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# Consensus for the Early Identification of Secondary Progressive Multiple Sclerosis in Portugal: a Delphi Panel

# Consenso Português para a Identificação Precoce de Esclerose Múltipla Secundária Progressiva: Painel Delphi

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## ABSTRACT

**Introduction:** Multiple sclerosis is a disease with a heterogeneous evolution. The early identification of secondary progressive multiple sclerosis is a clinical challenge, which would benefit from the definition of biomarkers and diagnostic tools applicable in the transition phase from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis. We aimed to reach a Portuguese national consensus on the monitoring of patients with multiple sclerosis and on the more relevant clinical variables for the early identification of its progression.

**Material and Methods:** A Delphi panel which included eleven Portuguese Neurologists participated in two rounds of questions between July and August of 2021. In the first round, 39 questions which belonged to the functional, cognitive, imaging, biomarkers and additional evaluations were included. Questions for which no consensus was obtained in the first round (less than 80% of agreement), were appraised by the panel during the second round.

**Results:** The response rate was 100% in both rounds and consensus was reached for a total of 33 questions (84.6%). Consensus was reached for monitoring time, evaluation scales and clinical variables such as the degree of brain atrophy and mobility reduction, changes suggestive of secondary progressive multiple sclerosis. Additionally, digital devices were considered tools with potential to identify disease progression. Most questions for which no consensus was obtained referred to the cognitive assessment and the remaining referred to both functional and imaging domains.

**Conclusion:** Consensus was obtained for the determination of the monitorization interval and for most of the clinical variables. Most questions that did not reach consensus were related with the confirmation of progression taking into account only one test/domain, reinforcing the multifactorial nature of multiple sclerosis.

**Keywords:** Consensus; Multiple Sclerosis, Chronic Progressive/diagnosis; Portugal

## RESUMO

**Introdução:** A esclerose múltipla é uma doença de evolução heterogénea. A identificação precoce da forma secundária progressiva é um desafio clínico, carecendo da definição de biomarcadores e ferramentas de diagnóstico aplicáveis na fase de transição da forma surto-remissão para a forma secundária progressiva. Este trabalho teve como objetivo estabelecer um consenso nacional português sobre a monitorização dos doentes e das variáveis clínicas mais relevantes para a identificação precoce da progressão da esclerose múltipla.

**Material e Métodos:** Um painel Delphi constituído por 11 neurologistas portugueses respondeu a duas rondas de perguntas entre julho e agosto de 2021. Na primeira ronda foram incluídas 39 questões relacionadas com a avaliação funcional, cognitiva, imagiológica, de biomarcadores e outras, e na segunda, as questões para as quais não foi atingido consenso (menos de 80% de concordância) na primeira ronda voltaram a ser submetidas a avaliação pelo painel.

**Resultados:** A taxa de resposta foi de 100% em ambas as rondas e 33 das 39 questões (84,6%) atingiram concordância. Foi atingido consenso relativamente ao tempo de monitorização dos doentes, às escalas de avaliação a empregar e a variáveis clínicas tais como o grau de atrofia cerebral ou redução da mobilidade, cuja alteração é sugestiva de esclerose múltipla secundária progressiva. Adicionalmente, os dispositivos digitais foram considerados ferramentas com potencial para identificar a progressão da doença. A maioria das questões para as quais não foi obtido consenso dizem respeito à avaliação cognitiva, estando as restantes inseridas nos domínios funcional e imagiológico.

**Conclusão:** Foi obtido consenso para a determinação do intervalo de monitorização e para a maioria das variáveis clínicas. A maioria das questões sem consenso estavam relacionadas com a confirmação do diagnóstico de progressão tendo em conta apenas um teste/domínio, realçando a natureza multifatorial da esclerose múltipla.

