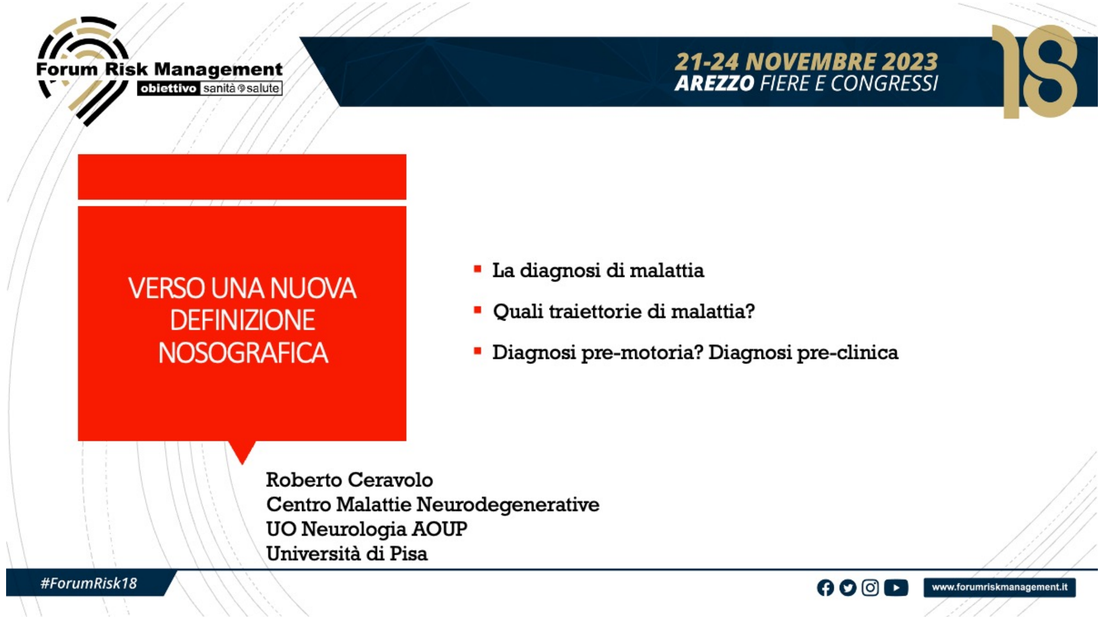


REVIEW

CME

MDS Clinical Diagnostic Criteria for Parkinson's Disease

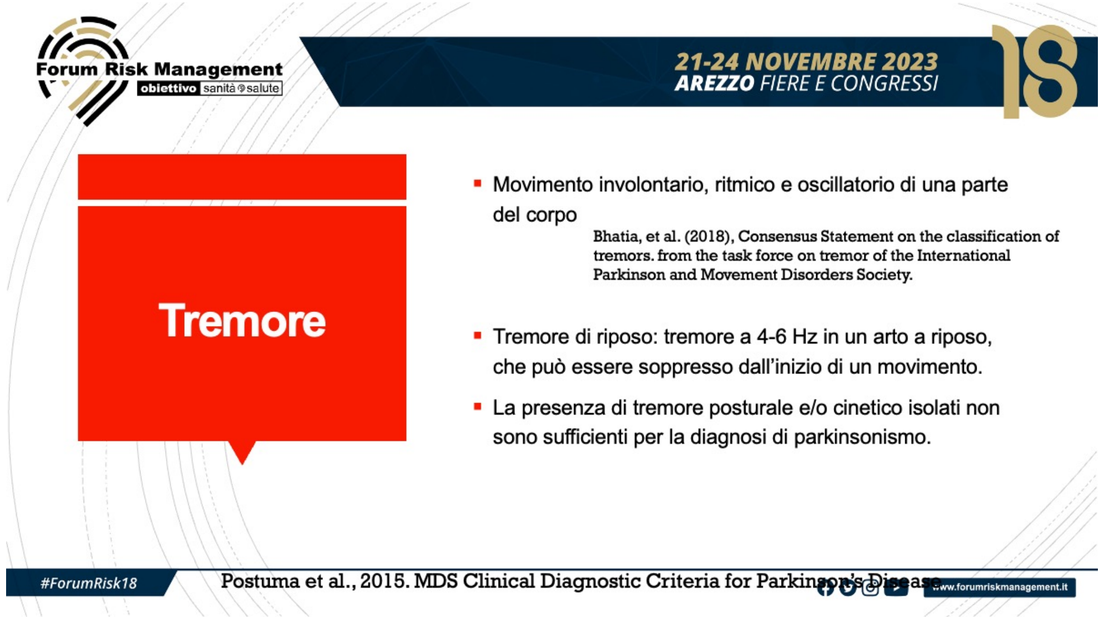
Ronald B. Postuma, MD, MSc,[1]* Daniela Berg, MD,[21]* Matthew Stern, MD,[3] Werner Poewe, MD,[4]
C. Warren Olanow, MD, FRCPC,[5] Wolfgang Oertel, MD,[6] José Obeso, MD, PhD,[7] Kenneth Marek, MD,[8] Irene Litvan, MD,[9]
Anthony E. Lang, OC, MD, FRCPC,[10] Glenda Halliday, PhD,[12] Christopher G. Goetz, MD,[13] Thomas Gasser, MD,[2]
Bruno Dubois, MD, PhD,[14] Piu Chan, MD, PhD,[15] Bastiaan R. Bloem, MD, PhD,[16] Charles H. Adler, MD, PhD,[17]
and Günther Deuschl, MD[18]

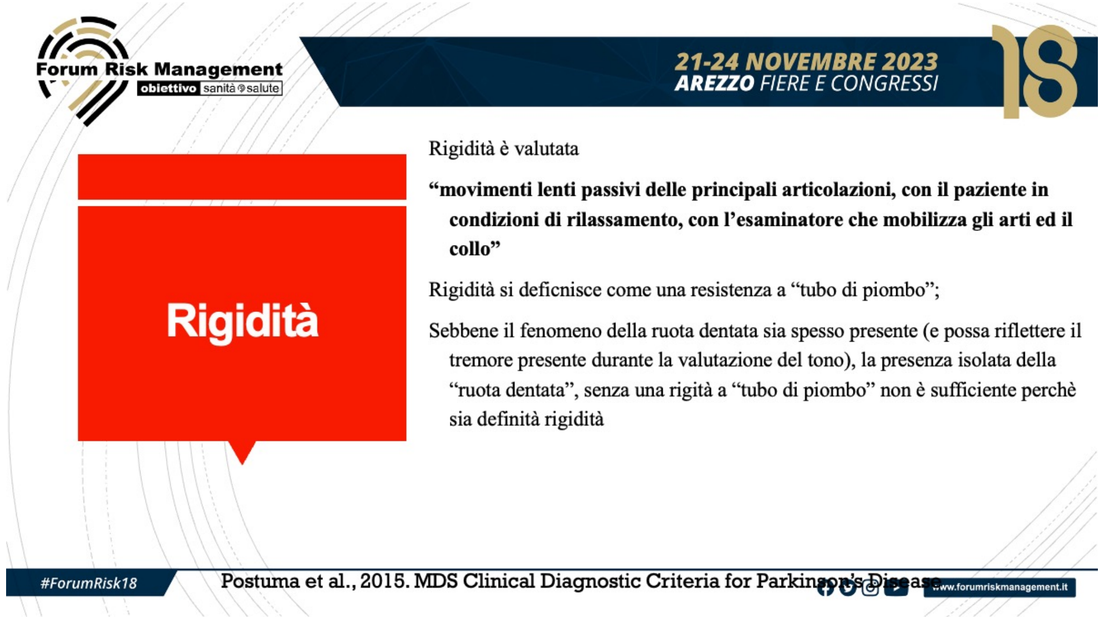
Centralità della sindrome motoria—Parkinsonismo e MP

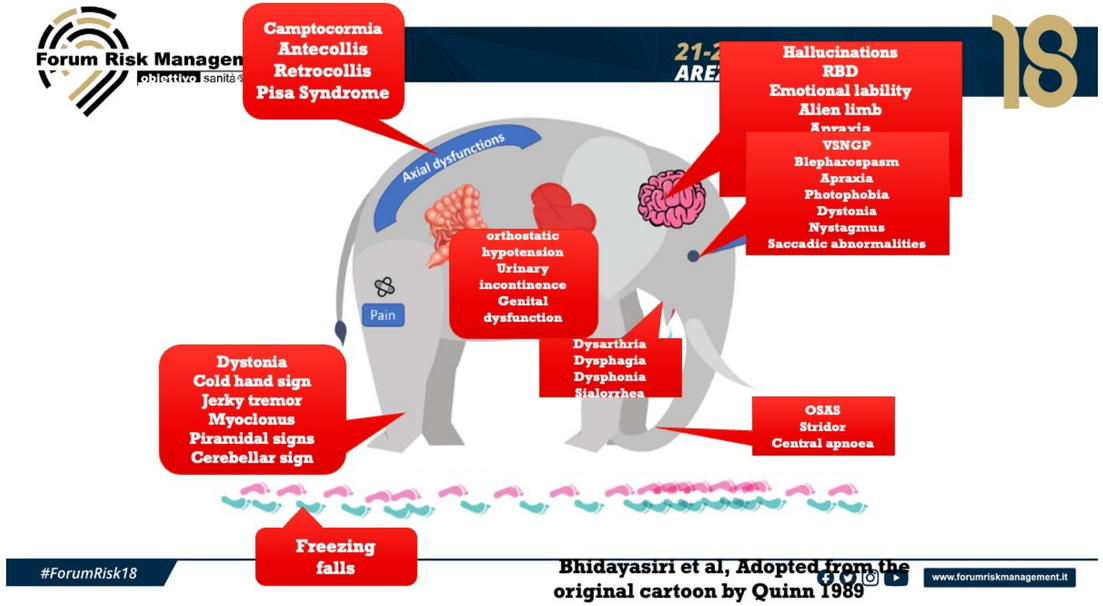
Approccio *Two step* ⊂ 1: c'è parkinsonismo?
2: è MP?

