ALS
Amyotrophic Lateral Sclerosis

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FRONTOTEMPORAL DEGENERATION

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Welcome

Welcome and thank you for participating in this, the 32nd International Symposium on ALS/MND.

Amid the difficulties, restrictions and constraints that COVID-19 has imposed on us, we hope you have managed to find some positives in these difficult times, and you and your family, friends and colleagues have been safe and well.

One thing that could not have escaped us has been the focus that COVID-19 has brought on science, healthcare, the power of collaborative working and the sharing of information between researchers, healthcare professionals, industry and government: the very ethos of the creation of the International Symposium on ALS/MND.

Last year we made the difficult decision to cancel the previous year’s ‘in person’ meeting in Montreal and were forced to dive head-first into the virtual world with our 31st International Symposium on ALS/MND. The event was held, for the first time, online, and was hosted under social distancing rules from the MND Association office in Northampton, UK.

The online format brought new challenges in serving the interests of such a diverse range of delegates located across multiple time zones, but in collaboration with the MND/ALS community, we rose to the challenge. The event was a great success and hopefully we will be able to bring such enthusiasm again, as we hold a virtual meeting for the second year in a row.

In a world of noise, the Symposium continues to play a fundamental role, not only in facilitating the exchange of exciting new knowledge and information, but also serving as an interdisciplinary ‘melting pot’, stimulating new ideas and fostering new collaborations. We really appreciate each and every one of you playing your part in that.

We have yet again included the traditional mix of basic and clinical science, therapy development and clinical management that is synonymous with the Symposium. We extend our thanks to our plenary speakers who have graciously agreed to deliver their presentations online; and this year we have been able to review and select submitted poster presentations to be ‘upgraded’ to oral presentations from the outstanding pool of poster abstracts submitted, to add to the program.

As last year, the Poster Sessions remain in the virtual world and are packed with extremely high-quality content. It will be a challenge to generate the ‘buzz’ of the face-to-face event, but we hope to encourage a similar feel between poster presenters and delegates through live online interaction, including Q & A sessions, networking, gamification and video presentations of each poster.

Finally, we thank the Symposium Programme Committee, chaired by Professor Ammar Al-Chalabi, for their tireless work and valuable advice.

We hope you will join us online in our collective effort to understand, treat and – ultimately – defeat ALS/MND.

We wish you a successful and enjoyable Symposium.

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Poster Communications

Poster Communications are available online via https://symposium.mndassociation.org and http://tandfonline.com/iafd

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SESSION 1 OPENING SESSION

C1 CRISPR: the science and opportunity of genome editing

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Fundamental research to understand how bacteria fight viral infections uncovered the function of CRISPR-Cas programmable proteins that detect and cut specific DNA or RNA sequences. I will describe our research showing how RNA-guided CRISPR-Cas proteins can be used for re-writing the DNA in cells and organisms, providing transformative technology for genome editing. Current research focuses on exploring the biochemical basis for genome editing and developing effective applications in medicine and agriculture. I will also discuss the development of CRISPR-based diagnostics technology to address the current coronavirus pandemic and improve future preparedness.
SESSION 2 CLINICAL TRIALS

C2 ALS Drug Development Programs 2021: overview of the international ALS drug development programs with the integration of Biomarkers in Early Phase development programs

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The number of therapeutics in development for ALS has exploded since the ice bucket challenge in 2014. In the last 18 months the programs from pharma, biotechs and academic institutions are tackling several different pathways and utilizing biomarkers and companion diagnostics to accurately predict safety and efficacy in advance of clinical benefits. This presentation will review the current drug development event highlighting the programs which are using these techniques until the emergence of CSF and serum neurofilament levels as biomarkers potentially indicative of response to therapy. Drug development programs were dependent upon clinical response to therapy to determine whether to move an investigational product forward. There is now a concerted effort in many programs to include measures of response in the early phase programs. This presentation will review the current ALS programs in the preclinical and early clinical space highlighting the key outcome measures in each program which are specific to the proposed mechanism of action in addition to neuropilament levels and to other more general aspects of trial design. Academic, Biotech and pharma sponsored trials will be covered in this presentation. Programs presented will include programs in the neurodegenerative, neuroinflammatory, hyperexcitability, toxic protein, oxidative stress, neuromuscular as well as the gene specific programs. Recommendations for future trial designs will be included in the concluding remarks.

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C3 Long-term functional benefits and safety of a fixed-dose coformulation of sodium phenylbutyrate and taurursodiol in amyotrophic lateral sclerosis

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Background: An oral, fixed-dose sodium phenylbutyrate (PB)/taurursodiol (TURSO) coformulation was designed to reduce neuronal death by mitigating endoplasmic reticulum and mitochondrial dysfunction.

Objective: Report long-term functional and safety results from the CENTAUR trial of PB/TURSO in ALS.

Methods: CENTAUR encompassed a 24-week randomized, double-blind, placebo-controlled period and up-to-132-week open-label extension (OLE) period. Adults with definite ALS (revised El Escorial criteria) ≤18 months from symptom onset were randomized 2:1 to PB/TURSO or placebo. Participants completing all randomized period visits were eligible to enroll in the OLE period and receive PB/TURSO. Prespecified analyses compared changes in extended slope for continuous efficacy outcomes from randomization through week 24 of the OLE period (48 weeks total) in the originally randomized treatment groups within the modified intent-to-treat (mITT) population (ie, all randomized participants receiving ≥1 dose of study drug with ≥1 postbaseline efficacy assessment), using a mixed model with repeated measures. This model was used to estimate ALS Functional Rating Scale–Revised (ALSFRS-R) total score, upper/lower-limbAccurate Test of Limb Isometric Strength (ATLIS) scores, and slow vital capacity (SVC) in both groups at week 48. Safety was evaluated through week 24 in each period individually in the safety population (ie, all participants receiving ≥1 dose of study drug in the respective trial period).

