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# Initial screening for neuronal autoantibodies and their putative impact on survival in patients with small-cell lung cancer

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## Abstract

**Introduction:** Small-cell lung cancer (SCLC) may be associated with neuronal autoantibodies and paraneoplastic neurological syndromes. It has been suggested that neuronal autoantibodies, especially antineuronal nuclear antibody type 1 (Hu) autoantibodies, are associated with longer survival of patients with SCLC. The objective of this study was to determine the frequency and distribution of neuronal autoantibodies at the time of diagnosis of SCLC patients and assess survival rates in relation to autoimmunity.

**Methods:** In this retrospective study, serum from 40 patients with biopsy-proven SCLC at the time of diagnosis was studied prior to treatment. The sera originated from a cancer registry at the Oncology Department, Vejle Hospital from 2007 to 2010. The sera were analyzed blindly to clinical status for the presence of neuronal autoantibodies. Medical records were reviewed for neurological symptoms.

**Results:** Neuronal autoantibodies were detected in 22/40 (55%) of the SCLC patients. A broad range of neurological symptoms was recorded in 28/40 (70%) patients, of which 14/28 (50%) were positive for neuronal autoantibodies. The most frequently detected autoantibodies were Hu (7/40, 17.5%) followed by GAD65 (6/22, 15.0%). Striational and P/Q- or N-type voltage-gated calcium channel antibodies were less common, with each found in five patients (12.5%). Eight patients (20%) had coexisting autoantibodies. Autoantibody-positivity was not associated with survival.

**Conclusion:** Neuronal autoantibodies were at time of diagnosis found in approximately half of the treatment-naïve SCLC patients. Neither autoantibody positivity at diagnosis nor neurological manifestations correlated with survival and their clinical importance requires further studies in larger, prospective cohorts.

KEYWORDS
anti-neuronal antibodies, autoimmunity, paraneoplastic neurological syndromes (PNS), small-cell lung cancer (SCLC)

## INTRODUCTION

Paraneoplastic neurological syndromes (PNS) are mediated by an antitumor immune response to neuronal antigens expressed by the tumor and may result in neural antigen-directed immunoglobulin G that can be detected in serum.[1,2] In patients with cancer, the neurologic symptoms frequently precede tumor diagnosis by months.[3] Neuronal autoantibodies can also be detected in cancer patients without neurological symptoms and are frequently found in small-cell lung cancers (SCLCs).[4–7] The presence of antineuronal nuclear antibody type 1, so-called Hu autoantibodies, have been reported to be associated with improved survival of SCLC patients, and it has been speculated that antitumor immune responses targeting Hu and/or other neuronal antigens, expressed in tumor tissue, may improve

prognosis.[6,8–13] In this retrospective study, we aimed to examine the prevalence of neuronal autoantibodies in sera from treatment-naïve patients with SCLC at time of diagnosis, and to assess if the presence of neuronal autoantibodies correlated with prolonged survival.

## METHODS

### Patients

This retrospective study included a total of 40 treatment-naïve patients ≥18 years of age with biopsy-proven SCLC diagnosis, identified in a cancer patient registry with associated biobank at the Oncology Department, Vejle Hospital, Denmark. Patients were evaluated clinically at the Oncology Department, Vejle Hospital, from 2007 to 2010, and sera were collected from the patients at the time of diagnosis, prior to treatment. For the purpose of this study the medical records were reviewed individually by a resident immunologist and a neurologist, who were masked to results from the autoantibody status of patients. However, neurological examinations were not performed and patients were not screened for PNS at time of diagnosis. All blood samples were obtained with approval from the relevant ethical board (ref. no. S-20070014) and after informed consent of the patients. The Research Ethical Committees for the Region of Southern Denmark approved the study protocol (ref. no. S-20130026).

