IDP-01 ‘CONFIDO’: a pilot study of dog-assisted therapies in ALS patients

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Keywords: dog-assisted therapy, anxiety, physiotherapy and occupational therapy

Background: Animal-assisted therapy (AAT) is an intervention with precise therapeutic objectives in which the animal acts as a co-therapist. Few studies investigating animal-assisted therapy from the rehabilitation point of view are available (1–3).

Objectives: The aim of the present study was to assess the impact of dog-assisted therapies in rehabilitation programs in patients with neuromuscular diseases.

Methods: 50 hospitalized patients with Amyotrophic Lateral Sclerosis (ALS) were enrolled in the study. All patients ran a regular rehabilitation treatment in the morning for five days a week. 25 of them were assigned to receive, in addition, Pet Therapy protocol, consisting of dog-assisted physiotherapy or occupational therapy, according to type of motor disability, three afternoons a week, while 25 control patients performed the traditional physiotherapy/occupational therapy treatment three afternoons a week. Each participant was evaluated before (T0) and after 2 weeks of training (T1). Motor performance and psycho-emotional state were assessed. All patients underwent the following scales: HADS (hospital anxiety and depression scale), MRC (Medical Research Council score) and ALSFRS-R (Revised-ALS functional rating scale). Furthermore, patients enrolled in the occupational therapy sub-groups performed nine hole peg test (NHPT) and strength measurement assessed by dynamometer, while patients enrolled in the physiotherapy group underwent Short Physical Performance Battery (SPPB) and Six Minutes Walking test (6MWT). Two different dogs were used in the therapy protocol, both were Swiss White Shepherds, with excellent and advanced education, with peculiar skills such as the ability to relate emotionally and dynamically to the patient.

Results: By comparing pre-treatment (T0) vs post-treatment (T1) tests results, both pet-treated and control group and their respective physiotherapy and occupational therapy sub-groups have a trend, although not statistically significant, to improvement at all the scales taken into account. Level of anxiety results, evaluated by HADS, were, however, significantly reduced (p<0.05) in the pet-treated group compared with the control group.

Discussion and conclusion: This is a pilot study showing that trained dogs can be an additional tool for global rehabilitation of patients affected by ALS. The present study demonstrates a significant therapeutic effect on anxiety. In conclusion, pet-assisted physiotherapy and occupational therapy have the same benefit on functional parameters compared to standard therapies, but have the advantage of being very appreciated by most patients, positively affecting mood, by reducing in particular anxiety. More studies are needed to explore indications and limits of the intervention.

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IDP-02 The twin cities ALS research consortium: a model for regional collaboration in advancing research for people living with ALS

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Keyword: clinical trials
Background: There is a recognized need to increase participation in ALS clinical research among people living with ALS (PALS). One of the potential barriers to participation among PALS living in metropolitan areas is a perceived or real lack of collaboration across ALS research centers. The Minneapolis-St Paul metropolitan area has a unique opportunity to overcome this barrier, as ALS providers in four academic centers share University of Minnesota faculty appointments and participate actively in regular regional clinical and research meetings hosted by the ALS Association Minnesota/North Dakota/South Dakota chapter. Recognizing an opportunity to combine complementary strengths across centers, the ALS providers at the ALS Association Certified Treatment Centers of Excellence at Hennepin County Medical Center and the University of Minnesota have joined forces with the HealthPartners Neuroscience Center and the Minneapolis Veterans Affairs Medical Center to form the Twin Cities ALS Research Consortium (TCALSRC). All clinical research at TCALSRC centers endeavor to include principal- and co-investigators from at least two participating centers and, to whatever extent possible using courtesy appointments, investigators are encouraged to recruit and evaluate their own patients to all TCALSRC studies at whichever institution is contracted as the study site. Monthly meetings assure that all investigators and coordinators are up-to-date on current and planned projects and have an opportunity to share ideas.

Methods and results: The TCALSRC model encourages active investigator and PALS engagement throughout the metropolitan region, regardless of the study site, thus enhancing recruitment as well as value of the site to sponsors and consortia. Contracting sites are rotated among participating centers with a view toward equal participation, but also based upon the complementary research interests of individual principal investigators and the unique resources that might be available at certain institutions.

Discussions: The TCALSRC is currently exploring regional expansion to engage other outstanding ALS clinicians in Minnesota and the Dakotas. The TCALSRC is a model for advancing ALS local and regional clinical research, with several centers committed to advancing ALS research and care.

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Keywords: machine learning, diseases state prediction, ALSFRS

Background: Using past information about a patient, a physician can make more reliable future decisions regarding that patient. This is usually done by incorporating old with new information, giving the latter a higher weight. In this research, we use machine learning tools that mimic the physician’s line of reasoning and action.

Objectives: Anytime accurate prediction of a future ALS functional rating scale (ALSFRS) — a measure that reflects the patient medical condition — can help both physicians and their patients to adjust the treatment and living environment of the patients along the disease period.

Methods: Using data from several clinic visits of a patient in the PROACT database and a machine-learning algorithm that combines past information about this patient with new information, we produce an accurate prediction of the patient’s future state. The relevance of past information to the prediction dynamically adjusts the algorithm during training according to the level of contribution of this information to the prediction. In contrast to other machine learning models, our algorithm allows incorporation of dynamic variables, such as laboratory test results and vital signs, into the prediction.

Results: Data of 1,195 patients were used for training and testing the algorithm. Using information of all clinic visits of a patient within a period of 90 days, we predicted the ALSFRS value of this patient in a future visit, at least 270 days after the last observed visit. By comparing ALSFRS prediction values with the real ones for an examined visit, we demonstrate that our model achieves a higher accuracy than a model learned using another state-of-the-art prediction algorithm. The difference in performance between the two is statistically significant ($p$-value lower than $1e-06$). Even when changing the prediction range, ie. the period between the last observed visit and the predicted visit, the model maintained its superiority.

Drilling down into the results, we can determine that, due to their large number in the patient population, the prediction accuracy of patients whose disease is not very progressive is even higher than the average accuracy measured over the whole population.

Discussion and conclusion: Our suggested framework for predicting the ALS disease state is analogous to that practiced by physicians and is very accurate and, thus, may easily be adopted by the medical community.

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IDP-03 Dynamic weighting of old and new information for predicting future condition of ALS patients

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Keywords: machine learning, diseases state prediction, ALSFRS

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IDP-04 Displaced reality: the challenges of creating an ALS clinical study in which all data collection takes place in the patient's home

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Keywords: clinical trials, outcome measures, self-assessment

Background: Most ALS therapeutic clinical trials are organized in a fairly standard fashion; patients are screened and enrolled at an ALS center and return regularly for efficacy and safety evaluations. Efficacy evaluations occur every 2–3 months and include measures of physical function, questionnaires and blood tests. These visits are often supplemented by phone calls or emails. The total number of visits is usually less than eight over a 1-year period.

We sought to develop a new paradigm of clinical trial organization in which data collection takes place in the patient's home either by the patient or a dedicated caregiver on a very frequent basis using simplified versions of commonly used outcome measures. Our approach differs from other groups developing web applications in which data such as activity is monitored without specific actions required by the subject.

Objectives: To describe the challenges of setting up an at-home clinical study in which all the patient components, from pre-screening to consenting to data collection, are completed remotely.

Methods: We developed an Internet-based multi-component clinical study to assess ALS progression on a day-to-day basis. Recruitment is achieved mainly through Internet-based advertisements. A website (ALS-at-home.org) has been developed which contains a set of pre-screening questions. Upon successful completion of the pre-screening questions, the patient is contacted by a study liaison who further describes the study and arranges for medical records to be sent. After confirmation of eligibility, patients are consented via an online webinar. Subjects are then shipped devices that interact with their smart phones to allow them to collect data on speech performance, handgrip strength, multi-muscle impedance, vital capacity, functional status and activity. Ongoing compliance is monitored daily by study personnel and an automated reminder system ensures subject engagement.

Results and discussion: A variety of challenges have been identified that required a series of innovations. These included: 1) Ensuring complete anonymity during the consenting process and webinars via the use of a global unique identification (GUID) number; 2) The development of web based consenting and training videos; 3) The implementation of iOS and Android ALS-at-home apps that synced data from device-specific apps to a research electronic data capture (REDCap) database; 4) Syncing of the REDCap database with email servers to send automatic reminders to participants if they forget to collect data; and 5) Ensuring consistent performance of web and email servers to send reminders in a timely fashion.

Conclusions: The development of a completely remote clinical study is feasible. Our work identifies a number of potential challenges to successfully launching such an investigation and straightforward steps to solving them.

