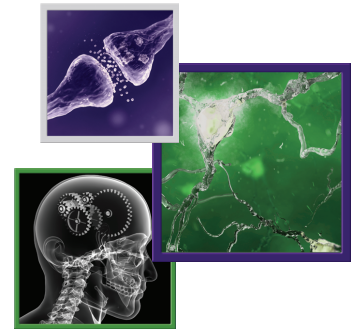
White Paper

For reprint orders, please contact: reprints@futuremedicine.com

Neurodegenerative Disease Management



Living with secondary progressive multiple sclerosis in Europe: perspectives of multiple stakeholders

Øivind Torkildsen*[,1], Ralf A Linker[2], Jose MM Sesmero[3], Simone Fantaccini[4], Rainel Sanchez-de la Rosa[4], Jerome de Seze[5], Martin Duddy[6] & Andrew Chan[7]

[1]Department of Neurology, Haukeland University Hospital, 5020, Bergen, Norway
[2]Department of Neurology, University Hospital, 93053, Regensburg, Germany
[3]Hospital Clínico San Carlos, 28040, Madrid, Spain
[4]Medical Affairs, Novartis Pharma AG, CH-4056, Basel, Switzerland
[5]University Hospital of Strasbourg, 67200, Strasbourg, France
[6]Department of Neurology, The Newcastle upon Tyne Hospitals Trust, Newcastle upon Tyne, NE7 7DN, UK
[7]Department of Neurology, Inselspital, Bern University Hospital, University of Bern, 3010, Bern, Switzerland
*Author for correspondence: oivind.fredvik.grytten.torkildsen@helse-bergen.no

Practice points

- Secondary progressive multiple sclerosis (SPMS) is characterized by a progressive accumulation of disability after an initial relapsing course. The diagnosis of SPMS is often established retrospectively owing to indistinct clinical features of disease progression, unclear diagnostic guidance and lack of imaging and biomarkers to monitor the transition.
- A holistic understanding of the current and future patient journey of SPMS across seven European countries was undertaken to identify overarching unmet needs encountered by all key stakeholders involved in the management of multiple sclerosis (MS).
- Elemental findings from the key stakeholders (nurses, neurologists, payers) who participated in this international expert group meeting highlighted an uncertainty among healthcare professionals over SPMS disease definition and its differentiation with relapsing-remitting MS, as well as a reluctance to diagnose due to the absence of effective therapeutic options. The standard of therapeutic care for a patient with SPMS also exhibits diversity across regions.
- Experts consider that inputs from physiotherapists, rehabilitation doctors, neuropsychologists and social workers are also beneficial in the detection and diagnosis of SPMS primarily performed by specialized neurologists.
- With an enriched pathophysiological knowledge of SPMS disease and a distinct disease definition in future, SPMS may not remain as devastating for patients and different stakeholders.
- The role of the pharmaceutical industry is important in enhancing SPMS disease awareness among patients and all stakeholders involved in the SPMS patient journey.
- The emergence of digital tools and robust real-world evidence will aid drug developers in the rapid advancement of novel therapeutics for SPMS.
- Prompt clinical evidence on the efficacy of novel treatments will also rapidly expand the SPMS treatment armamentarium. However, a strengthened treatment paradigm will require guidelines for the reassessment of treatment options. Combined with enhanced patient monitoring and consolidated caregivers support, the quality of life of patients with SPMS can be transformed.

The transition from relapsing-remitting multiple sclerosis to secondary progressive multiple sclerosis (SPMS) remains a clinical challenge owing to the heterogeneous course of the disease, indistinct disease progression and lack of availability of validated biomarkers and diagnostic tools. This article summarizes the outcomes from an international expert group meeting conducted to validate the preliminary research findings gathered through interviews with primary healthcare stakeholders and pharmaceutical representatives, and to understand the current and future patient journey of SPMS across seven European countries. We highlight the uncertainty in SPMS diagnosis and management and, consequently, the need for uniform assessment guidelines, enhanced awareness and a collaborative effort between the stakeholders associated with SPMS patient care and the pharmaceutical industry.

Future Medicine

Lay abstract: This article summarizes the findings from an international expert group meeting conducted to understand the current and future patient journey of secondary progressive multiple sclerosis (SPMS), across seven European countries. Although there are a number of challenges in the diagnosis and treatment of patients with SPMS, it is evident that the collaborative efforts of associated stakeholders (neurologists, nurses, caregivers, payers, patients and the pharmaceutical industry), along with proper knowledge on diagnosis/treatment, and availability of real-world data in the future, will allow for optimal care that will improve the quality of life of people living with SPMS.

Tweetable abstract: Uncertainty in SPMS diagnosis and management emphasizes the need for robust assessment guidelines, enhanced awareness and collaborative efforts among stakeholders to allow optimal care of SPMS patients

First draft submitted: 1 October 2020; Accepted for publication: 9 November 2020; Published online: 25 November 2020

Keywords: diagnosis • disease management • disease-modifying therapy • neurologists • nurses • secondary progressive multiple sclerosis

Multiple sclerosis (MS), a neuroinflammatory disease characterized by demyelination and axonal loss [1], is usually diagnosed at a young age (age: 20–40 years). MS prevalence rises with increase in latitude; it is the lowest in eastern sub-Saharan Africa (3.3 cases per 100,000), central sub-Saharan African (2.8) and Oceania (2.0), and the highest in North America (164.6), Western Europe (127) and Australasia (91.1). Additionally, there is a strong female preponderance [2]. As of 2015, approximately 700,000 people in Europe were living with MS [3], and, after traffic accidents, MS is the leading cause of disability in young adults globally [4]. MS manifests itself distinctively in patients and significantly affects their quality of life, healthcare costs, work capacity and productivity [5,6].

