Primary Progressive Multiple Sclerosis – Clinical progression and biomarkers

Student: Carolina Legarda

Mentors: Dr. Michael Gurevich

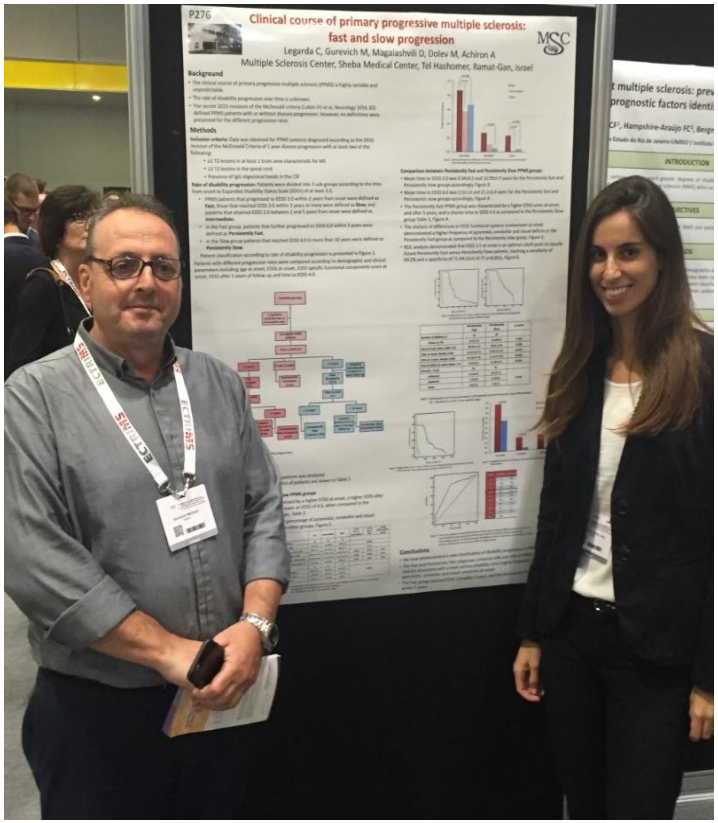
Prof. Anat Achiron

Brain lesion load and anatomic distribution in patients with juvenile clinically isolated syndrome predicts rapid conversion to multiple sclerosis

Shay Menascu, MD, Carolina Legarda, Shmuel Miron, MD, PhD, Lea Pollack, MD, Anat Achiron, MD, PhD

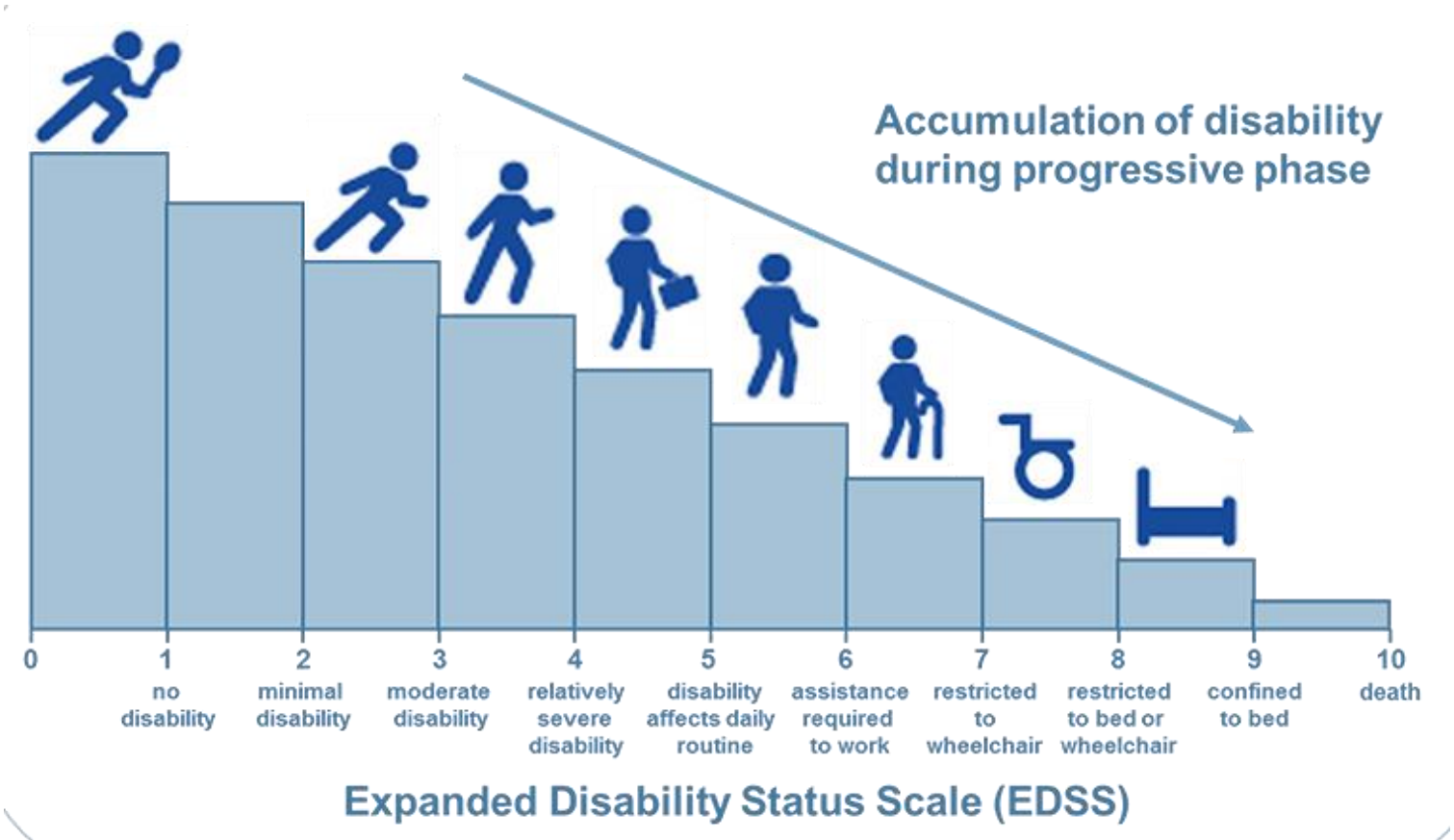
Clinical course of primary progressive multiple sclerosis: fast and slow progression

