# Consensus guidelines for the timely detection and diagnosis of disease progression in multiple sclerosis patients

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# Background and objective

- **Secondary Progressive Multiple Sclerosis** (SPMS) is a clinical form of MS characterized by gradual accrual of disability independent of relapses over time[1]
- Consensus guidelines for the timely detection and management of SPMS are **limited**[2]
- As a consequence, SPMS is frequently diagnosed **retrospectively**[2], potentially reducing treatment impact

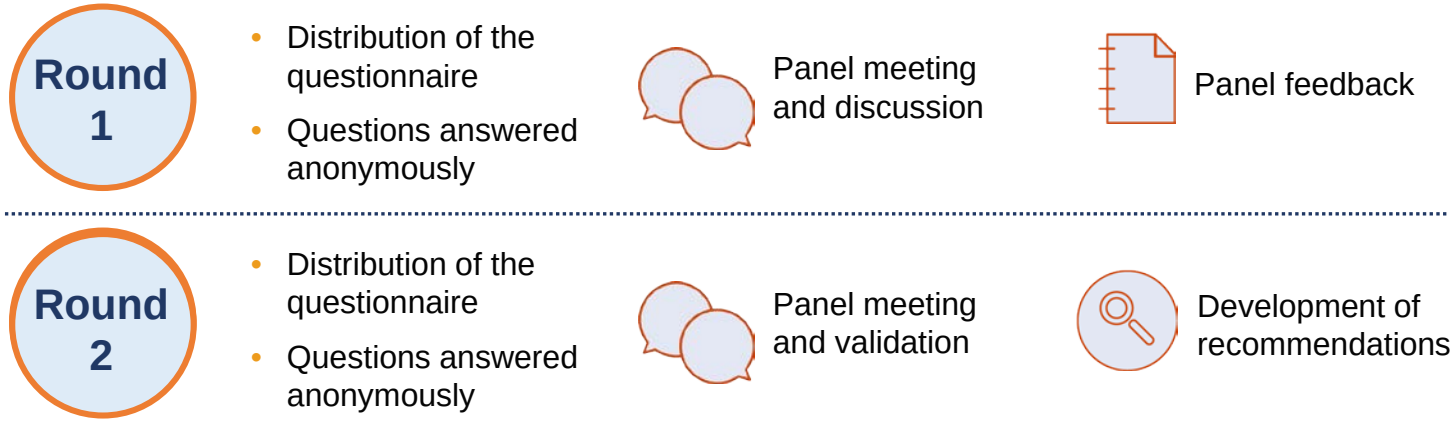
| Objective | **To establish consensus on patient monitorization and on the most relevant clinical variables for early identification of disease progression in MS** |
|---|---|

SPMS, Secondary Progressive Multiple Sclerosis

1. Lorscheider J, et al. *Brain*. 2016;139(Pt 9):2395-405. 2. Lublin FD, et al. *Neurology* 2014; 83: 278–86

# Methods

- A **two-round RAND-UCLA** method was used, involving a panel of **15 MS specialists** in **Spain**




- Consensus **questionnaire** characteristics

**Round 1:** 72 open-ended questions

**Round 2:** 11 additional questions were included based on panel feedback in Round 1

**3 dimensions**: Clinical (Monitoring and EDSS, Cognitive exploration, Other evaluations), Radiological and Biomarker detection

- Level of **agreement:**
  - Items were rated on a 4-point Likert scale
  - Consensus was defined as ≥ 66% agreement (sum of 3 and 4 scores) for each question

| 1 | 2 | 3 | 4 |
|---|---|---|---|
| Totally disagree | Disagree | Agree | Totally agree |

EDSS, Expanded Disability Status Scale; MS, multiple sclerosis

# Results

## Monitoring and EDSS

- Progression definition

| | Level of agreement |
|---|---|
| EDSS is the **best variable** to define progression | **93%** |
| Progression could be defined as: worsening of **1 point** when EDSS baseline is ≤ 5.5 or **0.5 points** if the EDSS baseline score is ≥ 6. Considering a minimum EDSS of 4, a pyramidal function system of ⩾2 and confirmation of progression for a minimum of 3 months | **100%** |

**Minimum time to confirm disability progression**

*Longer disease duration and age are not confirmatory of disease progression per se.*

| | 3 months | 6 months | 12 months | |
|---|---|---|---|---|
| Level of agreement (%) | Agree 73%* | Agree 87% | Disagree 73% | Potential exceptions: *patients clinically and/or radiologically unstable in relation with DMT and patients with non-confirmatory signs of progression. Patients with suspected progression (every 3 months) |

- Confirmatory variables of progression

| | Level of agreement |
|---|---|
| 20% time increase in **T25-FW** + 20% time increase in **9HPT**, with an increase in **EDSS** as defined above | **87%** |

