

# Disputes & Debates: Editors' Choice

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## Editors' Note: Serum Neurofilament Light Association With Progression in Natalizumab-Treated Patients With Relapsing-Remitting Multiple Sclerosis

In "Serum Neurofilament Light Association With Progression in Natalizumab-Treated Patients With Relapsing-Remitting Multiple Sclerosis," Bridel et al. evaluated serum neurofilament light chain (sNfL) levels serially after initiation of natalizumab in patients with relapsing-remitting multiple sclerosis (RRMS) and found that they do not capture or predict clinical/radiologic trajectory. Kropshofer et al. commented that their conclusion that sNfL is not a valid biomarker for disease progression is in opposition to the results from other large studies, noting that the editorial about this article, written by Goldschmidt and Fox, suggested that this may be because prior studies demonstrate natural history, without natalizumab treatment. Nonetheless, Kropshofer et al. noted that they found an association between baseline sNfL and 3-month disability progression in patients treated with siponimod, irrespective of prior disease activity, indicating that baseline sNfL can be used for neuroprognostication, regardless of treatment with anti-inflammatory therapy. Bridel et al. clarified that their conclusion was that sNfL may not be well suited to monitor or predict progression in patients with RRMS on natalizumab. They noted that their results may differ from those from other studies because their patients (1) all had RRMS and (2) were all treated with natalizumab. They also commented that almost half of patients on siponimod in the EXPAND study developed new or enlarging brain lesions on 2-year follow-up imaging, so that is not the ideal population to study the relationship between sNfL and progression. They recommend performance of additional larger studies on the relationship between sNfL and progression in patients on natalizumab and/or ocrelizumab.

Ariane Lewis, MD, and Steven Galetta, MD  
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## Reader Response: Serum Neurofilament Light Association With Progression in Natalizumab-Treated Patients With Relapsing-Remitting Multiple Sclerosis

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The results of the observational monocentric study by Bridel et al.<sup>1</sup> contrast with those from large phase 3 studies in progressive multiple sclerosis (MS) such as ASCEND, EXPAND, and INFORMS,<sup>2,3</sup> which suggest association of high baseline serum neurofilament light chain (sNfL) levels with increased risk of disability progression. In the accompanying editorial, Goldschmidt and Fox highlight that these earlier studies included a placebo arm where inflammation followed its natural course,<sup>4</sup> whereas Bridel et al.<sup>1</sup> studied patients on anti-inflammatory therapy by natalizumab. They hypothesized that the lack of association of sNfL with disability progression may result from suppression of inflammatory activity by natalizumab. They concluded that sNfL is not a valid biomarker for disease progression.

Author disclosures are available upon request ([journal@neurology.org](mailto:journal@neurology.org)).

We addressed this hypothesis in analyses by a treatment group in the EXPAND trial ( $\leq 5$  years follow-up) where patients with confirmed disability progression (CDP) events showed higher sNfL levels.<sup>2</sup> In the siponimod group ( $N = 946$ ), which controlled for inflammation, high baseline sNfL levels were associated with a higher risk of CDP events at 3 months (HR [95%CI]: 1.30 [1.06; 1.58],  $p = 0.0115$ ). A prognostic association between baseline sNfL and disability progression was also observed for patients with (1.28 [1.01; 1.61],  $p = 0.0397$ ) and without active disease before baseline (1.33 [1.06; 1.58],  $p = 0.0149$ ). In conclusion, increased baseline sNfL is prognostic of disability progression, irrespective of anti-inflammatory therapy.

1. Bridel C, Leurs CE, van Lierop ZYGJ, et al. Serum neurofilament light association with progression in natalizumab-treated patients with relapsing-remitting multiple sclerosis. *Neurology*. 2021;97(19):e1898-e1905.
2. Leppert D, Kuhle J, Kropshofer H, et al. Neurofilament light levels in the blood of patients with secondary progressive MS are higher than in primary progressive MS and may predict brain atrophy in both MS subtypes. Poster presented at: PACTRIMS. *Mult Scler J*. 2019;25(3):432-492.
3. Kapoor R, Smith KE, Allegratta M, et al. Serum neurofilament light as a biomarker in progressive multiple sclerosis. *Neurology*. 2020; 95(10):436-444.
4. Goldschmidt C, Fox RJ. Relationship between serum neurofilament light and multiple sclerosis disability progression: clear as mud. *Neurology*. 2021;97(19):887-888.

