# Multiple Sclerosis in the Era of the New McDonald Criteria

The updated diagnostic criteria for multiple sclerosis (MS) (2024 McDonald criteria) marks a paradigm shift in the understanding of this condition, including the recognition of radiologically isolated syndrome (RIS) (Montalban *et al.*, 2025). This publication could facilitate earlier diagnosis, the development of biomarkers, and potentially preventive measures.

Early detection and prevention of MS are strategic levers for optimizing the care pathway, thereby preserving the autonomy of people with the disease (Bebo *et al.*, 2022; Bebo *et al.*, 2024; Marrie *et al.*, 2026).

According to a 2020 report, more than 90,000 Canadians, or one in 400 people, live with MS (3rd edition of the Atlas of MS Atlas – (MS Canada)). More than 20,000 Quebecers are estimated to be living with MS, a large proportion of whom are between the ages of 18 and 64. Québec and Canada thus have the highest rates of MS in the world. This state of knowledge report is intended primarily to inform discussions on the implications of the updated McDonald criteria on care and service pathways for patients in Québec. The challenges and opportunities, the current landscape, and trends in the MS care pathway are explored.

The key points draw on multiple sources of information, including an exploration of the scientific literature, discussions with various stakeholders, and communications received.

The methodology is presented in Appendix A.

### The state-of-knowledge report presents

| 1 | 2 | 3 | 4 | 5 |
|---|---|---|---|---|
| The 2024 McDonald criteria | Treatments | Digital solutions | Economic findings | Considerations: challenges and opportunities |

**Keywords:** multiple sclerosis, 2024 McDonald criteria, continuum, radiologically isolated syndrome, early management, treatments, biomarkers

*The expedited nature of the work and the key findings arising therefrom are not based on an exhaustive literature review or an elaborate consultation process.*

**Note!**: This state-of-knowledge report does not claim to provide answers or recommendations regarding the topics it deals with, nor does it make value judgments about the relevance or applicability of the measures mentioned.

## Key points

- The 2024 revision of the McDonald criteria aims to enable earlier diagnosis of MS, particularly through the increased incorporation of biomarkers and the broadening of the diagnostic spectrum. While this change will likely increase sensitivity, its impact on specificity and the risk of overdiagnosis have yet to be determined.
- According to the new McDonald criteria, the different MS phenotypes, including RIS, share similar pathological mechanisms; the different clinical presentations of the disease are part of a continuum.
- Early diagnosis and treatment of RIS raise the possibility of delaying or preventing the onset of clinical symptoms and disability.
- According to a recent Canadian consensus statement, highly effective treatments are preferred as first-line therapy for all patients with an aggressive or severe form of MS.
- Specific MS markers, detected by magnetic resonance imaging (MRI), can help confirm an uncertain diagnosis, without the need for repeated follow-up assessments. However, their availability and diagnostic value vary according to local technical capacity.
- Kappa free-light chains (kFLCs) are an alternative diagnostic biomarker to oligoclonal bands (OCBs). The demonstration of positive cerebrospinal fluid (CSF) is fulfilled with either of these biomarkers. The more automated and faster nature of kFLC testing could reduce the use of OCBs and the costs associated with diagnosing MS.
- Neurofilament light chain (NfL) is a nonspecific blood biomarker that could help prioritize patients requiring an MRI, particularly those with active disease or new symptoms.
- Several categories of digital solutions for MS have been identified. These solutions have been designed to improve access, follow-up and patient involvement. However, the study results are subject to some uncertainty due to limitations and heterogeneity in the data.
- MS represents a significant economic burden in Québec, for both patients and the healthcare system. This burden stems from its high prevalence, the disability it causes in adults during important stages of their professional and family lives, and the rising costs of disease-modifying therapies (DMTs), a trend that is likely to intensify as clinical practices evolve.

# 1 2024 MCDONALD CRITERIA

In 2024, a revision of the McDonald criteria was undertaken to provide internationally applicable criteria for the diagnosis of MS.

The revised criteria represent a fundamental paradigm shift toward a biological definition of MS (Montalban *et al.*, 2025). They mark a transition from a disease whose diagnosis was heavily based on clinical symptoms to a framework grounded in biomarkers and immunobiology.

The diagnostic criteria for MS have evolved over time. Various reviews provide an overview of each iteration and the associated changes, including that by Agrawal (Agrawal *et al.*, 2025). The following are some of the new elements incorporated into the 2024 revision:

- The elimination of separate diagnostic pathways for relapsing MS and progressive MS, including RIS, treating them instead as a single, continuous biological spectrum (See Section 1.1).;
- The ability to diagnose MS in individuals with MRI-detected RIS who do not have any of the typical clinical symptoms of MS (also referred to as preclinical MS, according to the opinions expressed by some clinicians), when specific combinations of biomarkers are present (see Section 1.2 and Table 1);
- The addition of biomarkers:
  - Imaging (See Section 1.3):
    - The inclusion of the optic nerve as a fifth anatomical location to demonstrate dissemination in space (DIS), in the absence of a better explanation for optic nerve pathology;
    - The demonstration of dissemination in time (DIT) is no longer mandatory in certain situations;
    - Specific MRI findings, including the central vein sign (CVS) and paramagnetic rim lesions (PRLs). An accompanying companion paper to the 2024 McDonald criteria (Montalban *et al*., 2025) provides additional details (Barkhof *et al.*, 2025).
  - Molecular biomarkers (see Section 1.4):
    - The addition of the kFLC index as an alternative to OCBs.

The update also includes recommendations:

- Regarding the diagnostic workup of pediatric-onset MS;
- For the diagnosis of MS in people aged 50 or older with vascular comorbidities, in order to reduce misdiagnosis.

MS is a diagnosis of exclusion and should be periodically reassessed, given the harmful consequences of under- or misdiagnosis (Montalban *et al.,* 2025). Ongoing monitoring is necessary as diagnostic criteria change (Brownlee *et al.*, 2026).

Retrospective studies (Abad-Inchaurrondo *et al*., 2026; Bollo L., 2025; Brownlee *et al*., 2026; Hamdy *et al*., 2025) suggest that the 2024 McDonald criteria facilitate earlier diagnosis of MS compared with the 2017 McDonald criteria (Thompson *et al*., 2018). They also lead to more frequent diagnoses, including in patients with RIS. The 2024 criteria have greater sensitivity and maintain their clinical applicability, particularly in identifying disease activity through new MRI-visible lesions during follow-ups (Habek *et al*., 2025). This sensitivity is preserved in the pediatric population and in adults over 50 years of age (Brownlee *et al*., 2026; Tena-Cucala *et al*., 2025). The DIAG24 trial is designed to compare the application of the 2024 criteria with that of the 2017 criteria in a real-world setting (NCT07492667). The trial is currently underway, with primary completion expected in late 2028.

The 2024 revision marks a paradigm shift, allowing a diagnosis of MS to be made solely on the basis of paraclinical data.

Recent critiques have noted that the new criteria:

- Prioritize diagnostic speed at the expense of safety, and lack validation data from real-world settings (Toosy *et al*., 2026; Zettl *et al*., 2026);
- Have exceptionally high sensitivity but only moderate specificity. Thus, the criteria detect nearly all cases of MS but are prone to false positives (Brownlee *et al*., 2026);
- Carry the inherent risk of overdiagnosis and its consequences due to increased sensitivity and faster diagnosis (Solomon and Brodersen, 2025; Zettl *et al*., 2026);
- Are ahead of their time, although scientifically rigorous; bridging the gap they create requires the rapid implementation of new diagnostic techniques, industry support, and continuing medical education (Krieger, 2026).

According to Zettl (Zettl *et al*., 2026), future revisions should, among other things, prioritize diagnostic safety over diagnostic speed and establish the confirmation of chronic central nervous system (CNS) inflammation through CSF testing as a central diagnostic pillar.

In his response to recent critiques, Montalban (Montalban *et al*., 2026) notes that the specificity of the new criteria is enhanced by incorporating, for instance, additional considerations for older individuals or those with vascular risk factors, the assessment of anti-MOG antibodies in selected populations, and the inclusion of highly specific imaging features (e.g., CVS and PRLs).

## 1.1 The multiple sclerosis continuum

**Figure 1 MS continuum**

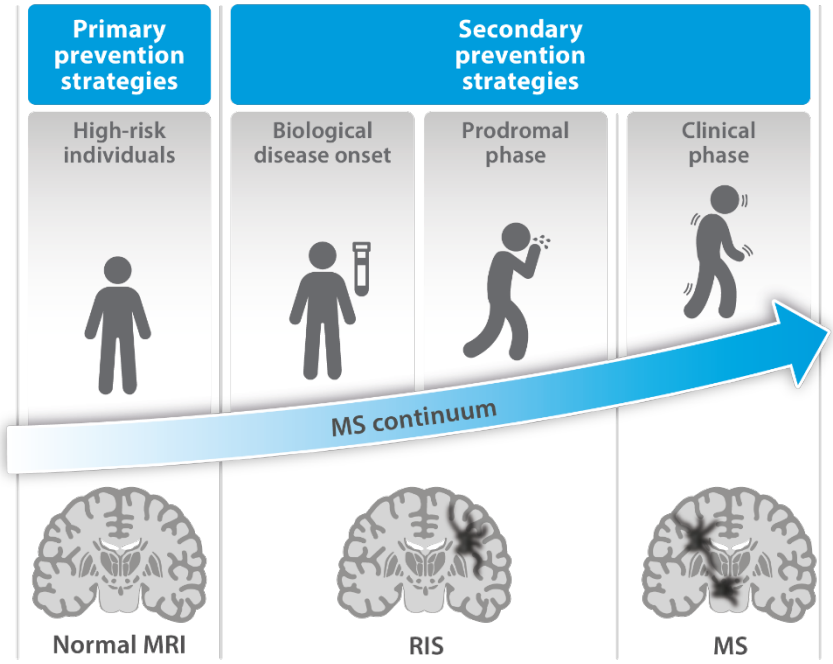


*Figure adapted from (Nociti et Romozzi, 2025)*

MRI: Magnetic resonance imaging; MS: Multiple sclerosis; RIS: Radiologically isolated syndrome.

