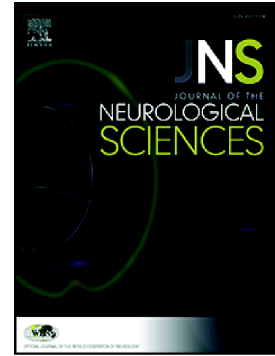# Journal Pre-proof

New technologies and Amyotrophic Lateral Sclerosis – Which step forward rushed by the COVID-19 pandemic?

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New technologies and Amyotrophic Lateral Sclerosis – which step forward rushed by the COVID-19 pandemic?

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Abbreviations

ADL: Activities of daily life; AI: Artificial intelligence; ALS: Amyotrophic Lateral Sclerosis; ALSFRS-R: Revised ALS functional rating scale; AAC: Augmentative and alternative communication; AR: Augmented Reality; BCI: Brain-computer interfaces; ECAS: Edinburgh Cognitive and Behavioural ALS Screen; EQoL-5D: European quality of life questionnaire; ENCALS: European Network for the Cure of ALS; ET: Eye tracking; EU: European Union; FVC: Forced vital capacity; GDPR: General Data Privacy Regulation; HAD scale: Hospital Anxiety and Depression scale; MIP: Maximal inspiratory pressure; ML: Machine Learning; QoL: Quality of life; LL: Lower limb; MIE: Mechanical insufflator-exsuflattor; NEALS: Northeast ALS Consortium; NIV: Non-invasive ventilation; PLS: Primary lateral sclerosis; pt: patient; pt: patient; UL: Upper limb; VR: Virtual Reality; WHO: World Health Organization.

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Abstract

Amyotrophic Lateral Sclerosis (ALS) is a fast-progressive neurodegenerative disease leading to progressive physical immobility with usually normal or mild cognitive and/or behavioural involvement. Many patients are relatively young, instructed, sensitive to new technologies, and professionally active when developing the first symptoms. Older patients usually require more time, encouragement, reinforcement and a closer support but, nevertheless, selecting user-friendly devices, provided earlier in the course of the disease, and engaging motivated carers may overcome many technological barriers. ALS may be considered a model for neurodegenerative diseases to further develop and test new technologies. From multidisciplinary teleconsults to telemonitoring of the respiratory function, telemedicine has the potentiality to embrace other fields, including nutrition, physical mobility, and the interaction with the environment. Brain-computer interfaces and eye tracking expanded the field of augmentative and alternative communication in ALS but their potentialities go beyond communication, to cognition and robotics. Virtual reality and different forms of artificial intelligence present further interesting possibilities that deserve to be investigated. COVID-19 pandemic is an unprecedented opportunity to speed up the development and implementation of new technologies in clinical practice, improving the daily living of both ALS patients and carers.

The present work reviews the current technologies for ALS patients already in place or being under evaluation with published publications, prompted by the COVID-19 pandemic.

Introduction

Amyotrophic Lateral Sclerosis (ALS) is a progressive neurodegenerative disease in which death occurs mainly due to respiratory insufficiency and respiratory infections. ALS patients are followed every 1.5-3 months by multidisciplinary teams, interval usually extended for slow progressors. Extra visits may be needed for respiratory, nutritional and psychological support (1).

Contrary to patients suffering a specific event in a specific moment, neurological or not, as a cerebrovascular injury or a fracture, in whom the natural course of the disease, assisted by co-adjuvant therapies including rehabilitation, progresses frequently from a considerable initial functional impact to higher levels of independence, ALS patients face the opposite track. From fully independent, patients with initial lower limb (LL) weakness need progressive assistance with gait and balance until being unable to climb stars, walk or maintain posture. Ankle-foot orthosis assist patients with drop foot but progressive disto-proximal LL weakness will require a cane/ walker, until wheelchair and bed confinement ensue. Upper limb (UL) involvement initially limits fine finger-hand motor skills, as needed for handling a needle. Other activities of daily life (ADL) are progressively affected as holding a pen and write, using the cutlery and self-feeding, grabbing a glass and drinking, using the computer or the cell-phone. From hand-wrist orthosis to assist on different

UL activities and positioning, many simple adapted devices facilitate ADL, including adapted cutlery with enlarged handles, sock aid sliders and button hook devices. Bulbar involvement leads to progressive language and communication deterioration with subsequent non-verbal compensation by writing and gestures, if and until UL functionality persists. Alphabet tables traditionally assist in communication, blinking the patients when the carer identifies the correct letter in a previous selected line to construct sentences. Drinking as well as chewing and swallowing food are also progressively impaired, as happens with the respiratory function, leading to total dependence of alternative nutritional and respiratory support, including nasogastric intubation or gastrostomy, and non-invasive (NIV)/ invasive ventilation and mechanical insufflation-exsufflation (MIE). Neck and trunk weakness have a negative impact in walking, standing, sitting, balance, UL activities, maintaining social interaction including communication, as well as eating and breathing, being ameliorated by orthosis.

ALS patients and carers have, nevertheless, already gained considerable individual independence as compared to other neurological diseases, regaining control of remote communication and operational manoeuvres by using domotics, augmentative and assistive communication (AAC) with eye-tracking (ET) and brain computer interfaces (BCI) support. The specificity of the ALS clinical impairment with loss of any motor initiative was one of the compelling reasons for ALS patients with preserved intellectual functions trying to maintain themselves active, creative, and even developing business plans. Every ALS Center has several examples of locked-in patients capable of communicating

and maintaining perfectly organized and efficient business. Young, instructed and professionally active patients are more sensitive to new technologies. Older patients, with lower education levels and not previously acquainted with new technologies, face considerable difficulties, requiring more time, encouragement, reinforcement and a closer support. AAC is a good example of this. Nevertheless, it has been shown that the earlier the adaptation, in earlier phases of the disease, the higher the compliance (2-4). More motivated patients, having younger motivated carers (5) and selecting user-friendly devices (4) are associated with better outcomes.

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 hospital visits. Its full impact is yet to be determined. It will surely provide the best benchmark for the fast implementation and development of emerging technologies in which telemedicine will have a central role. Telemedicine is particularly relevant for ALS patients with mobility limitations, especially as disease progresses, and for those living far from the tertiary ALS centres. Time, costs, and all the travelling logistics necessary to attend in-clinic visits, including carer absence from work and traveling with wheelchairs, respiratory and nutritional support, would be redundant. ALS patients are more than ready to be further fostered in the endeavour due to COVID-19.

The present work reviews the current technologies for ALS patients already in place or being under evaluation with published publications, prompted by the COVID-19 pandemic.

Definition of Emergent technologies and telemedicine

The Information and Telecommunications Revolution, also known as Digital Revolution or Third Industrial Revolution, was the most impacting technological revolution in the Human History so far, through the development and implementation of the Internet (6). "Emerging technology" is defined as a "radically novel and relatively fast growing technology characterised by a certain degree of coherence persisting over time and with the potential to exert a considerable impact on the socio-economic domain(s) which is observed in terms of the composition of actors, institutions and patterns of interactions among those, along with the associated knowledge production processes" (7). The development of new hardware/ software opened new opportunities in all fields, including in Medicine and Clinical Research, from robotics and BCI to artificial intelligence (AI).