**Palavras-chave:** Consenso; Esclerose Múltipla Crónica Progressiva/diagnóstico; Portugal

## INTRODUCTION

Multiple sclerosis (MS) is a chronic, autoimmune and neurodegenerative condition that affects approximately 2.8 million people worldwide and a range of 34.3 to 64.4 per 100 000 people in Portugal, being the most common cause of

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non-traumatic disability in young adults.[1-8] As symptoms usually appear in individuals who are between 30 and 40 years old and, therefore, at a highly productive stage of life, it can have a profound social and economic impact.[6,7,9]

In general, MS patients are initially diagnosed with relapsing-remitting MS (RRMS), characterized by the occurrence of relapses or lesions that cause neurological damage, followed by partial or complete recovery and no disease progression between relapses.[10,11] The duration of the RRMS phase is variable, but approximately 50% of untreated patients will progress to a later stage of disease, secondary progressive MS (SPMS), within 15 years after the onset of the first symptoms.[11] SPMS is associated with a higher degree of disability, an inherent deterioration of the patients' health status and with few or no relapses, as after the start of progression only approximately 30% of patients experience relapses.[12,13]

Due to the heterogeneous clinical presentation of MS and the lack of diagnostic tools and criteria, SPMS is usually retrospectively diagnosed considering increased disability and neuronal loss.[10,11] However, early SPMS diagnosis would allow patients to start treatments aimed at this phase of the disease before developing severe disability, thus maximizing the benefit of such drugs.[12] The identification of clinical presentations suggestive of progression to SPMS are, therefore, of the utmost importance for a timely diagnosis and treatment of SPMS.[10,12]

The aim of this study was to identify the clinical variables and the most adequate follow-up timings for the early identification of progression for SPMS.

## MATERIAL AND METHODS

A Delphi panel[14] with two rounds was conducted between July and August 2021, to evaluate the most appropriate timings and clinical variables to monitor and assess MS progression. Eleven Portuguese Neurologists with extensive expertise in the monitorization and treatment of MS were invited to the Delphi panel. The questionnaire was adapted from a survey developed to reach a national consensus on the relevant clinical variables to predict progression to SPMS in Spain[15] with the help from the two experts responsible for the coordination of the project. The survey was divided into 39 questions/statements that belonged to five different assessment domains: functional, cognitive, imaging, biomarkers and additional assessments.

All the questions/statements were rated using three Likert scales that evaluated levels of agreement (completely disagree, disagree, agree, completely agree), recommendation (do not recommend at all, do not recommend, recommend, fully recommend) and applicability (medium/long term applicability, short term applicability, not applied in clinical practice but useful, already applied in clinical practice). The questionnaire was made available online and the answers were anonymous. The questions were considered to have reached consensus at equal to or greater than 80% of agreement. In between rounds, the results were analyzed and sent to the Delphi panel. To facilitate the interpretation of the results, the evaluations completely disagree/disagree and agree/completely agree, as well as the evaluations do not recommend at all/do not recommend and recommend/fully recommend were pooled under the evaluations disagree, agree, do not recommend, and recommend.

## RESULTS

The response rate in both rounds was 100%. In the first round, consensus was obtained for 28 questions (71.8%). The remaining 11 questions were appraised during the second round and consensus was achieved for five questions (45.5%). Thus, in total, consensus was obtained for 33 of the 39 questions (84.6%) (Fig. 1). The percentages for each question are detailed in the Appendix 1 (Appendix 1: https://www.actamedicaportuguesa.com/revista/index.php/amp/article/view/18543/15036).

### Functional evaluation

Regarding the functional domain of SPMS, six and three months were consensually agreed as the most adequate time interval for monitoring patients under disease modifying therapies who are clinically and imagiologically stable or unstable, respectively. Nevertheless, it was also consensual that when progression is suspected the patient should be monitored on a case-by-case basis.

Consensus was also reached regarding the Expanded Disability Status Scale (EDSS) as the best measure to define progression. Moreover, an increase of 20% in the 25-foot walk test (25FTW) and in the 9-hole peg test (9HPT) or in EDSS Plus (which includes 25FTW, 9HPT and EDSS) was considered sufficient to suspect and confirm the diagnosis of progression. Even without changes in the EDSS,

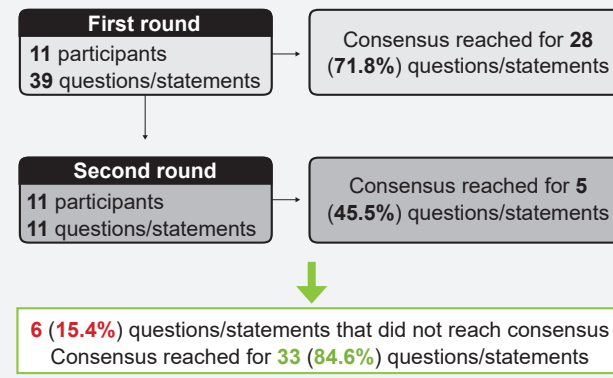


Figure 1 – Flow chart of the Delphi panel results

confirmed worsening of 2-points in any functional system (except the visual) was considered to allow the suspicion and confirmation of a progression diagnosis if disease duration was 10 to 20 years and/or if the patient was older (over 45 years-old).