### The MS Continuum

- RIS is discovered incidentally on MRI. At the time of diagnosis, the individual does not exhibit any of the typical clinical symptoms of MS.
- During the prodromal phase, nonspecific symptoms of MS appear (e.g., cognitive or psychiatric disorders, fatigue, headache or pain).
- MS is the culmination of a long and complex biological process that begins years before the onset of neurological symptoms.
- This understanding of MS paves the way for an earlier diagnosis, the development of biomarkers, and potentially preventive measures.

## 1.2 Radiologically isolated syndrome

The incidental discovery of demyelinating lesions suggestive of MS in individuals who do not exhibit any of the typical clinical signs of MS has been documented in several postmortem studies (Nociti et Romozzi, 2025). These lesions were detected in 0.1 to 0.3% of the autopsies (Preziosa *et al.*, 2024). The term “RIS” was coined to refer to these lesions when visualized on MRI.

Diagnostic criteria for RIS were proposed in 2009 (Okuda *et al.*, 2009) and updated in 2023 (Lebrun-Frenay *et al.*, 2023a), reducing the number of lesions required to meet the diagnostic criteria for RIS.

### Epidemiology

Although the prevalence of RIS is currently poorly established, it is rare in the general population (0.1 to 0.7%) (Lebrun-Frenay *et al.*, 2023a; Morris *et al.*, 2009; Yamout et Al Khawajah, 2017). The rate rises to 4% among asymptomatic first-degree relatives of patients with sporadic MS and up to 10% among those with familial MS (De Stefano et al., 2006). One study reported an estimated incidence of RIS of 0.8 cases per 100,000 person-years in a Swedish cohort (Forslin *et al.*, 2016).

### The conversion from radiologically isolated syndrome to multiple sclerosis: Probabilities and risk factors

In the MS continuum, certain individuals with RIS may remain asymptomatic throughout their lives, while others may develop clinical symptoms associated with MS. Observational studies show that approximately 19% of people with RIS develop clinical MS within 2 years (Lebrun-Frenay *et al.*, 2021), 34% within 5 years (Okuda *et al.*, 2014), 51% within 10 years (Lebrun-Frenay *et al.*, 2020), and 72% within 15 years (Lebrun-Frenay, 2025).

The risk factors for a higher likelihood of conversion include 1) being younger than 37 years of age; 2) the presence of infratentorial or spinal cord lesions on follow-up imaging; 3) the presence of gadolinium-enhancing lesions on follow-up imaging ; and 4) the presence of OCBs in the CSF (Lebrun-Frenay *et al.*, 2020).

The presence of risk factors increases the 10-year risk of conversion by 29%, 54%, 68% and 87% in individuals with 1, 2, 3 and 4 risk factors, respectively (Lebrun-Frenay *et al.*, 2020).

### Radiologically isolated syndrome – Pediatric population

Currently, there are no formal diagnostic criteria or therapeutic consensus for pediatric RIS. One cohort study found that RIS and MS are significantly rarer in children than in adults, with an estimated prevalence of RIS of 0.02% (de Mol *et al.*, 2021), while pediatric-onset MS is estimated to account for approximately 4.5 to 7.9% of individuals living with MS (Benallegue et Deiva, 2025).

Significant clinical consequences are associated with the conversion from pediatric RIS to pediatric-onset MS, as the latter is notably more inflammatory, with a higher relapse frequency and a greater lesion burden on imaging than in adults (Benallegue et Deiva, 2025).

Although recovery after a relapse is generally complete in pediatric MS, disability thresholds may nevertheless be reached earlier than in early-adult MS (Montalban *et al.*, 2025).

## 1.3 Magnetic resonance imaging biomarkers

The identification and characterization of CNS lesions by MRI are the main determinants of the diagnosis of MS (Barkhof *et al.*, 2025; Montalban *et al.*, 2025). The diagnostic criteria based on imaging are:

- DIS (number of CNS locations with lesions);
- DIT (progression of lesions);
- Specific MS markers (CVS and PRLs).

Recommendations regarding the operationalization of different combinations of criteria to diagnose MS are summarized in Table 1.

### Table 1 Diagnostic criteria for MS based on the number of affected anatomical sites and the clinical presentation

| Number of anatomical sites with lesions | Typical clinical presentation | Atypical clinical presentation or absence of typical clinical symptoms of MS (e.g., RIS) |
|---|---|---|
| **4 or 5** | Sufficient for a diagnosis of MS | Diagnosis of MS if DIT, CVS or CSF biomarker present |
| **2 or 3** | Diagnosis of MS if DIT, CVS or CSF biomarker present | |
| **1** | Diagnosis of MS if DIT or CSF biomarker **and** CVS or PRLs present | Insufficient for diagnosis |
| **0** | Insufficient for diagnosis | |

*Adapted from (Barkhof et al., 2025)*
CSF: cerebrospinal fluid; CVS: central vein sign; DIT: dissemination in time; MS: multiple sclerosis; PRL: paramagnetic rim lesion; RIS: radiologically isolated syndrome.

## Dissemination in space

The demonstration of DIS spans five possible anatomical locations typically affected by MS (e.g. cortical/juxtacortical, periventricular, infratentorial brain, spinal cord, and optic nerve) (Montalban *et al.*, 2025). The inclusion of at least two locations for the demonstration of DIS have shown high sensitivity (70 to 95%) and moderate specificity (60 to 80%) (Brownlee *et al.*, 2025; Hyun *et al.*, 2018). The impact of adding the optic nerve as a fifth anatomical location is uncertain. Depending on the cohort, including the optic nerve can increase sensitivity from 88% to 99% (while reducing specificity from 100% to 81%) (Pihl-Jensen et Frederiksen, 2025) or have no impact on diagnostic performance (Brownlee *et al.*, 2025). Detecting optic nerve lesions may require a dedicated orbital MRI, which extends the total acquisition time. In addition to MRI, optic nerve involvement can be assessed using optical coherence tomography or visual evoked potentials. An accompanying companion paper to the 2024 McDonald criteria (Montalban *et al.*, 2025) provides additional details (Saidha *et al.*, 2025).

The presence of lesions in at least four regions is associated with a reported specificity of 100% (Brownlee *et al.*, 2025) and is therefore considered sufficient for an MS diagnosis in the context of a typical clinical presentation, without the need for further confirmation (Montalban *et al.*, 2025). For patients with one to three affected regions (or two or more if the clinical presentation is atypical), a diagnosis requires at least one additional criteria (Montalban *et al.*, 2025), namely demonstration of DIT, lesions that are highly specific for MS on MRI, or a CSF biomarker (see Section 1.4).

## Dissemination in time

DIT is demonstrated by at least two distinct relapses. It often requires follow-up MRIs to monitor for the appearance of new lesions but can also be established retrospectively by the concurrent presence of lesions with and without contrast enhancement (active and old lesions at the same time). DIT is generally considered to be nonspecific, as a substantial proportion of patients in the preclinical stage fulfill it without progressing to clinical MS (Freedman *et al.*, 2014; Montalban *et al.*, 2025).

### Specific markers: central vein sign and paramagnetic rim lesions

The detection of the CVS in a certain proportion of lesions or the presence of at least one PRL can significantly contribute to confirming a diagnosis of MS (specificity of 80 to 95%) (Castellaro *et al.*, 2020; Maggi *et al.*, 2020; Sinnecker *et al.*, 2019). However, the diagnostic value of these two markers has mainly been demonstrated using high-field MRI scanners (3 Tesla [3T] and 7T). They can also be detected with a 1.5T scanner, but with reduced sensitivity (Castellaro *et al.*, 2020). Negative results with these scanners may therefore be considered inconclusive. Optimal detection requires susceptibility-weighted imaging (SWI) sequences for these two markers, for which there is no consensus in the literature (Barkhof *et al.*, 2025; Kerpel *et al.*, 2025). Lastly, detecting the CVS and PRLs requires a certain level of expertise on the part of the interpreting radiologist. The recommended diagnostic criteria are particularly cautious regarding the weight assigned to PRLs, noting that such expertise is not yet widespread (Barkhof *et al.*, 2025).