Results: A total of 137 participants were randomized (mITT, n = 135) [PB/TURSO, n = 87; placebo, n = 48]; randomized period safety [PB/TURSO, n = 89; placebo, n = 48]. Ninety of 98 eligible participants elected OLE period enrollment (started on PB/TURSO, n = 56; started on placebo, n = 34). At week 48, estimated least squares mean (LSMEAN) (SE) ALSFRS-R total score was 21.61 (1.18) points among participants starting on PB/TURSO and 17.38 (1.54) points among participants starting on placebo (difference, 4.23 points; 95% CI, 0.56–7.90; p = 0.02). Estimated LSMEAN upper- and lower-limb ATLIS scores were 7.83 (95% CI, 0.85–14.80; p = 0.03) and 4.74 (95% CI, −3.00–12.48; p = 0.23) points greater, respectively, in those starting on PB/TURSO. Estimated LSMEAN SVC was 10.66 percentage points higher in those starting on PB/TURSO (95% CI, 0.63–20.69; p = 0.04). The proportions of participants who experienced ≥1 treatment-emergent adverse event (TEAE) in the groups starting on PB/TURSO and placebo, respectively, were 97% and 96% during the randomized period and 73% and 82% in the OLE period. Gastrointestinal TEAEs were more common in the first 3 weeks among participants receiving PB/TURSO in the randomized period and in participants switching from placebo to PB/TURSO in the OLE period.

Discussion: Earlier initiation and longer duration of PB/TURSO were associated with long-term functional benefit, as measured by slope of ALSFRS-R total score progression over 48 weeks. Improved retention of measures of upper-limb and respiratory muscle strength was also observed in those initiating PB/TURSO 24 weeks earlier. TEAEs attributable to PB/TURSO were primarily gastrointestinal.

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C4 Long-term follow-up of masitinib study AB10015 shows prolonged survival in patients that start treatment prior to severe impairment of functionality

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Background: A randomized, placebo-controlled study (AB10015) previously demonstrated that masitinib (4.5 mg/kg/day), administered orally as an add-on to riluzole, slowed the rate of functional decline in ALS patients having an ALSFRS-R progression rate from disease-onset to baseline (AFS) of < 1.1 points/month (1). At the time of final readout, overall survival (OS) data were too immature for interpretation.

Objectives: Long-term OS analysis of study AB10015, testing whether a signal in OS is evident in an enriched patient population similar to that prospectively defined for ongoing confirmatory study AB19001.

Methods: Survival status of all patients originally randomized in AB10015 was collected from participating investigational sites. Survival analysis (using the multivariate log-rank test and Cox proportional-hazards model, with stratification factors as covariates) was performed on the intention-to-treat population and enriched subgroups, which were defined according to initial randomization, AFS and baseline disease severity.

Results: The survival analysis followed all patients originally randomized in study AB10015 for an average duration of 75 months (time of diagnosis until long-term OS analysis cutoff). Consistent with previously communicated results (1), no long-term survival advantage was observed for the overall masitinib 4.5 mg/kg/day cohort of study AB10015 (i.e. regardless of baseline disease severity or ΔFS) or for the low-dose (3.0 mg/kg/day) masitinib treatment-arm. Conversely, in ALS patients with mild or moderate disease severity at baseline and ΔFS < 1.1 points/month, masitinib 4.5 mg/kg/day (n = 45) prolonged survival by 25 months relative to those treated with riluzole alone (n = 62) (median OS of 69 versus 44 months, respectively, p = 0.037) with a 47% reduced risk of death (Hazard Ratio 0.53 (95% CI [0.31–0.92]); p = 0.025). People with mild or moderate ALS comprised patients that had not suffered a complete loss or severe impairment of ALSFRS-R-related functionality at the time of masitinib treatment initiation (i.e. patients with a score of at least 2 on each ALSFRS-R individual component). Survival data for this cohort of patients were corroborated by the effect observed in the endpoints of ΔALSFRS-R at week-48 and time-to-event analysis (TFS), further supporting the premise of greater treatment effect when masitinib is initiated at an earlier stage of disease.

Discussion: These positive survival results provide evidence that the main efficacy outcomes of study AB10015, i.e. ΔALSFRS-R at week-48 (according to the primary endpoint and sensitivity analyses based on multiple imputation jump-to-reference techniques) and PFS, are legitimate surrogate endpoints for long-term OS. Results are also consistent with masitinib’s mechanism of action, which is expected to provide better outcomes if administered early in disease progression (2). Confirmatory study AB19001 is ongoing with a primary endpoint of decline in ALSFRS-R from baseline to week-48 in the enriched patient population described herein.

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C5 NurOwn targets multiple disease pathways in ALS Phase 3 Trial

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Background: MSC-NTF cells (NurOwn\textsuperscript{3}) are autologous bone marrow derived mesenchymal stem cells that have been shown to favorably modify neuroprotective and neuroinflammatory cerebrospinal fluid (CSF) biomarkers following single intrathecal administration (1). We conducted a phase 3, randomized, placebo-controlled, clinical trial to evaluate the efficacy and safety of repeated administration of MSC-NTF cells in ALS patients. We have separately reported on the clinical effects of MSC-NTF cells from this trial. The goal of this analysis was to evaluate treatment effects on CSF biomarkers and their relationship to clinical outcomes.

Methods: MSC-NTF cells were administered intrathecally on 3 occasions, 2-months apart. CSF samples were obtained prior to the first treatment and at 6 additional times. CSF biomarkers were analyzed using validated multiplex or singleplex assays (Simoa, Procartaplex, and Proximity Extension). Bioinformatic tools were applied to investigate relationships between CSF biomarkers and clinical outcomes. Principal component analyses (PCA) were performed on neuroinflammation, neurodegeneration, and neuroprotection pathways,
identified by their contribution to clinical data models to efficiently assess the treatment effects on each pathway separately. A pre-specified stepwise regression model was used to select biomarkers that were predictive of the primary efficacy endpoint, from all biomarkers measured, and assess the treatment effect in a combined model.

