Reaching an evidence-based prognosis for personalized treatment of multiple sclerosis

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Abstract | Personalized treatment is ideal for multiple sclerosis (MS) owing to the heterogeneity of clinical features, but current knowledge gaps, including validation of biomarkers and treatment algorithms, limit practical implementation. The contemporary approach to personalized MS therapy depends on evidence-based prognostication, an initial treatment choice and evaluation of early treatment responses to identify the need to switch therapy. Prognostication is directed by baseline clinical, environmental and demographic factors, MRI measures and biomarkers that correlate with long-term disability measures. The initial treatment choice should be a shared decision between the patient and physician. In addition to prognosis, this choice must account for patient-related factors, including comorbidities, pregnancy planning, preferences of the patients and their comfort with risk, and drug-related factors, including safety, cost and implications for treatment sequencing. Treatment response has traditionally been assessed on the basis of relapse rate, MRI lesions and disability progression. Larger longitudinal data sets have enabled development of composite outcome measures and more stringent standards for disease control. Biomarkers, including neurofilament light chain, have potential as early surrogate markers of prognosis and treatment response but require further validation. Overall, attainment of personalized treatment for MS is complex but will be refined as new data become available.

Multiple sclerosis (MS) is an inflammatory disease of the CNS known for its wide spectrum of symptoms, severity and response to therapy. To date, 12 distinct drugs have been approved for relapsing–remitting MS (RRMS) and 1 has been approved for primary progressive MS (PPMS). The clinical diversity of MS and the expanding array of disease-modifying therapies (DMTs) for RRMS combine to make MS a pre-eminent example of the need for a personalized approach to medical therapy.

The terms 'personalized medicine' and 'precision medicine' are often used interchangeably in MS and in other fields[1–4], but we believe it is important to distinguish between these terms with respect to MS care. We define personalized medicine as an approach to treatment that accounts for an individual's characteristics, environment and disease features and biomolecular traits. Precision medicine involves the same principles but genomics and pharmacogenomics are key[5]. Precision medicine has been most successful in oncology[6,7], but its application to MS has been limited by the complexity of the disease and a lack of sensitive and specific genomic and other biomarkers.

As is the case for cancer, MS can be a severely disabling disease. Widespread use of MRI and revisions to MS diagnostic criteria have enabled earlier diagnosis and therapy, and outcomes are improving as a result (although the Will Rogers phenomenon might play a role in this trend)[8]. Prioritization of the highest-efficacy therapies is likely to be beneficial in severe, and possibly most, cases, but these therapies can pose considerable risks. Personalization of MS therapy therefore involves three key components: prognostication soon after diagnosis, an initial treatment decision based on risk–benefit trade-offs and patient preferences, and assessment of early treatment response and the need to switch therapy. In this Review, we discuss the factors that should be taken into account for each component and how these factors influence treatment decisions.

Prognostication

Prognostication is the foundation of personalized treatment and enables individuals to be grouped on the basis of their demographic and environmental characteristics, clinical features, MRI measures and biomarkers (FIG. 1). Some of the first clinical studies in MS aimed to predict prognosis, but subsequent large, prospective longitudinal cohort studies have incorporated multivariate analyses and are likely to be more accurate.

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Key points

- Personalized treatment of multiple sclerosis (MS) depends on prognostication at baseline, a shared treatment decision between the physician and patient, and early assessment of response to therapy.
- Prognosis can be evaluated soon after diagnosis on the basis of demographic and environmental factors, clinical features, MRI measures and biomarkers.
- Individuals with poor prognostic features should be recommended high-efficacy therapies early on; studies are underway to investigate whether most patients with relapsing–remitting MS could benefit from initial aggressive therapy.
- During the treatment discussion between the neurologist and patient, factors such as comorbidities, pregnancy planning, patient preferences, risk tolerance, safety, cost and treatment sequencing should be considered in addition to prognosis.
- Early assessment of treatment response is important to identify the need to switch therapy; composite outcome measures that incorporate clinical and MRI data are best for predicting long-term disability.
- Personalized MS therapy is currently limited by a lack of evidence-based biomarkers; newer biomarkers, such as neurofilament light chain, have potential, but further validation and standardization of assays are required.

Disease subtype

The first step in MS prognostication is confirmation of the diagnosis and disease subtype. After a single demyelinating attack, evidence of dissemination in space (DIS) and dissemination in time (DIT) on MRI enables a diagnosis of RRMS according to the McDonald diagnostic criteria[9]. In the 2017 revision of these criteria, the presence of cerebrospinal fluid (CSF)-specific oligoclonal bands (OCBs) can substitute for DIT[9] because OCBs are predictive of future relapses[10]. If the MS diagnostic criteria are not met after a single attack, clinically isolated syndrome (CIS) can be diagnosed. Most, but not all, cases of CIS eventually convert to RRMS[11], but DMT can delay the conversion to clinically definite MS (CDMS)[12].

PPMS is associated with more rapid disability accumulation than RRMS[13,14]. PPMS is considered by some to be analogous to the secondary progressive phase that follows RRMS, as both have similar ages of onset and rates of disability accumulation[15,16]. DMTs that are effective in RRMS have generally not been effective for PPMS and secondary progressive MS (SPMS), with the exception of two positive studies in the past 2–3 years[17,18]. For these reasons, we focus on prognostic factors and management of CIS and RRMS for the remainder of this Review.

Demographic and environmental factors

Demographic factors. Early attempts at prognostication in MS focused on demographic and clinical factors at presentation[19]. Older age at onset has been associated with faster disability progression in multiple studies[19–21]. This effect of age is observed even when individuals with PPMS are excluded[21]. However, in a large, prospective multivariate analysis (the Barcelona study), older age at onset of CIS was associated with a lower risk of conversion to CDMS[22]. Evidence suggests that individuals whose first relapse occurs at a young age reach disability milestones at a younger absolute age than individuals with later onset, although the intervals from disease onset to these milestones are usually longer among younger patients[20].

Sex is another prognostic indicator in MS. MS is more common among women, but in most, although not all[23], prognostic studies, disability milestones are reached sooner and the onset of progression is earlier in men[19,20,24]. However, sex did not predict the risk of conversion from CIS to CDMS in one study[22]. Ethnicity has also been associated with rates of disability accumulation in several studies. In particular, faster accumulation has been observed among African-American[25], Hispanic-American[26] and North-African[27] people.

Environmental and modifiable factors. Environmental exposures contribute to the risk of developing MS[28], and some environmental or modifiable factors — in particular vitamin D deficiency, smoking and some comorbidities — also affect prognosis in patients with established CIS or MS. Other environmental and modifiable factors of interest include obesity[29], diet[30] and levels of antibodies against Epstein–Barr virus[31], but conflicting results mean these factors require further investigation.