Secondary progressive MS (SPMS) is characterized by a progressive accumulation of disability after an initial relapsing course, with approximately 80% of patients initially diagnosed with relapsing-remitting MS (RRMS) transitioning to SPMS within 20 years if not adequately treated [7,8]. The diagnosis of SPMS is often established retrospectively owing to indistinct clinical features of disease progression, unclear diagnostic guidance in the 2017 revised McDonald criteria, and lack of imaging and biomarkers to monitor the transition [9–11]. SPMS is further distinguished as either active (with relapses and/or evidence of new MRI activity) or nonactive, with progression (accumulation of disability over time, independent of any relapse) and without progression [12] assessed generally using the Expanded Disability Status Scale (EDSS) [9,13]. The recent explanation on classification criteria of MS phenotypes emphasizes the inclusion of time frame, while defining the current disease state through assessment of activity (evidenced by clinical relapses or imaging) and assessment of progression (clinical evidence of disability worsening that is independent of relapses) over a given period of time in patients who are in a progressive phase of the disease. In addition, the terms worsening and progressing, or disease progression, should be used more accurately when describing the MS disease course [11]. The recommended time frame for evaluating active disease or a progressing disease is at least once in a year.

Periodic monitoring of disease activity and progression, as well as availability of potential disease-modifying therapies (DMTs), govern treatment decisions [12,14,15]. Hence, a holistic understanding of the SPMS patient journey is critical to identify overarching unmet needs encountered by all key stakeholders involved in the management of MS. This paper is based on a meeting of MS experts held in December 2019 and highlights unmet needs and country-specific idiosyncrasies in order to identify key priority areas to improve the MS ecosystem across Europe.

Methods

The detailed step-by-step methodology followed for this study is described below.

Primary & secondary research

Primary and secondary research was conducted across seven European countries (France [FR], Germany [DE], Italy [IT], Spain [SP], the UK, Switzerland [CH] and Norway [NOR]) to gather a preliminary understanding of the unmet needs and future expectations across different stakeholders. Primary research comprised in-depth qualitative interviews with 58 randomly selected local experts encompassing the main stakeholders involved in the management of SPMS (specialized neurologists, MS nurses and payers) (Figure 1).

Preferred SH profile							
Specialized neurologist	• Large hospitals • Office-based (n=6)	• CHU + CHG • Office-based (n=5)	• Reference centers and small hospitals (n=4)	• Large and small hospitals (n=5)	• Reference centers and small hospitals (n=6)	• Centers of excellence (n=2)	• Centers of excellence (n=3)
MS nurse	• MS nurses in large hospitals (n=2)	• MS nurses in CHU + MS networks nurses (n=2)	• MS nurses in large university hospitals (n=3)	• MS nurses in large university hospitals (n=2)	• MS nurses in large university hospitals (n=2)	• Nurses in CoE (n=2)	• Nurses in CoE (n=1)
Payer	• SHI funds (n=2)	Former representatives from CT/CEESP/CEPS (n=2)	• Former national advisor + local payers (n=2)	• Regional payers + former national advisors (n=2)	• Regional payers + former national advisors (n=2)	• National/local payers (n=2)	• Local payers (n=1)
n=58	10	9	9	9	10	6	5

Figure 1. Respondent profiles of stakeholders from different countries.
CEESP: Commission Évaluation Économique et de Santé Publique (Committee for Economic and Public Healthcare Evaluation); CEPS: Comité Economique des Produits de Santé (Economic Committee of Healthcare Products); CHG: Centre Hospitalier Générale (general or local hospital); CHU: Centre Hospitalier Universitaire (university hospital); CoE: Centers of excellence; CT: Commission de la Transparence (Transparency Committee); MS: Multiple sclerosis; SH: Social health; SHI: Social health insurance.

International expert group meeting

Validated findings from the primary research were used to identify key topics and develop a discussion guide for the faculty of experts invited to the international expert group meeting. The meeting was organized into three workshops: healthcare professionals (HCPs) – six international MS clinical experts from SP, DE, CH, FR, UK and NOR; payers – six experts in access and price negotiation from SP, UK, FR, DE and NOR; and nurses – four MS nurses from centers of excellence in the UK, DE, FR and IT. Early interviews during the primary research revealed that the patient journey could be divided into five steps – prediagnosis, diagnosis, work-up and treatment decision, monitoring and re-assessment, and this was adapted for subsequent interviews. Different aspects were discussed separately with neurologists and nurses, including current and future expectations regarding SPMS disease awareness and epidemiology, patient identification, diagnosis, disease management, treatment decisions and monitoring, and the role of treatment cost, as well as the role of multi-stakeholders in the patient journey. The payers' discussion was focused on disease awareness and epidemiology, current treatment options and unmet needs, disease and economic burden, access level and restrictions, current and future value drivers, and future pricing and reimbursement drivers in MS.

Consensus

The outcome of the expert group meeting validated the preliminary understanding of the unmet needs and future expectations across different stakeholders. An alignment and consensus around the main topics characterizing the current SPMS patient journey is presented in the following sections.

Results

Current patient journey through SPMS

SPMS disease awareness: perception versus reality

An integral part of the SPMS patient journey is to identify the disease transition from RRMS to SPMS. With the definition of clinical MS courses in 1996, the latest revision in 2020 emphasized the importance of a time-based assessment of the current disease status of an MS patient. However, an ambiguity around the disease definition was seen among neurologists, payers and nurses across the participating European countries [9,11]. SPMS is largely perceived as a continuum of RRMS, and an increasing tendency exists among clinicians to diagnose the disease based on the cessation of inflammatory activity (relapses or MRI activity), rather than the recognition of progressive clinical disability independent of relapses (even when they are still occurring), as described by the 2013 consensus criteria [9,11].