**Results:** Robust and statistically significant CSF biomarker changes from baseline were observed with MSC-NTF treatment compared to Placebo in biomarkers related to neuroinflammation, neurodegeneration, and neuroprotection, consistent with earlier trials. For example, there were statistically significant treatment differences in VEGF-A and MCP-1 at all post-treatment time points \( (p < 0.05) \), with MSC-NTF increasing VEGF-A two-fold following treatment \( (p < 0.0001) \) and MCP-1 decreased by 74% compared to Placebo post treatment \( (p < 0.0001) \). NfL values on MSC-NTF were 82% relative to Placebo following treatment. PCA analyses retain most of the information provided across all biomarkers collected with 5 PCA components. PCA confirmed the conclusions across biomarkers that MSC-NTF increased neuroprotection and decreased neuroinflammation and neurodegeneration relative to Placebo. A statistical model demonstrated that MCP-1, Fetuin-A, VEGF-A, MSR1, and NfL were all important predictors of treatment response \( (p < 0.05) \), as defined by the primary efficacy endpoint of the trial. The Receiver Operating Curve highlights strong model performance with 82.5% accuracy. Analysis of the primary clinical efficacy endpoint leveraging this model reveals a significant treatment response \( (p = 0.003) \), with more MSC-NTF participants meeting the clinical response definition than Placebo participants.

**Discussion:** The significant post-treatment CSF biomarker changes observed in this study and their relevance to clinical response suggest MSC-NTF cells have important effects on multiple ALS disease pathways. The data also suggests that simultaneously targeting multiple ALS disease pathways may be necessary to achieve meaningful clinical outcomes.

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**Reference**

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Bioenergetic failure is increasingly considered as a unifying pathogenic mechanism in a number of ALS sub-types with energy depletion in high energy demanding neurons making them sensitive to apoptosis (1). One potential response to bioenergetic failure is to increase the energy supply to neurons and other CNS cells. There is encouraging evidence from mouse models and clinical trials that meeting the energy deficit with a high calorie diet in pwALS may affect disease progression.

Malnutrition and weight loss are well recognised poor prognostic factors in amyotrophic lateral sclerosis (ALS). In people living with ALS (pwALS) weight loss of 5% or more there is associated with a two-fold increase in risk of death. The weight loss is multifactorial and is compounded by hypermetabolism with resting energy expenditure being, on average, 20% higher than in healthy individuals (2). A lower pre-morbid BMI in ALS patients and a 40% risk reduction of ALS in obese patients support the role of weight and energy homeostasis in influencing ALS pathogenesis.

Current nutritional management is often not evidence-based with little guidance on nutritional management regarding assessment of nutritional status, total daily energy expenditure calculations, appropriate dietary intake or oral nutritional supplementation. We have identified a lack of knowledge in healthcare professions regarding the nutritional management of ALS (3). The poor evidence base explains the poor nutritional outcomes observed.

If we accept increasing energy intake is a potential therapeutic option, then there are complex challenges to be overcome; not least a need to consider how to influence the nutritional behaviours and knowledge of pwALS and also the staff and services that support them.

We have undertaken a user centred design approach to create OptiCALS (Optimal Calories in ALS), a complex nutritional intervention. OptiCALS supports pwALS to increase their calorie intake using a food first approach and behaviour change techniques. Additionally, the OptiCALS tool provides an evidenced based framework for healthcare professionals to assess nutritional status and set calorie goals for pwALS. The effectiveness of the OptiCALS intervention is being assessed in a large randomised controlled trial (ISRCTN - No. 30588041).

Assessment of nutritional status is largely based on weight which is problematic given the challenges of using weighing scales as disease progresses. Therefore more practical assessment methods are needed. Advances in bioimpedance techniques and nutritional biomarkers may provide alternative information about body composition and energy status.

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C7 The combined study of gut microbiota and metabolomics of early-stage ALS patients

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Objectives: Amyotrophic lateral sclerosis (ALS) is a fatal neurodegenerative disease lacking curative therapeutic approaches. Clinical diagnosis of ALS has an average 11-month latency due to complication of clinical symptoms. In recent years, the concept of gut-brain axis inspires novel perspectives of diagnosing and curing neurological diseases. However, studies from several groups worldwide reported the gut microbiota results for ALS patients with either small sample size or inconsistent conclusions. This study aims to explore the link between gut microbiota and pathological mechanisms of ALS.

Methods: In current study, we conducted the 16S ribosomal RNA gene sequencing microbiota sequencing in fecal samples of 35 ALS diagnosed early-to-middle stage ALS patients and 35 condition-matched healthy controls, a subgroup of samples (29 ALS and 23 controls) was conducted untargeted metabolomics mapping.

Results: β-diversity of gut microbiota indicated significant difference between ALS and controls (p < 0.05). A higher median ratio of Firmicutes/Bacteroidetes (F/B) was found in ALS patients (ALS: 29.07 vs HC: 18.32). With untargeted metabolomics mapping, significantly different metabolites between ALS and HC were enriched in nicotinate and nicotinamide metabolism pathway, retrograde endocannabinoid signaling, inflammatory mediator regulation of TRP channels, sphingolipid metabolism and thiamine metabolism (p < 0.05). Nicotinate and nicotinamide metabolism pathway was down-regulated in ALS patients, while retrograde endocannabinoid signaling, inflammatory mediator regulation of TRP channels, sphingolipid metabolism and thiamine metabolism were up-regulated in ALS patients.

Conclusions: The major findings of the current study indicate that, gut microbe in ALS changes in a pro-inflammation direction, oxidative stress in ALS may be aggravated by the dysregulation of bacterial metabolites. Our study provides an in-depth view of gut microbiota and substance characteristics based on decent sample sizes with multi-omics strategies. It would strengthen the link between gut microbe/metabolic substance and ALS pathogenesis.

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Elevated levels of HDL-cholesterol at diagnosis are associated with shorter survival in patients with amyotrophic lateral sclerosis

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Objective: To determine the prognostic value of the serum lipid profile for survival time in patients with amyotrophic lateral sclerosis (ALS).

Methods: We conducted a systematic review and meta-analyses to summarize previous literature that determined the prognostic value of the lipid profile in patients with ALS. Subsequently, we evaluated the relationship between the lipid profile and survival time in a large population-based registry. We used Cox proportional hazards models to assess the prognostic value of total cholesterol (TC), LDL-, HDL-cholesterol, and triglycerides (TRI), adjusted for known prognosticators.