Legarda C, Gurevich M, Magalashvili D, Dolev M, Achiron A
Multiple Sclerosis Center, Sheba Medical Center, Ramat-Gan, Israel

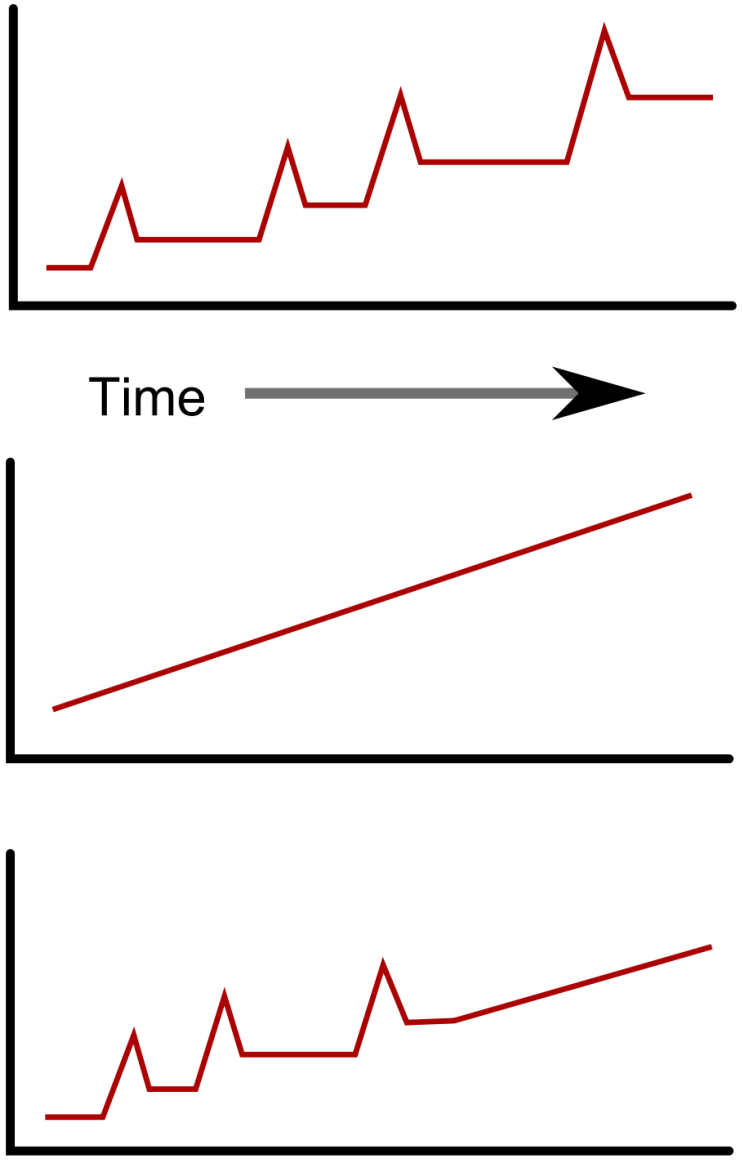


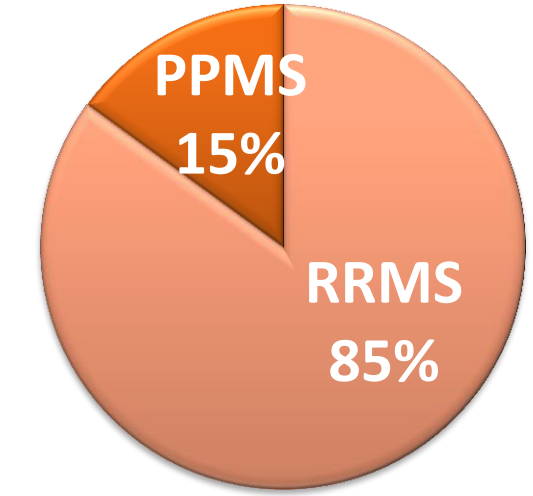
Background

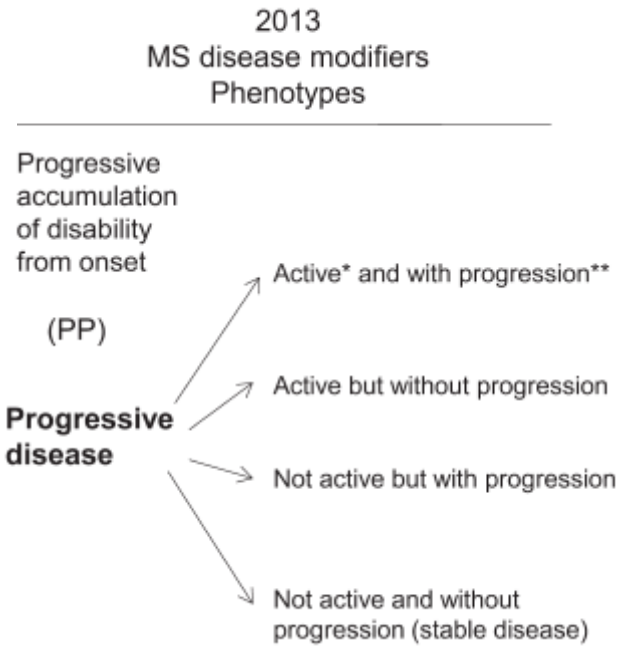
- Most frequent demyelinating disease and leading cause for permanent disability in young adults
- 2.5 million people are affected
- Onset and clinical course are unpredictable
- Disability is measured with EDSS



What is PPMS?

