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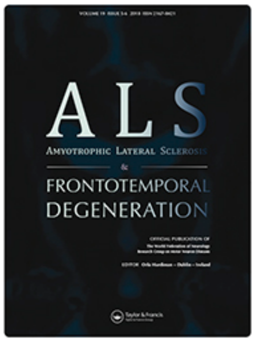

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RESEARCH ARTICLE

Respiratory measures in amyotrophic lateral sclerosis

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Abstract

Objective: Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease that causes skeletal muscle weakness, including muscles involved with respiration. Death often results from respiratory failure within 3–5 years. Monitoring respiratory status is therefore critical to ALS management, as respiratory/pulmonary function tests (PFTs) are used to make decisions including when to initiate noninvasive ventilation. Understanding the different respiratory and PFTs as they relate to disease progression and survival may help determine which tests are most suitable. *Methods*: This review describes the tests used to assess respiratory muscle and pulmonary function in patients with ALS and the correlations between different respiratory measures and clinical outcomes measures. *Results*: The most commonly used measurement, forced vital capacity (VC), has been shown to correlate with clinical milestones including survival, but also requires good motor coordination and facial strength to form a tight seal around a mouthpiece. Other tests such as slow VC, sniff inspiratory pressure, or transdiaphragmatic pressure with magnetic stimulation are also associated with distinct advantages and disadvantages. *Conclusions*: Therefore, how and when to use different tests remains unclear. Understanding how each test relates to disease progression and survival may help determine which is best suited for specific clinical decisions.

Keywords: *Non-invasive ventilation*, *amyotrophic lateral sclerosis*, *pulmonary function tests*, *slow vital capacity*

Measuring respiratory function in amyotrophic lateral sclerosis

Amyotrophic lateral sclerosis (ALS) is a progressive neuromuscular disease that causes skeletal muscle weakness, including muscles that aid in respiration, due to central and peripheral motor neuron degeneration. Respiratory failure associated with declining muscle strength is the primary cause of death in ALS patients and typically occurs within 3–5 years (1). Moreover, approximately 3–5% of ALS patients present with respiratory failure (2,3). As respiratory function is directly related to skeletal muscle function and patient survival, it is anticipated that change in respiratory performance is reflective of ALS progression.

However, measurement of respiratory function in ALS patients is complicated by several factors. For example, loss of facial muscle strength often makes it difficult for patients to form a tight lip-seal around a tube (4). Although a facemask or flanged mouthpiece may be used in these patients (5,6), there is still the potential for falsely low readings. Additionally, marked spasticity associated with concomitant upper motor neuron involvement, cognitive impairment, and difficulties coordinating

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respiratory movements also have the potential to confound respiratory measures (7). Bulbar muscle dysfunction may result in nonvolitional glottic closure during forced expiratory maximal measures, which can alter measurement accuracy (8,9). Finally, the presence of concomitant diseases such as obstructive lung disease can modify results of pulmonary function tests (PFTs) (10), making it difficult to estimate the contribution of respiratory impairment for each illness.

Obstructive pulmonary disorders such as chronic obstructive pulmonary disease (COPD) require PFTs. However, because respiratory failure in ALS is a result of neuromuscular weakness rather than diseased airways, evaluation of respiratory function in ALS requires different assessments than standard PFTs. For example, obstructive pulmonary disease is defined by a reduction in the rate of forced expiration in 1 second (FEV_1) as a function of forced vital capacity (FVC) (FEV_1/FVC) (11) and as such this measurement is included in the diagnostic criteria for COPD (12). However, patients with restrictive lung diseases such as ALS may have a normal FEV_1 (13), making FEV_1/FVC ratio of limited value in these patients.

Clinical practice guidelines recommend routine monitoring of respiratory symptoms in ALS patients because symptoms of respiratory decline may be masked by overall weakness. ALS patients frequently have severe limb weakness before the onset of respiratory involvement and therefore are unable to exert themselves to the point of dyspnea, rendering respiratory symptoms an insensitive marker for pulmonary impairment (14). This is most evident in patients with decreased mobility who may be unable to walk (15).

According to American and European guidelines (16,17), all ALS patients should have spirometry measurements performed regularly after diagnosis. Other recommendations include nocturnal pulse oximetry, arterial blood gases (ABGs), polysomnography, maximal inspiratory pressure (MIP)/maximal expiratory pressure (MEP), transdiaphragmatic pressure (P_{di}), or sniff nasal pressure (SNIP) if patients are symptomatic and FVC is >50% predicted (14). The inclusion of these tests, in addition to FVC, may assist with detecting changes in respiratory function early in the disease course (18) and lead to institution of supportive therapy with noninvasive ventilation (NIV) (16,17).