Results: The systematic review comprised eight articles; four studies (50%) found a beneficial effect on survival in patients with high levels of TC, LDL/HDL ratio or TRI, corrected in each study for different confounders. Therefore, it is difficult to draw an overall conclusion. Our prospective cohort study included 1,346 consecutively patients with ALS of whom a lipid profile was determined at diagnosis. A dose-response relationship between HDL-cholesterol and survival (HR 1.35 (95% CI 1.15–1.57, p < 0.001)) was found, increasing the risk of death with 35% per every point increase in HDL-cholesterol. None of the other lipid components were significantly associated with survival when adjusted for known prognosticators.

Conclusions: Our large population-based study shows that HDL-cholesterol is an independent prognosticator of survival. Gaining further insight in cholesterol metabolism, HDL functioning, and metabolic stress, might reveal novel aspects of ALS pathogenesis and potential targets for treatment.

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C9 Dysfunction to proteostasis mechanisms in ALS

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Protein folding is managed by the ‘protein homeostasis’ or ‘proteostasis’ machinery, which comprises the cellular pathways that control the biogenesis, trafficking, folding, degradation of proteins. These integrated pathways are distributed across several subcellular compartments that interact in a coordinated way. Efficient and balanced proteostasis is essential to maintain cellular health and viability and to protect against environmental challenges. Furthermore, compared to other cell types, neurons are large, long-lived cells with complex morphologies. These characteristics can present unique demands on the proteostasis network to dynamically regulate the motor neuronal proteome. Loss of proteostasis is central to protein misfolding diseases and not surprisingly, dysfunction of this network is implicated in pathogenesis of ALS. Furthermore, collapse of proteostasis also occurs during normal aging, which is the main risk factor for ALS. Here I will review recent studies linking the intricate proteostasis mechanisms to ALS, and how this is related to other emerging cellular mechanisms implicated in ALS pathophysiology. Therapeutic strategies based on restoring proteostasis or on targeting specific components of the proteostasis network, therefore, offer potential for future approaches for ALS and other protein misfolding diseases.

C10 Sporadic ALS disease initiation and targeted therapy: nuclear accumulation of CHMP7 initiates nuclear pore complex injury and subsequent TDP-43 dysfunction in sporadic and C9orf72 ALS

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Alterations in the components (nucleoporins, Nups) and function of the nuclear pore complex (NPC) have been implicated as contributors to the pathogenesis of genetic forms of neurodegeneration including C9orf72 Amyotrophic Lateral Sclerosis/Frontotemporal Dementia (ALS/FTD). We hypothesized that Nup alterations and the consequential loss of NPC function may lie upstream of TDP-43 dysfunction and mislocalization widely observed in ALS, FTD, and related neurodegenerative diseases. We now have accumulated evidence that CHMP7, a critical mediator of NPC quality control, is increased in nuclei of C9orf72 and sporadic ALS induced pluripotent stem cell (iPSC) derived spinal neurons (iPSNs) and postmortem human motor cortex prior to the emergence of Nup alterations. Using a large cohort of Answer ALS supplied sporadic ALS iPSC (n > 30) and human autopsy specimens, we also determined that CHMP7 has enhanced nuclear localization, in the same neurons with nuclear TDP43 depletion. Inhibiting the nuclear export of CHMP7, triggered Nup reduction and TDP-43 dysfunction and pathology in human neurons. Knockdown of CHMP7 alleviated disease associated Nup alterations, deficits in Ran GTPase localization, defects in TDP-43 associated mRNA expression, and alleviated downstream glutamate induced neuronal death. Analytics of the pathway over time revealed that CHMP7 nuclear location, preceded nuclear pore complex degradation which in turn preceded the loss of nuclear tDP43 in human spinal neurons. Thus, our data support a role for altered CHMP7 mediated Nup homeostasis as a prominent initiating pathomechanism for sporadic as well as C9orf72 ALS/FTD and highlights the potential for CHMP7 as therapeutic target. Importantly, these studies identify a molecular target for sporadic ALS and one that may repair the common molecular defect in nuclear pores as well as TDP43. The evaluation of this ASO target for clinical utility is now underway.

C11 Perivascular fibroblasts activity precedes the onset of ALS neurodegeneration with high plasma SPP1 associated with short patient survival

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Background: Apart from the well-defined neuron-centric factors, few reports consider that variability of sporadic ALS progression can depend on the less-defined contributions from non-neuronal cell types including glia and blood vessels (1). Nonetheless, variability of ALS patient survival continues to confound clinical trial design and estimations of disease dynamics remain based only on neuronal cell derived outcomes.

Objectives: To better understand how non-neuronal cells contribute to ALS aetiology.

Methods: We inferred cell activity in ALS spinal cord transcriptomes using single-cell guided profiling, vascular histopathology and plasma profiling.
Results: Here we report that perivascular fibroblast cell gene activity during presymptomatic disease stage remodels blood vessel matrix and provides distinct plasma protein biomarker that can independently predict short ALS patient survival at diagnosis (2). We determined that sporadic ALS patients present cellular changes consistent with two mouse models in which gene expression patterns from vascular cells precede the blood-brain barrier dysfunction and microglial response. Notably, perivascular fibroblast cells elicited the strongest pre-onset gene enrichments and their marker proteins SPP1 and COL6A1 accumulated in enlarged perivascular spaces in sporadic ALS patients. Moreover, in 574 ALS patients from four independent cohorts, increased plasma levels of SPP1 at disease diagnosis repeatedly predicted shorter survival with a stronger effect than established indications of bulbar onset or neurofilament levels in cerebrospinal fluid.

Discussion: Although vascular dysfunction has previously been proposed as an epidemiological risk factor in humans (3) and contribute to the multi-step ALS hypothesis (4), our results instead provide a plausible molecular and cellular explanation for these associations and a potential target for therapy. We propose that the activity of the recently-discovered perivascular fibroblast can predict ALS patient survival and provide a novel conceptual framework to re-evaluate definitions of ALS aetiology.

