Extranigral Aspects of Parkinson Disease**

Arch Neurol. 2009;66(2):167-172. doi:10.1001/archneurol.2008.561

Time Course of Symptom Onset

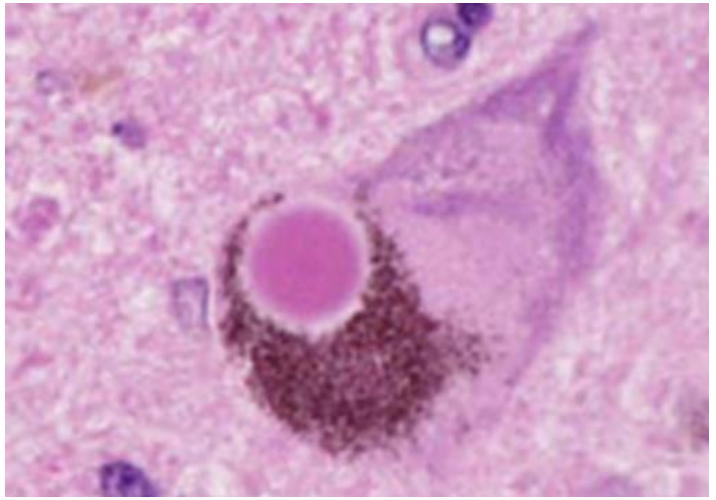


-Kalia & Lang, The Lancet, 2015
-Savica et al. JAMA Neuro 2010

Diagnosis of Parkinson's Disease

U.K. Brain Bank Criteria:

- **Required:**
  - Bradykinesia
  - At least one of the following:
    - Muscular rigidity
    - 4-6 Hz rest tremor
    - postural instability
- **Supportive criteria:**
  - Unilateral onset
  - Rest tremor present
  - Progressive disorder
  - Excellent response (70-100%) to levodopa



**From: Hughes AJ, Daniel SE, Kilford L, Lees AJ. Accuracy of clinical diagnosis of idiopathic Parkinson's disease. A clinico-pathological study of 100 cases. JNNP 1992;55:181-184.*

MDS Criteria for PD diagnosis

- Parkinsonism is defined as bradykinesia, in combination with either rest tremor, rigidity, or both.
- Bradykinesia is defined as slowness of movement AND decrement in amplitude or speed (or progressive hesitations/halts)
- Rigidity: “lead-pipe” resistance (velocity-independent resistance to passive movement). Isolated “cogwheeling” without “lead-pipe” rigidity does not fulfill minimum requirements for rigidity.
- Rest tremor refers to a 4- to 6-Hz tremor in the fully resting limb
- Absence of absolute exclusion criteria
- At least two supportive criteria
- No red flags

MDS Supportive Criteria

- Clear and dramatic beneficial response to dopaminergic therapy (>30% improvement in UPDRS III)
- Unequivocal on/off fluctuations
- Presence of levodopa-induced dyskinesia
- Rest tremor of a limb, documented on clinical examination (in the past, or on current examination)
- Olfactory loss (in the anosmic or clearly hyposmic range, adjusted for age and sex)
- Metaiodobenzylguanidine (123I-MIBG) scintigraphy showing cardiac sympathetic denervation

