'No evidence of disease activity' – is it an appropriate surrogate in multiple sclerosis?

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The increasing number of disease-modifying treatments available for multiple sclerosis has broadened treatment options for patients, but also challenges clinicians to select the best therapy for each individual at the appropriate stage of the disease. Early prediction of treatment response still remains one of the main difficulties in the management of multiple sclerosis patients. The concept of 'no evidence of disease activity' (NEDA) has been proposed as a surrogate for treatment response based on the absence of relapses, disability progression and radiological activity. Although there are several apparently logical arguments for the NEDA approach, there are also some major concerns that have to be considered and that are not sufficiently addressed yet. Amongst others, each parameter's limitations are not eliminated solely by its use within a composite score, and the contribution of each parameter to NEDA is not well balanced, as the detection of, for example, a single new magnetic resonance imaging lesion is considered as significant as the occurrence of a severely disabling relapse. NEDA in its current form also neglects underlying pathophysiology of the disease, has not been shown to fulfil formal criteria of a surrogate marker and its prognostic value has not been sufficiently evidenced yet. From a clinical point of view, 'evidence of disease activity' seems the more relevant surrogate; however, its implications are even less clear than those of NEDA. Here, existing literature on NEDA is critically reviewed and improvements are discussed that value its potential use in clinical trials and, even more importantly, treatment decision making in daily routine.

Introduction

Multiple sclerosis (MS) is an immune-mediated chronic inflammatory demyelinating and neurodegenerative disorder of the central nervous system and the most frequent cause of neurological disability in young adults [1]. Several disease-modifying treatments (DMTs) have been shown to ameliorate the relapsing disease course; nevertheless MS remains a serious condition as none of these treatments is able to halt the disease as evidenced by ongoing – even though reduced – clinical deterioration and para-clinical disease activity in treated patients [2–19].

A high degree of disease heterogeneity extending from its clinical course [20], radiological features [21] to underlying pathology [22] might partially explain the limited efficacy of different DMTs at a group level as well as variable individual treatment response. This has generated the need for surrogate markers able to reliably evaluate the impact of therapeutic interventions [23]. Clinical parameters such as relapse rate and disability progression were supplemented by various magnetic resonance imaging (MRI) parameters in earlier studies, and a multitude of body fluid markers were investigated with regard to their predictive capability. However, only a few parameters have been introduced into clinical routine so far, all of them reflecting a certain aspect of MS disease activity or response to treatment.

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With the emergence of more effective DMTs, the treatment paradigm of MS has been shifting in recent years from aiming at partial response to complete remission [24,25]. To achieve complete remission in an immune-mediated inflammatory disease is not a new concept, as this is already an important goal, for example, in the treatment of rheumatoid arthritis, and combinations of clinical and laboratory assessments became accepted as measures of treatment success [26–29]. In relapsing MS, the concept of 'no evidence of disease activity' (NEDA) – previously termed 'disease activity free' (DAF) – has been proposed based on the absence of clinical deterioration and MRI activity [24]. The combination of these parameters enables a more comprehensive assessment of treatment effects than by using just one singular parameter [25,30–32]. Although it seems logical to use this composite as a treatment goal in MS, there are some concerns that are not sufficiently addressed in the current debate.

Surrogate marker for treatment response in MS

A surrogate is defined as 'a biomarker intended to substitute for a clinical end-point' [33]. Different parameters such as MRI metrics [34], body fluid markers [35] or even clinical characteristics [36–39] might be used as a surrogate in order to assess a pre-specified clinical end-point. As clinical end-point, one might use for example disability as assessed by the Expanded Disability Status Scale (EDSS) [40], because disability represents the sustained consequence of disease activity and failure of treatment response in MS.

One of the main requirements of a surrogate marker is its capacity to mediate, in the short term, the effects seen on the clinical (true) outcome in the long term [34]. A proper surrogate marker of treatment response would also discriminate between the natural history of the disease (i.e. disease activity) and a true response to the treatment (i.e. the net effect of the DMT in reducing disease activity) [41].