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SESSION 5 AUTONOMY AND DECISION MAKING

C12 Medical assistance in dying in Switzerland

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In Switzerland, assistance to suicide is legal, unless the assisting person incites a person for selfish reasons (Article 115 of the Swiss Penal Code). Euthanasia, thus active killing, is forbidden. Assisted suicide is increasingly accepted in Swiss society. Since the 1980s, right-to-die organisations have institutionalized the process of assisted suicide for adult patients. Whereas the rate of suicide without assistance has decreased in the years of 2000–2018 (from 19.8 to 12 per 100,000 inhabitants), the rate of medically assisted suicide has risen continuously, from 1.5 to 14.3. So far, the national monitoring of suicide acts provides little information about underlying diagnoses and patients’ origin (suicide tourism). We will present data about the development and circumstances of assisted suicide in patients of the ALS Clinic Basel, led by Kathi Schweikert and localized in the University Hospital and the REHAB Basel, respectively. In this setting, patients have access to a multiprofessional network of care, including advance care planning and early palliative care, and parallelly to right-to-die organizations. Trends for assisted suicide of patients cared for by the ALS Clinic Basel are compared to those nationwide.

Wishes to die in patients with incurable disease are grounded on personal motivations, but also on trajectory-related patterns, problems and concerns (1). Wishes to die may be a mean to preserve agency in a situation of uncertainty and loss of control. In ALS patients, wishes to die statements seem to be more frequent than for example in patients with cancer. In our interview-study on 62 patients with incurable disease (7 patients with ALS) wishes to die in ALS were directed to a future that is likely to come along with suffocation or heavy dependency, but also with psychosocial and spiritual obstacles, as hopelessness, loss of control, loss of role or the self-perception of being a burden (SPB). Patients with SPB showed an altered self-understanding that did not meet mutual expectations within their relationships (2). Family caregivers felt deeply touched by SPB and tried to unburden patients by giving care and compassion. SPB were not only associated with feelings of self-doubt, shame or guilt, but also with important feelings of solicitude and love. Acknowledging this seemed to unburden patients from wishes to die.

The relational aspect is important in ALS, since patients’ extensive care and cognitive impairment can foster unbalanced relationships. The relational dimension of a wish to die implicates that the situation and concerns of family caregivers should be addressed early in dialogue and decision-making. Supporting family caregivers actively may alleviate patients’ burdensome wishes to die.

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C13 Discussing personalized prognosis of survival in amyotrophic lateral sclerosis: a qualitative study of experiences of patients, caregivers, and physicians

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Background: The ENCALS survival prediction model offers patients with ALS the opportunity to receive a personalized prognosis of survival at diagnosis (1). We developed a communication guide to support physicians in tailoring prognostic discussion to the individual needs and preferences of patients with ALS (2).

Objectives: To explore experiences of patients with ALS, caregivers, and physicians with discussing personalized prognosis in ALS.

Methods: We conducted a qualitative study using semi-structured interviews with patients and caregivers, and a focus group with physicians. We invited recently diagnosed patients with ALS, referred to one of three ALS care teams in the Netherlands and with whom the personalized prognosis was discussed. The focus group consisted of five physicians involved in the recruitment of participants. Interviews and focus group were conducted by researchers not involved in the care of patients (RvE, LK, AB), and transcribed and analysed thematically (RvE, LK).

Results: Data saturation was reached after interviewing twelve patients and nine caregivers. Patients’ prognosis ranged from short to very long. Three overarching themes with eight subthemes emerged. I Tailored communication. Physician’s tailoring of communication style and information provision mediated the emotional impact of prognostic disclosure and increased satisfaction with communication. Regardless of good or bad news, most patients and caregivers were satisfied with the communication. II Personal factors. Coping style, illness experiences, and information needs affected how patients and their caregivers coped with the
Background: There is a focus on patient and caregiver engagement within regulatory review processes, especially in relation to determining clinically meaningful outcomes. The IMPACT ALS Europe survey of people with amyotrophic lateral sclerosis (ALS) and their caregivers collected data from over 1500 people from 9 European countries on the burden of disease, psychological distress, and the loss of function over the disease course.

Objective: To improve understanding of the functional burden of disease in ALS to ensure that the patient and caregiver voice is included in the development and evaluation of new therapies.

Methods: The survey materials used in a 2017 US survey were adapted for use in Europe. Most questions were directly comparable, with relevant amendments for local contexts. A steering committee consisting of industry partners, clinical and methodological experts, with input from patients and caregivers advised on the contents of the survey. Recruitment of patients and caregivers was carried out with the partnership of European Organization for Professionals and Patients with ALS (EUPeALS) and advocacy groups in each country. The online survey questionnaires – one for people with ALS, one for current caregivers and another for bereaved caregivers – were hosted on a Qualtrics platform. Ethical approval was received from Trinity College Dublin, participant confidentiality was agreed, and all relevant GDPR regulations were followed during survey processing, analysis, and dissemination of findings.

Results: Data from 1538 people in nine European countries – Belgium, France, Germany, Ireland, Italy, Netherlands, Spain, Sweden and the UK provide a detailed understanding of the functional burden of living with ALS. Respondents were people with ALS (n = 870), caregivers (n = 450) and bereaved caregivers (n = 218) who identified several clinically meaningful symptoms beyond muscle weakness such as respiratory function, mobility, fatigue, and communication difficulties which could be the focus for future therapies. Fears for the future were detailed. Caregivers – current and bereaved – described their health status, levels of stress, and their own perspectives on patient-related factors. A series of specialized analyses are planned by clinical members of the advisory group. Results of the European survey will be viewed in comparison with results from the 2017 US survey.