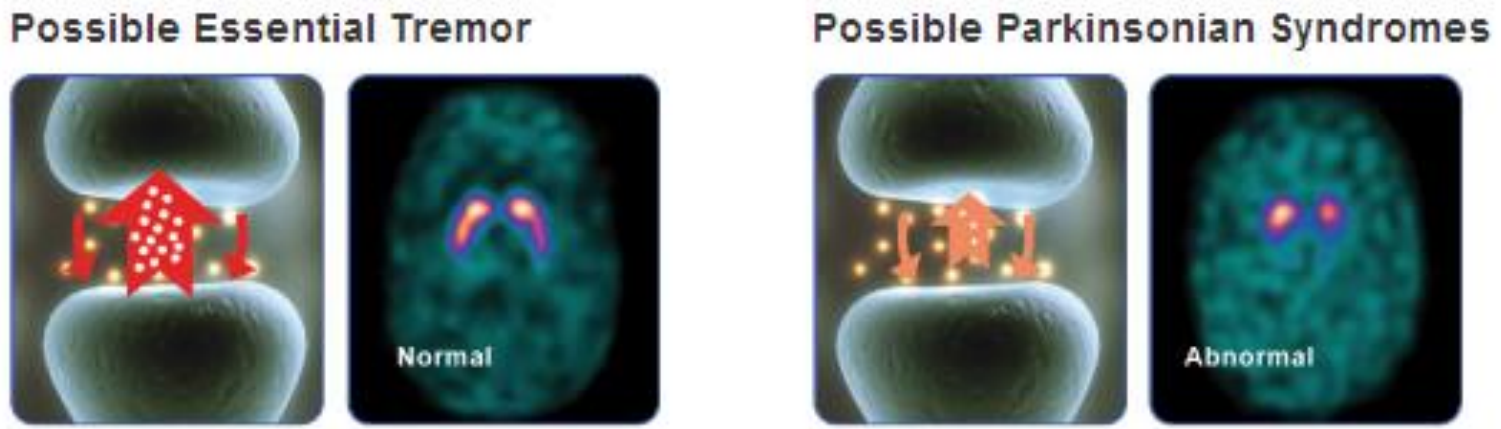
MDS Exclusion Criteria

- Unequivocal cerebellar abnormalities on examination, such as cerebellar gait, limb ataxia, or cerebellar oculomotor abnormalities (eg, sustained gaze-evoked nystagmus, macro square wave jerks, hypermetric saccades) (MSA-C)
- Downward vertical supranuclear gaze palsy, or selective slowing of downward vertical saccades (PSP)
- Diagnosis of probable behavioral variant frontotemporal dementia or primary progressive aphasia, defined according to consensus criteria within the first 5 y of disease (FTD-P)
- Parkinsonian features restricted to the lower limbs for more than 3 y
- Drug-induced parkinsonism (antipsychotic agents, anti-emetics, VPA)
- Absence of observable response to high-dose levodopa despite at least moderate severity of disease (≥600 mg/d).
- Unequivocal cortical sensory loss (ie, graphesthesia, stereognosis with intact primary sensory modalities), clear limb ideomotor apraxia, or progressive aphasia (CBS)
- Normal functional neuroimaging of the presynaptic dopaminergic system (DaT)

Recommended Testing

- MRI
  - Rule out stroke, NPH, midbrain (PSP) or pontine or cerebellar atrophy (MSA)
- FDG-PET
  - Rule out Corticobasal Degeneration (CBD), MSA-C, Frontotemporal Dementia (FTD), Alzheimer's Disease
- Dopamine Transporter Imaging:
  - DaTscan™ approved by FDA Jan 2011 to differentiate PD from essential tremor

Dopamine Transporter Imaging



www.datscan.com

- DaTscan™: Ioflupane I 123 combined with SPECT imaging for the detection of dopamine transporters (DaT)
- 50% reduction in Striatal Dopamine uptake was ~80% sensitive for Parkinson's Syndromes (PD, MSA, PSP)

DaT Scan Does Not Differentiate PD from Atypical PD

Disease Entity	Imaging Modality			
	MR Imaging	FDG PET	Amyloid PET	^{123}I Ioflupane SPECT
Parkinson disease	Often normal, occasional diffuse atrophy	Usually normal, preserved putaminal activity, occasional decreased uptake in the parieto-occipital cortex	Normal	Decreased striatal activity (usually asymmetric)
MSA	Putaminal atrophy and marginally increased T2 signal, "hot cross bun sign"	Decreased putaminal or cerebellar uptake, subtype dependent	Normal	Symmetric or asymmetric decreased striatal activity
PSP	"Hummingbird sign," "Mickey Mouse sign"	Decreased uptake in the posterior frontal lobes, midbrain, and basal ganglia	Normal	Symmetric or asymmetric decreased striatal activity
DLB	Diffuse atrophy	Generalized decreased uptake (more prominent in the occipital lobes)	Positive in most cases	Symmetric or asymmetric decreased striatal activity
CBD	Asymmetric parietal and/or frontal cortical atrophy	Asymmetric decreased uptake in the parietal and/or frontal lobes	Normal	Decreased striatal activity (usually asymmetric)