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IDP-05 NeuroGUIDization of PALS population as a necessary condition for patient-centric research and care

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Keywords: NeuroGUID, NeuroBANK, patient-centric research

Objective: To establish an approach and processes to facilitate international collaboration in patient-centric research and care while protecting patients' privacy by adopting a Neurological Global Unique Identifier (NeuroGUID) platform.

Background: Medical research relies on the multitude of data accumulated from various sources such as health records, clinical trials and self-reported patient information, which needs to be aggregated and records for individual patients must be linked across data sources. However, Health Insurance Portability and Accountability Act (HIPAA) regulations present significant difficulties with regard to sharing the protected health information (PHI) preventing from using PHI or any directly derived information for patient identification.

Methods: The Neurological Global Unique Patient Identifier (NeuroGUID) technology and platform make it possible to link separate datasets into a coherent harmonized data-sharing environment, while maintaining HIPAA compliance. To achieve this goal, a domain-specific central authority for generating NeuroGUIDs suitable for inclusion in de-identified datasets is set up by the Neurological Clinical Research Institute. The advantages of using NeuroGUIDs are: (a) PHI does not leave the client computer; (b) The generated ID is a random string that is not derived from the PHI; (c) IDs are centrally generated and available for use in multiple applications and on various platforms (d) Independently
produced datasets can be linked together; (c) In the case of insufficient patient information for a successful NeuroGUID generation, a pseudo-ID may be generated and later be replace with a real NeuroGUID, which is advantageous for legacy datasets integration; (f) Generated NeuroGUIDs are unique yet untraceable back to the patient; and (g) Recently introduced NeuroTOKEN generation capability allows one to use unique identifiers within datasets that may contain PHI data, such as EHR/EMR systems, mobile apps, etc., i.e. in any environment where the association of PHI with NeuroGUIDs should be prevented.

Results: NeuroGUIDs are widely accepted among researchers in rare neurological diseases, especially in ALS/MND. NeuroGUIDs and their derivatives (NeuroTOKENs) are utilized to connect clinical and research data to biospecimen collections (embedded into bar-coded labels on biofluids and post-mortem tissues), images (introduced into image headers), WGS files, cell lines, EHRs and mobile apps.

Conclusions: NeuroGUID technology is uniquely suitable for use with de-identified datasets. It links biosamples and images with clinical data and electronic health records. Clinicians and researchers utilize this technology, which facilitates international scientific collaboration.

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IDP-06 PRO-ACT: meta-analysis of concomitant medications and active ingredients on disease progression

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Keywords: PRO-ACT, concomitant medications, disease progression, active ingredients

Objective: To analyze influence of concomitant medications on disease progression in the PRO-ACT database.

Background: The Pooled Resource Open-access ALS Clinical Trials (PRO-ACT) platform and database houses the largest harmonized dataset from 23 completed clinical trials in ALS (10,724 subjects). PRO-ACT™ approach proved its efficiency and serves as a de-facto reference knowledge base with tens of published papers, developed models and performed analyses to its credit. Still, it contains a lot of information that has not been yet utilized.

Methods: There are almost 112K records of concomitant medications (ConMed) in PRO-ACT, which we converted to the standard WHO-supported dictionary, identified active ingredients in those medications and analyzed ALSFRS-(R) slopes as follows: 1) Converted 111,848 records per WHO-DRUG dictionary; 2) Generated list of drug name and their ingredients from WHO-DRUG; 3) Converted drug names in PRO-ACT to drug ingredients, (a) ConMed records in PRO-ACT: 111,848, (b) Unique ConMeds in PRO-ACT: 6,569, (c) ConMed ingredients records in PRO-ACT: 377,163; 4) Created list of ingredients present in 25+ patient ConMed records, (a) Unique ingredients in PRO-ACT (25+ patient records): 964; 5) Created list of records for subjects with more than one ALSFRS/ALSFRS-R record: (a) Subjects: 6,565, (b) Records: 60,288; and 6) Generated matrix of ingredients present per subject in ConMeds records: (a) Average number of ingredients per subject: 27. Empirical Bayes estimates of ALSFRS-R slopes and their standard errors were obtained from a random-slopes model that included 3,504 participants who had at least 2 ALSFRS-R observations. Estimated participant-specific slopes, weighted by the inverse of their squared standard error, were regressed on known predictors of differential rates of progression (baseline ALSFRS-R, bulbar onset, age at symptom onset and symptom to diagnosis lag) and indicators for baseline use of 964 distinct medical ingredients. The data set was split 1:1:1 to training, validation and test sets. Least-angle regression was used to identify medical ingredients predictive of differential rates of ALS progression, based on reductions in averaged squared error of predictions in the validation data set.

Results: Results of meta-analysis for top 20 medical ingredients identified to potentially influence disease progression slopes will be presented.

Conclusions: With more clinical trials datasets becoming available, standard methods and approaches shall be developed to rapidly screen updated dataset for new discoveries. Data from clinics and natural history studies may improve results.

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IDP-07 The ALS stratification challenge: using big data and predictive computer models to identify clinically significant ALS patients sub-populations

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Background: One of the biggest challenges in ALS treatment and research is the disease’s heterogeneity: ALS patients have widely different patterns of disease manifestation, rate of progression and clinical prognosis. This heterogeneity has detrimental effects on clinical trial planning and interpretation and on attempts to uncover disease biological mechanisms. Thus, stratifying ALS patients into clinically meaningful sub-groups can be of great value for advancing the development of effective treatments and achieving better care for ALS patients.

Objectives: We aimed to use the power of state-of-the-art machine learning algorithms applied to large-scale clinical databases of ALS patients to uncover and characterize homogeneous sub-populations of ALS patients with respect to two important clinical targets: ALSFRS progression and survival.

Methods: The 2015 DREAM ALS Stratification Prize4Life Challenge was a crowdsourcing initiative that invited participants to create algorithms to identify sub-groups of patients and through that improve prediction of ALS disease progression and patients’ survival. To achieve a diverse dataset, we used two data sources: ALS clinical trials data from the PRO-ACT database and community-based ALS clinical data from ALS registries in Italy and Ireland. Thus, the challenge was divided into 4 sub-challenges in which participants predicted either disease progression or survival while using data from either the PRO-ACT database or ALS registries. We assessed submitted algorithms’ performance against 2 baseline algorithms, using three evaluation metrics: Pearson’s correlation, concordance index, and root-mean-square-deviation.

Results: The challenge ran between June—October 2015, and final submissions were made by 30 teams, with a prize of $28,000 divided equally between the 4 best performing algorithms. For almost all teams, predictions were substan-
ially better than random and top performing teams significantly outperformed the baseline algorithms. Patient clustering gave the most accurate predictions of disease progression for the registry data and performed generally better when applied to fast progressing patients. We used challenge participants’ clustering results to detect patients who were consistently grouped together. This analysis identified, for each of the four sub-challenges, small sets of discrete ‘consensus clusters’. Each of these novel sub-groups of patients had distinct clinical and physiological characteristics and disease outcome profiles. A few of the most distinctive features separating the clusters were: age, time from disease onset, disease progression rate and survival, mobility, bulbar function, creatinine levels and the prevalence of bacterial infection and its biomarkers. Notably, we identified similar sub-groups of patients across different data-sets and predicted outcome measures.

Conclusions: These results demonstrate the value of large datasets and crowdsourcing challenges for developing a better understanding of ALS. We showed that ALS patients can be stratified into a few consistent and clinically-significant sub-groups, which can be used for improving prediction algorithms and guiding clinical care, research and drug development efforts.

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IDP-08 Stratifying ALS patients by disease progression patterns

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Keywords: disease progression rate, disease progression pattern, patient stratification

Background: A predominant problem with designing clinical trials is the heterogeneity of the ALS population. Issues such as disease progression rate, pattern of progression and more vary greatly among patients so that it is often extremely difficult to reach statistically sound conclusions in clinical trials and large numbers of participants are required for these.

In the past, studies have attempted to find meaningful sub-groups among the patient population. These studies have usually concentrated on specific features or rate of disease progression.

Objectives: Our goal was to suggest a new method of stratifying ALS patients. We aimed to show that it is important to inspect disease progression patterns as characteristics of the disease and that patients can be usefully stratified with respect to such patterns.