Discussion: The IMPACT ALS Europe patient and caregiver surveys provide a robust evidence base for the burden of ALS from the perspectives of people living with ALS and those providing care, and will provide guidance into drug development processes.
SESSION 6 DISEASE MODELS

C15 iPSCs as a model for neurodegenerative disease: myths and truths

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Human pluripotent stem cells (hPSCs) offer a powerful new system to model neurodegeneration that can capture the precise genetic background of a given patient and can yield access to the specific neural cell types affected. Over the last few years, techniques for generating patient-specific induced pluripotent stem cells (iPSCs) have become routine with large libraries of iPSC lines established – including from patients suffering from neurodegenerative disorders such as ALS, Parkinson’s disease or Alzheimer’s disease. In parallel, protocols for the directed differentiation of hPSCs into a myriad of cell types have been established, and it is foreseeable to such protocols will become available for accessing literally any cell type on demand. In the current presentation, I will discuss the state of hPSC-based models for neurodegeneration with a particular focus on ALS.

Human PSC technology has matured to the level where some of the very first clinical trials based on results obtained in iPSC-based studies have been initiated, and where iPSC-derived lineages are becoming a routine tool for genomewide genetic screens or in drug discovery studies. However, many serious challenges remain to realize the potential and make iPSC technology truly predictive of human neurodegenerative disease. Those include cell line to cell line variability both between and within individuals that can impact differentiation potential and induce or mask the emergence of disease phenotypes. Another major drawback is the immature (fetal to neonatal) stages of neuronal maturation that can be achieved using current iPSC-differentiation approaches, that is a mismatch from the adult or aged state at which neurodegenerative disease typically occurs. This is reflected in immature physiological properties of human iPSC-derived lineages and the lack of adult or age-related genetic and epigenetic signatures. Finally, most iPSC-based studies are focused on modeling disease features in a given neuronal lineage such as spinal motoneurons in ALS, midbrain dopamine neurons in PD or cortical neurons in AD. However, it is important to capture the role of glial cells including the modeling of neuroinflammatory interactions in iPSC-based models. Furthermore, it will be critical to study neuronal function in the context of an appropriate target such as neuromuscular interactions in ALS or nigrostriatal interactions in PD.

In my presentation, I will provide an update on the technologies developed in my lab to address some of those key challenges including our goal to achieve a better control of cell type composition and studying neuronal/glia interactions in defined proportions using a novel tri-culture system. I will also present strategies under development to induce enhanced levels of maturation in iPSC-derived lineages. Those are just a few of the remaining challenges to be addressed for realizing the full potential of iPSC-technology in modeling disease and in personalized medicine.

C16 ALS drug discovery using AI platform with patient iPSC panel

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Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that causes progressive loss of motor neurons. The disease progresses quickly, and the development of effective medicine is urgently required. The discovery of induced pluripotent stem cell (iPSC) technology enabled us to analyze the pathophysiology of ALS and screen therapeutic drugs using patient motor neurons. We have constructed a phenotypic screening system to evaluate the efficacy of compounds with a readout of motor neuron survival using ALS patient iPSCs.

Methods: To find a potent drug for many ALS patients, we developed an artificial intelligence (AI)-based drug discovery algorithm with patient iPSCs. Although it is still a challenge to apply machine learning to achieving sufficiently complex phenotypic drug screening due to imbalanced datasets, non-linear prediction, and unpredictability of new chemotypes, we could overcome these issues by constructing a prediction model based on a heat diffusion equation (PM-HDE), a novel non-linear approach that uses a partial differential equation describing heat distribution for prediction of the efficacy of compounds.

Results: The algorithm of PM-HDE was verified as being feasible for virtual compound screening using biotest data of 946 assay systems registered with PubChem as benchmark sets. PM-HDE presented high prediction performance showing high AUC levels even in datasets with a bias of the active ratio. Furthermore, the performance of PM-HDE was compared with the k-nearest neighbor (kNN), random forests (RF), and support vector machine (SVM), and showed higher accuracy compared to those of the well-known in silico hit predictors. PM-HDE was applied to actual screening to evaluate compounds to rescue ALS motor neurons. Based on supervised learning of the data of about 50,000 compounds from biological phenotypic screening with ALS motor neurons derived from patient iPSCs, virtual screening of >1.6 million compounds was implemented, followed by a second screening which confirmed that PM-HDE enriched the hit compounds and identified new chemotypes. Finally, the compounds identified by PM-HDE demonstrated broad and potent effectiveness against motor neuron death in ALS patient iPSC panels.
Discussion: This AI platform using patient iPSCs could be a powerful tool for discovering promising compounds for drug development. It may be possible to screen unlimited numbers of compounds, and spread of the application to the drug discovery for various other diseases is also expected.

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SESSION 7 TRANSLATING RESEARCH FROM TARGETS TO TRIALS

C17 Cortical hyperexcitability causes TDP-43 proteinopathy

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Background: Neuronal hyperexcitability is an early and intrinsic feature of ALS patients, induced pluripotent stem cell-derived motor neurons and mouse models. Motor neuron hyperexcitability is linked to ALS pathophysiology, although no direct evidence exists in vivo.

Objectives: To directly test the impact of motor neuron hyperexcitability in ALS pathophysiology using chemogenetics in mice.

Methods: AAV5 vectors expressing either excitatory hM3Dq receptors, or mCherry, were injected into layer 5 neurons of motor cortex in adult C57BL/6 mice (n = 8 per group). Mice were treated with the synthetic ligand CNO or saline (IP injection, daily) for 6–12 months. Mice were analysed using whole cell patch clamping electrophysiology, behavioural testing and neuropathology. Brains and spinal cords were collected for TDP-43 analysis using biochemical fractionation, immunoblotting and immunohistochemistry.

Results: Chronic activation of hM3Dq receptors in cortical motor neurons induced significant hyperexcitability, progressive motor deficits and degeneration of cortical motor neurons, spinal motor neurons, axons and neuromuscular junctions in mice. Cortical hyperexcitability also lead to astrocyte and microglia activation in brain and spinal cord. Importantly, cortical hyperexcitability triggered TDP-43 phosphorylation and cytoplasmic aggregation of TDP-43 in both cortical and spinal motor neurons.

Discussion: These results establish that cortical hyperexcitability is sufficient to drive TDP-43 pathology in the brain and spinal cord, associated with sequential degeneration of cortical motor neurons, spinal motor neurons and their peripheral synapses, consistent with a ‘dying-forward’ mechanism of ALS onset.

