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REVIEW ARTICLE

The future of ALS diagnosis and staging: where do we go from here?

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Abstract

Amyotrophic lateral sclerosis (ALS) is a rare, progressive multi-system neurodegenerative disorder. Its clinical presentation varies considerably leading to delays in diagnosis, which has dire consequences in a disease where early intervention is key to optimize outcomes and limit care giver burden. There are a range of diagnostic criteria available to aid ALS diagnosis, as well staging methods to assess disease progression. However, they all suffer from inter-rater variability, complexity, and confusion in use. Such difficulties, when medical appointment times are limited and becoming more virtually based, have the potential to amplify uncertainty and errors in ALS diagnosis and prognosis. This review provides a clinical overview of the best way to balance the needs of evidence-based medicine and the patient. We focus on ALS diagnostic criteria and staging systems currently in use in clinical practice and explore factors that could enhance diagnostic efficiency and assessment of disease progression.

Keywords: *ALS, diagnosis, prognosis, clinical stage, clinical trials*

Introduction

Amyotrophic lateral sclerosis (ALS) is a rare, progressive neurological disorder that primarily affects the motor neurons in the brain and spinal cord resulting in muscle weakness and loss of muscle control (1). The pathology underlying ALS remains unclear, but it is likely that multiple factors contribute to the development and progression of the disease (Figure 1). The worldwide incidence and prevalence of ALS ranges between 0.6–3.8 cases and 4.1–8.4 cases per 100,000 people, per year respectively (2). The onset of symptoms usually occurs between the ages of 50–65 years (3), and median survival from symptom onset is 2–3 years (4). As ALS is a multi-system neurodegenerative disorder, there is considerable variability in its clinical presentation, (5), which can overlap with other neurological disorders (6). Such variability causes delays in diagnosis (7), which has dire consequences in a disease where early intervention is key to optimize outcomes and limit care giver burden (8,9). Indeed, it has been shown that timely treatment with one of the three approved

disease-modifying medications, namely riluzole, edaravone and sodium phenylbutyrate (PB) and taurursodiol (also known as ursodoxicoltaurine; TURSO), can slow disease progression (10,11), and prolong survival duration (12). Given the different modes of actions, the combination of these therapies could have additive benefit, but this is yet to be proven. Noninvasive ventilation in subjects with moderate respiratory failure (13), gastrostomy feeding when dysphagia is present (14), and attendance at an ALS multidisciplinary clinic (15–17), also confer survival benefits. Optimizing the combination of these medical treatments to give the greatest survival benefit would be key for patients (18). Alongside managing disease progression and symptom control through palliative care (19).