Defining progression as an increase in confirmed disability, measured by EDSS, regardless of the existence of relapses, achieved 90.9% of consensus. In addition, the minimum time needed to confirm the diagnosis of progression not associated with relapses, independently of the variable used, was considered to be 12 months.

Decreases in mobility, such as the transition from walking independently to needing support or help and a reduction from 500 to 300 m in the distance that the patient can walk without needing rest, were regarded as suspicious of disease progression, but the panel unanimously highlighted the need to use more accurate progression diagnostic tools. Accordingly, the experience of repeated falls, reflecting a clear loss of physical endurance, even without changes in the EDSS score or other evaluation tools, was deemed to suggest the diagnosis of progression. Nevertheless, consensus was not reached on the use of this clinical evaluation as confirmation of a disease progression diagnosis.

**Cognitive evaluation**

Regarding the cognitive domain, consensus was reached for performing at least one cognitive assessment per year since MS diagnosis. In addition, the frequency of this assessment was considered to depend on the clinical situation of the patient and on the recommendation of the neurologist. Moreover, it was considered that the cognitive assessment should include the largest number of domains possible, being recommended the application of at least one battery of intermediate duration, such as the Brief Repeatable Battery of Neuropsychological tests (BRB-N). However, if it is not possible to apply a battery of intermediate duration, a short duration battery such as the Brief International Cognitive Assessment for MS (BICAMS) should be applied. If this short battery can also not be applied, it was considered appropriate to apply a test such as the Symbol Digit Modalities Test (SDMT). Consensus was not reached on whether a battery like BICAMS needed to be applied by a neuropsychologist to obtain a reliable assessment. Nevertheless, if progression of cognitive decline is suspected after application of a short or intermediate battery of tests, it was considered that a comprehensive neuropsychological study by a neuropsychologist should be performed.

Concerning the changes in the cognitive domain suggestive of SPMS, consensus was obtained for how a confirmed worsening of 20% in at least two subtests of the BRB-N or BICAMS battery of tests, after exclusion of other factors, is sufficient to confirm a progression diagnosis. Also, a confirmed 20% reduction in SDMT was considered sufficient to suspect disease progression. No consensus was obtained on whether an isolated worsening of cognitive function was sufficient to diagnose or even suspect disease progression. Likewise, a confirmed 20% reduction in SDMT was not considered sufficient to confirm a diagnosis of progression.

**Imaging evaluation**

Changes in the degree of brain or spinal cord atrophy which are maintained and/or confirmed over time were consensually considered to be suggestive of disease progression. However, no consensus was reached on the presence of diffuse hyperintensity leading to the suspicion of disease progression.

**Biomarkers**

Increased levels of serum neurofilament light chain (sNfL) and changes in optical coherence tomography (OCT) were considered important biomarkers to identify disease progression. Additionally, digital devices were regarded as relevant tools for the early diagnosis of SPMS.

**Additional assessments**

It was consensually agreed that, since the diagnosis of MS, patients should complete a scale/questionnaire which evaluates depression, fatigue and quality of life, as well as a scale that assesses spasticity (if changes in the pyramidal function system occur), at least once a year. Accordingly, deterioration of the patient's quality of life and/or worsening of spasticity were considered to be good indicators for the need to use more precise diagnostic tools. However, changes in scales that measure fatigue and depression were considered insufficient to confirm an SPMS diagnosis. Regarding the informal assessment of patients, it was agreed that patients should be asked proactively and in a structured manner if they noticed some change in their symptoms that could suggest disease progression.

