Clinical Measures of Disease Progression in Amyotrophic Lateral Sclerosis

Seward B. Rutkove

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Abstract Progressive weakness remains the clinical hallmark of amyotrophic lateral sclerosis (ALS). Accordingly, a variety of tools has been developed to capture this disease feature, including questionnaires, such as the ALS-functional rating scale, strength testing, pulmonary function tests, electrophysiologic measures, including motor unit number estimation, and imaging techniques. Despite this plethora of approaches, there is little agreement as to what measures to use in a given clinical trial or in the clinic during routine patient care. Part of the reason for this uncertainty is that ALS is a remarkably protean disease. Some individuals progress rapidly, others slowly; some patients have considerable upper motor neuron dysfunction, whereas others have little; and there is considerable variation in the sequence of body regions affected, in some the disease beginning in the bulbar musculature and in others in one arm or one leg. Here, I present a variety of basic and more complex clinical measures for potential use in therapeutic trials with the aim of offering a balanced and practical set of recommendations, as well as considerations for future studies.

Key Words Amyotrophic lateral sclerosis · functional measures · biomarkers · electrophysiology

Introduction

At first consideration, measuring the progression of amyotrophic lateral sclerosis (ALS) appears to be a straightforward problem. In contrast to nearly all other degenerative neurological and neuromuscular conditions, the progression is so rapid that

patients or caregivers can often describe progressive loss of capabilities from month to month or even week to week. In contrast, other diseases, such as inclusion body myositis or adult forms of muscular dystrophy, progress so slowly that patients have to compare carefully their functioning from year to year or decade to decade to determine whether they have actually worsened. Moreover, as ALS eventually affects all motor systems throughout the body, there are many potential regions and techniques that can be applied, from simple dynamometry, to assess appendicular function, to pulmonary function tests, to assess the muscle of respiration. One would think that with this abundance of measures, there should be little challenge to identifying sensitive measures of deterioration.

Yet despite its speed of progression and the plethora of potential assessment tools at our disposal, ALS presents unique challenges. In fact, choosing which tests to utilize when testing therapeutics in a clinical trial is not a simple matter. Most of these challenges relate to the disease's remarkably protean nature: 2 people with the same disease can have extremely different presentation and courses. Such heterogeneity adds a challenge that is not present for many other neuromuscular conditions.

The first and most obvious challenge in ALS is that the body regions affected by the disease vary from patient to patient. Clearly, someone with primary bulbar symptoms early in the course may require a different outcome measure than someone with predominantly lower extremity limb weakness. This variability creates a therapeutic testing challenge as during the 6–12 months of a typical clinical trial, 2 people could have very different areas deteriorating.

A second challenge is the variation in upper *versus* lower motor neuron involvement in different people. Certain tests may be better geared toward evaluating lower rather than upper motor neuron involvement, such as motor unit number estimation. In contrast, progressive dysarthria due to upper motor neuron loss, may be challenging to quantify.

S. B. Rutkove (✉)
Beth Israel Deaconess Medical Center, Harvard Medical School, 330
Brookline Avenue, Boston, MA 02215, USA
e-mail: srutkove@bidmc.harvard.edu

A third clear challenge is the remarkable variability in the rates of decline across patients. Some patients with ALS may live less than a year from the onset of symptoms, whereas others will live for more than a decade. This variability proves to be an especially challenging component in clinical therapeutic trial design and in determining the most appropriate outcome measures to employ.

In this review, I will work my way through from the most “subjective” measures (clinical questionnaires) to functional measures, electrophysiological tools, and, finally, muscle imaging (central nervous system imaging is discussed elsewhere in this special issue). A summary is also provided in Table 1.

Rating Scales and the ALS Functional Rating Scale-Revised

Several early efforts at developing a functional rating scale for clinical trial use were pursued in the 1970s and 1980s, including a scale described by Norris, first used in a study of

guanidine (1974) [1], and then, a decade later, the Appel Scale (1984) [2]. However, both of these early scales were complex and time consuming to administer. Thus, in the 1990s the most well-known and utilized measure of disease progression, the ALS functional rating scale (ALSFRS) was developed [3]. The scale was based on responses to 10 questions, each graded on a scale of 0 to 4, in all the different domains that might be affected by the disease, including bulbar function, respiratory function, and upper and lower limb function. The original ALSFRS was replaced with the ALSFRS-revised (ALSFRS-R) just a few years later when it was recognized that additional measures of respiratory decline were needed [4]. The new scale consists of 12 questions that total 48 points.