Diagnosis of ALS has largely remained unchanged over the last decade (20). Biomarkers have not been incorporated into routine clinical care despite evidence that elevation of neurofilament levels in both plasma (NfL) and cerebrospinal fluid (pNfH) are confirmatory of the
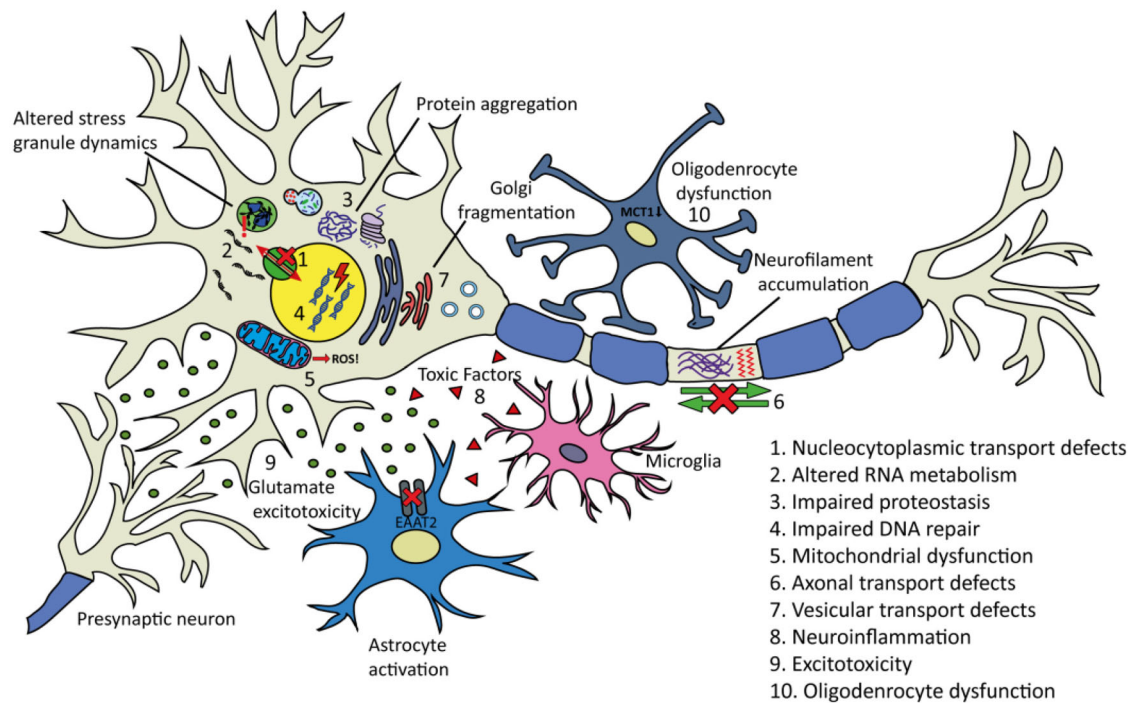
Figure 1. Proposed mechanisms underlying amyotrophic lateral sclerosis. (1) Nucleocytoplasmic transport defects including altered transport of RNA molecules and RNA-binding proteins. (2) Altered RNA metabolism. RNA-binding proteins including TDP-43 or FUS may become mislocalized in the cytoplasm leading to altered transcription and splicing. Stress granule dynamics are also affected. (3) Proteostasis is impaired with aggregating proteins including TDP-43 accumulating in the cytoplasm. There is evidence that the two main protein clearance pathways, autophagy and the UPS may be involved. (4) Impaired DNA repair: several ALS-linked genes including FUS, TARDBP, TAF15, SETX, and EWSR1 are involved in DNA repair. (5) Mitochondrial dysfunction resulting in the increased formation of reactive oxygen species (ROS) has been proposed as an initiating factor in ALS. Several ALS-linked proteins including SOD1, TDP-43, and FUS interact with mitochondria. (6) Axonal transport defects have been implicated in ALS pathogenesis. Neuropathological evidence has shown evidence of this including neurofilament accumulation and cytoskeletal disorganization. (7) Several ALS-linked genes including OPTN, VAPB, CHMP2B, and UNC13A are involved in vesicular transport. Impaired vesicular trafficking can lead to protein accumulation and golgi fragmentation which has been observed in ALS patients. (8) Neuroinflammation: the secretion of inflammatory proteins by activated microglia leads to the potentially neurotoxic activation of astrocytes, which may contribute to the death of neurons and oligodendrocytes. (9) Excitotoxicity: glutamate receptor overstimulation has been proposed to occur via several mechanisms including increased synaptic glutamate release, alterations to AMPA receptors and reduced clearance of glutamate by astrocytes. (10) Oligodendrocyte dysfunction may lead to reduced support for neurons. Changes in lactate production and transport via MCT1 have been implicated. Taken from Mejzini et al. (37). Copyright © Mejzini, Flynn, Pitout, Fletcher, Wilton and Akkari. This is an open-access article distributed under the terms of the Creative Commons Attribution License (CC BY).
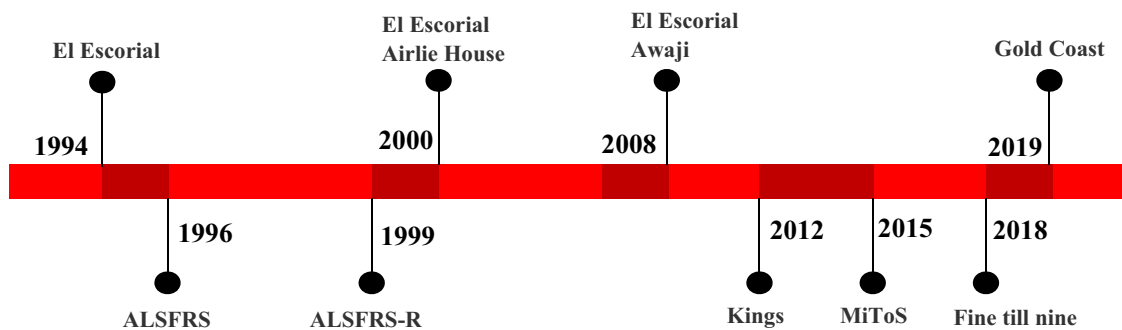
Figure 2. Timeline of amyotrophic lateral sclerosis diagnostic criteria and prognosis staging. Top timeline shows diagnostic criteria; bottom timeline shows prognostic staging. ALSFRS: ALS Functional Rating Scale; ALSFRS-R: ALS Functional Rating Scale-Revised; MiToS: Milano-Torino functional staging.