Low intake of vitamin D[32] and low serum concentrations of the metabolite 25-hydroxyvitamin D (25(OH)D)[33] were initially linked to an increased risk of developing MS but have subsequently been studied in the context of established MS. Lower 25(OH)D concentrations have been associated with higher relapse rates[34] and a higher frequency of new T2 and gadolinium-enhancing lesions[35] in RRMS. A large post hoc analysis of the BENEFIT clinical trial, in which patients with CIS were receiving IFNβ1b treatment, showed that baseline vitamin D status was associated with brain volume loss, relapse rate, new T2 and gadolinium-enhancing lesions and 5-year disability progression[36]. In another analysis of the BENEFIT cohort, presented only in an abstract to date, higher vitamin D levels and an absence of smoking at CIS onset predicted better cognitive performance after 11 years[37]. On the basis of these results, vitamin D supplementation can be an inexpensive and safe intervention to modify MS prognosis, although no consensus has been reached on an ideal dose and randomized controlled trials are ongoing.

Some evidence suggests that smoking tobacco leads to earlier onset of SPMS, although this trend fell just short of statistical significance in one meta-analysis[38]. A subsequent meta-analysis demonstrated a relationship between ever smoking and scores on the Expanded Disability Status Scale (EDSS)[39], and another study showed that smoking was associated with brain atrophy in CIS and early RRMS[40]. Among established smokers with RRMS, quitting seems to prolong the time to onset of SPMS[41].

Conditions that are common comorbidities of MS include anxiety and mood disorders, hypertension, dyslipidaemia and migraine[42,43]. A higher comorbidity burden has been associated with greater risks of relapse[42] and progression[44,45]. In addition, the presence of physical comorbidities, in particular ischaemic heart disease and epilepsy[45,46], and psychiatric comorbidities[44] predict earlier attainment of higher EDSS scores.

Clinical factors

Some clinical features of MS are associated with the extent of long-term disability and therefore provide prognostic information. In one of the largest longitudinal prognostic studies, which included 28,000 patient-years of follow-up, the relapse frequency in the first

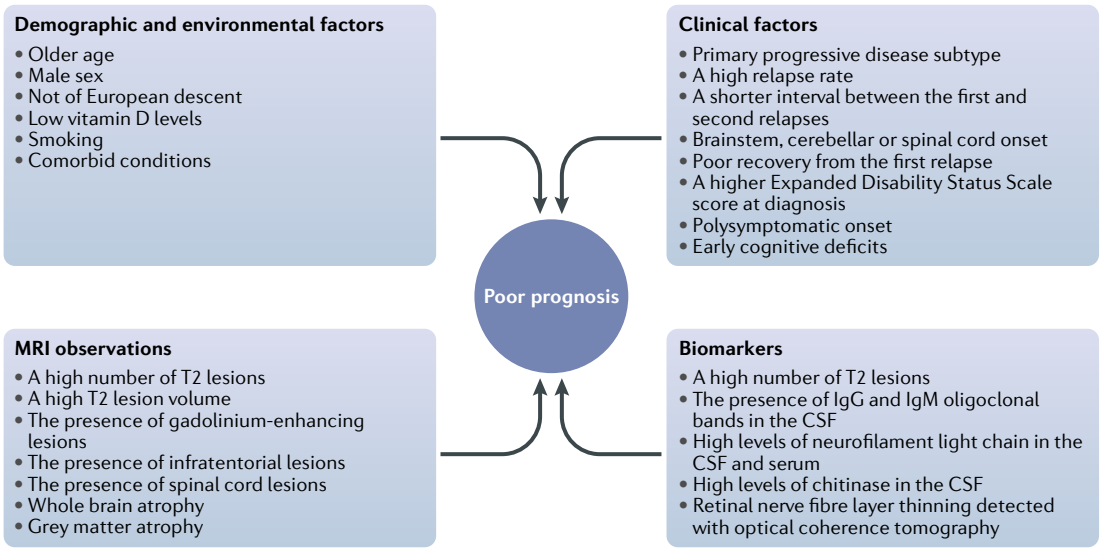


Fig. 1 | **Predictors of a poor prognosis in multiple sclerosis.** The demographic and environmental factors, clinical factors, MRI observations and biomarkers that have been associated with a poor prognosis in multiple sclerosis are listed. CSF, cerebrospinal fluid; IgG, immunoglobulin G; IgM, immunoglobulin M.

2 years and the time between the first and second attacks were both important predictors of long-term disability outcomes[47]. Patients who experienced three or more relapses in the first 2 years reached an EDSS score of 6.0 a mean of 7.6 years earlier than patients who experienced only one attack in this time. The total number of relapses and the relapse frequencies beyond year 2 were not predictive in this study[47], although prior work suggested that relapse frequency up to year 5 was predictive[20,48]. In a multi-national study that included 2,466 individuals in MSBase, most of whom were receiving DMT, annualized relapse rate (ARR) in the first 10 years — particularly relapse rate when on therapy — strongly predicted changes in EDSS scores after 10 years of follow-up[49]. In another MSBase investigation that encompassed >80,000 patient-years of follow-up, common predictors of disability progression in patients who were already receiving therapy included older age, more severe baseline disability, more severe gait impairment and incomplete recovery from relapses regardless of DMT type[1]. Polysymptomatic onset has been a predictor of time to disability in some studies[50] but not others[24,47]. The extent of recovery from the first relapse has been a predictor of later disability in most studies[20,24,51].

The localization of the first relapse and the associated disability seem to affect the subsequent disease course. In one study, factors related to an unfavourable disease course (defined as an EDSS score of ≥5.0 after 5 years of follow-up) were motor onset (OR 2.78, $P=0.03$), sphincter onset (OR 5.52, $P=0.01$) and a higher EDSS score at inclusion (OR 3.84, $P<0.001$), although CIs were wide[23]. Sensory onset was associated with a favourable prognosis (OR 0.40, $P=0.048$). A large study conducted in France showed a favourable effect on prognosis of an optic neuritis onset, an intermediate effect of brainstem onset and a negative effect of long-tract examination findings at presentation[20]. In the Barcelona study, an optic neuritis presentation of CIS was associated with slower progression to an EDSS score of 3.0 than were other presentations[22]. Early cerebellar involvement has been associated with faster progression to disability milestones[52].

Another clinical feature with prognostic potential is cognitive impairment, which is increasingly recognized as an important aspect of MS-related disability despite being poorly measured by the EDSS. Cognitive impairment in MS is associated with lower quality of life scores and higher rates of unemployment[53,54]. In addition, early cognitive impairment is associated with poorer long-term functional status[54] and with global cortical thinning[55].

When evaluating the conclusions of older natural history studies, the fact that most were not multivariate analyses and did not control for MRI findings must be considered. In the most recent studies in this area (for example, BREMSO[56] and EBDiMS[57]), scores have been derived from baseline clinical and demographic features to predict later disease course. These scores will be refined through future research that incorporates other relevant data, such as MRI measures, and techniques, such as machine learning.