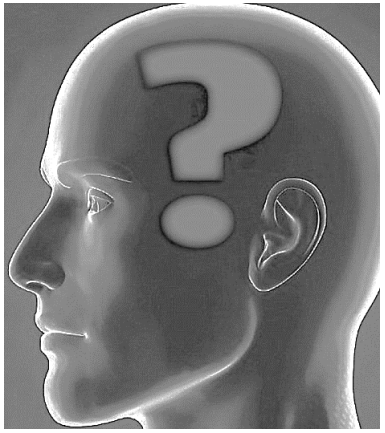

Time

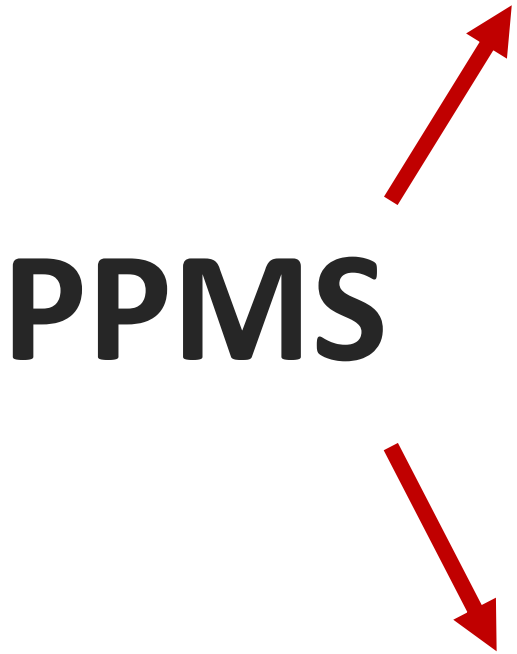

PPMS
15%
RRMS
85%


2013
MS disease modifiers
Phenotypes
Progressive accumulation of disability from onset
(PP)
Progressive disease
Active* and with progression**
Active but without progression
Not active but with progression
Not active and without progression (stable disease)

PPMS patients are the most challenging group of MS to diagnose and treat

1. High **variability** of clinical and radiological behavior
2. **Diagnosis** is retrospective
3. No clinical or laboratory **biomarkers**