diagnosis of ALS and give an indication of the speed of progression of the disease (21). Diagnosis of ALS is based primarily on clinical signs, symptoms, and exclusion of other causes of progressive upper motor neuron (UMN) and lower motor neuron (LMN) dysfunction (22). A range of diagnostic criteria have been developed over the years (Figure 2). However, they each have different levels of certainty leading to inter-rater variability, confusion, and errors in use (23). ALS staging methods have also been developed (Figure 2) to aid assessment of disease progression. These

systems vary in the number of stages used, as well as the assessment of functional ability or clinical stage of disease (22). Such complexity, when medical appointment times are limited and becoming more virtually based, has the potential to amplify errors in ALS diagnosis and prognosis. This review focuses on ALS diagnostic criteria and staging systems currently in use in clinical practice and explores factors that could enhance diagnostic efficiency and assessment of disease progression.

A brief history of diagnosis in amyotrophic lateral sclerosis

The variability in the course of ALS and the lack of diagnostic biomarkers make absolute diagnosis difficult, in clinical practice, research and clinical trial settings. Whilst the diagnosis of ALS may be straightforward for ALS specialists, it can be delayed in the medical community outside of specialist centers, as well as in cases with atypical clinical picture or slow progression (24). Over the course of the past few decades, several diagnostic criteria have been proposed to aid clinical diagnoses, patient management and research (Figure 2). The El Escorial criteria, (25), have been widely accepted and undergone revisions to increase sensitivity (26,27). The criteria provide a set of guidelines based on patterns of disease spread to diagnose - clinically definite ALS, clinically probable ALS, clinically probable ALS laboratory supported, and clinically possible ALS. Clinically suspected ALS was removed during the first round of revisions to enhance sensitivity of diagnosis (26), with clinically probable ALS laboratory supported removed in the second round of revisions to further enhance sensitivity (27). Although studies reported that the revisions increased sensitivity of the El Escorial criteria (28), the fact remained that applying the criteria in clinical practice (18,29,30) or trials (10,12,31) was not simple. Test-retest reliability of diagnoses based on the El Escorial criteria have been shown to be relatively low and the criteria are often mis-interpreted by patients and clinicians as the likelihood of ALS rather than the stratification of diagnosis (28). This, in turn causes significant delays in providing the diagnosis to the patient and delays referral (32), meaning patients miss out on therapy and access to clinical trials. Several other limitations have been identified in the El Escorial criteria (Table 1), which led to the development of new ALS diagnosis criteria called the Gold Coast criteria. The Gold Coast criteria aimed to simplify ALS diagnosis while considering cognitive and behavioral impairments that play a critical part of the disease course (33); and progressive muscular atrophy (PMA), a highly specific form of ALS affecting only the lower motor neurons (34).