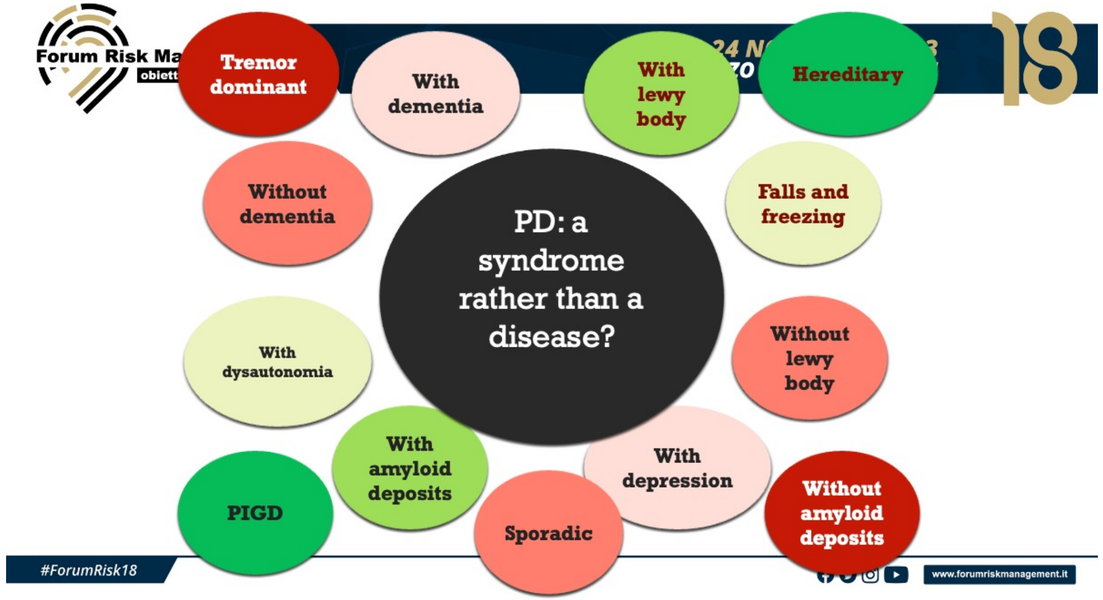
The first essential criterion is parkinsonism, which is defined as BRADYKINESIA, in combination with at least 1 of rest tremor or rigidity

Queste caratteristiche devono essere chiaramente dimostrabili e non attribuibili a fattori confondenti.
Anche se l'instabilità posturale è una possibile caratteristica del parkinsonismo, non è considerata parte dei criteri MDS per il parkinsonismo attribuibile a MP



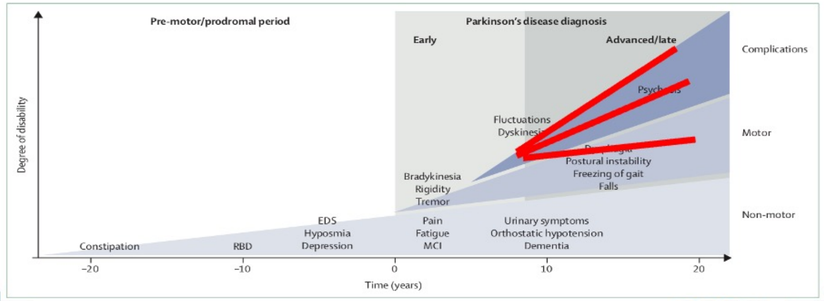






What does it matter?

CLINICAL predictors of outcome → Early detection of disease trajectories



Tremor: a marker of benign PD

OUTCOME

MORE FAVOURABLE for TD

Hoehn et al, Neurology 1967

Zetusky WJ et al, Neurology 1985

Huber SJ et al. J Neurol Neur Ps1988

Jankovic J, et al. Neurology 1990

Marttila RJ, Acta Neurol Scand 1991

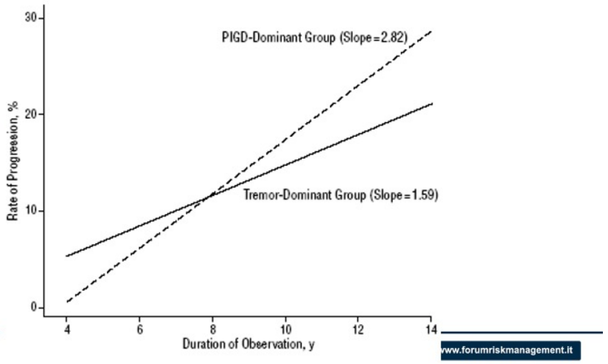
Jankovic J, Arch Neurol 2001

Marras et al Arch Neurol 2002

Alves G et al., Mov Disord 2006

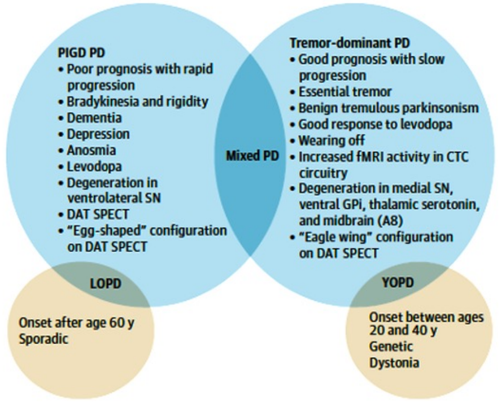
Rajput AH et al. Neurology 2009

Eggers et al, Plos One 2012



Motor Phenotypes

Postural Instability Gate Disorder (PIGD) *versus* Tremor Dominat (TD)



#ForumRisk18

Thenganatt & Jankovic, 2014

www.forumriskmanagement.it

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21-24 NOVEMBRE 2023
AREZZO FIERE E CONGRESSI
18

RESEARCH PAPER

Mild cognitive impairment and cognitive-motor relationships in newly diagnosed drug-naive patients with Parkinson's disease

Poletti 2011

18 pts PD-MCI (14.8%) *Tröster criteria , 2011*

7 pts MCI single domain

Amnesic. ***not-amnesic***

11 pts MCI multidomain

Amnesic. ***not-amnesic***

7 MCI control group (5%)

Petersen criteria, 2004

Motor phenotype and cognition

According to Jankovic's criteria

48 (39.7%) patients were classified as TR-D, 56 (46.3%) patients as PIGD-D

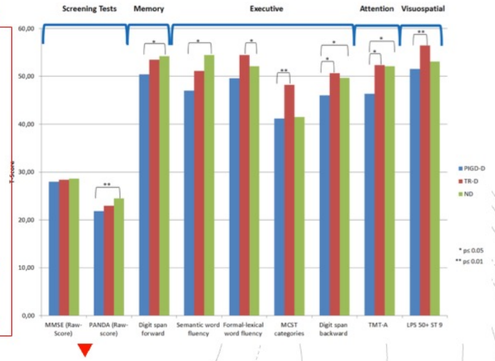
PIGD-D patients presented a higher frequency of MCI (23.2%) relative to TR-D patients (6.3%) (p<0.05).