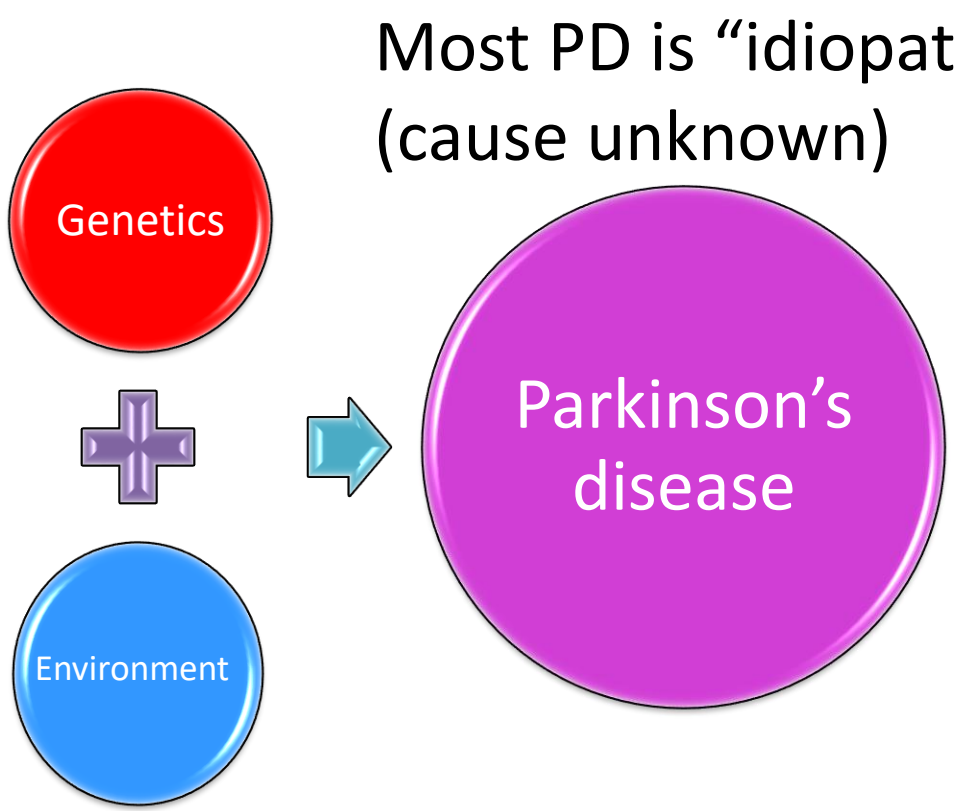
-Broski et al, Radiographics, 2014

Sinemet Responsiveness

- Test up to 1000 mg/day (or 300 tid) before determining “non-responsive”
- Sinemet Trial/Levodopa Challenge:
  - 100-200 mg levodopa x 1
  - Test motor symptoms pre and 30 minutes after dosing

