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REVIEW

The Use of Patient-Reported Outcome Measures in Developmental Age: A Complementary Tool for Pediatric Multiple Sclerosis Prognosis

Paola Zaratin · Maria Pia Amato · Giampaolo Brichetto · Anne Helme · Brenda Banwell · Angelo Ghezzi

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ABSTRACT

In pediatric multiple sclerosis (MS), assessment of disease burden predominantly relies on outcome measures developed and validated in adult populations. The application of these tools to children and adolescents may compromise sensitivity and specificity, potentially resulting in an underestimation of disease impact. Symptoms such as fatigue, mood disorders, and cognitive impairment may present subtly in younger patients and are therefore prone to underrecognition in routine clinical practice. Comprehensive evaluation of pediatric MS requires integration of the perspectives of both patients and their caregivers to fully capture the multidimensional effects of the disease, including psychosocial and functional consequences. Incorporation of patient-reported outcome measures (PROMs) into routine clinical care enables a more patient-centered assessment and supports informed clinical decision-making and personalized disease management. Furthermore, PROMs may provide insight into long-term health trajectories and help identify early predictors of adult outcomes. In recognition of the need for a coordinated global approach, the PROMS Initiative was established in 2019 to promote the development, validation, and implementation of PROMs in both research and clinical settings. Its objectives include facilitating the integration of PROMs into clinical trials, routine care, and regulatory frameworks across adult and pediatric populations. To optimize clinical utility, PROMs should demonstrate validity, reliability, and responsiveness, and their use should be standardized while remaining developmentally appropriate and tailored to age and disease stage. This article summarizes the current landscape of PROM use in pediatric MS and highlights key gaps to guide future research and clinical implementation.

P. Zaratin (✉) · G. Brichetto
Research Department, Italian Multiple Sclerosis Foundation, Genoa, Italy
e-mail: paola.zaratin@aism.it

M. P. Amato
Department NEUROFARBA, University of Florence, Florence, Italy

M. P. Amato
IRCCS Fondazione Don Carlo Gnocchi, Florence, Italy

A. Helme
Multiple Sclerosis International Federation, London, UK

B. Banwell
Department of Pediatrics, Johns Hopkins University, Baltimore, MD, USA

A. Ghezzi
Dipartimento di Scienze della Salute, Università di Novara, Novara, Italy

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Key Summary Points
Pediatric multiple sclerosis (MS) occurs during critical brain development, making early cognitive monitoring essential.
Digital patient-reported outcome measures (PROMs) support remote monitoring, real-time data collection, faster scoring, and improved integration with digital health systems.
Challenges of digital PROMs implementation: responsible research and innovation (RRI) and youth engagement are essential for tool development.
Greater PROMs' integration is needed in clinical trials, routine care, and regulatory decision-making in pediatric MS.
Recommendations for core PROMs and performance measures for pediatric-onset MS will be co-produced using structured multistakeholder consensus, aligned with the Global PROMS Initiative objectives.

PEDIATRIC-ONSET MULTIPLE SCLEROSIS (POMS)

Recent data from national MS registers indicate that the onset of multiple sclerosis (MS) before the age of 18 occurs in 4.4–8.7% of all MS cases [1, 2] and there are at least 30,000 people with MS under the age of 18 worldwide [3]. Pediatric-onset MS (POMS) shares many clinical features with adult-onset MS, but there are some distinctive characteristics that differentiate the two forms: in children with MS the course is predominantly relapsing–remitting, with progressive forms being quite rare [4, 5]; the frequency of relapses is approximately twice as high [6, 7]; relapses tend to recover more promptly with fewer residual deficits [8]; disability accrual is slower and takes about 10 years longer, although the patients are younger when reaching mild and severe disability milestones [1, 9, 10]. Moreover, in three studies assessing disability progression in POMS, the shift from mild to severe disability occurred relatively quickly (mean of 7 years), despite the prolonged time to achieve mild disability (mean of 23.9 years). Children who develop MS before the age of 12 may constitute a subgroup with unique characteristics [11]. A study comparing patients with POMS with onset before age 12 ($n=172$) to those with onset between ages 12–18 ($n=1821$) revealed significant differences: the younger group had a higher proportion of male patients, more isolated brainstem involvement, longer intervals between episodes, slower conversion to secondary progression, and extended time to reach disability milestones. Additionally, clinical and magnetic resonance imaging (MRI) prognostic factors varied between the two groups [10].

The relapsing–remitting course with high relapse rate is consistent with findings of heightened inflammatory activity in POMS compared to adult MS, as indicated by MRI data. The pronounced inflammation driving the demyelinating process underscores the urgency of early treatment with disease-modifying drugs (DMDs) in patients with POMS to halt inflammation, protect the brain, and prevent progression to the degenerative phase. Advances in the management of patients with POMS—namely the shorter time between disease onset and diagnosis, the earlier initiation of DMDs, and the increasing use of high-efficacy DMDs—have led to a significant delay in disability progression and a reduced risk of relapses [12], with an overall positive effect on quality of life [13]. These improvements may also play a role in reducing the proportion of patients with cognitive difficulties, once reported at around 30% (see Table 2) and estimated at 22–26% in recent US studies (see the last two references in Table 2) [14].

