



# Emerging technologies for management of patients with amyotrophic lateral sclerosis: from telehealth to assistive robotics and neural interfaces

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## Abstract

Amyotrophic lateral sclerosis (ALS), also known as motor neuron disease, is characterized by the degeneration of both upper and lower motor neurons, which leads to muscle weakness and subsequently paralysis. It begins subtly with focal weakness but spreads relentlessly to involve most muscles, thus proving to be effectively incurable. Typically, death due to respiratory paralysis occurs in 3–5 years. To date, it has been shown that the management of ALS patients is best achieved with a multidisciplinary approach, and with the help of emerging technologies ranging from multidisciplinary teleconsults (for monitoring the dysphagia, respiratory function, and nutritional status) to brain-computer interfaces and eye tracking for alternative augmentative communication, until robotics, it may increase effectiveness. The COVID-19 pandemic created a spasmodic need to accelerate the development and implementation of such technologies in clinical practice, to improve the daily lives of both ALS patients and caregivers. However, despite the remarkable strides that have been made in the field, there are still issues to be addressed. This review will be discussed on the eureka moment of emerging technologies for ALS, used as a blueprint not only for neurodegenerative diseases, examining the current technologies already in place or being evaluated, highlighting the pros and cons for future clinical applications.

**Keywords** Amyotrophic lateral sclerosis · Motor neuron diseases · Clinical management · Emerging technologies · Telemedicine · Brain-computer interface · Eye tracking · Robotics · Internet of things

## Introduction

Amyotrophic Lateral Sclerosis (ALS) is a rapid progressive neurodegenerative disease characterized by the degeneration of both upper and lower motor neurons, leading to motor and extra-motor symptoms with death usually occurring 3–5 years after the onset of symptoms [1, 2]. Recent studies suggest a worldwide incidence of 2/100,000 individuals with ALS per year and a prevalence of 3–8 cases per 100,000 inhabitants [3]. The early detection of ALS can vary between patients: some present with spinal-onset

disease characterized by muscle weakness of the limbs, other patients present with bulbar-onset disease, which is characterized by dysarthria and dysphagia [4]. Although the primary symptoms of ALS are associated with motor dysfunction (i.e. muscle weakness, spasticity, and dysphagia), up to 50% of patients develop cognitive and/or behavioral impairment during the course of disease, and 13% of patients present with concomitant behavioral variant frontotemporal dementia (FTD) [5, 6]. Anyhow, loss of respiratory muscle innervation and associated complications are the most frequent causes of death [7]. The mechanism of neurodegeneration in ALS is not entirely clear yet (there are several cellular and molecular processes that are implicated) [8, 9], and despite the continuous efforts to develop curative therapies, to date there is no effective cure to reverse the disease except for Riluzole [10, 11], Edaravone [12, 13], and non-invasive ventilation (NIV) [14, 15] that can improve quality of life and survival in ALS patients.

Currently, the main effort that is made regarding this pathology concerns patient care management, which

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includes extensive symptomatic and support therapies throughout the course of the disease and requires constant counseling to the patient and caregiver. Indeed, the current practice of caring for patients with ALS involves a multidisciplinary team consisting of neurologist, pulmonologist, physiatrist, nurse, physical and occupational therapists, speech pathologist, dietitian, social worker, mental health counselor, and respiratory therapist [16, 17]. This type of care aims to optimize patients' quality of life and survival. For this reason, patients must be monitored closely and have continuous access to multidisciplinary centers during their disease. However, many ALS patients have access issues in the multidisciplinary clinics—mostly related to long travel distances, difficulty traveling, and long days at the clinic—and, in addition, there is a lack of monitoring patients between clinic visits. These critical issues could limit the continuity of multidisciplinary management of ALS patients, negatively affecting the course of the disease.

In this context, emerging technologies such as teleconsults, Internet of things (IoT), wearable devices, augmentative and assistive communication with brain-computer interfaces (BCI) and eye tracking (ET) support, and robotic rehabilitation can fill this gap [18–20] (Fig. 1). Such technologies could allow a specialist team to care for patients throughout their disease regardless of patients' ability to travel to the multidisciplinary centers. It should be also emphasized that the COVID-19 pandemic has rushed the need to remotely continue providing the best care to patients, therefore diminishing the risk for nosocomial infection during hospitalization [21]. However, to be successful and effective these emerging technologies must be accessible to all patients who may be frail, have severe disabilities, or have communication difficulties, and must be user-friendly to obtain better outcomes. Furthermore, to have a widespread and consolidated adaptation of these technologies—starting from the early stages of the disease—it is necessary to ensure that either ALS patients or