Notwithstanding, respiratory muscle strength tests and pulmonary function assessments are not routinely used (19). In a 2009 survey of consultant neurologists in the United Kingdom investigating NIV use in patients with ALS, only 38% of respondents reported assessing respiratory function initially and only 20% routinely monitored it (20). Therefore, it is clear that increased education about, and standardization of the pulmonary measures that are most useful in ALS, are needed.

Respiratory muscle and PFTs used in ALS (Table 1)

Inspiratory measures

Inspiratory measures most commonly involve measurements at the mouth (MIP) or nose (SNIP) during a sudden rapid inhalation; to obtain the maximum value, three trials are recommended for MIP (21) and up to 10 trials for SNIP (21,22). A normal value on either test requires both intact central motor processing and a normally functioning phrenic nerve. Both the diaphragm and sternocleidomastoid muscles participate in inhalation; sternocleidomastoid muscles contribute more strongly to MIP, whereas the diaphragm generates most of the force generated during SNIP (23). MIP requires patients to inhale against an occluded airway with maximum pressure generated measured by a pressure transducer. This test is simple for healthy subjects to perform, noninvasive, portable, and inexpensive (24–26), and has well-established reference values (24). However, it is effort-dependent and difficult for some patients, especially for those with facial weakness (25,26) and low values can be difficult to interpret. Patients with significant upper motor neuron burden may also find it difficult to generate a rapid and coordinated forceful inhalation. To perform a SNIP maneuver, patients inhale through their noses (sniff) with one nostril occluded with a probe connected to a pressure transducer (26). There has been uncertainty about whether the contralateral nostril should be occluded or not (27). A recent study demonstrated that SNIP performed with the contralateral nostril occluded yields higher values and these correlate more closely with MIP, demonstrating that the occluded technique is preferable (27). This test is also simple, noninvasive, portable, inexpensive (24,25), and easier for most patients with facial weakness to perform (25); however, it also requires effort (6), good central motor control, and appears to be associated with a learning effect in some patients over time (28).

P_{di}, performed by inserting balloon catheters in the stomach and mid-esophagus, and recording the pressure difference across the diaphragm while patients volitionally inspire, is the most accurate and reproducible volitional inspiratory test, but is also invasive and may not be well-tolerated (26). However, P_{di} with magnetic stimulation of the phrenic nerve (29) is a passive test of the peripheral nervous system, thus bypassing issues related to central motor control. Although this test may provide a more direct view of spinal motor neuron integrity, it has the potential to under-represent disease burden as central processes are not assessed. In addition, although this measure is not effort- or coordination-dependent, it does require equipment that is not readily available and can be technically challenging (24).

Table 1. Measures of respiratory function in ALS.

Test	Volitional (Y/N)	Invasive (Y/N)	Advantages	Disadvantages	Comments
Inspiratory					
MIP	Y	N	Simple, portable, and inexpensive; has well-established reference values	Requires effort/coordination; hard to perform with facial/bulbar weakness	
SNIP	Y	N	Simple, portable, inexpensive; easier to perform than MIP	Requires effort; is associated with learning effect; cannot be used in mechanically ventilated patients	
P_{di}	Y	Y	Accurate; the strength of the diaphragm has well-established reference values in different groups	May not be well tolerated; not readily available and not practical for serial measurements; depends on clinician experience	Considered the “gold standard” measure of diaphragmatic strength
Phrenic nerve stimulation	N	N	Not dependent on effort or coordination; simple to perform; well-tolerated with surface electrodes	Not readily available; costly; can be technically challenging; overlaps substantially between normal subjects and those with muscle weakness; can be nonspecific; gross obesity may hamper	Phrenic nerve stimulation may be electrically or magnetically and recordings invasive or noninvasive
Expiratory					
MEP	Y	N	Simple, convenient	Requires effort/coordination; hard to perform with facial/bulbar weakness	
PCF	Y	N	Simple, convenient	Requires effort/coordination	
Cough P_{ga}	Y	Y	Excellent measure of expiratory muscle strength	Invasive: balloon catheter is placed in the stomach; requires effort/coordination	
Inspiratory/expiratory					
Spirometry[a]					
Forced expiratory flow 25–75%	Y	N	Simple and easy to perform; portable	Requires effort/coordination; dependent on FVC	
FEV at timed intervals: 0.5, 1 (FEV_1), 2, and 3 seconds	Y	N	Simple and easy to perform; widely used with age- and sex-related normal values; portable	Requires effort/coordination; does not reflect disease progression as well as FVC and does not provide any useful information on a longitudinal basis in ALS	
FVC	Y	N	Simple and easy to perform; good for serial measurements over a long time to evaluate disease progression	Requires effort/coordination; may be masked/modified by comorbid diseases; not sensitive to mild/moderate weakness	In healthy subjects, supine VC is generally lower than seated VC. This difference is greater in patients with diaphragmatic weakness
MVV	Y	N	Simple and convenient	Difficult to follow over time; requires effort/coordination; not sensitive to small changes in early disease	
SVC	Y	N	Simple and easy to perform; good for serial measurements over a long time to evaluate disease progression	Requires effort/coordination although less than with FVC; not sensitive to mild/moderate weakness	