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C18 AI-augmented search for disease-modifying treatments: a new era in ALS drug discovery

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The complex aetiology and heterogeneity of neurodegenerative diseases, such as ALS, has proved a formidable barrier to the translation of basic research into effective treatments. With a rapidly aging global population, the need to address this unmet medical need becomes ever more pressing. The exponential increase in biomedical data generation and research output, however, offers confidence that we are on the cusp of making substantial progress. BenevolentAI combines advanced AI and machine learning with cutting edge science to decipher complex disease biology, generate novel insights and discover more effective medicines. The company’s unique AI-applied drug discovery platform spans every step of the drug discovery process, powering an in-house pipeline of over 25 drug programmes from early discovery towards clinical phases. This presentation will examine how the application of this technology is helping to enhance the mechanistic understanding of human disease, therapeutic target identification and uncover more effective disease-modifying treatments for ALS and other neurodegenerative diseases.

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C19 How important are biomarkers in drug development?

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ALS biomarker research has been ongoing for over 30 years, with early studies focused on targeted amino acids or proteins that may be elevated in the blood or cerebrospinal fluid (CSF) of ALS patients when compared to healthy controls or disease control groups. Newer technologies permitted large, unbiased studies to identify protein, metabolic or genomic changes in ALS patients. These discoveries uncovered numerous biologic pathways altered in ALS that have been targets for therapeutic development. Beyond identifying pathways targeted for drug development, biomarkers contribute in many ways to the ALS drug development process. Pathologic markers identified in ALS models of disease that recapitulate the pathology of the human disease (i.e. TDP-43 pathology) permit preclinical studies that target pathology and hopefully can be translated to the human disease. An important use of biomarkers to demonstrate target engagement in preclinical and clinical studies has only more recently been incorporated into ALS drug development. Biomarkers that can be measured and monitored in biofluids (blood, CSF, urine) may highlight downstream impact of drug treatments both in preclinical models and during a clinical trial. More recently, biomarkers have been used to select a patient population that may best respond to a particular treatment, or to
monitor the efficacy of the treatment during a clinical trial. This impacts the design of a trial and may also lower the number of participants necessary to evaluate the efficacy of the treatment. Finally, the use of biomarkers to identify ALS at a pre-symptomatic phase or to monitor disease progression has great potential to impact future clinical trials. While much work remains till ALS biomarkers are used by regulatory agencies to make drug approvals, there is little doubt that biomarker research has greatly accelerated ALS drug development and has been a key factor in the expanding pipeline of ALS clinical trials during the past decade.

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C20 Innovative trial design considerations for ALS proof of concept and beyond

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Background: Drug development in ALS poses multiple challenges. Not only is the disease biology complex, but disease biomarkers suitable for pharmacodynamic (PD) studies have yet to be identified, the established clinical endpoints show poor sensitivity to change and require lengthy clinical studies to demonstrate efficacy and there is significant competition for clinical trial participants. These challenges require innovative solutions if drug development efforts for ALS are to be successful.

Objectives: To develop an integrated approach to the development of novel pharmaceuticals for drug development.

Methods: Novartis has formed a matrixed ALS team in order to develop an integrated research and clinical ALS strategy. In contrast to the traditional project-teams that focus on the development of a single novel drug candidate, the ALS team is instead indication focused. This team works internally in close alignment with the respective molecule-focused teams; establish biomarkers and align trial design. And externally, the team works to build relationships with ALS patient groups and clinical consortia, in order to ensure patient-centric clinical trial designs and optimal research, and clinical study efficiency.

Results: In the absence of disease-related PD biomarkers, TSPO PET imaging, using the PET tracer [11C] PBR28, is being used as an early PD biomarker to determine proof of mechanism of neuroinflammatory agents. Such proof of mechanism approaches are needed to select promising drug candidates and justify the costs of larger, later-phase studies. Home-based digital biomarkers that allow for the collection of digital endpoints by study participants and their caregivers in their own home environment are being evaluated in a dedicated observational study. These digitally collected endpoints have the potential to increase the sensitivity of clinical trial endpoints and improve trial efficiency, in addition to decreasing trial participant burden. A master study design protocol is being developed that can be applied across multiple drug candidates with the goal of facilitating clinical operations. For Ph2 and 3 studies, platform designs that maximize the ability of patients to receive potentially helpful treatment and reduce placebo exposure are important. The establishment of strategic alliances with ALS consortia including collaborating with existing platform trials will similarly facilitate clinical operations. An ALS patient advisory board, convened during the trial protocol drafting stage, provided guidance related to the patient-centric design consideration, which increased the attractiveness of clinical trials to prospective study participants.

Discussion: Novartis is developing an integrated research and clinical development strategy that includes coordination with both internal and external partners. Coordinated efforts such as these are necessary in order to overcome the significant challenges to drug development for ALS.

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SESSION 8 COGNITIVE CHANGE

C21 Measuring cognitive change in ALS

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ALS is a frontotemporal spectrum disorder affecting multiple systems. Symptoms include a range of cognitive impairments and behaviour abnormalities. Measuring these symptoms is crucial for accurate phenotyping, identifying and monitoring change including the effect of drug treatment and for adapting clinical care. What we should assess depends on the purpose; clinic, research, or clinical trials. Assessments should comprise testing of multiple cognitive domains, including executive and language functions; a range of behavioural abnormalities as found in behavioural variant FTD and in particular apathy. Psychiatric symptoms and disorders are also gaining prominence. Tools for assessment include the Edinburgh cognitive and behavioural ALS screen, ECAS (1), the Dimensional Apathy Scale DAS (2), the Beaumont Behavioural Interview BBI (3), the Reading the Mind in the Eyes (4) amongst others. There are many hurdles and pitfalls to overcome, including how to measure behavioural change (semi-structured interview or tick box questionnaire), translation and cultural adaptations (validity in the local population), what is normal and abnormal and how to measure change over time. Furthermore interpretation can be hazardous, there is a difference between cognitive and capacity assessment. Measurement has enabled understanding of disease stage (7), differentiating between different dementias (8), and has had an impact on clinical care (9).