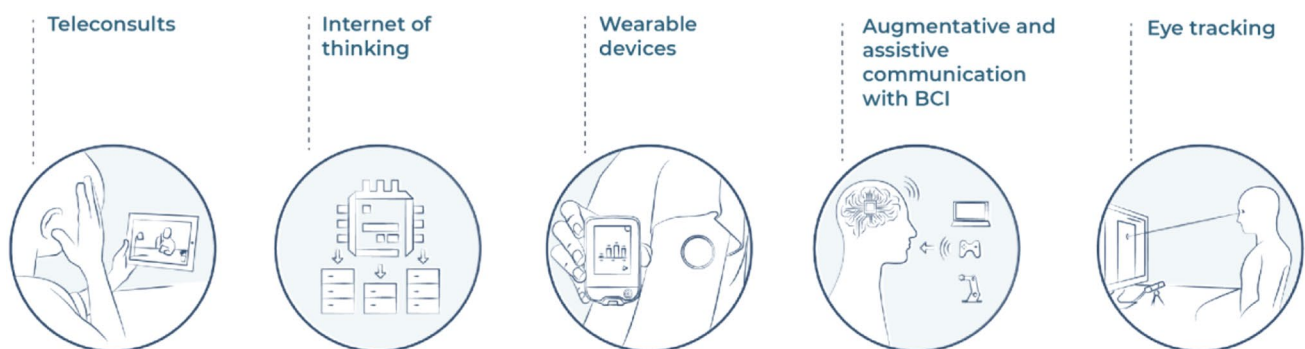
caregivers acquire considerable control and independence in their use. Hence, it will be necessary to keep in mind that young, educated and professionally active patients will be more sensitive to emerging technologies, while older patients, not previously trained about such technologies, will face considerable difficulties, requiring more time, encouragement, and greater support by specialists from multidisciplinary centers.

Here will be evaluated the potential benefits and challenges of using emerging technologies (already in place or under evaluation) to facilitate care access and to improve the daily living of both ALS patients and caregivers.

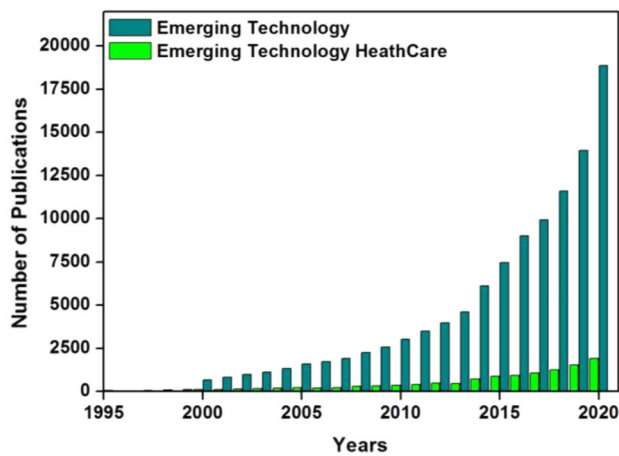
### A Eureka moment to emerging technologies: matters and pitfalls

There is considerable and growing interest in emerging technologies, especially from the social, economic, industrial, healthcare, and policy perspective [22, 23]. The evidence of the increasing attention being paid to the phenomenon of emerging technologies is clearly visible in the growing number of publications dealing with this topic, as depicted in Fig. 2. In the last two decades, there has been an exponential growth in publications focused on emerging technologies in general, with a total of 18,856 publications, as well as on emerging technologies for healthcare applications (1919 publications).

However, to date, there is a lack of consensus—among the scientometric community—on the definition of emerging technology [24]. To the best of our knowledge, Rotolo et al., have attempted to contribute to this ongoing debate through the conceptual clarification of the emerging technology phenomenon [25]. They identified five attributes that characterize emerging technologies: (1) radical novelty, (2) relatively fast growth, (3) coherence, (4) prominent impact, and (5) uncertainty and ambiguity. Furthermore, the authors defined emerging technologies as: “a relatively fast-growing



**Fig. 1** Schematic representation of emerging technologies already used for the management of ALS patients



**Fig. 2** Timeline of publications dealing with the topic of emerging technologies (in dark green) and emerging technologies in healthcare (light green) retrieved by querying PubMed. As inclusion criteria for the search on said database, the following key terms were used: “emerg\* technol\*” or “emerg\* technol\* in healthcare”

and radically novel technology characterized by a certain degree of coherence persisting over time and with the potential to exert a considerable impact on the socio-economic domains which is observed in terms of the composition of actors, institutions and the patterns of interactions among those, along with the associated knowledge production processes. Its most prominent impact, however, lies in the future and so in the emergence phase is still somewhat uncertain and ambiguous” [25].