Methods: We suggest a feature representation based on the multi-dimensional nature of the amyotrophic lateral sclerosis functional rating scale (ALSFRS), which allows us to capture these patterns. We leverage the natural correlation between the ALSFRS items to reduce the dimensionality of the space we are searching. We represent each patient as a vector of ALSFRS grouping derivatives (ie. deterioration rates) and then identify these patterns using unsupervised learning techniques. Specifically, we apply K-means clustering in a bootstrap sampled fashion to the database (n=2,475) and evaluate the results with the Davies-Bouldin index (an evaluation metric for clustering partitions).

Results: We show that the best stratification as measured by the Davies-Bouldin index on the PROACT data yields an interesting division into four distinct groups of patients. These groups are differentiated by the rate of disease progression (ie. fast, moderate and slow progressors) and
also by the pattern of progression. Among the groups, two can only be differentiated among by looking at specific patient functions (as represented by the different ALSFRS items) and divided into those with rapid bulbar deterioration and those with rapid limb functionality deterioration. Further, to test the validity of our distinctions, we visualized the stratification in a set of 2-dimensional spaces (ie. scatter plots) and compared characteristics of the groups. We then suggest three methods for predicting a patient’s future progression pattern using features from early stages of the disease and evaluate these methods on patient data. Finally, we evaluate the usefulness of the clustering to improve predictive performance on a benchmark disease progression prediction task.

**Discussion and conclusions:** Our work suggests two important results: 1) inspecting disease progression patterns yields a novel, interesting and useful manner of stratifying patients, and 2) this stratification can then be used to improve performance of systems that predict future disease progression rate, thus further validating the usefulness of our results.

**Methods:**

**Objectives:** To improve our ability to assess treatment influence, to decrease the sample size needed for clinical trials, and to shed more light on unknown mechanisms in the disease, we suggest a machine-learning algorithm for prediction of the ALS progression rate and creation of reliable clustering, ie. grouping of patients according to their deterioration patterns.
Methods: Since patients’ condition and, thus, the ALSFRS value deteriorate over time, it is vital for a prediction algorithm to model ALS in a fully-temporal approach, namely using data from as many clinic visits as possible. An implementation of a fully-temporal machine-learning algorithm for learning a graphical model of disease trajectories is presented. The model predicts a future ALSFRS value using four components that capture the complexity of the disease trajectories: (A) Population component – Shared by all patients and represents a general disease progression; (B) Sub-population component – Added to the population component to reflect a progression rate of patients with similar characteristics; (C) Individual component – Affects the prediction by incorporating past information regarding the individual we are making the prediction for; and (D) Noise component – Models events that do not stem from the disease, but affect the patient’s condition.

Results: Data of 3,925 patients from the PROACT database was used for training and testing the model. The main results of our experiments are: 1) Online prediction – Our model improves prediction (its prediction error decreases) as more data regarding a patient is available for the model; 2) Clustering – Using the error of future prediction as a measure, patient stratification into 10 groups/clusters gave the best performance. Visualizing the clusters’ disease trajectories showed a significant difference between them, which suggests that the model has managed to group the patients well; and 3) Predicting by ALSFRS items or groups – Three prediction set-ups were examined: (a) Prediction of the total ALSFRS; (b) Prediction of each ALSFRS item separately; and (c) Prediction of ALSFRS for five groups of items. Using set-ups (b) and (c), we were able to maintain the level of accuracy of set-up (a), while giving a more informative prediction.

Discussion and conclusions: To the best of our knowledge, this is the first research study in which ALS disease progression has been modeled using a fully-temporal approach. The results show that, by using the suggested model, we are able to improve our predictions and better cluster patients.

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IDP-11 Modeling neuroanatomic propagation of ALS in the spinal cord
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Keywords: stochasticity, computational models, anatomical progression

Background: Last year at this meeting we proposed a stochastic diffusion model of ALS progression. Here, we extend the model to connect the molecular/cellular level model with the patient level by mapping patterns of neuronal degradation in the spinal cord with progression patterns in clinical assessment data. Our model is based on the hypotheses of amyotrophic lateral sclerosis (ALS) progression that posits a point source origin of motor neuron death with neuroanatomic propagation either continuously to adjacent regions or along networks via axonal and synaptic connections. Although molecular mechanisms of propagation are unknown, one leading hypothesis is a ‘prion-like’ spread of misfolded and aggregated proteins, including SOD1 and TDP43.

Aim: To use mathematical models combined with clinical assessment data to quantify and characterize the cellular and molecular spread of ALS in the human spinal cord.

Methods: Our mathematical model utilizes the stochastic reaction-diffusion master equation approach on a discretized human spinal cord reconstructed from magnetic resonance (MR) images. To inform and evaluate our model on human data, we will use the ALSFRS-R score progressions (eg. swallowing, walking) mapped to somatotopic regions to create progressions for our simulated ALS model trajectories. Then, by comparing these simulated trajectories to patient progressions, we infer model parameters using the approximate Bayesian computation procedure.

Results: Our model recapitulates features of the spread of ALS in the human spinal cord. Specifically, a constant spread of ALS, despite an exponential increase in the amount of misfolded protein. We observe ~20% neurons remain after the front of neurons affected by the disease has passed, which qualitatively corresponds to observations from post-mortem analysis. Combined with our analysis of the PRO-ACT clinical progression data to identify rates and classifications of disease progression and the most probable patterns of cellular degeneration, our model make it possible to test (in silico) hypotheses concerning proposed mechanisms of disease degeneration and validate them against the progression patterns derived from patient data.

Conclusion: Future studies will extend our preliminary model of ALS propagation to better explain variability of this disease and to address open questions in the field, namely: 1) the validity of the prion-like hypothesis of ALS, as it relates to predicting topographical propagation of neurodegeneration in ALS; 2) relative importance of contiguous/network spread in phenotypic and genetic variants of ALS; 3) relative importance of parameters in determining phenotypic variability; and 4) the role of selective vulnerability of motor neurons and other cell types in the spinal cord. Finally, we anticipate our modeling framework of disease progression will be useful in predicting the phenotypic effect of putative pharmacotherapies that may inhibit production and/or accelerate degradation/clearance of abnormal proteins in ALS and possibly other neurodegenerative disorders.

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IDP-12 Validation of predictive ALS machine learning models with a contemporary, external dataset

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Keywords: machine learning, predictions

Background: Patient disease heterogeneity is widely believed to be a confounding factor in the analysis of ALS clinical trials. In particular, deaths and, at the other extreme, slowly progressing patients may be the root causes of the observed heterogeneity. As a step towards solving this problem, we report on several ALS predictive models.

Objective: To validate the models using the BENEFIT-ALS placebo arm data set.

Methods: We have developed baseline and run-in gradient boosting machine regression models (GBM) for the prediction of ALSFRS-R, gross motor sub-score, fine motor sub-score, bulbar sub-score, respiratory sub-score and vital capacity using the PRO-ACT ALS database and determined the performance characteristics of each model. Internal 10-fold cross validation was performed to assure the reproducibility of the model. The BENEFIT-ALS placebo data set (ClinicalTrials.gov trial # NCT01709149) was used as a contemporary external data set to validate and assess the generalizability of the models. Criteria for the validation of the models was set a priori to be that the root-mean square difference (RMSD) using the BENEFIT-ALS data set was to be no more than 5% greater than the RMSD of the internal validation and that the model shall not exhibit signs of bias as evidenced by a bootstrap mean prediction error for the BENEFIT-ALS data set that includes zero within the 95% confidence interval.

Results: Both run-in and baseline models were validated using the BENEFIT-ALS placebo arm data set.

Conclusions: A GBM model platform capable of predicting several key ALS disease progression metrics has been developed. This platform has applicability for both patient care and drug development.

Acknowledgments: Data used in the development of the models used in this study were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database. This work was funded by the Amyotrophic Lateral Sclerosis Association, grant 17-LGCA-333.

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IDP-13 Machine learning models for the assessment of potential ALS biomarkers

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Keywords: machine learning, predictive model, biomarkers

Background: This is the first step of a research study that aims to develop a machine-learning-based platform against which potential biomarkers of ALS disease can be tested as surrogate markers of disease progression. Recently developed baseline and longitudinal forced vital capacity (FVC) models are used as base models for the assessment of potential prognostic ALS biomarkers. These methods have been successfully applied to the evaluation of imaging markers in Parkinson’s Disease.

Objective: We hypothesize that machine-learning-based FVC models can be used as tools to assess the relative importance of potential biomarkers as predictors of ALS disease progression.

Methods: We previously reported the development of gradient boosting machine learning models (1) for the predictions of FVC at future timepoints. These models are used to evaluate the importance of potential prognostic biomarkers relative to other predictors in the model. The performance characteristics of the models will be assessed prior to and following the addition of the potential biomarkers, alone and in combination. In addition, the importance of the biomarkers relative to other predictors in the model will be determined. Markers with predictive potential will ideally improve the overall performance of the models and rank highly in relative importance.