### Autoantibody assays

All samples were analyzed in two independent laboratories, the Autoimmune Laboratory, Department of Clinical Immunology, Odense University Hospital, Denmark and the Mayo Clinic's Neuroimmunology Laboratory, Minnesota, USA. Autoantibody testing in both laboratories was performed by investigators who were masked to results from autoantibody analysis and to the clinical status of patients. Serum samples were tested for neuronal autoantibodies using tissue-based indirect immunofluorescence assays (IFAs) or cell-based assays (CBAs). Analyses such as line immunoassays (LIAs), enzyme-linked immunosorbent assays (ELISAs), and radioimmunoprecipitation assays were additionally used to test for neuronal autoantibodies and to determine the specificity of the neuronal antigen. Samples tested positive for neuronal autoantibodies in any one assay were counted as positive. At Odense University Hospital, autoantibodies targeting intracellular neuronal antigens were detected by commercially available tissue-based IFA using monkey and enteric nervous tissue and immunoblots with recombinant antigens for amphiphysin, Yo, CRMP5 (CV2/DRP-5), Hu, PNMA2 (Ma-2/Ta), and NOVA1 (Euroimmun AG, Lübeck, Germany). Samples were diluted 1:10. Sera was also evaluated by LIA for amphiphysin, CRMP5 (CV2/DRP-5), PNMA2 (Ma-2/Ta), Ri, Yo, and Hu (Euroimmun AG). These samples were diluted 1:100. Autoantibodies targeting extracellular neuronal antigens were tested by IFA using CBA on HEK293 cells transfected with plasmids including CASPR2, LGI1, NMDAR1, GABAbR, AMPAR1/2, and AQP4. Samples were diluted 1:10. Radioimmunoprecipitation assays were used to detect muscle acetylcholine receptor (AChR) antibodies on undiluted and 1:10 diluted sera samples (IBL International (Tecan), Huissen, The Netherlands).

Assays at Mayo Clinic have been reported in a previous study.[7] Sera diluted 1:480 were analyzed by tissue-based IFA using mouse tissue and immunoblots with recombinant antigens for amphiphysin, Hu, Ri, Yo, ANNA-3, PCA2, PCA-Tr, CRMP5 (CV2/DRP-5), and SOX1 (Euroimmun AG). Sera diluted 1:10 were also tested for autoantibodies specific for NMDAR, AMPAR, $GABA_BR$, and AQP4 by CBA on HEK293 cells transfected with the respective antigens (Euroimmun AG). Radioimmunoprecipitation assays for muscle acetylcholine receptor antibodies, acetylcholine ganglionic receptor antibodies (α3-AChR), voltage-gated calcium channel antibodies (P/Q-type and N-type calcium channels), voltage-gated potassium channel (VGKC), and glutamic acid decarboxylase 65-kilodalton isoform (GAD65) were performed on undiluted sera samples.[14,15] Striational autoantibodies were detected by ELISA on undiluted sera samples.

### Statistical analysis

Comparison of the SCLC patients was performed by Fisher's exact test for categoric variables and *t*-tests for numerical data. Data were summarized as frequencies and percentages or medians and ranges as appropriate. The Kaplan–Meier survival curves were used to estimate survival after SCLC diagnosis for the autoantibody-positive and autoantibody-negative patient groups. The log-rank test was used to evaluate the association of autoantibody status and survival. Cox proportional hazards regression was applied to evaluate differences in survival incorporating several factors simultaneously and to estimate hazard ratios. The analyses were performed with Prism version 9.3.0 for Windows (GraphPad Software, CA, USA).

## RESULTS

### Neuronal autoantibodies at time of diagnosis

The demographics and clinical characteristics of the SCLC patients are summarized in Table 1. Neuronal autoantibodies were detected in 22/40 (55%) of the patients at the time of diagnosis of biopsy-proven SCLC (Table 2 and Supporting Information file 2). Using tissue-based IFA, no autoantibodies against currently unknown antigens were detected. A broader range of neurological symptoms including paresthesia, central vertigo, weakness or paralysis,