No evidence of disease activity – NEDA

Since the first clinical study using combined assessments in MS [42], definitions of NEDA and its component measures applied in clinical trials have varied markedly. Generally, NEDA is defined by the absence of relapses, disability progression and MRI activity (thus termed NEDA-3). For this purpose, disability progression was defined as increase in the EDSS score usually confirmed after 3–6 months. Radiological activity was defined as occurrence of contrast-enhancing lesions (CELs) in T1-weighted or new/enlarging hyperintense lesions on T2-weighted MRI [24,25] (Table S1). Some authors suggested including further parameters such as brain volume loss (BVL) determined by MRI (NEDA-4) or, recently, neurofilament levels in cerebrospinal fluid to better reflect a complete view of MS disease activity [25,43].

To understand the capability of NEDA, one has to look first at the limitations and drawbacks of the single component measures, which – contrary to common opinion – are not automatically eliminated when combined in a composite. Whilst the sensitivity to detect MS disease activity is higher applying a composite such as NEDA than single component measures by capturing different aspects of MS disease activity (e.g. inflammatory activity and neurodegenerative damage), the intrinsic limitations of these measures still remain.

Relapses – the first domain of NEDA

The number of relapses and the annualized relapse rate represent the oldest descriptors of MS disease activity and are used as outcome measures both in clinical trials and clinical routine [20,44]. The occurrence or non-occurrence of relapses carries significant prognostic value for long-term accumulation of disability and risk for conversion to secondary progressive MS as evidenced by large natural history studies stemming from both the pre- and post-DMT era [36–39,45–47]. These studies clearly demonstrate that relapses have a prognostic impact especially if occurring in the early disease phase [48].

However, the use of relapses as an outcome measure has major limitations. In general, relapses are relatively rare events. In recent trials, untreated MS patients showed an annual relapse rate of ~0.4 [5,11–13,16]. As a consequence, long observation periods (of at least 2 years) are needed to establish whether a treatment is effective in reducing relapse rate. Furthermore, the mere counting of relapses does not account for differences in relapse severity and extent of remission. Several studies reported an unfavourable prognostic impact of a severe relapse with incomplete remission compared to a mild relapse with complete remission regarding the time to reach a certain disability level or the progressive disease phase. Also, type of relapse symptoms as well as the presence of monofocal or multifocal symptoms imply some prognostic value [36–39,49–51]. Brainstem, cerebellar or spinal cord syndrome is associated with poor recovery from relapse [52] and multifocal symptoms with shorter time to reach a certain level of disability [39]. Finally, relapse rates differ significantly

depending on whether relapses are defined as equivalent to an increase in functional system or EDSS score (confirmed by neurologist), or whether relapses are just reported by the patient without the need of objective change in neurological function. This difference of documentation may account for a more than 2-fold higher relapse rate in the reported versus confirmed relapse group [53].

Disability progression – the second domain of NEDA

Physical disability and its worsening over the disease course can be measured by a large armamentarium of scales and tools with the EDSS the most widely used [40]. It has been consistently shown that the extent of disability accumulation as measured by the EDSS 2 and 5 years after MS diagnosis is predictive for the level of disability later [38,39,48]. Also, shorter time to disability progression is associated with higher disability in the long term [54] and sustainability of disability accumulation is highly predictive for long-term outcome not only at the group but also at an individual level [42].

Assessment of disability by the EDSS has some well-known limitations as it measures a mixture of disability and impairment, is strongly driven by walking impairment and mostly disregards neuropsychological disability and upper-extremity function [55–57]. MS patients with stable EDSS score might show cognitive deterioration [58]. Worsening of upper-extremity function as assessed by the nine-hole peg test is observed in ~20% of higher disabled MS patients with stable EDSS [57]. Furthermore, EDSS does not reflect an increase of disability in a linear manner, as greater rates of change are observed for lower EDSS scores [59,60]. There are also certain constellations where an acute relapse does not result in a change of EDSS score [61], and long observation periods are usually needed to record disability progression.