Cognitive decline in Parkinson's disease: the impact of the motor phenotype on cognition

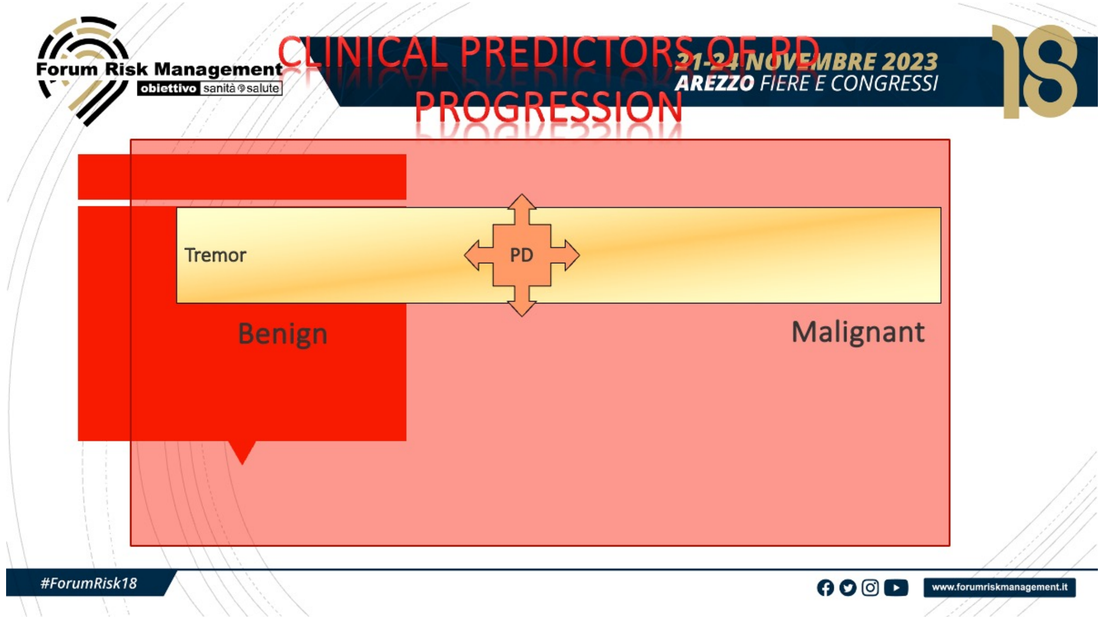
528 PD

Cognitive deficits seem to be less severe in TD PD

AR PD patients showed greater cognitive decline in executive function, as well as attention/speed of processing and verbal fluency



Wojtala J et al JNNP 2018



Clinical predictors of worse outcome

REVIEW

Orthostatic hypotension and REM sleep behaviour disorder: impact on clinical outcomes in α-synucleinopathies

Andrea Pilotto,[1,2] Alberto Romagnolo,[3] Jasmine A Tuazon,[4,5] Joaquin A Vizcarra,[4] Luca Marsili,[4] Maurizio Zibetti,[3] Michela Rosso,[6] Federico Rodriguez-Porcel,[4,7] Barbara Borroni,[1] Maria Cristina Rizzetti,[2] Carlo Rossi,[8] Darwin Vizcarra-Escobar,[9] Jennifer R Molano,[10] Leonardo Lopiano,[3] Roberto Ceravolo,[11] Mario Masellis,[12] Alberto J Espay,[4] Alessandro Padovani,[1] Aristide Merola[4]

JNNP 2019

Objective Review the effect of orthostatic hypotension (OH) and rapid-eye-movement sleep behavioural disorder (RBD) on survival, cognitive impairment and postural stability, and discuss pathogenic mechanisms involved in the association of these two common non-motor features with relevant clinical outcomes in α-synucleinopathies.

Methods We searched PubMed (January 2007–February 2018) for human studies of OH and RBD evaluating cognitive impairment, postural instability, and survival in Parkinson's disease (PD), dementia with Lewy bodies (DLB), multiple system atrophy (MSA) and pure autonomic failure (PAF). Included studies were analysed for design, key results and limitations as per the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.

Results OH and RBD showed a positive association with cognitive impairment in PD and DLB, conflicting association in PAF, and no association in MSA. OH was correlated with incident falls and postural instability in PD and DLB but not in MSA. The association between RBD and postural instability was inconclusive; positive in five studies, negative in seven. OH, but not RBD, correlated with reduced survival in PD, DLB and MSA. The combination of OH and RBD was associated with cognitive impairment and more rapid progression of postural instability.

Conclusions OH and RBD yielded individual and combined negative effects on disability in α-synucleinopathies, reflecting a 'malignant' phenotype of PD with early cognitive impairment and postural instability. Underlying mechanisms may include involvement of selected brainstem cholinergic and noradrenergic nuclei.

Dysautonomia and REM sleep behavior disorder contributions to progression of Parkinson's disease phenotypes

Giulietta Maria Riboldi[1], Marco J. Russo[1], Ling Pan[2], Kristen Watkins[3] and Un Jung Kang[1,4✉]

Non-motor symptoms of Parkinson's disease (PD) such as dysautonomia and REM sleep behavior disorder (RBD) are recognized to be important prodromal symptoms that may also indicate clinical subtypes of PD with different pathogenesis. Unbiased clustering analyses showed that subjects with dysautonomia and RBD symptoms, as well as early cognitive dysfunction, have faster progression of the disease. Through analysis of the Parkinson's Progression Markers Initiative (PPMI) de novo PD cohort, we tested the hypothesis that symptoms of dysautonomia and RBD, which are readily assessed by standard questionnaires in an ambulatory care setting, may help to independently prognosticate disease progression. Although these two symptoms associate closely, dysautonomia symptoms predict severe progression of motor and non-motor symptoms better than RBD symptoms across the 3-year follow-up period. Autonomic system involvement has not received as much attention and may be important to consider for stratification of subjects for clinical trials and for counseling patients.

npj Parkinson's Disease (2022)8:110; https://doi.org/10.1038/s41531-022-00373-0

Non Motor Predictors of Dementia

Neurology®

Anang et al, 2014

	All patients (N = 80)	Without dementia (n = 53)	With dementia (n = 27)	Odds ratio (90% CI)	*p* Value
RBD, %	59	40	96	49.7 (7.4-333.5)	0.001
% Tonic REM	43.1 (34.0)	30.6 (30.3)	68.0 (27.0)	1.04 (1.02-1.05)	0.001
% Phasic REM	26.0 (19.3)	22.9 (18.0)	32.1 (20.6)	1.03 (1.00-1.05)	0.053
Epworth score	9.4 (4.8)	9.0 (4.9)	10.2 (4.4)	1.07 (0.94-1.22)	0.364
Insomnia Severity Index	11.1 (7.2)	10.9 (7.6)	10.2 (5.8)	1.02 (0.94-1.11)	0.663
Mild cognitive impairment, %	52	32	82	18.13 (3.96-83.05)	0.002
UPDRS 1.1: cognition	0.66 (0.69)	0.46 (0.57)	0.94 (0.78)	2.57 (1.26-5.30)	0.030
Hallucinations, %	17	6	37	10.20 (2.40-44.00)	0.009
Illusions, %	21	9	40	8.20 (2.40-28.40)	0.005
UPDRS 1.2: hallucinations	0.46 (0.78)	0.31 (0.62)	0.94 (1.00)	2.44 (1.33-4.50)	0.015
UPDRS 1.3: depression	0.47 (0.70)	0.36 (0.63)	0.69 (0.79)	2.27 (1.15-4.46)	0.047
UPDRS 1.4: apathy	0.60 (0.83)	0.53 (0.81)	0.73 (0.87)	1.11 (0.66-1.88)	0.74
Orthostatic symptoms yes:no, %	56	47	70	3.16 (1.60-6.51)	0.008
Orthostatic symptoms UMSARS score	0.79 (0.81)	0.58 (0.67)	1.24 (0.91)	2.69 (1.37-5.29)	0.016
Systolic BP, mm Hg	136 (19)	132.1 (18.0)	142.23 (18.95)	1.38 (1.10-1.70)	0.032
Systolic BP drop, mm Hg[a]	15 (17)	8.6 (14.2)	26.77 (16.80)	1.84 (1.40-3.30)	<0.001
Systolic BP drop ≥10 mm Hg, %[a]	60	47	82	7.30 (2.50-21.30)	0.002
Systolic BP drop ≥20 mm Hg, %[a]	39	26	63	4.80 (2.00-11.40)	0.003
Color vision, F-M 100 error score	172 (97)	147.3 (74.4)	236.7 (126.1)	1.01 (1.00-1.02)	0.016
Color vision, % expected values	136 (70)	128.5 (64.3)	176.39 (85.5)	3.32 (1.49-7.38)	0.014
Olfaction, UPSIT-40	18 (7.0)	19.4 (6.4)	15.4 (5.8)	0.94 (0.87-1.03)	0.26
Olfaction, UPSIT-40, % expected values	54.3 (20)	56.2 (18.3)	48 (17)	0.19 (0.01-3.03)	0.321

Differential impact of individual autonomic domains on clinical outcomes in Parkinson's disease