Telemedicine is an open and constant evolving science incorporating new information and communication technological advancements to adapt and respond to the changing health care needs of the societies. The word "telemedicine" is used since the 1970s, initially meaning "healing at a distance" (8) and defined by the World Health Organization (WHO) as "The delivery of health care services, where distance is a critical factor, by all health care professionals using information and communication technologies for the exchange of valid information for diagnosis, treatment and prevention of disease and injuries, research and evaluation, and for the continuing education

of health care providers, all in the interests of advancing the health of individuals and their communities" (9). Home tele-management for chronic disease surveillance is of main concern for the European Community and the "vision for Europe 2020" calls for the implementation of telemedicine collaborative arrangements. In high income countries, it is mostly focused on diagnosis and therapeutics but, nowadays, it can be as wide as including evaluation, assessment, monitoring, prevention, intervention, supervision, education, consultation, and coaching (10), with the potentiality to transform health care delivery by shifting it from hospitals/ clinics to home care (11).

Already implemented or ongoing studies on emergent technologies and telemedicine in ALS

A. Telemedicine

a) Multidisciplinary consults

Multidisciplinary ALS consults have been sparsely done through telemedicine, either by live videoconferences on real-time, synchronous (12-24) or though the store-and-forward method, asynchronous (25). Videoconferences connect the multidisciplinary ALS teams at the tertiary centres to the patients at home, or to the local community hospitals/ health centres (12,21,22)

Two Australian tertiary hospitals established regular videoconferences with the local hospitals or community health services assisting ALS patients living far from the hospitals, thereby replacing the regular multidisciplinary in-clinic 3-mo consults (12). Videoconferences were considered feasible, although respiratory

and palliative concerns arose (12). Feasibility, even in advanced stages, was also reported by the tele-visit program as a supplement of the regular visits developed by the Massachusetts General Hospital ALS clinic (13). Patients lived 211 miles from the clinic (median) and the consults involved the contact with a physician and a nurse. Frequent addressed issues were medication management (89%), discussion of goals of care (74%), research (55%) and equipment use (50%). However, acute care issues were rarely discussed (13). Adjusted cost-savings to medical usefulness of those video tele-visits as compared to in-clinic visits were further addressed (14), representing, per visit, $997 for the patients (in-clinic visit $1116; video tele-visit adjusted for medical usefulness $119) and $327 for the institution (in-clinic visit $799; video tele-visit adjusted for medical usefulness $472). Patients and providers rated medical usefulness modestly lower for video tele-visits, despite following the American Academy of Neurology Guidelines (26), as compared to in-clinic visits. On the contrary, a study conducted by the Veterans Affairs ALS Center in Ohio addressing outcomes, disease progression, malnutrition and survival, reported that videoconsult multidisciplinary care provided by physicians, nurses and other health providers when needed, had the same quality and similar clinical outcomes as in-clinic visits (15). The latter group had previously used direct mobile videoconsults with patients or interaction through platforms with healthcare providers at the hospital in close connection with the ALS team referring economic and time benefits (22). High levels of satisfaction were reported in a prospective study addressing the feasibility and satisfaction of ALS patients, carers and healthcare providers with multidisciplinary tele-visits,

conducted by the Penn State Health Hershey ALS Center (16). Despite negative aspects (video/audio problems; no physical examination; no body language cues; more impersonal, less emotional connection; lack of privacy in individual conversations between the patient/ carer and the team), benefits included continuing providing care, understanding home dynamics of patients/ carers dynamics, no travel requirements, time savings in addition to less fatigue and stress for the patients, who were more comfortable and talkative (16). Two modalities of care were further assessed - full multidisciplinary visits with the ALS team on ALS clinic days or 1-on-1 visits with individual ALS healthcare providers on other days (17). The tele-visit modality was preferred by the patients living farthest, also the ones having poorer physical and respiratory function and more likely to use NIV (17). Despite patients' satisfaction, good acceptance and reduced time burden, psychological and emotion issues have also been identified as needing to be discussed with face-to-face contact. Therefore, teleconsults (performed through a platform with access to a chat room and videoconsults) were considered to be an addition to the face-to-face consult and not to replace them (20).

In Sheffield, questionnaires on the condition of patients and carers weekly collected by the Tele-health in Motor Neuron Disease (TiM) were evaluated by a nurse from the multidisciplinary ALS team, who could, afterwards, clarify the information by phoning the patient/ carer, expedite clinic appointments or establish a liaison with the team. Recordings included weight and balance, the revised ALS functional rating scale (ALSFRS-R), pain and saliva assessments, quality of life (QoL) scales, the Hospital Anxiety and Depression (HAD) scale, in

addition to the carers' strain, depression and anxiety (18,19). Reported potential benefits included improved communication and care coordination, reassurance, identification of complications and being an alternative or addition to clinic, although a friendlier algorithm to deal with clinical alerts was needed (18,19).

A store-and-forward method (25) by having nurse home-visits video-recorded and later discussed by the multidisciplinary team was considered to be feasible and gathering a good team satisfaction. The less positive points included lack of physical examination and being time consuming to review the videos, write recommendations and further discuss the plan with the patient, in addition to the necessary technological, financial and ethical support and considerations as well as the time required to train the nurse (25).

Multidisciplinary consults *via* telemedicine due to COVID-19 pandemic have been started in multiple centers worldwide. In Italy, a group has recently followed 32 patients with motor neuron disease (29 with ALS, 4 of whom with associated fronto-temporal dementia) with a structured questionnaire collecting demographics, clinical information and functional scale (ALSFRS-R) but also information addressing possible signs/symptoms of COVID-19 infection (23). The questionnaire was reported to be feasible and the team was able to detect respiratory deterioration at distance, including respiratory decompensation requiring urgent hospitalization. No patients were diagnosed with COVID-19. In the satisfaction survey via email or WhatsApp, 90% of the patients or carers were satisfied with the teleconsult (70% very satisfied), 85% felt as being talking to the neurologist face-to-face, and 90% were interested in continuing

the the follow-up visits through teleconsult, which could overcome social isolation, "abandoned" feelings during the illness as well as economic and time constraints associated to in-hospital visits (23). Telephone and/or videoconsults has also been reported to be implemented/ ongoing in ALS centres integrating ALS consortiums/ networks, namely the Northeast ALS Consortium (NEALS) (24) and the European Network for the Cure of ALS (ENCALS) during the COVID-19 (unpublished data).