The CVS and PRLs can therefore be considered optional markers. Nevertheless, when available, they can be useful in certain cases for confirming a diagnosis of MS more quickly, without the need for imaging monitoring or a lumbar puncture. However, the usefulness of these markers depends heavily on the MRI field strength, the specific acquisition sequences used, and the specialist interpreting the images. The vast majority of MRI scanners in Québec are 1.5T, with approximately 12.5% being 3T scanners while 7T scanners are not currently used in routine clinical practice (Agence des médicaments du Canada, 2021). Furthermore, the acquisition sequences are generally determined by individual radiology departments, leading to heterogeneity across the healthcare system.

### Access to magnetic resonance imaging

In addition to the variability in technical imaging capacity mentioned above, access to MRI may itself present certain challenges. In 2023, 48% of elective MRI examinations in Quebec (all anatomical regions and clinical indications combined) had a wait time exceeding 90 days. Depending on the health and social services region, this proportion ranged from 12% to 71%.

Investigating an uncertain diagnosis of MS often requires multiple MRI examinations. According to some clinicians, these cases can be monitored annually or semi-annually for a period of 2 to 5 years. If such follow-up is performed too broadly in patients with a very low probability of progressing to MS (e.g., vague symptoms, incidental discovery of lesions that are not typical of MS), there is a risk of generating consultation requests and MRIs with little added value, with consequences for the patient (anxiety and time spent on follow-up examinations) and for the health and social services system (increased workload and longer waitlists).

## 1.4 Molecular biomarkers

### Diagnostic molecular biomarkers

The 2024 McDonald diagnostic criteria now include kFLCs as an alternative to OCBs and the demonstration of positive CSF is fulfilled with either of these biomarkers (Montalban *et al*., 2025). An accompanying companion paper to the 2024 McDonald criteria (Montalban *et al*., 2025) provides additional details (Deisenhammer *et al*., 2025).

OCBs and kFLCs are two biomarkers that must be analyzed in both blood and CSF. The OCB test provides a qualitative assessment of intrathecal immunoglobulin production. It relies on specialized electrophoresis techniques, requires highly qualified personnel, and involves a longer analytical process, with examiner-dependent interpretation (Konen *et al*., 2025). As for kFLC measurement, it relies on automated methods that provide quantitative results faster but may require larger sample volumes and is highly dependent on the analytical thresholds used (Hegen *et al.*, 2023; Konen *et al.*, 2025).

Several studies support a sequential strategy starting with kFLC measurement, followed by OCB testing for negative cases, which could reduce costs and turnaround time while maintaining good diagnostic performance (Abid *et al*., 2023; Crespi *et al*., 2017; Hannich *et al*., 2022; Sanz Diaz *et al*., 2021). According to some clinicians, this strategy could reduce the number of OCB tests in Québec by more than half.

### Prognostic molecular biomarkers

NfL is a nonspecific blood biomarker associated with neuroinflammation and axonal damage. When used in conjunction with MRI, NfL could provide information on subclinical MS activity, treatment response, and, in some cases, disease progression. According to some clinicians, longitudinal NfL monitoring could be useful in individuals with active MS or when new symptoms appear, particularly to help prioritize the use of MRI. Furthermore, certain national and international expert consensus statements recommend a baseline NfL measurement, followed by repeat testing every 3 to 12 months (Consortium of Multiple Sclerosis Centers, 2023; Freedman *et al.*, 2025; Freedman *et al.*, 2024; García Domínguez *et al.*, 2026).

### Access to molecular biomarker tests

According to some clinicians who shared their perspectives:

- There are few, if any, barriers to accessing OCB testing;
- kFLC testing is not currently performed in Québec for the diagnosis of MS;
- NfL testing is currently performed in several Canadian provinces. In Québec, its use remains emerging and variable. In fact, some of the province's university hospitals have access to it by sending specimens outside Québec.

# 2 TREATMENTS

## 2.1 Disease-modifying therapies: categories and therapeutic approaches

Disease-modifying therapies (DMTs) are a class of drugs designed to alter the course of MS by targeting the underlying immune-mediated inflammatory process. Unlike symptomatic treatments (e.g., fampridine), DMT are intended to reduce the frequency and severity of relapses, limit the formation of new brain and spinal cord lesions, and slow the progression of physical disability (Bellanca *et al.*, 2024). There is presently no curative treatment.

The currently listed DMTs can be divided into two categories (Freedman *et al.*, 2025). These exclude sphingosine-1-phosphate receptor modulators because of insufficient data (Freedman *et al.*, 2025):

- Lower-moderate efficacy DMTs (e.g., glatiramer acetate, interferon beta-1A, interferon beta-1B, dimethyl fumarate and teriflunomide);
- Higher-efficacy DMTs (e.g., alemtuzumab, cladribine, ofatumumab, ocrelizumab and natalizumab).

The two main treatment strategies are the escalation approach and the early approach (Ontaneda *et al.*, 2019).

- The escalation approach starts with less effective treatments that have a better safety profile and then moves on to more effective treatments if the disease progresses. This approach can lead to cumulative, irreversible disability.
- The early approach starts with a higher-efficacy DMT, especially for the aggressive forms of the disease. This approach, initiated at the onset of MS, may have a long-term positive effect on disease progression (Al-Araji *et al.*, 2025; Filippi *et al.*, 2022). This approach is favoured by some of the clinicians who shared their perspectives.

The early approach is associated with less frequent and generally less severe relapses, as well as better long-term outcomes in terms of disability, compared with waiting for a relapse before changing treatments (escalation approach). However, higher-efficacy DMTs may cause more adverse effects (Freedman *et al.*, 2025).

Canadian specialists have issued recommendations as part of a consensus process focusing, in particular, on the optimal use of higher-efficacy DMTs (Freedman *et al.*, 2025). They recommend that these treatments be preferred as first-line therapy for patients with an aggressive or severe form of the disease at the time of diagnosis. This approach marks a paradigm shift, advocating immediate and more intensive treatment for high-risk patients. Furthermore, this approach is recommended elsewhere in the world, as reported in the 2024 second edition of the series *Brain Health: Time Matters* (Butzkueven *et al.*, 2025), in an opinion piece by Italian neurologists (Filippi *et al.*, 2022) and in the guidelines of the Association of British Neurologists (Rashid *et al.*, 2025). Observational, cohort and population-based studies, as well as reviews, consistently support this approach (Al-Araji *et al.*, 2025; Baroncini *et al.*, 2016; Brown *et al.*, 2019; Buron *et al.*, 2020; Edan et Le Page, 2023; Freeman *et al.*, 2022; Hanninen *et al.*, 2022; Harding *et al.*, 2019; He *et al.*, 2020; Hrnciarova *et al.*, 2023; Iaffaldano *et al.*, 2021; Merkel *et al.*, 2017; Norborg *et al.*, 2025; Selmaj *et al.*, 2024; Spelman *et al.*, 2021; Vudumula *et al.*, 2023). Although there is a preference for initiating higher-efficacy DMTs upon diagnosis of MS, opinions regarding the most appropriate

treatment paradigm are divided (Roberts *et al*., 2025). Consequently, the results of the ongoing TREAT-MS (NCT03500328) and DELIVER-MS (NCT03535298) trials, which compare higher-efficacy DMTs with lower or moderate efficacy DMTs, could provide useful information.

## 2.2 Treatment of patients with radiologically isolated syndrome

Chronologically, RIS occurs at the beginning of the MS continuum. However, although several DMTs for the treatment of MS are listed on the drug formularies, no treatment has been approved by Health Canada for the treatment of RIS.

According to the Canadian consensus recommendations (Freedman *et al*., 2025), treatment should be considered for patients diagnosed with RIS who meet the 2024 McDonald diagnostic criteria (Freedman *et al.*, 2025). In the earliest stage of MS, a diagnosis of RIS offers the possibility of delaying the onset of or preventing clinical symptoms and disability, through early pharmacological intervention (Freedman *et al*., 2025).

### Data on the treatment of patients with radiologically isolated syndrome

There is little data on the use of DMTs in patients with RIS.

The only two DMTs that have been evaluated in a randomized controlled trial are dimethyl fumarate in the ARISE study (Okuda *et al*., 2023) and teriflunomide in the TERIS study (Lebrun-Frenay *et al*., 2023b) (treatments with lower or moderate efficacy), although many others have been used in observational cohort studies (Ripsman *et al*., 2025).

According to the Canadian consensus (Freedman *et al*., 2025), the results of the TERIS and ARISE studies have demonstrated that, compared with placebo, treatment may prolong the time to a first clinical event in subjects with RIS. INESSS has conducted an assessment of dimethyl fumarate and teriflunomide for the treatment of RIS. For a comprehensive description of the evidence and findings, readers are referred to the published assessment (INESSS, 2026; available in French only).

## 2.3 Treatments for pediatric-onset multiple sclerosis

With the exception of fingolimod (Gilenya®), no treatment has been approved by Health Canada for use in the pediatric population. Clinical trials evaluating treatments (e.g., fenebrutinib, fingolimod, ocrelizumab, ofatumumab and siponimod) in this population are currently underway. As for pediatric-onset RIS, a few case reports have been published (Barbuti *et al.*, 2023; Tzempetzis *et al.*, 2025).