The use of more sophisticated clinical tools to accurately assess the burden of the demyelinating process, including measures based on the

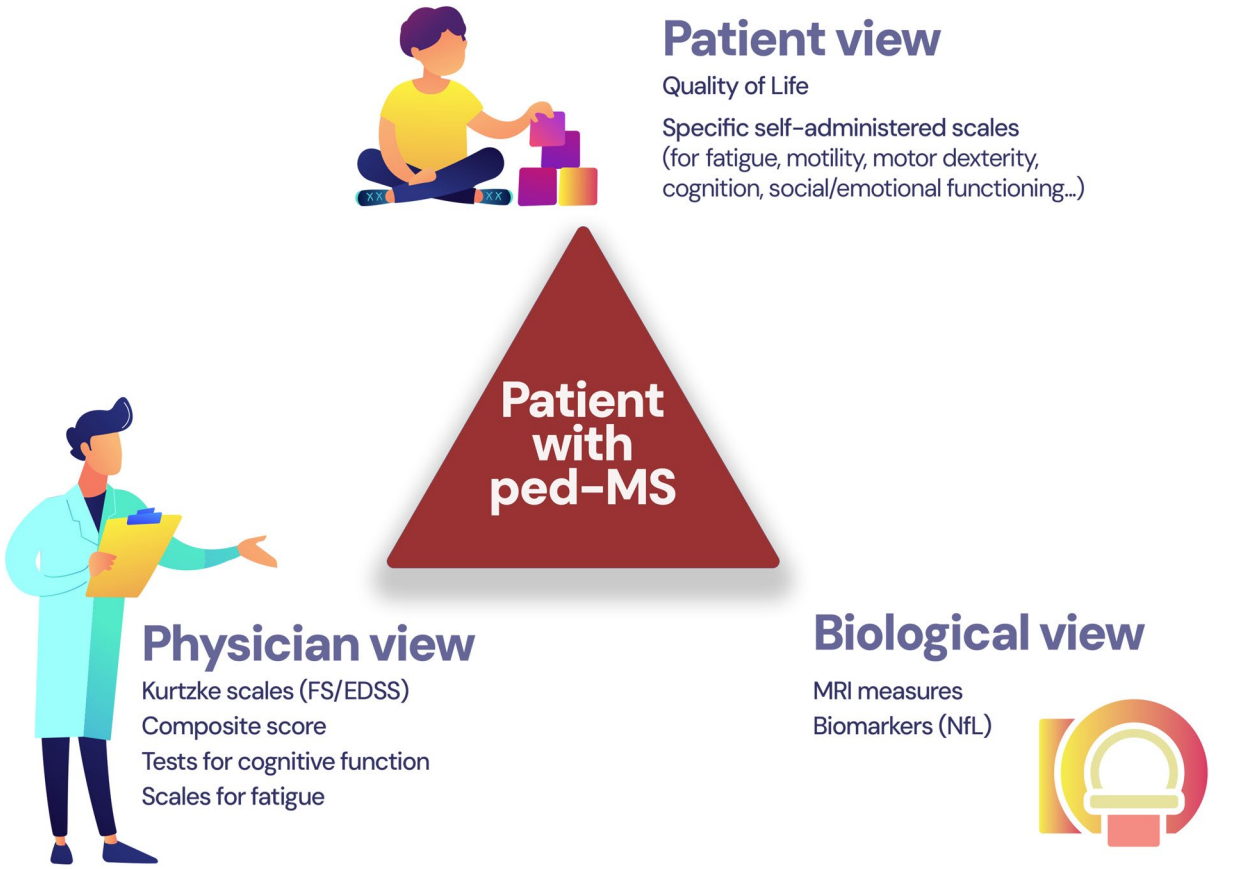

Fig. 1 Multidimensional assessment of patients with pediatric-onset multiple sclerosis. This figure illustrates the three complementary perspectives involved in evaluating patients with ped-MS: *Patient view*: Focuses on quality of life and uses specific self-administered scales to assess fatigue, mobility, motor dexterity, cognition, and social/emotional functioning. *Physician view*: Includes clinical assessment tools such as Kurtzke scales (FS and EDSS), composite scores, cognitive function tests, and fatigue scales. *Biological view*: Encompasses objective biomarkers including MRI measures and NfL levels. *ped-MS* pediatric-onset multiple sclerosis, *FS* Functional Systems, *EDSS* Expanded Disability Status Scale, *MRI* magnetic resonance imaging, *NfL* neurofilament light chain

patient perspective, would enable a more precise evaluation of the impact of MS on patients, as well as the effectiveness of therapeutic interventions not limited to pharmacological approaches. Using a patient-reported approach in addition to neuroimaging or biomarker measurements [15] could help capture the progression that is independent of the occurrence of clinical relapses, which is also present in the pediatric form [16]. As a result of the long interval required for the development of mild disability, patients with POMS remain at low levels of disability for a long time, making it challenging to detect subtle changes or fluctuations in neurological status [17] with commonly used clinical scales (see "Physician view" in Fig. 1).