(continued)

Test	Volitional (Y/N)	Invasive (Y/N)	Advantages	Disadvantages	Comments
Measurements of gas exchange[b]	N	Depends	Useful for specific aspects of the disease (e.g. sleep disturbance/ hypoventilation)	Not sensitive early in disease course; some are invasive	
Diaphragm ultrasound	N	N	Does not require coordination or collaboration; can be repeated several times over a short period of time; uses a basically configured ultrasound system, common in many hospitals and clinics	Operator-dependent method; can be difficult to obtain in obese patients with abdominal distension or extensive dressings	

Cough P_{ga}: cough gastric pressure; FEV_1: forced expiration in 1 second; FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MVV: maximum voluntary ventilation; PCF: peak cough flow; P_{di}: transdiaphragmatic pressure; SNIP: sniff inspiratory pressure; SVC: slow vital capacity.

[a]Other measures that can be obtained with spirometry include FEV_1/FVC ratio (FEV1%), forced inspiratory flow 25–75% or 25–50%, peak expiratory flow, tidal volume, total lung capacity, diffusing capacity, static lung compliance, and mean transit time.

[b]Pulse oximetry, arterial blood gases, and transcutaneous/end tidal CO_2.

Expiratory measures

Expiratory tests including MEP, cough peak flow (CPF), peak expiratory flow (PEF), and cough gastric pressure (cough P_{ga}) require activation of diaphragm and intercostal muscles and are affected by impaired central motor control in the same manner as volitional inspiratory tests. MEP requires subjects to exhale maximally against an occluded airway as the pressure is measured (14). Similar to MIP, MEP is simple, noninvasive, and convenient (30) with five trials recommended to obtain maximum value. However, it has the same limitations as MIP (26). Thus, low MEP values may require additional assessments such as CPF and cough P_{ga} (31). CPF uses a standard peak flow meter adapted to an anesthesia face mask to measure a subject's ability to cough (26), whereas PEF is the maximum flow rate generated during a forceful exhalation from full inspiration (32,33). Cough P_{ga}, measured by passing a balloon catheter nasally to the stomach and asking subjects to cough maximally until no further increase of cough P_{ga} is observed, is considered an excellent measure of expiratory muscle strength; however, it is invasive and might not be well-tolerated (31).

Vital capacity

Spirometry, which allows for the measurement of vital capacity (VC), is the most frequently used measure in ALS clinics (26). FVC is routine in the clinical care of ALS patients (34) and is simple and easy to perform (31,35). To perform a VC maneuver, subjects must both inhale maximally and exhale either rapidly (FVC) or slowly (SVC), recruiting more muscle groups than either inspiratory or expiratory tests. However, in addition to the need for the facial muscle strength to form a tight seal around the mouthpiece and good motor control (4,6,36), VC is nonspecific in that it is reduced by both obstructive and restrictive pulmonary disease as well as by nonpulmonary factors such as obesity (35). Clinicians should also be aware of the differences between supine versus upright readings and how each reading can be helpful in monitoring ALS (26). Specifically, supine FVC is typically lower than upright FVC in both healthy subjects (up to 6.5%) and in patients with restrictive lung diseases such as ALS (up to 15%) (37–39); this suggests that supine FVC may reveal abnormalities in diaphragm functioning that upright FVC does not (40), thus allowing clinicians to initiate NIV sooner. Finally, a normal VC does not exclude the presence of muscle weakness (14).