The validity of the scale has been shown in several studies to be high, in its being relatively sensitive to disease progression and being reliable [5–7]. The rate of deterioration also correlates with survival [8]. An obvious advantage of such a measure is that it is very quick to perform and can even be completed over the telephone or online, making it simple to obtain regular data, even

Table 1 Summary of measures to evaluate progression of amyotrophic lateral sclerosis

Category	Specific method	Advantages	Disadvantages
Clinical measures	ALSFRS-R	<ul style="list-style-type: none"> • Easy to employ • Has been shown to correlate to survival and is robust in several trials 	<ul style="list-style-type: none"> • Relatively insensitive to progression over short periods of time • Affected by mood/effort
	Strength testing	<ul style="list-style-type: none"> • Universally available • Can be used to evaluate limbs effectively 	<ul style="list-style-type: none"> • Affected by mood/effort • Reliability uncertain • Insensitive early and late in disease • Bulbar testing less clear
	FVC	<ul style="list-style-type: none"> • Repeatable and quantifies the health of the most critical activity for sustaining life 	<ul style="list-style-type: none"> • Only evaluates 1 region • May not show changes early in disease • Later in disease it may be affected by bulbar weakness and poor lip closure
	Bulbar-specific measures	<ul style="list-style-type: none"> • Easy to perform 	<ul style="list-style-type: none"> • Not as well studied as longitudinal metrics
Electrophysiological	CMAP/NI	<ul style="list-style-type: none"> • Easy to obtain • May be very sensitive to decline 	<ul style="list-style-type: none"> • Has not been employed extensively • Limited to distal muscles
	MUNE	<ul style="list-style-type: none"> • Provides approximation of actual motor neuron number and rate of actual motor neuron loss 	<ul style="list-style-type: none"> • Technically challenging • Potentially insensitive early in disease • Limited to distal muscles
	EIM	<ul style="list-style-type: none"> • Easy to utilize • Can assess many muscles 	<ul style="list-style-type: none"> • Mechanisms of change over time not intuitive • Limited studies evaluating its potential at this time
	Excitability testing	<ul style="list-style-type: none"> • Potentially useful for early diagnosis • Some measures correlate with survival 	<ul style="list-style-type: none"> • Limited data on progression • Requires specialized equipment • May be challenging to use in multicentered studies
Muscle imaging (MRI and US)		<ul style="list-style-type: none"> • Relatively easy to use, (especially for US) • Conceptually straightforward 	<ul style="list-style-type: none"> • Studies have suggested that they are insensitive to change
Serum and CSF markers		<ul style="list-style-type: none"> • If biomarkers can be identified in serum, high ease of use • Correlate to rate of progression 	<ul style="list-style-type: none"> • None currently effective at showing longitudinal change
Survival		<ul style="list-style-type: none"> • The ultimate outcome of clinical value 	<ul style="list-style-type: none"> • Not really a biomarker, but rather an endpoint • Can be impacted by factors unrelated to the rate of disease progression

ALSFRS-R = Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised; FVC = forced vital capacity; CMAP/NI = compound motor action potential/neurophysiological index; MUNE = motor unit number estimate; EIM = electrical impedance myography; MRI = magnetic resonance imaging; US = ultrasound; CSF = cerebrospinal fluid

if the patient is unable to return to the clinic for evaluation [5]. It also ensures that all realms of potential disease progression are being captured. On average, patients lose about 1 point per month as the disease progresses [9, 10]; thus, it offers a relatively simple and easily applied measure of progression. The US Food and Drug Administration (FDA) also approved incorporation of the questionnaire as an outcome measure (in conjunction with survival via joint-rank study design) in a large trial of dexamipexole in ALS [10]. Thus, the scale's value has recently taken on added significance.