In addition to classical neurological manifestations—motor, sensory, balance, visual impairments, etc.—patients with MS may present disturbances such as fatigue (reported in 9—76% of cases, and more frequently than in healthy controls [18], mood disorders, particularly depression (in 5–25% of cases [19]), and cognitive dysfunction (see Sect. "Cognitive Impairment and the Role of Digital PROMs"): these symptoms are often subtle and may be challenging to detect, assess, and quantify, particularly in this pediatric population. It is noteworthy that most clinical

scales have been developed and validated for use in adult populations and are not specifically designed for pediatric subjects. While their application in pediatric cohorts allows for standardized comparisons across age groups, these tools may lack sensitivity and specificity when applied to children and adolescents, potentially underestimating the true burden of disease in younger patients.

The diagnosis and symptoms of MS affect individuals' self-perception of well-being, as well as their family and social relationships, academic life, and sporting or other leisure activities. The effects of MS on both patients and their familial/social environment are similarly difficult to assess and quantify. Capturing patients with POMS' experiential knowledge and making it scientifically relevant through patient-generated health data (PGHD) [20] will enable the holistic approach needed to make earlier diagnosis, promote preventive treatment strategies, and monitor disease progression, enabling quicker treatment switching or symptomatic support as needed. This approach requires assessing MS comprehensively, summarizing the overall burden of the disease by measuring and quantifying different aspects (Fig. 1):

- Clinical manifestations (symptoms/signs/evolution), as assessed by physicians.
- Clinical manifestations and their impact on everyday activities, psychological and social functioning, as assessed by patients and their parents, for pediatric patients with MS, as discussed later (see Sect. "Conclusions").
- Biological burden of the disease, assessed via MRI measures and humoral biomarkers. As this aspect is beyond the scope of this paper, we refer the reader to a recent study evaluating the role of biological markers in comparison with neuroimaging findings [21].

For assessing neurological clinical status, Kurtzke's scales (Functional Status [FS] and Expanded Disability Status Scale [EDSS]) [22], primarily developed for adults, are also widely applied in POMS. These scales remain the most widely used measures of neurological impairment in spite of the well-known limitations, such as the intra- and interrater variability, nonlinear relationship between impairment extent and clinical scores, subjective assessment of gait and sphincteric functions, and predominant focus on motor function and ambulation [23]. An additional limitation in their use in POMS is the inability to capture subtle changes of neurological status: since patients with POMS spend a long time at the lower levels of EDSS, the US Network of Pediatric MS Centers proposed the Ped-Multiple Sclerosis Severity Score (MSSS) to increase the sensitivity of Kurtzke's scales. This score relates the EDSS scores to the distribution of disability in patients with comparable disease durations [14]. To date, no other study has been published using this modified Kurtzke scale. As stated by the International Pediatric MS Study Group (IPMSSG) around 10 years ago, "some relevant outcome measures in pediatric MS may be different from those traditionally used in adult MS trials, and may require new and currently unvalidated measures. It would be desirable to have more accurate tools to better define the burden and impact" [24]. Limited advances have been made in this area and this remains a priority for POMS stakeholders [25]. The Multiple Sclerosis Functional Composite Measure (MSCF), which aims to integrate neurological assessment by introducing measures of walking ability, manual dexterity, and cognition [26], has been proposed as an additional tool in POMS evaluation [27–29] but, except for research studies, these tests are not currently applied in clinical practice. FS, EDSS, and MSCF only measure part of neurological impairment. Scales for cognitive function, mood disorders, and fatigue in POMS are suggested but rarely used in clinical settings, though they feature in national projects [30].

In recognition of the need for a common strategic agenda and roadmap shared by all relevant stakeholders, the Global Patient-Reported Outcome for Multiple Sclerosis (PROMS) Initiative was born in 2019 [31] to shape and develop the field [32–34] to increase the uptake of PROMs from research to care and in decision-making processes by regulatory agencies in both adult and pediatric patients. Various stakeholders, including regulators, have been concentrating their efforts into examining obstacles to the integration of patient experience data (PED),

including PROMs, in medicines development and regulatory decision-making [35, 36]. A summary of these efforts is provided below.

Literature Search Approach

To inform this narrative review, we performed a structured, non-systematic literature search primarily in PubMed/MEDLINE, complemented by targeted searches in multidisciplinary databases and manual screening of reference lists of relevant publications. The search covered the period from January 2000 to October 2025 and combined terms related to pediatric-onset MS and patient-/observer-reported outcomes. Given the narrative scope of this manuscript, no PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) workflow was applied and no formal risk-of-bias assessment was performed. This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

PROMS AND OTHER CLINICAL OUTCOME ASSESSMENTS (COAS)

General Measures

According to the US Food and Drug Administration (FDA) working group on COAs [37], classifications include clinician-reported outcomes (ClinRO), performance outcomes (PerfO), observer-reported outcomes (ObsRO), and patient-reported outcomes (PROs).