New focal lesions on brain MRI – the third domain of NEDA

The valuable contribution of MRI – visualizing the typical inflammatory demyelinating lesions in the white (and grey) matter – to diagnosis [44] and differential diagnosis [62] of MS is unquestionable. It is widely agreed that MRI measures are more sensitive indicators of MS disease activity than clinical measures, as the ability of MRI to visualize lesions is an order of magnitude greater than the ability of clinical observation to detect relapses or disability progression – especially in the early disease phase. This phenomenon, referred to as the clinico-radiological

paradox, has been consistently observed throughout a multitude of MS clinical trials [63]. The higher sensitivity of MRI to detect new lesions has led to revisions of MS diagnostic criteria and is the basis for earlier diagnosis by establishing dissemination in time much more quickly than would be possible only by 'waiting' for occurrence of a further relapse [44,64].

Detection of new lesions on follow-up MRI scans has also been suggested as a surrogate for treatment effects [25], as DMTs significantly reduce the occurrence of new T2 lesions [2,5,7–12,14,15,17–19,65] and as the number of new T2 lesions correlates with future disability [66,67]. However, the burden and accumulation of T2 lesions in MS patients correlate only weakly with clinical measures of disability [65–67]. The studies indicating a stronger correlation included patients with clinically isolated syndrome [68–70]; hence, the correlation between T2 lesions and future disability was artificially strengthened by adding a group of subjects without MS. In interferon-β trials, it has been shown that MRI metrics mediate only about 50% of the treatment effect on relapses [71] and disability progression [67]. Furthermore, one has to consider that there is a difference between the simple correlation of T2 lesion load or new T2 lesions with future disability and the ability to predict disability progression by an increase in T2 lesions at a certain time point using a pre-specified cut-off. Accordingly, highly variable results have been reported on the relevant number of new T2 lesions to predict disability progression. Whereas the Rio score proposed >2 new/enlarging T2-hyperintense lesions or T1-CELs determined after 1 year of treatment as relevant (and weighted this number of new MRI lesions as significant as the occurrence of relapse or disability progression) [30], the modified Rio score suggested >4–5 lesions to predict disability progression during follow-up [31]. A Canadian group stated that treatment modification should be considered when one to three new T2-hyperintense or T1-CELs occur within 1 year [32]. Whilst it is self-explanatory that occurrence of new MRI lesions principally reflects MS disease activity, a validated and reliable cut-off for prediction of long-term disability progression being the basis for treatment decision making has yet to be determined. Predictive capabilities of different scores are displayed in Table 1. At this point, it has to be stated that evidence on the predictive value of new MRI lesions is limited mainly to MS patients treated with interferon-β.

Brain volume loss – the fourth domain of NEDA?

The occurrence of relapses and new focal MRI lesions provides useful information about the inflammatory

Table 1 MRI criteria for treatment response prediction in interferon-β treated relapsing–remitting multiple sclerosis patients

Reference	Surrogate		Clinical end-point		Results	
	Criteria for treatment response	Time point	Definition	Time point	Sensitivity	Specificity
Río *et al.* (2008) [104]	≥3 new/enlarging T2 or contrast-enhancing lesions	Year 1	Disability progression	Year 3	71%	77%
Río *et al.* (2009) [30]	≥3 new/enlarging T2 or contrast-enhancing lesions plus ≥1 relapse or confirmed increase ≥1 point in EDSS	Year 1	Relapse and/or disability progression	Year 3	Odds ratio 3.3–9.8 for relapses Odds ratio 6.5–7.1 for progression	
Sormani *et al.* (2013) [31]	≥5 new T2 lesions and ≥1 relapse; or ≥2 relapses	Year 1	≥1 relapse and/or disability progression	Year 4	24%	97%
Prosperini *et al.* (2014) [105]	≥1 relapse plus ≥9 T2 lesions or ≥1 contrast-enhancing lesion	Year 1	Relapse and/or disability progression	Year 4	34%	90%
	≥1 relapse or ≥1 contrast-enhancing lesion or ≥2 new T2 lesions	Year 1	Relapse and/or disability progression	Year 4	68%	80%
	≥1 contrast-enhancing lesion or ≥2 new T2 lesions	Year 1	Relapse and/or disability progression	Year 4	61%	83%