Despite its clear benefits, the ALSFRS-R has a number of limitations, which should be highlighted. First, it is not especially sensitive to disease progression, and in those patients who are progressing relatively slowly, capturing any change may require several months. Accordingly, phase 3 clinical trials, such as the recent dexamipexole study [10], may need to be relatively long (i.e., 1 year) in order to identify significant disease progression. Second, it is by its nature a subjective test and thus it has the potential to be affected by mood, potential unblinding, and therapeutic optimism [11]. For example, patients in a drug study may report less progression than those not on an experimental drug simply because they believe the drug might be working. Indeed, a natural history study evaluating ALSFRS-R along with other measures actually showed the ALSFRS-R to be more sensitive to progression than had been reported in other studies [12], perhaps because there was no subjective bias toward a drug having a therapeutic effect. Another limitation of the ALSFRS-R is that it may be affected by the degree of social support and the presence of depression [13]. Finally, a recent Rasch analysis found that the test failed rigorous measurement standards, with the authors of this analysis calling for its revision [14].

The ALSFRS-R is not the only questionnaire or scale in use to evaluate disease status in the ALS. Self-reported outcomes have been studied, including a recent investigation that successfully used the “patientslikeme” website (www.patientslikeme.com) to prove lithium's ineffectiveness in the disease [15]. However, such an approach could not substitute for a placebo-controlled study to achieve FDA approval. Similarly, quality-of-life measures could also be valuable [16, 17], but have not garnered general acceptance as a clinical trials metric. The undeniable value of such scales and questionnaires is that they are incredibly cost-effective, can be done from a distance, can be comprehensive in their assessments, and can capture an element of personal well-being not possible with all of the other approaches to be discussed next.

Strength Measurements, Including Handheld Dynamometry, Maximal Voluntary Isometric Contraction Testing, and Manual Muscle Testing

As weakness is the major clinical feature of ALS, the quantification of strength in a patient over time would appear to be a

robust and sensitive approach for assessing disease progression. The most obvious and basic measure is standard manual muscle testing [18], with grading of muscle strength in each individual limb on a 0–5-point Medical Research Council scale [19]. Whereas this approach works, is generally considered reliable [20, 21], and was used for a number of ALS studies, even as recently as 2007 [22], it has mostly fallen out of favor. This is true because of the technique's inability to detect subtle degrees of weakness and because it is affected by examiner strength [23]. For these reasons, approaches for improving the quantification of weakness have represented a longstanding effort.

The first major innovation in this regard was the development of the Tufts Quantitative Neurological Examination. This test basically consisted of a measure of maximal voluntary isometric contraction testing using an electronic strain gauge in conjunction with pulmonary and bulbar measures [24]. The isometric strength aspect of this work was further improved by the creation of a “megascor,” or a z-averaged score across a predefined set of muscles [25]. Such maximal isometric voluntary contraction was incorporated into a variety of trials in the 1990s and early 2000s [9, 26–28]. While providing good data, the methodology was very challenging to institute, as it required a large plinth upon which the debilitated patient needed to be placed; this became especially challenging as patients became too weak to transfer. Moreover, testing required highly trained personnel not only in using the apparatus effectively, but also in ensuring that the patient was not moving during the procedure. It was also limited to a relatively small set of muscles and one study even suggested that it performed no better than manual muscle testing [29]. Given that the costs of the systems were relatively high (approximately \$10,000) and the entire system quite bulky, their use fell out of favor in most clinical trials by the mid-2000s.

A newer approach to performing such isometric testing has recently been introduced using the ATLIS system [30]. Based on similar principles, it is also a form of isometric contraction testing, but one that is considerably easier to employ as the system is smaller and the outcomes easier to obtain. Several upper and lower extremity muscle groups can be measured using this approach and a normalized score (akin to those used in pulmonary function testing) is obtained for easier data interpretation [31]. This promising effort continues to be under study at this time.