MRI measures

Several MRI measures have been evaluated as prognostic markers in MS. Conventional MRI measures do not completely correlate with disability in MS[58], but their ability to predict disease course has consistently been greater than that of early clinical features[22,59].

The Optic Neuritis Treatment Trial (ONTT) was one of the first prospective studies to demonstrate that the number of T2 lesions at baseline could predict conversion from CIS to CDMS, and this finding has been replicated with an extended follow-up of 15 years[60]. Multiple subsequent studies have confirmed that a high number of T2 lesions at baseline is associated with an increased risk of conversion to CDMS[22,59,61–63]. In addition, three studies have shown that T2 lesion volume at presentation of CIS can predict EDSS scores at 10 years[64], 14 years[65] and

20 years[61]. The presence of gadolinium-enhancing lesions predicts conversion from CIS to CDMS[66], although a meta-analysis showed that the number of such lesions did not predict changes in EDSS scores at 1–2 years[67].

Evidence suggests that lesion topography is an independent predictor of prognosis for patients with CIS. Cerebellar and brainstem lesions are associated with a higher risk of conversion to CDMS and greater long-term disability than are lesions in other brain regions[22]. In individuals who present with optic neuritis, infratentorial and spinal cord lesions were predictive of disability status after a median of 6 years of follow-up[59]. In one relatively small cohort of patients with CIS, the presence of two or more infratentorial lesions was the MRI feature with the greatest predictive value for disability after a median follow-up of nearly 9 years[68]. The presence of spinal cord lesions in CIS predicts conversion to RRMS whether or not the lesions are symptomatic[69,70]. Spinal cord lesions are also the strongest predictive factor for development of a first clinical event in radiologically isolated syndrome (RIS) subjects[71].

Brain atrophy has been observed in the earliest stages of RRMS[64,72,73], even in RIS[74], and in multiple studies baseline whole-brain and grey matter volume measurements have correlated well with long-term disability progression[64,72,73]. One study has shown that cortical grey matter lesion load at baseline in particular correlates with baseline EDSS score and changes in EDSS score over 5 years[75] and that a greater load is associated with a shorter time to onset of SPMS[76]. Nevertheless, baseline brain volume measurements have not been widely adopted as prognostic measures in clinical practice, probably because these measurements can be difficult to assess on routine clinical scans and can be influenced by other factors, including age, lifestyle factors and comorbidities[77]. In addition to baseline measures, early rates of brain volume loss have been associated with subsequent disability in several studies[64,73,78], but this metric can be confounded by short-term pseudoatrophy that can occur with initiation of some DMTs[79].

Biomarkers

Biomarkers can be helpful for diagnosis, prognostication and monitoring of treatment responses and adverse events. Despite a long history of biomarker research in MS, no wholly sensitive or specific biomarker has emerged for MS diagnosis, but some biomarkers, discussed below, hold promise for prognostication. Further research and validation are necessary for their widespread implementation.

Oligoclonal bands. The presence of immunoglobulin G (IgG) OCBs in the CSF is an independent predictor of conversion from CIS[10,22] to CDMS or from RIS to CIS[80]. One study has shown that the presence of OCBs is also an independent risk factor for disability accumulation (HR 2.0, 95% CI 1.2–3.6) in CIS[22]. In another study, an absence of OCBs was associated with less whole-brain and grey matter atrophy than was the presence of OCBs[81].

The number of CSF IgG OCBs might also have prognostic value. In one study, patients who developed severe disability (EDSS score >7.5) as a result of MS after ≥10 years of follow-up had higher numbers of OCBs at diagnosis than patients who developed less disability[82]. In another study, patients with CIS who had 8–12 OCBs had a 2.5-fold greater risk of conversion to CDMS than patients with fewer OCBs[83].

Some evidence suggests that immunoglobulin M (IgM) OCBs could also be prognostic markers in MS. In one study, patients with CIS who were positive for IgM OCBs had greater disease activity than patients who were negative, although the cohorts were relatively small and duplication is required by other groups to confirm the finding[84,85]. In another study, the presence of IgM OCBs was associated with a lower risk of progressive multifocal leukoencephalopathy (PML) in patients who were treated with natalizumab, independent of JC virus (JCV; or John Cunningham virus) antibody status[86].

Neurofilament light chain. Neurofilament light chain (NfL) is released into the blood and CSF as a result of axonal cytoskeleton damage. High NfL levels are not specific to MS but occur in other neurodegenerative diseases[87], and NfL concentration increases with age even in healthy controls[88]. The level of NfL in the CSF has been identified as a predictor of conversion from CIS[89,90] to CMDS and from RIS[80] to a first clinical event. High CSF levels of NfL are also associated with higher relapse rate[91], greater T2 lesion volume and more gadolinium-enhancing MRI lesions in patients with CIS[92] and with higher MRI measures of white matter disease severity in RRMS[93]. In one study, CSF levels of NfL correlated ($r = 0.47$, $P < 0.001$) with long-term Multiple Sclerosis Severity Score (MSSS) in patients with RRMS over a median of 14 years of follow-up[94]. In the same study, higher CSF levels of NfL were associated with a greater likelihood of conversion from RRMS to SPMS[94].

The development of highly sensitive single molecule array (Simoa) has facilitated measurement of NfL in the serum, and serum levels correlate well with CSF concentration; therefore, analysis of serum levels could enable non-invasive assessment[88,93,95]. Early studies have shown that serum levels of NfL at baseline are associated with T2 lesion volume, the number of gadolinium-enhancing lesions and brain parenchymal volume[92,96]. In a study of >2,000 serum samples from >250 individuals, serum levels of NfL greater than the 90th percentile of values in healthy controls independently predicted an increase in EDSS score over the following year[96]. In the Swiss MS cohort study, which has been reported in abstract form, serum NfL levels in >200 patients with RRMS were higher with older age and higher EDSS scores and if patients had experienced a recent (<120 days) relapse[97]. Each 10 pg/ml increase in serum NfL concentration was associated with a 29% increase in the risk of a relapse over the subsequent 2 years. In another study reported in abstract form — a pooled analysis of blood samples from >1,400 individuals across four phase III clinical trials — high baseline serum NfL levels (>16 pg/ml) were associated with new T2 lesions in the subsequent year (positive predictive value 91%)[98]. In the same study, higher baseline serum NfL levels were associated with greater T2 lesion volumes at 5 years and 10 years and with greater brain atrophy over 5 years.

Uncertainty remains about whether critical thresholds should be established for serum NfL levels or whether levels should be compared with age-based norms. Moreover, applying serum NfL levels to individual decision-making could be challenging owing to confounders, such as age, other neurological diseases and minor head injury[99]. Reproducibility studies are ongoing, including efforts to standardize serum NfL assays and to define abnormal values.