ClinRO is a measurement based on information from qualified health professionals following observation of the patient's health condition. Most ClinRO measures involve clinical judgment or interpretation of observable signs, behaviors, or other health manifestations. Unlike PROs, ClinRO measures cannot directly evaluate symptoms that are known exclusively to the patient. ClinRO data can be acquired electronically via usual digital platforms on mobile devices or personal computers. ClinRO measures include specific clinical findings (e.g., skin lesion presence or enlarged lymph nodes) and evaluation scales, such as the EDSS for MS.

PerfO is a type of clinical outcome assessment defined as a measurement based on standardized activities actively performed by a patient following predetermined instructions. PerfO assessments can be administered by trained professionals or independently performed by the patient. Notably, technological evolution enables PerfO data collection through mobile and wearable devices, which can be either clinician-controlled or independently managed by the patient. PerfO data collected electronically, as well as traditionally, are discrete measures acquired during predefined events (medical visits, clinical trial assessments). Alongside discrete PerfO evaluations, continuous measures using wearable devices can also be classified within PerfO [38]. PerfO assessments include measures of walking speed (e.g., timed 25-foot walk test using a stopwatch) and some cognitive domain measurements (e.g., word recall tests).

ObsROs are reported by someone other than the patient, typically a caregiver or family member, who can report on observable behaviors or aspects of health. This type of outcome is often used when the patient is unable to report for themselves, such as in the case of young children or individuals with cognitive impairments. Note that observer reports are different from proxy reports. Proxy reports are also completed by someone other than the patient, such as a caregiver, but proxy reporting also includes assessment of aspects of health that cannot be comprehensively observed and are only truly known by the patient themselves, such as the degree of fatigue or pain. We will discuss the challenges with proxy reporting in POMS later in this article.

PROs are defined as any direct report from patients about the status of their health condition, without the interpretation of their responses by clinicians or anyone else. This concept was outlined by the FDA in 2009 and similarly by the European Medicines Agency (EMA) 2014. PRO measures (PROMs) refer to any tools, such as questionnaires or instruments, that record health-related data collected from patients' self-reporting. The FDA PRO definition includes both active and digital passive

measurements. These definitions underscore the importance of the patient's voice in assessing health outcomes and the effectiveness of medical interventions. In POMS research, PROMs selection is particularly complex. Study teams must consider not only the treatment effects being measured but also whether the POMS population can understand the questions and response scales. However, symptoms or domains "invisible" to clinicians—known only to the patient—can only be assessed using PROMs. Notably, there has been significant progress in the adoption of digital technologies for collecting PROs electronically (ePRO). In this context, electronic PROs rather than traditional paper-based forms may facilitate wider adoption both in clinical practice and trials. PRO measures include rating scales (e.g., numeric rating scale for pain intensity) and event counting (e.g., patient-completed logs of urinary incontinence episodes).

PROMs assessing relevant domains have been validated in adult MS (see Table 1 with literature) and are currently used in clinical studies and trials (however, a systematic presentation and discussion of data on this topic are outside the aims of the present publication). When considering the implementation of PROMs in pediatric age groups, factors such as cognitive ability, willingness to cooperate, and the availability of validated instruments for the specific indication must also be considered. Selecting the right measures is key to developing a COA strategy that supports reliable, POMS-centered outcomes.

In line with International Society for Pharmacoeconomics and Outcomes Research (ISPOR) recommendations [39], PROMs should be use whenever possible. A challenge with using proxy-reported outcomes is that it is common to see discrepancies between self-reports and proxy reports, a phenomenon known as cross-informant variance, and the use of proxy-reported outcomes is discouraged by the FDA [40]. However, depending on the indication and the ability of the patient to answer, proxy-reported outcomes might be the only option to obtain patient insight. Parent-reported outcomes may introduce potential sources of bias, for instance due to influence of parental distress, and reduced perception of subjective patient experiences that are not directly observable. On the other hand, the reliability of self-reported outcomes in children strongly depends on age, is influenced by cognitive and emotional development, as well as disease awareness. In cases of disagreement between self- and parent-reported outcomes, parallel collection and longitudinal interpretation of both perspectives may provide complementary insights and help interpret differences in symptom perception, coping strategies, or family impact.

Cognitive Impairment and the Role of Digital PROMs

Increasing evidence indicates that cognitive and neurological patterns established during developmental years often serve as indicators of later-life health outcomes. This growing body of evidence has increased interest in the use of digital cognitive PROMs during childhood and adolescence as potential early indicators of adult-onset disease, particularly for conditions in which cognitive decline or impairment is a prominent feature, such as MS, dementia, and certain neuropsychiatric disorders. This evidence has led to increasing interest in using digital cognitive PROMs during the pediatric and adolescent period, particularly for conditions in which cognitive decline or impairment is a prominent feature, such as MS, dementia, and certain neuropsychiatric disorders [41, 42].