We foresee a number of great opportunities for future research in this field, especially for the home management of patients with neurodegenerative, and cardiovascular diseases. First, future research should pay more attention to the origins of emerging technologies and should involve specialists from different fields such as engineers, physicians, biotechnologists, data scientists, and physicists (to name a few), to limit the risk factors and get better results in a short time. Second, the growing access to big data could help in the rationale of research on emerging technologies by delineating also the counterfactual samples (if present), thus providing a significant opportunity to develop indicators and methods for the evaluation and feasibility of emerging technologies, for which the current state of the art provides only a limited contribution. Finally, regarding the use of emerging technologies for the management of patients with neurodegenerative diseases such as ALS, spinal cord injuries (SCI), Alzheimer’s, and Parkinson’s, these should broaden their horizons not only on diagnostics but also on assessment, monitoring, prevention, education, consultation, and coaching, with the ultimate goal of transforming healthcare by moving it from hospitals/clinics to home care.

## Telemedicine: a breakthrough on predictive, personalized, preventive and participatory (4P) medicine

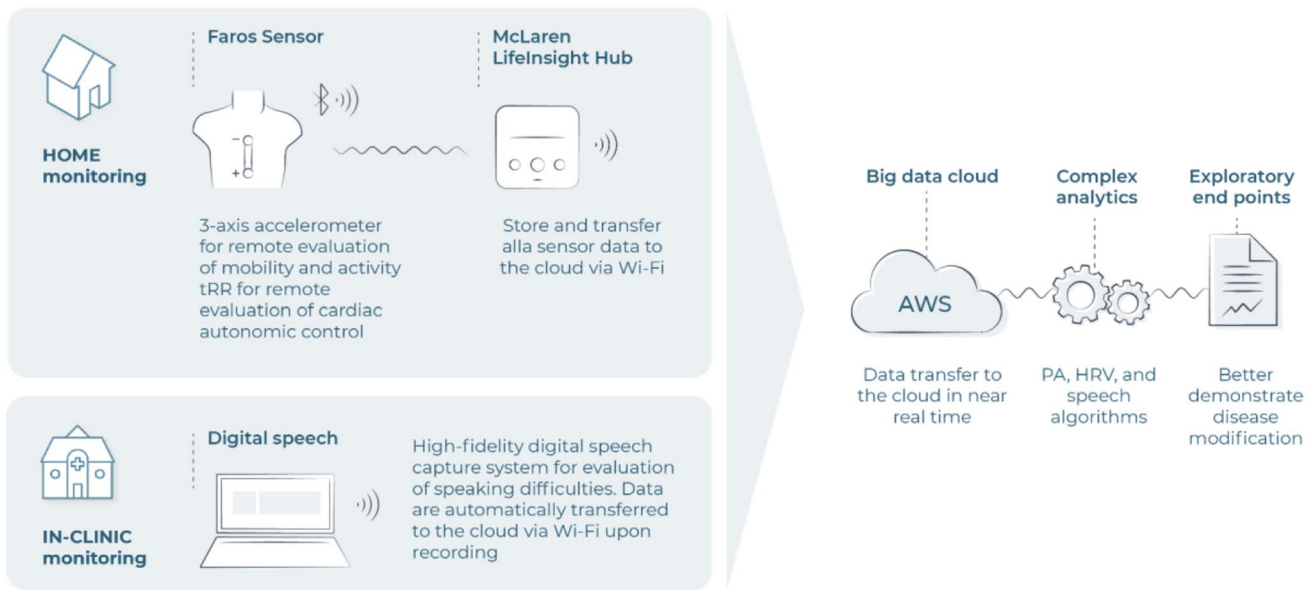
Telemedicine is a general term, first introduced in the 1970s, to indicate the use of telecommunications technology to provide health care services to persons who are at some distance from the healthcare professional provider [26]. Analogous to the long-established physician–patient relationship, telemedicine must comply with all the rights and duties of any health act for prevention, diagnosis, treatment, rehabilitation, and monitoring. Furthermore, telemedicine must not replace traditional health services but rather to integrate them to improve effectiveness. The COVID-19 pandemic has accelerated this process and forced researchers and clinicians to reshape the telehealth strategies with the use of emerging technologies, and to accelerate its development for home care purposes. Indeed, the healthcare systems have suddenly faced an enormous and complete rearrangement of resources and spaces, and most visits for chronic diseases have been canceled or postponed. In this context, patients affected by chronic neurological diseases, such as ALS, are at risk of being lost at follow-up with a consequently higher morbidity and mortality.

Therefore, it is important to establish a well-structured telemedicine service to replace face-to-face visits, monitor disease’s progression, and manage complications like life-threatening ones.