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## Author Response: Serum Neurofilament Light Association With Progression in Natalizumab-Treated Patients With Relapsing-Remitting Multiple Sclerosis

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We are grateful for the interest in our study.<sup>1</sup> We did not conclude that serum neurofilament light chain (sNfL) is not a valid biomarker for disease progression. Rather, we indicated that it may not be well suited to monitor or predict progression in people with relapsing-remitting multiple sclerosis (RRMS) treated with natalizumab. At least 2 reasons may explain the discrepancy between our findings and those reported by Kropshofer et al.<sup>2</sup> First, the population we investigated consisted exclusively of people with RRMS, as opposed to people with secondary progressive multiple sclerosis in the EXPAND study.<sup>3</sup> The rate of progression differs greatly between these 2 populations, and prediction of progression in people with RRMS may require more sensitive tools. Second, in our study, all patients were treated with natalizumab, which silences acute focal inflammatory disease activity in a vast majority of patients compared with placebo.<sup>4</sup> In the EXPAND study, 43% of the siponimod-treated patients had new or enlarging T2 lesions during the 24 months follow-up.<sup>3</sup> Thus, siponimod-treated patients are less well suited to investigate the biological underpinnings of progression because of residual focal inflammatory disease activity. We contend that larger studies investigating natalizumab and/or ocrelizumab patients are needed to determine the prognostic and monitoring potential of sNfL in terms of progression.

1. Bridel C, Leurs CE, van Lierop ZYGJ, et al. Serum neurofilament light association with progression in natalizumab-treated patients with relapsing-remitting multiple sclerosis. *Neurology*. 2021;97(19):e1898-e1905.
2. Leppert D, Kuhle J, Kropshofer H, et al. Neurofilament light levels in the blood of patients with secondary progressive MS are higher than in primary progressive MS and may predict brain atrophy in both MS subtypes. Poster presented at: PACTRIMS. *Mult Scler J*. 2019;25(3):432-492.
3. Kappos L, Bar-Or A, Cree BAC, et al. Siponimod versus placebo in secondary progressive multiple sclerosis (EXPAND): a double-blind, randomised, phase 3 study. *Lancet*. 2018;391(10127):1263-1273.
4. Polman CH, O'Connor PW, Havrdova E, et al. A randomized, placebo-controlled trial of natalizumab for relapsing multiple sclerosis. *N Engl J Med*. 2006;354(9):899-910.

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## Quality Improvement in Neurology

### Epilepsy Quality Measurement Set 2017 Update

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In the Special Article “Quality Improvement in Neurology: Epilepsy Quality Measurement Set 2017 Update” by Patel et al.,<sup>1</sup> there are several errors in Table 1. The table is republished here. The authors regret the errors.

**Table 1** Epilepsy Quality Measurement Set 2017 Update

Title	Denominator	Numerator	Exclusions
Counseling for Women of Childbearing Potential with Epilepsy	All women, including all individuals of childbearing potential (12–44 years) with a diagnosis of epilepsy	Patients or caregivers counseled at least once a year about how epilepsy and its treatment may affect contraception and/or pregnancy. Measure is met if the patient has documentation they are premenstrual, postmenopausal, surgically sterile, or reproductive organs absent.	None
Comprehensive Epilepsy Care Center Referral or Discussion for Patients with Intractable Epilepsy	Patients diagnosed with intractable epilepsy (see Appendix of Codes) OR patients diagnosed with epilepsy who were prescribed 3 or more distinct antiseizure medications in past 2 years	Patients with an order for referral to a comprehensive epilepsy care center, who had a discussion of evaluation at a comprehensive epilepsy care center, OR who received treatment at a comprehensive epilepsy care center during the measurement period.	None
Quality of Life Assessment for Patients with Epilepsy	Patients aged 4 years and older diagnosed with epilepsy	Patients with age-appropriate condition-specific quality of life assessed at least once in the measurement period.	Patients who are unable or decline to complete the instrument and for these patients, a caregiver is not present to provide a proxy report.
Quality of Life Outcome for Patients with Epilepsy	Patients aged 18 years and older diagnosed with epilepsy who had 2 office visits during the 2-year measurement period, which occurred at least 4 weeks apart	Patients whose most recent QOLIE-10-P score is maintained or improved from the previous QOLIE-10-P score obtained in the measurement period.	None
Depression and Anxiety Screening for Patients with Epilepsy	Patients age 12 and older diagnosed with epilepsy	Patients with epilepsy who were screened for both depression and anxiety at every office visit.	<ul style="list-style-type: none"> <li>• Patients who are unable or decline to complete the epilepsy-specific screening tool</li> <li>• Patient has a diagnosis of depression or anxiety on the active problem list.</li> </ul>
Seizure Frequency for Patients with Epilepsy	All visits for patients with a diagnosis of epilepsy	Patient visits with current seizure frequency documented for each seizure type.	<ul style="list-style-type: none"> <li>• Caregiver is unavailable for a patient who is noncommunicative or has an intellectual disability.</li> <li>• Patient or caregiver declines to report seizure frequency.</li> </ul>

## Reference

1. Patel AD, Baca C, Franklin G, et al. Quality improvement in neurology: Headache Quality Measurement Set 2017 update. *Neurology*. 2018;91(18):829–836.

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## Quality Improvement in Neurology: Epilepsy Quality Measurement Set 2017 Update

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