# Analysis of current multiple sclerosis registries

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## ABSTRACT

**Background:** Patient registries are valuable because they provide data that cannot be captured in any other way. Observations from registry studies are particularly informative if multiple registries confirm similar findings. A selection of multiple sclerosis (MS) registry studies were reviewed, and results and consistency of those studies are presented.

**Methods:** A panel of experts analyzed the study findings of established MS registries and presented their conclusions on the overall results and consistency of those studies.

**Results:** A review of evidence from MS registry studies reveals similar findings with respect to patterns of disability progression, predictors of disability progression, and changes in lifespan. Several registries show that progression after Expanded Disability Status Scale (EDSS) 4 occurs at a predictable rate, and once EDSS 4 is reached, subsequent progression rates are similar regardless of the type of MS at onset. Clinicians, payers, and patients need to understand that MS may shorten life expectancy. The mortality data derived from registries reveal higher death rates in patients with MS compared with the general population, indicating that MS is an important public health issue.

**Conclusions:** The key findings in registries should be utilized in conjunction with data from clinical trials to optimize treatment and improve long-term outcomes. **NEUROLOGY 2011; 76(Suppl 1):S7–S13**

## GLOSSARY

**BCMS** = British Columbia Multiple Sclerosis; **CDMS** = clinically definite multiple sclerosis; **DMT** = disease-modifying therapy; **EDMUS** = European Database for Multiple Sclerosis; **EDSS** = Expanded Disability Status Scale; **IFN** = interferon; **MS** = multiple sclerosis; **NYSMSC** = New York State Multiple Sclerosis Consortium; **PPMS** = primary progressive multiple sclerosis; **PRMS** = primary relapsing multiple sclerosis; **RRMS** = relapsing-remitting multiple sclerosis; **SPMS** = secondary progressive multiple sclerosis.

Multiple sclerosis (MS) registries have been established worldwide, and are valuable repositories of information on the long-term course and characteristics of MS. These longitudinal or cross-sectional databases provide important information that may promote a better understanding of risk factors and prognosis, and serve as an important guide for both clinical and socioeconomic decision-making. These registries provide insight into the disease process and its progression as well as the effect of MS on patients' functional status, quality of life, morbidity, and mortality. Detailed descriptions of established MS registries were presented previously in this supplement. This article summarizes the current findings from key registry studies.

## GENERAL ISSUES FOR ALL MS REGISTRIES

Registries are valuable because they provide data that cannot be captured in any other way, due to such issues as the extensive time and funding that would be required in order to recruit such a large number of patients into a study. This method of prospective, standardized accumulation of data overcomes the limitations of power present in many clinical trials. However, these observational databases have been criticized for their lack of power in addressing weak associations and in predicting rare events, and for ascertainment bias because most of the registries are not complete.[1] In addition, the gathering and maintenance of high-quality data requires a huge commitment. This is made even

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more difficult by limited funding, which can be difficult to obtain because registry data are not required for product registration. Therefore, registries are generally funded by agencies seeking health statistics or actuarial data, or are a dedicated effort by clinicians seeking a better understanding of MS. All registries are subject to similar methodologic challenges.[1]

In the case of data collection, it is more practical to collect a minimum amount of information consistently. Consistent data on past medical history, comorbidities, number of relapses, MRI lesions, and medications may be particularly difficult to capture over the long term. If extra data are required, one possibility is to collect this over a limited time period. For example, small complete registries of relatively stable populations (such as the Framingham or Olmsted County databases) are very valuable and can produce high-quality data.[2–4] Forms for data entry should be unambiguous in order to capture information effectively and without unnecessary effort. Clear guidelines, training, and careful monitoring are essential for those providing and entering patient information. Efficient methods for obtaining missing data and validation are essential.

In order to provide accurate and robust data, the characteristics of a registry should encompass many factors. Ongoing longitudinal data collection is needed to observe the long-term MS disease course. Maximum possible ascertainment in a region or population should be attained to avoid selection bias.[1] There should be systematic follow-up of each patient, with the ability to identify patients if necessary, in order to complete missing data. Data entered into the databases should be consistently validated and confirmed to increase the rigor of registries. Maintenance must be done to ensure complete and accurate information.[1] Information on deaths should go beyond what is written on the death certificate to try to identify not only the cause of death but also contributing factors. These measures would help in the creation and maintenance of registries with greater research potential.