In this context, the American Academy of Neurology published some advice for improving a telemedicine service and suggested tools to perform a neurological examination remotely [27].

Luis Garcia-Gancedo et al. [28] reported a pilot observational study to investigate the feasibility of a digital platform for remote data collection of multiple symptoms, such as physical activity, heart rate variability, and digital speech characteristics, in 25 patients with ALS over 48 weeks (mean age of the overall population is:  $53.1 \pm 9.93$ ). Such platform comprised three main components: (1) the commercially available Mega Faron 180 accelerometer and 2-lead ECG sensor, attached to the chest; (2) a Life-Insight Hub, that received data from the sensor via a secure Bluetooth wireless signal every 2 min, and which in turn automatically uploaded data in real time to secure cloud servers; (3) a digital speech capture system comprising a high-fidelity microphone connected to a computer, with bespoke software that instructed the patients to say a series of vowels, words, and paragraphs, which were then recorded and immediately automatically transferred to a secure server via mobile connectivity (Fig. 3).

Overall, the authors reported that the amount and quality of the data collected and the accuracy of the algorithms



**Fig. 3** Schematic representation of the monitoring platform reported by Luis Garcia-Gancedo et al. which comprises: Mega Faron 180, Life-Insight Hub, and a digital speech capture system

developed were sufficient to evaluate changes over time in patients’ activities of daily living. In addition, the equipment was generally well tolerated by patients with no or minimal impact on their daily activities. Although, 6 of 25 patients had mild or moderate adverse events in the skin and subcutaneous tissue disorders category caused by the electrode patch. A limitation of this study—as specified by the authors themselves—was a lower than expected reception on the amount of home monitoring physical and speech activity data, partly because of a number of patients withdrawing from the study early, which limited the ability to draw robust clinical conclusions, and partly due to poor contact between the sensor and the skin.

Instead, other studies have been conducted to assess the feasibility and acceptability of telemedicine for treating ALS via real-time videoconferencing from the clinic to patients’ homes [29–34]. Globally, these studies (one of

which conducted in Italy during the COVID-19 pandemic) [31] found that patients, caregivers, and clinical staff members are satisfied with the telemedicine service, although improvements in technology and methods are needed to provide satisfactory person-to-person contactless remote assistance (Table 1).

Another key issue to be addressed in ALS patients is the monitoring of the nutritional status, which is a relevant prognostic factor [32]. Despite countless nutrition-based mobile health applications being available, only a few were clinically assessed [35–37]. In a recent randomized trial, Anne Marie Wills et al., compared remote nutritional counseling with or without mobile health technology in ALS patients [35]. In this randomized clinical trial, patients were randomly assigned one of three nutritional interventions, namely: (1) counseling by their physician or nurse (“standard care”); (2) counseling by a registered

**Table 1** Advantages, disadvantages, and possible improvements experienced by the patient, caregivers, and clinical staff during the pilot studies

Advantages	Disadvantages	Improvements
No travel	No personal touch	Better appointment options
In home	No emotional connection	Additional software options
Less time	Poor eye contact	Limit to necessary providers
Less effort	Video/audio	Better coordination of onsite support
No bad weather	Wait time between providers	Better video/audio
More convenient	Privacy	
Less stress	Not leaving house	
Saw clinical staff	Coordination with onsite support	
No overnight stay	No physical examination	
No childcare worries		

dietitian (“in-person”); (3) counseling supported by a nutrition-based application (“mHealth”). All nutritional interventions received tailored nutrition recommendations and recorded dietary intake and weight biweekly (for mHealth) or monthly (for in-person). Moreover, based on patients’ gain or loss weight, the nutritionist could remotely access the app and modify dietary recommendations. The primary outcome of weight and secondary and tertiary outcomes of calorie intake, ALS Functional Rating Scale Revised (ALSFRS-R), and quality of life were recorded at each clinic visit and analyzed in an intent-to-treat (ITT) mixed model analysis.

Interestingly, patients with mHealth app-supported counseling increased their dietary intake and percent of recommended calories compared to patients who received standard-of-care treatment. Furthermore, the rate of disease progression measured by ALSFRS-R total score over 6 months, was half as fast among mHealth participants compared to participants in the standard care.

Based on these assumptions, in our opinion, Telemedicine in ALS is poised to monitor everyday life and potential life-threatening aspects of the disease, while creating new challenges and opportunities without replacing the traditional clinical procedures. As underlined by the aforementioned pilot studies, remote neurological examination, heart rate assessment, speech analysis, nutritional status monitoring via mHealth application, are useful and accessible tools and should be applied to all patients at the follow-up teleconsultation. While the digital evaluation of motor functions through digital devices, such as the accelerometer, are not completely reliable at the moment and should be better developed to be well tolerated by patients. A future perspective could be the development of a clinical app linked to a wearable device to achieve a complete self-assessed evaluation of nutritional status, respiratory function, motor ability, and subjectively perceived health status.