EDSS, Expanded Disability Status Scale; T25-FW, Timed 25-Foot Walk; 9HPT, 9-Hole Peg Test

# Results

## Cognitive and other explorations

- To perform an **annual** cognitive exploration such as SDMT, BRB-N or BICAMS
- To evaluate **once annually with scales**:
  - **Quality of Life (QoL)**
  - **Depression**
  - **Fatigue**
  - **Spasticity** (if there is an alteration on the piramidal system)
- Patients should be proactively asked about their symptoms and impairment, as it allows for **suspected progression**
- BICAMS and BRB-N can be performed by a qualified team member when a neuropsychologist is not available
- A complete neuropsychological study should be performed when progression is suspected

## Radiological identification

- A sustained **change in** both **brain and medullary atrophy suggests progression** but **more precise techniques** should be used to confirm a **diagnosis**
- Main biomarkers to detect progression:
  - Presence of **ectopic lymphoid follicles** in the meninges of patients
  - Quantification of **Neurofilament Light Chain** in blood
  - **Optical coherence tomography (OCT)** test



BICAMS, Brief International Cognitive Assessment for Multiple Sclerosis; BRB-N, Battery of Neuropsychological Tests; OCT, Optical Coherence Tomography; QoL, Quality of Life; SDMT, Symbol Digit Modalities Test

# Results

## Variables of suspected progression

| | Level of agreement |
|---|---|
| • Worsening of 2-points in any functional system | 80% |
| • Worsening of 2-points in functional system , < 10 years of disease | 93% |
| • Worsening of 2-points in functional system , 10-20 years of disease | 87% |
| • Worsening of 2-points in functional system , < 35 years of disease | 73% |
| • Worsening of 2-points in functional system , 35-45 years of disease | 87% |
| • >20% time increase in T25-FW | 93% |
| • > 20% time increase in 9HPT | 87% |
| • >20% time increase in T25-FW + >20% time increase in 9-HPT | 100% |
| • > 20% in 2 minutes walk test | 87% |
| • Repeated falls to the floor | 100% |
| • < 20% in SDMT | 93% |
| • Worsening 20% in 2 battery sub-test | 87% |
| • Worsening 20% in 2 battery sub-test | 87% |
| • Cognitive function worsening | 87% |
| • Change in brain atrophy degree | 80% |
| • Diffuse hyperintensity / confluent lesions | 80% |
| • Lymphoid follicles | 67% |

## Variables NOT confirmatory of progression

| | Variables | Level of agreement |
|---|---|---|
| Functional assessment and EDSS | • Worsening of 2-points in any functional system | 67% |
| | • Worsening of 2-points in functional system , < 10 years of disease | 67% |
| | • >20% time increase in T25-FW | 93% |
| | • >20% time increase in 9-HPT | 100% |
| | • > 20% in 2 minutes walk test | 93% |
| Cognitive exploration | • Repeated falls to the floor | 93% |
| | • < 20% in SDMT | 93% |
| | • Worsening 20% in 2 battery sub-test | 80% |
| | • Worsening 20% in 2 battery sub-test | 77% |

EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; T25-FW, Timed 25-Foot Walk; 9HPT, 9-Hole Peg Test

# Results

## Variables that need more precise techniques to confirm a diagnosis

| | Variables | Level of agreement |
|---|---|---|
| Functional assessment and EDSS | • Worsening of 2-points in any functional system | 67% |
| | • Worsening of 2-points in functional system , < 10 years of disease | 67% |
| | • > 20% time increase in T25-FW | 93% |
| | • >20% time increase in 9-HPT | 100% |
| | • > 20% in 2 minutes walk test | 93% |
| Cognitive exploration | • Repeated falls to the floor | 93% |
| | • < 20% in SDMT | 93% |
| | • Worsening 20% in 2 battery sub-test | 80% |
| | • Worsening 20% in 2 battery sub-test | 77% |
| Radiological detection | • Sustained medullary atrophy | 93% |

EDSS, Expanded Disability Status Scale; SDMT, Symbol Digit Modalities Test; T25-FW, Timed 25-Foot Walk; 9HPT, 9-Hole Peg Test

# Conclusions

- The expert panel agreed that EDSS is the best variable to define progression in MS. Increase in EDSS together with a 20% time increase in 25FT-WT and 9-HPT is confirmatory of disease progression.
- Monitorization of cognitive status, QoL and patient reported outcomes and anamnesis can guide the early detection of disease progression
- With a consensus agreed on 73 of a total of 83 questions (87.6%), these areas of collective agreement could guide neurologists in anticipating progression and planning informed clinical and therapeutic interventions

# Thank you