**Table 1** Life expectancy of patients in years from the Canadian MS databases from London, Ontario and Vancouver, British Columbia[7]

| | Life expectancy (women), y | | Life expectancy (men), y | |
|---|---|---|---|---|
| Age, y | All MS | Insured population[a] | All MS | Insured population[a] |
| 20 | 52.5 | 59.7 | 46.6 | 54.3 |
| 40 | 33.7 | 40.4 | 28.7 | 35.6 |
| 60 | 17.0 | 22.5 | 13.0 | 18.5 |
| 80 | 5.2 | 8.4 | 4.1 | 7.0 |

Abbreviations: MS = multiple sclerosis.
[a] Insured population data are age- and sex-matched data from the Canadian Institute of Actuaries Standard Insured Mortality, 1969–1995.

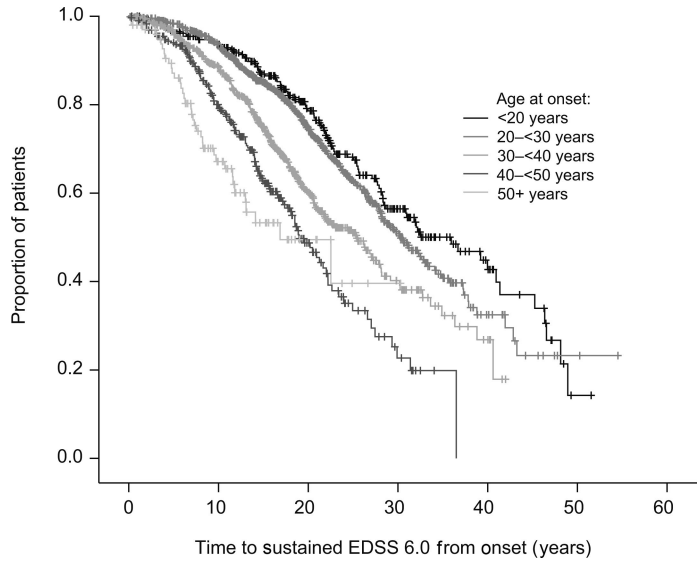
## RESULTS FROM KEY MS REGISTRY STUDIES

**London, Ontario database.** In 2006, the London, Ontario database assessed time to disability in 1,043 patients with different progressive forms of MS between 1972 and 1984.[5] Disability was measured by the Disability Status Scale (DSS), which was subsequently enhanced to produce the Expanded Disability Status Scale (EDSS), and the progressive phase of the disease was defined as at least 1 year of continuous deterioration. The study found that, when stratified by DSS score at progression onset, patients with a single attack before progression (n = 140), primary progressive MS (PPMS; n = 219), and secondary progressive MS (SPMS; n = 146) all took a similar amount of time to reach DSS 6, 8, and 10. Neither the number of relapses prior to entering the progressive phase nor subsequent relapses affected this rate of progression. The study showed the importance of focusing on delaying time to reach the progressive stage of MS, as controlling patient relapses at and from that point is less likely to have an effect on the disease course.[5] In a different study examining potential predictors of future disability, a greater number of attacks in the first 2 years after onset, a shorter interval between first and second attacks, and a shorter time to reach DSS 3 were found to be predictive of reaching DSS 6 earlier.[6]

In 2 studies combining registry data from the Canadian southwestern Ontario London and the British Columbia Vancouver clinics, MS was reported to be associated with increased mortality. In one study, survival was approximately 6 to 7 years less in the MS population than the normal population aged 20 to 60 years. After the age of 60 years, there was less of a difference between those populations, with only about a 4-year or less difference in mortality by the age of 70 years.[7] However, this was a small dataset of 115 deaths in a population of 2,348 patients with MS from 1972 to 1985, and before the use of disease-modifying therapy (DMT) (table 1).[7] A second study using data from this registry demonstrated that approximately half of the deaths with a known cause (56/119 patient deaths) of a total population of 3,126 registered patients with MS were due to MS-related complications. Furthermore, the risk of suicide in this MS population was observed to be 7.5 times higher than that of age-matched controls.[8]

**British Columbia Multiple Sclerosis database.** Patients participating in the British Columbia Multiple Sclerosis (BCMS) registry had their EDSS score measured once every 1.1 years (SD 0.97).[9] The median time from first onset of symptoms to EDSS 6 (re-

**Figure 1** Time to a cane from first-onset symptoms by age at onset[9]




At 15 years after onset, 21% required a cane, increasing to 69% by 40 years after onset. EDSS = Expanded Disability Status Scale.[9]

quiring a cane) was 27.9 years. At 15 years after onset, 21% required a cane, increasing to 69% by 40 years after onset (figure 1). Significant predictors of increased disability progression to EDSS 6 when analyzed from onset of first symptoms were male gender, younger age at onset, and PPMS disease course ($p < 0.0005$). Progression to EDSS 6 for men was 38% more rapid than for women.