Odds ratios refer to the probability that patients meeting the criteria will demonstrate the outcome measure, relative to patients who do not meet the criteria; Table adapted after Wattjes, M. P. *et al. Nat Rev Neurol* 2015; 11: 597–606. EDSS, Expanded Disability Status Scale.

activity of MS, but does not adequately account for neurodegenerative disease progression. Also, disability assessment by the EDSS only partially reflects neurodegenerative damage. Evidence for this is provided from studies that observed cognitive deterioration amongst patients achieving NEDA-3 [58].

The macroscopic correlate of neurodegeneration is brain atrophy, which defines irreversible loss of brain volume. It is the result of various destructive pathological processes, including irreversible demyelination, axonal and/or neuronal loss, and astroglial scarring [72]. BVL occurs already in the earliest stage of MS and may progress to brain atrophy throughout the disease course [73,74]. BVL correlates with cognitive impairment [75] and disability progression [76–79]. BVL determined by MRI has been suggested to complement NEDA stratification (termed NEDA-4).

There are some limitations of this MRI parameter. The effect size of BVL is usually small, especially if determined within a short time period (of 1–2 years). Timing of MRI scans with regard to the start of DMT has also to be considered, as brain volume excessively decreases within the first 6–12 months of treatment, followed by a certain degree of stabilization during later periods (so called pseudoatrophy) [78]. In addition to disease-specific changes, standardization of respective MRI techniques and read-outs [80] as well as lifestyle-related factors (including alcohol consumption or smoking), medication (e.g. lamotrigine, diuretics) and concomitant pathophysiological conditions (e.g. diabetes or vascular risk factors) have been shown to impact brain volume [72,81,82]. Altogether,

clinical interpretation of BVL in patients with MS might be difficult in the context of the above discussed variables. The MAGNIMS consensus guidelines currently state that 'the use of longitudinal brain volume assessment as a marker of disease progression in individual patients cannot be considered to be reliable at present' [72].

No evidence or evidence of disease activity (NEDA vs. EDA)?

Determination of the prognostic impact of relapse(s), disability progression, new MRI lesion(s) or BVL still remains a considerable unresolved problem in the management of MS patients, partially due to the parameters' limitations discussed above. With the development of the composite NEDA, one's focus might shift on selection of patients who do not show any disease activity. Indeed, a recent study showed that NEDA-3 status allows better early prediction (e.g. after 2 years) of long-term stability (i.e. EDSS score change ≤0.5 after 7 years) than its individual component measures (relapses, disability progression or MRI activity), reaching a positive predictive value of 78% [83]. Another study including interferon-β treated MS patients even revealed a positive predictive value of NEDA at year 1 of 86% to predict stable disease [84]. However, patients without disease activity, i.e. fulfilling NEDA criteria, constitute a small proportion, especially in the long term or if receiving first-line DMT, and do not pose a challenge in clinical routine, because in these patients no change of treatment strategy is necessary.