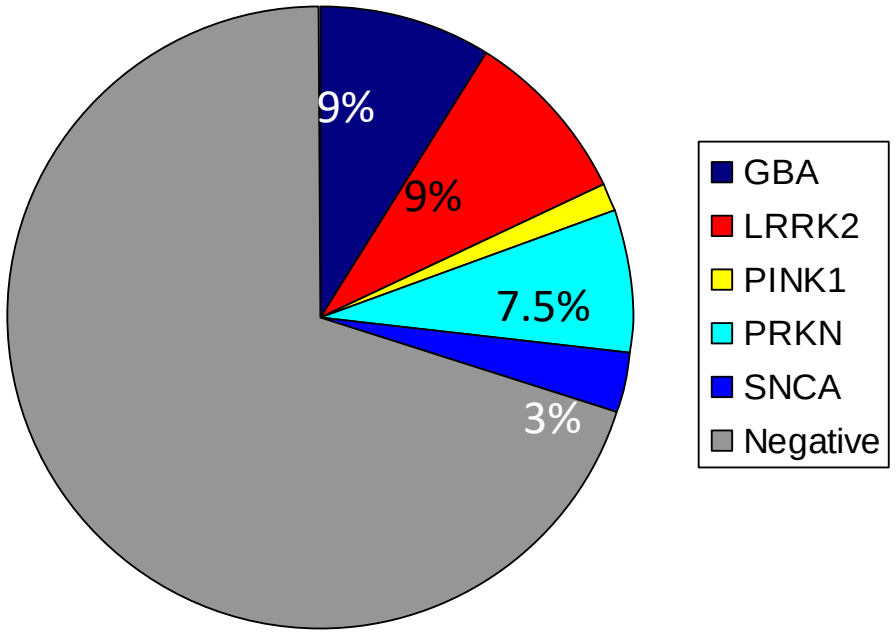
What about Genetic Testing?

- 15-20% of PD is thought to be "familial" with a positive family history
- 10-15% of PD is thought to be "monogenic" (caused by a single gene)
- Environmental risk factors: pesticides, metallurgy, head trauma