b) Respiratory support

Initial works on telemedicine in ALS focused on home monitoring of the respiratory function when NIV was required. At the ALS Clinical Center in Lisbon, home telemonitoring was considered to be feasible and safe (27), decreasing the need for NIV parameter adjustments until achieving compliance and during afterwards monitoring. It increased survival, while decreasing health care costs as determined by the number of in-office and emergency room visits and hospital admissions (28,29). The authors used NIV devices with an integrated software, with internet access by TCP/IP connection and a modem station, allowing for real-time bidirectional tele-medical assistance, with immediate exchange of the ventilator data as well as parameter adjustments at distance. Home tele-monitoring and tele-assistance of home ventilated patients, not only with ALS but also with other neuromuscular disorders, were also effective by using a modem and a phone line connection to acquire patients' symptomatology and data from pulse oximeters at the Pulmonology Rehabilitation Center, IRCCS, in Brescia (30-32). The number of hospitalizations

and costs decreased, which was also reported when telemedicine was used to determine the need, on-demand, for MIE (33,34). In both the Portuguese and the Italian groups, telemedicine relied on a central control station, run by rehabilitation physicians in the Portuguese setting and by nurses with close connection to pulmonologists in the Italian group. In addition, both groups developed specific red flag alerts to call for a rapid medical response when needed. Hazenberg *et al.* (2014) followed patients with neuromuscular disorders using telemedicine (telephone calls in addition to data transmission from ventilator, nocturnal pulse oximeters and capnography) not only for monitoring NIV follow-up but also for its initiation, which was safe, feasible and cost-effective, with improvements in blood gas and in QoL not inferior to hospital initiation (35). Transmission of data from spirometry was also feasible with high acceptability by patients, carers and respiratory therapists, showing forced vital capacity (FVC) and maximal inspiratory pressure (MIP) a strong correlation between remote and the standard assessments (36). Recently, data from a self-reported questionnaire together with weekly ventilator and oximetry monitoring facilitated the maintenance of ventilation and SpO2 levels despite ALS progression (37). In patients with Duchenne Muscle Dystrophy (38) and Facio-Scapulo-Humeral Muscle Dystrophy (38,39) tele-monitoring for home ventilatory support through videoconferencing with a multidisciplinary team and tele-monitoring of cardiorespiratory variables (oxygen saturation, heart rate, blood pressure and electrocardiogram) was feasible, user-friendly, efficient and reduced the need for hospital admissions. Weaning a patient with Duchenne Muscle Dystrophy off the ventilator using telemedicine to connect the in-patient

visits by a nurse with a specialist at distance was also successful (40). In accordance with the statement of the European Respiratory Society Telemonitoring of Ventilator-Dependent Patients Task Force (41), more evidence is needed for the applicability and efficacy of telemedicine in ventilated-dependent patients. Nonetheless, its developments (including hardware, software and cloud platforms) are considered to be likely to change future home NIV management (41,42). Despite improving healthcare access, particularly in rural/ remote areas, a risk of reducing standard services in health systems of developed countries is a concern (41).

c) Physiotherapy

Pinto *et al*. (2012) established a home respiratory training program with compliance assessed every week by telephone calls and review of the every-day charts filled-in by the ALS patients (43). In-clinic visits at month 4 and 8 assured the clinical assessments. The protocol was feasible and safe, with high compliance. Braga *et al* (2018) monitored a home–tailored personalized exercise program, in a treadmill or walking outside. Heart rate and pulse oxygen saturation during the exercise were transmitted via Bluetooth from a non-intrusive biosensor to a mobile phone, wireless connected to a digital platform, being the data directly available for analyses (44). Telephone calls and email contacts with the multidisciplinary team were provided if necessary. The exercise monitored at distance through telemedicine was safe, feasible, with good compliance (44).

Controlling physical activity overtime in ALS is also feasible by its remote evaluation through accelerometers, with good compliance (93%), being the results strongly correlated with ALSFRS-R, with low variability (45). Physical activity has also been successfully assessed at-home through accelerometers and an ECG sensor in addition to in-hospital evaluations every 3-months, also including speech recording in the latter setting (46). Although comfortable and well tolerable, sensors can be associated to skin and subcutaneous lesions, specially dermatitis (46).

The Penn State Health Hershey ALS Center is presently assessing movement in relationship to falls in ALS at home through UL and LL wearable devices as well as a pendant monitor assessing general activity (17). Developing an automated fall detection algorithm is planned (17).

d) Nutritional support

A randomized open-label standard of care controlled trial compared nutritional counselling in ALS through an app to provide tailored nutrition recommendations as compared to counselling by a physician/ nurse (standard of care) and to in-person counselling provided by a dietician (in-person) (47). App recordings were done biweekly for dietary intake and weight or monthly if in-person. The app nutritional counselling was feasible, safe, but not superior to the in-person or standard of care at 6-mo follow-up (47). On the contrary, another group studied self-reporting through an app of weight (weekly) in addition to daily well-being and monthly functional status and considered it

easy, helpful and not burdensome, with an 83% adherence, adding value to the in-clinic visits and providing additional personalized feedback (48).

e) Telephone calls, emails, apps, and clinical trials

Surprisingly, immediate telephone calls to the healthcare team or emails are not a frequent resource for getting medical care, as represented respectively by 27% and 17% in a clinical survey carried out in the United Kingdom and Australia involving ALS patients (49-51). The exponential growth of telephone apps and different platforms have, however, been frequently used. Physicians can monitor, at distance, patient's symptoms, functional status through functional scales, and medication. It also engages and empowers patients in their clinical status and medical decisions and directly connects the patients one-another, as exemplified by the PatientsLikeMe platform (52). Defining automatic alerts to track clinical changes could allow the health teams to rapidly act upon them (16)

The need to promote patient recruitment in ALS clinical trials, at distance, decreasing the burden on patients/ carers, drove the Barrow Neurological Institute and the Beth Israel Deaconess Medical Centers to develop the ALS AT HOME web portal (53). Patients were recruited all over US, enrolled, consented and trained entirely at distance with online videos. The data from handgrip dynamometry, actigraphy, spirometry, electrical impedance myography, ALSFRS-R and patient reported experience measures, as well as speech trough a different application, were recorded and analysed (53).

B. Other emerging technologies

a) Augmentative and alternative communication (AAC) and cognitive assessments through Eye tracking (ET) and Brain-Computer Interfaces (BCIs)

AAC systems complement (augment) and substitute (alternative) verbal communication. Touch screen mobile phones and ipads, with software incorporating symbols/ words, frequently used words,' phrases, text prediction and synthesized speech, improve communication and QoL in ALS patients when introduced in early stages of the disease (4).

ET and BCIs allow ALS patients and others with severe motor involvement, particularly locked-in syndrome, to live, communicate and control the surrounding with software, electronic or electromechanical systems through brain activity, without muscle contribution. Controlling computers or wheelchairs and switching on-off electrical devices is thereby possible. In ALS, studies in ET and BCIs focus on its applicability in AAC and, lately, on the administration of neuro-cognitive tests/ tasks.