Table 2 Predictive value of the NEDA composite

Reference	N	Disease type	DMT	Baseline characteristics		Predictor: NEDA			Outcome: disability progression			Predictive value of NEDA	
				Prior relapses	EDSS	Time point	Definition of NEDA	% reaching NEDA	Time point	Definition of disease progression	% with stable disease	PPV (NEDA predicting stable disease)	NPV (EDA predicting disease progression)
Rotstein et al. (2015) [83]	219	RRMS/CIS[a]	Various (47.9% had no DMT at baseline)	n.a.	1.3[j]	Year 2	NEDA-3[c]	27.5%	Year 7	SDP (≥1 EDSS point, 6 months confirmed)	56.6%	78.3% (superior to individual measures)	43.1%
Cree et al. (2016) [93]	407	RRMS/CIS[a]	Various (38.1% had no DMT at baseline)	0.5 per year[i]	1.5[i]	Year 2	NEDA-3[d]	17.9%	Year 10	Disability progression (≥1 EDSS point[g])	44.7%	NEDA-3 at year 2 was not statistically significantly associated with disability progression	
Uher et al. (2017) [85]	192	CIS[b]	IFN-β	n.a.	1.5[i]	Year 1	NEDA-3[e]	40.1%	Year 4	SDP (≥1 EDSS point,[h] 12 months confirmed)	86.7%	n.a.	HR 2.4 (1.1–5.3)
						Year 2	NEDA-4[f]	16.3%				NEDA-4 at year 2 was not statistically significantly associated with SDP	
	162	RRMS	IFN-β IFN-β/AZA IFN-β/AZA/CS	≥2 relapses in prior 1 year, or ≥3 relapses in prior 2 years	2.0[i]	Year 1	NEDA-3[e]	20.4%	Year 6	SDP (≥1 EDSS point,[h] 12 months confirmed)	74.1%	n.a.	38.8%
						Year 2	NEDA-4[f]	4.3%				NEDA at year 2 was not statistically significantly associated with SDP	
Río et al. (2018) [104]	233	RRMS	IFN-β	1.9[j] relapses in prior 2 years	2.0[i]	Year 1	NEDA-3[d]	24%	Year 7[j]	SDP (≥2 EDSS points, confirmed at end of follow-up)	80%	86%	23%

AZA, azathioprine; CIS, clinically isolated syndrome; CS, corticosteroids; HR, hazard ratio; IFN, interferon; NPV, negative predictive value; PPV, positive predictive value; RRMS, relapsing-remitting multiple sclerosis; SDP, sustained disability progression. [a]Patients with CIS were diagnosed according to McDonald Criteria 2001; [b]Patients with CIS had ≥2 T2 hyperintense lesions on MRI and ≥2 oligoclonal bands in the cerebrospinal fluid; [c]NEDA-3 was defined as absence of relapses, EDSS worsening and brain/spinal cord MRI activity (no new/ enlarging T2 hyperintense and/ or contrast-enhancing lesions); [d]NEDA-3 was defined as absence of relapses, EDSS worsening and brain MRI activity (no new/ enlarging T2 hyperintense and/ or contrast-enhancing lesions); [e]NEDA-3 was defined as absence of relapses, EDSS worsening and brain MRI activity (no new/ enlarging T2 hyperintense lesions); [f]NEDA-4 was defined as absence of relapses, EDSS worsening, brain MRI activity (no new/enlarging T2 hyperintense lesions) and increased whole brain volume loss (>0.4% between year 1 and year 2); [g]In patients with a baseline EDSS score of 0 an increase of ³1.5 points, or in patients with a baseline EDSS score >5.5 an increase ³0.5 points was considered as disability progression; [h]In patients with a baseline EDSS score of 0 an increase of ³1.5 points was considered as disability progression; [i]median; [j]mean.

The remaining patients, i.e. those with evidence of disease activity (EDA), would be especially in need of a surrogate marker supporting treatment decision making. Unfortunately, capability of 'loss of NEDA-3' to predict long-term disability is quite low (up to 40%; Table 2) [83–85], i.e. loss of NEDA does not automatically imply poor prognosis. There might be several reasons for this. In the current version of NEDA, clinical information of disability progression and MRI disease activity are strongly reduced by dichotomization. It seems obvious that there is a prognostic difference between an EDSS increase of, for example, 2 vs. 0.5 points. Similarly, in the case of new MRI activity, the detection of for example one as opposed to nine new T2 lesions implies a different MS disease activity and higher risk for disease progression at the individual level. Regarding BVL, prognostic value is also probably not appropriately reflected if dichotomized by the suggested annual threshold of 0.4% [85,86]. In a recent study, the predictive value of NEDA-3 was even lost if BVL was added [85]. Furthermore, the different component measures building NEDA are not well balanced amongst each other, e.g. the detection of a single new MRI lesion is considered as significant as the occurrence of a severe disabling relapse. Besides the different impact in terms of severity, the probability of worsening in one of the three component measures is different with MRI being the most sensitive and EDSS the least sensitive [83,86] (Table S1).