Handheld dynamometry (also called quantitative myometry) is now probably the most commonly used methodology for assessment of muscle strength in clinical trials. Its use was first suggested as an alternative to the more complex maximal isometric contraction systems in 1999 [32]. In handheld dynamometry, the examiner holds a small-strain gauge that the patient pushes against using a variety of muscle groups, and a force measurement is obtained. The concept dates back, remarkably, to 1763, when the The Graham-

Desaguliers force dynamometer was first introduced [33]. The test is usually repeated 2–3 times to ensure consistency of the data for a given muscle; then the examiner moves on to the next muscle. This approach is appealing as it requires no bulky equipment, relatively limited training (mostly geared toward ensuring the patient is positioned appropriately for each type of contraction being performed), and can be performed on a variety of muscle groups. However, a major limitation of handheld dynamometry, which also holds true with simple manual muscle testing, is that it is challenging to measure people who are relatively strong, as it is difficult to create sufficient force to overcome their contraction (a necessity to achieve good quality data). Indeed, the testing can become quite uncomfortable in patients who are not clinically weak in a given muscle group; the end result will be that the examiner's own strength rather than the patient's is being measured, and the data may be entirely unreliable [34]. In patients who are very weak reliability also may be challenging [35]. Thus, in a given patient, there is only a limited range over which the technique is reliable—namely those muscles that are mildly-to-moderately weak. And as even in the best of circumstances there is considerable noise in each measurement, it does require that multiple muscles be measured and averaged to ensure consistent data. Despite these limitations, given its ease of performance, handheld dynamometry is likely to still be the preferred method of strength examination in clinical trials for the foreseeable future.

All forms of strength testing have some limitations worth considering. First, they are effort and mood dependent, and a depressed patient may have difficulty in performing at his/her peak performance. Moreover, a patient with any cognitive issues, including frontotemporal dementia, may not be able to follow commands effectively. Second, the metrics cannot evaluate bulbar or other cranial nerve weakness effectively. Third, increased tone associated with upper motor neuron degeneration may make it difficult to obtain accurate strength measurements. Finally, as ALS often progresses most conspicuously in a subset of limbs in a given patient during a clinical trial, the data from the nonprogressing limbs may only add noise to the measurement. Performing strength testing on just a subset of muscles in just 1 or 2 limbs may be an approach to correcting this issue, but has not been studied.

Respiratory Function

As respiratory dysfunction remains the usual cause of death in ALS, measurement and quantification of respiratory function in these patients is, on the face of it, one of the most important measures to obtain [36, 37]. As respiratory dysfunction is mainly caused by muscle weakness and produces a restrictive pattern, one of the most utilized measures in clinical trials is the forced vital capacity (FVC) [22, 27, 38]. FVC essentially measures the full extent of a breath capable by a patient,

excluding the dead space of the lung and upper airways. Other measures of pulmonary function in ALS have also been studied, including maximal voluntary inspiratory or expiratory pressures, but it is not clear that these offer any advantage over the FVC [39].

A major challenge to all forms of pulmonary testing is that the test becomes increasingly unreliable if there is bulbar weakness and the patient cannot achieve a good mouth seal around the device. In addition, FVC testing is generally unhelpful in patients with early disease as the values may be relatively insensitive to change early on.

Measures of Bulbar Dysfunction

Clinical measures of bulbar dysfunction represent a separate category of testing procedures. But as much of the effort in characterizing disease progression in ALS is focused on progressive weakness of the limbs, the bulbar-specific measures continue to be relatively limited in number. First, the ALSFRS-R bulbar subscore has been utilized as a simple test [4], but only contains 2 items, so is fairly limited in its granularity. In lieu of this rough assessment, a battery of tasks has been described as useful in assessing ALS [40, 41], including the Iowa Oral Performance Instrument measurements of tongue, lip, and cheek strength [42]. The Sydney Swallow Questionnaire may also be useful in this regard [43]. Other approaches, including magnetic resonance imaging (MRI), electrical impedance myography, and quantification of standard swallowing studies are also being explored as potential markers of disease status, but will not be discussed here further.

Peripheral and Central Electrophysiological Biomarkers

As nerve conduction studies and needle electromyography remain the main methods for confirming a diagnosis of ALS, it is perhaps not surprising that electrophysiologic methods also provide excellent approaches for monitoring clinical disease progression. However, needle electromyography, which is so critical in helping establish the diagnosis of ALS, is not very useful in identifying disease progression. This is because the technique is generally employed in a subjective fashion and quantitative methods are time-consuming to perform and require considerable expertise [44].