## DISCUSSION

The transition between RRMS and SPMS is difficult to identify due to the overlap between the two conditions. The different modulation by environmental, genetic and epigenetic factors affects the clinical course, symptoms, and therapy. Additionally, the central nervous system compensatory processes can cause a delay in the manifestation of progressive disease.[11] Thus, the time between the onset of disease progression and confirmation of diagnosis has been estimated to be three years, on average.[13,16] This delay can result in needless deterioration of quality of life and increase in costs, as patients may continue relapse-reducing disease modifying therapies, which are ineffective for slowing SPMS, and, therefore, lose the opportunity to

tackle early SPMS with therapies that may delay disability progression.[13,16]

In this Delphi panel, consensus for disease monitoring time intervals was dependent on the degree of stability of patients. Nevertheless, the achievement of 100% of agreement for a case-by-case analysis reflects the heterogeneity of MS, impacting the timing for medical appointments. This tailored-made medicine is especially relevant if there is suspicion of progression.

EDSS is widely regarded as the most used tool to measure MS outcomes, having been accepted internationally as a primary endpoint in clinical trials, allowing cross-study comparisons.[17] Similarly, it was deemed the best measure available in clinical practice to define progression in this study. The definition of progression has been challenging due to the difficulties in identifying SPMS early.[18] Recently, a new definition has been suggested: it considers that if a patient presents a minimal value of 4 in the EDSS score, a pyramidal function system of ≥ 2, and had confirmation of progression for at least three months, an increase of 1 point in the EDSS score if the initial score was ≤ 5.5, or an increase of 0.5 points if the initial score was ≥ 6, confirms disease progression.[19] However, no consensus was reached by this panel, with only 63.6% of the participants considering that this is an appropriate definition of progression. This might be explained by the observation that this definition implies that disability progression can be confirmed during the follow-up at three months.[18] It has been previously suggested that, at this time, diagnosis should be done carefully and confirmed in a later follow-up.[18] Accordingly, this panel considered that 12 months was the minimum time needed to confirm the diagnosis of disability progression not associated with relapses. The selected time interval is explained by the observation that 30% of patients which had a confirmed progression at the three or six months follow-up can still show clinical improvements during the 12 or 24 months follow-up, especially if the EDSS changes are small or if patients are younger.[18] However, and given that waiting 24 (or 18) months could delay treatment[18], 12 months was the selected time interval. In this case, the definition of progression as an increase in confirmed disability at three, six or 12 months, measured by EDSS, regardless of the existence of relapses, reached consensus.

It has been previously shown that the risk of developing SPMS increases with age.[20] Moreover, it was shown that approximately two thirds of untreated RRMS patients will progress to SPMS within 10 to 20 years.[6] Thus, this panel also agreed that for patients who are over 45 years old and have had MS for 10 to 20 years, a worsening of 2-point in any functional system (except the visual), even without changes in the EDSS, can confirm a diagnosis of progression.

Multiple sclerosis causes motor symptoms such as muscle weakness, abnormal walking mechanisms and balance problems.[21] Thus, it is not surprising that consensus was reached for suspicion of progression when patients experience repeated falls, which reflect a clear loss of balance, even without changes in other evaluation tools; when patients reduce the distance that they are able to walk without help or rest from 500 to 300 m; or when the patient transitions from walking independently to needing support or help to do so. However, repeated falls with evident loss of balance alone were not considered sufficient to confirm a progression diagnosis. Changes in other tests would be needed to confirm it. Accordingly, consensus was obtained for confirmation of progression diagnosis when there is a confirmed 20% increase in the 25FTW (which measures ambulation) and 9HPT (which measures upper limb function) or in the EDSS Plus (which combines the two previously mentioned tests and EDSS).[18]

Most questions for which no consensus was obtained belonged to the cognitive performance domain. Cognitive impairment can manifest itself early in the course of the disease and impacts the patients' employability, social interactions, and quality of life.[22] Additionally, it affects approximately 40% to 70% of MS patients in North America and Europe.[23] Thus, it is a major contributor to the burden of MS. However, assessment of cognitive dysfunction is a challenge as it is difficult to define what is considered normal cognition.[22] Moreover, impairment in cognitive function is present in various neurological diseases and depends on the involvement of different brain structures, extent of neuronal damage, and the cognitive reserve and performance of patients.[22,24] Therefore, the importance of cognitive impairment, on one hand, and the difficulty in defining it, on the other hand, may explain why no consensus was reached on the suspicion or confirmation of SPMS diagnosis based on the isolated worsening of cognitive function. Also, no consensus was reached on confirmation of progression based only on a 20% worsening measured by SDMT. This lack of agreement may be due to SDMT being a test that only evaluates one aspect of cognitive impairment (cognitive processing speed) and thus might not reflect the decline of cerebral functions over time which might occur in MS patients.[25] Moreover, the frequency of use of this test seems to impact the results. A recent study, which used original data from the ASCEND trial, where the SDMT test was applied every four weeks during follow-up, reported a steady increase of SDMT scores during this period, which suggests the existence of a practice effect and, thus, the inability to correctly reflect the steady cognitive decline that MS patients experienced.[26] However, in the EXPAND trial, where the original SDMT and two alternative forms (shown to have the same degree of difficulty), were presented in