Primary and secondary research shows that neurologists confined to a limited number of MS centers have a robust understanding of SPMS diagnosis. However, the less specialized HCPs and nurses may have suboptimal knowledge regarding the SPMS diagnosis and its clinical course. In addition, it is noteworthy that the clinicians exhibit a reluctance to confirm the SPMS diagnosis owing to the lack of effective treatment. Experts in MS management consider symptomatic cognitive decline/depression/fatigue, along with MRI findings, and EDSS assessment, vital for the assessment of SPMS. However, there is a time lag in worsening of symptoms and evaluation of disease activity

10.2217/nmt-2020-0054

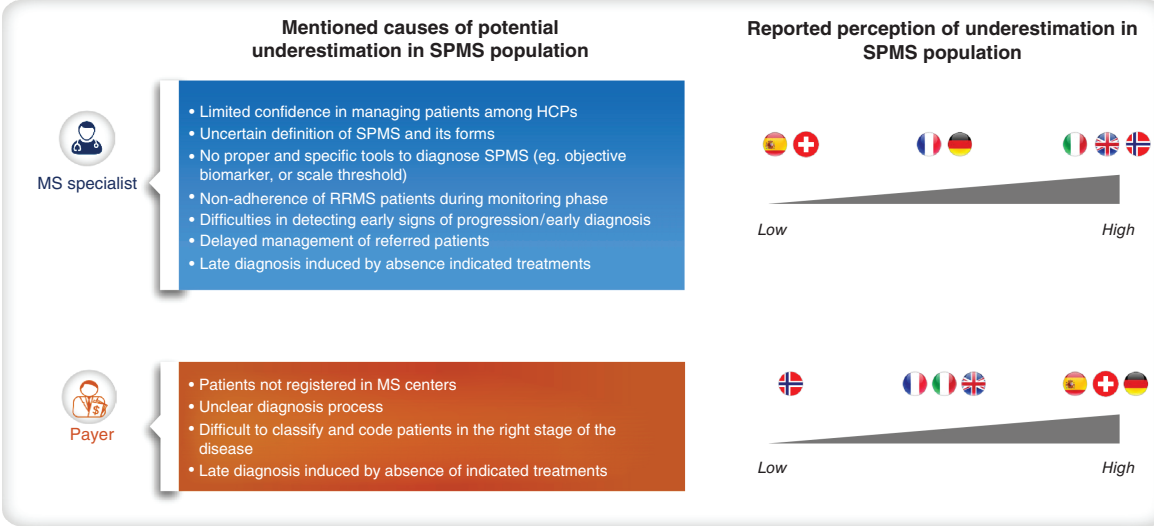


Figure 2. Perspectives of multiple sclerosis specialists and payers toward perception of secondary progressive multiple sclerosis population.
HCP: Healthcare professional; MS: Multiple sclerosis; RRMS: Relapsing-remitting MS; SPMS: Secondary progressive MS.

with MRI [16]. The prolonged patient journey and symptomatic variability also make it challenging to distinguish the point of transition from RRMS to SPMS. In this regard, nurses play a significant role in determining the first signs of disease progression and relaying the information to the neurologists. Community nurses have better clarity on the patient's symptomatic transition as they dedicate more time to and closely monitor their patients [17,18]. Therefore, although the diagnosis of SPMS is primarily a neurologist's role, the responsibility of the nurses in providing insights on symptomatic self-reporting cannot be undermined.

Across the seven countries, approximately 20–30% of the currently DMT-standard of care-treated MS patients are diagnosed with SPMS. The uncertainty in disease definition across clinicians, insufficient MS-specialized neurologists, delayed diagnosis, drug label constraints and unavailability of effective treatment options suggest under-reporting of the SPMS disease burden. Moreover, payers rely on real-world evidence (RWE) studies to estimate MS prevalence, which can be a concern since the data from controlled settings may not truly represent the real-world burden. Figure 2 summarizes the perspectives of MS specialists and payers toward perception of SPMS population by country.

SPMS: symptoms to diagnosis

In the UK and Germany, nurses are frequently the first to recognize and record the symptomatic changes that support the diagnosis of SPMS. Furthermore, in the UK, nurses involved in the initial patient assessment are mostly involved in diagnosis.

In Italy, SPMS diagnosis relies exclusively on the patient's response, due to the absence of an objective tool for quantification of progression. Because of the slow progression of SPMS, disease worsening is nonapparent in terms of EDSS scores during the initial progressive phase. To confirm an SPMS diagnosis, patients' clinical symptoms are first reviewed, followed by evaluation of disease activity through MRI.

In the UK, the National Institute for Health and Care Excellence (NICE) guidelines recommend at least one annual MS consultation and therefore, it is difficult to see a patient every 3–6 months to confirm disease worsening. Occasionally, it may take up to 3–4 years to determine the progression as the interval between doctor visits and MRI is approximately a year. Most patients initially experience a denial phase toward the SPMS diagnosis owing to the unavailability of effective treatment options and potential loss of motor function.

Apart from specialized neurologists, physiotherapists in Germany and the UK, rehabilitation specialists and social workers in France and the UK, and neuropsychologists in Italy, are usually involved in the detection and diagnosis of SPMS. In Germany and the UK, detection of disease progression depends on the size and dynamic of the center. The role of the caregiver is also important in comprehending the signs of progression, although currently it is overlooked (Figure 3).