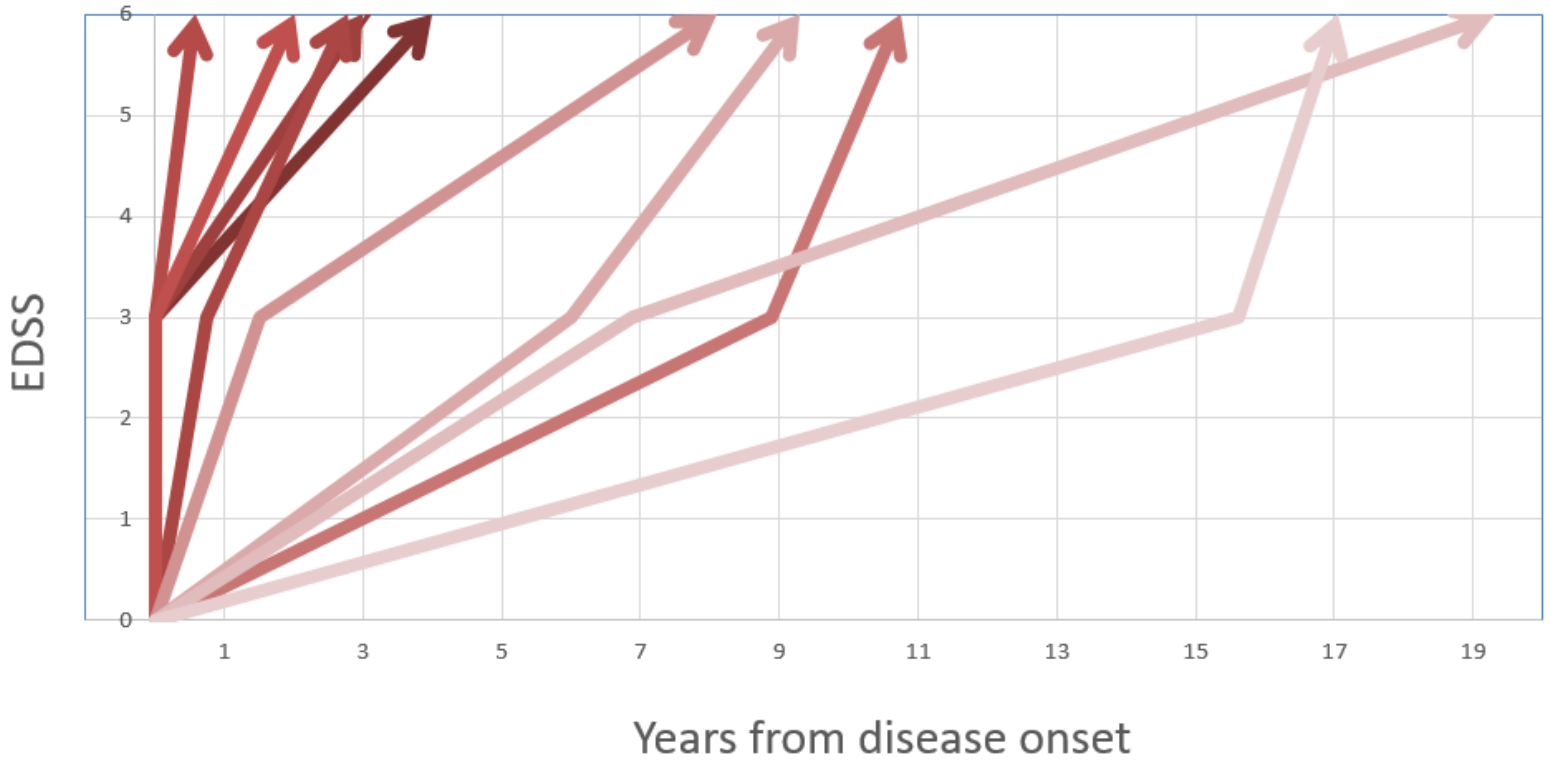
Clinical PPMS –

Variability of progression

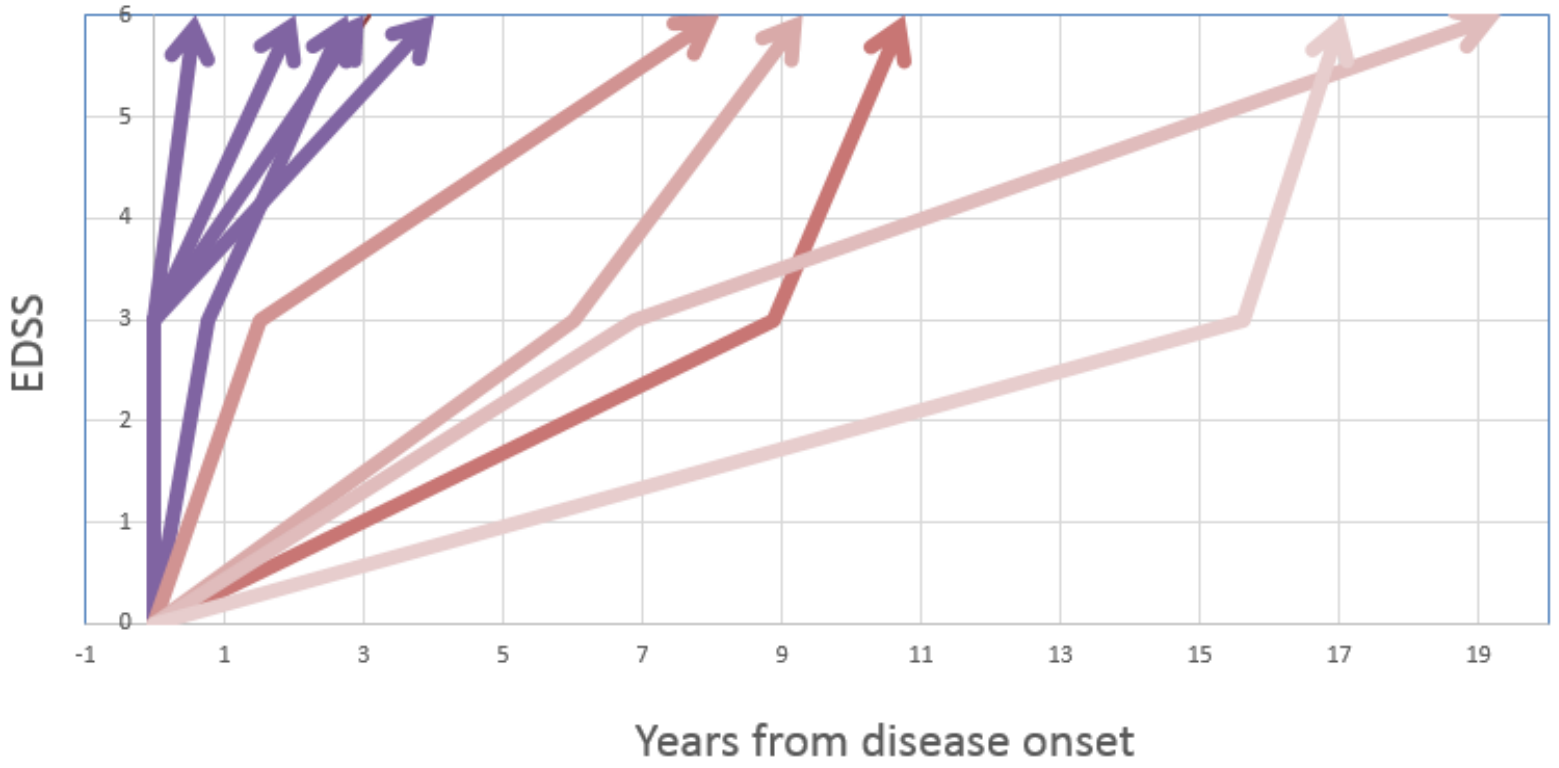
Gene expression –

PPMS biomarkers

Clinical PPMS – high variability of progression rate



Clinical PPMS – fast vs slow progression



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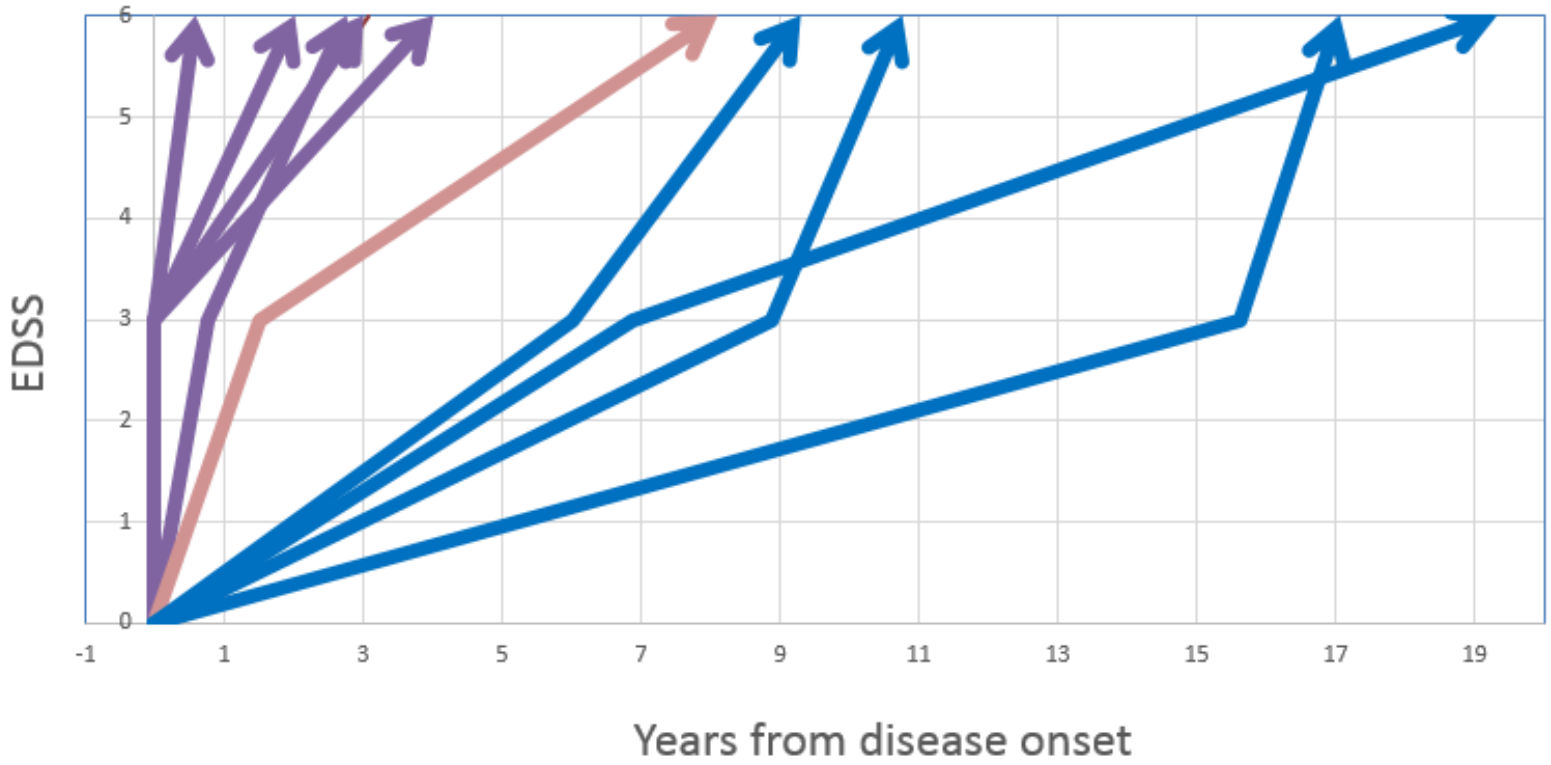


Evidence in the literature

The natural history of primary progressive multiple sclerosis

Marcus Koch, MD, PhD
Elaine Kingwell, PhD
Peter Rieckmann, MD
Helen Tremlett, PhD