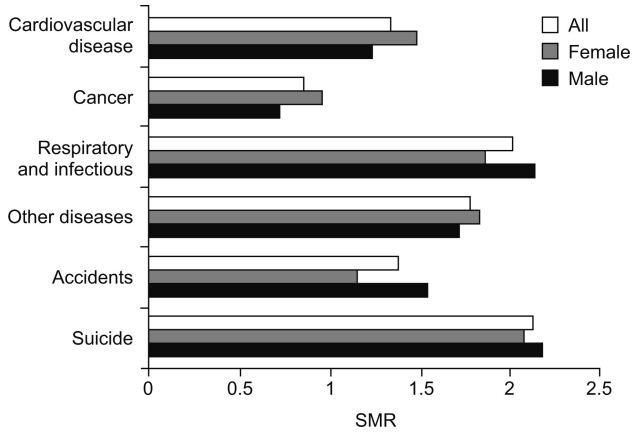
The impact of DMT use was minimal in this dataset, as only 17.7% (439/2,484) of patients with relapsing-remitting MS (RRMS) and 17.9% (259/1,445) with SPMS were ever prescribed a DMT, with a mean duration on DMT of 3.9 years out of a total of 20.5 years mean follow-up time.[10] The relatively low proportion of patients prescribed DMTs in this population may be because, at the time of this study, DMTs were reported to have been prescribed mainly to patients with a more aggressive disease course, thus limiting their use and potentially diluting the appearance of any efficacy when compared with patients with more benign forms of MS.[11] An additional reason not reported in this study may be that all patients in this registry were first registered prior to 1988, 5 years before the first DMT was commercially available.

**New York State Multiple Sclerosis Consortium database.** In 2003, a total of 5,602 patients were registered in the New York State Multiple Sclerosis Consortium (NYSMSC) database. The study analyzed the prevalence of MS in patients of African American origin and other non–African American registrants. The majority (>56%) of both these MS patient populations had RRMS. Of the remaining MS types, SPMS was the next most common (28.9% of African American origin, 30.5% non–African American), with relatively fewer patients with PPMS (6.7% of African American origin, 7.8% non–African American) and primary relapsing MS (PRMS; 6.1% of African American origin, 4.1% non–African American). Longer disease duration (95% confidence interval for odds ratio 1.14–1.23) was found to be a predictor of worse disability outcomes, and African American origin was found to be associated with greater disability as disease duration increased (95% confidence interval for odds ratio 0.92–0.99).[12] A prior study using the NYSMSC database found evidence that patients with MS had worse disability outcomes when they had progressive types of MS when compared with RRMS (65% vs 9% with EDSS 6.0 or greater, respectively).[13] Duration of disease was also found to be significantly longer for patients with SPMS (12.5 years) than those with PRMS (9.2 years) or PPMS (8.8 years) ($p < 0.01$).[13]

**Department of Veterans Affairs registry.** Information obtained in this database was cross-sectional, correlating the patient information from the Veterans Affairs national administrative database with a 1999 mailed national health survey. The majority of patients with MS in the Veterans Affairs registry are men (86.5%); additionally, 86.7% of patients are white and 13.3% are nonwhite. There is evidence that this cohort has a high comorbidity burden. Measures of comorbidity (mean ± SD) included a Seattle Index of Comorbidity (which can be predictive of rates of mortality and hospitalization) of 3.69 ± 2.73, a body mass index of 26.17 ± 4.82, and a Veteran RAND 36-Item Health Survey pain intensity item (1–6) of 3.84 ± 1.34.[14]

**North American Research Committee on Multiple Sclerosis.** In response to criticism that patients with MS are incapable of accurate self-reporting, small validation studies of the North American Research Committee on Multiple Sclerosis registry were undertaken.[15–18] In the validation of MS diagnosis, 142 out of 240 random samples of registry participants were in active status and eligible for the study. Of the 142 patients, 109 were in active registry status with accurate contact information, of which 52 patients consented to participate. All patients were interviewed by telephone, and medical records, including imaging studies, CSF examinations, evoked potentials, bloodwork, and clinical history and examination, were also reviewed. Based on the physician questionnaire or review of medical records, the diagnosis of MS was confirmed in 98.9 ± 1.3% of patients.[15] Additional studies determined that the