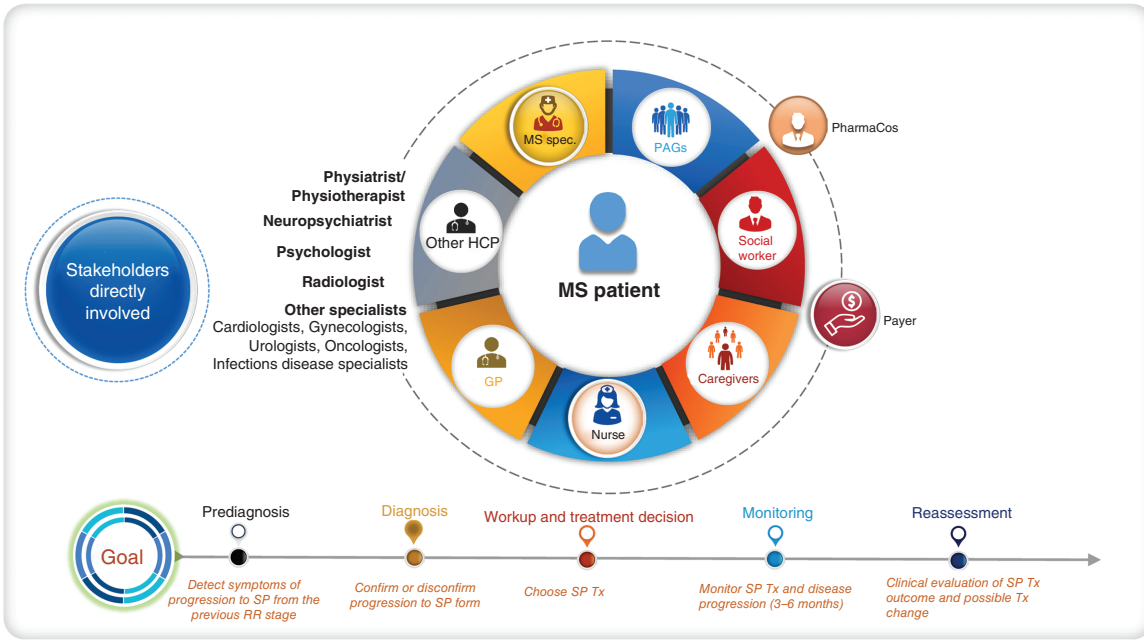


Figure 3. Secondary progressive multiple sclerosis patient's ECOSYSTEM.
GP: General practitioner; HCP: Healthcare professional; MS: Multiple sclerosis; PAG: Patient advocacy group; PharmaCo: Pharmaceutical company; RR: Relapsing-remitting; SP: Secondary progressive; Spec: Specialist; SPMS: Secondary progressive MS; Tx: Treatment.

Management of SPMS

There was a general agreement that the current treatment goal for SPMS is to halt disease progression (defined as no change in the EDSS score) and prevent worsening of symptoms. The management of SPMS includes: pharmacological management of the disease, in other words, drugs with a relapsing indication or symptomatic drugs; and nonpharmacological management, in other words, rehabilitation and physiotherapy to manage symptoms such as fatigue, brain fog and spasticity [19].

Although several DMTs are approved for the relapsing form of the disease, very few DMTs are specifically approved for SPMS [20]. Cladribine received European Commission (EC) approval in 2017 for relapsing MS (RMS and active SPMS) [21]. Siponimod, a selective modulator of sphingosine-1-phosphate receptor, was also approved by the EC in 2020 for the management of active SPMS [22]. Mitoxantrone is approved by the US FDA and recommended as per the American Academy of Neurology and European Committee for Treatment and Research in Multiple Sclerosis guidelines for the treatment of SPMS [15,23]. In some cases, neurologists view ocrelizumab (and other high-efficacy therapies) as an alternative to treat RMS patients, as it can be prescribed without confirmation of SPMS diagnosis and patients can be switched back to other RRMS treatments if they do not respond to ocrelizumab.

Multiple barriers exist in the management of patients with SPMS. A huge knowledge gap concerning SPMS and its management exists among general neurologists. In all countries, neurologists are reluctant to switch treatment during transition, mainly owing to the lack of safe and cost-effective treatment options. Recent therapeutic agents faced challenges in reimbursements, which in turn increased the off-label use of MS drugs. The key barriers to treatment reimbursement vary from country to country. In Germany, lack of information on recommended treatments in health insurance and no acceptance of indirect comparisons by the Federal Joint Committee (GBA – Gemeinsamer Bundesausschuss) are the key deterrents to SPMS treatment reimbursement. In France, unavailability of robust epidemiology data to justify volume estimations acts as a barrier to treatment reimbursement. In Italy and Spain, RWE may be useful in optimizing drug positioning, and in facilitating patients' treatment access and outcomes. With regard to budget impact analysis and cost–effectiveness, payers from all countries primarily focus on direct medical and nonmedical costs. The indirect medical costs play a secondary role in cost–effectiveness analysis, and societal costs do not impact price and reimbursement decisions. The heterogeneity in the active