## 2.4 Emerging therapies

A search of the ClinicalTrials.gov database of the U.S. National Institutes of Health (NIH) in March 2026 identified 121 clinical trials pertaining to MS. Among the emerging therapies are chimeric antigen receptor (CAR) T-cell (CAR-T) immunotherapies, stem cell transplantation, and monoclonal antibodies directed against targets not addressed by monoclonal antibodies currently listed on the drug formularies. There are 23 studies involving CAR-T therapies, all of which are early-phase trials. These trials have different targets, including CD19, the CD19/CD20 combination, BCMAs (B-cell maturation antigens), the CD19/BCMA combination, and the CD20/BCMA combination. As for stem cell transplantation (hematopoietic and mesenchymal), there are 11 studies underway, most of which are early-phase trials. Regarding monoclonal antibodies, there are four trials (two Phase II and two Phase III) of frexalimab, an anti-CD40L antibody, one Phase II trial of obexelimab, an anti-CD19/FcγRIIb antibody, and one Phase II trial of foralumab, an anti-CD3 antibody. For further details, see Appendix C, where therapies are presented according to their respective mechanisms of action.

Furthermore, the low risk of MS among individuals who are seronegative for Epstein-Barr virus (EBV) suggests that most cases of MS may be caused by EBV. An EBV vaccine would therefore be a promising therapeutic approach (Bebo *et al.*, 2022; Bellucci *et al.*, 2026; Bjornevik *et al.*, 2022; Maple *et al.*, 2022; Zane *et al.*, 2025). Phase I and II trials evaluating EBV vaccines are currently underway (e.g., NCT05164094, NCT04645147 and NCT06735248).

# 3 DIGITAL SOLUTIONS FOR MULTIPLE SCLEROSIS

## The potential of digital tools in multiple sclerosis

Digital solutions could serve as a catalyst for the delivery of more personalized, proactive and coordinated care that supports self-management and treatment optimization. (Tseriotis *et al.*, 2026; Voigt *et al.*, 2026; Wenk *et al.*, 2024).

Not all digital solutions included in the systematic reviews have the same objectives. It is not possible to determine from the main findings of these studies which functionalities provide the greatest benefits.

The results of these studies describe potential benefits of digital solutions for MS, including:

- Better remote access for people living in geographically isolated communities and for those who have difficulty accessing rehabilitation services (De Angelis *et al.*, 2021);
- Standardization of assessments, more frequent data-gathering, improved detection of fluctuating or invisible symptoms, more objective monitoring of treatment adherence, and greater patient engagement (De Angelis *et al.*, 2021);
- Reduction in depression and improvements in fatigue and anxiety, including among caregivers (Giusto *et al.*, 2026; Heesen *et al.*, 2023);
- Improved balance, postural control, walking speed, and endurance, (De Keersmaecker *et al.*, 2025; Triolo *et al.*, 2026);
- High usability, acceptability, and satisfaction (Triolo *et al.*, 2026).

The limitations reported in the studies include, the still limited evidence base owing to the small number of studies, the high proportion of pilot or feasibility trials, and the high degree of heterogeneity in the technologies, protocols and comparators (De Angelis *et al.*, 2021; De Keersmaecker *et al.*, 2025; Giusto *et al.*, 2026; Heesen *et al.*, 2023; Triolo *et al.*, 2026), and a lack of large-scale trials with standardized criteria to confirm clinical efficacy (Triolo *et al.*, 2026).

An overview of clinical trials involving digital solutions for MS is presented in Appendix D.

## Categories of multiple sclerosis digital tools

There are various categories of digital solutions designed for different purposes, such as:

- Diagnostic assistance (De Angelis *et al.*, 2021; Dillenseger *et al.*, 2021; Dini *et al.*, 2025; Michaud *et al.*, 2023; Voigt *et al.*, 2026);
- Tracking progression with remote monitoring (Dillenseger *et al.*, 2021; Dini *et al.*, 2025; Gashi *et al.*, 2024; Michaud *et al.*, 2023; Oh *et al.*, 2024; Tseriotis *et al.*, 2026; Ziemssen et Haase, 2021);
- Self-management and relapse management (Dillenseger *et al.*, 2021; Salimzadeh *et al.*, 2019; Tseriotis *et al.*, 2026; Zaratin *et al.*, 2026);
- Treatment and functional rehabilitation (De Angelis *et al.*, 2021; De Keersmaecker *et al.*, 2025; Heesen *et al.*, 2023; Triolo *et al.*, 2026; Wender *et al.*, 2022).

Tracking progression by means of remote monitoring appears to be the category with the most extensively studied tools in the literature, which may indicate that their development is more advanced. A detailed description of the various categories is provided in Appendix E. Depending on the category of digital solution, the primary users are health professionals, patients or both. Most solutions, however, involve health professionals.

One study identified 16 digital solutions in various categories for MS (some of which are described in Appendix E), 12 of which are currently used in 108 hospitals across 13 countries in Europe and North America (Tseriotis *et al.*, 2026).

Furthermore, an info-MS page (March 2026) was created by the Société suisse de la sclérose en plaques to list digital applications relevant to patients.

**In Québec**

There is a Health Canada-approved solution that was developed in Québec. It is based on the automated analysis of eye movements captured by a tablet camera during noninvasive visual tests. The collected data is processed by artificial intelligence (AI) to provide clinicians with indicators of neurological progression (scores derived from the Expanded Disability Status Scale (EDSS) and cognitive functions).

# 4 ECONOMIC FINDINGS

MS is associated with a significant economic burden in Québec. This burden is due mainly to its high prevalence, the cost of treatments, and the fact that it primarily affects young adults, during critical stages of their professional and family lives.

MS leads to significant productivity losses for people living with the disease and their caregivers, mainly because of absenteeism and presenteeism. According to a Canadian study, more than half of employed people with MS reported productivity losses, averaging $2,968 (2025) per patient over a 3-month period (Rodriguez Llorian *et al.*, 2022).

Approximately 80% of Canadians with this disease may find themselves unemployed (Amankwah *et al.*, 2017). RAMQ billing statistics (Appendix A) show, in fact, that most (77%) MS patients are in the 18-to-64 age group, a population that is generally active in the labour market.

DMTs constitute a major component of this economic burden, both for the healthcare system and for patients, because of their high cost, with annual treatment costs ranging from $5,849 to $50,105 (Appendix F), despite being associated with a reduction in hospitalizations (Khakban *et al.*, 2023). According to some patients, DMTs represent a financial burden because of the deductible and coinsurance they must pay, which can amount to as much as $102.64 per month or $1,232 per year (RAMQ).

An overview of the use of DMTs and their cost to the basic prescription drug insurance plan in recent years, based on billing statistics, is presented and supplemented with tables in Appendix G.

### A brief overview of MS treatments covered by the Basic Prescription Drug Insurance Plan over the past 3 years

| | 2023 | 2024 | 2025 |
|---|---|---|---|
| **Public Prescription Drug Insurance Plan**[a] | | | |
| Number of new patients treated | 231 | 266 | 309 |
| Total number of patients treated | 4015 | 4146 | 4379 |
| Cost[b] | $63,085,208 | $69,725,663 | $77,849,699 |
| **Private insurers**[c] | | | |
| Cost[b] | $103,379,367 | $116,252,105 | $124,122,284 |

a The billing data are derived from RAMQ billing statistics.

b Includes the cost of the drug, of the pharmacist's professional services, and the wholesaler's profit margin.

c The billing data are from the IQVIA Pharmastat™ database, which had a completion rate of approximately 78% over the 3-year period. The reported costs are therefore underestimated.

An increase in the use of DMTs, as well as their costs, has been observed over the past 3 years and could, if the trend continues, lead to increases in annual expenditures of up to nearly $8 million for the RAMQ and $10 million for private insurers.

The predominant use of ocrelizumab and ofatumumab observed in recent years appears to reflect a shift in clinical practice toward the early use of higher-efficacy DMTs (Butzkueven *et al.*, 2025; Filippi *et al.*, 2022; Freedman *et al.*, 2025; Rashid *et al.*, 2025). According to some clinicians, this trend can be attributed mainly to their superior clinical efficacy, a safety profile considered favourable, low frequency of administration, and ready accessibility.

# 5 CONSIDERATIONS: CHALLENGES AND OPPORTUNITIES

The considerations presented in this section are based on perspectives gathered from clinicians, patients and a patient organization during a half-day discussion on MS held in the spring of 2026, and during *ad hoc* consultations. The methodology is presented in Appendix A. Needs, challenges, and opportunities were identified, particularly in light of the paradigm shift in MS, as defined in the 2024 McDonald criteria (Montalban *et al.*, 2025).

## 5.1 Considerations concerning health needs

### Needs pertaining to prevention, diagnosis and clinical follow-up

- According to some patients, there is a need for interventions aimed at preventing MS. Furthermore, the period of diagnostic uncertainty between the onset of the first nonspecific symptoms (e.g., depressive disorders, cognitive disorders and fatigue) and the diagnosis of MS is lengthy and affects many aspects of life.
- According to some patients, patient associations and clinicians, early disease detection is needed to enable timely initiation of appropriate treatment.
- According to some clinicians, there is a need for equitable access to MRI services and for MRI wait-time targets to be met across all regions of Québec .