Compound Motor Action Potential and the Neurophysiological Index

The compound motor action potential (CMAP) is generated by the near-simultaneous depolarization of all muscle fibers in a muscle (or group of muscles) via supramaximal stimulation of a single nerve [45]. The CMAP is a standard fixture of nerve conduction studies, with reductions in amplitude

usually corresponding to motor axon-loss neuronal pathology. Despite this, most ALS studies have not evaluated the use of the CMAP as a measure of disease progression; rather, they have focused on motor unit number estimate (MUNE). However, there are considerable CMAP data as a CMAP is needed in order to calculate the MUNE. And, in fact, the median and ulnar CMAPs actually show substantial decline over time in most patients with ALS, as demonstrated by 2 recent MUNE-focused studies [46, 47]. The biggest challenge to the CMAP is its reliability, which is sensitively dependent on electrode positioning, limb and hand positioning, and temperature. Not surprisingly several studies that have looked at CMAP reliability have shown mixed results [48, 49]. However, by carefully trying to maximize the CMAP value and being consistent about electrode placement and limb position, it may be possible to more effectively use the CMAP as a primary marker of disease progression.

Another approach that incorporates the CMAP was first suggested by Swash and de Carvalho in 2004 [50]. Termed the “neurophysiological index” (NI), it is defined as $NI = (\text{ulnar CMAP amplitude} / \text{distal motor latency}) \times \text{F wave persistence}$ [50]. By dividing the CMAP by the distal motor latency and then multiplying by the F wave persistence (the former gradually increasing in progressive disease and the latter gradually decreasing), the premise was that the NI would be a sensitive marker of disease progression. As these data are easily obtainable with a standard nerve conduction system and only require a few more stimuli beyond a typical nerve conduction study, it is easy to apply. Unfortunately, there has been relatively little follow-up research of this suggested biomarker. However, a recent study has shown that it is very sensitive to disease progression over a several-month period [51], but it also showed its sensitivity was mainly due to the CMAP amplitude rather than the F wave persistence or the distal motor latency. In addition, there has been no longer-term study and its test–retest repeatability is unknown. Nonetheless, I believe that further, more carefully performed studies of both CMAP and NI are warranted.

MUNE

MUNE remains one of the most theoretically compelling electrophysiologic measures of disease status in ALS. In MUNE, an attempt is made to estimate the number of motor neurons innervating a muscle or muscle group [52]. This is achieved by first obtaining a CMAP using standard supramaximal nerve stimulation usually from the median or ulnar nerves. Then, using one of several techniques, an effort is made to obtain the average size of the single motor unit potentials (SMUPs) that contribute to the CMAP. The most obvious and first-described approach is by incremental stimulation [52], in which the stimulation intensity over the nerve is gradually increased from subthreshold values and the size of the steps in amplitude with successive elevations in stimulation

is noted. The average size of a step is then measured and that size divided into the CMAP to obtain the MUNE. Another approach is what has been called the multipoint stimulation technique in which the nerve is stimulated at different points along the length of the nerve at very low levels with an effort to obtain different low threshold SMUPs and measuring the individual amplitude of each [53]. After collecting data and averaging 10 such SMUPs, the values are divided into the CMAP to obtain the MUNE. Other methods incorporate various versions of these basic approaches, some incorporating the use of F waves or needle recording of the action potential [54]. One other, more recent, version combines both multipoint stimulation and incremental techniques [46]. Another variation, termed MUNIX, has been developed in which, after obtaining the CMAP, contraction of the muscle is made at various intensity levels and the surface interference pattern measured and divided into the CMAP value [55].

While MUNE is conceptually appealing, it is challenging to implement as it requires considerable training and can be time consuming to perform well, with a great deal of real-time decision-making (although this remains less of an issue with MUNIX). With practice it does become fairly easy to perform, but to the uninitiated the procedure can seem daunting. While studies have suggested good repeatability across a group of individuals [56], test–retest variation for individual data can be higher, with variation of up to 20 % [57]. Indeed, one of the potential advantages of MUNE over CMAP is that it is capable of capturing disease progression very early in the disease course, presumably when reinnervation may still be preserving CMAP size but the MUNE is already decreasing [58]. Yet this is offset by the fact that repeatability of MUNE is usually worst early in the disease and improves as the disease reaches end stage and there are fewer, larger SMUPs. Nonetheless, MUNE has been used in several clinical studies and remains a topic of investigation in ALS and in other motor neuron disorders, including spinal muscular atrophy [54].