There are several advantages to the Gold Coast criteria (Table 1), such as reduced disease categories for diagnosis and increased sensitivity (requires assessment in clinical trials). Indeed, these criteria represent the minimum necessary abnormalities to arrive at a diagnosis of ALS (33). Despite the advancements in the genetics of ALS, no specific mutation or biomarker was included in the Gold Coast criteria (33).

A brief history of prognosis in amyotrophic lateral sclerosis

To improve the clinician ability to establish the severity of ALS, several scoring and staging systems have been developed. In clinical practice, most clinicians rely on the ALS Functional Rating Scale-Revised (ALSFRS-R) (35), a scoring system that monitors rate of disease progression. However, limitations of the ALSFRS-R have been noted (Table 2), e.g. it does not provide information of the stage of the disease nor the expected speed of progression (20). Staging systems can help identify where patients are in their disease course. The most widely accepted are the Milano-Torino (MiToS) functional staging (39) and the King's clinical staging (38). The MiToS system uses six stages (0 = normal function; 5 = death) and assesses functional burden of the disease using scores from the ALSFRS-R (35). Even though the ALSFRS-R has been shown to have a floor effect and lack sensitivity in later stages of ALS disease course (7), these limitations are removed when using MiToS, as it combines different parts of the ALSFRS-R to assess functional burden (22). The King's system uses five stages (1 = symptom onset; 5 = death) and assesses the clinical or anatomical spread of the disease. The King's system is not based on the ALSFRS-R scores. Studies have shown that the MiToS and King's staging systems are complimentary and should be used together as they summarize different aspects of disease information (22). Presently, MiToS and King's staging systems are not utilized as primary outcomes in clinical research. In 2018, an empirical ALS staging approach was developed based on how many of the patients ALSFRS-R sub scores were 9 or less (normal = 12) (40). This staging system is called "fine til 9" and consists of 5 stages (0 = 0 ALSFRS-R sub scores ≤9; 4 = 4 ALSFRS-R sub scores ≤9). It has been shown to have some advantages to other staging systems (Table 2), e.g. it is more sensitive to disease progression than MiToS and it can be easily applied to retrospective data (40). However, as fine til 9 is based on the ALSFRS-R scoring system it suffers the same inherent weakness as the ALSFRS-R (Table 2), with misclassifications and reversals in stages reported (40). Fine till 9 has not been used in

Table 1. Amyotrophic lateral sclerosis diagnostic criteria overview.

	El Escorial criteria (25)	El Escorial criteria revised, Airlie House (26)	El Escorial criteria revised, Awaji Criteria (27)	Gold coast criteria (33)
Presence of ALS	√	√	√	√
Definite ALS	√	√	√	x
Probable ALS	√	√	√	x
Clinical probable ALS: Laboratory-supported	x	√	x	x
Possible ALS	√	√	√	x
Suspected ALS	√	x	x	x
Benefits	• Widely accepted first criteria developed for diagnosis • Includes UMN and LMN signs	• Increased sensitivity vs 1994 criteria • EMG data supplements clinical findings	• Increased sensitivity vs 1994 and 2000 criteria • Enhanced integration of EMG data • Increased reliance on neurophysiology for diagnostic utility in early disease stages	• Increased sensitivity vs 1994, 2000 and 2008 criteria • Reduced categories for diagnosis • High specificity • Sensitivity across motor neuron disease phenotypes • EMG data retained • Cognitive and behavioral data included • Simple criteria for ease of clinical and research use
Limitations	• Lacks diagnostic sensitivity • Low test-retest reliability • Complex to apply • Disease may not evolve through all identified categories • No electrophysiology, neuro-imaging or immune-chemistry analysis	• Concerns on sensitivity during early disease stages • Complex to apply due to multiple categories • Disease may not evolve through all identified categories • Low inter-rater variability • Cognitive and behavioral data not included	• Concerns on sensitivity due to elimination of clinical probable ALS: Laboratory-supported • Complex to apply due to multiple categories • Disease may not evolve through all identified categories • Low inter-rater variability • Cognitive and behavioral data not included • No genome analysis	• Should be used in conjunction with a staging system to preserve prognostic information • Limited research on the accuracy of criteria in clinical practice and trials • No genetic testing or biomarkers included so will require revision once tests/tools are validated for ALS

ALS: Amyotrophic lateral sclerosis; EMG: electromyography; LMN: lower motor neuron; UMN: upper motor neuron.

clinical trials nor has it been tested in large multicenter longitudinal observational programs therefore the usefulness has not been determined or validated.