ET applicability for AAC in ALS patients addressed internet surfing, e-mailing, phone-calls and social networking, with good performance (54,55). In regular ET users, in late-stage ALS with tetraplegia and anarthria, ET increased communication abilities, QoL and patients' satisfaction (56). Not only ET for AAC improves Qol but it diminishes significantly caregivers' burden (57). QoL in locked-in state ALS patients is maintained on the cost of the QoL of their next

of kin, as assessed by ET (58), with well-being usually underestimated by carers (59).

Assessing cognition in non-verbal, unable to write ALS patients led to the development of neuropsychological assessments to be performed through ET. Keller *et al.* (2015) showed that performance accuracy in Raven's coloured progressive matrices was significantly correlated, as verified for d2-test only in controls but not in ALS (60). Results either in paper or through ET were lower in patients and discriminative of cognitive impairment. In a second study (61), similar results were reported when comparing the paper and ET-version of the Edinburgh Cognitive and Behavioural ALS Screen (ECAS) in ALS and controls, with a 95% specificity for cognitive discrimination. A ET-based cognitive battery assessing language, attention, executive and social cognition abilities developed by Poletti et al (2017), showed good levels of diagnostic accuracy and usability (62). The same group (63) used an ET-based cognitive assessment to perform a verbal-motor free cognitive flexibility test (Arrows and Colours Cognitive Test) in addition to other cognitive measures, showing significant correlations between them. Lower prevalence of perseverative errors was also observed and a successful discrimination between patients and controls, mainly in execution times, was recorded.

The development of eye-gaze fatigue and oculomotor impairment impairs ET's functional usage (55). Oculomotor movements are usually considered spared in ALS. Nevertheless, patients can present ophthalmoparesis, specially at late stages of the disease in long-surviving cases. Defective persuit movements, saccadic movements, nystagmus and abnormal Bell phenomenon

can also be present (64). P300 evoked potentials, steady state visual evoked potentials, mu rhythm or slow cortical potentials have been addressed in BCI overpassing ET's ocular limitations.

McCane *et al.* (2014) showed that most severely disabled ALS patients could use the Wadsworth BCI (P300-based) home system (65). Good BCI accuracies measures were achieved, despite disease severity, age, EEG montages or recording quality, with higher P300 amplitudes and more anterior located (fronto-centrally) in patients with good accuracies. Auditory and eyes-closed steady-state visual evoked potentials were suggested as an alternative if visual impairment was not overcome (by ptosis-glasses or eye-patch for diplopia). Using P300-based auditory BCI in ALS was feasible by using visual and/or auditory P300-based BCI to test controls and 3 patients in a four-choice oddball paradigm ("yes", "no", "pass", "end") (66). Nevertheless, the visual and visual plus auditory modality had higher accuracy levels, with higher speed.

By using a P300-based matrix speller, Nijboer et al. (2008) showed that severely disabled ALS patients could communicate producing both cued and spontaneous text, with relatively stable performance over a 40-week period, as demonstrated by P300 amplitude and latency (67). Not only in late stages of the disease but also in early and middle stages can ALS patients use a P300-BCI system for AAC, with a visual paradigm to choose between 4 icons representing basic needs (68). In the 1-year follow-up, BCI skills, including cognitive abilities, were maintained, despite disease progression, being patients' motivation higher when higher immediate benefit in its usage was obtained and in the elderly (68).

In USA, 42 male ALS patients without verbal and/or written communication were recruited to assess home function reliability and extent of use of the Wadsworth BCI home system for communication, using email and audio/ video programs (69). Telemedicine allowed for daily transmission of data on BCI use, including EEG activity, while home interviews and technical support were done at 3-month intervals. Fourteen patients (33%) completed the training and became BCI users. Eight completed the study. Death, rapid disease progression and decreased interest for BCI (in 6) conditioned study abandon. The system was reliable and useful for home communication. Patients' QoL did not decline overtime despite ALSFRS-R decay. According to most patients/ carers, BCI benefit exceeded burden. Rare technical problems were reported. Addressing speed, accuracy of selection (also dependent on carers' technical ability) and having more diverse computer applications were the suggested improvements while a dry-electrode technology, with easier usable caps, improved portability and telemetry would increase compliance and reduce its burden.

In Utrecht, subdural electrocorticographic electrodes (2 strips on the primary motor cortex, and two additional on the dorsolateral prefrontal cortex) were implanted in a 58-year-old late-stage ALS patient (70,71). Home communication use was frequent after initial training, mainly replacing an ET in unfavourable light conditions, especially outdoors, with progressive less effort although both having high levels of satisfaction. A reliable long-term functional stability was reported, despite slight increase in impedance until month 5 and a slowly decline of the power in the high frequency band (71). Performance was

high consistently, increasingly steadily overtime.

Cognitive functions in late-stage ALS patients were assessed by Iversen et al. by developing a SCPs EEG-BCI system, which required extensive initial training for controlling EEG components to move a cursor on a monitor (72). A series of two-choice cognitive discriminative tasks as well as matching-to-sample paradigm, assessing performance in discriminating numbers, letters and colours, and simple computations was addressed. In a second study (73), a conditional-associative learning task with arbitrary associations among visual stimuli (signs, coloured disks, geometrical shapes) was tested. Good levels of accuracy in performance and good verbal instruction-task response were achieved.

The development of neurophysiological batteries for ALS patients in late stages of the disease has been also addressed. After studying the feasibility of applying a modified version of the Phonemic and Semantic Verbal Fluency test as well as psychological and usability questionnaires through BCI and ET (74), Poletti et al. 2016 (75) applied a motor-verbal free neuropsychological battery, adapted from traditional neuropsychological tests (Token Test, Modified Card Sorting Test, Raven Coloured Progressive Matrices (Figure 1), d2-Test) using BCI (75). The battery correlated to the standard cognitive assessments, especially in the execution times, which was lower and discriminative in ALS patients than in controls. High rate of calibration accuracy, satisfactory levels of usability and sensitivity, independent from clinical factors (disease onset and clinical deterioration, using ALSFRS-R), and psychological factors (anxiety and

depression) were observed. However, reliability could be reduced by the length of time required for the administration of the tests and patients' cognitive effort.

Few studies have directly compared ET with BCI. When comparing ET with P300 BCI, Pasqualotto *et al.* (2015) showed that the information transfer rate and System Usability Scale score were significantly higher for ET, with a significantly lower cognitive workload (76). Therefore, ET seems to be more suitable for patients when no ocular involvement limits it, which can be overcome by BCI. The comparison of electrooculography, ET and auditory BCI for AAC tested by a regular low-tech AAC user in locked-in stage, was feasible but none were considered of an additional use although auditory BCI was recognized as favouring independence from eye control, but more tiring (77).

b) Controlling the environment

A robot tele-operated by ALS patients with a joystick and buttons and able to move around obstacles, pick up objects (despite different configurations and various types of flooring) and deliver them back (78) was successfully tested with high overall satisfaction (6.7 out of 7). It was considered to be significantly easier to use than the patients' own hands, asking family members for help or using mechanical reaching devices.