Chitinase-3-like protein 1. Chitinase-3-like protein 1 (CHI3L1) is a glycoprotein thought to be related to inflammatory pathways and tissue remodelling. As is the case for NfL, CHI3L1 is found in the CSF and serum, and high levels have been observed in various conditions, including neurodegenerative, neoplastic and other autoimmune diseases. Most, but not all, studies have demonstrated that high CSF concentrations of CHI3L1 predict conversion from CIS to CDMS[80,100–102]. Moreover, higher CSF concentrations of CHI3L1 predicted faster development of disability in patients with CIS[101]. One study has shown that CSF concentrations of CHI3L1 correlate with those of NfL in patients with CIS[91].

Retinal nerve fibre layer thickness. Optical coherence tomography (OCT) is an easily administered and reliable technique for characterization of axonal and neuronal layers within the retina. Of the various measures studied with OCT, retinal nerve fibre layer (RNFL) thickness and the composite thickness of the ganglion cell and inner plexiform (GCIP) layers have correlated best with contrast visual function in MS[103]. Evidence indicates that GCIP and, in particular, RNFL atrophy reflect neurodegeneration in the CNS more broadly. In a large study of 879 patients with MS, a baseline RNFL of <88 µm in the eyes of patients without a history of optic neuritis was associated with a twofold greater risk of disability progression after the first year and up to the third year of follow-up (HR 2.06, 95% CI 1.36–3.11)[104]. In some small early studies, RNFL atrophy was associated with disability progression[105] and cognitive impairment[106], and, more recently, with failure to meet the no evidence of disease activity (NEDA) end point[107] (see No evidence of disease activity below) in MS. Although many of the cohorts in OCT studies have included people with various disease durations, RNFL thinning has also been documented in people with CIS[108].

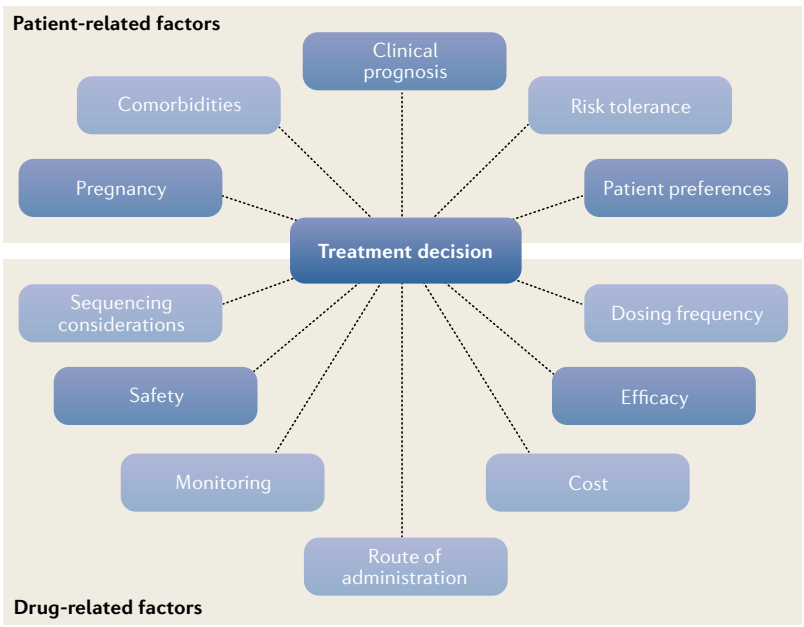


Fig. 2 | **Factors that influence the initial treatment decision for patients with multiple sclerosis.** Patient-related factors (top) and drug-related factors (bottom) are shown. Dark blue indicates factors that are typically most important. These factors should be weighed in a shared discussion between the physician and patient.

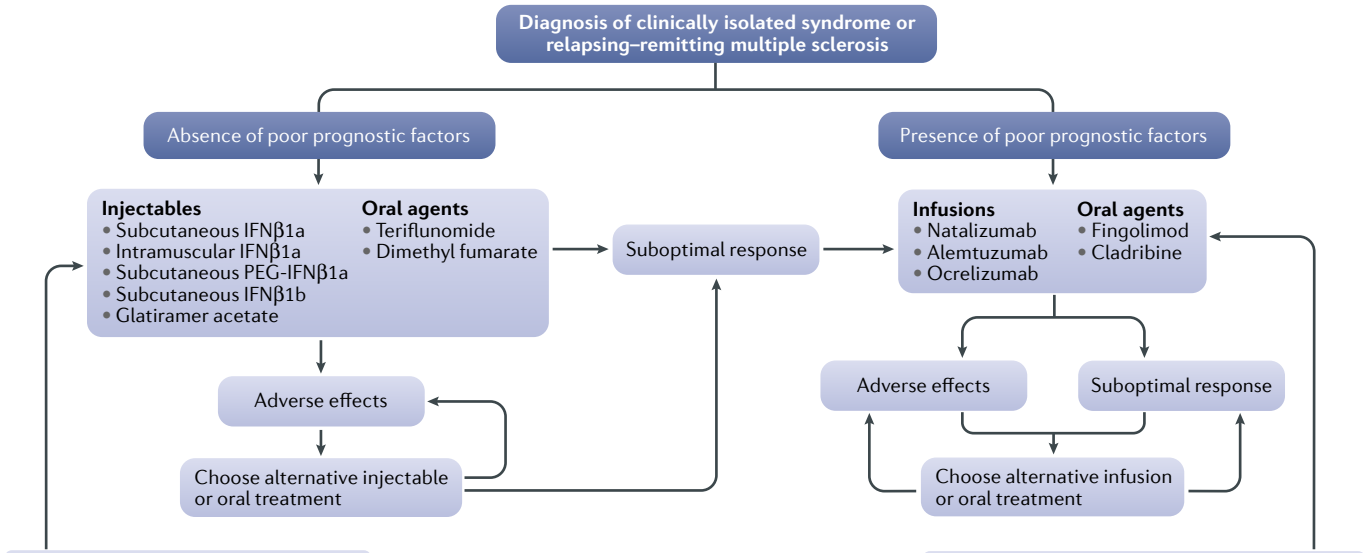
Personalized treatment plans

Patients with MS are triaged soon after diagnosis using the prognostic factors discussed above. Currently approved drugs for RRMS include the various IFNβ formulations, glatiramer acetate, teriflunomide, dimethyl fumarate, fingolimod, cladribine, natalizumab, alemtuzumab and ocrelizumab. Mitoxantrone and haematopoietic stem cell transplantation (HSCT) can be used in the most aggressive cases. High-efficacy MS therapies — fingliomod, cladribine, natalizumab, alemtuzumab and ocrelizumab — carry a greater risk of adverse events and are often reserved for patients in whom a first-line injectable or oral agent has failed, but they might be selected at the outset for patients with RRMS and poor prognostic features. Head-to-head clinical trials would provide evidence to compare DMTs and grade their efficacy precisely, but such data are limited. Patient-related factors and drug-related factors (discussed below) need to be weighed in the treatment discussion between the neurologist and patient (FIG. 2). These factors are then prioritized to identify a favourable DMT within the given treatment group (FIG. 3).