### Needs pertaining to pharmacotherapy

- Patients report a need for effective treatments with a favorable safety profile to prevent or reduce relapses.
- According to some clinicians, choosing the right treatment for the right patient is a challenge, for which decison-support tools are needed.
- According to some clinicians, delaying the onset of or preventing clinical symptoms and disability in MS during the RIS stage is ideal but difficult to get patients to accept because they do not exhibit any typical clinical symptoms of MS. They point out that the window for diagnosing RIS is very narrow, particularly in patients with multiple risk factors.
- Some clinicians and patients expressed a desire for reimbursement of certain drugs and changes to the coverage criteria for others:
  - Coverage of drugs for the treatment of RIS and for the pediatric population;
  - Simplified treatment transitions based on disease course, especially when de-escalating treatment;
  - The option of using higher-efficacy DMTs as first-line therapies in special circumstances (e.g., immediate and more intensive treatment for high-risk patients);
  - The option of continuing treatment despite an EDSS score of 7 or higher (e.g., to maintain hand function in a patient who uses a wheelchair).

### Needs pertaining to non-pharmacological therapy

- According to some patients, it is important to promote physical activity.
- According to some clinicians, timely access to the services of a psychologist, neuropsychologist or kinesiologist would be beneficial.
- More personalized, coordinated care that supports self-management (e.g., through the use of digital solutions) (Dillenseger *et al.*, 2021; Tseriotis *et al.*, 2026; Voigt *et al.*, 2026; Wenk *et al.*, 2024).

## 5.2 Organizational and economic considerations

- According to the Québec Division of MS Canada, the new McDonald criteria are raising concerns, particularly with regard to a potential increase in diagnosed cases amid limited resources and long wait times.
- According to some clinicians, technical capacity are needed for using specific markers (CVS and PRLs) in MRI and for measuring kFLCs (a fluid biomarker) for the diagnosis of MS.
- Broadening the diagnostic criteria and adopting new treatments are likely to increase the demand for neurology consults and MRIs, particularly for monitoring patients diagnosed with RIS (follow-up that can last for up to 10 years), and thus exacerbate challenges in accessing specialist consults and medical imaging services.
- In addition to MRI, access to NfL testing is considered important by some clinicians for clinical follow-up.
- Uncertainties regarding the organization of care should cellular therapies such as CAR-T and stem cell transplants, be introduced were noted (see Appendix C). It is difficult to gauge the healthcare system's capacity, in terms of human and material resources, to provide equitable and timely access to these therapies across the province.
- Digital solutions for monitoring MS progression are the most extensively studied, which could support their integration into clinical practice. However, it would be prudent for any future deployment to be preceded by an evaluation grounded in the INESSS framework for assessing the value of digital technologies (INESSS, 2026). This framework identified several considerations related to the use of these technologies, including strategic alignment, interoperability, data management, governance and professional oversight.
- The rising costs of DMTs, combined with the eventual entry of new treatment options into the Canadian market, such as Bruton's tyrosine kinase (BTK) inhibitors and cell therapies such as CAR-T, which are expected to be more costly than currently reimbursed treatments, could exacerbate the economic burden. However, simplifying the coverage criteria (recognized indications) could increase the use of currently available DMTs, thereby reducing the need for even more costly options.
- The soon-to-be-marketed biosimilar versions of ocrelizumab could reduce the costs associated with this drug.
- Increased demand for MRIs could prolong wait times and, should corrective measures be implemented, lead to higher costs for the healthcare system.

- Broadening the definition of MS to include RIS could lead to additional expenditures, raising questions about the sustainability of care for symptomatic individuals. However, it should be noted that incidental detection of RIS is rare in the general population.
- Clinicians emphasize the importance of multidisciplinary teams, noting that a lack of human resources has a direct impact on patient care.They also highlight the significant administrative burden.

## 5.3 Ethical considerations – Radiologically isolated syndrome

Several publications discuss various ethical considerations regarding RIS and its treatment (Amato *et al.*, 2022; Leeuwenberg *et al.*, 2026; Nociti et Romozzi, 2025; Okuda *et al.*, 2026; Reynolds *et al.*, 2026; Smets, 2023; Solomon et Brodersen, 2025).

### The disclosure dilemma, the risk of overdiagnosis, and indirect consequences

According to some clinicians, the diagnosis of RIS is important for patient management and for delaying or preventing the onset of disability associated with MS. According to others, labeling a person who does not exhibit any typical MS symptoms can cause significant psychological distress, years before the disease potentially manifests. Still other clinicians feel that not disclosing an RIS diagnosis may be more harmful, since the course of the disease can be altered at this stage with early pharmacotherapy.

According to some clinicians, in situations where an MRI was performed and led to an incidental finding of RIS, radiologists often immediately state that the demyelinating lesions are “suggestive of MS”. The indirect consequences for patients (e.g., insurability, prognostic uncertainty and anxiety) are therefore already present, according to some clinicians.

### Therapeutic uncertainty

According to some clinicians, the lack of data on the use of many DMTs for the treatment of RIS raises concerns about long-term safety, given that some patients will never develop typical clinical manifestations of MS. Furthermore, uncertainty regarding the actual long-term benefits of early treatment complicates decision-making.

No validated guidelines or tools for stratifying patients with RIS who are most likely to benefit from initiating treatment have been identified. However, according to some clinicians, many patients would be good candidates for therapeutic management. Furthermore, data from studies deemed to be of good quality by clinicians show that certain treatments do have an impact. The goal at this stage is to alter the course of the disease, a goal that is often shared by patients.

## 5.4 Conclusion concerning all the considerations

The optimal implementation of biomarkers—both imaging-based and molecular—and their accessibility to all Quebecers with MS would benefit from a phased approach. It seems prudent for implementation to be preceded by prioritization and an assessment based on the five value dimensions of the INESSS framework. The availability of material, human and financial resources; compliance with standards and requirements; an appropriate data collection plan, data availability and the capacity for adaptation and sustainability; and stakeholder leadership and commitment are among the conditions that can support the successful prioritization and deployment of these

projects. Furthermore, the following elements, among others, could be documented as part of the assessment: priority health needs, the quality and maturity of available data, and the system's ability to incorporate these new tests without compromising existing care services for other patients.

The optimal application of the 2024 McDonald criteria (Montalban *et al.*, 2025), both for diagnosis and disease monitoring, could thus contribute to creating value for patients, the healthcare system and Québec society, provided that their implementation is accompanied by a relevance assessment, ongoing monitoring, rigorous oversight, and sustained dialogue among the different stakeholders.

Furthermore, the potential adoption of the concept of an MS continuum, including RIS, would require a review of the approved indications for drugs listed in the formularies. Particular attention could also be paid to the various challenges and opportunities identified in order to mitigate the risks that may be associated with such a review.

Lastly, both non-pharmacological and pharmacological treatments, including emerging therapies, could contribute to a significant improvement in the management of Quebecers living with MS.

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# ABBREVIATIONS AND ACRONYMS

| | |
|---|---|
| AI | Artificial intelligence |
| BTK | Bruton's tyrosine kinase |
| CAR-T | Chimeric antigen receptor (CAR) T-cell (CAR-T) |
| CNS | Central nervous system |
| CSF | Cerebrospinal fluid |
| CVS | Central vein sign |
| DIS | Dissemination in space |
| DIT | Dissemination in time |
| DMT | Disease-modifying therapy |
| EDSS | Expended Disability Status Scale |
| INESSS | Institut national d'excellence en santé et en services sociaux |
| kFLCs | Kappa free-light chains |
| MRI | Magnetic resonance imaging |
| MS | Multiple sclerosis |
| MSPA | Ministère de la Santé, de la Prévention et des Aînés |
| NfL | Neurofilament light chain |
| NIH | National Institutes of Health |
| OCBs | Oligoclonal bands |
| PASAT | Paced Auditory Serial Addition Test |
| PRL | Paramagnetic rim lesion |
| RAMQ | Régie de l'assurance maladie du Québec |
| RIS | Radiologically isolated syndrome |
| SDMT | Symbol Digit Modalities Test |
| SWI | Susceptibility-weighted imaging |
| TUG | Time Up and Go |

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# APPENDIX A

## Methodology

*The appendices are presented without having undergone an in-depth linguistic review. The French version takes precedence over the translation.*

The approach includes an exploratory review of the scientific and grey literature on MS. In addition, this report draws on input gathered through a stakeholder consultation that brought together neurologists, a nurse who works with MS patients, patients with MS, a representative from the Québec Division of MS Canada, the Association québécoise des pharmaciens propriétaires, the Regroupement des pharmacies de médicaments de spécialité du Québec, Innodem Neurosciences and Roche Diagnostics, and industry representatives. Participants were selected following a call for interest published in February 2026. The purpose of the 3-hour multidisciplinary meeting was to gather different perspectives on the MS care pathway, with a particular focus on the therapeutic arsenal, drug coverage criteria, and the additional examinations required. The objectives of the meeting were as follows:

- To establish a shared, high-level overview of the MS care pathway, the treatments used, their coverage, and upcoming innovations;
- To share the perspectives of stakeholders with an interest in this project (patients, clinicians and industry representatives);
- To identify the priority issues and avenues for improvement regarding the therapeutic options, coverage criteria, and the additional tests or examinations required.

The meeting was held in a hybrid format on April 2, 2026. Selected participants were allotted a specific speaking time in one of the four following categories: patients, clinicians, diagnosis, and manufacturers or partners.

Certain participants were allotted a specified amount of speaking time The event did not include a question period. Observers were allowed to attend the event but were not included among those consulted.