Requirements for standardization

Definitions of NEDA and its component measures used in clinical trials have varied substantially (Table S1). Profound evaluation of NEDA or EDA is impossible without harmonization of definitions of relapse, disability progression and MRI activity.

Whilst the core definition of relapse, i.e. symptoms typical of an acute inflammatory demyelinating event in the central nervous system (CNS), with duration ≥24 h, in the absence of fever or infection, has been used relatively uniformly as specified in the MS diagnostic criteria [44], there are differences in terms of relapse confirmation. Some studies included relapses reported by the patient, whereas others required an objective change in neurological function. As a recent study showed a more than 2-fold differing relapse rate depending on whether relapses were confirmed or reported [53], this issue is of high relevance and impacts on the rate of NEDA.

For definition of disability progression, some studies considered an increase of ≥1 step in the EDSS scale as deterioration, whereas others took baseline EDSS score into account, i.e. considering an increase ranging between 0.5 and 1.5 as significant depending on the previously determined EDSS score. Sustainability of disability progression was also used inconsistently in different studies, i.e. the time period after EDSS progression requested for confirmation varied between 3 and 12 months. It is obvious that a uniform and unequivocal definition for disability progression is required before its use within a composite.

Regarding MRI metrics, image acquisition techniques (e.g. pulse sequence or spatial resolution) as well as image analyses require standardization. In particular, the reliable determination of new/enlarging T2 lesions and BVL requires high-quality imaging and an experienced neuro-radiologist, a circumstance that is not achievable in every region of the world. Detection of new/enlarging T2 lesions can be hindered by multiple factors, including a high load of T2 lesions, inadequate repositioning of serial scans and inter-observer variability [87]. Moreover, there are no standardized protocols for T2 lesion counting, which can be performed manually or (semi-)automatically. The value of CELs in addition to T2 lesion load is also not fully elucidated. Whereas older studies performing weekly MRI reported an increase in sensitivity for detection of new MRI lesions when contrast-enhanced T1-weighted imaging was done in addition to T2-weighted imaging [88–90], a recent study using a large population of patients from the FREEDOMS trials indicated that T2 lesion changes almost invariably coincided with CELs [86]. MRI frequency is another issue of utmost importance, especially if the occurrence of CELs is counted, as they only appear for a certain time period (up to several weeks) [91]. Infrequent assessments may be biased by chance pick-up or underreporting of lesion load changes. The consequences are clear: the more frequently assessments are performed, the less favourable NEDA outcome is recorded. Thus, time points of assessments have to be standardized. With regard to brain atrophy assessment, differences in the quality and capabilities of MRI hardware as well as in software packages used for analysis or processing can generate notable variability [72,92].

No evidence of disease activity as an additional outcome measure versus predictive surrogate marker for treatment response

The majority of studies on NEDA have simply performed *post hoc* analyses each combining the

percentage of patients remaining free of relapses, free of disability progression and free of MRI activity. In this context, NEDA is solely an additional outcome measure for disease activity at the end of an observation period. These studies were not designed to investigate whether the proportion of patients achieving NEDA was higher in any treatment arm (e.g. active treatment versus placebo; Table S1).

Only a few studies investigated the predictive value of NEDA for future disability [83–85]. Whilst in some studies early loss of NEDA status (after 1–2 years) was associated with higher risk of disability in the middle to long term (7–12 years), these findings were not confirmed in a recent large prospective cohort study [93].

Conclusions and perspectives

The increasing number of DMTs available for MS has broadened treatment options for patients, but also challenges clinicians to select the best therapy for each individual at the appropriate stage of disease. Whilst it is widely agreed to initiate early and effective treatment in order to improve long-term outcome [94–99], some of the more efficacious DMTs pose considerable risks such as progressive multifocal leukoencephalopathy or secondary autoimmunity [100,101]. The optimal time point to switch from a first-line to an escalation treatment considering the patient's individual risk−benefit balance is still an unresolved issue. Most product labels still require clinical disease activity such as occurrence of relapse(s) (partially reflecting inclusion criteria of pivotal trials). In the last decade, there was and still is great research interest in identification of surrogate markers allowing early determination of failure or response to a certain DMT (e.g. Rio score) and legitimating rational treatment switch.