**Figure 2** Standardized mortality ratios (SMRs) for underlying causes of death[21]



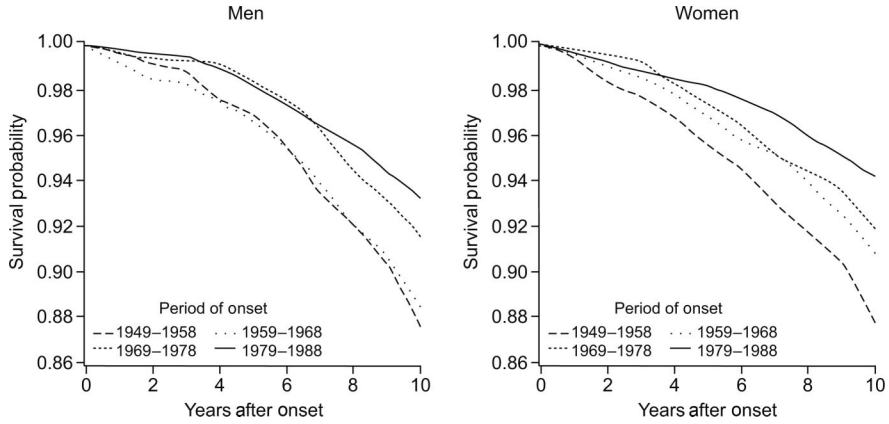

subscales of the disability measure have adequate criterion and construct validity, and that the questionnaire item used to assess pain is also a valid self-report measure in MS.[16–18]

**European Database for Multiple Sclerosis.** In an analysis of the European Database for Multiple Sclerosis (EDMUS) Burgundy database, better MS prognosis was associated with younger patients, initial presentation of optic neuritis, fewer MS attacks during first year, and a longer interval between first and second attacks.[19] The risk of advancing to EDSS Grading Scale ≥3 (a simplified version of the EDSS, to which it is highly correlated) increased with atypical clinical presentation at onset (hazard ratio = 2.97; $p = 0.047$), older age at onset (hazard ratio = 1.04; $p < 0.00001$), and every additional relapse by 21% ($p = 0.007$). It was concluded that frequent relapses, which are a sign of inflammation, in the first years of MS influence long-term disability when observed through the measurement of axonal degeneration.[19]

From the EDMUS Lyon database, data were obtained on disability progression and its predictors.[20] In patients with PPMS, disability progression, as measured by the Kurtzke DSS, was found to occur more rapidly from disease onset to DSS 4, 6, and 7 than for patients with RRMS. Disability progression was also more rapid for patients who were male, had an older age at disease onset, were diagnosed with RRMS as compared with a progressive onset, had an incomplete recovery from their first relapse, or had a shorter duration between first and second neurologic attacks. The initial symptom of isolated dysfunction of long tracts was also associated with faster time to disability (DSS 4, 6, and 7)[20] when compared with isolated optic neuritis at onset. Time from DSS 4 to DSS 6 or 7, or from DSS 6 to DSS 7, occurred at a similar rate in patients with PPMS and RRMS. While the early phases of the PPMS and RRMS disease course differed, a common disease progression process occurred once a certain disability threshold had been reached.[20]