Sparato *et al.* (2017) studied the performance of locked-in ALS patients as compared to controls in controlling a humanoid robot through P300-BCI, to reach, grasp and give a glass of water (79). Three out of the 4 patients and all

controls succeeded in the task, without differences in the number of correct commands, percentage of success and accuracy, which was easy to use and comfortable for all participants finishing the task.

In Seattle, an eye-controlled power wheelchair prototype for ALS patients, integrating software-hardware technology not dependent on preserved motor function or speech, rather only on oculomotor function, has been developed (80). Twelve patients in different stages of the disease, without cognitive impairment, significant neck weakness, significant respiratory involvement or nystagmus, completed 3 trials of going forward and backward, stopping, turning and moving left and right. Eight performed the trials without errors. Errors were not related to clinical deterioration or glasses' usage although patients who committed errors were older. The rate of successful completion was 98.3% and the overall performance was excellent (4.6 out of 5), thus showing that the eye-controlled power wheelchair prototype was feasible, safe and with the potentiality of improving the mobility and independence in ALS.

c) Neurological evaluation using robots

Eleven ALS patients were studied in Colombia University with a robotic dynamic neck brace to characterize head motion with simultaneous surface recording of neck muscle activity (81). The microcontroller of the robot was wireless synchronized with the electromyography receiver. Maximal neck movements in the 3 anatomical planes were repeated 5 times each, at self-selected speeds. Compared to controls, the head of ALS patients failed forward quicker and required early activation of the extensor muscles to be decelerated.

In addition, there was a longer recruitment of splenius capitis muscle in lateral bending and sternocleidomastoid muscles in axial rotation, probably causing excessive fatigue.

Simmatis *et al*. (2019) used the KINARM robot to quantify UL sensorimotor and cognitive involvement in 17 ALS patients (82). Cognitive involvement was correlated to the MoCA and FAB tests and sensorimotor and proprioceptive impairments were identified.

d) Neurorehabilitation in ALS using robotics

Multi-functional robotics can not only be used for assisting the patients but also for their assessment, training and reassessment overtime, possible by using the same robot. Robotic rehabilitation in ALS is giving its first steps. Contrary to other non-progressive diseases that begin as an acute event, the required support by the robot in ALS patients would be minimal at early stages of the disease, when the intensity and frequency of the training can be higher. The progressive physical weakness in ALS requires higher support provided by the robot and successive adjustments in the intensity and frequency of the training (decrease effort). More complex robots and software will provide a wider range of programs, relevant for motor learning as it is task-specific. Associating visual and auditory biofeedback, as provided by softwares with task-specific exercises/ games, increase the efficacy of the training. In a recent study, a 2-mo specific task-oriented right-UL exoskeleton training (Armeo® Power®, Hocoma® AG, Switzerland) combined with conventional physiotherapy for the training of a 69-year-old woman with flail-arm syndrome, improved right

UL strength as compared to the initially stronger left UL (83).

For further information on the mentioned articles on other emergent technologies, please refer to Table 1.

Present moment at the COVID-19 pandemic and future developments

In the context of a highly contagious virus, for which the world population had not previous contact with, and without vaccines or effective therapies, more than 3.9 billion people (half of the world population) have been home confined in more than 90 countries/ territories. The population was asked to seek medical help only in acute cases to prevent being infected at healthcare infrastructures, with special advice for high risk patients, as ALS patients (84). Mask usage, home confinement and hand hygiene, in addition to the identification of a primary carer to coordinate and provide the care and an additional carer to cover for, if needed, were recommendations provided by an European group of experts for the ALS patients and their families/carers during this period (84). Hospital contact was promoted in the presence of symptoms suggestive of COVID-19, *de novo* respiratory symptoms or clinical respiratory deterioration related to the progression of the disease as well as respiratory emergencies (84). Medical conditions for when to physically contact the ALS team or the emergency room instead of relying on at-distance technologies are

proposed (Table 2). Planning, creativity and adaptability are essential to maintain the clinical care to these patients.

Steps have already been done in the way to move forward, being the widespread of telemedicine crucial. It has been shown to be feasible and safe, with good compliance and with time and cost savings for both patients/ carers and healthcare systems. The creation of platforms for bidirectional transmission of encrypted data, synchronization of devices, storage and data analyses, accordingly to ethical and political policies across countries, is essential. The availability of hardware and software, with the necessary adaptabilities to the patients during the progression of the disease, and the training of patients/ carers is a limiting factor. Nevertheless, tele-consults via internet or even over the phone (if no internet/ hardware availability), more focused on symptomatology and functional assessments, including nutritional, respiratory and psychological functional assessments, is feasible from day 1. In the market, not-so expensive sensors or basic devices are already available, which can, wireless or not, be connected to smartphones, to measure different biological parameters, including cutaneous temperature, heart rate, blood pressure, peripheral oxygen saturation, FVC, body positioning and even non-invasive ventilators and EEG. Many patients have already access to high-tech AAC devices (through ipads or or computers with specific writing programs and synthesized voice). ET can be feasible through goggles and adapted neurophysiological batteries tests are being developed. The implementation and the broad usage of what has already been validated in ALS is necessary. The creation of tighter clinical and scientific bounds between different ALS centers

highly recognized for their own specific competencies fundamental for the holistic care of ALS patients can surely boost the process, more orientated and with greater efficacy.

Robots are mainly used for scientific proposes, available only to a limited number of patients, under strict protocols. The costs of robotics represent the main limitation for its usage. However, exoskeletons are already being used in some neurorehabilitation clinics, either for UL and cognitive training (as the UL robots), or for balance and gait training (as the stationary, in a treadmill, or the over ground exoskeletons), with studies published mainly on stroke and spinal cord injury (85,86), as in virtual reality (87).

ALS patients represent a human population suffering from one of the most devastating diseases causing a progressive physical deterioration and leading to immobilization, while most maintain intact or mild-involved cognition. This, in pair with the fact that many patients are relatively young, instructed, professionally active when developing the first symptoms and sensitive to new technologies, offers the ideal field to the development of those technologies, thereby also offering a referral for other neurological diseases. Technologies used in video games and entertainment may have, in the near future, useful applications in telemedicine. Virtual (VR) and augmentative reality (AR) are already stablished, widespread on multiple devices and developing at a fast pace. VR fully immerses the user in a virtual world who interacts with it through wearable headset covering the field of vision with screens placed in front of the eyes. Through joysticks or other gadgets, virtual world interaction includes moving in virtual spaces, interacting with objects and people, having sensorial