Address correspondence and reprint requests to Dr. Marcus Koch, Department of Neurology, University Medical Center Groningen, Hanzeplein 1, 9713 GZ Groningen, the Netherlands
m.w.koch@neuro.umcg.nl

ABSTRACT

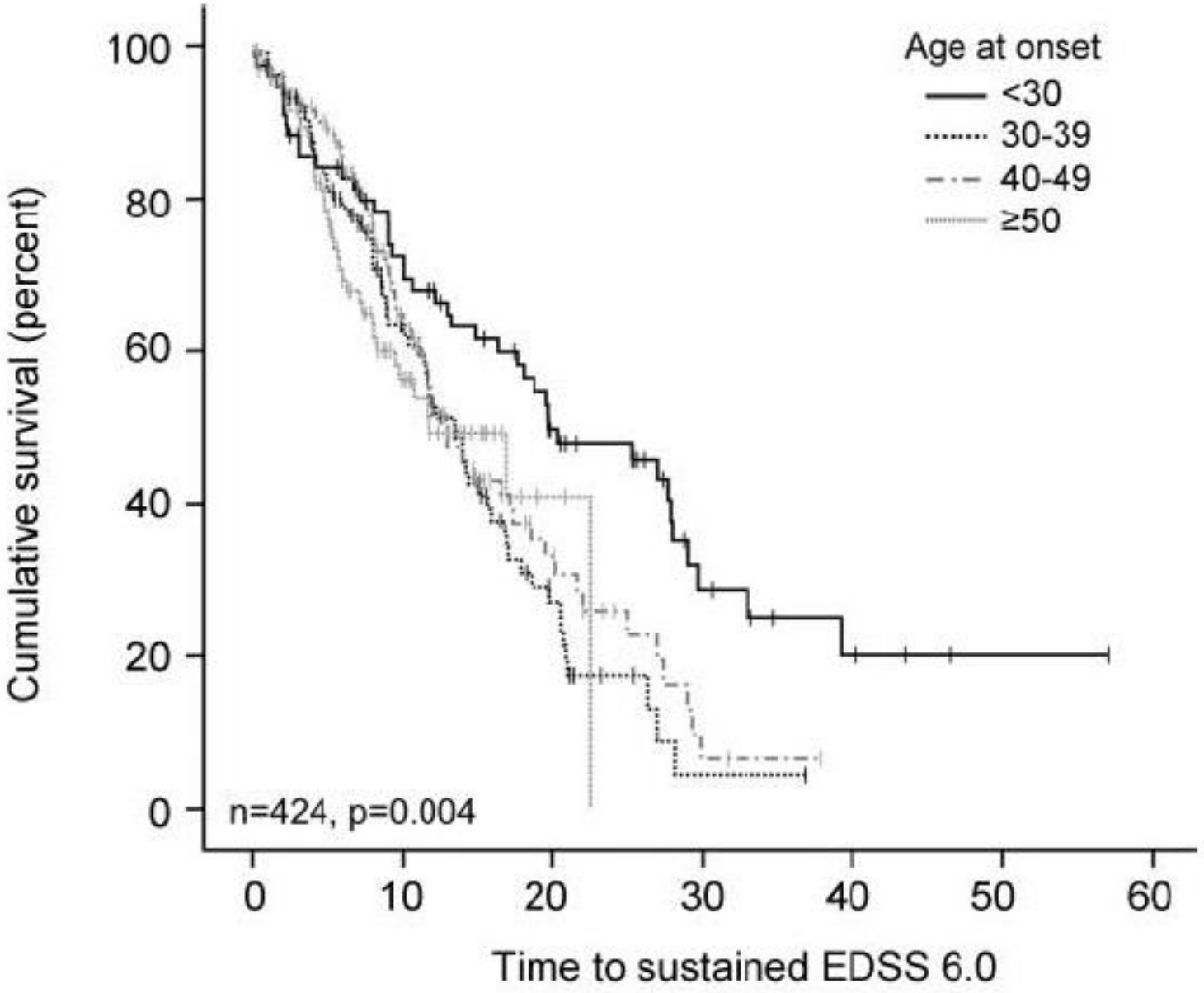
Background: Primary progressive multiple sclerosis (PPMS) carries the worst prognosis of the multiple sclerosis (MS) subtypes and is currently untreatable. A previous analysis of the British Columbia MS database challenged the view that disability progression is rapid in PPMS, but identified few predictors of disease progression. Here, we extend previous analyses in an updated PPMS retrospective cohort study of prevalent cases.