Finally, despite the high enthusiasm for telemedicine, must be kept in mind that if widespread use of telemedicine technology is to be achieved for the ALS clinical care, a well-structured multi-center telemedicine service with a high levels of expertise from clinical organization will have to be built; such expertise is still being built by most organizations. Despite these pitfalls, rapid progress is being made on several forefronts and different innovative ways forward are being developed. It is expected that continued exploration and validation of outcome measures, coupled with continued engagement of physician, nurse, speech pathologist, dietitian, respiratory therapist, engineers, biotechnologists, data scientists, physicists, and regulators, will facilitate the core goals of maximizing opportunities for patient involvement, minimizing patient and caregiver burden, and providing accurate data for analysis of outcomes.

## High-tech augmentative and alternative communication (HT-AAC) technologies

The HT-AAC is a compensation form, with the aims to help and improve communication abilities of individuals with difficulties in using common channels of communication, especially verbal and written [38]. Such technologies are defined augmentative because they extend or replace means of communication for physically impaired people, but at the same time, they are defined alternative as they use multimodal methods of communication, which are different from the traditional ones, giving to patients the opportunity to maintain their communicative function by producing written or spoken messages.

Since ALS patients may completely lose the ability to articulate words and phrases (dysarthria occurs in 80–95% of ALS patients), and have impaired limb mobility (so they may be deprived to use gesture communication), they could gain enormous benefit from the HT-AAC technologies to continue communication, despite the physical impairment that otherwise would prevent it. In particular, the development of HT-AAC, such as brain-computer interface (BCI) and eye tracking (ET), could be a useful tool to bypass the important motor difficulties present in ALS patients [39].

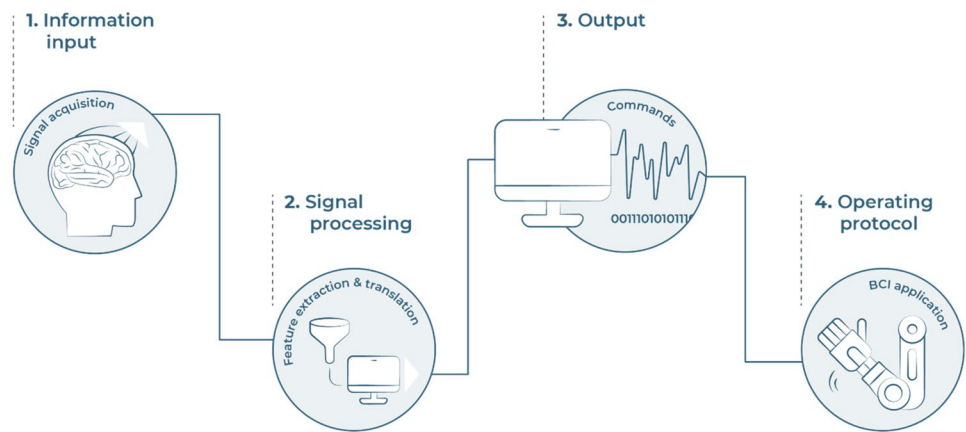
Additionally, HT-AAC can help maintain emotional connection within families, and support social roles, thereby decreasing the caregiver burden and increasing the patient’s psychosocial well-being or quality of life.

## Brain-computer interface (BCI) in ALS: a P300-based case study

The BCI is a communication system, independent of the brain’s normal output pathways, that enables the generation of a control signal from brain responses such as sensorimotor rhythms and evoked potentials, thus conveying messages directly to a computer, which performs the desired action. Brain activity can be monitored by several methods as: electroencephalography (EEG), magnetoencephalography (MEG), positron emission tomography (PET), functional magnetic resonance imaging (fMRI), and functional near-infrared spectroscopy (fNIRS). However, these latter two are expensive, and they have a slow time resolution that does not allow rapid communication. While EEG has a relatively short time constant, can be operated in many environments, and requires inexpensive devices, so it is the most practical and suitable method for BCI development.

Typical BCI techniques include the use of evoked potentials (such as P300) [40] or motor imagery [41], and

**Fig. 4** Process and elements of BCI system



enable the user to communicate with a speller device or to control the movement of an end effector. Briefly, BCI is a communication system that does not depend on the brain’s normal pathways of peripheral nerves and muscles [42, 43]. In brief, a BCI system consists of four essential parts: (1) information input (i.e. recorded brain activity from the user), (2) signal processing (i.e. the components that translate raw information into output), (3) output (i.e. the commands administered by the BCI system), and (4) operating protocol that determines the timing of operation (Fig. 4). These elements interact to produce the user’s intention [44].