Where do we go from here?

Despite the three currently available disease-modifying therapies, ALS remains a rapidly debilitating, fatal disease (41). Even though there have been some advances in genetic testing and biomarkers, there has been minimal clinical uptake and a 10–16-month diagnosis delay remains (32). This highlights the need for clinicians and researchers to reflect and assess practice. It is crucial to diagnose ALS early in the disease course, not only to optimize disease management and patient outcomes, but to enhance recruitment into clinical trials aimed at developing new disease-modifying therapies which are key to tackling ALS. So, where do we go from here?

A diagnosis perspective

We believe the Gold Coast criteria should be adopted into routine clinical practice. It is the only diagnostic criteria to describe the minimum necessary abnormalities to arrive at an ALS diagnosis, while maintaining sensitivity and specificity (33). It is simple to use, provides diagnostic accuracy regardless of disease duration, functional status, or site of disease onset, and differentiates atypical phenotypes (23). By applying the Gold Coast criteria, you can diagnose ALS earlier, enable patients and families to plan and cope with the disease, and decrease the risk of unnecessary procedures/treatments leading to increased patient burden (23). Using the Gold Coast criteria in clinical research would also have substantial benefits. As ALS symptoms are variable, it makes definitive diagnosis difficult impacting ALS diagnosis and inclusion criteria for clinical trials. For example, the El Escorial and Awaji criteria are complex with poor inter-rater variability increasing diagnosis error

Table 2. Amyotrophic lateral sclerosis prognostic scoring and staging systems overview.

	ALSFRS (36)	ALSFRS-R (35)	Kings clinical staging system (38)	Milano–Torin, MiToS (39)	Fine till 9 (40)
Overview	• Scoring system • Monitors rate of disease progression	• Scoring system • Monitors rate of disease progression • Based on symptom management and medical decisions	• Staging system • 5 stages assess disease progression (clinical and anatomical) • 1 (symptom onset) – 5 (death)	• Staging system • 6 stages assess functional burden of disease • 0 (normal function) –5 (death)	• Staging system • 5 stages assigned by number of ALSFRS-R sub scores $\leq$9 points • 0 (0 ALSFRS-R sub scores $\leq$9) – 4 (4 ALSFRS-R sub scores $\leq$9)
Benefits	• Useful to measure functional decline	• Useful to measure functional decline • Can be administered virtually	• Discrete stages of disease progression • Superior staging in earlier disease vs MiToS • Simple to apply • Stages occur in order with forward progression only • Less vulnerable to misclassification vs ALSFRS-R	• Discrete stages of disease progression • Superior staging in later disease vs Kings • Based on ALSFRS/ ALSFRS-R so familiar to clinicians and based on patient function • Less vulnerable to misclassification vs ALSFRS-R	• Superior staging in earlier disease vs MiToS • More sensitive to disease progression vs MiToS • Easily applicable to retrospective data • Permits estimation of multidimensional effects of variables on treatment outcome
Limitations	• May not fully capture functional characteristics of later stage ALS • No agreed upon thresholds for transitions in functional status • No respiratory data	• May not fully capture functional characteristics of later stage ALS • No agreed upon thresholds for transitions in functional status • Multidimensions limit clinical utility • Low responsiveness during plateaus • Does not provide information of the expected speed of disease progression	• Based on clinical milestones rather than functional ones	• Reversion in stages has been noted	• Same weaknesses as ALSFRS-R • Misclassifications and reversals in staging lead to instability • No validation in clinical trials or research