Recently, there has been a trend in ALS trials to measure SVC rather than FVC (41). SVC has been shown to provide interchangeable information with FVC regarding respiratory function in ALS patients (42), but is easier to perform, especially in patients with significant upper motor neuron burden or with severe respiratory dysfunction. Patients with severe bulbar disease have difficulties with FVC because the upper airway collapses when maximal effort is exerted (43), and patients in general have a tendency to cough during forced exhalation (44). In addition, FVC but not SVC, has been shown to underestimate true VC in the presence of concomitant obstructive lung disease (45).

Maximum voluntary ventilation

Maximum voluntary ventilation (MVV), a measure of respiratory muscle endurance, requires patients to breathe as deeply and quickly as possible for 12 seconds (10) for at least two trials. Although it has been shown to be a sensitive measure of ALS disease progression overall (46), it is not sensitive to small changes in muscle strength early in the disease (18) and is difficult to follow over time because some patients have difficulty performing the maneuvers (14). In addition, it may also be reduced in patients with coexisting obstructive lung disease and interstitial lung diseases (10), complicating the interpretation of the results. MVV generally does not provide information not found with standard spirometry. Given the challenges of performing this test, it is not frequently used.

Other measures of pulmonary function

Measurements of gas exchange (e.g. pulse oximetry, ABGs, transcutaneous/end tidal carbon dioxide [CO_2]) are also used to monitor respiratory function in ALS patients and are recommended for patients with severe bulbar impairment (47,48). Nocturnal pulse oximetry, which involves measuring oxygen saturation throughout the night via transcutaneous finger probes (49), and ABGs, assessed from blood samples drawn from the radial artery while patients breathe room air, are used to evaluate nocturnal hypoventilation, which is an indicator for urgent evaluation for NIV or palliative care (48). Nocturnal pulse oximetry values are a prognostic indicator of survival (50); however, arterial hypoxemia occurs relatively late in hypoventilation (51). ABGs also have limited value in early disease (14) as CO_2 levels generally rise late in ALS disease course (1).

Phrenic nerve motor response assessed by percutaneous electrical stimulation at the neck is a simple, nonvolitional test that provides information about the functional preservation of the diaphragm. Motor amplitude is an independent predictor of hypoventilation (52) and survival (53), and the size of the motor response is related to respiratory symptoms in ALS (54). Non-invasive transabdominal ultrasonography allows for direct, dynamic assessment of diaphragm motion (55), and diaphragm thickness has been correlated with FVC (56).

The evaluation of respiratory muscle function in ALS is critical for the timing of respiratory interventions and for overall prognosis. However, routinely performed tests, for example, FVC, need to be specifically correlated with clinical outcomes and may be poorly informative particularly in patients with severe bulbar dysfunction or frontotemporal dementia, limiting their usefulness.

Correlations between different respiratory measures and between the measures and clinical outcomes

Overview

Given the wide range of tests available determining which respiratory function test(s) to use and when is critical, especially when making decisions regarding initiating NIV, which can increase survival (57–61) and improve quality of life (58,61,62). Optimal timing of NIV initiation remains controversial (16). Additional research may provide a more complete understanding of the relationships among the different tests as they relate to disease progression and ultimately survival and may help determine which test is best suited.

Respiratory measures and survival

Some respiratory tests have been shown to predict survival in ALS (1,60,63–70). For example, a single FVC value obtained at an initial visit was shown to serve as a clinically meaningful predictor of survival (1,65), and a retrospective analysis of placebo-treated ALS patients from two large clinical trials (EMPOWER and BENEFIT-ALS) and an ALS trial database (PRO-ACT) found that rate of decline in SVC strongly predicts the likelihood of death (63). Another study found that the decrease in the percentage of predicted values of both FVC and SVC are strong predictors of survival in patients with ALS (67). A review of results from numerous PFTs from ALS patients over 8 years found that the risk of death was significantly associated with the decline in pulmonary function, regardless of the PFT parameter (e.g. SVC, MIP, SNIP, MEP, PFC), although compared with SVC, the MIP, SNIP, and MEP values were decreased earlier in disease course, decreased more rapidly within months before death, and were affected by learning effect (66). Maximal esophageal pressure (Ppl, max), which is used to assess respiratory mechanism, has also been shown to be predictive of survival, with a Ppl, max <30 cmH_2O associated with significantly greater mortality (70). Finally, a cohort study of ALS patients at a single, tertiary care academic medical center from 1997 to 2002 found that supine FVC, and upright FVC, MIP, MEP, and P_{di}-sniff values to be significantly associated with tracheostomy-free survival, and that normal supine FVC, MIP, or MEP values were highly predictive for 1-year survival (68).