The limitations to all electrophysiological methods that rely on nerve conduction include the fact that they are limited to nerves that can be effectively stimulated and muscles that can be effectively measured. Most methods have been used only the median and ulnar nerves, but there is no reason that peroneal or tibial motor conduction studies could not also be performed and evaluated. However, superimposed compression neuropathies, common in ALS, could also affect the accuracy of these measures.

Electrical Impedance Myography

In electrical impedance myography (EIM), a minute electrical current is applied across electrodes placed over a muscle or muscle group of interest and the consequent surface voltages measured [59]. These surface voltages reflect the conductivity of the underlying tissue, as well as the size, number, and health

of the underlying muscle fibers. Thus, the method is not truly electrophysiological, in the sense that it is not producing excitation of muscle fibers, but is rather electromorphological. Studies of EIM to date have shown substantial sensitivity to ALS disease status and rate of progression, and high reliability [60–62]. Animal work has also strongly supported this concept [63, 64]. Another advantage of the technique is that it is easy to perform quickly and requires minimal training. And, unlike nerve conduction studies, it can be readily applied to most superficial muscles, including proximal and even bulbar muscles (e.g., the tongue is currently being studied). A recent study has also shown that it correlates to strength testing in patients with ALS [65]. One simple way of conceiving EIM is that it provides data that can be considered a surrogate for CMAP, but, unlike CMAP, does not require nerve stimulation to obtain, and thus can be performed on any sufficiently large superficial muscle.

Thus, while EIM remains promising, it has only been used to a limited extent and has been mostly studied by just a single laboratory (under my direction). Therefore, additional research incorporating the technology into clinical trials is needed to confirm its long-term value in tracking ALS progression.

Peripheral Nerve Excitability Testing

Excitability testing of peripheral nerves has recently garnered increased attention as studies have demonstrated alterations of excitability of motor neurons in ALS [66, 67]. In addition, 1 study showed that the degree of excitability at baseline predicted long-term survival in humans, with higher levels of excitability predicting shorter survival [68]. Whereas these data appear promising, the value of excitability metrics for serving as markers of disease progression still requires further study.

Transcranial Magnetic Stimulation Measures

Nearly all the measures discussed in this review have focused on the lower motor neuron in the anterior horn of the spinal cord. And, unfortunately, methods for assessing upper motor neuron dysfunction in the disease are decidedly limited. However, in the early 1990s, several studies showed that cortical excitability was altered in ALS by the use of transcranial magnetic stimulation (TMS) [69–71]. Many studies since then have been pursued, and a number of measures appear to be altered in ALS, including motor threshold (generally reduced early in the disease, supporting the presence of increased excitability), motor-evoked potential (generally also increased early in the disease), central motor conduction time (generally prolonged in the disease), and cortical silent period (reduced in the disease) [72]. While such differences in ALS are identifiable, how well each tracks disease progression is less well

studied. Whereas 1 investigation has suggested that TMS could serve as a biomarker to evaluate disease progression [73], another failed to show a clear longitudinal change in TMS parameters [74].

Peripheral Nerve and Muscle Imaging with Ultrasound and MRI

As motor neuron loss and muscle atrophy are primary features of ALS, it is not surprising that radiological techniques will identify reductions in nerve and muscle size. In the case of ultrasound, cross-sectional changes are readily observable [75]. Moreover, ultrasound studies have demonstrated the presence of fasciculations [76, 77], and even fibrillations [78, 79]. And while it has the potential to serve as useful measure to assist with disease diagnosis, its value as a biomarker of disease progression is less certain. One study suggested that it was not sufficiently sensitive to capture disease progression, at least by measuring muscle thickness [80]. Further work in this field, however, is clearly needed.

Most MRI studies in ALS have focused on imaging the brain and spinal cord and not muscle, and this topic is discussed in a separate article included in this issue. Given the cost and other challenges of using MRI (including the fact that patients generally must remain supine during a study, a posture that becomes increasingly challenging with progressive disease) it has not been used routinely to assess muscle condition. Nonetheless, studies have shown increased T2 signal in muscle [81], and 1 study has shown progressive loss of muscle volume in ALS mice [82]. However, like ultrasound, its sensitivity to progression in the human disease again appears dubious in that subclinical disease progression was not identifiable [83].