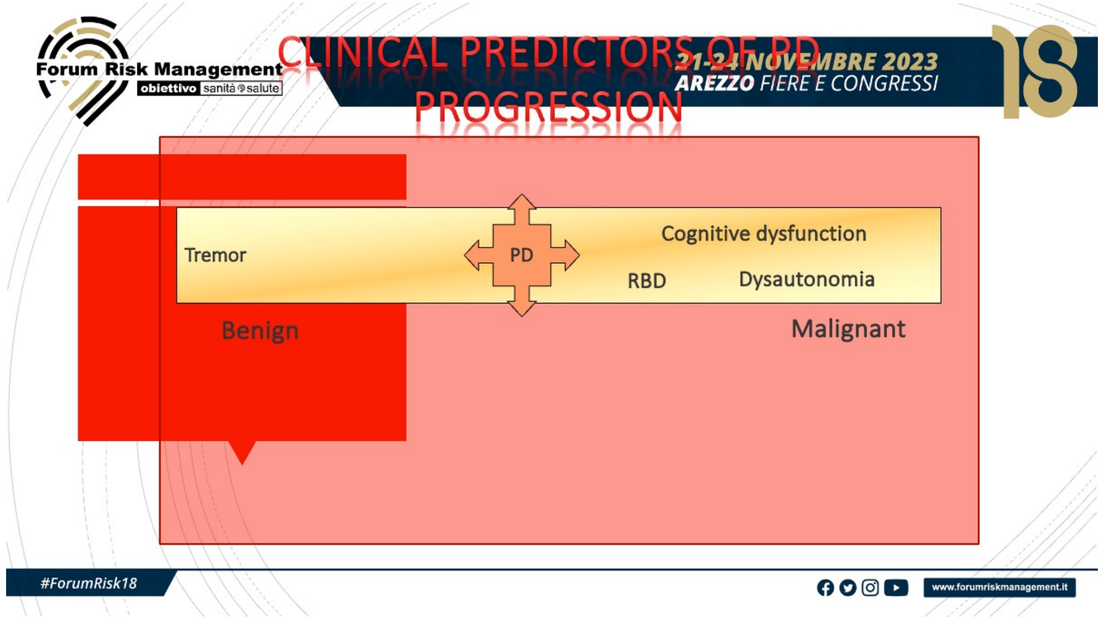
Table 3 Analysis of association between dysautonomia and disability milestones

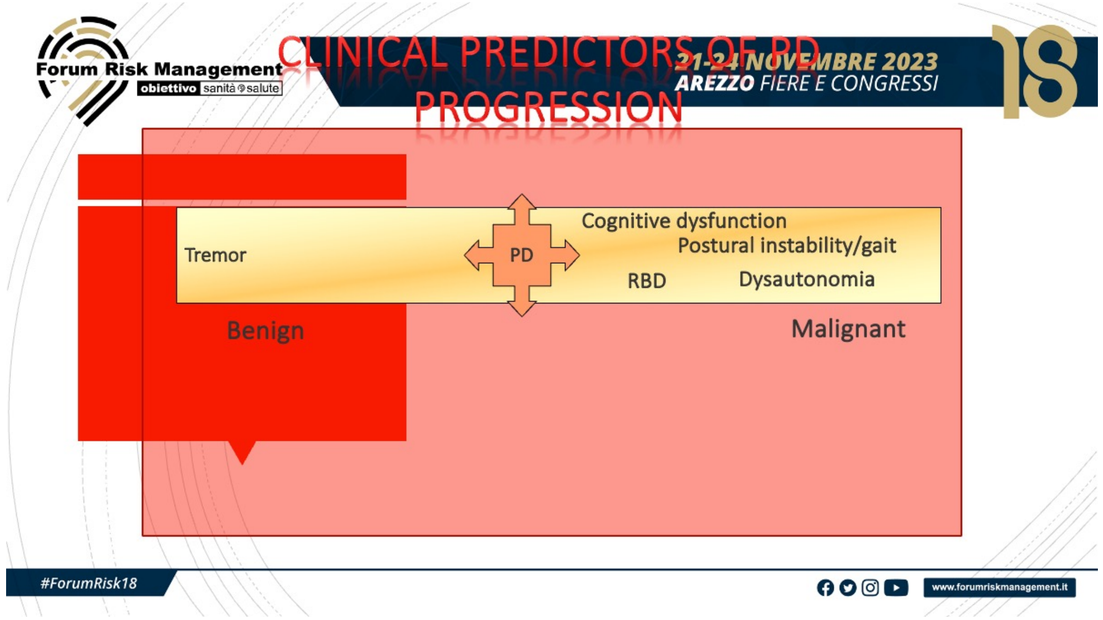
Dysautonomic features	Univariate		Multivariate	
	OR (95%CI)	*p* value	OR (95%CI)	*p* value
Dementia				
SCOPA-AUT (total score)	1.032 (0.948–1.123)	0.470	–	–
Gastrointestinal domain impairment	3.123 (0.480–20.310)	0.233	2.186 (0.221–21.603)	0.503
Urogenital domain impairment	0.541 (0.105–2.777)	0.462	0.493 (0.066–3.660)	0.489
Cardiovascular domain impairment	8.473 (1.476–48.638)	**0.017**	6.955 (1.113–43.475)	**0.038**
Thermoregulatory domain impairment	3.843 (0.699–12.089)	0.131	2.055 (0.324–13.043)	0.445
Pupillomotor domain impairment	1.327 (0.231–7.634)	0.751	0.988 (0.115–8.488)	0.991
After removing patients with dementia at baseline				
SCOPA-AUT (total score)	1.032 (0.946–1.126)	0.478	–	–
Gastrointestinal domain impairment	2.409 (0.382–15.211)	0.350	1.424 (0.138–14.739)	0.767
Urogenital domain impairment	0.414 (0.077–2.220)	0.303	0.383 (0.049–2.973)	0.359
Cardiovascular domain impairment	9.058 (1.548–53.000)	**0.014**	7.630 (1.154–50.436)	**0.035**
Thermoregulatory domain impairment	4.389 (0.822–19.834)	0.091	2.281 (0.286–18.164)	0.436
Pupillomotor domain impairment	1.599 (0.279–9.179)	0.599	1.190 (0.137–10.370)	0.875
Falls				
SCOPA-AUT (total score)	1.011 (0.932–1.096)	0.790	–	–
Gastrointestinal domain impairment	2.028 (0.489–8.401)	0.330	1.417 (0.278–7.232)	0.675
Urogenital domain impairment	1.255 (0.310–5.084)	0.750	1.196 (0.250–5.712)	0.823
Cardiovascular domain impairment	5.701 (1.099–18.940)	**0.039**	4.294 (0.413–44.609)	0.222
Thermoregulatory domain impairment	1.672 (0.425–6.581)	0.462	1.639 (0.291–9.226)	0.575
Pupillomotor domain impairment	0.328 (0.268–1.588)	0.266	0.290 (0.051–1.656)	0.164
Dysphagia				
SCOPA-AUT (total score)	1.069 (0.953–1.199)	0.253	–	–
Gastrointestinal domain impairment	10.093 (0.641–58.872)	0.100	13.352 (0.793–65.771)	0.072
Urogenital domain impairment	1.025 (0.257–3.622)	0.539	0.810 (0.113–5.554)	0.755
Cardiovascular domain impairment	4.808 (0.601–38.447)	0.139	6.082 (0.546–44.745)	0.142
Thermoregulatory domain impairment	1.285 (0.246–6.700)	0.766	0.416 (0.051–3.417)	0.414
Pupillomotor domain impairment	0.626 (0.070–5.626)	0.676	0.757 (0.047–12.092)	0.844
Dysarthria				
SCOPA-AUT (total score)	1.080 (0.996–1.170)	0.061	–	–
Gastrointestinal domain impairment	4.375 (0.874–21.904)	0.073	3.160 (0.552–18.082)	0.196
Urogenital domain impairment	2.883 (0.640–9.990)	0.168	2.898 (0.539–15.588)	0.215
Cardiovascular domain impairment	2.980 (0.680–13.053)	0.147	2.226 (0.453–10.933)	0.325
Thermoregulatory domain impairment	1.599 (0.463–5.520)	0.457	1.310 (0.280–6.129)	0.732
Pupillomotor domain impairment	1.121 (0.250–5.026)	0.882	1.248 (0.224–6.943)	0.800
Postural instability				
SCOPA-AUT (total score)	1.040 (0.961–1.126)	0.326	–	–
Gastrointestinal domain impairment	1.853 (0.470–7.298)	0.378	1.204 (0.259–5.602)	0.813
Urogenital domain impairment	1.268 (0.331–4.851)	0.729	1.551 (0.345–6.968)	0.567
Cardiovascular domain impairment	2.928 (0.513–16.727)	0.227	2.181 (0.358–13.306)	0.398
Thermoregulatory domain impairment	2.462 (0.661–9.174)	0.179	2.331 (0.492–11.055)	0.286
Pupillomotor domain impairment	1.112 (0.252–4.908)	0.888	0.955 (0.191–4.782)	0.955

65 consecutive PD
5-year cohort study

Cardiovascular dysautonomia was associated with a ***sevenfold*** higher risk of developing ***dementia*** and fivefold higher risk of falls

Longardner K…Romagnolo A, J Neurol 2022

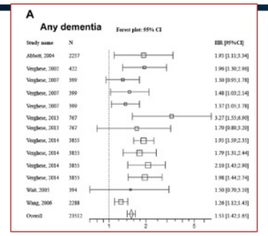


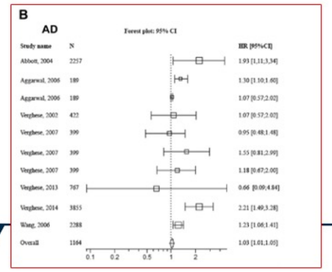


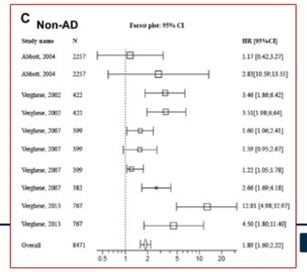
Review Article

Poor Gait Performance and Prediction of Dementia: Results From a Meta-Analysis

Beauchet O et al, 2016

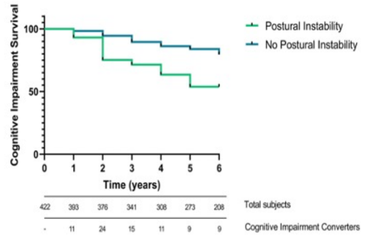






Disentangling the PIGD classification for the prediction of cognitive impairment in de novo Parkinson's disease