### Objectives

This state-of-knowledge report aims to provide an overview of the different potential considerations (e.g., clinical, organizational, economic and ethical) to inform discussions on the opportunities and challenges related to the optimal application of the 2024 McDonald criteria (Montalban *et al*., 2025). In particular, it presents an overview of the literature as well as the data needed for a potential assessment of the value of these new criteria.

### Strategy for identifying scientific data and grey literature

The approach includes an exploratory review of the scientific and grey literature on MS conducted by the project team members in connection with the recent publication of the McDonald criteria. The review focused primarily on recent articles on MS published in French or English between 2022 and April 2026. The literature review was conducted using a search engine (e.g., Google), the PubMed database, and a manual search of references in bibliographies or tables of contents in reviews. The keywords used for each section are as follows:

- The McDonald criteria and treatments: “multiple sclerosis, prevalence, McDonald criteria, multiple sclerosis continuum, radiologically isolated syndrome, pediatric-onset radiologically isolated syndrome, treatment of radiologically isolated syndrome, treatment optimization, preclinical MS, early management, high-efficacy therapies, risk factors for cumulative probability of a first clinical event, prognosis, disease-modifying agents (DMT), biosimilars, stem cell transplantation, CAR-T therapy, pediatric-onset multiple sclerosis, prodromal phase of multiple sclerosis, prevention, environmental factors, Epstein-Barr virus”;
- Imaging biomarkers: “multiple sclerosis, diagnostic criteria, magnetic resonance imaging, dissemination in space, dissemination in time, central vein sign, paramagnetic rim lesion, diagnostic accuracy, follow-up imaging”;
- Molecular biomarkers: “multiple sclerosis, MS, biomarkers, diagnostic, prognostic, oligoclonal bands, cerebrospinal fluid, CSF, kappa free light chains, kFLC, serum neurofilament, McDonald criteria”;
- Digital solutions: “multiple sclerosis digital health, multiple sclerosis telemedicine, multiple sclerosis telehealth, multiple sclerosis mHealth, multiple sclerosis eHealth, multiple sclerosis mobile apps, multiple sclerosis wearable devices, multiple sclerosis remote monitoring, multiple sclerosis digital biomarkers, multiple sclerosis artificial intelligence, multiple sclerosis digital therapeutics, multiple sclerosis virtual care, multiple sclerosis tele-rehabilitation, multiple sclerosis digital interventions, multiple sclerosis symptom tracking apps, multiple sclerosis patient-reported outcomes digital, multiple sclerosis self-management apps”;
- Economic findings: “multiple sclerosis, MS, economic burden, Canada, Quebec, healthcare costs, productivity loss, DMT”;
- Ongoing clinical trials of treatments for multiple sclerosis (Appendix C): “Multiple Sclerosis OR MS OR Disseminated Sclerosis OR Relapsing-Remitting Multiple Sclerosis OR RRMS OR Primary Progressive Multiple Sclerosis OR PPMS OR Secondary Progressive Multiple Sclerosis OR SPMS OR Clinically Isolated Syndrome OR CIS OR Radiologically Isolated Syndrome OR RIS OR Demyelinating Autoimmune Diseases OR CNS OR Neuroinflammation OR Myelin Repair OR Demyelination OR Quality of life OR MS Fatigue OR MS Spasticity OR Walking improvement OR CAR-T OR Chimeric Antigen Receptor OR CAR T-cell therapy OR CD19 OR CD20 OR BCMA OR Autologous OR Allogeneic OR Universal OR KYV-101 OR Obecabtagene autoleucel OR Obe-cel OR AUTO1-MS1 OR CC 97540 OR

BMS-986353 OR YTB323 OR Azercabtagene zapreleucel OR Azer-cel OR AZD0120 OR Zamtocabtagene Autoleucel OR Zamto-cel OR MB-CART2019.1 OR CT103A OR Disease-Modifying Therapy OR DMT OR Immunotherapy OR Immunomodulators OR Immunosuppressants OR Monoclonal Antibodies OR Sphingosine 1-phosphate (S1P) Receptor Modulators OR Autologous Hematopoietic Stem Cell Transplantation OR aHSCT OR Ocrelizumab OR Natalizumab OR Ofatumumab OR Alemtuzumab OR Interferon beta-1a OR Ublituximab OR Rituximab OR Fingolimod OR Siponimod OR Ozanimod OR Ponesimod OR Teriflunomide OR Cladribine OR Dimethyl fumarate OR Diroximel fumarate OR Monomethyl fumarate OR Interferon beta-1b OR Peginterferon beta-1a OR Glatiramer acetate OR BTK inhibitors OR Fenebrutinib OR Evobrutinib OR Tolebrutinib OR Frexalimab OR Vidofludimus calcium OR Fampridine OR Dalfampridine OR Surgeries OR Medical devices OR Neuromodulation implants OR Wearable devices OR Software-based tools OR Diet OR Ketogenic diet OR Dietary supplements OR Vitamins".

Other specialized sources, including sources in the grey literature, were consulted. The websites of professional societies, health technology assessment agencies, government agencies, and professional associations in countries whose healthcare systems and clinical practices are similar to those in Québec (e.g., the United States, Australia, New Zealand, France, England and Scotland) were consulted. The list of the sources consulted is provided in Appendix B.

The generative AI tool Microsoft 365 Copilot Chat was used in accordance with INESSS's *Balises de l'utilisation responsable de l'IA générative* to explore topics and concepts, to support the strategic drafting of this report, including the rephrasing and summarizing of sentences, and to translate concepts relating to foreign health policies and healthcare systems.

### Gathering and synthesis of contextual and experiential data

INESSS values the experiential and contextual knowledge contributed by various stakeholders.

The information cited in the report is drawn from perspectives gathered from clinicians, patients, and a patient association during a half-day discussion on MS held in the spring of 2026, and from *ad hoc* consultations (narrative synthesis), a review of the scientific literature, and scientific and clinical-administrative data.

### Clinical-administrative data

The clinical-administrative data used for this project are drawn from RAMQ databases, which are accessed through a tripartite agreement between the MSPA, RAMQ and INESSS. The main data sources used are as follows:

- **The Fichier d'inscription des personnes assurées (FIPA).** This registry contains demographic characteristics (age, sex, date of death, etc.) on individuals covered by the Québec health insurance plan, and their address history.
- **Services médicaux des pharmaciens rémunérés (SMED).** This database contains information on each drug prescription dispensed by a pharmacist to individuals

covered by Québec's Basic Prescription Drug Insurance Plan (prescriptions for individuals covered by a private plan are therefore not included in this database). For each prescription, the database includes its date, the prescriber, and details about the drug (name, DIN code, dose, duration of treatment, cost, etc.).

### Scientific support and critical peer review

The report underwent critical review by theScientific Coordination and the department responsible for its production. A final review of the report was carried out by INESSS's Vice-présidence scientifique and Bureau – Méthodes, données et éthique.

### Prevention, disclosure and management of conflicts of interest and role conflicts

The individuals who participated in the consultation disclosed any personal interests that could place them in a situation that could give rise to conflicts of interest, whether commercial, financial, career-related, relational or otherwise. They also disclosed any professional activities or roles that could place them in a situation that could give rise to role conflicts. The disclosures were examined by INESSS. Management measures were taken in accordance with INESSS's Policy on the Prevention, Identification, Assessment and Management of Conflicts of Interest and Role Conflicts among External Collaborators (*Politique de prévention, d'identification, d'évaluation et de gestion des conflits d'intérêts et de rôles des collaborateurs*).

# APPENDIX B

## List of the sources consulted

### Table B-1 Other sources consulted

| |
|---|
| **Agency websites**<br>Date consulted: May 13, 2026 |
| Canada's Drug Agency (CDA, Canada) |
| Patented Medicine Prices Review Board (PMPRB, Canada) |
| European Medicines Agency (EMA, Europe) |
| Food and Drug Administration (FDA, United States) |
| Haute Autorité de Santé (HAS, France) |
| Institut national d'excellence en santé et en services sociaux (INESSS, Québec) |
| Medicines and Healthcare products Regulatory Agency (MHRA, United Kingdom) |
| National Institute for Health and Care Excellence (NICE, United Kingdom) |
| Régie de l'assurance maladie du Québec (RAMQ, Québec) |
| Health Canada (Health Canada, Canada) |
| Therapeutic Goods Administration (TGA, Australia) |
| **Other websites** |
| The U.S. NIH clinicaltrials.gov database |
| **Search engines**<br>Date of last search: May 13, 2026 |
| Google |

# APPENDIX C

## Ongoing clinical trials for the treatment of multiple sclerosis

A search of the U.S. NIH ClinicalTrials.gov database in March 2026 identified 121 clinical trials involving MS. Figure C-1 below shows the number of ongoing clinical trials. Therapies and drugs for the treatment of MS are categorized by therapeutic target or intervention. Most ongoing MS clinical trials focus on CAR-T therapies, stem cell transplantation, and monoclonal antibodies.

### Chimeric antigen receptor T-cell therapy (all early-phase; phases I and II) (Fischbach *et al.*, 2024; Li *et al.*, 2026)

In MS, CAR-T therapy is a major step forward, shifting from chronic suppression to a potential reset of the immune system. This approach uses modified T cells to achieve deep depletion of pathogenic B cells, an objective that is often unattainable with existing treatments. The goal of CAR-T therapy research in MS is to achieve an immune reset that would allow long-term control of MS without the need for subsequent treatment.