Many neurodegenerative diseases, including MS, have a long prodromal phase of several years, providing a window of opportunity to identify cognitive decline when impairment is nonexistent or has little impact on daily function [43]. MS in children occurs during a critical period of ongoing brain growth, myelination, and maturation of neural networks, all of which are essential for cognitive development. Cognitive impairment has been reported in approximately 25–30% of pediatric patients with MS. The neuropsychological profile in children is broadly similar to that observed in adults, with predominant deficits in information processing speed and memory, although language abilities and general intelligence may be affected in some cases. In addition, children and adolescents with

Table 1 List of relevant patient-reported outcome measures (PROMs) used in adult MS

Domains	PROM	Short description	References
Upper limb functions			
	Manual Ability Measurement 36 (MAM-36)	Individuals are asked to rate 36 unilateral and bilateral daily life tasks on a 4-point scale	I. Lamers, S. Kelchtermans, I. Baert, and P. Feys, "Upper limb assessment in multiple sclerosis: a systematic review of outcome measures and their psychometric properties.," Arch. Phys. Med. Rehabil., vol. 95, no. 6, pp 1184–1200
	The Arm Function in Multiple Sclerosis Questionnaire (AMSQ)	Individuals are asked to rate 31 items on arm function on a 6-point scale	L. B. Mokkink, D. L. Knol, F. H. van der Linden, J. M. Sonder, M. D'hooghe, and B. M. J. Uitdehaag, "The Arm Function in Multiple Sclerosis Questionnaire (AMSQ): development and validation of a new tool using IRT methods.," Disabil. Rehabil., vol. 37, no. 26, pp 2445–51
Walking functions			
	Multiple Sclerosis Walking Scale-12 (MSWS-12)	MSWS-12 provides a patient-reported measure of MS impact on walking through 12 items	J. C. Hobart, A. Riazi, D. L. Lamping, R. Fitzpatrick, and A. J. Thompson, "Measuring the impact of MS on walking ability: the 12-Item MS Walking Scale (MSWS-12).," Neurology, vol. 60, no. 1, pp. 31–36, Jan. 2003
Dual tasks functions			
	Dual-task Impact on Daily-living Activities-Questionnaire (DIDA-Q)	DIDA-Q consists of 19 items presenting task combinations commonly performed in daily activities	L. Pedullà et al., "The patients' perspective on the perceived difficulties of dual-tasking: development and validation of the Dual-task Impact on Daily-living Activities Questionnaire (DIDA-Q).," Mult. Scler. Relat. Disord., vol. 46, p. 102601, Nov. 2020

Table 1 continued

Domains	PROM	Short description	References
Fatigue			
	Fatigue Severity Scale (FSS)	PRO focusing on motor aspects of fatigue and its influence on daily activities consisting of nine items	L. B. Krupp, N. G. LaRocca, J. Muir-Nash, and A. D. Steinberg, "The fatigue severity scale. Application to patients with multiple sclerosis and systemic lupus erythematosus.," Arch. Neurol., vol. 46, no. 10, pp. 1121–1123, Oct. 1989
	Modified Fatigue Impact Scale (MFIS)	Multidimensional approach assessing cognitive, physical, and psychological fatigue consisting of 34 items	D. Kos, E. Kerckhofs, I. Carrea, R. Verza, M. Ramos, and J. Jansa, "Evaluation of the Modified Fatigue Impact Scale in four different European countries.," Mult. Scler., vol. 11, no. 1, pp. 76–80
Mood			
	Hospital Anxiety and Depression Scale (HADS)	Identifies and quantifies anxiety and depressive disorders through 14 questions	K. Honarmand and A. Feinstein, "Validation of the Hospital Anxiety and Depression Scale for use with multiple sclerosis patients.," Mult. Scler., vol. 15, no. 12, pp. 1518–1524, Dec. 2009

Table 2 Cognition in pediatric-onset MS (POMS): overview of the main cross-sectional studies and major areas of impairment

Study	Region	MS/HC	Definition of CI	% CI	Major areas of impairment
MacAllister, 2005 [57]	USA	MS 37	≥ 2 test scores > 1.5 SDs below normative data	35.1%	Complex attention, verbal memory, naming
Amato, 2008 [58]	Italy, multicenter	MS 63 HC 63	Performance on≥ 3 tests < 5th percentile of HC performance	31%	Verbal and visual memory, complex attention, executive functions, language, reduced IQ
Till, 2011 [59]	Canada	MS 35 HC 33	≥ 3 test scores < 1.5 SDs below normative data	29.4%	Attention, IPS, visuomotor integration, verbal fluency, spelling abilities
Julian, 2013 [60]	USA, multicenter	MS 187 CIS 44	≥ 33% of test scores < 1 SD below normative data	35% CIS 18%	Fine motor speed, visuomotor integration, IPS
Wallach, 2020 [61]	USA, multicenter	MS 616		22%	IPS (single test assessment on the SDMT)
Krupp, 2023 [62]	USA, multicenter	MS 72 HC 99	≥ 1 test out of 3 impaired	26% on both BICAMS and CBB (in HCs 24% and 32%, respectively)	IPS, memory, reaction times

BICAMS Brief Cognitive Assessment for Multiple Sclerosis, *CBB* CogState Brief Battery, *CI* cognitive impairment, *CIS* clinically isolated syndrome, *HC* healthy controls, *IPS* information processing speed, *MS* multiple sclerosis, *SD* standard deviation, *SDMT* Symbol Digit Modalities Test

MS are at increased risk of psychiatric comorbidity [4]. These cognitive difficulties often emerge early in the disease course, while children are still undergoing critical academic and developmental milestones, and may adversely affect daily functioning, school performance, and behavior. Notably, declines in academic performance may serve as an early indicator of emerging cognitive impairment.