**TABLE 1** Summary of demographics and clinical information on SCLC patients (SCLC).

| | SCLC patients positive for neuronal antibodies | SCLC patients negative for neuronal antibodies | *P*-value |
|---|---|---|---|
| *N* | 22 | 18 | |
| Females/males | 11/11 (50 %) | 4/14 (28 %) | 0.104 |
| % females | | | |
| Follow–up data unavailable, *N* | 6 | 2 | |
| Alive/deceased at most recent follow-up, *N* | 0 / 22 | 1 / 18 | |
| Median, age at time of diagnosis[a] | 63 (50.0 – 77.5) | 65 (51.1 – 79.5) | 0.815 |
| Median, survival from time of diagnosis, moths (range)[a] | 10 (2.98 – 27.4) | 9 (1.41 – 25.0) | 0.763 |
| Unknown, *N* | | | |
| | 3 | | |
| Cerebral/cerebellar metastasis, *N* Unknown, *N*[b] | 7 (36.8 %) | 8 (50 %) | 0.506 |
| | 3 | 2 | |
| Presence of neurological symptoms at any timepoint, *N* | 14 (63.6 %) | 14 (77.8 %) | 0.491 |
| Prevalence of autoimmune co-morbidities, total, *N* | 3 (13.6 %) | 1 (5.56 %) | 0.613 |
| Type 1 diabetes mellitus | 1 | 0 | |
| Hyperthyroidism | 1 | 1 | |
| Systemic lupus erythematosus | 1 | 0 | |
| Prevalence of other cancers, total, *N* | 0 | 3 (16.7 %) | 0.0967 |
| Breast cancer | 0 | 1 | |
| Malignant melanoma | 0 | 1 | |
| Chronic lymphocytic leukemia | 0 | 1 | |

[a]Time or age are given as (median [(2.5 – 97.5 percentiles)]).
[b]Patients with missing information are not included in the percentage calculations.

cognitive decline, cranial nerve disorder, or brainstem disorder was recorded in 28/40 (70%) patients. Of these, 14/28 (50%) were positive for neuronal autoantibodies. There were no significant differences in terms of the percentage of female patients, median age at time of diagnosis, median survival, cerebral/cerebellar metastasis, reported neurological symptoms, or other autoimmune manifestations in patients with or without neuronal autoantibodies (Table 1 and Supporting Information files 1 and 2). Clinical information about cerebral/cerebellar metastasis was not available for five patients and survival data were missing for three. A total of 15 patients had cerebral/cerebellar metastasis as documented by computed tomography/magnetic resonance imaging scan. Median time from SCLC diagnosis to confirmed brain metastasis was 7 months (−1–24 months). Median time from diagnosis to death was 8 months (range 1–27 months). One patient was still alive at the end of the study period and 10 years after diagnosis.

The frequency of neuronal autoantibodies in sera from patients with SCLC at diagnosis is given in Table 2 (see also Supporting Information file 2). Eight out of 40 samples tested positive for neuronal autoantibodies at Odense University Hospital and 19 samples tested positive at the Mayo Clinic. The majority of samples only tested positive in one assay, with the exception of anti-Hu, which in most cases was detected with both tissue-based indirect IFA and with LIA. Based on data from both laboratories, anti-Hu was the most frequently detected autoantibody (17.5%), followed by anti-GAD65 (15.0%), striational autoantibodies (12.5%), anti-VGCC (P/Q- and N-type) (12.5%), anti-ganglionic acetylcholine receptor (α3-AChR) (10.0%), and VGKC autoantibodies (7.5%). Acethylcholine receptor (muscle AChR), PCA2, anti-amphiphysin, and PNMA2 (Ma-2/Ta) autoantibodies were each detected in one patient (2.5%). Multiple autoantibodies were detected in eight patients (20%), and the specificities of coexisting autoantibodies are listed in Supporting Information Table S1.

## Disease survival and neuronal autoantibodies

The presence of one or more neuronal autoantibodies among SCLC patients did not correlate with survival ($p = 0.738$, univariate analysis). Similarly, there was no correlation between the presence of Hu antibodies and survival in SCLC patients ($p = 0.975$) nor the presence of GAD65 or VGCC (P/Q-type and N-type) ($p = 0.422$ and $p = 0.699$, respectively). The survival data for SCLC patients with and without autoantibodies as well as SCLC patients with and without neurological symptoms are illustrated by Kaplan–Meier curves in Figure 1a–c. In