10.2217/nmt-2020-0054

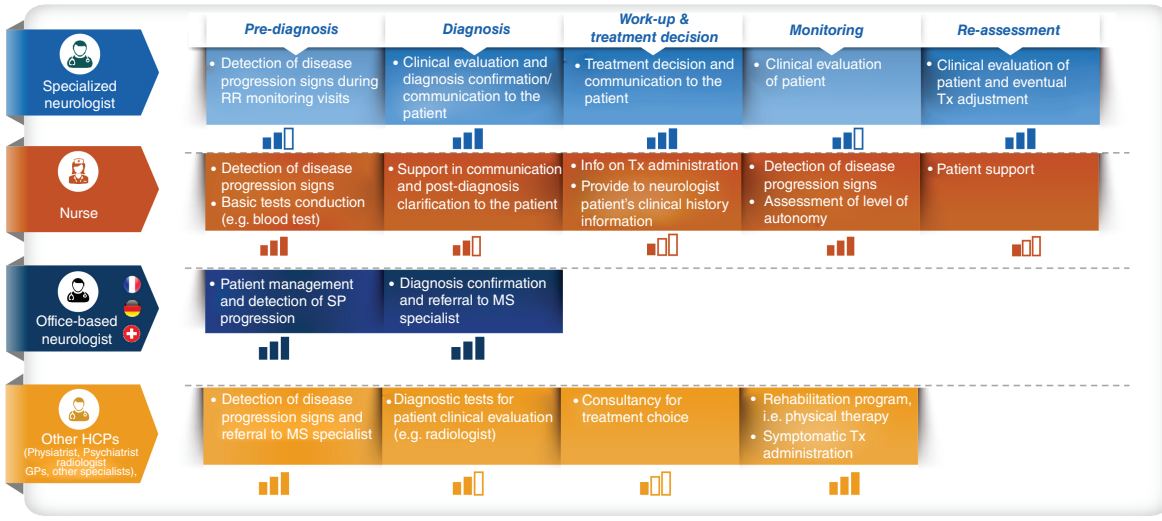


Figure 4. Different stakeholders involved and their role in the management of secondary progressive multiple sclerosis patients.
GP: General practitioner; HCP: Healthcare professional; MS: Multiple sclerosis; RR: Relapsing-remitting; SPMS: Secondary progressive MS; Tx: Treatment.

SPMS population that includes rapidly progressive and older patients who are without treatment access, hinders the cost/benefit evaluation of a therapeutic agent.

Monitoring & reassessment

Owing to the long patient journey, continuous monitoring to check disease progression is vital in MS, and nurses play a primary role in this regard. A higher monitoring frequency for patients with RRMS, which usually varies from 3 months to a year, could help identify new SPMS cases. While neurologists play a key role in diagnostic and treatment decisions, nurses and other HCPs are important for prediagnosis and monitoring (Figure 4). Moreover, the role of nurses is not so much focused on the detection of progression signs and diagnosis of SPMS, but rather on monitoring. In the UK, nurses can provide critical information to the MS physicians, which may be relevant during the diagnosis. In Germany, nurses are usually involved in monitoring patients every 3–6 months, which may help in detecting transition to SPMS. In all seven countries, monitoring depended on the size and dynamics of the MS center. The patient's caregiver and family also play a pertinent role in monitoring, in terms of support and assessment of the symptoms of disease progression. Neurologists are largely involved in the treatment, monitoring and periodical reassessment of patients with SPMS. In Spain, Italy and France, most patients are managed at MS centers of excellence. In the UK, in addition to neurologists, general practitioners with expertise in neurology play an important role in patient management; while in Germany, monitoring and reassessment is done by neurologists at MS centers, as well as office-based neurologists. However, the responsibilities of the multidisciplinary teams and rehabilitation specialists in monitoring patients with SPMS are currently limited.

According to the panel discussion, nearly 10–30% of patients with SPMS (UK and Norway: 10–20%; France: ~30%; Italy, Switzerland and Spain: <10%; Germany: ~20%) are lost in the system after SPMS detection owing to apprehension regarding the lack of effective treatment, long waiting times for MRI and mobility issues. However, once patients start receiving their SPMS treatment, adherence is not a grave concern unless there are cognitive or emotional issues, ineffective treatment or any adverse effects. As per the experts' opinion, only 5–10% of patients with SPMS reportedly display nonadherence to treatment.

Future patient journey

Expectations from neurologists

The primary objective for neurologists should be early diagnosis of SPMS and timely initiation of appropriate treatment, with no anticipation of major disruptive events impacting diagnosis. However, this remains aspirational considering the time it takes to confirm SPMS.

Expectations from MS nurses

Nurses play an active role in the recognition of disease transition and often discuss this with their patients. Consistent communication with patients and increased awareness of the disease among nurses may facilitate an earlier diagnosis. Patient-reported outcomes (PROs) are essential in the identification of the right signs of disease progression [24]. In the UK, although the focus is on RRMS, an increased awareness of SPMS is imperative for early diagnosis.

More DMT options necessitate safety monitoring of new drugs, progression monitoring and patient education on the expanded drug access. During the treatment phase, a greater workforce, digital tools and setting the right expectations on the effectiveness of emerging therapies among patients, neurologists and caregivers could galvanize SPMS management [25].

Overall, change in the relapsing-remitting monitoring approach, greater attention to SPMS detection, and increased contact and collaboration between nurses and physicians will potentially expedite SPMS reporting. Digital applications to support remote patient tracking may aid in patient monitoring, and nurses would need to be trained in using these platforms.

Expectations from payers

To shape a distinct SPMS landscape in the future, clarity on SPMS definition, epidemiological data and increased awareness on SPMS is essential. Availability of data on indirect comparisons, RWE and subgroup of patients with rapid progression will be useful in decision-making on disease budget allocations [26]. More adaptive trial designs that can demonstrate satisfactory effect sizes in subgroups of patients with rapid progression are imperative.

Payers expect EDSS scores to remain as the gold standard for their evaluations. A composite end point that measures both inflammation and disease progression could be useful for physicians, but not for payers as it will not allow for comparisons with already existing products. Payers do foresee value in digital tools and applications, although with a low impact on price and reimbursement. However, digital applications independent of patient input are preferred as patients tend to get demotivated about feeding in their data after a few months of treatment.

Role of pharmaceutical industry

Although significant progress has been achieved in RRMS treatment, the same is yet to be replicated in SPMS disease diagnosis and treatment. This lack of development can be explained by an insufficient understanding of SPMS pathophysiology [27] and unclear diagnostic criteria [28]. The pharmaceutical industry is expected to provide support for minimizing the ambiguity in SPMS disease definition [13] and improving patients' disease awareness. Pharmaceutical companies must remain highly involved in raising awareness and continue educational initiatives, such as congresses, symposiums and workshops, training programs, patient networks and digital applications for tracking patients' evolution and detection of disease progression. Digital tools [29] can gather real-world data that can encourage patient education and transcend barriers to disease awareness.