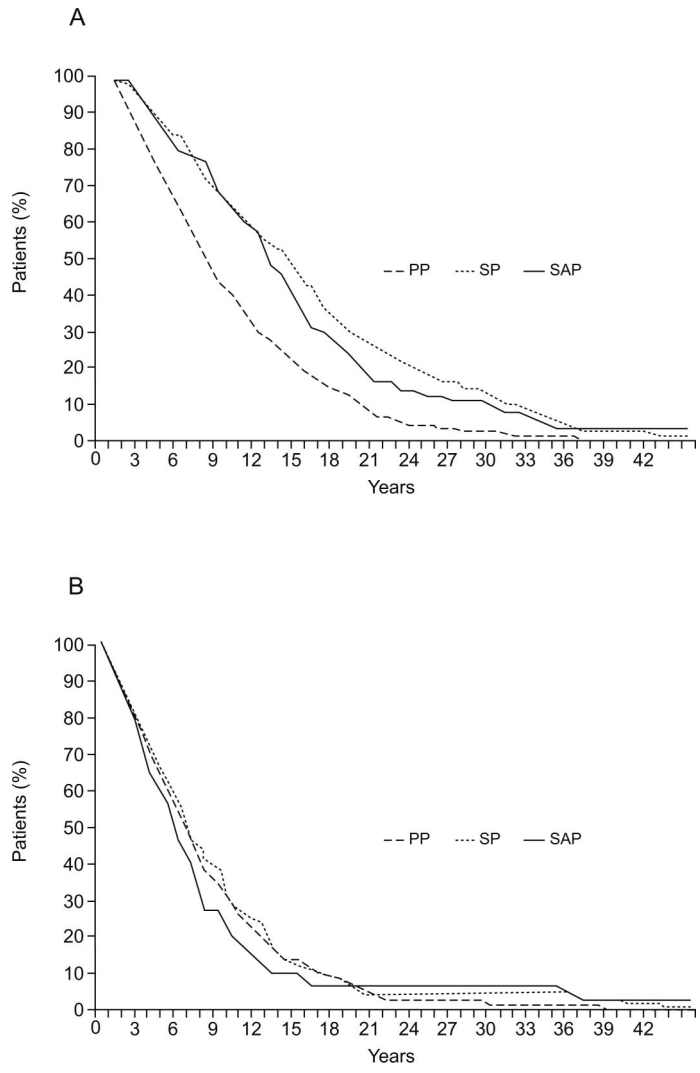
**Danish Multiple Sclerosis Treatment registry.** Mortality data from the Danish registry have been determined in 9,881 patients with MS (with an onset of disease between 1949 and 1996).[21] By the end of the follow-up, there were a total of 4,254 deaths. In more than half (56.4%) of those who died, MS was recorded as the underlying cause. There was an average excess of 13 MS deaths from any cause per 1,000 patient-years, when compared with an age-matched, general Danish population. On average, patients with MS were found to lose 10 to 12 years of life compared with an age-matched population. This increased mortality rate was due to a relative increase in

**Figure 3** Trend in survival probability over time in the Danish MS population[21]




From Bronnum-Hansen H, Koch-Henriksen N, Stenager E. Trends in survival and cause of death in Danish patients with MS. Brain 2004;127:844–850, by permission of Oxford University Press.

**Figure 4** Disability progression in patients with progressive MS




(A) Time to Expanded Disability Status Scale (EDSS) 6 from the onset of MS. (B) Time to EDSS 6 from the onset of progressive MS.[5] PP = primary progressive MS; SAP = single-attack progressive MS; SP = secondary progressive MS. From Kremenchutzky M, Rice GP, Baskerville J, Wingerchuk DM, Ebers GC. The natural history of MS: a geographically based study 9: observations on the progressive phase of the disease. Brain 2006;129:584–594, by permission of Oxford University Press.

deaths from cardiovascular disease, respiratory and infectious disease, accidents, and suicide, with a relative reduction in cancer-related deaths, when compared with an age-matched Danish population (figures 2 and 3).[21]

The first DMT for MS, interferon β-1b (IFNβ-1b), was approved in Denmark in June 1996. Data from Danish patients treated since then, and as other DMTs were approved thereafter, have been incorporated into a Danish Multiple Sclerosis Treatment Registry. In a 2006 study, IFNβ-1b, IFNβ-1a, and glatiramer acetate were compared using registry data from 1996 to 2003. All DMTs were shown to have reduced relapses over the first 2 years of use when compared to pretreatment relapse rates. The study showed that only treatment with IFNβ-1a 44 mcg SC was associated with a greater likelihood of disease progression. The authors of the study believed this may have been due to selection bias. It has been suggested that such bias may be a problem for all open-label, observational studies, making it difficult to compare efficacy between different DMTs in such studies.[22]

## ARE RESULTS CONSISTENT BETWEEN REGISTRY STUDIES?

**Rates of mortality.** Combined British Columbia and Vancouver[7,8] and Danish registries have observed reduced lifespan in patients with MS.[21,23,24] For more than half the Danish MS patient population, MS was reported as the underlying cause of death, which is similar to observations from the Vancouver registries.[8] However, the Danish registry has shown that survival time has improved in the last 3 to 4 decades, probably due to multiple medical advances, including treatment for respiratory infections (figure 3). However, it should be noted that these mortality data are taken from non-DMT-treated patients.[7,8,21]

**Rates of disability progression.** Multiple registry studies provide relatively consistent findings on the rate of disability progression in patients with MS. The EDMUS and BCMS databases have observed that, for MS patient populations in France and Canada, the median time to disability progression (EDSS 6) was 23 years (EDMUS Lyon) and 27.9 years (BCMS), respectively.[9,19,20] These findings were similar to those found in registry studies concerning Olmsted County, MN, USA (28.6 years, n = 201), and Newcastle, Australia (27.0 years, n = 159).[3,25] However, median time to disability progression of EDSS 6 in a cohort of patients with MS from the Vancouver registries (London, Ontario MS database) was shorter at 15 years,[1] which may indicate not only a selection bias but also a changing MS population.