Methods: We used Kaplan-Meier survival analyses and Cox regression models to investigate the influence of gender, age at onset, and onset symptoms on time to and age at Expanded Disability Status Scale (EDSS) 6.0 in patients with PPMS.

Results: Of 5,779 patients with definite MS, 552 (10%) had PPMS. Median time to EDSS 6.0 was 14.0 years (95% confidence interval [CI] 11.3–16.7), reached at a median age of 58.6 years (95% CI 56.8–60.3). Sensory onset symptoms were associated with a longer time to and an older age at EDSS 6.0 (multivariable hazard ratios 0.55 [95% CI 0.35–0.87] and 0.54 [0.35–0.85]). Younger age at disease onset was associated with a longer time to but a younger age at EDSS 6.0. Gender and other onset symptoms were not associated with these outcomes. Fifty patients with PPMS (9%) fulfilled criteria for benign MS (EDSS ≤3.0 after 10 years' disease duration).

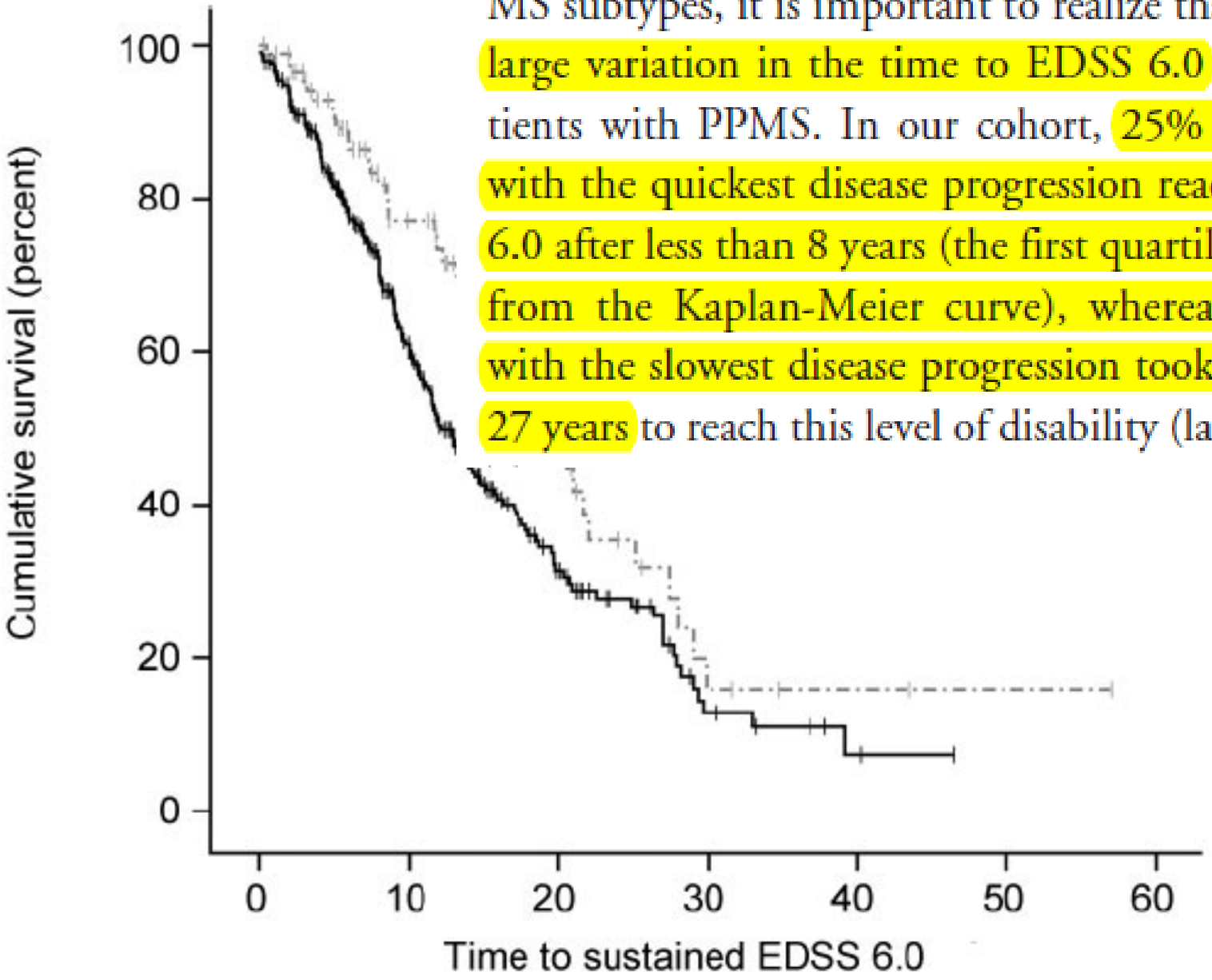
Conclusions: We identified 2 predictors of a slower disease progression in primary progressive multiple sclerosis. Sensory onset symptoms were associated with both a longer time to and a higher age at Expanded Disability Status Scale (EDSS) 6.0. A younger age at disease onset was associated with a longer time to EDSS 6.0, but patients with an early disease onset reached EDSS 6.0 at a younger age. *Neurology*® 2009;73:1996–2002