Serum and Cerebrospinal Fluid Biomarkers

The search for “wet” biomarkers continues to be a major effort by a number of laboratories. A number of easily measured and obtainable tests such as creatine kinase [84], uric acid [85], and serum cholesterol [86] have been studied, but none have been identified as effective biomarkers of disease progression. Some, however, such as uric acid [85], and triglyceride and cholesterol levels [86, 87], do correlate to survival.

In addition to these readily obtained laboratory tests, a variety of disease-specific biomarkers have been sought including neurofilament heavy subunit, both in serum and cerebrospinal fluid (CSF) [88, 89], and CSF cystatin C [90, 91]. Cystatin C levels have also been found to correlate with the rate of disease progression and are predictive of survival [90]. While these proteins are increased in ALS patients, neither has yet been shown to be better than other established markers, such as the ALSFRS-R or electrophysiological measures for following disease progression. Still, much research is ongoing

in the hope of identifying an easily obtainable biomarker from serum or CSF that can be used to quantify disease progression and the impact of an effective therapy.

Survival

Strictly speaking, of course, the length of survival from the time of symptom onset cannot be considered a clinical marker of disease progression. Yet the 1 drug that has been approved for use to slow the progression of ALS, riluzole, was proven not with any of the approaches discussed above, but rather survival [92]. Moreover, the recent trial of dexamipexole in ALS utilized a rank combination of ALSFRS-R and survival as the trial's outcome measures [10]. However, there are problems using survival as an outcome measure. First, it requires that the study be sufficiently long and large enough to have a substantial number of subjects die or require full ventilation during the study period. Second, the timing of death/full ventilatory support may be affected by a variety of factors ranging from the use of supportive therapies, including bilevel positive airway pressure and gastrostomy tubes, to the patient's socioeconomic status [93]. Thus, survival does not represent a true gold standard as it also can be influenced by a variety of outside factors.

Conclusions: Taking Stock and Future Directions

So where are we when it comes to monitoring disease progression in ALS clinical trials? It appears that while there is a plethora of potential tools, there continues to be debate as to which is most promising. Clinical measures that are closely tied to patient health status, including the ALSFRS-R and handheld dynamometry, are certainly useful. However, in my opinion, neurophysiologic measures may offer the best compromise, capturing an outcome closely related to function but that is effort independent. But given ALS's variable involvement of the central *versus* peripheral nervous system and the limb most affected, applying these in a consistent fashion still offers unique challenges.

The US FDA has defined a program of biomarker qualification, in which biomarkers can be developed as tools to assist in drug testing and, ultimately, drug approval [94]. The idea is that such measures, which are defined as "pharmacodynamic biomarkers" and cannot be influenced by patient effort or mood, can make clinical trials more efficient than by employing standard measures. And if one of these markers is proven out sufficiently, it can achieve the designation of being a "surrogate marker", in which it can be used in lieu of standard clinical outcomes in a phase 3 clinical trial to gain regulatory approval. While all of the nonclinical biomarkers discussed here are far from reaching surrogate status, it is

worth considering pursuit of this designation as a worthwhile effort.

Another challenge to consider is the application of localized biomarkers depending on the therapy offered. For example, in studies of stem cell transplantation, utilizing whole-body measures of disease progression may be problematical. If injection of stem cells into the cervical spine is employed specifically with the goal of improving pulmonary function, measuring the FVC is probably more important than evaluating ALSFRS-R or strength. Parallel arguments can be made for the lumbar injection of cells, where directed measurements of the lower limbs are needed. Indeed, one completed stem cell study relied on a combination of localized functional and physiological measures to achieve these goals [95].

Finally, just as we focus on identifying new therapies to halt or reverse the progress of the disease, it is also important for us to consider these studies as opportunities to test and improve biomarkers on an ongoing basis. As noted, the ALSFRS-R, while useful, could likely be improved to yield a tool with improved sensitivity and greater reliability. Similarly, individual or combinations of electrophysiological markers may offer greater value than the ones tested to date. It is only through the concurrent testing of biomarkers along with therapies that we can hope to identify an optimized set of tools for the evaluation of ALS progression and, ultimately, the effect of therapy.

Required Author Forms [Disclosure forms](#) provided by the authors are available with the online version of this article.

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