Compared to adult-onset patients, pediatric-onset patients exhibited a higher frequency of cognitive difficulties [44]. This suggests that early disease onset may place individuals at a higher risk of cognitive problems later in life. A larger registry-based study in Sweden, involving more than 5700 individuals with MS (300 with pediatric onset MS), reinforced these findings [45]. The study analyzed performance on the Symbol Digit Modalities Test (SDMT) and found that although initial differences were not significant, over time, patients with pediatric-onset exhibited reduced information-processing efficiency. A 12-year follow-up study found that individuals with cognitive impairment had poorer social and occupational outcomes in adulthood [46]. Two registry-based studies also highlight these long-term consequences. A Swedish study [47] found that pediatric-onset

MS was associated with lower educational attainment, lower income, and greater reliance on disability benefits. A Danish study [48] compared children with MS to both healthy children and those with other non-neurological diseases (e.g., inflammatory bowel disease). Although school performance was comparable, fewer children with MS attended high school, suggesting lower educational achievement. Additionally, these children had an increased risk of psychiatric comorbidities, with a 3.4 times higher likelihood of developing depression, anxiety, or bipolar disorder. Pediatric-onset MS may therefore have long-term consequences for social participation and vocational outcomes, including lower educational attainment [49] and reduced occupational achievement in adulthood, as well as persistent cognitive difficulties. As children with MS tend to accumulate physical disability more slowly than adults, cognitive impairment may represent a more prominent and disabling feature than physical deficits in this population [50, 51].

The most commonly used cognitive assessment tools (cognitive PerfO) in pediatric MS research include the SDMT [52] and the Brief Cognitive Assessment for Multiple Sclerosis (BICAMS) [53, 54], both validated in pediatric populations as well as the CogState Brief Battery [55], which is computer-based and also validated for pediatric patients. Longitudinal studies have demonstrated the validity and reliability of these tools for assessing cognition in patients with POMS [56] (Table 2).

One major challenge in selecting the relevant COA and PROMs in POMS is due to the long interval required for the development of mild disability, making it difficult to detect subtle changes or fluctuations in neurological status with commonly used clinical scales. Within this framework the use of digital cognitive PROMs and PerfO, together with QoL measurements, is a promising research field to help in meeting the challenges of outcome assessments in children and young people. Digital cognitive PROMs enable convenient remote assessment with faster scoring, improved data quality, real-time monitoring, and better integration into digital health systems. Digital interventions for the retraining of cognitive deficits with PerfO-like outputs are also being developed for use in the pediatric population. A promising example in this field is COGNI-TRAcK, a tablet-based application developed by the Italian Multiple Sclerosis Foundation, tailored for young people with MS. The tool allows for self-administered, home-based cognitive training through adaptive working load algorithms that regulate task intensity based on user performance. Initial pilot testing in adults with MS showed high usability, motivation, and compliance with the intervention [63]. More recently, a randomized, multicenter study in pediatric-onset MS confirmed the feasibility of COGNI-TRAcK for remote attention training, showing a statistically significant improvement on the SDMT in the specific training group compared to controls [64]. These preliminary findings suggest that COGNI-TRAcK could represent a scalable, patient-centered approach for early cognitive monitoring and intervention in POMS.

Pro and Cons of Using Digital Cognitive PROMs in Young People with MS

Adolescents are typically comfortable with the use of digital tools and this makes it easier for them to reliably report their symptoms, challenges, and well-being. Importantly, digital PROMs can also reduce the need for in-person hospital visits, minimizing the impact on school attendance and social activities. Digital cognitive PROMs not only could provide insights currently lacking from the main clinical outcome measures but also align with a holistic view of well-being, provide real-time data and thus data-driven, personalized care.

Digital cognitive PROMs could improve the involvement of family members in monitoring and supporting the patient journey. Above all, these measures could provide predictive insights into adult life and help us identify individuals at higher risk of disease progression or poor health outcomes.

The increasing use of digital and AI technologies [65] to measure cognition poses challenges [66] for anyone living with MS and potentially even more for children and adolescents. Similarly to the use of any PROM, as mentioned in

Sect. "General Measures," factors such as cognitive ability, willingness to cooperate, and validation of any tool for this age group must be considered. Access to digital technology may vary across age groups within this population, and motivation to collect and share personal data may be very different to that of the adult population. The issue of consent for data collecting and sharing may also be more complex when considered for under-18s. It will therefore be essential to apply responsible research innovation models of engagement of young people with MS from research to care [67, 68].

Engaging young people living with the disease in the research and development of digital cognitive PROMs—taking the necessary steps to understand participation with digital PROMs from their perspective and avoiding assumptions—will also enable the measurement of patient preference information (PPI) on the acceptability of the digital device.