Neurology 2009



Neurology 2009

Although PPMS carries the worst prognosis of all MS subtypes, it is important to realize that there is a large variation in the time to EDSS 6.0 among patients with PPMS. In our cohort, 25% of patients with the quickest disease progression reached EDSS 6.0 after less than 8 years (the first quartile estimated from the Kaplan-Meier curve), whereas the 25% with the slowest disease progression took more than 27 years to reach this level of disability (last quartile).



Clinical course of primary progressive multiple sclerosis: fast and slow progression

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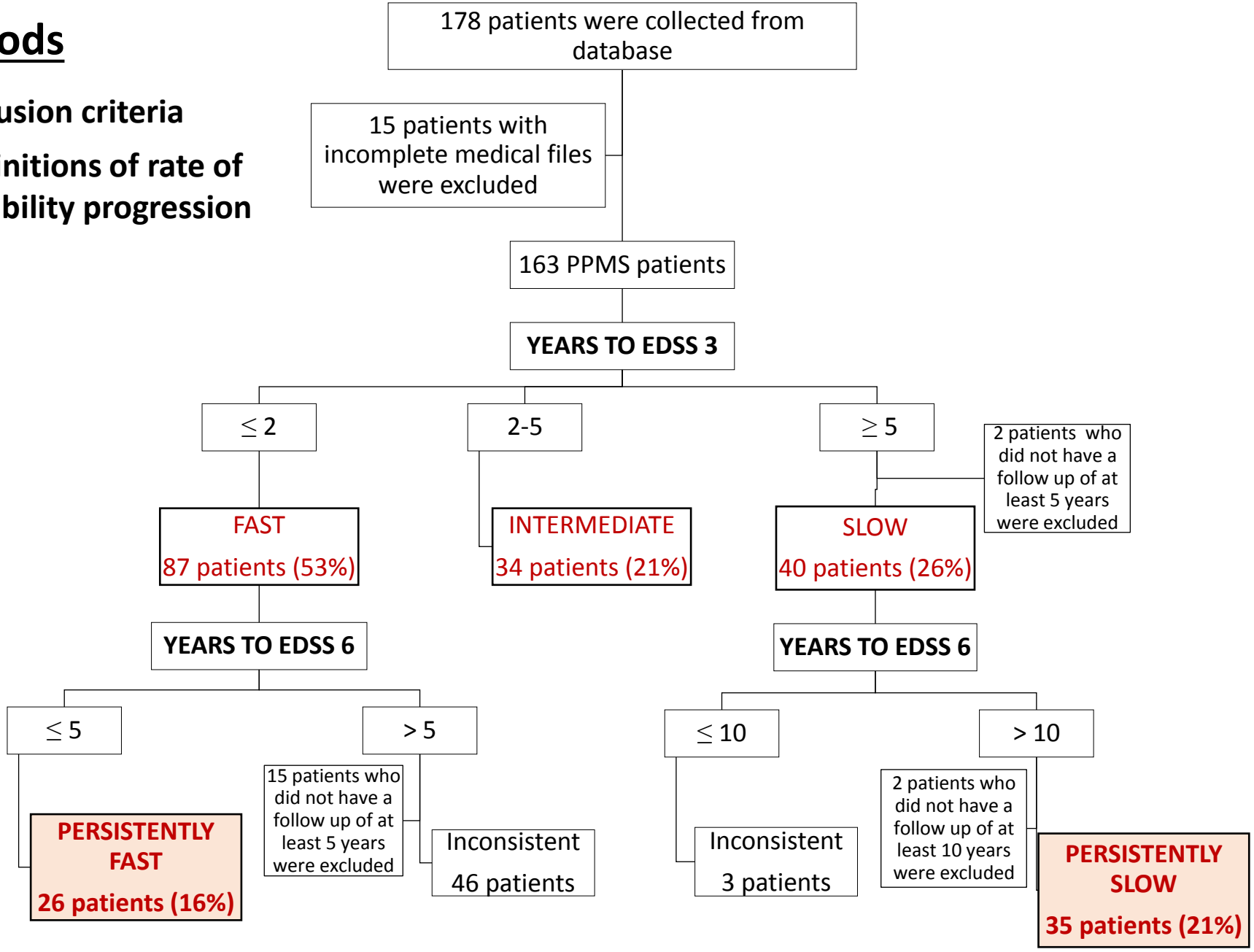
AIM:

Characterize clinical and demographical parameters that affect the variability of progression rate in PPMS