For SPMS research to be compelling and clinically impactful, collaborative efforts are needed between the pharmaceutical industry and multi-stakeholders involved in SPMS patient care. There is a pressing need for pharmaceutical companies and HCPs to support nurse education, particularly on the psychological impact of SPMS on patients. Increased awareness in patients and caregivers on the disease and its treatments through dedicated communities is also necessary. Furthermore, inclusion of PROs in the clinical trials will highlight the real-added value of new treatments. Pharmaceutical resources for the training and education of HCPs must be strengthened (Figure 5).

Discussion

A high level of heterogeneity exists in current clinical practice regarding the diagnosis and standard of care for SPMS. In most countries, neurologists are the key prescription decision-makers, and payers have limited control in this regard, except in complex SPMS cases for which neurologists may seek advice from multidisciplinary teams while choosing the right treatment. Furthermore, regulating neurologists' treatment decisions is challenging, given the lack of clarity in differentiation between MS phenotypes and lack of head-to-head treatment comparisons in clinical trials. Therefore, it is essential to address different aspects in the patient journey of SPMS.

Essentially, disease monitoring in an SPMS patient involves patient history, clinical examination and MRI markers of disease progression when available. Patients' feedback regarding the worsening of their condition and side effects of the ongoing treatment is fundamental in understanding the efficacy of any therapy. Therefore, it

10.2217/nmt-2020-0054

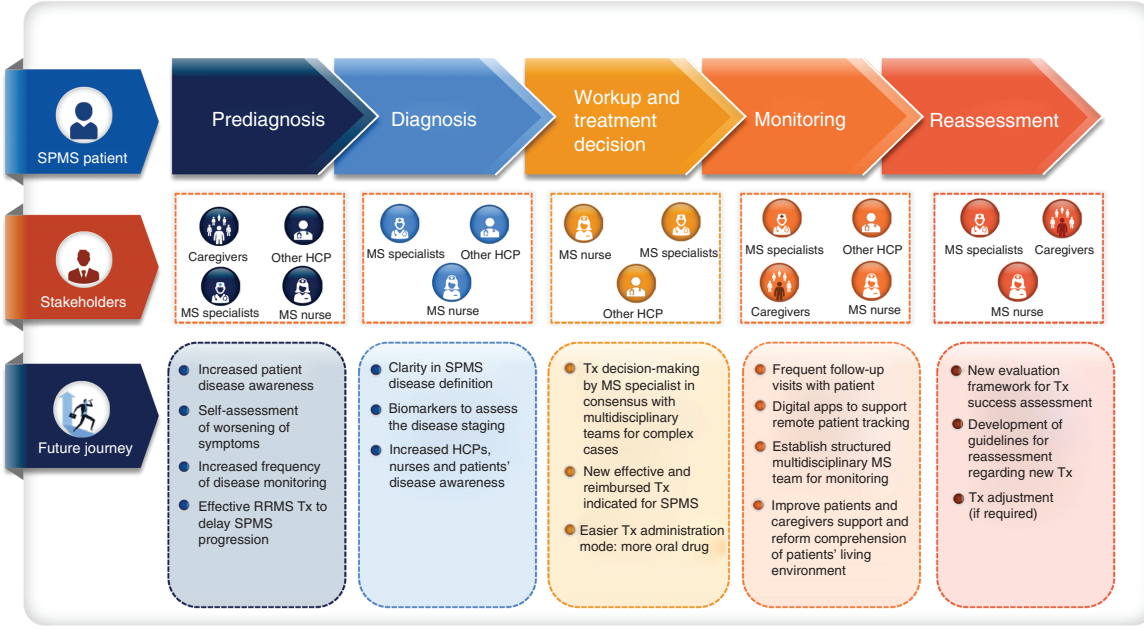


Figure 5. Future patient journey with secondary progressive multiple sclerosis.
HCP: Healthcare professional; MS: Multiple sclerosis; RRMS: Relapsing-remitting MS; SPMS: Secondary progressive MS; Tx: Treatment.

would be desirable to take into consideration more PROs together with MRI and other clinical outcomes, in particular, the outcomes relevant for patients. Additionally, increased awareness of SPMS and advancements in monitoring the approach of patients with RRMS may help detect SPMS earlier. In this regard, digitals tools are key, as patients could monitor themselves and report outcomes. The universal implementation of digital tools, validated with long-term cohort data and the opinions of allied multidisciplinary teams, remains vital for the monitoring and reassessment of patients with SPMS [25].

Complete MS biosignature development will be crucial, which could lead to the use of serum levels of neurofilament light chain, GFAP, along with the established MRI markers of disease progression to monitor disease advancement instead of waiting for the clinical worsening [30,31]. It is also essential for clinicians managing patients with SPMS to improve collaboration and referral pathways as patients display multiple symptoms and potential organ toxicities due to DMTs. The recent emergence of oral medications, an easier mode of administration specifically approved for SPMS, offers new therapeutic options and potentially improved treatment adherence. Neurologists also discussed the potential of combination therapies that would reduce inflammation and simultaneously improve myelin regeneration; however, such therapies are not anticipated in the near future.

The outcome of pipeline products for SPMS remains uncertain, predominantly due to the lack of treatment sequencing and the prospects of overlapping drug labels. For novel SPMS drugs, the indications to include younger as well as older patients remain an enigma owing to the lack of evidence. Positioning of potential DMTs for SPMS would ideally be based on populations investigated in controlled settings. Clear communication of the value of DMTs will be key for optimizing price and reimbursement. For emerging therapies in SPMS, a detailed analysis of the clinical profile is essential to make a precise price assessment [30]. Moreover, studies on the possibility of using RRMS drugs for SPMS have revealed unsatisfactory outcomes [31–34].