**TABLE 2** Frequency of neuronal autoantibodies in small-cell lung cancer (SCLC) patients.

| Autoantibody specificity | SCLC[a] patients ($n = 40$) |
|---|---|
| Antineuronal nuclear antibody type 1 (Hu) | 7 (17.5%) |
| Glutamate decarboxylase 65 (GAD65) | 6 (15.0%) |
| Skeletal muscle | 6 (15.0%) |
| Striational | 5 (12.5%) |
| Muscle acetylcholine receptor (AChR) | 1 (2.50%) |
| Voltage-gated calcium channel (VGCC) | 5 (12.5%) |
| P/Q-type VGCC | 4 (10.0%) |
| N-type VGCC | 3 (7.5%) |
| Nicotinic ganglionic acetylcholine receptor (α3-AChR) | 4 (10.0%) |
| Voltage-gated potassium channel (VGKC) | 3 (7.50%) |
| New Purkinje cell antibody (PCA2) | 1 (2.50%) |
| Amphiphysin | 1 (2.50%) |
| Paraneoplastic antigen Ma2 (PNMA2) | 1 (2.50%) |
| Total number of patients with coexisting antibodies | 8 (20%) |
| Two autoantibodies | 5 |
| Three autoantibodies | 0 |
| Four autoantibodies | 3 |
| Total number of positive patients[a] | 22 (55%) |

[a]The total number of antibody positive patients 21 is different from the total number of antibody positives 33 because of coexisting antibodies in eight patients.

a multivariate Cox-regression model, adjusting for sex, age, cerebral/cerebellar metastasis, the presence of one or more neuronalautoantibodies, and reported neurological symptoms did not correlate with survival ($p = 0.6221$). Data are summarized in Supporting Information Table S2.

## DISCUSSION

In this study a high prevalence of neuronal autoantibodies as well as a broad range of neurological symptoms were observed among SCLC patients at time of diagnosis and prior to treatment. This data suggest the usefulness of a neurological examination with a uniform diagnostic algorithm for PNS as a routine part of an SCLC patient's care. In this study, neither the presence of one or more neuronal autoantibodies nor neurological manifestations among SCLC patients were associated with survival.

Neuronal autoantibodies are clinically used as markers of an underlying tumor in patients with PNS with variable neurological presentations depending on the affected site of the nervous system, but they can also be found in patients with various cancers without PNS.[4,5,17–21] In contrast, neuronal autoantibodies have been reported to occur very rarely in healthy controls.[4,22–25] Neuronal autoantibodies in patients with different types of cancers, including SCLC, may facilitate early diagnosis of SCLC. Neuronal antibodies have been found to be associated with cognitive impairment, and accurate diagnosis of PNS may improve therapeutic interventions.[19–21] In the present study, 70% of patients had one or more neurological symptoms recorded in their medical records, but this should be interpreted with caution as no neurological examinations were performed. Possibly, cognitive deficits and/or mild PNS manifestations were overlooked by clinicians due to more pressing clinical matters and lack of PNS awareness at the time of sampling.

Hu autoantibodies have most commonly been associated with SCLC, with a reported prevalence of 4–25% in patients with SCLC and without PNS.[4,5,7,9,26,27] When testing for multiple neuronal autoantibodies, 41–53% of SCLC patients without PNS harbored at least one neuronal autoantibody.[6,12] Consistent with these findings the frequency of Hu antibodies in the present study was 17.5% (7/40) and 55% (22/40) patients were positive for at least one neuronal autoantibody. We observed a significant diversity in the anti-neuronal antibody repertoire detected by different methodologies, possibly explained by technical differences in antigen preparation and detection.

GAD65 autoantibodies have been associated with PNS and SCLC, but have also been found in SCLC patients without neurological symptoms as well in low titers in healthy subjects.[28,29] GAD65 autoantibodies are seen in up to 80% of prediabetic and recent onset type 1 diabetes mellitus (T1DM) patients.[30] In our study, the six patients (15.0%) with GAD65 autoantibodies were not diagnosed with T1DM, suggesting that the GAD65 autoantibodies were associated with their SCLC.[31]

P/Q- and N-type VGCC autoantibodies were found in 12.5% of patients (5/40 patients). These autoantibodies are primarily specific for Lambert Eaton myasthenic syndrome, but have also been reported in patients with paraneoplastic cerebellar degeneration and SCLC.[24,32] Muscle AChR and striational autoantibodies may be present in the serum of patients with myasthenia gravis and myositis, but their presence has also been associated with underlying malignancy.[33] Autoantibodies towards striational muscle and/or AChR autoantibodies were found in in 15% of SCLC patients.