Results: We designed a predictive modeling platform for validation of potential biomarkers predictive of FVC progression in ALS patients. The baseline FVC model was used to evaluate the potential diagnostic value of biomarkers and the longitudinal FVC model was used to evaluate the potential prognostic value of biomarkers.

Conclusions: A machine-learning-based model platform for validation of potential biomarkers in ALS disease was developed. Our preliminary data support the hypothesis that these models can be used to assess the diagnostic and prognostic potential of ALS biomarkers.

Acknowledgments: Data used in the development of the models used in this study were obtained from the Pooled Resource Open-Access ALS Clinical Trials (PRO-ACT) Database.

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IDP-14 Utility of the ALSFRS-EX to measure function in advanced ALS: the VA biorepository brain bank

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Keywords: ALSFRS-R/EX, clinical assessment, outcomes

Background: The Amyotrophic Lateral Sclerosis Functional Rating Scale - Extension (ALSFRS-EX) is an enhanced version of the ALSFRS-Revised (ALSFRS-R) developed to better assess function in advanced ALS. The ALSFRS-EX contains 3 additional items; one item to further assess bulbar, fine motor and gross motor functions, respectively. The additional items are each scored via a 0–4 rating as in the ALSFRS-R, with a possible maximum score of 12. Since its introduction in 2009, little work has examined the utility of ALSFRS-EX.

Objectives: To examine the utility of ALSFRS-EX versus the ALSFRS-R in persons with advanced ALS in the VA Biorepository Brain Bank (VABB) prospective ALS cohort study.

Methods: From July 2012 to the present, persons with ALS (PALS) or their caregivers were administered the ALSFRS-R with the three additional items from the ALSFRS-EX via semi-annual telephone calls. We examined the utility of the ALSFRS-EX to extend the floor of the ALSFRS-R in those participants who attained a score of 0 on the ALSFRS-R over a 60-month observation interval.

Results: 20 of 175 PALS attained a 0 on the ALSFRS-R over the observation interval. Sixteen of these 20 cases obtained greater than 0 scores on ALSFRS-EX items. The scores on the EX items ranged from 1–5, with 13 PALS maintaining a greater than 0 score between 6–54 months. The bulbar item from the ALSFRS-EX exhibited the best utility in extending the floor of the ALSFRS-R over time.

Discussion and conclusions: We found that the ALSFRS-EX improved the assessment of advanced ALS severity; particularly in the assessment of bulbar function. The ALSFRS-EX extended the floor of the ALSFRS-R for up to 54 months in the present study. Given this, and the relatively short time to administer the three additional items in the ALSFRS-EX, we recommend the use of the ALSFRS-EX, particularly in advanced ALS in clinical and research settings.

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IDP-15 The ALS mobile analyzer: monitoring ALS disease progression via smartphone app and identifying novel digital biomarkers

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Keywords: clinical assessment, digital health, disease progression

Background: The rapidly evolving mobile technology offers a unique opportunity for the development of much needed novel tools for continuous, accurate and accessible monitoring of ALS patients in their home environment. Such tools will generate large scale functional data for ALS research, facilitate better and more responsive clinical care for patients and accelerate ALS drug development by supporting faster, smaller and more efficient clinical trials.

Objectives: We aimed to use the widely available smartphone mobile technology to develop an application that collects objective, detailed and frequently sampled information about patients’ clinical and functional status. The collected data can be used to better characterize disease course and to develop novel digital biomarkers of disease progression.

Methods: The ALS Analyzer mobile app was launched in November 2015 and is available as a free mobile app for Android and iOS platforms. The app includes a self-reported digital version of the ALSFRS-R questionnaire and a series of tasks that estimate patients’ functional abilities in all relevant functional domains: breathing capacity tests, speech tests to evaluate dysarthria, line tracing and finger tapping tests (fine motor skills), arm gross motor test and walking test. All relevant demographic information and self-reported ALSFRS-R scores are also collected through the app. The app’s tasks can be completed by patients anytime, anywhere and require none or minimal assistance. All functional data is recorded via the phone’s built-in sensors with no additional devices needed, making the app readily available for use by patients all over the world with only the click of a button. A range of task-specific performance parameters are recorded, allowing the development of in-depth informative analysis schemes.

Results: Over 200 ALS patients and 300 controls used the app since its launch, roughly a quarter of them using it repeatedly. Unique algorithms were developed to analyze performance in each functional task. The accumulated data was used to find thresholds separating patients from controls and to detect different levels of dysfunction in ALS patients.

Discussion and conclusions: The ALS Analyzer mobile app harnesses the latest technology to collect large scale real world functional data from ALS patients worldwide and to create a novel ALS disease progression digital biomarker. These objective, frequently collected, sensitive
digital measurements could revolutionize ALS research, clinical care and clinical trials.

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IDP-16 An exploratory study to investigate the use of biotelemetry to identify markers of disease progression in subjects with amyotrophic lateral sclerosis – pilot phase

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Keywords: clinical trial, biotelemetry, exploratory marker

Background: In addition to conventional clinical examination, biotelemetric monitoring of people with Amyotrophic Lateral Sclerosis (ALS) has the potential to provide an important source of information to assess the impact of the disease on aspects of functional capacity and activities of daily living, which may be a useful outcome measures in clinical trials.

Methods: This exploratory, non-controlled, non-drug study in ALS aims to investigate novel objective measures of physical activity, night-time rest, heart rate variability (HRV) and speech. There were two study phases: a variable length Pilot Phase (completed; reported here) and a 48 week Core Study Phase (ongoing; NCT02447952).

The objectives of the Pilot Phase were to (i) test the reliability, ease of use and acceptance of a wearable sensor capable of measuring simultaneous acceleration and inter-beat interval (R-R), (ii) confirm that the wireless data transfer methodology (sensor-data hub-cloud) was working correctly and (iii) optimise algorithms to identify physical activities and measure HRV. Tolerability of the technology was assessed.

Results: 5 subjects attended at least one clinical visit to perform a set of pre-defined activity reference tasks while wearing the sensor on the sternum. Subjects also wore the sensor in their routine home-life setting for ~3 days after the clinical visit (home monitoring). Clinic reference task acceleration data was available for four of the five subjects and home monitoring was successful for three out of five subjects; recording periods with at least 18 hours of data varied from 1–3 days. The charging routine (2 hours each day) was successfully adopted by three of the five subjects. The physical activity algorithms reliably classified ‘lying’ and ‘stationary but not lying’. However, sensitivity for prediction of ‘walking’ was 93% and ‘going up or down stairs’ 40.5%. The acceleration data was, therefore, re-examined, combining ‘walking’ and ‘stairs’ into an ‘active’ category. With this new classifier, all three states ‘lying’, ‘stationary but not lying’ and ‘active’ achieved 100% accuracy for sensitivity, specificity and accuracy. HRV data were available for four of the five subjects. Acceptable quality HRV data permitting analysis varied from 74.8–100% for root mean square of the successive differences (RMSSD) analyses and 53.2–100% for the ratio between low and high frequency components (LF/HF) ratio analyses.

One of the five subjects experienced moderate skin irritation and removed the sensor ~5 hours before the end of the three day home monitoring recording period.

Discussion and conclusions: Overall, the sensor was generally well tolerated. User acceptance for the new technology, combined with the successful validation of the physical activity and HRV algorithms, enabled the study to continue to the Core Study Phase which is currently ongoing.

Acknowledgments: This study was sponsored by GSK and done in collaboration with McLaren Applied Technologies.

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IDP-17 Effects of socio-economic and cultural factors on the ALSFRS-R in South African ALS patients: a pilot study

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Keywords: disease progression, assessment, non-invasive ventilation
Background: The respiratory sub-score of the ALSFRS-R assesses respiratory function through items 10 (dyspnea), 11 (orthopnea) and use of non-invasive ventilation (NIV) or tracheostomy (item 12). In the South African context, NIV usage is largely related to availability, which is dependent on socioeconomic and/or cultural circumstances.

Aim: To investigate the presence of potential bias in the respiratory sub-score introduced by non-use of NIV related to availability, resulting in an apparent flattened decline in the score.

Methods: We reviewed the records of 103 people with ALS (PALS) who are part of a prospective longitudinal study at Tygerberg Academic Hospital, South Africa, and analyzed a sub-group of patients that presented with a FVC <80% of predicted and/or respiratory symptoms, as assessed by items 10 and 11 of the ALSFRS-R. We then compared NIV usage (<4 on item 12) to respiratory symptoms and FVC at the first visit (T0), T1 (up to 6 months) and T2 (up to 12 months).