	TD (n = 299)	PIGD (n = 76)	p value
Demographic variables			
Age	61.89 ± 9.47	61.91 ± 9.23	0.988
Sex (male %)	66.6%	61.8%	0.440
Disease duration, months	6.76 ± 6.64	6.22 ± 5.48	0.841
Age of onset, years	59.75 ± 9.77	60.30 ± 9.54	0.572
Age of diagnosis, years	61.33 ± 9.44	61.40 ± 9.22	0.958
Clinical variables			
MDS-UPDRS Part I	5.17 ± 3.80	6.93 ± 4.75	**0.008***
MDS-UPDRS Part II	5.27 ± 3.88	7.42 ± 4.57	**0.00082***
MDS-UPDRS Part III	21.14 ± 9.042	21.00 ± 8.38	0.728
H&Y stage 1, 2, and 3 (%)	46.5, 53.5, 0	39.5, 57.9, 2.6	**0.0234***
UPSIT	22.16 ± 7.86	22.50 ± 9.43	0.782
SCOPA-AUT	9.31 ± 6.315	9.59 ± 5.48	0.565
RBDSQ	4.02 ± 2.64	4.46 ± 2.94	0.480
STAI	63.74 ± 18.12	70.58 ± 17.49	**0.0045***
GDS	2.06 ± 2.24	3.24 ± 2.87	**0.0078***
DaTSCAN			
Mean caudate	2.01 ± 0.53	1.89 ± .63	0.067
Mean putamen	0.83 ± 0.27	0.79 ± 0.32	0.063
Mean striatum	1.42 ± 0.37	1.34 ± 0.45	0.079
Neuropsychological assessment			
MoCA	27.08 ± 2.34	27.15 ± 2.43	0.799
Benton judgment of line orientation	12.76 ± 2.13	12.61 ± 2.10	0.447
Symbol digit modalities score	41.16 ± 9.83	40.58 ± 10.00	0.771
Semantic fluency total score	48.35 ± 11.43	49.46 ± 13.41	0.493
Letter number sequencing raw score	10.55 ± 2.67	10.50 ± 2.73	0.842
HVLT immediate/total recall	24.46 ± 5.09	24.20 ± 4.888	0.829
HVLT delayed recall	8.42 ± 2.48	8.03 ± 2.79	0.362
HVLT delayed recognition	11.18 ± 1.30	11.14 ± 1.05	0.399
HVLT false alarms	1.30 ± 1.41	1.04 ± 0.93	0.493
HVLT recognition discrimination	9.51 ± 2.87	10.07 ± 1.41	0.877
HVLT retention	0.86 ± .197	0.82 ± 0.23	0.206

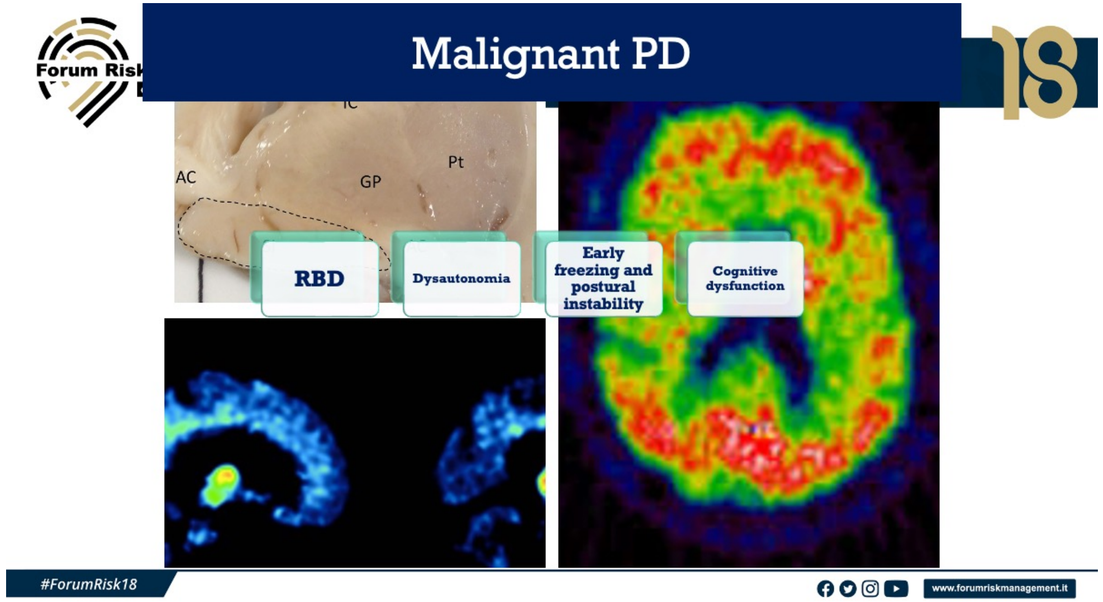


Postural instability is appropriate for the prognostication of cognitive impairment in early de novo PD pts

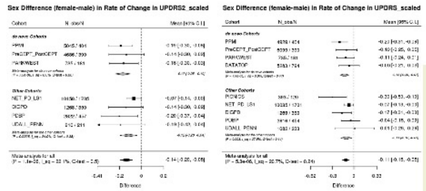
Urso D et al, 2022

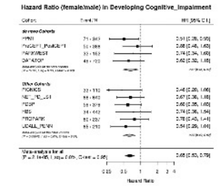
#ForumRisk18

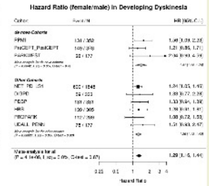
www.forumriskmanagement.it



Gender and disease phenotype





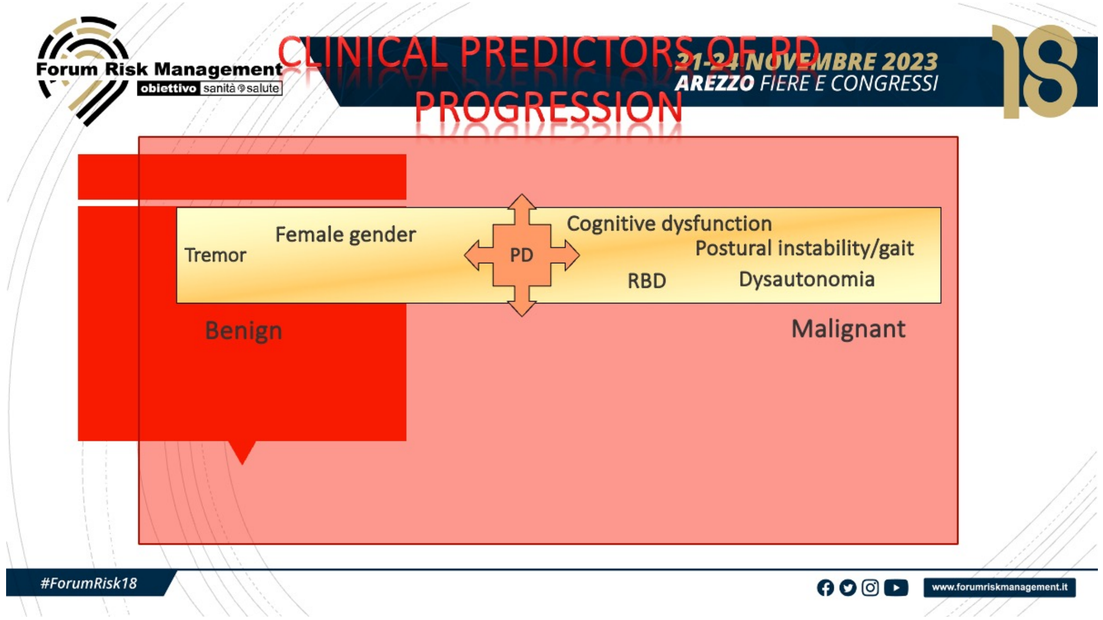


RESEARCH ARTICLE

Differences in the Presentation and Progression of Parkinson's Disease by Sex

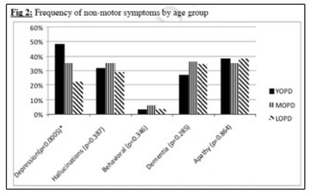
- We examined **sex associations** to PD phenotypes cross-sectionally and longitudinally in largescale Data (**5946** Patients) with a median follow-up of 3.1 years
- **Female PD** patients had a **higher risk of developing dyskinesia** early during the follow-up period
- **Female PD** patients had a **slower progression in activities of daily living difficulties**
- Female PD patients a **lower risk of developing cognitive impairments** compared with male patients