However, the use of BCI in ALS patients still shows some limitations, related to both technical and neuropsychological issues. In fact, the number of clinical trials on BCI is still relatively low [45–48]. Violaine Guy et al., evaluated in a clinical study the usability of P300 speller BCI on 20 patients with ALS [47]. The study consisted of two 3-block sessions (copy spelling, free spelling and free use) with the system in several modes of operation to evaluate its usability in terms of effectiveness, efficiency and satisfaction. Globally, the P300 speller BCI system was effective in that all participants successfully achieved all spelling tasks. All participants expressed satisfaction regarding comfort, ease of use and utility. Furthermore, all participants decided to try word prediction; the authors observed that the spelling rate (in symbols per minute) was improved with word prediction. For a few patients, word prediction decreased the spelling rate, which could be attributed to their difficulty in scanning the proposed words fast enough and in switching between typing strategies. In this regard, word prediction even if it brings a benefit may require some extra training to be fully effective. Despite these findings, the authors raised a number of technical and practical concerns that need to be addressed for regular daily use of the system. First, their system was designed to be set up by physicians and caregivers, so it should be further simplified to allow anyone to set it up easily. Second, the installation time of 13 min should

**Table 2** Values of speller size parameters used by Teresa Medina-Julιά et al. [49]

Size	Speller size (cm)	Symbol size (cm)	Symbol distance (cm)
Small	5.27	0.42	0.55
Medium	9.98	0.79	1.04
Large	14.69	1.17	1.53



**Fig. 5** Example of speller’s size parameters. SS stands for “symbol size” and SD for “symbol distance”

be reduced to < 5 min to be practical. Finally, electrode positions should be selected to provide both good signals and good comfort even for patients who need support for holding their head (e.g. patients with the dropped head syndrome).

Recently, Teresa Medina-Julià et al., assessed the usability of three speller sizes (Table 2, and Fig. 5) in ALS patients (mean age:  $64.43 \pm 11.1$ ) [48]. This is because, the authors thought that speller size might be limiting for some locked-in state patients, where they have restricted head and eye movements [49].

In particular, the authors evaluated the effect of these three different speller sizes, in terms of effectiveness, efficiency, and satisfaction as proposed by ISO 2000, highlighting that the medium size is the most usable and the small size is the least usable in terms of satisfaction. Furthermore, the error performance evaluation showed that the medium size as the only speller that enables efficient communication according to the MEP30 criterion [50]. Finally, the medium speller was selected as the least temporal demanding and the one that required less effort to control; on the contrary the small size was selected as the most physically demanding and the one that required more effort, based on the NASA-TLX scores [51].

### Eye-tracking in ALS: assessment of cognitive functions

In advanced ALS disease, phonatory impairment seriously hinders the patient's interpersonal communication [52–56]; for this reason ET communication devices are used to aid communication in the later stages of ALS. The main advantage of ET devices is that they are independent of the caregiver allowing social communication and interaction with the environment. As reported by Caligari et al. the most used device is the Eye Tracking Communication Device (ETCD), which is able to detect and interpret, through an infrared camera, the patient's eye movements [57]. ETCDs merely require the patient's capability of pointing and holding the gaze on various commands displayed on the monitor. The

authors showed an easy and regular use of the ETCD in ALS patients with tetraplegia and anarthria, highlighting that this device is an effective option for the management of communication deficits in the advanced stage of the disease, and it would be important to provide it as standard care since improves the quality of life of the patient who is affected by the deprivation of communication. Furthermore, ET-based technology can be used for neuropsychological and cognitive assessment in non-verbal ALS patients [58–60]. For instance, Poletti et al. reported the use of an ET-based cognitive battery assessing language, attention, and social cognition abilities, showing good levels of diagnostic accuracy and usability in ALS patients [61]. The same group used an ET-based cognitive assessment to perform a verbal-motor free cognitive flexibility test (Arrows and Colors Cognitive Test) [62].