Results: Our sample (n=37) included 31 PALS with spinal onset, with mean age at diagnosis of 56.6 years (±10.6) and mean disease duration at inclusion in the study of 16.5 ± 12.7 months. The mean ALSFRS-R (±SD) was 35.7 ± 7.45 at T0, 29.4 ± 9.35 at T1 (up 6 months after T0) and 27.4 ± 9.78 at T2 (up 12 months). A FVC <80% of predicted was present in 83.8% of patients at T0, 86.7% at T1 and 94.1% at T2. Respiratory symptoms consisted of: dyspnea (item 10; score <4) in 56.8% of patients at T0, 75.7% at T1 and 81.0% at T2. Orthopnea (item 11; score <4) in 18.9% at T0, 48.6% at T1 and 61.9% at T2. At T0, 22 patients (59.4%) had both FVC <80% of predicted and respiratory symptoms; but only 5 of these were using NIV at T1. At T2, 21 patients (56.7%) of the initial sample were alive, 17 of whom had both criteria to start NIV, but only 6 patients were using NIV. Eleven patients met criteria for introduction of NIV, but failed to do so.

Discussion: As ALSFRS-R does not make provision for non-use of NIV in patients with respiratory impairment, item 12 may not be representative of actual respiratory involvement in situations where NIV use is limited by cultural or socioeconomic factors, such as resource-constrained environments. This has the potential to lead to flattening of the decline, as measured by the ALSFRS-R, and thereby result in inaccurate assessment of progression in therapeutic trials or cohort studies.

Conclusion: Researchers should be aware of the shortcomings of the ALSFRS-R with regards to the evaluation of respiratory function. Our findings suggest that ALSFRS-R should be restructured or adapted for use in situations where cultural or socioeconomic factors influence the management of respiratory failure in ALS patients.

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IDP-18 The aim and development of the primary lateral sclerosis functional rating scale (PLSFRS)

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Keywords: PLSFRS, primary lateral sclerosis, ALSFRS-R

Background: Primary Lateral Sclerosis (PLS) is the rarest among motor neuron diseases. There is currently no clinical outcome assessment to monitor the progression of the disease other than the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R), created for use with Amyotrophic Lateral Sclerosis (ALS) patients. Patients with PLS experience a longer disease trajectory and slower progression than those with ALS. For this reason, there is a need for a scale that captures the subtle changes that occur in PLS for use in future clinical trials.

Objectives: To develop a clinical outcome assessment similar to the ALSFRS-R that more accurately demonstrates PLS disease progression.

Methods: The ALSFRS-R was used as the foundation for the PLSFRS; we preserved the levels of function in each domain of the ALSFRS-R. Two additional options were added to each question (except orthopnea and respiratory insufficiency), accounting for less overall functional change than is accounted for in the ALSFRS-R. The question regarding gastrostomy was removed. Once an initial draft of the PLSFRS was developed, a patient focus group was held to determine whether the scale was meaningful to them in regard to functional change and elicit suggestions. After these suggestions were incorporated in a second draft, 20 patients from a previous study (PLS COSMOS) were contacted for feedback. This feedback was used for the final draft of the PLSFRS. The questions now provide functional choices focused on early symptoms. The speech section accounts for changes not detectable to others and efforts to improve speech. The salivation section includes increased swallowing and coughing. 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Results: The PLSFRS prototype was created for use in future clinical trials. A webinar was held to train evaluators from 21 sites to administer the scale. We have started the process of validating the scale with intra- and inter-rate reliability, internal consistency, construct validity and in-person and telephone-based test–re-test reliability.
Conclusions: We hope to find that the PLSFRS prototype will prove useful to measure progression in patients with PLS. Using the highly validated ALSFRS-R as a framework, we hope the PLSFRS will prove beneficial for future use in clinical trials and other studies in PLS.

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IDP-19 Clinical relevance of quantitative upper motor neuron burden (UMNB) scales in ALS

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Keywords: upper motor neuron burden, ALSFRS-R, vital capacity

Background: Multiple quantitative clinical scales are used to objectively measure upper motor neuron burden/dysfunction (UMNB) in ALS (1–4). The MGH-UMNB (1) and UPenn-UMNB (3) scales have shown strong correlation with glial activation and cortical thinning in motor cortices of people with ALS (1,3,4). The clinical relevance of these scales remains unknown (1,3,5).

Objectives: (a) Correlate the two UMNB scales with ALS disease severity. (b) Measure longitudinal changes in UMNB over time. (c) Evaluate the predictive value of UMNB scales on future functional decline and survival.

Methods: 49 ALS subjects underwent longitudinal UMNB, ALS functional rating scale (ALSFRS-R) and slow vital capacity (SVC) measurements for up to 20 months. The MGH-UMNB (1) ranges 0–45 and measures hyperreflexia. The UPenn-UMNB (3) ranges 0–32 and measures hyperreflexia, pseudobulbar affect using modified-Ashworth-scale.

MGH- and UPenn-UMNB scores were correlated with ALSFRS-R and SVC cross-sectionally using Pearson’s correlation, longitudinally using linear mixed effects model and with disease duration at baseline using non-parametric Spearman’s. For prediction analysis, a mixed model using baseline UMNB and all ALSFRS-R and SVC collected over a mean 11-months (n=26 and 19 subjects with baseline MGH- and UPenn-UMNB, respectively) was performed.

Results: 25 subjects completed both UMNB scales by the same rater, ALSFRS-R and SVC. Mean (SD) for MGH-UMNB was 25.2 (6.6) and UPenn-UMNB was 11.1 (6.3).

UPenn-UMNB inversely correlated with ALSFRS-R (r=−0.52, p=0.01). Among its sub-scores, a significant correlation was observed with hyperreflexia alone (r=−0.5, p=0.01). MGH-UMNB did not correlate with ALSFRS-R (r=−0.26, p=0.20). Conversion of MGH-UMNB reflex items from a 0–4 to 0–1 grading scheme to model UPenn-UMNB improved the correlation with ALSFRS-R (r=−0.52, p=0.01). MGH-UMNB (r=−0.21, p=0.32) or UPenn-UMNB (r=−0.4, p=0.05) did not correlate with SVC. UMNB scores did not correlate with disease duration or change significantly over time, despite disease progression. Baseline UMNB did not predict survival, future ALSFRS-R or SVC changes.

Discussion: The UPenn-UMNB scores correlate with functional status in ALS, as measured by ALSFRS-R; MGH-UMNB does not. This correlation is mainly driven by hyperreflexia and not spasticity or PBA. Converting MGH-UMNB reflex items (biceps, triceps, patellar, ankle, Hoffman, Babinski and Jaw jerk) to binary scale to model UPenn-UMNB improved its construct validity and the correlation with ALSFRS-R was significant. Upper motor neuron dysfunction in ALS does not change over short durations. Further evaluation in a larger sample and longer follow-up is required to better characterize longitudinal changes and prediction potential of UMNB scales in ALS.

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IDP-20 Multistate modeling of ALS stages: estimating risks of transition and death

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Keywords: staging, King’s, MITOS

Background: Partitioning the course of ALS into stages facilitates clinical description, allocation of care and research. Two proposed approaches, namely King’s and
MITOS, stage by regions involved and functions lost, respectively.

Objectives: To propose an additional empirical staging system (Fine ‘til 9 or FT9) drawing upon ALSFRS-R sub-score trajectories dropping to a threshold of 9 (of normal 12). To explore the applicability of these 3 staging systems to the PRO-ACT database.

Methods: Distribution of stages by each system in the PRO-ACT database was examined at initial assessment and throughout the observed course, using published algorithms to convert ALSFRS-R responses to King’s and MITOS stages. Markov multistate models were employed to model distribution of stages over time, estimate risks of transition from stage to stage and estimate survival by stage.

Results: In 3,199 patients with at least 2 ALSFRS-R records, a balanced distribution of King’s and FT9 stages at initial assessment (1=21.1%, 2=28.0%, 3=25.1%, 4a=21.4%, 4b=4.4% and 0=8.8%, 1=36.1%, 2=38.4%, 3=14.1%, 4=2.5%, respectively) and throughout the course (1=14.1%, 2=23.1%, 3=28.7%, 4a=17.3%, 4b=16.8% and 0=4.2%, 1=22.7%, 2=35.9%, 3=23.9%, 4=13.2%, respectively, for all observations) was noted, whereas MITOS stages were heavily skewed (0=80.3% initially and 0=53.3% of all observations). Moderate correlation was observed between FT9 and King’s as well as FT9 and MITOS stages (r=0.63 for each). Markov multistate models adequately described transitions from stage to stage and showed increasing mortality with increasing stage for each system. These models, however, underestimated overall mortality. Variability in ALSFRS-R scoring in the PRO-ACT database sometimes resulted in stage misclassification.