'No evidence of disease activity' has been proposed as a disease activity marker based on the absence of relapses, disability progression and radiological activity. Some authors have even suggested NEDA as a predictive marker for treatment response and long-term disability. However, NEDA has some considerable, conceptual limitations. Whilst NEDA as a composite score – in contrast to individual parameters – captures different aspects of MS disease activity, valuable clinical information is lost through dichotomization. Another main drawback amongst others is the imbalance between the different component measures (Table 3).

'No evidence of disease activity' might be used as an additional outcome parameter in clinical trials besides the established primary end-points relapse rate and EDSS progression and the various secondary

Table 3 Strengths and limitations of NEDA

Limitations	Strengths
Low predictive value of EDA for future disability progression	High predictive value of NEDA for no future disability progression
Extent of disease activity is disguised by dichotomization (e.g. one versus nine new T2 lesions)	Aim to capture and combine different assessments of MS disease activity
Component measures not balanced (e.g. one new T2 lesion versus severe relapse)	A composite score would describe treatment outcomes easier than its single parameters
Loss of NEDA is mainly driven by MRI activity	
Intrinsic limitations of component measures still present if combined	
No standardized definition of NEDA and its components	

EDA, evidence of disease activity; MRI, magnetic resonance imaging; MS, multiple sclerosis; NEDA, no evidence of disease activity.

MRI end-points. As loss of NEDA is mainly driven by MRI activity (Table S1) which is still not accepted as a surrogate marker of CNS inflammatory activity by regulatory authorities such as the European Medicines Agency or the US Food and Drug Administration, it seems unlikely that the significance of NEDA will increase and top those of clinical end-points in the near future.

Evidence on NEDA to predict future disability and treatment response, respectively, is insufficient and contradictory [83–85,93]. NEDA has not been shown to fulfil the criteria of a surrogate marker [102] and has yet to be validated in prospective trials. Therefore, NEDA is far from being implemented in clinical routine for treatment decision making. A special caveat regards the use of NEDA for comparisons of different treatments to choose which is best. Such drug marketing driven comparisons are currently scientifically dishonest. Furthermore, the majority of patients do not reach NEDA-3 after 2 years. Inclusion of more parameters into the composite leads to lower proportions of patients fulfilling NEDA criteria (e.g. the proportion of patients with NEDA-3 is relatively reduced by ~40% upon addition of BVL) [85,86,103]. This narrows the group of patients with no disease activity indicating optimal treatment response, but does not allow prediction of long-term outcome in the large majority of patients.

In the process of developing a surrogate marker for MS disease activity and treatment response, first the real and independent value of each individual parameter has to be clarified and weighted appropriately. Then, the more promising approach requires a

statistical model that includes this pre-defined bundle of parameters and considers their different predictive capabilities, returning a probability for disease progression within a specified time period instead of returning only a 0 or 1 result.

Finally, despite the high and still evolving importance of MRI in MS, other measures such as body fluid markers might be included in a composite score. Body fluid markers allow insights into the underlying pathological disease process. In contrast to NEDA, which solely indicates disease activity, body fluid markers can specifically indicate response or failure to a certain DMT based on its mode of action. The already established and potentially evolving body fluid markers have recently been reviewed elsewhere [41]. Also, patient-related outcome measures might be considered in developing a composite score to capture the quality of life of MS patients whose improvement is obviously one of the most important treatment goals.

In conclusion, there is still an urgent and unmet need of a surrogate marker for prediction of disease activity and response to DMT. Unquestionably, 'absence of disease activity' is the main goal for MS, but NEDA in its current form does not come up to the set requirements.

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Supporting Information

Additional supporting information may be found online in the Supporting Information section at the end of the article.

Table S1. Summary of different disease activity measures – singular and combined.

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