Another important consideration is that the adoption of a digital approach risks worsening the already known differences between regions and countries in the provision of social and health services. Therefore, a national definition of Essential Levels of Digital Technology Access needs to be developed, which guarantees that digital opportunities are accessible everywhere and not only in the social and health services of the richest countries and regions in Europe and beyond. PPIs will be instrumental in meeting this challenge and creating core indicators for a multidisciplinary model of care for young people with MS [17].

Moreover, when developing models or interventions based on a sample of digital PRO data, an important consideration is that the data need to be representative of the population in which the digital PROMs will subsequently be implemented [69]. This is particularly relevant for cognitive PROMs, where the type of cognitive challenge experienced may vary across demographics, and where the measurement of cognition could be subject to cultural effects. Existing methods for detecting cognitive decline are best suited for scenarios where symptoms have already manifested (e.g., a referral following subjective cognitive impairment) but are not appropriate when longitudinal monitoring of asymptomatic individuals is required. Therefore, the development and validation of digital cognitive PROMs that are meaningful and valid for children and adolescents with MS, and potential indicators of later-life health outcomes, represents a breakthrough area of research progress towards effective multidisciplinary management of POMS.

Quality of Life Outcome Measures

The assessment of quality of life is crucial for the clinical management of patients with POMS. The PedMS Inventory Pediatric Quality of Life Inventory (PedsQL) scales, including self-reported and parent-reported versions, are the most widely used tool used for measuring quality of life [70]. A systematic review found PedsQL to be the most frequently used scale for pediatric MS [71, 72], adopted by 10 out of 12 authors, with KIDSCREEN-52 [73] and TACQoL [74] being less common. PedsQL has been used to assess fatigue and depression [28, 75–77], cognitive dysfunction [78], comparisons with acute demyelinating disorders [75, 79–81], effectiveness and tolerability of DMTs [82, 83], and clinical follow-up of patients [84]. The PedsQL is designed to measure the core dimensions of health as delineated by the World Health Organization [70], covering four domains:

- Physical Functioning (8 items, e.g., "it is hard for me to run")
- Emotional Functioning (5 items, e.g., "I feel sad or blue")
- Social Functioning (5 items, e.g., "other teens don't want to be my friends")
- School Functioning (5 items, "I have trouble keeping up with my schoolwork")

The two versions of the questionnaire, one for the patient and one for their parents, are validated for different age ranges (ages 5–7, 8–12, 13–18). Respondents are asked to indicate how much of a problem each of the 23 items in the questionnaire has been over the past month, on a scale from 0 (Never a problem) to 4 (Almost always a problem). The items are reverse scored and linearly transformed to a 0–100 scale, so

higher scores indicate better health-related quality of life. A Total Scale Score is generated, including all 23 items, which can be divided into a Physical Health Summary Score (8 items) and a Psychosocial Health Summary Score (15 items). The scales are available in both paper and tablet-based formats.

In summary, the PedsQL questionnaire offers the following features:

- It is brief, generally taking no more than 5 min to complete.
- It shows good inter-rater agreement and has been widely used in many chronic disorders of children and adolescents.
- It is available in self- and parent-report forms and caters to various age ranges.

The assessment by parents has an important role in the holistic management of patients, as it offers a view on the impact of MS in the family [85, 86].

Quality of life assessment adds meaningful information on the effects of medications, beyond clinical and neuroimaging measures. Fingolimod has been shown to improve HRQoL compared with IFNβ1 (interferon beta-1) in patients with POMS as evidenced by the self-reported and parent-reported PedsQL score [28]. In patients treated with fingolimod, both the Physical Health Summary Score and Psychosocial Health Score improved whereas both worsened in those treated with IFNβ. The same trend was observed with the Social Functioning Score, whereas a mild but lower increase of the Emotional Functioning Score was also observed in patients treated with IFNβ. Two findings deserve attention: (a) HRQoL assessment provides additional information on DMT effects—in this trial fingolimod showed a more pronounced effect compared with IFNβ not only in clinical and neuroimaging measures but also in a more extensive health dimension, particularly in the perceived physical dimension, probably because of the stronger effect to prevent relapses and disease progression, the higher tolerability of the oral administration, and the lack of injection-related side effects; (b) the scores of self-reported scales showed a more marked effect in patients' perception compared to parents. A similar finding was observed in a paper evaluating the tolerability of IFNβ [74] administration and in another one evaluating fatigue and QoL [87] indicating, from one side, the strong negative impact of MS on the family, and, from the other side, the high level of patients' resilience [88].

The profound destabilizing effect of MS on family relationships is well documented in other studies [70, 89, 90], highlighting how differently patients and their relatives perceive and weigh the impact of the disease on the patient's life. This aspect should be carefully assessed and integrated into the holistic management of POMS [70], which should address not only the needs expressed by patients but also should consider the perspectives of proxy, paying attention to the factors underlying potential discrepancies: if they are really due to objective circumstances or to subjective perception.