SCLC is an aggressive disease with poor prognosis. Previous studies have found that survival from SCLC is improved in patients with PNS, suggesting that the antitumor immune response may have a protective effect.[34] In these patients, the diagnosis of the neurological syndrome often antedates that of the tumor, suggesting that the immune system is able to detect the presence of SCLC at an early stage.[3] Hu autoantibodies in patients without PNS have previously been associated with longer survival of patients with SCLC,[4,6,35] whereas others report no association.[7,9,35] Increased survival time has been reported in patients with SCLC associated with CRMP5 autoantibodies compared to patients with Hu autoantibodies or both.[10] These findings suggest that the prognosis of SCLC may differ according to the type of neuronal autoantibodies. We

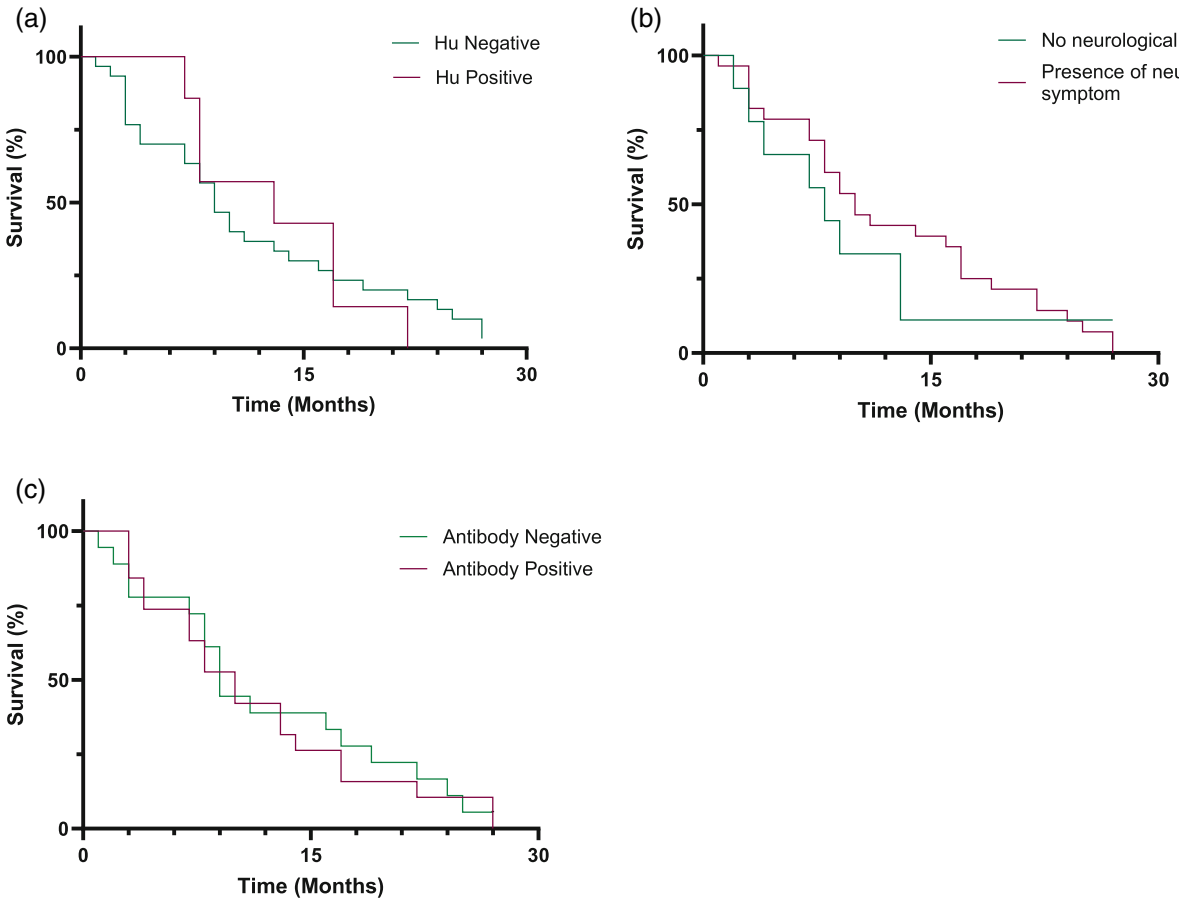


**FIGURE 1** (a) Kaplan–Meier survival curves for anti-Hu positive and anti-Hu negative small-cell lung cancer (SCLC) patients. (b) Kaplan–Meier survival curves for SCLC patients with and without reported neurological symptoms. (c) Kaplan–Meier survival curves for neuronal autoantibody-positive and -negative SCLC patients.