hand experience through gloves (for example feeling vibration), or connecting and browsing the internet. Positive effects were already shown in patients with different neurological disorders (88). Contrary to VR, AR does not fully immerse the user in a virtual world but adds information to the real world. Filming an object with a smartphone triggers the object recognition software and adds information about it on the screen. Interactions with the information or other displayed things are also possible. AR is used in gaming and in other industries, for example to check if furniture fits physically and aesthetically into one's room. Other technologies offer great potentials by making objects "smart" without triggering actions by interacting in a virtual world. Hypersurface is a new technology combining vibration sensors to ML/ AI, transforming any object of any material, shape, and size in an intelligent object able to recognize physical interactions. In ALS, an array of gestures could be instantly recognized and trigger specific commands, ridding the patients of unnecessary keyboards, buttons, and touch screens. It may also quantify physical activity with placed referrals and may have unpredictable further applications to improve QoL in ALS patients thus deserving further consideration. Finally, AI is not one technology, but rather a collection of them with different processes and tasks. ML is a one of the most common forms of AI, a statistical technique for fitting models to data and to 'learn' by training models with data, with high importance to healthcare. The most common application of traditional ML in healthcare is precision medicine – predicting which treatment protocols are likely to succeed based on various patient attributes and the treatment context. A more complex form of ML is the neural network, available since the 1960s,

well established in healthcare research and used for categorising applications like determining whether a patient will acquire a particular disease. The most complex forms of ML involve deep learning or neural network models with many levels of features or variables that predict outcomes and future developments. It may also predict outcomes of the individual ALS patients. In the form of ML, AI is the primary capability behind the development of precision medicine, widely agreed to be a sorely needed advance in care.

Clinical trials represent a challenge in the era of COVID-19, as the existing protocols, in already on-going studies, have to be adjusted and new clinical trials are being postponed. The development of a new patient assessment, home-centred, by telemedicine and with access to the new emergent technologies, including end-effectors will allow for most evaluations to be performed. ML models/ AI will allow appraising candidate diagnostic, monitoring, and prognostic markers, as well as accurate patient stratification into well-defined prognostic categories, especially if large data sets of patients with exhaustive clinical characterization are available (89). The identification of the most likely medications and dosages that would be most effective to administer to ALS patients with specific identified phenotypes would certainly open new opportunities and bring new hope to the ALS community. COVID-19 pandemia may result in an unprecedented need to reset data managements and the high predictable clinical evolution of the ALS patients according to scales of functional evaluation (ALSFRS-R, 90) and stage progression (King's (91) and MitoS' (92) staging), already recorded for thousands of patients may

represent a previous referral to better define the impact of a new agents (SARS-CoV-2) on the clinical evolution of a high predictable disease.

Legal issues

From the intersection of technology and medicine emerges the generation and processing of people-related data. Although no global regulation exists, in many jurisdictions there are limitations, sometimes particularly strict on how to handle and use this data. In some countries, health data is treated as personal data while, in others, as particular personal data. In the United States, in general, personal data is considered marketable. In Europe, as opposed to the previous directive (European Directive 95/46/EC) (93) in which the protection of personal data was regulated with specific limitations on health data processing, the General Data Privacy Regulation (GDPR), European Union (EU) Regulation n.2016/679 (94,95), has no specific regulation regarding health data, beyond specific references related to the application of certain standards or institutions.

"Health-related data" or "data concerning health" is the "personal data related to the physical or mental health of a natural person, including the provision of health care services, which reveal information about his or her health status" (94,95). "Personal data concerning health should include all data pertaining to the health status of a data subject which reveal information relating to the past, current or future physical or mental health status of the

data subject". "This includes information about the natural person collected in the course of the registration for, or the provision of, health care services as referred to in Directive 2011/24/EU of the European Parliament and of the Council" (94-96) "to that natural person; a number, symbol or particular assigned to a natural person to uniquely identify the natural person for health purposes; information derived from the testing or examination of a body part or bodily substance, including from genetic data and biological samples; and any information on, for example, a disease, disability, disease risk, medical history, clinical treatment or the physiological or biomedical state of the data subject independent of its source, for example from a physician or other health professional, a hospital, a medical device or an in vitro diagnostic test." (94,95)

"Health data" is "Sensitive data" and, therefore, worthy of specific protection regarding fundamental rights and freedoms. Genetic and biometric data is considered in sensitive data (94,95), the processing of which, like for health data, may be subject to additional conditions and/or limitations, freely maintained or introduced by individual European Member States. Further fragmentation of the legal European regimes can occur, with potential legal uncertainties for the scientific research. Nevertheless, if the processing of health data is necessary to pursue scientific research purposes, GDPR requires the data controller to take technical and organisational security measures to ensure data minimisation (94,95). Minimum amount of data that may be lawfully processed is not indicated and does not expand the scope of scientific research to any type of activity carried out in the health sector. Researchers and organizations may carry out scientific research without seeking the consent

of the interested party (94,95). In some isolated cases, researchers could even transfer the data of the data subject abroad as the research purpose, to which society entrusts the improvement of knowledge, prevails (94,95). Organisations processing sensitive data for scientific research purposes may be exempt from the restrictions on the processing of sensitive data. Processing, further than that for which the data were originally collected, is lawful but compatible with the GDPR if also carried out for scientific research purposes and other requirements are met, including appropriate safeguards for the data subjects (94,95). Despite seeming comforting, doubts of interpretation regarding the suitability of the guarantees for the data subjects still persist, which must be provided by those carrying out the research, and regarding the very concept of scientific research, essentially left to the interpretation of the national regulation authorities, which are required to apply European and national law in each specific case.

Acknowledging the above obstacles, it is the intention of the Council of the EU German's presidency to improve pan-European access to and the exchange of health-related data, laying the groundwork for a transparent European healthcare data space that provides legal security and to set in motion efforts to draft a code of conduct for the use of healthcare data in line with data protection legislation (97).

Technology can be instrumental in reducing the legal interpretative uncertainty through anonymisation techniques. In some applications, current anonymization techniques for statistical databases exhibit significant limitations, related to the utility-privacy trade-off, the introduction of artefacts, and the

vulnerability to correlation. Some "recolouring" techniques have been proposed in order to preserve the same statistical characteristics of the original data up to the second order, but making data not directly linked to records of single individuals (98). The recolouring procedure considers the database as an instance of a random population and applies statistical signal processing methods to it. In response to a query, the technique estimates the covariance matrix of the original data and builds a linear transformation of the data, producing an output that has the same statistical characteristics of the original data (98).

Advanced life directives have been regulated in different countries. New technologies can overcome communication limitations in late stages of the disease, thus allowing for the patients to express their wills on one hand and, on the other, to perform cognitive–behavioural assessments that can influence their decisions (59, 99).

Conclusions

ALS represents a model to further develop telemedicine and new technologies, being the COVID-19 pandemic an unexpected opportunity to speed up the process. Telemedicine has already been successfully implemented in some ALS centers, mostly to provide multidisciplinary care and specific respiratory monitoring. Being feasible, safe, with positive cost-benefit aspects, its wide implementation worldwide should be promoted. Parallel to telemedicine, new technologies especially projected to facilitate ALS patients

and carers in communication, mobility, interaction and control of the environment, as well as cognitive assessment are ongoing and many already available for daily usage. Nevertheless, costs are usually a limiting factor, which can be overcome if more companies invest in their applicability in clinical settings and their usage is widely spread. Their control through telemedicine would provide a more planned and day-to-day adjustability to the patients' clinical needs in addition to advanced life decisions. Legal issues deserve more attention in the near future.