Selection of treatment based on prognosis

The benefits of early initiation of DMT in RRMS have been demonstrated repeatedly in large, randomized clinical trials[109] and real-world cohorts[22,110,111]. The 2018 guidelines for MS treatment from the European Committee for Treatment and Research in Multiple Sclerosis (ECTRIMS)[112] and the American Academy of Neurology (AAN)[113] both emphasize the importance of early DMT in RRMS. However, controversy remains around how treatments should be sequenced, in particular whether high-efficacy therapy should be used at the outset, and in which cases.

Early initiation of high-efficacy therapy is supported by consistent evidence from head-to-head randomized controlled trials that these therapies are superior to first-line options, evidence that treatment has greater efficacy at earlier stages of the disease course, evidence that the risk of serious adverse events (such as opportunistic infections) with these DMTs are lower at younger ages and the absence of therapeutic options to reverse disability in MS[114,115]. An escalation paradigm — in which safer first-line therapies are used initially and higher-efficacy DMTs are used when the response is inadequate — can be defended on the grounds that MS is a chronic disease, early high-efficacy therapy exposes patients to substantial risks that increase with longer use and the recent



Factors that influence drug selection

Factors	Favoured drug(s)
Needle phobia	• Teriflunomide • Dimethyl fumarate
Monitoring	Glatiramer acetate
Pregnancy	• Glatiramer acetate • IFNβ
Safety	Glatiramer acetate

Factors that influence drug selection

Factors	Favoured drug(s)
JCV positivity	All but natalizumab[a]
History of poor adherence	• Natalizumab • Ocrelizumab
Monitoring	• Cladribine • Ocrelizumab
Efficacy	• Alemtuzumab • Natalizumab • Ocrelizumab
Pregnancy (with planning)	• Alemtuzumab • Cladribine • Natalizumab
Oral route of administration preferred	• Cladribine • Fingolimod
Induction preference	• Alemtuzumab • Cladribine

Fig. 3 | **Treatment algorithm for personalized therapy of relapsing–remitting multiple sclerosis.** This algorithm can be used to guide care for patients with clinically isolated syndrome or relapsing–remitting multiple sclerosis. Patients are triaged soon after diagnosis according to baseline prognostic factors, then factors for personalizing therapy are taken into account for choosing a specific drug. When adverse effects develop or the response to the selected drug is suboptimal, patients should be re-directed to another disease-modifying therapy as shown. The listed factors for personalizing therapy are illustrative and others should be incorporated as appropriate. Such algorithms are yet to be validated in relation to long-term outcomes. [a]Natalizumab can be chosen for some patients with JC virus (JCV; or John Cunningham virus)-positive serology, but greater caution and surveillance are required when the JCV titre is >0.9 and natalizumab has been used for >2 years. PEG-IFNβ1a, polyethylene glycolated form of IFNβ1a.

introduction of high-efficacy therapies means they could have unknown long-term effects, such as risks of malignancy or chronic immunodepletion. In most cases, a suboptimal response to therapy can be identified within 1–2 years, before disability worsens substantially. In addition, the long-term impact of DMTs, including high-efficacy therapies, on disability status remains uncertain because disability can take decades to accumulate.

This issue is sometimes referred to as the 'induction versus escalation' debate, although the term 'induction therapy' more specifically refers to approaches that induce long-lasting immunological changes that protect against future disease activity after a limited number of courses. Induction therapies, including alemtuzumab, HSCT and possibly cladribine, might have advantages over other early high-efficacy therapies, but studies with longer follow-up periods are necessary to determine the durability of their effects and favourable risk–benefit profile. A systematic review published in 2017 provided evidence that suppression of relapses was greater when high-efficacy therapy was initiated earlier after MS onset, but MRI and disability outcomes were inconclusive[116]. Formal randomized clinical trials in which high-efficacy therapies are compared with lower-efficacy therapies as initial treatments will provide further answers in the coming years[117].

Owing to successive revisions of the McDonald diagnostic criteria enabling earlier diagnosis of RRMS, the available clinical information at the point of initial treatment choice is often sparse and from a single relapse. For this reason, we suggest that patients are categorized at the outset according to prognostic signs rather than whether they have 'highly active' MS, which implies familiarity with disease behaviour over time. Furthermore, neither the ECTRIMS nor AAN treatment guideline panel reached a consensus definition of highly active MS[112,113]. However, the way in which

prognostic measures should be weighed in treatment decisions remains incompletely defined. We favour early high-efficacy therapy for patients with poor prognostic factors overall and in selected patients with one or two poor prognostic indicators for which evidence suggests a strong association with later disability, although this approach is speculative.

Our treatment algorithm (FIG. 3) is based on current knowledge of DMT efficacy and sequencing practices, with an illustration of factors that influence personalization of treatment. Such algorithms must be validated through future research into comparative drug efficacy, ideal timing of high-efficacy therapy and definition of a 'suboptimal response' in relation to long-term outcomes.

Patient-related factors

The initial treatment decision should be based on shared decision-making between the clinician and patient and should take into account patient-related factors beyond their clinical prognosis. Several patient-related factors can affect the success and safety of DMT, discussed in detail below.

Comorbidities. A patient's medical history must be carefully reviewed before selection of a DMT. Certain comorbidities are considered to be contraindications for specific DMTs; for example, a history of PML contraindicates natalizumab[118] and cardiac or cerebrovascular disease contraindicates fingolimod[119]. IFNβ therapy can exacerbate depression[120] and lead to thyroid dysfunction, particularly in people with pre-existing thyroid autoantibodies[121]. Fingolimod and teriflunomide can each increase blood pressure, which might be important in patients with vascular comorbidities. For patients with a previous or current malignancy, immunomodulators (IFNβ or glatiramer acetate) are thought to be safest[122]. Further study is required to establish whether any of the newer DMTs are associated with a risk of malignancy. Smoking has been associated with an increased risk of developing neutralizing antibodies against IFNβ and natalizumab, therefore this association should be taken into account in treatment selection[123,124].

Clinicians should also be alert to comorbidities as potential barriers to adoption of DMT. In a large population-based analysis, the likelihood of initiating a DMT declined with an increasing total number of comorbidities, and in particular with concomitant anxiety or ischaemic heart disease[125]. Patients with these conditions might require more education, frequent follow-up and interventions for psychiatric comorbidities.