an alternate pattern every six months, a steady increase in SDMT scores was not observed for patients under treatment with placebo.[27] Thus, although a 20% confirmed reduction on SDMT can suggest progression, it cannot alone confirm the diagnosis. A more thorough evaluation using batteries of tests such as the BRB-N (preferentially) and BICAMS could provide more information on the cognitive status of patients.

No consensus was reached on whether a battery of tests such as BICAMS should be applied by a neuropsychologist to obtain a reliable cognitive assessment. The lack of agreement may be explained by the fact that this battery of tests was developed to be applied by an individual without expertise in cognitive assessment, even though the person applying the test needs to be able to interpret the results, taking into account several confounding variables (MS physical symptoms, demographic factors, other neurological disorders, concurrent medication, and a modest degree of depression).[28]

Due to the relevance and prevalence of cognitive problems, evaluation of the patients' cognitive abilities is recommended in order to monitor disease progression and predict cognitive impairment.[18] In this case, a consensus of one evaluation per year was reached, while also considering that the condition of the patient and the opinion of the neurologist should be taken into account to adjust this time period, if needed.

Magnetic resonance imaging (MRI) is the most common tool for routine surveillance of MS patients, and in a study where Neurologists were interviewed, 68.8% of the physicians reported that their SPMS diagnosis was usually based on MRI scans.[29,30] Our panel reached consensus for suspecting progression when there were changes in the degree of brain atrophy or of spinal cord atrophy. However, no consensus was reached on whether the presence of diffuse hyperintensity in the brain white matter or confluence of lesions would suggest progression. This might be explained by the fact that white matter hyperintensities are not specific to MS and can be detected in individuals with other disorders and even in seemingly healthy individuals, especially with aging.[31] Thus, to reach a diagnosis, it is necessary to combine the characteristic clinical presentations of SPMS with images of lesions that have the morphology and location that are usually associated with MS.[31]

The identification of biomarkers would advance the monitoring of MS and facilitate SPMS diagnosis. However, only a small number of biomarkers are validated, and even a lower number have been translated into clinical practice.[32] Increased sNfL has been associated with brain fraction loss and consequently with cognitive ability, with the increase in sNfL levels being significantly faster, in MS patients experiencing disability worsening, when compared with MS patients that remained stable.[32-34] Also, OCT has been increasingly applied for the study of MS, as it allows quantification of neuronal loss.[35] Accordingly, the Delphi panel agreed that changes in these biomarkers could suggest disease progression. Moreover, the panel considered that digital devices could be relevant for the early detection of SPMS. This is in line with the results of Ziemssen *et al*, that reported that 11 in 16 Neurologists would prefer a digital tool to help evaluate the early and subtle symptoms that are suggestive of SPMS.[30] Also, digital devices, such as wrist accelerometers to measure gait, which allow real-time monitoring, are considered promising for the early detection of progression.[18]

As MS can cause spasticity and fatigue, and usually promotes feelings of depression, highly impacting the quality of life of patients,[21,36] the need to assess these variables was discussed by this panel. Consensus was reached on the importance of frequently assessing these symptoms and how their worsening can be suggestive of progression. However, due to the variety of factors that can cause depression and fatigue, their changes alone cannot confirm progression.