ALS: Amyotrophic lateral sclerosis; ALSFRS: amyotrophic lateral sclerosis functional ratings scale; ALSFRS-R: amyotrophic lateral sclerosis functional rating scale-revised; MiToS: Milano–Torino functional staging.

and variability across sites in multi center trials (23). Up to 22% of patients classified as possible ALS using the El Escorial Awaji criteria progress to death without progressing further through the diagnostic categories (42). These patients would be excluded from clinical trials where inclusion criteria mandated a "probable" or "definite" ALS diagnosis as requested by the FDA (43). If regulatory agencies base treatment approval and reimbursement on clinical trial inclusion criteria, the result would be almost ¼ of people living with ALS (PLWALS) who would benefit from treatment (the "possible" patients), would be denied access. For example, the phase II CENTAUR trial found that TURSO treatment resulted in slowing of disease progression in patients with definite ALS as determined by the revised El Escorial criteria (12). The investigators chose definitive ALS as the inclusion criteria based on several reasons. First, it is the principle functional end point referenced in the FDA guidance for ALS clinical trials and correlates with survival outcomes (35). Second, using survival outcomes would result in unmanageable sample sizes and long follow-up to achieve statistical power, and third, due to the heterogeneity of ALS an enriched population attempts to decrease variability and thus sample size and time required to run a trial. These are all legitimate reasons to balance evidence and science with the patients need for additional effective and safe treatments. However, if regulatory agencies translate this inclusion criteria to approval and reimbursement it would create a barrier to treatment access for a considerable number of patients who already have limited treatment options in a rapidly progressing disease with death as an endpoint within 3 years. Whilst it is understandable that regulatory agencies need to balance risk and benefit and not over generalize clinical trial findings, it does seem overly restrictive in an environment where there is an urgent need for more effective treatment options. If the Gold Coast criteria was utilized in clinical trial settings, these issues would be overcome and enable one to balance the need for scientific rigor and the needs of patients. It could lead to earlier diagnoses and better health outcomes sooner, reducing trial duration without increasing risk of false positive diagnoses (23). It could also help trials recruit a wider, more representative ALS trial population vs the "real world" (44). If the Gold Coast criteria was used in clinical trials and clinical practice, you would have specific patient and diagnostic data to base treatment decisions and disease management on.

A prognosis perspective

The ALSFRS-R scoring system is limited. It captures where the patient sees themselves at a moment in time; but it is not verified by a caregiver or a clinician and does not meet criteria for a staging system. We believe the other staging systems are better suited to clinical use and can better identify where a patient is in their disease course. MiToS and King's staging systems have many desirable characteristics that lend themselves to clinical practice (Table 2). For example, they are relatively easy to use and apply, and higher stages are associated with increased mortality (40). They each utilize different data to determine stage and thus are useful in different ways and could be combined to improve power. Of course, there are challenges with each staging system (Table 2), but the benefits outweigh the limitations for clinical utility. If the clinician assigns a disease stage, and takes into consideration the limitations associated with the method, the information can help guide a personalized conversation with patients and families about risks of disease progression and health outcomes, thereby informing disease management, appropriate interventions and planning of care (39). From a clinical trial and research perspective, staging the disease will show the affects of treatments on specific disease stages (45). This will not only help guide the most appropriate treatment for the right patient at the right time (46), but as transition times between stages are short the use of stage duration as an endpoint could result in shorter trial durations (47). It could also aid in the cost/risk/benefit assessments due to therapeutic benefit being greater in the earlier stages of the disease (45,48). Post hoc analyses of the original riluzole data applying MiToS and Kings staging reported the ALS stage at which benefit occurs is important to understand and impacts patients' response to therapeutic treatment (45,49). Using a staging system as an endpoint in clinical trials could result in large sample sizes, since they transform continuous data into binary variables. A post hoc analysis of the Edaravone phase III study reported that despite this, the information provided by the staging systems made them useful end points (50). Moreover, MiToS staging has been found to be equally sensitive to clinical change as the ALSFRS-R, maintaining a similar statistical power (49). As with any clinical trial, investigators would need to power the study adequately for the chosen endpoints to include sufficient sample sizes and retain statistical power (50).We suggest using Kings and MiToS staging in future ALS clinical trials as objective measures of disease progression to assess the stage at which (1) survival benefit, and (2) and improved quality of life, occurs. One last point to consider is the growing recognition of the involvement of non-motor functions (e.g. cognitive impairment, pain, fatigue, and suicidal ideation), and the detrimental effects on PLWALS (51,52). These non-motor symptoms negatively impact patients' function, quality of life and disease outcome (52). In both clinical practice and trial settings, we recommend