found that the presence of neuronal autoantibodies is not an independent predictor for survival in SCLC patients, reflecting data in the litterature.[4,7,9,35–37]

CRMP5 autoantibodies have been reported to be almost as frequently associated with PNS and SCLC as Hu autoantibodies (47%), whereas the prevalence has been reported as 5–9% in SCLC patients without PNS.[7,16,37–39] Monstad et al. reported CRMP5 antibodies in 5% of 200 patients with SCLC, but found no correlation with survival of the disease.[37] None of the SCLC antibody-positive patients had apparent PNS, but the presence of neurological symptoms was not reported. In a more recent study, Zekeridou et al. did not detect CRMP5 antibodies in 45 SCLC patients without neurological manifestations, but did detect them in six out of 71 (8.5%) SCLC patients with neurological symptoms.[7] These reports suggest that SCLC patients with neurological symptoms may have higher titers than those without. CRMP5 autoantibodies were not detected in our study.

In our study, nine (22.5%) of the SCLC patients had two or more types of autoantibodies. The most common coexisting autoantibodies were Hu, striatonal, and P/Q- and N-type VGCC (Supporting Information Table S1). In a previous study, it was reported that 87.5% of all SCLC-related PNS was associated with SOX2, Hu or P/Q-type VGCC autoantibodies compared to 28.8% in SCLC patients without PNS.[5] These findings indicate that screening for SOX2, Hu, and P/Q-type VGCC autoantibodies could capture the majority of SCLCs in patients with a related PNS, but this is insufficient to be a useful tumor marker in the absence of PNS. In contrast, another study did not find SOX2 antibodies in SCLC patients with PNS.[40] We found that 20% had P/Q-tye VGCC or Hu autoantibodies, but did not include an SOX2 autoantibody assay in our study. The frequency of SOX2 autoantibodies has been reported to be 24–30% in SCLC patients without neurological symptoms, and it should be prioritized to be included in further studies.[5,41]

Neuronal autoantibodies, observed in this and other studies, are frequently associated with SCLC patients without PNS, suggesting that these autoantibodies are not always followed by neurological autoimmunity or cellular immune responses that could improve cancer survival.[5,7,9,11,12] Autoantibodies do not always equal autoimmune disease, and typically a so-called "second hit" is crucial for the inflammatory process to proceed that allows autoantibodies to exert their pathogenic potential. In our study, these autoantibodies were present at the time of SCLC diagnosis, and as

such they are of important diagnostic value as tumor-associated autoantibodies. They might even be present before the tumor becomes symptomatic, as seen in patients with PNS, which holds promise for early tumor detection.[3]

One important strength of our analysis was that the laboratory investigations were performed blinded, to strengthen data reliability. Furthermore, this study was performed in patients with biopsy-proven SCLC at the time of diagnosis and prior to treatment. The limitations of this study include the retrospective nature and cross-sectional study design instead of a longitudinal study with multiple samples, which are necessary for further validation, including treatment effects. Furthermore, the study had a small sample size and the serum samples sent for testing at the Mayo Clinic were limited in amount, which may explain some of the discrepancies observed between the two laboratories.

## CONCLUSION

In summary, neuronal autoantibodies frequently present at the time of diagnosis, prior to treatment of SCLC and irrespective of neurological symptoms. In this admittedly small study the presence of neither neuronal autoantibodies nor neurological symptoms correlated with survival. Larger prospective studies with systematic investigation of well-characterized patient groups are needed to establish the clinical significance of the presence of neuronal autoantibodies at SCLC diagnosis.

### AUTHOR CONTRIBUTIONS

N.A.: Conceptualization. N.A., S.T.L., A.C.N., and H.T.B.: Investigation or acquisition of data. A.W.M.: Analysis of data, visualization. S.T.L., A.W.M., N.A., A.C.N.: Interpretation of data. W.M., A.C.N., and N.A.: Writing-original draft. A.W.M., S.T.L., A.C.N., H.T.B., and N.A.: Writing – review and editing. N.A.: Funding acquisition.

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### CONFLICT OF INTEREST STATEMENT

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

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## SUPPORTING INFORMATION

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

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