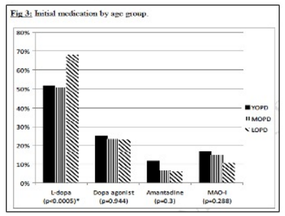
Movement Disorders, 2020

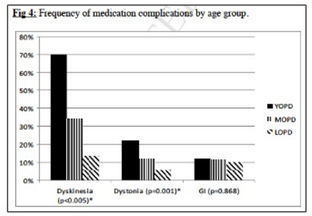


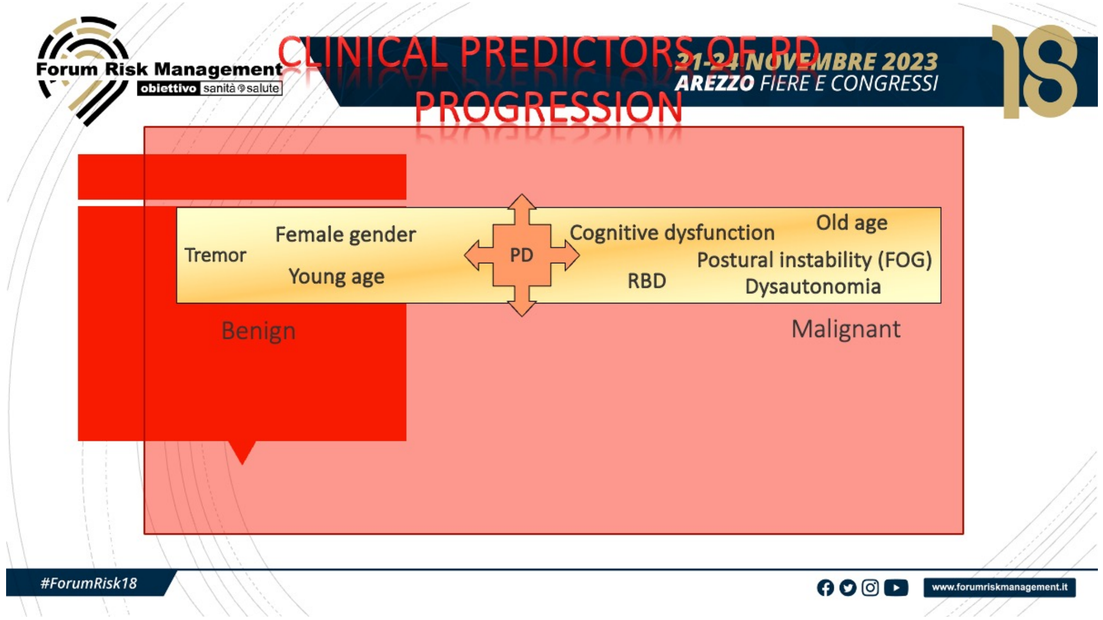
Young-onset/Early-onset PD: a distinct clinical phenotype

Mehanna et al 2013, 2022









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Genetics in PD

- In the last decades, emerging role of genetic in PD
- PD as multifactorial model
  - Role of genetic variant in sporadic PD

- Familial PD represents 10-16% of the pts
- Monogenic PD: unravelled beyond 20 genes loci (10% PD)

- Genetic role in definite population:
  - Ashkenazi Jewish: GBA, LRRK2
  - African Berbers: LRRK2
- Risk pathogenetic variants contribute to increase 'PD risk' development up to 5-6 times
  - GBA role as a 'risk factor' for PD development
  - Detected up to 90 variants associated to PD risk in GWAS studies

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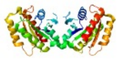
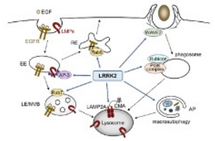
LRRK2 – PARK 8 (12p11.2-q13.1)

- Large gene, 51 exons, over 100 mutations



- Most frequent AD PD
  - -both familial and sporadic cases
- p.G2019S frequently expressed in Ashkenazi e Berbers (up to 40%)
- p.R1441G frequent in Basque Country
- Caucasian: 5-8 % familial PD, 0,5-2% sporadic PD
- Incomplete penetrance, increasing with age
- Similar to iPD
- More prevalent PIGD phenotype
- Good levodopa response
- LIDs risk
- Lower behavioral impairment



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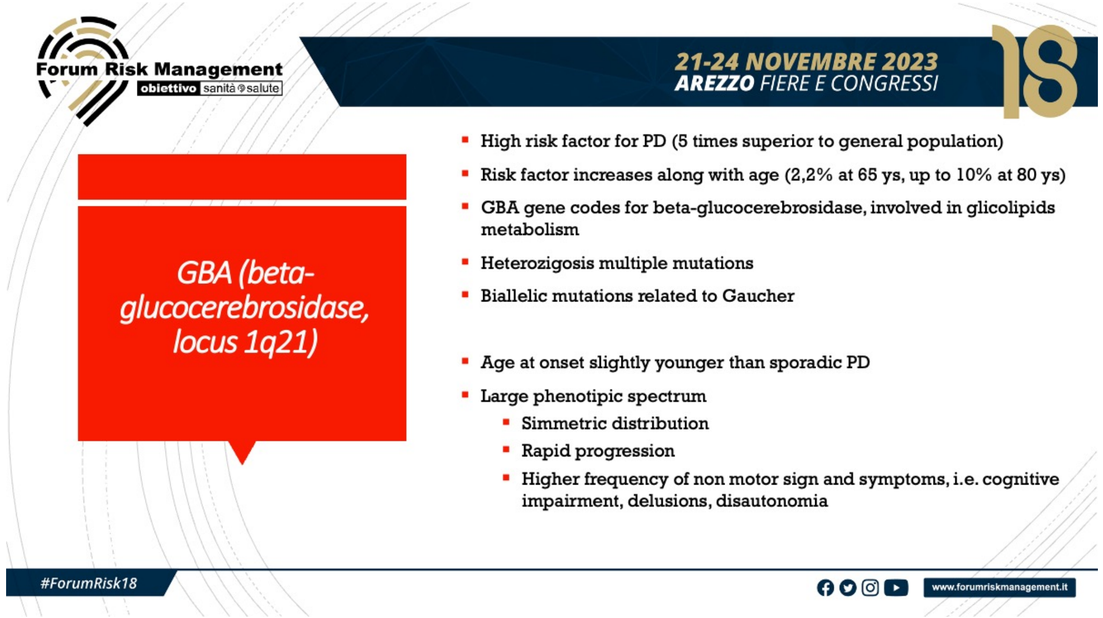