The reduced efficacy of RRMS biologics in SPMS is unlikely to have an impact on the price potential of therapies specifically approved for SPMS, as drug prices are compared within the same indication. However, due to budget constraints, the emerging oral therapies for SPMS are most likely to compete with interferons on drug price and should be priced lower than ocrelizumab; for instance, to secure access at both national and regional levels across the major countries in Europe.

Patient access to novel effective treatment options will facilitate and encourage the diagnosis of SPMS. Therefore, it is fundamental for drug developers to explicitly communicate the added value of new drugs and make the

information readily available to patients and stakeholders involved in SPMS patient care. Pharmaceutical companies can substantiate treatment usefulness through RWE generation and obtain broad access for patients with SPMS. The long-term cohort data would be helpful to validate the use of digital tools and aids [35].

Limitations

This is a qualitative research study. The participants responded to the questions and provided their feedback based on their expertise. We included a panel of 58 local experts, randomly selected from seven European countries, to get a balanced regional view; however, it would be beneficial to include the opinions of the stakeholders from other countries as well. The perspectives of SPMS patients and caregivers were not included in this expert panel discussion.

Conclusion

The perception of MS as 'one disease' has undergone a paradigm shift, with no clear differentiation between RRMS and SPMS. Ambiguity also exists regarding the definition of SPMS and identification of active versus nonactive forms of the disease. Although there are a number of challenges in clinical management (diagnosis and treatment) of patients with SPMS, it is evident that the collaborative efforts of the associated stakeholders (neurologists, nurses, caregivers, payers, patients and the pharmaceutical industry), along with advances in the understanding of SPMS pathophysiology and diagnostic criteria, robust assessment guidelines, enhanced disease awareness and availability of RWE in the future, will allow for optimal care that will improve the quality of life of people living with SPMS.

Author contributions

All the authors edited the manuscript for intellectual content, provided guidance during manuscript development, and approved the final version submitted for publication, and meet the criteria for authorship as recommended by the International Committee of Medical Journal Editors (ICMJE).

Acknowledgments

The authors thank the IQVIA team for their collaboration on project design, primary and secondary research, expert meetings and project reports. The authors also thank G Minhas and S Thammera (Medical Communications, Novartis Healthcare Pvt. Ltd., Hyderabad, India) for writing assistance, editorial review assistance and coordinating author review.

Financial & competing interests disclosure

This project was funded by Novartis Pharma AG. The authors have received no payment to write this article. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

G Minhas and S Thammera (Medical Communications, Novartis Healthcare Pvt. Ltd., Hyderabad, India) and was funded by Novartis Pharma AG. Medical writing assistance and the page processing charges for this article have been financially supported by Novartis Pharma AG.

References

Papers of special note have been highlighted as: • of interest; •• of considerable interest

1 Kamm CP, Uitdehaag BM, Polman CH. Multiple sclerosis: current knowledge and future outlook. *Eur. Neurol.* 72(3–4), 132–141 (2014).

2 Collaborators GBDMS. Global, regional, and national burden of multiple sclerosis 1990–2016: a systematic analysis for the Global Burden of Disease Study 2016. *Lancet Neurol.* 18(3), 269–285 (2019).

3 European Multiple Sclerosis Platform. MS Barometer 2015: raising the voice of people with MS (2015). http://www.emsp.org/wp-content/uploads/2017/02/BAROMETER-2015-28.02.2017.pdf

4 European Multiple Sclerosis Platform. Under pressure: living with MS in Europe. http://www.underpressureproject.eu/web/living-with-ms-in-europe

5 MS International Federation. Global MS employment report. https://www.msif.org/wp-content/uploads/2016/05/Global-MS-Employment-Report-2016.pdf

6 Kobelt G, Thompson A, Berg J, Gannedahl M, Eriksson J. New insights into the burden and costs of multiple sclerosis in Europe. *Mult. Scler.* 23(8), 1123–1136 (2017).

• **This European burden of illness study reported that high correlation between costs/utility disease burden in multiple sclerosis (MS) patients with disease severity. However, resource consumption was severely affected by healthcare systems organization and availability of services.**

7 Editorial. Setting new standards in multiple sclerosis care and research. *Lancet Neurol.* 11(10), 835 (2012).

8 Brown JWL, Coles A, Horakova D *et al.* Association of initial disease-modifying therapy with later conversion to secondary progressive multiple sclerosis. *JAMA* 321(2), 175–187 (2019).

9 Lublin FD, Reingold SC, Cohen JA *et al.* Defining the clinical course of multiple sclerosis: the 2013 revisions. *Neurology* 83(3), 278–286 (2014).

10 Thompson AJ, Banwell BL, Barkhof F *et al.* Diagnosis of multiple sclerosis: 2017 revisions of the McDonald criteria. *Lancet Neurol.* 17(2), 162–173 (2018).

11 Lublin FD, Coetzee T, Cohen JA, Marrie RA, Thompson AJ, International Advisory Committee on Clinical Trials in MS. The 2013 clinical course descriptors for multiple sclerosis: a clarification. *Neurology* 94(24), 1088–1092 (2020).

12 National Mulitple Sclerosis Society. Secondary progressive MS (SPMS). https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS

13 Lorscheider J, Buzzard K, Jokubaitis V *et al.* Defining secondary progressive multiple sclerosis. *Brain* 139(9), 2395–2405 (2016).