Comparing the agreement and recommendation scales, they both follow the same trend, with the questions that reached agreement being also the most recommended. In terms of applicability there was a more varied distribution, reflecting different clinical practices of the members of the Delphi panel. Interestingly, there were some measures not applied in clinical practice, whose applicability was deemed to be useful, namely: confirmation of the diagnosis of progression due to worsening of 2-points in any functional system (except the visual), even without changes in EDSS, if disease duration is greater than 20 years and if the patient is between 25 to 45 years old; suspicion of progression due to 20% worsening in at least two subtests of the BRB-N or BICAMS battery of tests, after excluding other factors; suspicion of progression due to change of the degree of brain atrophy maintained and/or confirmed over time; applying at least once per year a scale/questionnaire that evaluates fatigue and depression or fatigue and spasticity; and the use of more accurate progression diagnostic tools if there is a worsening in spasticity.

In summary, the main recommendations of our panel for the early identification of SPMS are as follows:

- Timing of clinical monitoring of disease modifying-treated patients: determined by the physician on a case-by-case basis, being recommended every three or six months, in cases of clinical and radiological instability or stability, respectively.
- Definition of progression: increase in confirmed disability measured by EDSS, regardless of relapses; if progression is suspected, the patient should be evaluated on a case-by-case basis. A 20% increase in the EDSS Plus or in 25FTW and 9HPT suggests disease progression and a decrease in the ability to

move independently indicates the need to use more accurate progression diagnostic tools.

- Cognitive evaluation: should be performed annually, ideally with a comprehensive battery; progression can be suspected upon a confirmed worsening of 20% in at least two subtests of the BRB-N or BICAMS battery of tests.
- Imaging: a maintained change in the degree of brain or spinal cord atrophy should lead to the suspicion of disease progression.
- Biomarkers: increased levels of sNfL and OCT changes can be important biomarkers of progression.
- Additional evaluations: the assessment of depression, fatigue and quality of life must be performed annually, although changes in those parameters should not be considered as isolated prognostic factors; a scale that assesses spasticity should be applied in patients with worsening of pyramidal functions.

### Strengths and limitations

The composition of a Delphi panel is a determining question for ensuring its validity. In this study, the specialists involved have extensive clinical practice in treating MS patients, and work in some of the largest hospitals in the country. Additionally, these hospitals included the main regions of mainland Portugal and Madeira, being therefore representative of the Portuguese reality. Nevertheless, to adapt the questionnaire to the realities of different hospitals in different regions of the country, some specific techniques and/or resources were not included in the questionnaire. Moreover, the multifactorial nature of MS makes it difficult to approach all domains in detail. Thus, due to feasibility constraints, some more specific statements such as the types of digital devices that could be useful and how to perform specific assessments were not included.

## CONCLUSION

Consensus was achieved for most of the questions/statements included in this Delphi panel. From all the analyzed domains, the cognitive domain was the one for which more uncertainty was present, possibly due to both the complexity and difficulty in cognitive assessment. Nevertheless, cognitive assessment is clinically relevant as highlighted by the consensus obtained for annual cognitive assessment, with a 20% reduction in SDMT considered sufficient to suspect SPMS progression. The questions for which no consensus was achieved focused mainly in SPMS diagnosis using only one clinical variable, which reflects the multidomain nature of MS. Assessments using imaging techniques and biomarkers seem very promising, even though more research is needed to establish them as diagnostic tools. Also, development of digital tools and devices might facilitate the early diagnosis of SPMS.

This study increases awareness about the importance of early identification of progression and the reached consensus provides a complete set of criteria for the early diagnosis of SPMS.

## AWARDS AND PRIOR PRESENTATIONS

Part of the data described in this manuscript were orally presented at the Congresso Nacional de Neurologia 2021, Albufeira, Portugal, Oct. 27-30, 2021.

## AUTHOR CONTRIBUTIONS

MJS and LS: Conception of the work, members of Delphi panel, critical review and approval of the final version to be published.

CB, CC, JJC, IM, AM, JCS, VS, AMS, JV: members of the Delphi panel, critical review and approval of the final version to be published.

## COMPETING INTERESTS

CC received fees from Janssen, Merck e Roche, Almirall, Biogen, Bristol Myers Squibb, Novartis, Sanofi-Genzyme, Teva and Bayer.

JJC has received fees from Biogen, Novartis, Roche, Merck, Bial Foundation, Fundação para a Ciência e Tecnologia, Almirall, Zambon, Bristol Myers Squibb and Janssen, and is a member of the Multiple Sclerosis Study Group.

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