Pregnancy and breastfeeding. A large proportion of patients who are newly diagnosed with RRMS are women aged 20–45 years. For these patients, clinicians should discuss their plans for future pregnancies because many of the DMTs are not safe in pregnancy and should be stopped before attempting to conceive; specific recommendations depend on the DMT[126]. Some prospective studies indicate that glatiramer acetate and IFNβ are safe in the first trimester and do not increase the risk of a miscarriage or of fetal malformations[127,128]. Natalizumab is also likely to be safe in the first trimester[126,129] and can be continued relatively safely through the third trimester for women with a history of highly active disease, although mild to moderate haematological abnormalities in the newborn baby are a risk[130]. Animal studies have linked teriflunomide with developmental abnormalities, and fetal malformation has been reported with fingolimod treatment in the first trimester[131].

In general, if women with a new diagnosis of CIS or RRMS have good prognostic signs and wish to become pregnant within a short period, DMT can be delayed until after pregnancy. Women who have commenced injectable therapy can continue their DMT while trying to conceive to minimize the chance of breakthrough disease activity. Pregnancy itself is associated with a lower risk of MS disease activity, although the risk of a relapse is slightly increased in the first few months post-partum[126].

For women with poor prognostic signs or highly active disease, several strategies can be used for pregnancy planning. Use of induction agents, such as alemtuzumab and cladribine, might increase the chance that a woman with highly active MS will remain disease-free while pregnant and breastfeeding, although this hypothesis has not been proved and this approach requires careful planning to ensure an interval of ≥4–6 months between the last course of therapy and conception[132,133].

Only glatiramer acetate and IFNβ are considered to be safe during breastfeeding[126]. Exclusive breastfeeding might partially protect against disease activity[134] but is unlikely to be sufficient in women with highly active MS. A woman must decide with her neurologist when to initiate or re-start DMT after pregnancy, balancing MS prognostic factors and past disease activity against the potential benefits of breastfeeding.

Patient preferences. Patient preferences often pertain to many aspects of DMT, including route of administration, dosing frequency and intensity of monitoring. In an investigation into patient preferences related to injectable DMTs in Germany, patients with MS placed the greatest emphasis on dosing frequency and therapeutic benefit for disability progression in hypothetical treatment choice scenarios[135]. In a large multi-centre study of 2,500 patients, 25% were non-adherent to therapy (defined as missing more than one injection dose in the 4 weeks preceding the study), and the most commonly cited reasons were injection-site reactions and forgetting injections[136]. Discontinuation rates for injectable therapy are similar, reported at 16–27% in a systematic review[137]. Flu-like adverse effects and injection-site reactions most often limited use. In one study, 83% of patients with MS stated a preference for oral medication over injectable medication[138], but whether oral therapy has improved adherence and persistence remains unclear[139]. In several real-world studies of oral DMTs, persistence with fingolimod has been superior to that for dimethyl fumarate[140,141]. For the most recently approved therapies, such as alemtuzumab, ocrelizumab and cladribine, dosing is infrequent; the administration of alemtuzumab and ocrelizumab by infusion means that clinicians can be sure that patients took the medication and when they took it. Further follow-up is needed to determine the rates of discontinuation with these agents and the reasons. Situational factors, such as

geography, profession, socio-cultural factors and travel requirements, may influence patient preferences. Patient preferences regarding monitoring intensity (see Safety below) also influence treatment choice.

Risk tolerance. People have individual risk-taking profiles, and risk aversion is associated with older age, female sex and socio-economic status[142]. High-efficacy MS therapies have been associated with serious adverse events and could be associated with risks that are unknown until the post-marketing phase, as was the case for immune-mediated encephalitis associated with daclizumab[143]. An individual's risk-taking profile therefore affects their comfort with these more-aggressive approaches to DMT and should be taken into account in shared decision-making.

Age and withdrawal of therapy. The age of a patient can affect the decision of whether to initiate or stop therapy. In a meta-analysis of 28,000 patients with MS across 38 clinical trials, the efficacy of DMT declined markedly with increasing age[144]. Similarly, a focused, observational study of >1,800 patients receiving natalizumab showed that the beneficial effects of the treatment were lower for patients aged >50 years[145]. Together, these observations suggest that DMTs have lower efficacy in RRMS at older ages.

These observations might arise because older age is associated with the onset of progressive disease and the waning of inflammatory processes. None of the currently approved DMTs has consistently provided benefits in clinical trials in SPMS. Even in patients whose condition continues as RRMS, the risk–benefit ratio of DMT might shift towards risk with increasing age owing to the decline in inflammatory events and an increased frequency of adverse events such as infections. In a retrospective, observational study of 178 patients aged ≥60 years, discontinuation of therapy led to only one relapse, and 89% of patients remained off treatment[146]. An ongoing randomized controlled multi-centre trial (DISCO-MS) in the USA will determine the effects of DMT discontinuation in patients with RRMS aged ≥55 years who have not had any new relapses or MRI lesions in the previous 5 years[147]. Further work is necessary to determine how age should be used in combination with other disease characteristics to inform individual treatment decision-making.

Drug-related factors

Safety. Risk–benefit analysis became a priority in MS treatment decision-making with the introduction of natalizumab, which was withdrawn owing to an association with PML and re-introduced with a risk mitigation programme. The risk of PML with natalizumab has been estimated at 0.07–10 per 1,000 individuals, depending on their JCV antibody status[148]. Established risk factors for PML with natalizumab treatment include the presence of JCV antibodies in the serum, a duration of therapy >2 years and prior immunosuppressant use[149]. JCV antibody status and JCV index can be used for PML risk stratification when considering natalizumab use[148]. In a large, post hoc pooled analysis of four clinical studies, the risk of PML over 6 years was 0.07 (95% CI 0.00–0.40) per 1,000 individuals among JCV-negative patients (n = 13,996) and 2.7% (95% CI 1.8–4.0%) among JCV-positive individuals (n = 21, 696)[148]. JCV titres ≤0.9 were associated with a low risk of PML (0.01–0.6 per 1,000) during years 1–6. Some studies have also shown that serum levels of the cell adhesion molecule L-selectin (CD62L) and CSF levels of IgM OCBs correlate with the risk of PML in patients receiving natalizumab[86,150,151]. For JCV-negative individuals receiving natalizumab, recommended monitoring includes serum JCV re-testing every 6 months and an annual brain MRI; for JCV-positive individuals, these tests should be repeated more frequently[152].

Some cases of PML have been reported in patients with MS who are receiving teriflunomide, dimethyl fumarate, fingolimod and ocrelizumab and in other patient populations receiving cladribine and alemtuzumab[153]. However, many of these instances are considered to be crossover cases from previous treatment with natalizumab. JCV status and older age might affect the risk of PML with DMTs other than natalizumab, but risk factors remain poorly defined[153,154].