However, not all test results appear to be equally predictive of survival. Schmidt et al. (68), for instance, found no significant association between partial pressure of CO_2 and survival. This finding is supported by a retrospective study that found that although abnormal daytime partial pressure of oxygen, partial pressure of CO_2, and oxygen saturation from daytime arterial gas analyses appeared to be associated with shorter survival, this association was not statistically significant (60). In addition, two studies from Europe found that SNIP value was a good predictor of tracheostomy or death compared with FVC (71,72).

Respiratory measures and clinical outcomes/milestones

The use of respiratory measures to predict the time to ventilation and/or death has also been studied (63,69,71,73). For example, the recent retrospective analysis of placebo-treated patients from EMPOWER, BENEFIT-ALS, and PRO-ACT also found that a decline in SVC strongly predicted respiratory failure and tracheostomy (63). Additionally, a retrospective analysis of serial data of five respiratory function tests (FVC, PCF, MIP, MEP, and SNIP) in ALS patients found that although all five tests showed a descending trend during disease progression, SNIP showed the greatest decline within the latest 3 months before NIV was indicated and that PCF at referral to the first home ventilation service visit was significantly associated with NIV indication (73). A study of ALS patients enrolled at a multidisciplinary tertiary care center for motor neuron disease found that those who underwent tracheostomy or who had died presented with significant differences in SNIP ($p<0.001$) and FVC values at baseline ($p=0.023$) compared with patients who did not reach these outcomes (71). These results suggest the possibility that certain respiratory function tests might better predict survival or time to certain disability milestones in ALS patients than others. However, as analyses comparing all available tests and in all ALS stages have not been performed, one specific respiratory test with the greatest predictive value for respiratory decline and patient survival cannot be identified at this moment, indicating that additional research is warranted.

Studies examining the use of respiratory measures to predict clinical outcomes and measurements, including strength, respiratory failure, and/or the revised ALS Functional Rating Scale scores have generally focused on VC (38,42,69,74). For instance, Shefner et al. found that changes in hand-held dynamometry megascores, as measured in two double-blind, randomized, placebo-controlled phase 3 studies of ceftriaxone (75) and dexpramipexole (76), were well-correlated with SVC (74), and Pinto and de Carvalho found a weak yet significant correlation between the revised ALS Functional Rating Scale and FVC/SVC ($p<0.001$) (42).

Cross correlations of respiratory measures

Due to its extensive use in clinical trials, FVC has historically been the most commonly used comparative measure (Table 2). However, studies examining the relationships between VC and other respiratory measures have yielded variable results likely related to different methodologies used in the different studies. For example, when pulmonary function (FVC) and respiratory muscle strength (MIP, MEP, and SNIP) were assessed in ALS patients and matched healthy subjects, a positive correlation was recorded between FVC/SNIP, FVC/MIP, and FVC/MEP in ALS patients (19). However, a prospective, randomized study of 20 ALS patients found no correlation between FVC and MIP, MEP, or peak cough expiratory flows (38). A recent study of ALS patients found a strong correlation between FVC and SVC; both were also correlated with MIP and MEP (42).

Conclusions

Measuring respiratory function is clearly critical for monitoring ALS progression. Although multiple tests have been shown to predict survival, they measure different aspects of pulmonary function. In addition, although some studies have shown correlation between different measures and with clinical outcomes these conclusions are generally derived from data collected in clinical trials and, as such, from a specific population of ALS patients who are typically younger, more motivated, and without cognitive involvement.

Additional research, especially population-based respiratory studies, is needed to provide information to support decisions regarding which respiratory tests are most useful and at which stage of disease. In addition, it would be helpful to establish the relative sensitivity of each test to specific aspects of respiratory function to know if some tests are more sensitive to early changes in respiratory muscle function and whether others are more useful as disease progresses.

It is the opinion of the authors that FVC or SVC should be measured at ALS diagnosis and every 3 months thereafter. As noted, although FVC and SVC are highly correlated, there is some evidence that some patients perform one more reliably than the other. It is reasonable to measure both tests and use the one yielding a higher result with lower variability between efforts. Furthermore, it is important that whoever is administering the tests is trained and familiar with guidelines for acceptable test quality and should work to ensure high-quality

Table 2. Correlations between measures of respiratory function[a].