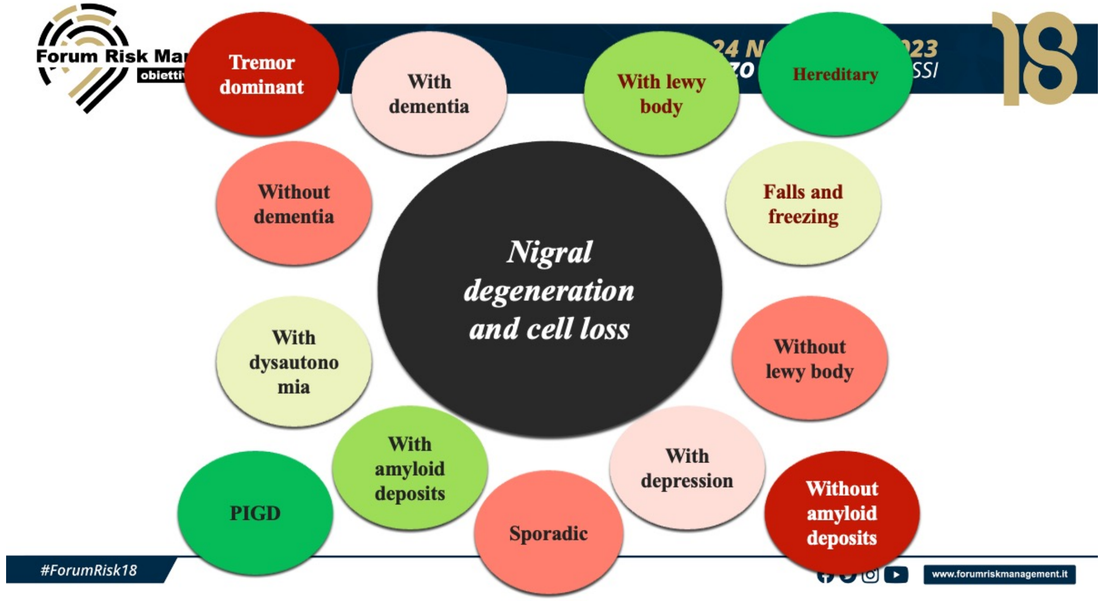

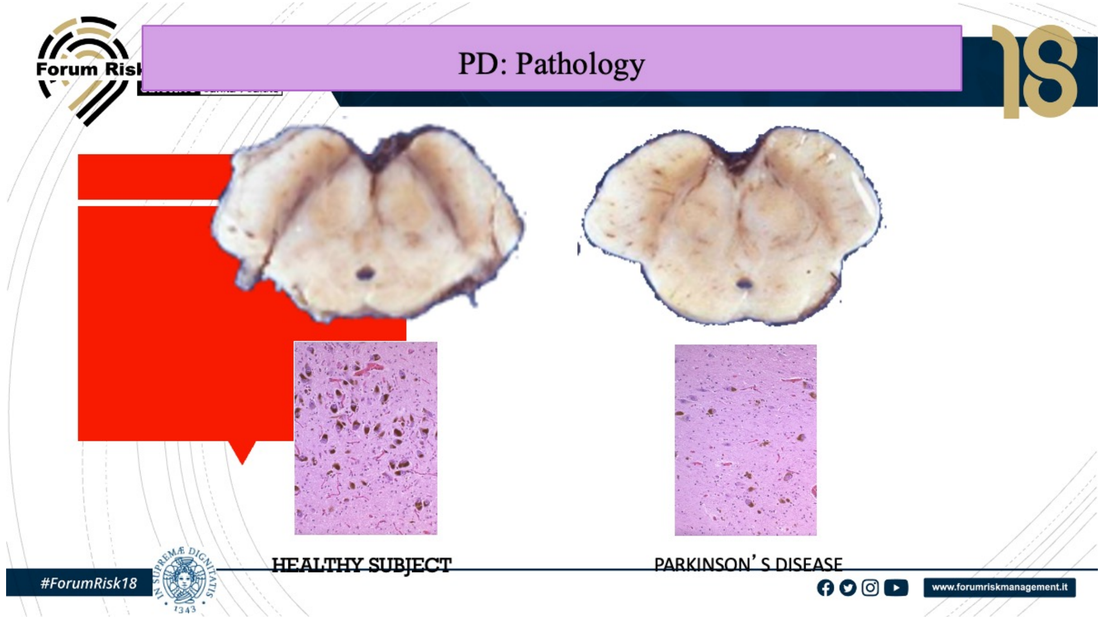

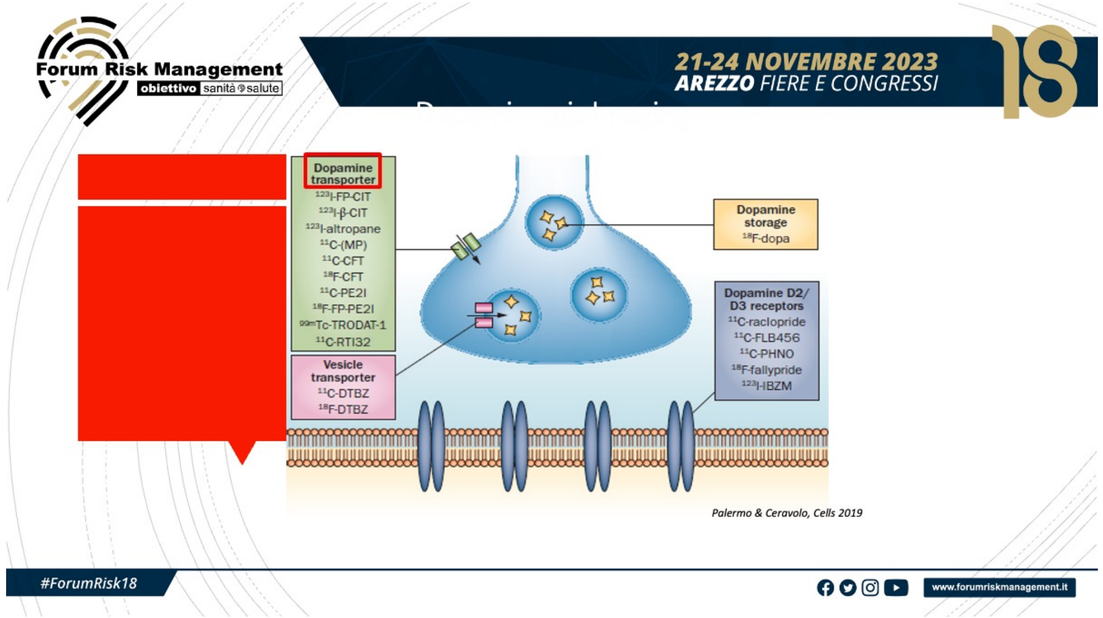

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Imaging dopamine terminal function
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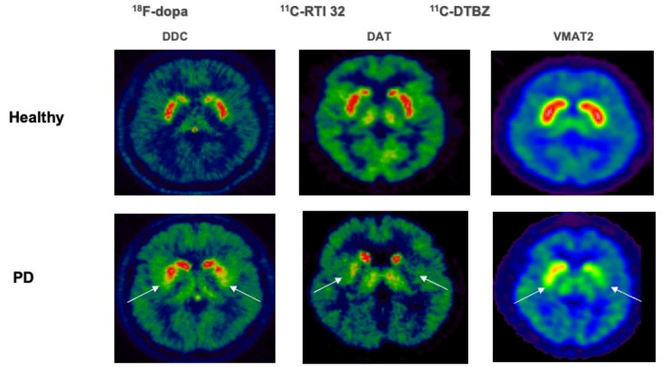

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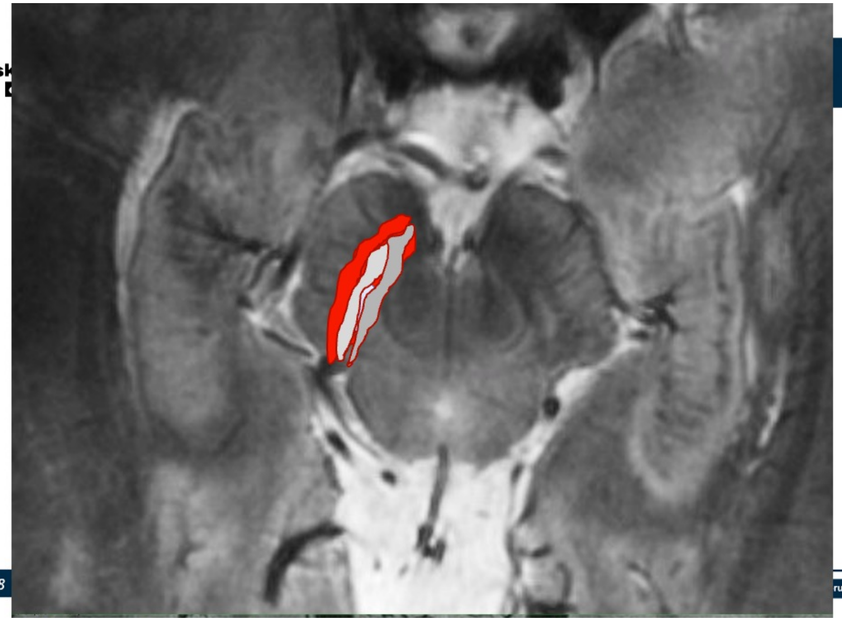

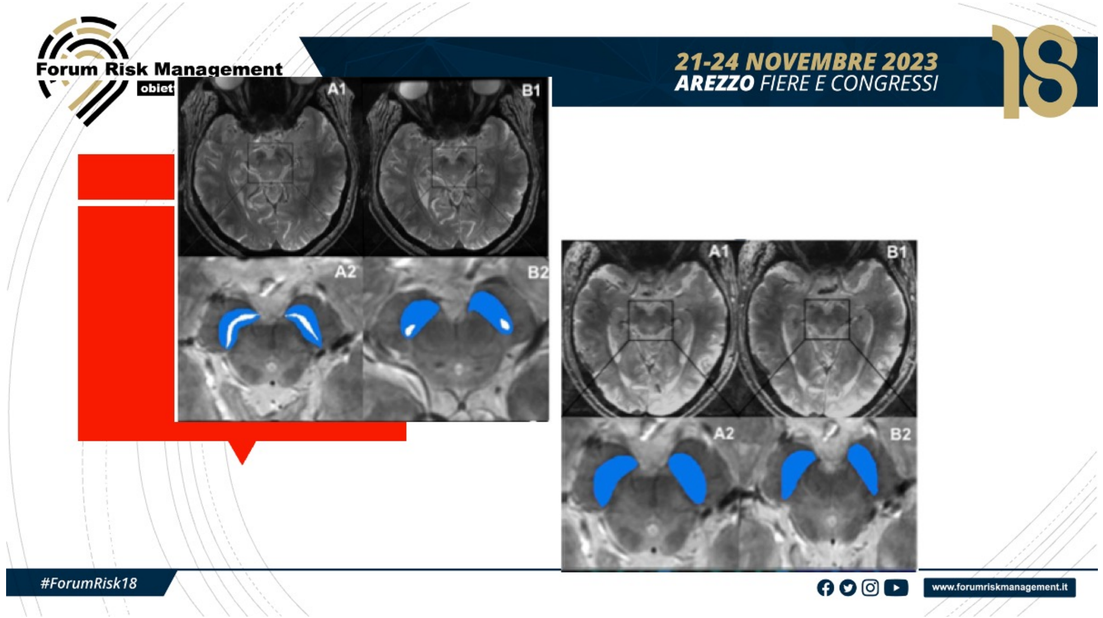

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Neurodegeneration – α-synuclein accumulation