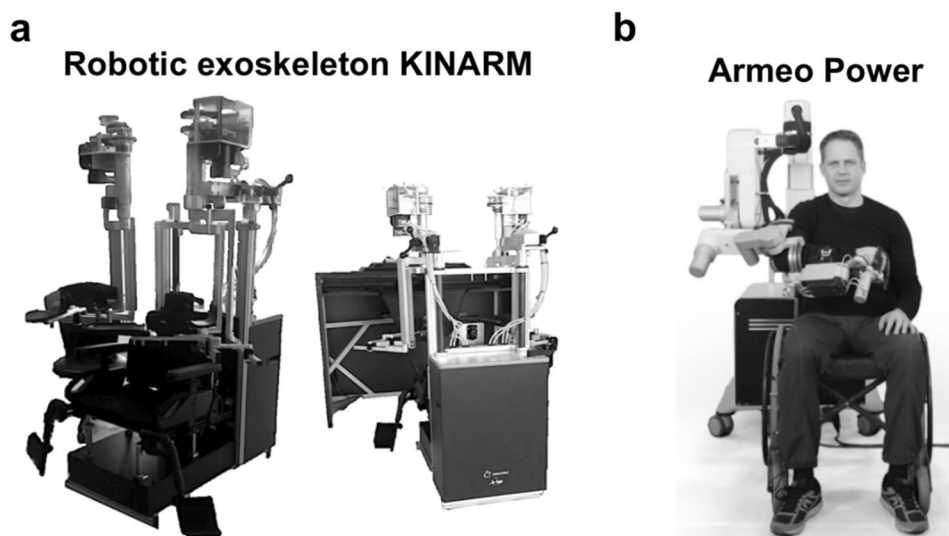
Overall, these efforts, although seminal, can provide a comprehensive assessment of cognitive functions, and the detection of cognitive impairment throughout the course of ALS disease, revealing ET technology as a useful diagnostic tool for the near future.

### Neuro-rehabilitation in ALS using robotics

Robotic rehabilitation is another emerging technology that is giving its first steps in ALS, and represents a promising tool that can be used not only to assist patients but also for their assessment and training throughout the course of the disease, as it is increasingly clear that either progressive motor weakness and cognitive decline play a significant role in ALS disability [63–65]. To date, only a few robot-assisted therapies have been tested in randomized clinical trials.

A prominent example on the feasible use of robotic technology to quantify the sensory, motor and cognitive

**Fig. 6** (a) KINARM exoskeleton apparatus, and (b) Armeo Power exoskeleton apparatus



impairments of ALS patients has been reported by Leif Simmatis et al. [66]. By using the robotic exoskeleton KINARM (BKIN, Canada) (Fig. 6a) on 17 patients with ALS (mean age:  $64.4 \pm 7.7$ ), the authors assessed: five tasks for upper-limb sensorimotor functions {visually guided reaching [67], object hit [68], object hit-and-avoid [69], ball-on-bar [70], and elbow stretch test [71]}; one task for upper limb proprioceptive function {arm position matching [72]}; three tasks for cognition {visually guided reaching, spatial span, and trail-making [72, 73]}. Most patients were able to perform the robotic tasks, showing that 56% of participants displayed motor-related impairments, 77% impairment in either arm, 69% sensorimotor impairments, and 25% proprioceptive impairments. The feasibility of using robotics (in good agreement with clinical tests, such as MoCA and FAB test), to assess motor and cognitive performance, highlight the potential of such technology in providing key additional information that can be useful for therapeutic decision-making and for clinical trials. In addition, from our point of view, it will be interesting in the future to correlate robotic motor task findings with disease stage, to have novel digital-biomarkers.

Furthermore, treatment with Armeo Power (Hocoma, Switzerland) (Fig. 6b), a robotic rehabilitation exoskeleton for upper limb training, was reported on a 69 year-old woman affected by flail arm ALS [74]. In particular, the Armeo Power is a 3D rehabilitation exoskeleton for upper limbs, allowing the treatment of motor function impairment by enhancing the residual function and neuromuscular control, assisting active movement across a large 3D workspace [75]. The Armeo Power protocol involved arm and elbow movement exercises to improve shoulder abduction, arm flexion, and elbow extension. After two months of treatment the authors observed a significant improvement in the patient's strength, together with a motor improvement of the upper limb. Although this is a single case study, this robotic neuro-rehabilitation approach with Armeo Power is a promising example of how such technology can be useful in chronic, progressive and untreatable degenerative disorders, such as flail arms ALS. Overall, robotic devices could support conventional rehabilitation, improving the patient's motor performance and enhancing plasticity phenomena within the damaged areas. However, one of the main limitations of the robotic approach is that the improvement is limited to the region of the body involved in the training, and it is difficult to imagine the combination of different robotic devices in the patient who has an impairment affecting multiple body areas.

Furthermore, it is not possible to accurately quantify the sensorimotor performance during exercise in terms of movement kinematics and exchanged forces; In the future, robotic therapies could incorporate models of the recovery process to predict the outcome of rehabilitation for adapting them to

the patient's features [76, 77]. Finally, another stimulating challenge is the development of lightweight robots suitable for the domestic environments: this implies a modular structure, which facilitates donning and transportability.