	Cough P_{ga}	DUS	Gas exchange	FVC/SVC	MEP	MIP	MVV	PCF	P_{di}	Phrenic	SNIP
Cough P_{ga}					0.61 (77)						
DUS			−0.4859 to −0.6618 (78)	0.3533–0.6501 (55,78)	0.471–0.510 (55)	0.442–0.453 (55)	0.315–0.377 (55)				0.427–0.504 (55)
Gas exchange		−0.4859 to −0.6618 (78)		0.5768 (79)							0.41 (80)
FVC/SVC		0.3533–0.6501 (55,78)	0.5768 (79)		0.431–0.826 (19,42,81,82)	0.446–0.736 (19,42,82,83)		–	0.71–0.91 (40,81)	0.396 (84)	0.47–0.748 (19,71,80,82)
MEP	0.61 (77)	0.471–0.510 (55)		0.431–0.826 (19,42,81,82)		0.59–0.835 (38,79,82)		0.528 (39)	0.42–0.78 (40,81)		0.612 (82)
MIP		0.442–0.453 (55)		0.446–0.736 (19,42,82,83)	0.59–0.835 (38,79,82)			0.339–0.53 (38,39)			0.646–0.94 (19,77,80,82,85)
MVV		0.315–0.377 (55)									
PCF					0.528 (39)	0.339–0.53 (38,39)					
P_{di}				0.71–0.91 (40,81)	0.42–0.78 (40,81)						0.9 (72)
Phrenic				0.396 (84)							
SNIP		0.427–0.504 (55)	0.41 (80)	0.47–0.748 (19,71,80,82)	0.612 (82)	0.646–0.94 (19,77,80,82,85)			0.9 (72)		

Cough P_{ga}: cough gastric pressure; DUS: diaphragm ultrasound; FVC: forced vital capacity; MEP: maximal expiratory pressure; MIP: maximal inspiratory pressure; MVV: maximum voluntary ventilation; PCF: peak cough flow; P_{di}: transdiaphragmatic pressure; SNIP: sniff inspiratory pressure.

[a]Only significant ($p < 0.05$) correlations included.

test results. Unreliable results can be misleading and may result in unnecessary interventions.

Declaration of interest

NL serves as a consultant/advisor for Cytokinetics, Hill-Rom, Vertex, and PMD Healthcare and lectured and participated at meetings on behalf of Cytokinetics and Hill-Rom; MEC serves as a consultant/advisor to Biogen, Biohaven, Cytokinetics, Lilly, Karyopharm, Denali, Wave, and Mitsubishi; MdC serves as a consultant/advisor for Biogen, Cytokinetics, and Kedrion, is an investigator at the Institute of Molecular Medicine, is involved with scientific studies/trials sponsored by AB Science and Cytokinetics, and serves as a board member/officer/trustee for *Amyotrophic Lateral Sclerosis & Frontotemporal Degeneration*, Clinical Neurophysiology-Neurophysiologie Clinique, and Neurology Research International; AG is an investigator for AB Sciences, Alexion, AL-S Pharma, Baxter, Bioblast, Biogen, CSL Behring, Cytokinetics, Genzyme, Grifols, Ionis, Novartis, Roche, Sanofi, and UCB; OH is an investigator for Cytokinetics and has served as a consultant for Biogen, Cytokinetics, Novartis, Roche, Merck and Mitsubishi. She is editor in chief of the journal *Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration*; HM is an advisory board member for Cytokinetics, Mitsubishi-Tanabe, and Sunovion and is an investigator for CDC, Cytokinetics, NIH, and Tsumura; JSM serves as a consultant/advisor for AB Science, Biogen, and Cytokinetics and is involved with scientific studies/trials sponsored by AB Science, Biogen, and Cytokinetics; JS is a consultant to Biogen, Inc., Cytokinetics, Inc., Mitsubishi Tanabe Pharma, Denali, Neuraltus Pharmaceuticals, Inc, and Biohaven and has received grant funding from Cytokinetics, Neuraltus, Biogen, ALS Association, Muscular Dystrophy Association, and the ALS Finding a Cure Foundation. LHvdB serves as an advisory board member for Biogen, Cytokinetics, and Orion; and JAA is a consultant/advisor for Cytokinetics and is an investigator for Neuraltus and Roche. This work was supported by Cytokinetics, Inc., which provided funding for writing and editorial support provided by Deb Stull, PhD, on behalf of Evidence Scientific Solutions, Philadelphia, PA, USA.

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