Conclusion: FT9, an empirical staging system drawing upon ALSFRS-R sub-scores, can partition the course of ALS similar to King’s system, and may have the advantage of easy applicability to retrospective data. King’s as well as FT9 are sensitive to observed progression of disease in the PRO-ACT cohort, whereas MITOS, being skewed towards more advanced disease, is not. Estimated transition intensities from stage to stage may be of value for counseling and research design.

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IDP-21 Estimating QALYs from the ALSFRS-R: mapping to the EQ-5D-5L from clinical data in people with motor neurone disease/amyotrophic lateral sclerosis

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Keywords: health economics, Euroqol EQ5-D5-L, TONiC

Introduction: Limited literature exists on preference-based health utilities, required for the calculation of quality-adjusted life-years (QALYs) in motor neurone disease (MND). Trials of potential MND treatments often use the Amyotrophic Lateral Sclerosis Functional Rating Scale-revised (ALSFRS-R), which provides valuable information on disease progression, allows the sorting of patients by disease stage and is a predictor of survival (1). It does not, however, provide a preference-based health utility score, required for estimating QALYs in economic evaluations for health technology assessments. The ALS Utility Index (ALSUI) can be used to derive patient preferences from the ALSFRS-R, but has not been validated or used in MND patient populations. When preference-based data have not been collected directly, it may be possible to map estimated utilities from generic measures; hitherto the validity of such an approach has never been reported for MND data.

Objectives: We undertook mapping from ALSFRS-R and ALSUI to EuroQoL EQ-5D-5L domains and utility values. Furthermore, we performed indirect mapping to the EQ-5D-5L domains using the Neuropathic Pain Scale (NPS) and Hospital Anxiety and Depression Scale for MND (HAD-MND) (2).

Methods: We developed direct mapping models using Ordinary Least Squares (OLS) and Tobit regression techniques to estimate EQ-5D-5L utilities (based on UK tariffs) with ALSFRS-R total, domain and item scores used as explanatory variables, along with ALSUI values, using patient-level data from the UK TONiC study. To map EQ-5D-5L domains, we also used indirect mapping models using the same variables, along with the NPS and HAD-MND using multinomial logistic regression techniques. We followed published mapping guidelines and reported goodness-of-fit along with predicted values for each mapping model.

Results: The best performing model predicting EQ-5D-5L utilities used the ALSFRS-R items as explanatory variables in an OLS regression. The mean squared error was 0.0245 and the absolute mean error was 0.1228.

Discussion: Prediction was excellent with 78% of estimated values within 0.1 of the observed EQ-5D-5L utility value. Indirect mapping using the NPS and HADS provided less predictive power than direct mapping models.

Conclusions: This is the first study to present mapping algorithms to `crosswalk’ between ALSFRS-R to EQ-5D-5L. This analysis, based on TONiC data, demonstrates that the ALSFRS-R can be used to estimate EQ-5D-5L utilities when they have not been collected directly within a trial.

Acknowledgments: We thank our participants for their contribution, and the Motor Neurone Disease Association (UK) and NIHR for support.
Results:

SC correlated with the 6MWT (6MWT distance and MVIC were obtained. Pearson correlation coefficients between SC level to 160 ambALS (106 in stage I and 54 in Stage II). Pairwise division of the lower extremities (MVIC) were obtained from 6MWT, SC and maximum voluntary contraction of the lower extremities as a measure of ambulation.

Methods:

Objective: To determine if SC correlate with the 6MWT measured by ALSFRS-R walking item score.

Predicted change in ambulation measured by ALSFRS-R and FVC only in stage I, but not in stage II, indicating that the 6MWT is an independent measure of ambulatory function in both stages of ambulation. The 6MWT provides a quantitative, simple and inexpensive outcome measure of walking capacity for early stage clinical trials in ALS which correlate with muscle mass.

Discussion and conclusion: The 6MWT is an independent measure of ambulatory function in both stages of ambulation. The 6MWT provides a quantitative, simple and inexpensive outcome measure of walking capacity for early stage clinical trials in ALS which correlate with muscle mass.

IDP-22 Six-minute walk test (6MWT) correlate with serum creatinine (SC) in ambulatory individuals with amyotrophic lateral sclerosis (ambALS)

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Keywords: 6MWT, creatinine, walking capacity

Background: We previously reported that the 6MWT is a valid quantitative measure of walking capacity in ambALS who ambulate without (stage I) and with (stage II) assistive devices. The 6MWT was associated with measures of lower extremity muscle strength and function in both stages and with ALSFRS-R and FVC only in stage I, but not in stage II, indicating that the 6MWT is an independent measure of lower extremity function across both stage of ambulation. We also reported that serum creatinine (SC) level, a biomarker of muscle mass, predicted change in ambulation measured by ALSFRS-R walking item score.

Objective: To determine if SC correlate with the 6MWT as a measure of ambulation.

Methods: 6MWT, SC and maximum voluntary contraction of the lower extremities (MVIC) were obtained from 160 ambALS (106 in stage I and 54 in Stage II). Pairwise Pearson correlation coefficients between SC level to 6MWT distance and MVIC were obtained.

Results: SC correlated with the 6MWT (r=0.27, p ≤ 0.0012) and MVIC (r=0.23, p ≤ 0.02) in all patients. When ambALS were stratified by stage of ambulation, SC was associated with 6MWT in stage I (r=0.23, p ≤ 0.024) and stage II (r=0.36, p ≤ 0.012). Conversely, SC was associated with MVIC only in stage II (r=0.37, p ≤ 0.028) but not in stage II (r=0.14, p ≤ 0.279).

IDP-23 ALS dashboard — cognitive, affect, bulbar, respiratory, arm, leg staging algorithm — single center longitudinal assessment comparing 1998–2001, 2009–2011 and 2013–2016 cohorts

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Keywords: disease staging, pseudobulbar affect

Background: Clinical Disease Trajectory is currently evaluated per-patient by ALS Functional Rating Scale—Revised (ALSFRS-R) without attention to cognitive and behavioral (depression/pseudobulbar affect-PBA) domains that are not included in current proposed staging algorithms. From 2009–2011, 181 patients (101 M; 80 F) were referred to the Carolinas Neuromuscular/ALS-MDA Center; 17 were found not to have ALS. The remaining patients were staged according to the ‘ALS Dashboard’ staging algorithm in cognitive, affect, bulbar, respiratory, arm and leg domains. Age at diagnosis, site of onset, time from onset to diagnosis, vital capacity at diagnosis, ALSFRS-R total and bulbar, arm, leg and respiratory sub-scores at diagnosis were calculated. Domain-specific

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stage at diagnosis and at 3-month intervals after diagnosis were established for each patient. Distribution of domain-specific staging at first clinic visit was compared with a previous cohort from 1998–2001, indicating difference in Bulbar and Respiratory domains.

**Objective:** To assess Clinical Disease Trajectory with ‘ALS Dashboard’ longitudinally to define differences in rate of clinical stage changes in different domains in 422 patients from 2013–2016 compared with two previous cohorts.

**Methods:** From 2013–2016, 422 patients (256 M; 166 F) were referred to the Carolinas Neuromuscular/ALS-MDA Center; 38 were found not to have ALS. The remaining patients were staged according to the ‘ALS Dashboard’ staging algorithm in cognitive, affect, bulbar, respiratory, arm and leg domains. Age at diagnosis, site of onset, time from onset to diagnosis, vital capacity at diagnosis, ALSFRS-R total and bulbar, arm, leg, respiratory sub-scores at diagnosis, ALS-Cognitive Behavioral Scale, Center for Neurological Study - Lability Scale and Patient Health Questionnaire-9 were calculated. Domain-specific stage at diagnosis and at 3-month intervals after diagnosis were established for each patient. Distribution of domain-specific staging at first clinic visit was compared with a previous cohort from 1998–2001 and 2013–2016.