non-motor scales be incorporated in the patients' workup. Instruments assessing non-motor symptoms should be adapted, validated, and used in person-centered web-based platforms or installed on smartphones.

The utility of real-world evidence

The importance of real-world evidence (RWE) in ALS is increasing. While randomized clinical trials remain the gold standard for high-quality data, they limit generalizability of outcomes to a real-world population. Conducting clinical trials in ALS can also be challenging due to the limited number of patients available for trials (2). Worldwide regulatory authorities realize the need for RWE in rare diseases and are working to optimizing the use of RWE in decisions. Health Canada is working with the Canadian Agency for Drugs and Technologies in Health (CADTH) and the Institut national d'excellence en santé et en services sociaux (INESSS) to understand how RWE can improve the extent and rate of access to prescription drugs in Canada (53). The FDA is using RWE to monitor post marketing safety, support drug coverage decisions and support clinical study data to generate new treatment approaches (54). In addition, the number of ALS registries around the world are increasing (Figure 3). Whilst registries have many unique strengths, lack of standardization and uniform data collection protocols could limit the analysis and applicability of the findings. Developing collaborative platforms across a range of stakeholders allowing for a variety of data to be collected (e.g. clinical and biological specimens, disease course, treatment patterns and survival) is no easy feat (29). However it is vital to ensure the applicability of findings (54). We recommend registries incorporate collection of ALS diagnosis using the Gold Coast criteria and prognosis using the staging systems of MiToS and King's.

Genetic testing and biomarkers

There are excellent reviews on genetic testing and biomarkers in ALS (6,55,56), so we will only briefly touch on the subject here. Since 1993, 40 genes for ALS have been identified, accounting for approximately 15% of cases (6). Whilst genetic testing is growing, it is not yet an integrated tool in ALS diagnosis. As the cost of genetic testing falls it is anticipated that this will change. Routine genetic profiling would allow precision medicine in practice and clinical trial stratification for targeted therapies (57). All of which would facilitate ALS diagnosis, prognosis and disease management. Biomarkers can play a crucial role in diagnosis, prognosis, predictive research studies and patient stratification and monitoring (58). Fluid and imaging studies may ultimately lead to specific diagnosis, however at present such modalities are at the experimental stage only (46).