The advantage of a somehow predictable disease as ALS for what it concerns the clinical progression combined with the acquired familiarity with new devices offered by the modern technologies indicated ALS as a prototype for neurodegeneration to further address the issue of the most efficient care of progressively disabled patients in the modern era.

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Table 1. Other emerging technologies being tested in ALS

Table 2. Proposed conditions for when to seek physical contact with the medical personnel at health facilities *vs* when to maintain remote contact.

Figure1. A BCI session - the BCI version of Raven's Colored Progressive Matrices exemplifying the potential application of new technologies in providing tools for diagnosis and cognitive rehabilitation of ALS patients.

Legend of figure 1
Courtesy of Barbara Poletti

Table 1. Other emerging technologies being tested in ALS

Technology	Nr subjects	ALS staging	Study duration	Positive aspects
Communication				
Touch screen mobile phone/ ipad (symbols/ words, frequently used words/ phrases, text prediction, synthesized speech), internet	26 bulbar-onset ALS pts (27 recruited); 17 carers	Early stage	7-10 months	Positive effects in communication including performance and QoL for both pts and carers G1(users) as compared to G2 (non-users)
ET (ERICA) (face-to-face interaction, group communication, phone calls, email, internet surfing)	15 ALS pts	Different stages	nd	Good performance in all pts but 1.
ET Questionnaire on its home usage	35 ALS pts	Late-stage	One time questionnaire	Improvement in Communication ability, QoL; patients' satisfaction
ET (communication with relatives/carers, email, internet surfing, social networking) Questionnaire on its home usage	30 ALS pts	Late-stage, non-demented	One time questionnaire	Valuable for ALS pts using it for 15 months (median); daily usage: 300min (100-720); Good performance
ET (communications with carers, email, internet surfing)	20 ALS pts; 20 carers	Late stage	nd	Improvement in QoL of patients and decrease carers' burden of those using the devices (10p
ET (Questionaire on QoL)	11 ALS pts (30 screened); 9 next of kin	Late-stage	One time questionnaire	Feasible to assess pts. Pts reported good QoL apparently at the cost of their next of kin QoL. of kin and pts' QoL rated similarly by next of ki with different relevant identified areas)
ET Blink response (Questionnaire on QoL and end-of-life preferences)	19 ALS pts (out of 25 respondents); 19 carers	Late-stage	One time questionnaire	9 answered by ET, 3 by ET and eye-blink, 6 by blink and 1 verbally. Only 1 regular ET-user an previous user. ET and eye-blink were feasible acquire the answers Pts reported good QoL an non-significant depression, underestimated by carers, and being content to maintain life susta measures
BCI, non-invasive, visual and/or P300-based (4-choice oddball paradigm - attend to 1 stimulus and disregard the other 3. Stimuli: visual, auditory, or both)	3 ALS pts; 3 controls	Different stages, but retaining communication	6 weeks (10 sessions)	Feasible as a non-muscular communication de Higher accuracies and speed in visual and vis auditory modalities
BCI, non-invasive, P300-based matrix speller (copy-spelling; free-spelling)	6 ALS pts (9 recruited)	Late-stage	40 weeks	Home stable performance in communication producing both cued and spontaneous text.
BCI, non-invasive, P-300 based (visual paradigm with 4 icons in the screen, representing basic needs)	21 ALS pts (first assessment); 5 ALS pts (assessed longitudinally)	Early and middle stages	12 months, initial training period	BCI skills, including cognitive abilities, maintai overtime
BCI, non-invasive, P300-based (Wadsworth BCI home system, 8- and 16-channel montage); telemedicine	17 ALS pts (25 recruited)	Late-stage	One time evaluation	Feasible. Good BCI accuracies, despite diseas severity, age, EEG montages or recording qua
BCI, non-invasive, P-300 based (Wadsworth BCI home system, 8-channel); telemedicine	27 ALS pts	Late-stage	12-18 months, initial training period	Reliable, useful. Benefits exceed burden Patients' QoL did not decline overtime.
BCI, non-invasive, P300-based; ET, SeeTech Pro set,7×7 grid (copy-spelling task, online encyclopedia search task, playing 2 songs on a Web site task)	11 ALS pts (2 with bulbar-onset), 1 pt with Duchenne muscular dystrophy	Different stages, from Early to late-stages	2 sessions for BCI and 2 for ET	ET: faster and more accurate, with higher info pts, requiring less cognitive workload, and less BCI: more fatigue, probably affecting performa
EOG; ET; Auditory BCI.	1 ALS pts	Late-stage	3 sessions for EOG and BCI, 1 for ET	Cost, communication speed, carer' burden: low BCI: is the only that allows muscle-independen
BCI, invasive (subdural electrocorticographic electrodes);	1 ALS pt	Late-stage	36 months	BCI high consistent performance, increasing s overtime, replacing ET in unfavourable light