Among the main approaches under investigation, cells can be harvested from the patient (autologous) or from a healthy donor (allogeneic). After harvesting and laboratory processing, lymphodepleting chemotherapy is required before the reprogrammed cells are reintroduced into the patient. T cells can cross the blood-brain barrier, which enables them to target inflammation and ectopic B-cell follicles hidden within the CNS. By eliminating the population of autoreactive B cells, CAR-T therapy enables the immune system to reconstitute itself with new naive B cells that neither recognize nor attack the body's nervous system.

### Stem cell transplantation (mostly early-phase) (Condamoor *et al.*, 2026; Muraro *et al.*, 2017; Sheikhi *et al.*, 2025)

The ongoing trials (autologous or allogeneic) concern the transplantation of:

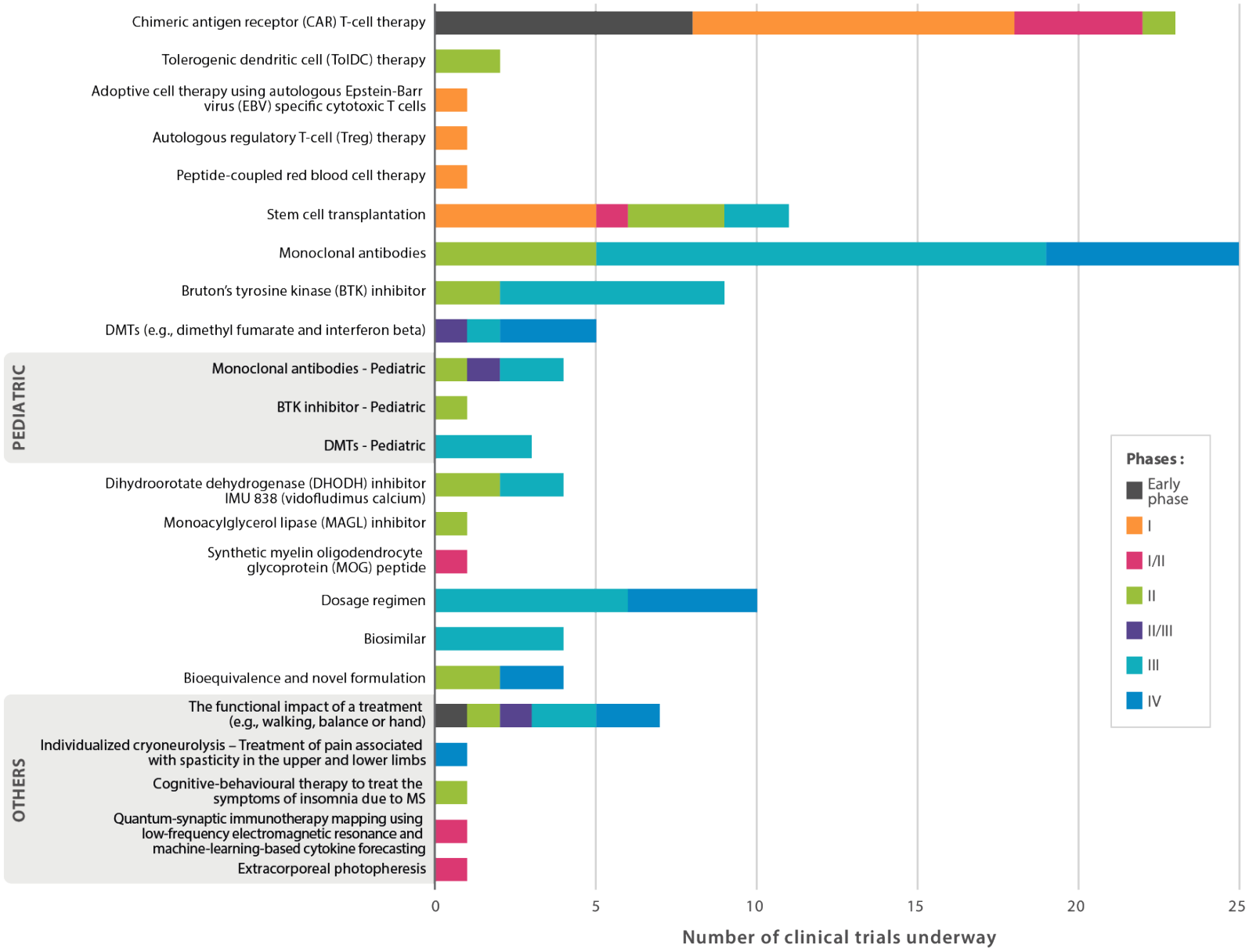
- Hematopoietic stem cells involving, among other things:
  - A reset of the immune system;
  - Typically high-dose chemotherapy (immunoablation) to destroy the autoimmune immune system, particularly T and B cells;
  - The harvesting of stem cells from bone marrow or blood, which are then frozen;
  - The reintroduction of the stored cells for the purpose of developing a new, healthy immune system;
  - The body's production, over several months, of new immune cells that are no longer programmed to cause attacks;

- Mesenchymal stem cells involving, among other things:
  - Repair (e.g., remyelination and neuroprotection);
  - The fact that chemotherapy is (typically) not required, allowing the patient's original immune system to be preserved;
  - The harvesting of stem cells from various sources (e.g., bone marrow, adipose tissue, umbilical cord or placenta), which are then frozen;
  - The reintroduction of naive or modified cells in order to initiate repair.

### Monoclonal antibodies

Among ongoing monoclonal antibodies trials, new targets are being investigated in early-phase trials (e.g., anti-CD3, anti-CD40L and anti-CD19/FcYRIIb). As regards non-inferiority trials (ocrelizumab vs. rituximab), they are all currently Phase III studies.

## Figure C-1 Ongoing clinical trials concerning MS

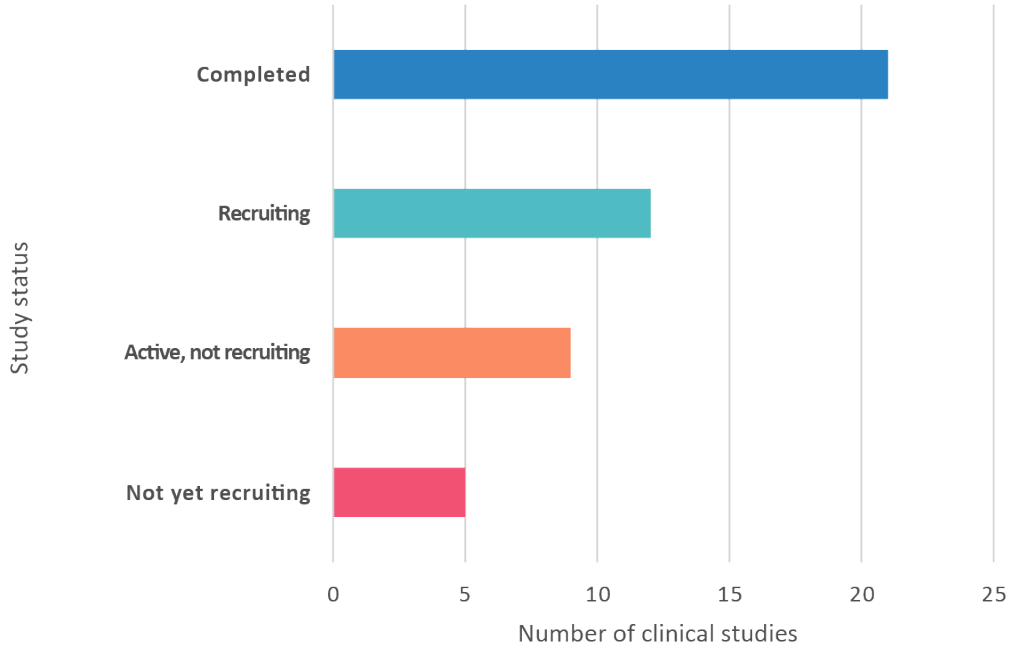


# APPENDIX D

## Clinical trials involving digital solutions in multiple sclerosis

A search in the U.S. NIH ClinicalTrials.gov database in April 2026 identified 47 clinical studies of digital solutions for MS with various recruitment statuses (not yet recruiting, active and not recruiting, recruiting, completed). Figure D-1 below shows the number of clinical trials by status.

**Figure D-1 Number of clinical trials involving digital solutions in MS**



# APPENDIX E

## Categories of digital solutions identified

### Digital solutions for assisting with diagnosis

***Users:*** *Health professionals* | ***Examples:*** *icobrain MS, Pixyl.Neuro, Neurophet AQUA* and *NeuroQuant.*

Used to objectively assess the patient's baseline condition and establish a baseline functional profile. These solutions include software for quantifying brain lesions, lesion volume, and atrophy; tools for measuring retinal thickness; and digital assessments of vision, cognition, motor skills, ocular motility, and gait (De Angelis *et al*., 2021; Dillenseger et al., 2021; Michaud et al., 2023). AI could be incorporated into standardized solutions, for example, to predict MS progression with high overall diagnostic performance (in terms of sensitivity, specificity and accuracy) (Darrudi *et al.*, 2025; Dini *et al.*, 2025; Nabizadeh *et al.*, 2022) or to anticipate risks or better guide treatment decisions (Voigt *et al.*, 2026).