High-efficacy therapies are also associated with an increased risk of infections other than PML. Many of the DMTs have been associated with increased rates of herpes zoster virus infection[154]. Severe opportunistic infections associated with particular agents include herpes encephalitis[155] and cryptococcal meningoencephalitis[156] with fingolimod treatment and listeria meningitis with alemtuzumab treatment[157]. Little evidence is available to guide risk stratification for such infections[154]. Pharmacogenomic studies offer some promise in this area but can be challenging owing to the low frequency of serious adverse events[158].

Monitoring programmes during treatment with DMTs are essential for safety, and patient preferences in relation to this monitoring might affect treatment choices. Monitoring programmes vary for different DMTs, and the most intensive is currently that for alemtuzumab, which involves monthly bloodwork and urine testing during treatment and for 4 years after the last dose. A high rate of secondary autoimmune diseases has been observed with alemtuzumab treatment: ~40% of treated patients are affected[159,160]. Thyroid disease is most common, but more serious autoimmune diseases include immune thrombocytopenic purpura and Goodpasture syndrome. A family history of autoimmune disease and an individual history of smoking are predictors of autoimmune disease risk with alemtuzumab treatment and should be considered in treatment decision-making[159]. For other DMTs, bloodwork is currently recommended every 3–6 months during dimethyl fumarate or fingolimod treatment, every 2–4 weeks for the first 6 months during teriflunomide treatment and at least once annually during cladribine treatment; no recommendation is specified for ocrelizumab treatment[133,161,162]. Less-intensive monitoring might appeal to patients, but further post-marketing experience is necessary to validate the safety profiles of these agents and their monitoring schedules.

Cost. The costs of DMT are high and access varies widely by country[163]. DMT costs and reimbursement rules have a considerable impact on treatment selection and should be addressed at the outset in an open dialogue between

the patient and physician. Newer DMTs commonly cost more than existing treatments[164]. The insurance coverage environment dictates which DMTs are reimbursed and can be based on disease subtype, previous use of DMT and/or individual clinical and radiographic features. In countries in which DMT is publicly funded, the initial treatment choice is often restricted to less-expensive first-line drugs[163]. Individuals without drug coverage usually cannot afford DMT, but compassionate drug provision can be requested.

Treatment sequencing. The increase in available DMTs has led to greater emphasis on treatment sequencing paradigms and the need for a strategic approach to the initial treatment choice that accounts for future switching. Shorter washout periods between agents can reduce the risk of new disease activity but can be hindered by prolonged pharmacokinetic action or immunological effects of the previous agent. The subcutaneous and intramuscular injectable agents are the only DMTs that rarely require a washout. For this reason, they can be attractive as first-line therapies, as the transition to a higher-efficacy agent is easy. By contrast, dimethyl fumarate[165] and fingolimod[166] can lead to lymphopenia that can last ≥6 months after drug withdrawal. Teriflunomide has a long half-life and can be detected in the serum for up to 2 years after discontinuation, although it can be eliminated within 11 days by use of a rapid, albeit uncomfortable, elimination procedure with cholestyramine or charcoal[167]. This procedure should be considered before switching to a high-efficacy agent to avoid additive immunosuppresive effects.

For cell-trafficking DMTs such as natalizumab and fingolimod, withdrawal of the treatment can lead to rebound disease activity[168,169]. Consequently, these agents might not be appropriate if a break in treatment for pregnancy or because of coverage issues, for example, is anticipated. The risk of rebound activity might be mitigated by a shorter washout period[170], but the benefit must be balanced against a potential increased risk of PML upon initiation of the subsequent agent[171].

If used in succession, cell-depleting agents such as ocrelizumab, rituximab, alemtuzumab and cladribine can have dose-related adverse events such as lymphopenia and, possibly, hypogammaglobulinaemia and malignancy[122,172]. These unknown risks should be considered when deciding when to introduce these agents.

When considering a switch of DMT, the mechanism of action of the new drug should inform the washout duration. For example, when transitioning from fingolimod to alemtuzumab, at least 4 weeks between drugs is advisable to provide sufficient time for lymphocytes to exit the lymph nodes so that alemtuzumab can act upon them[171].

Treatment response

A key aspect of personalized medicine in MS is monitoring the response to therapy to determine when a treatment switch might be necessary. Various short-term outcome measures have been studied as surrogate markers of long-term disability progression. There has been a move towards composite outcome measures that incorporate both clinical and MRI measures, which allow for greater stringency regarding acceptable levels of disease activity while on treatment. Biomarkers such as NfL and RNFL atrophy are being validated in the treatment context as well.

Traditional measures

Traditional measures of treatment response include relapse rate, new T2 and T1 gadolinium-enhancing lesions and disability progression; ARR has most often been adopted as the primary outcome measure in clinical trials[173]. A high ARR and new T2 and T1 gadolinium-enhancing lesions during IFNβ treatment have been associated with subsequent progression to disability milestones[174]. However, although relapses are arguably the most clinically relevant intermediate-term outcome measure in RRMS, they can be difficult to confirm in the absence of a neurological examination and recent MRI.

New T2 and gadolinium-enhancing lesions are more sensitive measures of disease activity[175,176], but the number of new lesions detected depends on the frequency of MRI scans; lesion size, location and T1 hypointensity might be as informative as the number of lesions[77]. Disability progression is difficult to assess over 1–2 years because apparent progression might be related to relapses and patients might subsequently recover[173].

Composite outcome measures

Rio score and modified Rio score. One of the first composite outcome measures to be suggested was the Rio score, which was derived from longitudinal real-world data. Rio and colleagues evaluated the ability of various combinations of relapses, disability progression and at least three active MRI lesions (new T2 or gadolinium-enhancing lesions) in the first year of IFNβ therapy to predict sustained EDSS progression at 3 years[177]. To derive the Rio score, 1 point was allocated for each of any relapse, any disability progression and development of at least three MRI lesions; patients were categorized as being at low risk (a score of 1) to high risk (a score of 3) of a poor treatment response. None of the individual measures alone correlated with the outcome measure, but the combination of all three or of MRI measures with either of the other measures provided significant predictive power.

The modified Rio score was developed several years later through use of a training set from the PRISMS trial[178]. Statistical methods were used to model the best fit between various numbers of new MRI lesions and relapses and the probability of a subsequent increase in EDSS score over 3 years. The score was derived by allocating 1 point for more than five new T2 lesions on MRI and 1 point for each relapse up to two. After 1 year of IFNβ therapy, 28.7% of patients had a score of 2 or more, with an associated HR of 4.60 for progression by 3 years[178].

Analysis of the Rio score study[177] cohort after further follow-up demonstrated that persistent clinical disease activity in the first 2 years of IFNβ therapy in treatment-naive patients predicted disability at 12 years[179]. Analysis of a subgroup of 209 patients for whom MRI data collected over 8 years were available showed that a Rio score of at least 2 (HR 3.3, 95% CI 1.7–6.4), at least three new T2 lesions (HR 2.9, 95% CI 1.5–5.6) or at least two

gadolinium-enhancing lesions (HR 2.1, 95% CI 1.1–4.0) in the first year of therapy were associated with EDSS progression, although modified Rio scores and NEDA (see No evidence of disease activity below) were not. These findings provide important insights into early indicators of long-term disability outcomes in IFNβ-treated patients.