The impact of COVID-19 on clinical practice

The pandemic has significantly altered the clinical approach to PLWALS with expansion of virtual consultations (51). These practice changes will remain and place PLWALS at a greater risk of late diagnoses and/or loss to follow-up leading to higher morbidity and mortality if not addressed (19). Optimal patient management requires regular monitoring and interactions between the patient and clinical team which telemedicine can reliably
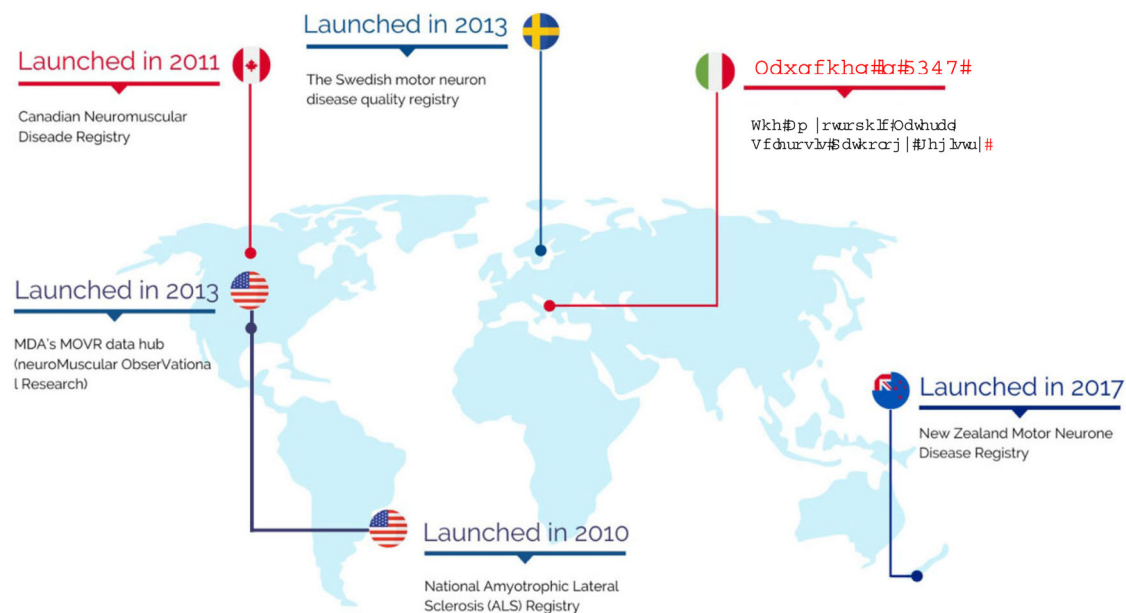

Figure 3. Map of worldwide registries in amyotrophic lateral sclerosis developed between 2010 and 2017. Adapted from Barbalho et al. (2).

support (59). Bombaci et al. (19) provide a good overview of what telemedicine for the management of PLWALS could look like in the future, while Govindarajan et al. (60) discuss optimizing telemedicine for clinical trials. It has been shown that the ALSFRS-R can be easily performed by video or phone (61–63).We believe the simpler Gold Coast criteria will also lend itself well to the telemedicine setting, although validation studies will be required for confirmation. Home-based assessments of disease progression will be vital for disease monitoring, and we believe MiToS should be added to the telemedicine core set of assessments. While King's would add information, it would require a visit to the patient for completion. The emergence of digital healthcare technology (e.g. wearable devices, assistive communication) has the potential to transform ALS care without requiring clinic visits. It is important to note the many advancements being made in this area (64).

Conclusion

ALS is a rare, complex, neurodegenerative disorder. No cure exists and new effective treatment strategies are required. The proposed changes in clinical practice and clinical trials suggested herein are vital not only for the development and translation of future treatment strategies in ALS into clinical practice, but to reduce patient, family, and caregiver burden. Such changes would enable clinicians to use their experience and medical training to balance the needs of evidence-based medicine and the needs of each PLWALS. Such personalization of patient care is crucial in managing this complex and multi factorial disease.

Declaration of interest

In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting that I, Dr Angela Genge have received funding from the following companies: Alexion, Als-Pharma, Amicus Therapeutics, Amylyx, Anelixis, Anexon, Apellis, Atlantic Research Group, Biogen, Calico, Cytokinetics, Eli Lilly, Ionis, Medtronic, Mitsubishi Tanabe Pharma, Orion, QurAlis, RA Pharma, Roche, Sanofi Genzyme, UCB, Wave Life Therapies. I am also a paid consultant for Amylyx Pharmaceuticals. I have disclosed these interests fully to Taylor & Francis, and I have in place a plan for managing any potential conflicts arising from these disclosures.

In accordance with Taylor & Francis policy and my ethical obligation as a researcher, I am reporting that I, Dr Adriano Chiò serve on scientific advisory boards for Mitsubishi Tanabe, Biogen, Roche, Denali Pharma, Cytokinetics, Lilly, and Amylyx Pharmaceuticals. I have also received a research grant from Biogen. I have disclosed these interests fully to Taylor & Francis, and I have in place a plan for managing any potential conflicts arising from these disclosures.

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