### Digital solutions for progression tracking or remote monitoring

***Users:*** *Health professionals and patients* | ***Examples:*** *ETNA™-MS (solution developed in Québec), MSCopilot, Floodlight™ MS,* ElevateMS and Konectom

These include mobile apps and connected devices that support remote functional assessments on mobile devices (monitoring cognitive function, fine motor skills, balance, gait, mood or fatigue) and to collect continuous data (mobility, physical activity, gait, sleep, or fall detection) (Dillenseger *et al.*, 2021; Dini *et al.*, 2025; Gashi *et al.*, 2024; Michaud *et al.*, 2023; Oh *et al.*, 2024; Tseriotis *et al.*, 2026; Ziemssen et Haase, 2021).

### Digital solutions for self-management or relapse management

***Users:*** *Patients* | ***Examples:*** *MS Sherpa, My MS Manager* and *iCompanion MS*

Used to collect patient data through electronic questionnaires or symptom diaries (fatigue, quality of life, mood, mobility and functional ability) (Dillenseger *et al.*, 2021; Tseriotis *et al.*, 2026; Zaratin *et al.*, 2026). Some mobile apps have been developed to help manage relapses (recording symptoms, generating or sending reports and recording notes) (Salimzadeh *et al.*, 2019).

### Digital solutions for treatment and functional rehabilitation

***Users:*** *Health professionals and patients* | ***Examples:*** *Elevida* and *Kinect*

Used for motor or cognitive rehabilitation. These include physical activity programs, digital psychotherapies, telerehabilitation, cognitive-motor training, and virtual reality-based tools (De Angelis *et al.*, 2021; De Keersmaecker *et al.*, 2025; Heesen *et al.*, 2023; Triolo *et al.*, 2026; Wender *et al.*, 2022).

# APPENDIX F

## Drug cost

| Drug | Dosage considered[a] | Unit price[b] | Annual cost of treatment[c] |
|---|---|---|---|
| Alemtuzumab<br>I.V. Perf. Sol.<br>Lemtrada® | First year:<br>1 I.V. infusion of 12 mg per day for 5 days<br><br>Subsequent years:<br>1 infusion per day for 3 days | $9,970/vial of 10 mg/mL (1.2 mL) | First year:<br>$50,105<br><br>Subsequent years:<br>$30,067 |
| Cladribine<br>Tab.<br>Mavenclad® and generic versions | 10 or 20 mg orally for 4 to 5 days, repeated after 1 month, according to body weight | $2,409/10 mg tab.[d,e] | $33,981[f] |
| Dimethyl fumarate<br>L.A. Caps.<br>Tecfidera® and generic versions | First 7 days:<br>120 mg orally twice daily<br><br>Subsequent days:<br>240 mg twice daily | $4.43/120 mg[d] caps.[d,e]<br>$8.69/240 mg caps.[d,e] | $6,872[g] |
| Fingolimod<br>Caps.<br>Gilenya® and generic versions | 0.5 mg orally once daily | $21.74/0.5 mg caps.[d,e] | $8,459 |
| Glatiramer<br>S.C. Inj. Sol.<br>Glatect® | 20 mg S.C. once daily | $32.40/syringe of 20 mg/mL (1 mL)[e] | $12,376 |
| Glatiramer<br>S.C. Inj. Sol.<br>Injectable glatiramer acetate | 20 mg S.C. once daily | $27.86/syringe of 20 mg/mL (1 mL)[e] | $10,742 |
| Interferon beta-1A<br>I.M. Inj. Sol.<br>Avonex Pen®, Avonex PS® | 30 or 60 mcg I.M. once weekly | $352.46/30 mcg syringe or pen | $19,100 to $38,065 |
| Interferon beta-1A<br>S.C. Inj. Sol.<br>Rebif® | 22 or 44 mcg S.C. thrice weekly | $358.69/cartridge of 22 mcg/0.5 mL (1.5 mL)<br>$436.66/cartridge of 44 mcg/0.5 mL (1.5 mL)<br>$119.56/22 mcg syringe (6 MIU)<br>$145.55/44 mcg syringe (12 MIU) | $19,424 to $23,478 |
| Interferon beta-1B<br>Inj. Pd.<br>Betaseron® and Extavia® | 0.25 mg S.C. every 2 days | $99.36/0.3 mg vial | $18,597 |
| Natalizumab<br>I.V. Inj. Sol.<br>Tysabri® | 300 mg by I.V. infusion every 4 weeks | $2,451.32/vial of 300 mg/15 mL | $32,639 |

| Drug | Dosage considered[a] | Unit price[b] | Annual cost of treatment[c] |
|---|---|---|---|
| Ocrelizumab<br>I.V. Perf. Sol.<br>Ocrevus® | 300 mg by I.V. infusion on days 1 and 15, then 600 mg every 6 months | $8,150/vial of 30 mg/mL (10 mL)[e] | $32,817 |
| Ofatumumab<br>S.C. Inj. Sol.<br>Kesimpta® | 20 mg S.C. on weeks 0, 1, 2 and 4, then every month | $2,208.33 $/pen of 20 mg/0.4 mL[e] | First year:<br>$33,985<br><br>Subsequent years:<br>$27,213 |
| Siponimod<br>Tab.<br>Mayzent® | 0.25 mg on days 1 and 2, 0.5 mg on day 3, 0.75 mg on day 4, 1.25 mg on day 5 and 2 mg on each day thereafter | $22.35/0.25 mg tab.<br>$89.32/2 mg tab.[e] | $33,283[g] |
| Teriflunomide<br>Tab.<br>Generic versions | 14 mg orally once daily | $14.93/14 mg tab.[d,e] | $5,849 |

Caps.: Capsule; GSP: Guaranteed selling price; I.M.: Intramuscular; I.M. Inj. Sol.: Solution for I.M. injection; Inj. Pd.: Powder for injection; I.V.: Intravenous; I.V. Inj. Sol.: Solution for I.V. injection; I.V. Perf. Sol.: Solution for I.V. perfusion; L.A. Caps: Long-acting Capsule; MIU: Million International Units; S.C.: Subcutaneous; S.C. Inj. Sol.: Solution for S.C injection; Tab.: Tablet;

a The dosage considered is the one recommended in the product monographs or the one commonly used in clinical practice.

b This is the guaranteed selling price on the *List of Medications* (April 2026).

c This calculation assumes continuous use and perfect adherence to treatment and includes the cost of the pharmacist's professional services and the wholesaler's profit margin.

d The lowest price method (LPM) applies.

e It should be noted that this drug was the subject of a listing agreement (RAMQ 2025).

f This calculation is based on a body weight of 77 kg. According to the product monograph, the recommended cumulative dose is 1.75 mg/kg per year (3.5 mg/kg over 2 years), administered in 2 treatment weeks: one at the beginning of the 1st month and one at the beginning of the 2nd month of the treatment year. For a patient weighing 77 kg, this corresponds to 14 tablets of 10 mg per year.

g For simplicity, only the cost associated with the maintenance dose was calculated.

# APPENDIX G

## RAMQ billing statistics

### Table G-1 Number of patients for whom an MS treatment was covered over the past 3 years, based on RAMQ billing statistics

| Drug | 2023 | 2024 | 2025 |
|---|---|---|---|
| Alemtuzumab | [redacted] | 0 | 0 |
| Cladribine | 61 | 67 | 60 |
| Dimethyl fumarate | 383 | 343 | 317 |
| Fingolimod | 391 | 357 | 323 |
| Glatiramer acetate | 480 | 404 | 359 |
| Interferon beta-1A | 321 | 289 | 255 |
| Interferon beta-1B | 57 | 50 | 39 |
| Natalizumab | 142 | 134 | 114 |
| Ocrelizumab | 993 | 1 099 | 1 209 |
| Ofatumumab | 378 | 630 | 918 |
| Siponimod | 119 | 115 | 111 |
| Teriflunomide | 876 | 830 | 824 |
| **Total**[a] | [redacted] | 4318 | 4529 |

a It should be noted that a given patient may be included in more than one year if they received one or more treatments during those years.

### Table G-2 Number of new patients who began an MS treatment in the past 3 years, based on RAMQ billing statistics

| Drug | 2023[a] | 2024[a] | 2025[a] |
|---|---|---|---|
| Alemtuzumab | [redacted] | [redacted] | [redacted] |
| Cladribine | 19 | 15 | [redacted] |
| Dimethyl fumarate | 23 | 10 | [redacted] |
| Fingolimod | [redacted] | [redacted] | [redacted] |
| Glatiramer acetate | 18 | 17 | 10 |
| Interferon beta-1A | [redacted] | [redacted] | [redacted] |
| Interferon beta-1B | [redacted] | [redacted] | [redacted] |
| Natalizumab | [redacted] | [redacted] | [redacted] |
| Ocrelizumab | 89 | 84 | 114 |
| Ofatumumab | 83 | 89 | 124 |
| Siponimod | 13 | [redacted] | [redacted] |
| Teriflunomide | 45 | 34 | 32 |

a A 1-year (365-day) lookback period was used to identify treatment-naive patients who were continuously enrolled in the Public Prescription Drug Insurance Plan during that period. Patients who had received a treatment during a previous study year were excluded.