ET				conditions. BCI with high levels of satisfaction, progressiv usage effort, reliable long-term functional stab
Cognition				
ET (Eye Link 1000) BCI, non-invasive, P300-based (modified version of the Phonemic and Semantic Verbal Fluency test, psychological and usability questionnaires;	1 bulbar-onset ALS pt; 8 controls	Late-stage	Evaluation sessions	ET perceived as more usable. No negative aff state or anxiety with BCI or ET but a small anx increase after BCI in controls. Exploratory use in the ALS pt.
ET (Raven's coloured progressive matrices, D2-test (60) and ECAS (61).	48 ALS pts; 32 controls (60) 46 ALS pt, 50 controls (61);	Late stage	Evaluation sessions	Feasible for administer cognitive tests. ET and paper versions with significant accurac correlations in controls and ALS pts (60,61), b significant for D2-test in ALS. Lower results in paper and ET in ALS pts (60). Discrimination of cognitive impairment (60,61) Similar results for ECAS in paper and ET (61).
ET (Eye Link 1000) (cognitive battery addressing language, attention, executive, social cognition)	21 ALS pts; 21 controls	Non-demented and non terminal-ill	Two sessions within a week for each subject	Feasible to apply the neuropsychological batte Good levels of diagnostic accuracy and usabil both groups. Lower results in ALS pts for frontal, social cog and verbal fluency domains. Disease involvem did not impact ET usage.
ET (Eye Link 1000) (Arrows and Colours Cognitive Test and other measures of cognitive functions)	21 ALS pts; 21 controls	Non-demented and non terminal-ill	Two sessions within a week for each subject	Successful discrimination between pts- contro mainly in execution times. Lower prevalence o perseverative errors, than other error-types. Significant correlations between ACCT and oth ET-based frontal-executive measures but limit correlations with paper cognitive tests.
BCI, non-invasive, SCPs EEG (2-choice cognitive discriminative tasks; odd/even numbers, consonants/vowels, nouns/verbs, large/small numbers, shapes and colours/ simple computations (72) and conditional-associative learning task with visual stimuli arbitrary associations (signs, shapes, colours) (73)	2 ALS pts (72) 1 ALS pts (73)	Late-stage	Training sessions and a evaluation session	Feasible. Good performance accuracy (near 90% in (72 near 100% in (73)) and verbal instruction-task response.
BCI, non-invasive, P300-based (BCI-based neuropsychological assessment - Token test, d2 test, Raven's Coloured Progressive Matrices, Modified Card Sorting Test), standard cognitive screening tools, psychological questionnaires, usability questionnaire	15 ALS pts; 15 controls	Non-demented and non terminal-ill	Evaluation sessions	Feasible, with high calibration accuracy, usabi satisfaction and sensitivity, independent from disease onset/ progression, anxiety/ depressi respiratory involvement. Correlations between standard cognitive and B based neuropsychological assessment, mainly concerning execution times in ALS. Execution useful to discriminate pts - controls (lower processing speed in pts).
Controlling the environment				
Robot tele-operated using a joystick and buttons (task: move around obstacles, pick up and deliver objects)	20 ALS pts (21 recruited)	Different stages, non terminal-ill	One evaluation session	High overall satisfaction (6.7 out of 7). Significantly easier to use than the pts' own ha asking family members or using mechanical reaching devices, probably more useful for mo disabled patients
Humanoid robot P300-BCI (task: reach, grasp and give a glass of water)	4 ALS pts; 4 controls	Late-stage, non-demented	3 sessions for each	Easy to use and comfortable. Task completed pts and all controls. Tested at home in 3 pts. No differences in number of correct command percentage of success and accuracy between and controls.
Power wheelchair prototype Eye control (task: going forward and backward, stopping, turning and moving left and right).	12 ALS pts	Different stages, without cognitive impairment, significant neck paresis, significant respiratory involvement, nystagmus	3 trials	Feasible, safe, potential of improving the mobi and independence in ALS. Trials without errors in 8 pts. Rate of successful completion: 98.3% Overall performance: excellent (4.6 out of 5)
Neurological evaluation				

Robotic dynamic neck brace Surface electromyography (characterize head function)	11 ALS pts; 10 controls	Different stages	One-time assessment (3 motions in each plane, each done in a cycle, for 5 times at self-selected speeds)	Wearable and comfortable. Feasible to assess drop and disease progression. Head in ALS pts: Fails forward quicker and red early activation of the extensor muscles for deceleration. Longer recruitment of splenius ca in lateral bending and sternocleidomastoid mu in axial rotation, with excessive fatigue. Muscl activation correlated to clinical functionality an
KINARM robot Virtual reality system for biofeedback (quantify UL sensorimotor and cognitive involvement)	16 ALS pts, 1 PLS pt	Different stages, frontotemporal dementia was not an exclusion criteria	One time assessment	Feasible to assess cognition, sensorimotor an proprioception Cognitive involvement correlated to MoCA and tests. Sensorimotor and proprioceptive impairm were identified.
Neurorehabilitation using robots				
Exoskeleton training supported with virtual reality + conventional physiotherapy (specific task-oriented)	1 pt with flail-arm	Early-stage	2 months	Improvement right UL strength as compared to initially stronger left UL

For Abbreviations, please see refer to Abbreviation section.

Contact with medical personal at health facilities	Neurological status	First consult, diagnostic EMG, exclusion image exams
		Rapid clinical deterioration
		Intractable spasticity associated with pain
		Advanced life directives discussion and end-of-life interventions
	Respiratory status	*De novo* respiratory symptoms
		Adaptation to non-invasive ventilation
		Intolerance to non-invasive ventilation
		Tracheostomy intervention
		Respiratory decompensation (respiratory infections)
		Respiratory emergencies (aspiration, pulmonary embolism)
	Bulbar/ Nutritional status	Frequent swallowing problems with coughing/ choking
		Rapid weight loss
		Dehydration
		Gastrostomy intervention
		Adaptation to AAC
	Limb status	Venous thrombosis
		Falls and fractures
		Adhesive capsulitis of the shoulder with pain
		Intractable spasticity associated with pain
	Other medical conditions	Fecaloma
		Other acute medical conditions requiring interventive measures (diagnostic and/or therapeutic)
Optimal remote visit in ALS	Neurological status	Regular follow-up consults
		Functional scales including ALSFRS-R, and QoL scales
		Therapeutic prescriptions
		Patient/carer support
	Respiratory status	Regular evaluation of the presence of respiratory symptoms/signs of respiratory involvement
		Respiratory tests if available (nocturnal pulse oxymetry, home spirometry, peak expiratory flow)
		Regular NIV follow-up
	Bulbar/ Nutritional status	Regular evaluation of bulbar symptoms with impact on the nutritional status
		Nutritional tests (weight recordings, caloric and hydric intake recordings, energy expendure)
		Regular follow-up on gastrostomy care
		Speech recordings
		AAC training
	Cognitive status	Regular assessments, including emotional lability and cognitive-behavioural involvement
		Regular cognitive training
	Limb status	Regular assessment (mobility and posture including with sensors if available, fasciculations, cramps, muscle atrophy, retractions, skin lesions, limb oedema)
		Regular evalution of maximal articular amplitudes performed actively
		Muscle strenght evaluation (subjectively as for localized weakness of the neck, hands, etc, and objectively if a home dynamometer is available)
	Other medical conditions	Regular checking on the stability of other medical conditions

For Abbreviations, please refer to "Abbreviations" section.

Highlights for review

- ALS is a model to further develop telemedicine and new technologies, being the COVID-19 pandemic an unexpected opportunity to speed up the process.

- Telemedicine has already been successfully implemented in some ALS centres, being feasible, safe, with positive cost-benefit aspects.

- New technologies especially projected to facilitate ALS patients and carers in communication, mobility, interaction and control of the environment, as well as cognitive assessment are ongoing and many already available

- The control of the new technologies by telemedicine will further promote the care to ALS patients.

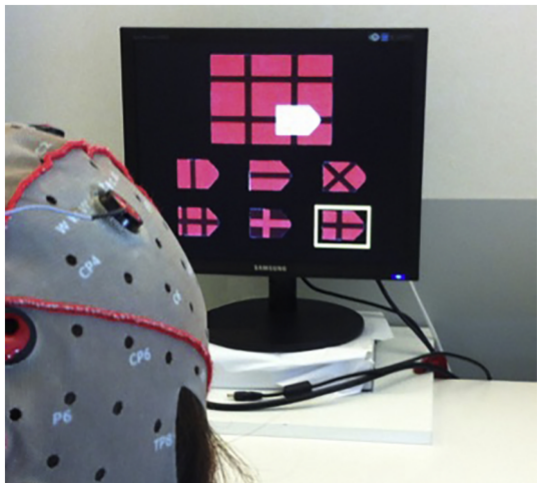- Legal issues deserve more attention in the near future.

Figure 1