Several registry studies have shown that progression after EDSS 4 occurs at a fairly predictable rate. One observational analysis of a cohort of patients with MS from the London, Ontario MS database, which compared time to disability progression (EDSS 6, 8, and 10) among patients categorized according to 3 progressive subtypes stratified at onset by EDSS (PPMS, single-attack progressive, and SPMS), showed that there were no differences between groups in the time from disease onset to EDSS 6, 8, or 10.[5] This suggests that progression, once it begins, is largely independent of preceding factors (figure 4). Key predictors of disability progression have been identified in multiple registry studies (table 2).[9,19,20,23,26] Similar observations have been reported in EDMUS Lyon,[20,26] which shows that, once

**Table 2** Predictors of disability progression

| Predictor | MS registry |
|---|---|
| Progressive course from onset | BCMS[9] |
| | EDMUS (Burgundy and Lyon)[19,20] |
| Older age at onset | EDMUS (Burgundy)[19] |
| | BCMS[11] |
| Long-tract/cerebellar symptoms at onset | Danish registry[21] |
| | EDMUS (Lyons)[20,26] |

Abbreviations: BCMS = British Columbia Multiple Sclerosis; EDMUS = European Database for Multiple Sclerosis.

an EDSS of 4 has been reached, preceding clinical variables that are predictors of time from onset of MS to time to irreversible disability are no longer predictive of subsequent disability progression. These findings imply that early treatment intervention may be important to prevent patients reaching this landmark (EDSS 4) and subsequent progression.

Other non-registry studies have also shown that early clinical variables can predict long-term disability in patients with early MS. Findings from a Barcelona cohort study show that baseline MRI is associated with an increased risk for converting to clinically definite MS (CDMS) and correlates with physical disability at 5 years.[27] A cohort study from Queen Square, London, UK, followed patients with a first clinical event suggestive of demyelinating disease for approximately 20 years. It was observed that an abnormal MRI, regardless of the number of lesions, strongly predicts development of CDMS, with about 82% of patients developing the disease within 20 years. MRI disease burden was useful in predicting the severity of disease over this time period, with 45% of patients with high lesion load (10+ lesions on MRI examination) reaching EDSS 6.[28] These findings indicate that the severity of MS can be influenced by clinical variables that can be detected early in the disease course, highlighting the importance of early diagnosis and treatment.

**DISCUSSION** MS registry studies are an important complement to clinical trial data because they provide valuable insight into the longitudinal course of MS. A review of evidence from MS registry studies revealed similar findings among registries with respect to patterns of disability progression, predictors of disability progression, and changes in lifespan. Several registries show that progression after EDSS 4 occurs at a predictable rate. Once EDSS 4 is reached, disability progression is similar, regardless of initial MS subtype at diagnosis. EDMUS reveals a similar rate of disability progression between progressive MS and RRMS after EDSS 4. The Vancouver registry shows no difference in the time to progression to EDSS 6, 8, or 10 among progressive types, suggesting that once progression begins it is largely independent of preceding factors. Long-term follow-up in registry studies will provide valuable insights into the long-term effectiveness of DMTs, and the value of early vs later initiation of treatment, as well as their sustained efficacy, such as a favorable long-term benefit: risk ratio and sustained efficacy of interferons. Clinicians, payors, and patients need to understand that MS may shorten life expectancy, and long-term treatment adherence may be critically important.

From the analysis, the recommendation is to improve inter-registry consistency. Registries currently do not provide much information on treatment effects. Because MS treatment has evolved over time, the impact of immunomodulatory therapy on the natural history of MS cannot be adequately assessed from current registry data. These treatment effects can only be rigorously assessed in well-designed clinical trials. However, because registry data provide valuable information on the long-term course of MS, they should be utilized in conjunction with clinical trial data to assess the impact of treatment on the course of MS and determine how we may optimize treatment to improve long-term outcomes.

## DISCLOSURE

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