MAGNIMS score. The Magnetic Resonance Imaging in Multiple Sclerosis (MAGNIMS) score was derived from the findings of a multi-centre study conducted at nine European centres. In this study, the relationship between clinical and MRI measures at 1 year and treatment failure (defined as sustained EDSS worsening of at least one point or a treatment switch due to inefficacy) was studied over 1–3 years[176]. A high risk of treatment failure was associated with one or more relapses and with at least three new T2 lesions in the first year of IFNβ therapy[176]. A score of 1 is allocated for one relapse or at least three new T2 lesions; a score of 2 is allocated for two relapses or one relapse and at least three new T2 lesions. A MAGNIMS score of 1 was associated with a 27% risk of treatment failure at 3 years and a 22% risk of disability progression; with a score of 2, the risk of treatment failure increased to 48% and of disability progression to 29%.

No evidence of disease activity. The concept of NEDA has come to MS through other medical specialities, such as rheumatology and oncology. The term NEDA was adopted instead of 'disease-free status' owing to our limited ability to detect the full extent of disease activity in MS. The most widely used iteration, NEDA-3, is defined as an absence of clinical relapses, new T2 or T1 gadolinium-enhancing lesions and sustained disability progression[180]. A newer iteration, NEDA-4, requires the same criteria plus an absence of brain atrophy[181], defined according to an annual brain volume loss threshold of 0.4%. NEDA-3 has been widely adopted as a treatment goal, used as a secondary outcome measure in clinical trials and studied in real-world settings[182]. In the context of clinical trials, cross-trial comparisons are difficult, therefore rates of NEDA with therapy should be compared with those in the control group.

In CLIMB, a real-world cohort study, NEDA over 2 years had a high positive predictive value (78.3%) for a lack of disability progression at 7 years of follow-up[180]. However, in EPIC, another large observational study, no relationship was seen between NEDA-3 in the first 2 years and disability end points after 10 years of follow-up[183]. Therefore, NEDA requires further validation as a surrogate marker of long-term disability. Moreover, the evidence suggests that the role of NEDA is most likely to be in intermediate-term rather than long-term prediction. For example, only 7.9% of patients had sustained NEDA-3 by year 7 in the CLIMB study, although most of these patients were treated with platform injectable therapy. For high-efficacy therapies, NEDA has been proposed as a realistic long-term treatment target[182].

NEDA-4 has not gained as much clinical traction as NEDA-3. This difference is probably because evaluation of brain volume loss with routine clinical MRI remains difficult and because the measure has not been validated against long-term disability outcomes.

Challenges. The evidence to support use of the aforementioned composite outcomes is lacking in several respects. First, the measures have often been validated against disability outcomes over relatively brief follow-up periods. Second, most studies have involved treatment with IFNβ or other first-generation injectable therapies. Third, the studies did not involve a re-baseline MRI at 3–6 months after starting therapy, as recommended under current European and American treatment guidelines[112,113]. Fourth, none of these measures account for the severity of relapses or the topography of lesions detected with MRI. Fifth, the measures have not been studied relative to the extent of disability worsening at the last follow-up. Other approaches have been proposed, such as that in the Canadian MS treatment guidelines, in which concern for treatment failure is based on relapse number, severity and the extent of recovery, and concern for disability progression is based on changes in EDSS score and the domains (for example, motor, cognitive or cerebellar function) affected[184].

Regardless of the exact approach, one general challenge with composite outcome measures is that greater complexity could impede their widespread application. The ideal composite outcome measure for early monitoring should be accessible in a routine clinical setting, have good inter-rater reliability and have a high positive predictive value for long-term disability status.

Biomarkers of treatment response

Serum neurofilament light chain. CSF levels of NfL can be used to predict clinical and radiographic outcome measures for patients receiving injectable therapies, natalizumab or fingolimod[95,185,186]. However, the test is too invasive for regular monitoring of treatment response. Consequently, validation of serum NfL levels as a biomarker of treatment response is underway[95].

In several prognostic studies, a correlation between serum NfL levels and clinical and MRI outcome measures has been consistently observed in patients receiving DMTs[88,187,188]. In one study, use of DMT was independently associated with lower serum NfL levels than those in untreated patients, and serum NfL levels were inversely associated with time on treatment[88]. Work presented in an abstract has shown an association of low serum NfL levels with NEDA-3 and NEDA-4 (REF.[189]). In other work presented in abstracts to date, more pronounced decreases in serum levels of NfL have been observed with high-efficacy therapies than with injectables[97,98]. Furthermore, analysis of blood from 589 participants in three phase III trials indicates that serum levels of NfL are associated not only with disease severity and progression but also with a decline with therapy[190]. Early studies suggest that NfL could also be a useful marker of treatment response in progressive MS[191,192].

Retinal atrophy. RNFL and GCIP atrophy over 1–2 years seems to correlate well with MRI and clinical outcome measures, including disability progression[104,107,193]. However, evidence that RNFL and GCIP atrophy respond to DMT is mixed. In one early study, rates of RNFL thinning were similar in patients with MS who were treated with IFNβ and those who were untreated[194].

However, in a 5-month study of patients with MS who were treated with fingolimod[195], macular volume increased with treatment, and in another study, rates of GCIP and macular thinning over a mean of 3 years were slower among patients receiving natalizumab than among those receiving injectable therapies[196]. Retinal thinning needs to be studied in the context of treatment with other DMTs and over longer follow-up periods before it can be used to inform treatment decisions.

Conclusion

MS is well suited to personalized treatment because of its wide range of clinical presentation and therapeutic responses. Successive revisions of the McDonald diagnostic criteria have led to earlier MS diagnosis and therapy, therefore we rely on evidence-based prognostication to predict disease course soon after onset and to direct therapy. In the future, prognostication will be refined as biomarkers are validated and incorporated into the assessment. We can then build models to optimize the benefits of DMT for individuals while minimizing the risk of adverse events.

This development of a personalized approach might be a scientific exercise, but some 'art' will remain in treatment choices, as personal concerns such as lifestyle preferences and risk aversion will have to be considered. Questions remain about whether initial high-efficacy treatment improves long-term outcomes, whether prolonged exposure to these agents increases adverse events and what the strongest early surrogate markers are for predicting long-term treatment responses to high-efficacy drugs. We have moved away from one-size-fits-all therapy to treatment algorithms with greater emphasis on individual attributes, but only when we answer these remaining questions will we fully enter the era of personalized medicine in MS.

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D.R. wrote the manuscript. D.R. and X.M. contributed equally to the conception of this work, literature review and revisions to the manuscript.

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