**Results:** Cognitive stage ≥3 present at diagnosis was similar in the 2013–2016 cohort compared with the 2009–2011 cohort and higher than the 1998–2001 cohort (18.9%/23.8%/11.4%; p<0.01). Affect stage ≥3 was increased in 2013–2016 compared to previously (19.5%/0.0%/7.5%; p<0.01). Bulbar stage ≥3 was unchanged (39.5%/42.9%/30.0%) and Respiratory stage ≥3 also continued to increase significantly (62.3%/57.1%/6.0%). Arm stage ≥3 (29.6%/23.8%/20.4%) and Leg stage ≥3 (43.3%/52.4%/44.5%) were not significantly different.

**Conclusions:** The ALS Dashboard is a novel tool for analyzing accumulation of disease severity within a single patient and across different patients. ALS severity in some, but not all domains, segregates differently with a higher proportion of ≥ stage-3 Bulbar Respiratory disease in the 2009–2011 and 2013–2016 cohort compared with previously. The ALS Dashboard provides a description of ALS milestone changes that permits more precision in comparing domains involved than rates of disability measured by ALSFRS-R.

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**IDP-24 Correlations between slow vital capacity and measures of respiratory function on the ALSFRS-R**

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**Keywords:** vitality capacity, respiratory function, ALSFRS-R

**Background:** Amyotrophic lateral sclerosis (ALS) is characterized by progressive muscle weakness; however, no established markers of disease progression exist. Disability and death commonly result from declining respiratory muscle function, suggesting that respiratory measures such as vital capacity (VC) should be useful in predicting disease progression. Although forced vital capacity (FVC) is more typically used when making the decision to initiate non-invasive ventilation (NIV), slow VC (SVC) has been shown to be equivalent to FVC and is easier for ALS patients to perform.

**Objective:** To determine correlations between SVC and symptoms as measured on the revised ALS Functional Rating Scale (ALSFRS-R) in order to evaluate the utility of SVC in clinical decision-making.

**Methods:** The placebo group from the EMPOWER trial (Clinicaltrials.gov identifier, NCT01281189) was analyzed in the present study. The Pearson product moment correlation coefficient (r) was used to evaluate the strength of association between percentage predicted SVC and the scores of the individual respiratory sub-domain items of the ALSFRS-R, the respiratory sub-domain score and total ALSFRS-R score, respectively. Of the 467 patients randomized to the placebo group, 453 had at least 1 post-baseline measurement of SVC and were used in this analysis.

**Results:** Percentage predicted SVC was significantly correlated with dyspnea (r=0.3611; p<0.0001), orthopnea (r=0.3230; p<0.0001), respiratory insufficiency (r=0.3496; p<0.0001) and the respiratory sub-domain score (r=0.4262; p<0.0001). The correlation between total ALSFRS-R score and percentage predicted SVC was the highest and was also significant (r=0.5519; p<0.0001). The percentage of the variance of SVC explained by dyspnea, orthopnea, respiratory insufficiency and the entire respiratory sub-domain was 13%, 10%, 12% and 18%, respectively. 30% of the variance of SVC was explained by the overall ALSFRS-R score.

**Discussion and conclusions:** SVC is significantly correlated with individual respiratory symptoms measured by the ALSFRS-R (ie. dyspnea, orthopnea and respiratory insufficiency); however, only a small percentage of the variance of SVC was accounted for by any of these individual items or the overall respiratory sub-domain score. The ALSFRS-R is often used to follow disease progression and the results of this analysis suggest that changes in SVC are associated with a considerable amount of change in ALSFRS-R over time. However, the relatively low correlations observed also indicate that it is important to do repeated pulmonary testing and directly measure pulmonary function when making decisions such as when to initiate NIV. In addition, SVC is more strongly correlated with the total ALSFRS-R score than it is with the respiratory sub-domain score, suggesting that the respiratory sub-domain may not be the best predictor of respiratory decline.
We studied correlations between the difference of T1 from onset to T1 (month).

(1) %FVCse-su; (2) % difference of seated-supine FVC and supine spirometry, measurement of Peak expiratory Cough Flow (PeCF), nocturnal pulse oximetry and ABG. ALSFRS-R total and sub-scores declines in an ALS population, during a 6-months follow-up period. Objectives: To evaluate the relationship among different routine respiratory measures decline and AFS and the ALSFRS-R total and sub-scores declines in an ALS population, during a 6-months follow-up period.

Methods: Lung functions were assessed at the first evaluation (T0) and after 6 months (T1), with seated and supine spirometry, measurement of Peak expiratory Cough Flow (PeCF), nocturnal pulse oximetry and Arterial Blood Gases analysis (ABG). ALSFRS-R total score and its bulbar (ALSFRS-Rb) and respiratory (RofALSFRS-R) sub-scores were analyzed. ΔFS was calculated as: 48 – ALSFRS-R at T1/disease duration from onset to T1 (month).

We studied correlations between the difference of T1–T0 (diff) of the following respiratory parameters: (1) % seated and supine Forced Vital Capacity (%FVCse and %FVCsu); (2) % difference of seated-supine FVC (%FVCse-su); (3) PeCF; (4) mean nocturnal SpO2 (%FVCsu); (2) % difference of seated-supine FVC (%FVCse-su); (3) PeCF; (4) mean nocturnal SpO2; (5) Oxygen Desaturation Index (ODI); and (6) ABG (pH, pO2, pCO2 and HCO3−) and ΔFS, diff ALSFRS-R, diff ALSFRS-Rb and diff RofALSFRS-R.

Results: Fifty-five patients (mean age: 61.6 ± 11.69 years; M/F ratio: 39/16; type of onset: 76.4% limb, 20% bulbar, 1.8% respiratory and 1.8% generalized) were studied. The longitudinal data analysis between T0 and T1 showed significant correlations between diff % FVCsu and ΔFS (p=0.0459; r=–0.31), diff ALSFRS-R b

Discussion and conclusions: Among the respiratory measures included in this study the FVCsu showed the best correlation with the disease progression in ALS. FVC is widely used as an indicator of the prognosis, of the need for non-invasive ventilation and for assessment of efficacy of treatments in ALS. FVCsu improves the detection of diaphragmatic weakness and was found to be associated with reduced survival in ALS.

Our data reiterate that FVCsu is superior to FVCse and suggest that it may help the clinicians to predict disease progression. Its decline is a sensitive measure of global functional deterioration over time in ALS patients.

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(95% CI = 12–47%) increased risks of death associated with each 10% decrease in FVC (p<0.001).

Conclusions: The measurement of FVC at the time of diagnosis and during follow-up may contribute to identify early-stage patients with poor outcome. FVC should be used to assist neurologists to adjust the clinical management for patients.

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IDP-27 Lingual and jaw kinematic abnormalities precede speech and swallowing symptoms in ALS

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Keywords: swallowing, speech, early identification

Background: Early identification of bulbar involvement in persons with ALS is critical for improving diagnosis and prognosis; however, efficacious diagnostic markers have not yet been identified. Changes in lingual biomechanics during swallowing may represent a good diagnostic target, because recent work suggests that the tongue is putatively more affected in ALS than other oral structures.

Objectives: The purpose of this study was to determine whether biomechanical changes of the tongue and jaw during swallowing, measured using 3D electromagnetic articulography, pre-date clinically identifiable symptoms of speech and swallowing impairment in persons diagnosed with ALS.

Methods: Data were collected from 19 adults diagnosed with ALS and 22 neuro-typical controls. All participants (both ALS and controls) were tolerating an unrestricted diet (FOIS = 7) and produced intelligible speech (>97%). There were no significant differences in age or speaking rate between groups. Participants completed a 3 mL water swallow task, during which an electromagnetic tracking device recorded biomechanical measures of the anterior and posterior regions of tongue including lingual speed, range of motion, duration, coordination and efficiency. Jaw speed and range of motion were also recorded.

Results: Persons diagnosed with ALS demonstrated slower posterior lingual speeds (78.87 mm/s, SD = 44.6 vs 136.20 mm/s, SD = 64.8, p<0.05), reduced posterior lingual range of motion (11.63 mm, SD = 4.9 vs 15.76 mm, SD = 4.5, p<0.05), increased lingual movement duration (15.95 s, SD = 10.2 vs 10.34 s, SD = 4.9, p<0.05) and reduced lingual coordination (0.06 s, SD = 0.1 vs 0.17 s, SD = 0.2, p<0.05) during the 3 oz water swallow task compared to controls. Furthermore, persons diagnosed with ALS demonstrated increased jaw speed (53.36 mm/s, SD = 37.9 vs 34.96 mm/s, SD = 18.0, p<0.05) and increased jaw range of motion (8.61 mm, SD = 5.2 vs 5.83 mm, SD = 4.1, p<0.05) during swallowing compared to controls.