Methods

1. **Inclusion criteria**
2. **Definitions of rate of disability progression**



Methods

1. Inclusion criteria
2. Definitions of rate of disability progression

Results

	Persistently Fast	Persistently Slow	p value
Number of patients – n. (%)	26	35	0.856
Males	15 (57.7%)	21 (60.0%)	
Age at onset – mean ± SE	40.46 ±1.9	39.51 ±1.8	0.656
EDSS at onset – median (IQR)	3.0 (2.0-3.5)	2.0 (2.0-2.5)	<0.001
EDSS at 5 years – median (IQR)	6.5 (6.0-7.0)	2.5 (2.0-3.0)	<0.001
Time to EDSS 4 – mean ± SE	0.50 ±0.2	11.93 ±1.6	<0.001
Ethnicity – n. (%)	26	33	
Ashkenazi	13 (50.0%)	24 (72.7%)	0.168
Sephardic	7 (26.9%)	6 (18.2%)	
Other	6 (23.1%)	3 (9.1%)	

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Number of patients	26	35	
EDSS Functional System - n (%)			
Pyramidal	25 (96.2%)	22 (62.9%)	0.002
Cerebellar	7 (26.9%)	2 (5.7%)	0.021
Brainstem	1 (3.8%)	3 (8.6%)	0.461
Sensory	7 (26.9%)	11 (31.4%)	0.703
Urinary	1 (3.8%)	2 (5.7%)	0.739
Vision	8 (30.8%)	1 (2.9%)	0.002

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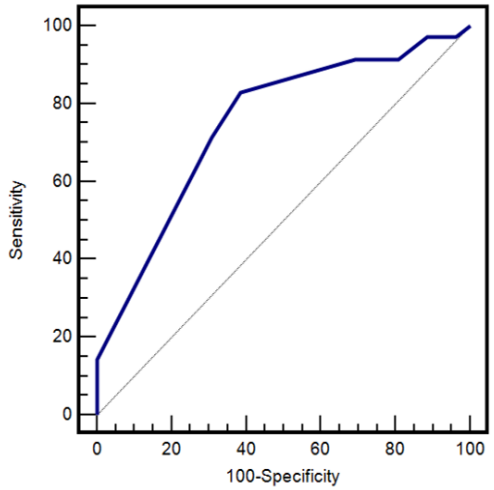

EDSS	Sensitivity	Specificity
1	0	100
1.5	14.3	100
2	71.4	69.2
2.5	82.7	61.5
3	91.4	30.8
3.5	91.4	19.2
4	97.1	11.5
4.5	97.1	7.7
6	97.1	3.9
6.5	100	0

Methods

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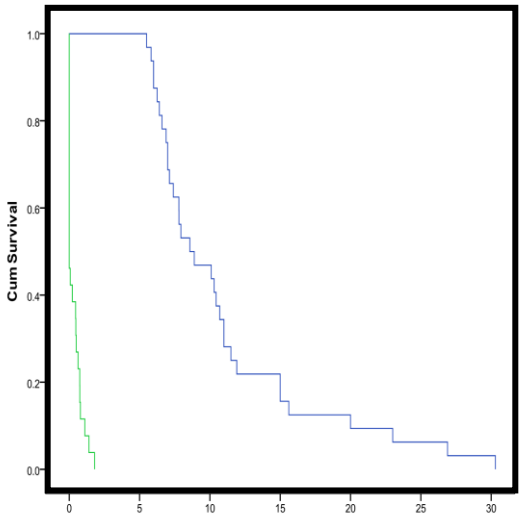
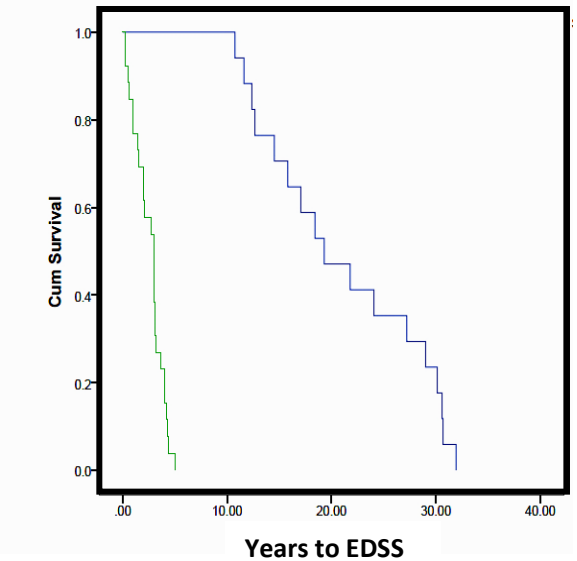


Years to EDSS 3.0

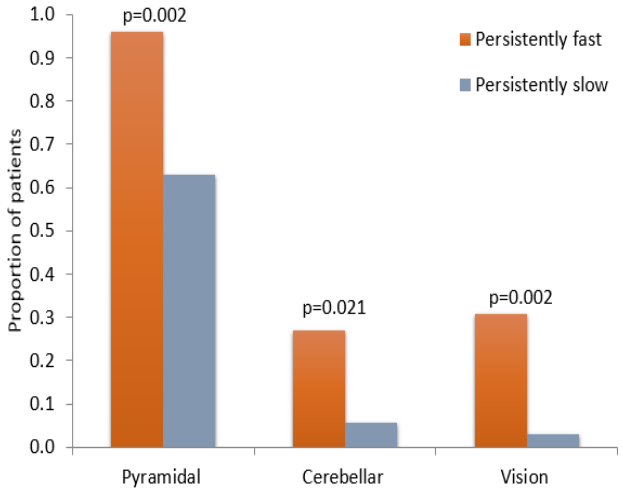


Years to EDSS 6.0

Results

Conclusions

- **PPMS patients demonstrate different rates of disability progression.**
- **The Fast and Persistently Fast groups comprises 54% and 24% of PPMS patients are associated with a higher disability and pyramidal, cerebellar and visual symptoms at onset.**



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Future

Gene expression – PPMS biomarkers

The Arrow Project – Benefits and tips

Learn different clinical, radiological and lab techniques

Learn how research works

Be a future clinical researcher

Advantage on your peers

1. Tips document
2. Have a plan
3. There is flexibility
4. Use the statistician
5. Use each other
6. Presentation
7. Summer work
8. Apply for next year