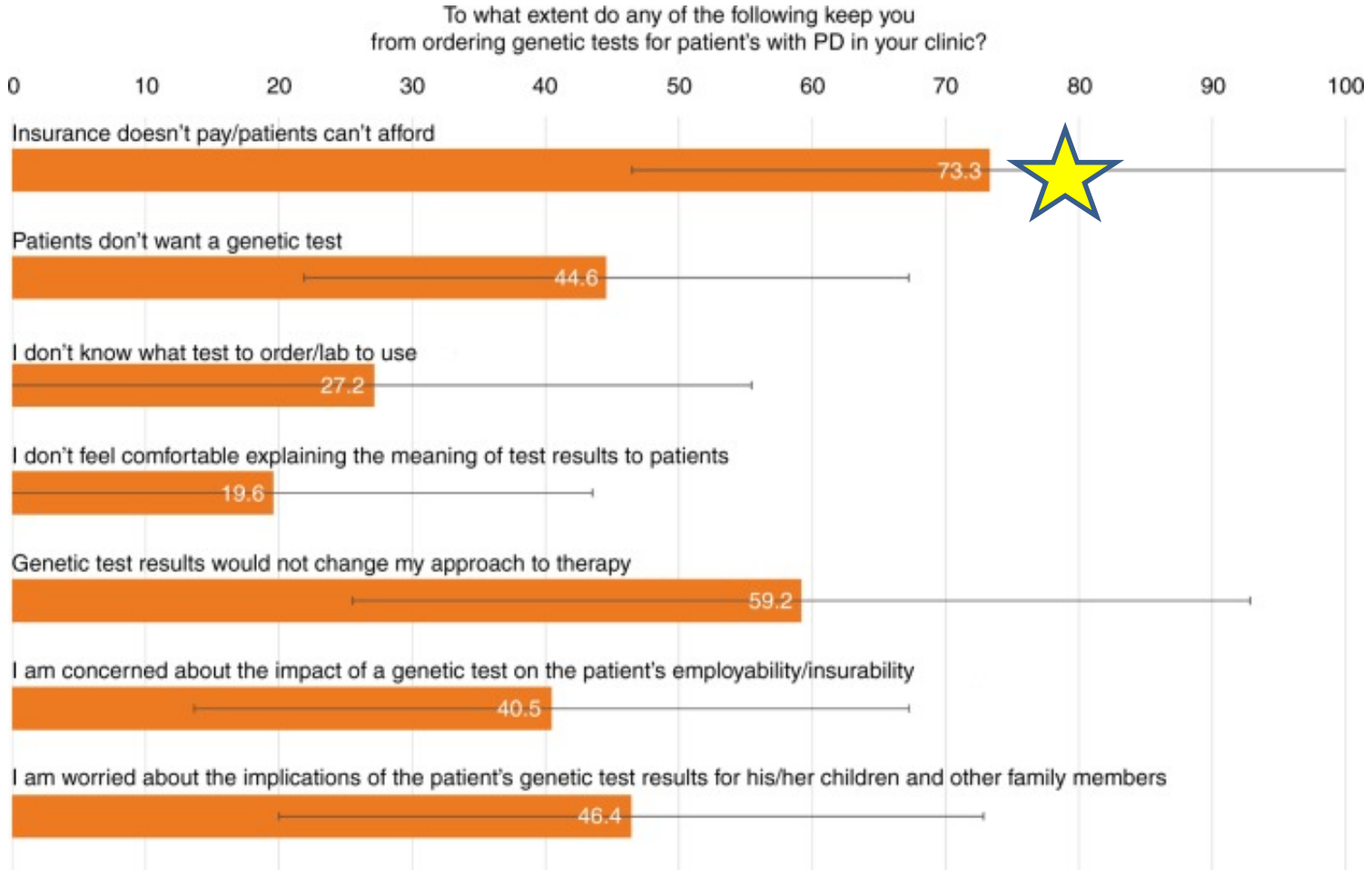


Frequency of Genetic Mutations

- 30% of monogenic PD is caused by a mutation in a known gene
- 25+ genes identified to date
- Penetrance of PD genes ranges from 10% (GBA) to 90% (SNCA)
- Of the first 291 participants enrolled in PDGENEration
- 17% reportable mutations in 7 genes
- 30% including VUS
- Genetic testing does not replace neurological exam



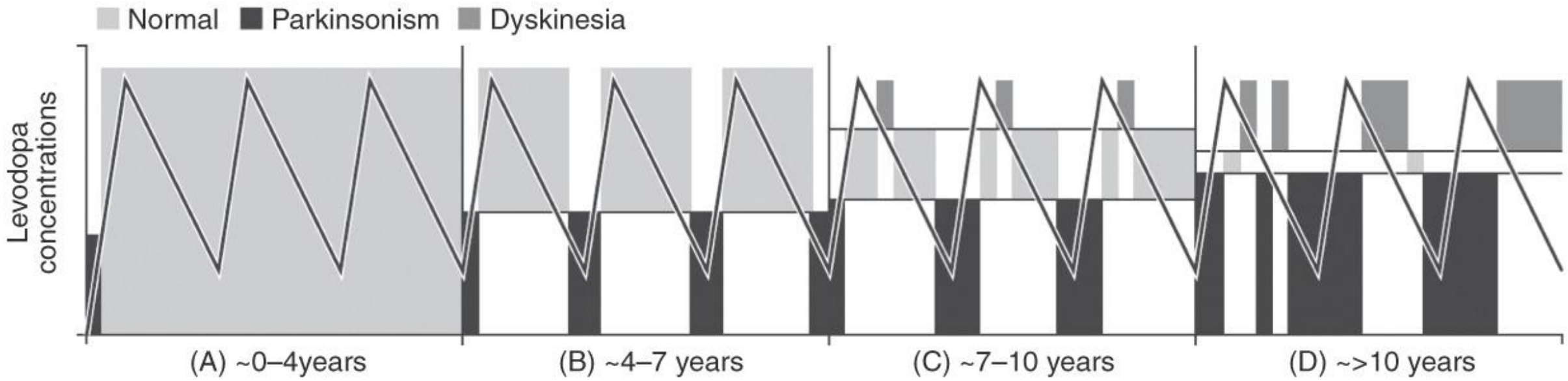
Genetic testing is currently rare in clinical practice



-Alcalay, Genetic Med (2020)

Wearing Off Symptoms

On-Off Fluctuations



- Early phase "the good years"
- Ability to store dopamine
- Threshold for morning dose only

- Wearing-off
- Short off-periods

- Wearing-off with dyskinesias
- Predictable fluctuations with peakdose dyskinesias
- Defined therapeutic window

- On-off fluctuations
- Unpredictable fluctuations
- Very narrow therapeutic window

Nyholm, Parkinsonism Relat Disord 2007

Wearing Off Symptoms

Return of Motor Symptoms:

- “Weakness”
- Tremor
- Reduced dexterity
- Impaired Gait
- Falls
- Stiffness, muscle cramps

Non-Motor Wearing Off

Return of Non-Motor Symptoms:

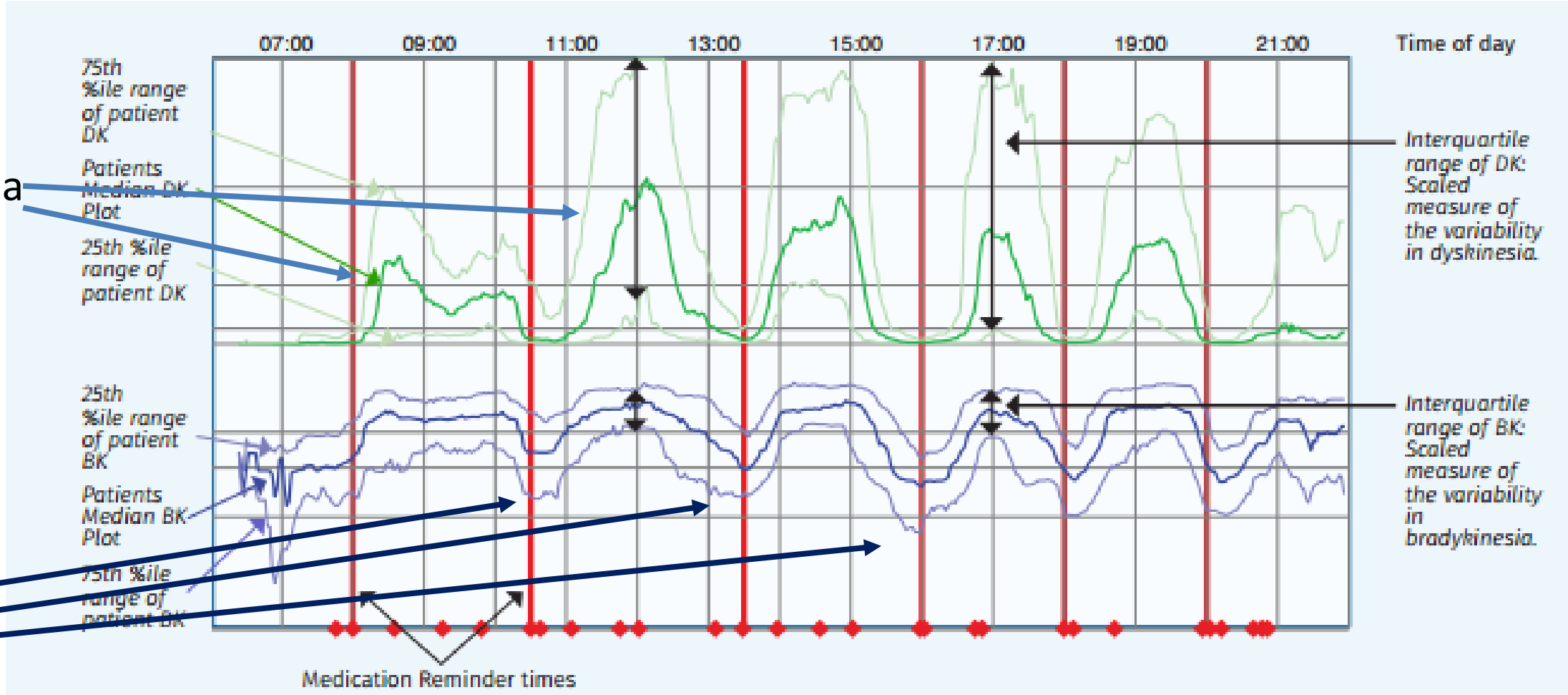
- Anxiety
- Pain/Paresthesia
- Fatigue
- Sweating/Thermal Dysregulation (heat intolerance)
- Cognitive Impairment

Wearing Off- visualized

- PKG watch:

Dyskinesia

Bradykinesia/
Wearing Off



Thank you!