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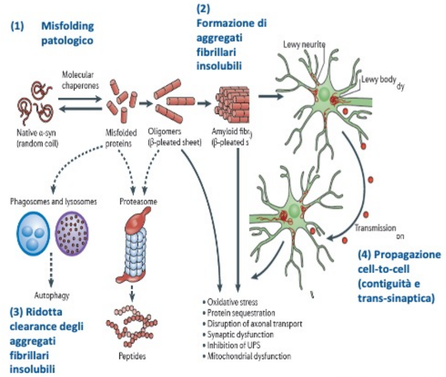

Irwin et al. *Nat Rev Neurosci* 2013

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Stages in the evolution of PD

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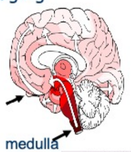
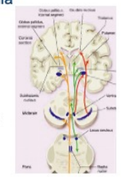
❑ Pathological staging



Parkinson's disease brain:
- dopamine
- serotonin
- norepinephrine
- acetilcholine



❑ Clinical staging

- *Stage 1*:
  - constipation (dorsal nucleus of vagus)
  - hyposmia (olfactory bulb)
- *Stage2*:
  - RBD (small pontine GABAergic nucleus)
  - depression (median raphe - locus coeruleus)
- *Stage 3*:
  - parkinsonism (midbrain)
- *Stage 4:*
  - cognitive deficits (basal forebrain)
- *Stage 5-6:* Braak et al. 2004
  - dementia (neocortex)

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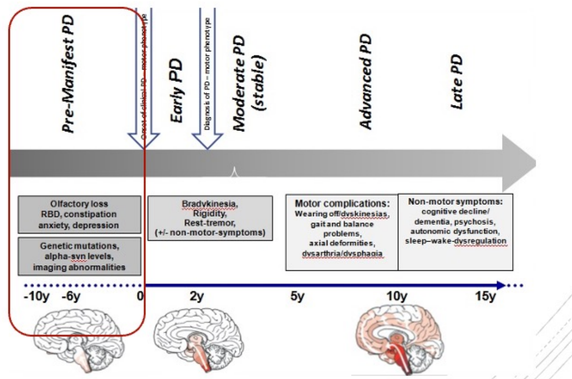
Natural history of degenerative parkinsonism

Prodromal parkinsonism and its markers: from bench to bedside



Adapted from BRAAK H et al., *Nat Rev Neurol* 2016

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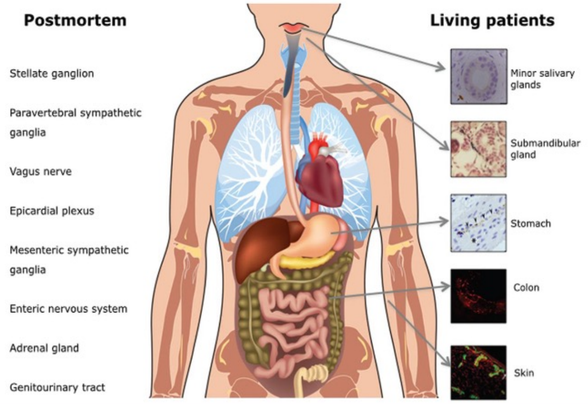
Multiorgan alpha-synuclein deposits in Parkinson's disease



Peripheral tissues

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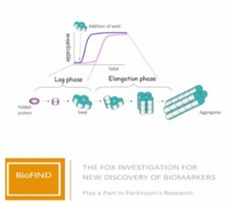
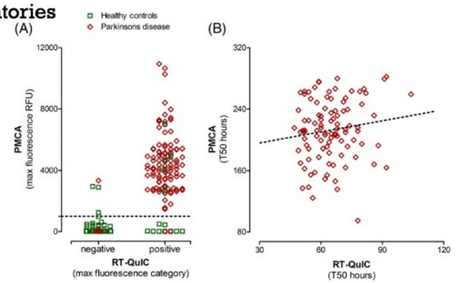
Seeding Aggregation Assays on CSF (SAA: PMCA/RT QuIC):

High sensitivity (up to 97%)
High specificity (up to 92 %)
High congruency between different laboratories





International Congress of Parkinson's Disease and Movement Disorders® August 27-31, 2023 Copenhagen DENMARK

Kang 2019, Mov Dis.

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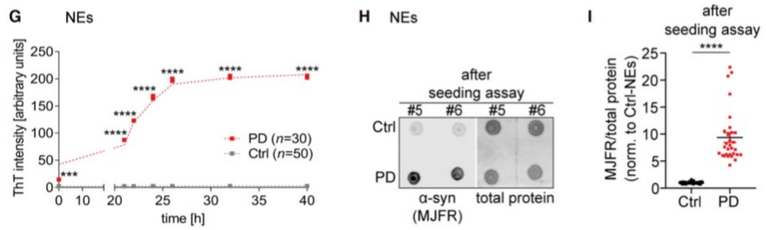
Alpha-syn SAA in peripheral blood (extracellular vesicles)



Klugge 2022

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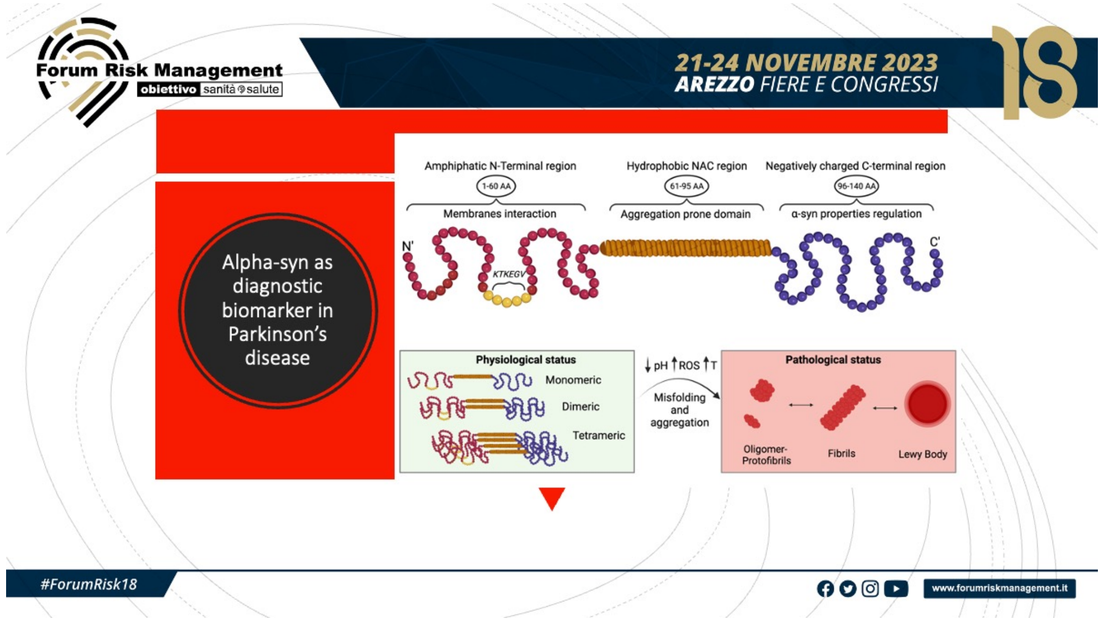

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- Messa a disposizione del pubblico, in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta, o di parte di essa (art. 171, legge n.633/1941 comma 1 lett. a) bis)
- Reati di cui al punto precedente commessi su opere altrui non destinate alla pubblicazione qualora ne risulti offeso l'onore o la reputazione (art. 171, legge n.633/1941 comma 3)
- Abusiva duplicazione, per trarne profitto, di programmi per elaboratore; importazione, distribuzione, vendita o detenzione a scopo commerciale o imprenditoriale o concessione in locazione di programmi contenuti in supporti non contrassegnati dalla SIAE; predisposizione di mezzi per rimuovere o eludere i dispositivi di protezione di programmi per elaboratori (art. 171-bis legge n.633/1941 comma 1)
- Riproduzione, trasferimento su altro supporto, distribuzione, comunicazione, presentazione o dimostrazione in pubblico, del contenuto di una banca dati; estrazione o reimpiego della banca dati; distribuzione, vendita o concessione in locazione di banche di dati (art. 171-bis legge n.633/1941 comma 2)
- Abusiva duplicazione, riproduzione, trasmissione o diffusione in pubblico con qualsiasi procedimento, in tutto o in parte, di opere dell'ingegno destinate al circuito televisivo, cinematografico, della vendita o del noleggio di dischi, nastri o supporti analoghi o ogni altro supporto contenente fonogrammi o videogrammi di opere musicali, cinematografiche o audiovisive assimilate o sequenze di immagini in movimento; opere letterarie, drammatiche, scientifiche o didattiche, musicali o drammatico musicali, multimediali, anche se inserite in opere collettive o composite o banche dati; riproduzione, duplicazione, trasmissione o diffusione abusiva, vendita o commercio, cessione a qualsiasi titolo o importazione abusiva di oltre cinquanta copie o esemplari di opere tutelate dal diritto d'autore e da diritti connessi; immissione in un sistema di reti telematiche, mediante connessioni di qualsiasi genere, di un'opera dell'ingegno protetta dal diritto d'autore, o parte di essa (art. 171-ter legge n.633/1941)
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