In addition, it should be emphasized that people with physical disabilities, such as ALS, have classified object retrieval as a high-priority task for assistive robots [78]. Indeed, when people are unable to recover a dropped object on their own, they ask for the assistance of a caregiver; however, this requires a caregiver to be close and available and can diminish an individual's sense of independence. Hence, assistive robots could potentially help people with motor impairments retrieve dropped objects, and thereby gain greater independence. Chih-Hung King et al. reported the use of a small-scale teleoperated mobile robot named Dusty, which is capable of reliably picking up objects from the floor and delivering them to motor-impaired users [79]. The authors evaluated this robot with 20 people with ALS and the results show that they can use Dusty to robustly, safely and effectively retrieve an object from the floor. The users reported high satisfaction with Dusty and reported that the robot was significantly easier to use than their current object retrieval methods. However, future studies involving long-term real-world use would be required to assess the true potential of this emerging form of assistive technology, since during real world use, the locations of the robot, obstacles, and target objects would vary, and multiple obstacles might present greater challenges for object retrieval. Furthermore, obstacles might also obscure the user's view of the robot or target object. All of these factors could influence the time required to retrieve an object in the real world setting. In order to overcome these issues for effective use of assistive robots in a real home environment, cameras could be included on the robots to allow user-friendly use, or artificial intelligence and machine-learning based-technology could be coupled to the robot [80, 81].

## Incorporating emerging technologies in ALS clinical trials: the road ahead

As we discussed in previous sections, clinical care for ALS patients increasingly incorporates emerging technologies to enable home-based care, improving access and quality of care in a progressively debilitated population. For this reason, we believe that today clinical investigators on ALS have the enormous opportunity to include such emerging technologies (e.g. televisits and home monitoring equipment) in trials to pave the way for an innovative trial design.

We are aware that these devices will require validation, but this great initial effort could improve: (1) the quality of the data (because allow to collect them in daily life and not just during the study visit), (2) minimize patient risk,



(3) reduce the frequency of study visits, (4) reduce study duration, and (5) increase study safety. Furthermore, while the incorporation of novel outcome measures and bio-markers have the potential to enhance study design, innovative trial incorporating emerging technologies that enable the real-time data analysis might improve the type of therapy, route of therapy delivery, or therapeutic plan, adapting (in a patient-specific manner) the best dosage/posology during data collection, thus promoting the predictive, personalized, preventive and participatory exciting era for clinical research in ALS.

## Conclusions

ALS may be considered a blueprint for neurodegenerative diseases to further develop and test emerging technologies, and the COVID-19 pandemic is squeezing up the development and implementation of such technologies in clinical practice. As it pointed out in this review, progress has already been made in the spread of telemedicine. In fact, it has been shown to be feasible and safe technology, with good compliance, and with time and cost savings for both patients/caregivers and healthcare systems. However, it will be essential the creation of a well-structured multi-center service for the bi-directional transmission of encrypted data, device synchronization, data storage and analysis, in accordance with ethical policies. On the other hand, BCI and ET expanded the field of augmentative and alternative communication in ALS but their potentialities still need to be verified so that they can become practical tools for the management of communication deficits, or diagnostic tools for the assessment of cognitive functions and the identification of cognitive impairment in the course of ALS disease. As well as robots are promising tools that can be used not only to assist patients but also for their assessment and training throughout the course of the disease. However, at the moment, they are mainly used for scientific purposes or available only to a limited number of patients, under strict protocols.

In our opinion, we have only scratched the surface of the development possibilities of these emerging technologies, and we foresee a number of great opportunities for future research in this field, in particular for the home management not only of ALS patients, but also for Parkinson's, Alzheimer's, strokes, traumatic brain injuries, and spinal cord injuries. To emphasize, nowadays, ALS is a disease that is inexorably progressive and without cure, and the gains that can be obtained with these emerging technologies can be wiped out by the subsequent loss of motor function. However, this should not be seen as a deterrent but on the contrary, the increasingly in-depth study of the mechanisms of neurodegeneration in ALS must be carried out to understand how

this disease can be clinically treated. In doing so, emerging technologies such as telemedicine, assistive robotics, HT-AAC, and neural interfaces will find their deserved role in enabling patients to have a dignified life with a chronic disease.

Finally, as previously reported by Semprini et al. [63]: when developing or implementing emerging technologies targeting a specific set of populations, it is extremely necessary that patients are involved in experimental studies, right from the start; in fact, their motto is “Nothing about us, without us”.

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## Declarations

**Conflicts of interest** The authors declare no competing interest.

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