14 National Multiple Sclerosis Society. Disease-modifying therapies for MS. http://www.nationalmssociety.org/NationalMSSociety/media/MSNationalFiles/Brochures/Brochure-The-MS-Disease-Modifying-Medications.pdf

15 Rae-Grant A, Day GS, Marrie RA *et al.* Practice guideline recommendations summary: disease-modifying therapies for adults with multiple sclerosis: report of the Guideline Development, Dissemination, and Implementation Subcommittee of the American Academy of Neurology. *Neurology* 90(17), 777–788 (2018).

16 Bakshi R, Thompson AJ, Rocca MA *et al.* MRI in multiple sclerosis: current status and future prospects. *Lancet Neurol.* 7(7), 615–625 (2008).

17 Healey K, Zabad R, Young L *et al.* Multiple Sclerosis at Home Access (MAHA): an initiative to improve care in the community. *Int. J. MS. Care* 21(3), 101–112 (2019).

18 Helleso R, Fagermoen MS. Cultural diversity between hospital and community nurses: implications for continuity of care. *Int. J. Integr. Care* 10, e036 (2010).

19 Macaron G, Ontaneda D. Diagnosis and management of progressive multiple sclerosis. *Biomedicines* 7(3), 56 (2019).

20 National Multiple Sclerosis Society. Treating SPMS. https://www.nationalmssociety.org/What-is-MS/Types-of-MS/Secondary-progressive-MS/Treating-Secondary-Progressive-MS

21 EMD Serono, Inc. Cladribine: prescribing information. https://www.accessdata.fda.gov/drugsatfda_docs/label/2019/022561s000lbl.pdf

22 Novartis Pharmaceuticals Corporation. Siponimod: prescribing information. https://www.pharma.us.novartis.com/sites/www.pharma.us.novartis.com/files/mayzent.pdf

23 Montalban X, Gold R, Thompson AJ *et al.* ECTRIMS/EAN guideline on the pharmacological treatment of people with multiple sclerosis. *Mult. Scler.* 24(2), 96–120 (2018).

24 Schriefer D, Haase R, Ettle B, Ziemssen T. Relapses in multiple sclerosis reported by patients versus physicians - insights from a large observational study. *Eur. J. Neurol.* 27, 2531–2538 (2020).

•• **Compared the patient reported-relapses with physician-documented relapses during quarterly visits and reported some disagreements, especially in patients with increased disability, decreased HRQoL or treatment satisfaction.**

25 Maillart E, Labauge P, Cohen M *et al.* MSCopilot, a new multiple sclerosis self-assessment digital solution: results of a comparative study versus standard tests. *Eur. J. Neurol.* 27(3), 429–436 (2020).

26 Samjoo IA, Worthington E, Haltner A *et al.* Matching-adjusted indirect treatment comparison of siponimod and other disease modifying treatments in secondary progressive multiple sclerosis. *Curr. Med. Res. Opin.* 36(7), 1157–1166 (2020).

•• **Utilized matching-adjusted indirect comparison to correct the cross-trial differences and demonstrated improved efficacy of siponimod over other disease-modifying treatments in secondary progressive MS.**

27 Faissner S, Plemel JR, Gold R, Yong VW. Progressive multiple sclerosis: from pathophysiology to therapeutic strategies. *Nat. Rev. Drug Discov.* 18(12), 905–922 (2019).

28 Katz Sand I, Krieger S, Farrell C, Miller AE. Diagnostic uncertainty during the transition to secondary progressive multiple sclerosis. *Mult. Scler.* 20(12), 1654–1657 (2014).

29 Midaglia L, Mulero P, Montalban X *et al.* Adherence and satisfaction of smartphone- and smartwatch-based remote active testing and passive monitoring in people with multiple sclerosis: nonrandomized interventional feasibility study. *J. Med. Internet Res.* 21(8), e14863 (2019).

•• **Assessed the adherence and satisfaction with FLOODLIGHT test battery and reported that patients with MS were engaged and satisfied with the test battery, which may enable continuous assessment of MS disease in clinical trials and real-world settings.**

30 Kappos L, Giovannoni G, Gold R *et al.* Long-term efficacy of siponimod treatment for up to 5 years in patients with SPMS: analysis of the EXPAND extension study. ePresentation sessions. *Eur. J. Neurol.* 27(S1), 103–522 (2020).

•• **Treatment benefit with siponimod (efficacy and safety) observed in the EXPAND-core study was sustained with long-term treatment for up to 5 years (EXPAND-extension study).**

31 Coles AJ, Cox A, Le Page E *et al.* The window of therapeutic opportunity in multiple sclerosis: evidence from monoclonal antibody therapy. *J. Neurol.* 253(1), 98–108 (2006).

32 Fitzner D, Simons M. Chronic progressive multiple sclerosis - pathogenesis of neurodegeneration and therapeutic strategies. *Curr. Neuropharmacol.* 8(3), 305–315 (2010).

33 Rice GP, Filippi M, Comi G. Cladribine and progressive MS: clinical and MRI outcomes of a multicenter controlled trial. Cladribine MRI study group. *Neurology* 54(5), 1145–1155 (2000).

34 Secondary Progressive Efficacy Clinical Trial of Recombinant Interferon-Beta-1a in MS (SPECTRIMS) Study Group. Randomized controlled trial of interferon-beta-1a in secondary progressive MS: clinical results. *Neurology* 56(11), 1496–1504 (2001).

35 Ziemssen T, Hoffmann O, Klotz L, Schreiber H, Weber M, Rauser B. Gaining first insights on secondary progressive multiple sclerosis patients treated with siponimod in clinical routine: protocol of the noninterventional study AMASIA. *JMIR Res. Protoc.* 9(7), e19598 (2020).

•• **Described the study design of AMASIA, a long-term study to assess the effectiveness and safety of siponimod in the clinical practice and evaluate the impact of disease burden on quality of life and socioeconomic conditions in secondary progressive MS patients.**

10.2217/nmt-2020-0054