For fatigue assessment, the PedsQL Multidimensional Fatigue Scale is commonly used, providing separate evaluations from both the patients and their parents [91]. Fatigue and quality of life were evaluated in 51 pediatric patients with MS (33 girls and 18 boys, mean age 14.8 and 15 years, mean EDSS 1.7) [87]. Compared to healthy controls, these patients experienced more fatigue, sleep issues, cognitive challenges, physical limitations, and academic difficulties. Parents reported additional problems with respect to emotional functioning, and reported a greater effect of fatigue, sleep, and cognitive difficulties than pediatric patients. According to this paper, fatigue was significantly correlated with sleep difficulties, cognitive problems, and quality of life variables. An Italian study found that while 14% of children and adolescents self-reported fatigue, against the rate of 39% reported by parents, again highlighting the different perception of health in patients and *their relatives*. In both cases, fatigue was associated with depression and cognitive problems [67]. The study compared the cognitive performance of patients with POMS with those diagnosed in adulthood.

The widespread use of PedsQL establishes it as the best tool for quantifying quality of life. However, unlike other chronic pathological conditions, MS has unique symptoms and specific characteristics (such as fatigue, mood and sleep

disorders, reduced participation in sports, recreational and social activities), and unpredictable evolution that can affect quality of life. To address these issues, the PedsQL Inventory Multiple Sclerosis Module has been developed [92]. This module includes items evaluating aspects such as general fatigue, sleep/rest fatigue, cognitive function, tingling sensations, numbness sensations, physical weakness, pain, speech, balance, fine motor skills, vision, urination, constipation, bowel incontinence, worry, communication, treatment, and medications. These items were identified through focus interviews with 23 pediatric patients with MS and 17 parents, cognitive think-aloud interviews, and pilot testing where the items were evaluated, modified, and confirmed. As the data have been generated from a single MS center, as also suggested by the authors, the PedsQL MS module should be validated in other clinical centers, countries, and across a wider age range, to assess its applicability also in children, and in those with cognitive impairment. To conclude, the PedsQL MS module is specifically designed to provide additional insights into the wide determinants of quality of life of patients with POMS and until now, on the basis of current data, it stands as the most promising and reliable tool to measure QoL and the perspective of patients and caregivers on the effects of MS. For this proposal to become operational and broadly adopted, it will necessarily need to receive a favorable assessment from a consensus of experts and from the relevant technical-scientific organizations.

CONCLUSIONS

PROMs should complement clinical measures when assessing children and adolescents with MS. Increasing evidence indicates that cognitive and neurological patterns established during developmental years often serve as indicators of later-life health outcomes. Patients with POMS often experience low levels of disability for a long time, requiring assessment of neurological dysfunction beyond clinical and neuroimaging measures, including fatigue, motor, emotional, psychological, and social limitations. Clinical MS scales mainly measure neurological deficits, whereas PROMs can provide essential measures of cognitive dysfunction, fatigue, sleep disorders, and psycho/social issues. In this context, the PedsQL—including the Inventory Multiple Sclerosis Module—is one of the most promising and meaningful tool. It integrates the assessment of the most prevalent symptoms and dysfunctions while offering the advantage of being standardized across different age groups. MS significantly impacts quality of life (QoL) of young people with MS (POMS), their parents and wider family members. Including patients' and parents' perspectives in assessing MS burden is therefore crucial. To respond to the practical need for outcome selection beyond EDSS, a pragmatic framework can be considered, integrating core domains frequently affected in POMS (fatigue, mood, sleep, cognition/school functioning, and participation/quality of life). In this context, PROMs (e.g., PedsQL Core and MS Module), complemented by age-appropriate PerfO measures for cognition (e.g., SDMT or BICAMS), and, when needed, parent-reported measures, may offer a multidimensional view of disease burden across developmental stages.

During the 2024 annual plenary meeting, the Global PROMS Initiative discussed how to help increase the uptake of PROMs in POMS within research and clinical settings and their use in decision-making processes by regulatory agencies. In alignment with the objectives of the Global PROMS Initiative agenda, recommendations for core PROMs and performance measures for POMS will be co-produced through structured multistakeholder consensus methodologies (e.g., Delphi processes, patient and caregiver engagement, regulatory and industry dialogue). The framework above represents an actionable bridge between current practice and future consensus, directly supporting the Initiative's goal to enable meaningful, standardized, and decision-relevant outcome measurement in POMS. The selection and implementation of PROMs in pediatric clinical trials demands careful consideration and adherence to regulatory guidelines. Recommendations from clinical outcomes experts and regulatory agencies emphasize the importance of age-appropriate instruments and standardized administration protocols, and

provide valuable guidance for effectively collecting COA data in pediatric clinical trials [89]. In line with this, the global survey performed by PROMS Initiative indicates that standardization of the use of valid, reliable, responsive PRO measures needs to happen together with their targeted (age-dependent personalized) use [20].

The field of PROs and PROMs needs to develop at speed in POMS. The PROMS Initiative will prioritize an education and training program for healthcare professionals working with children and adolescents with MS to ensure neutral administration and minimize potential biases. Digital tools for monitoring and data capture, together with the growing sophistication of artificial intelligence systems, could help meet the challenge of assessing hidden symptoms in POMS, as long as strict ethical principles are always applied. Co-designing MS-specific PROs with young people with MS is essential to ensure that any new PROs measure the symptoms and aspects of QoL that have the biggest impact on their lives at the current time and into their future adulthood.

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Declarations

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