Discussion and conclusions: The current findings suggest that changes in lingual and jaw kinematics during a simple water task can be detected using electromagnetic articulography prior to the onset of swallowing impairment or decline in speech intelligibility in persons with ALS. Future work aims to explore the impact of lingual impairment on swallow physiology, safety and severity.

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IDP-28 A study on relation of body mass index to survival in Chinese sporadic amyotrophic lateral sclerosis patients

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Keywords: body mass index, bulbar score, survival prognosis analysis

Background: Body mass index (BMI) is one of the possible influencing factors on survival of ALS. We studied the relationships of survival between BMI, reduction rate of BMI and the bulbar score of ALSFRS-R. We aimed to (1) find an appropriate criteria of BMI as a prediction of prognosis, (2) clarify the influence on survival of nutritional status in Chinese sporadic ALS patients and, finally, (3) provide guidance patients.

Methods: 789 ALS patients referred to and assessed at Peking University Third Hospital with complete baseline information between January 2011 and December 2013 were enrolled in this study. Of which, 265 patients had complete information of reduction rate of BMI. Baseline demographic details and clinical data were collected at the patients’ first visit. Each patient received follow-ups every 3 months by telephone that record the change of BMI and other relevant information until either August 31, 2015 as cut-off time or death or tracheotomy, which were the pre-defined primary outcome measures. We used Kaplan-Meier and COX proportional hazards regression models to analyze survival. All the data was analyzed by SPSS 18.0.
**Results**: Mean BMI was 22.78 kg/m², median BMI was 22.68 kg/m² in 789 ALS patients. Reduction rate of BMI in 265 ALS patients was 0.071 kg/m². The bulbar onset group and bulbar score ≤6 group had lower BMI than the non-bulbar onset group and bulbar score >6 group (separately p=0.006 and 0.000). Females had a lower reduction rate of BMI than males (p=0.025). There was no significant correlation between bulbar score and reduction rate of BMI by Spearman correlation (correlation coefficient was −0.099, p=0.109) and there was no significant correlation between percutaneous endoscopic gastrostomy (PEG) and reduction rate of BMI by Pearson Chi-Square test (Pearson value was 2.834, p=0.242, and Cramer V value were 0.013). A significant correlation could be seen between reduction rate of BMI and reduction rate of ALSFRS-R score (p=0.000) by linear regression and the same result also could be seen between reduction rate of BMI and reduction rate of bulbar score. Survival in the bulbar score ≤6 group was significantly shorter than the bulbar score >6 group, and survival in the BMI ≤22.78 kg/m² group was significantly shorter than with BMI >22.78 kg/m². Survival in the BMI increased or stable group was significantly longer than in the BMI rapidly-decreased group (Reduction rate of BMI >0.169 kg/m²/month) analyzed by Kaplan-Meier estimator and COX regression model. We also found that age and being male are risk factors to survival, while delay of diagnosis, BMI, ALSFRS-R score and non-invasive ventilator are protective factors to survival.

**Discussion**: BMI of Chinese sporadic ALS patients was lower than BMI of American and European patients. Survival in the BMI >22.78 kg/m² group was longer than in the BMI ≤22.78 kg/m² group. BMI increased or stable, and slow reduction rate of BMI were protective. Bulbar score ≤6 indicated a shorter survival.

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**IDP-29 Clinical stage of amyotrophic lateral sclerosis in Chinese patients**

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*Keywords: clinical stage, Chinese patients, sub-set analysis*

**Objective**: Amyotrophic lateral sclerosis (ALS) is a rapidly progressive neurodegenerative disease, so it is important to explore the use of a clinical staging system in ALS. Our aim was to evaluate the duration in each stage and its enlightenment in Chinese ALS patients.

**Methods**: From May 2008 to March 2016, patients whom the neurologist suspected had a likely diagnosis of ALS were registered. We assessed the progression of ALS patients in each stage, and calculated the disease duration at each stage.

**Results**: A total of 1,395 patients were included in the analysis. No patients moved backwards to an earlier stage and the majority of them progressed to the consecutive stage; only a small proportion skipped a stage as the disease progressed. There were 611 patients who experienced each disease stage with ALS progression and median duration at Stage 1 was 15.64 months, Stage 2 was 6.72 months, Stage 3 was 5.03 months and Stage 4 was 4.28 months. Sub-set analysis revealed that the limb-onset patients had a longer median duration in disease Stages 2 and 3 compared to the bulbar-onset patients group. Longer disease duration from Stage 3 to Stage 4 and longer survival were observed in ALS patients who initiated riluzole therapy more than 6 months in Stage 1 or 2, compared to those who started long-term riluzole use in Stage 3 or 4. The duration from Stage 4 to Stage 5 was longer in ALS patients treated with gastrostomy percutaneous endoscopy (PEG) than in ALS patients who did not receive PEG treatment.

**Discussion**: We have validated the King’s College staging system in a Chinese population and shown this system was useful in clinical practice and clinical trials. The results of sub-set analysis indicated that ALS patients with bulbar-onset progressed faster in the middle stages of ALS, PEG treatment was required when Stage 4B was reached and the effect of long-term use of riluzole may be more prominent at early disease stage.

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**IDP-30 Prediction of the presence of disease progression among Japanese ALS patients by discriminant analysis**

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*Keywords: epidemiological study, discrimination analysis, prediction*

**Purpose**: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative disease of unclear etiology involving spinal cord motor neurons, leading to atrophy of skeletal muscles, paralysis and rapidly-progressive death. So it needs to predict and prevent progression in severity early. However, to the best of our knowledge, a tool for the prediction of the presence of disease progression of ALS does not exist. It is very necessary and important to predict disease progression of ALS early and subsequently prevent the development of ALS. We, therefore, examine predictors to detect disease progression of ALS using a discriminant analysis study in Japan.
Methods: A total of 93 ALS patients who completed a structured self-administered questionnaire conducted in 2006 (baseline) and provided information on their degree of severity at follow-up 1 year later were analysed in this study. Self- or proxy-assessed changes in severity were classified as 0='stable' (severity same or better at follow-up compared with baseline) or 1='worse' (severity at follow-up worse). Linear discrimination analysis was used to construct a predictive model to select individuals who have a higher chance of disease progression. The strength of association between ALS and a potential risk factor was assessed by calculating odds ratios (ORs) and 95% confidence intervals (CIs).

Results: Patients with stable status had a significantly higher proportion of 'hate to lose', Type A behavior, subjective stress, with pain, mental instability, poor quality of sleep, much anxiety for one’s family, poor appetite and frequency of green and yellow vegetables in their diet than those with worse disease severity. Among those factors, five factors (subjective stress, Type A behavior, with pain, mental instability, poor appetite) were selected as the predictor of disease progression by stepwise regression analysis. The sensitivity with these predictors was 83.3% for stable and the specificity was 85.3% for worse by discrimination analysis.

Conclusion: The present study suggests that the calculated discriminant function may provide greater predictive accuracy for screening individuals at high risk of disease progression of ALS. Prospective studies are needed to confirm validity and feasibility of the model for earlier screening for disease progression of ALS.

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IDP-31 Prognosis of pathologically confirmed Japanese amyotrophic lateral sclerosis, a retrospective institute-based study

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Keywords: amyotrophic lateral sclerosis, prognosis, pathologically confirmed

Background: We provide long-term medical care for neuromuscular disease patients at a neuromuscular-disease center hospital in the Hokuriku area of Japan. We have also developed a multidisciplinary care team for amyotrophic lateral sclerosis (ALS) and we are supporting their own decision-making. It is necessary to understand the intervention effect by our care team for better decision-making.

Objective: We performed a retrospective institute-based prognosis study to clarify the clinical features of pathologically confirmed ALS patients.

Methods: To elucidate the clinical feature of pathologically confirmed ALS, we retrospectively reviewed medical records of 78 consecutive autopsied patients between 2008 and 2015.

Results: We identified 35 patients of pathologically diagnosed ALS in this period. The female to male ratio was 10:25. Average age of onset was 71.9 years old (SD = 9.0) and median survival time was 60.9 months (SD = 51.8). Twelve patients (34%) chose tracheostomy invasive ventilation (TIV) and 7 patients (20%) decided on using non-invasive ventilation (NIV). The female to male ratio of TIV patients was 2:10 and that of NIV patients was 1:6. TIV prolonged median survival time (106 months), as did NIV (51 months) when compared to non-ventilation supported patients (31 months). Female patients tended to choose non-ventilation support.

Conclusions: From this retrospective study, TIV and NIV support could improve prognosis of pathologically proved ALS patients. Female patients might tend to decide not to choose NIV or TIV.

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