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C22 Cognitive and neuropsychiatric endophenotypes among asymptomatic relatives from C9orf72 repeat expansion kindreds

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Background: With the advent of anti-sense oligonucleotide therapies, there has been much recent interest in delineating the pre-symptomatic stages of disease development among C9orf72 repeat expansion carriers. Asymptomatic familial non-carriers are frequently used as a comparison group for such studies (1). Yet, little is known as to what extent unidentified oligogenic inheritance patterns (2) may influence shared cognitive and neuropsychiatric profiles.

Objective: The Irish ALS Endophenotype Study directly assesses unaffected ALS relatives with the aim of characterising neuropsychological and neuropsychiatric traits which may serve as markers of increased genetic liability, helping to augment the statistical power of genotype-phenotype studies.

Methods: 231 asymptomatic relatives of Irish ALS patients (C9orf72 positive [37]; negative [194]) and 207 healthy controls completed a comprehensive neuropsychological battery and neuropsychiatric assessment. C9orf72 repeat expansion status was determined using repeat-primed PCR with ampli con length analysis (positive cut-off ≥ 30 repeats).

Results: Cognitive performance (ECAS language, verbal fluency and executive function) declined with increasing age among “pre-symptomatic” C9orf72 carriers (p = 0.003, p = 0.001 and p = 0.04 respectively). Furthermore, this cohort showed paradoxical high levels of self-control (BIS [p = 0.017]), and cognitive complexity (BIS [p = 0.034]) among younger repeat expansion carriers, with self-control rapidly declining with increasing age (p = 0.004). Similar patterns of declining cognitive performance (ECAS language [p = 0.033], executive function [p = 0.002]) with increasing age were observed for familial non-carriers. These C9orf72 negative relatives from C9orf72 kindreds also showed higher levels of anxiety (p = 0.033) and reduced openness to experience (p = 0.034). This finding was most apparent in those aged 65 years or older.

Discussion: The cognitive profile of ALS relatives broadly reflects that observed among C9orf72 positive ALS patient cohorts. The findings of this study of early and progressive cognitive and behavioural decline among C9orf72 carrier relatives is consistent with the evolution of underlying disease processes decades prior to motor onset. That similar patterns may be observed in familial non-carriers from C9orf72 kindreds suggests the presence of additional genomic variants that drive specific cognitive endophenotypes within these kindreds.

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C23 Non-motor impairment across the ALS-FTD spectrum: factors that influence disease severity and progression

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Background: The conceptualisation of ALS has changed dramatically over recent decades from one that was traditionally considered a pure motor disorder, to what is now deemed a multisystem neurodegenerative condition. The overlap across ALS and Frontotemporal Dementia (FTD) has been studied extensively, however the extent of similarities (or differences) across this spectrum in terms of non-motor impairment and associated modifying factors remains less well-explored.

Objective: This study aimed: (1) to identify the pattern of non-motor impairment (including neuropsychiatric symptoms, sleep and mood disorders) across behavioural and cognitive ALS phenotypes compared to behavioural-variant FTD (bvFTD); (2) to determine the overlapping non-motor features across ALS and FTD subtypes to ultimately confirm the extent of the ALS-FTD spectrum; and (3) to establish the contribution of age, sex, disease state and cognitive status on the severity of non-motor features.

Methods: Consecutive participants were recruited and underwent a detailed clinical, cognitive, behavioural, neurophysiological and neuroimaging assessment. Neuropsychiatric and other non-motor symptoms were determined using the Cambridge Behavioural Inventory (CBI-R). The scores were converted to define impairment in terms of symptom severity (mild, moderate and severe) for each subscale. Initially rate and severity of symptoms were determined and compared across groups, then contribution of age, sex and disease states were analysed and finally a regression model identified predictors of symptom severity.

Results: In total, 250 participants (115 ALS, 98 bvFTD, and 37 ALS-FTD) were recruited. A similar pattern of neuropsychiatric symptom severity was identified (apathy, disinhibition and stereotypical behaviour) for all behavioural phenotypes of ALS (ALS with behavioural impairment ([ALSbi], ALS with cognitive and behavioural impairment [ALSci], and ALS-FTD) compared to bvFTD (all \( p > 0.05 \)). Neuropsychiatric symptoms were also present in cases defined as ALS without cognitive and behavioural impairment (ALSPure) and the cognitive phenotype of ALS (ALSci), although they were less frequent and at the milder end of the spectrum. Disordered sleep and disrupted mood were common across all phenotypes (all \( p < 0.05 \)). The severity of sleep dysfunction was influenced by both sex and age (all \( p < 0.05 \)). All non-motor symptoms were common early in the disease process and deteriorated in line with progression on the Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised (ALSFRS-R; all \( p < 0.05 \)). Diagnostic phenotype, disease duration and global cognition scores were the strongest predictors of non-motor and neuropsychiatric impairments.

Conclusion: The current findings support the current nuanced concept of the ALS-FTD spectrum by identifying a strikingly similar pattern of non-motor symptoms across the subgroups of ALS and bvFTD. These findings further highlight the impact of non-motor, including neuropsychiatric symptoms, on both the disease trajectory and quality of life for people living with ALS. This advanced understanding of the ALS-FTD spectrum may accelerate the early identification of patient needs and improve clinical awareness of these symptoms.

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C24 Pathways to early diagnosis in ALS: can we do better?

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ALS is a rare disease, and diagnosis is currently made by exclusion of other conditions. The diagnostic pathway is determined by presentation to a healthcare professional with new symptoms: recognition of “red flag” symptoms /signs; appropriate investigations to exclude other diagnoses; timely and accurate disclosure of diagnosis; and referral to a specialist clinic. Patient journey studies have shown that those with ALS are seen by 3–5 healthcare professionals and average 4–5 investigations prior to definitive diagnosis. Early referral to a general Neurologist may not reduce diagnostic delay but reduces the costs of investigation. Ideally, all patients with ALS should be offered the opportunity to participate in clinical trials. However, with some notable exceptions, the majority of specialist clinics continue to describe a mean diagnostic delay of 12–15 months, which represents up to 30% of life expectancy for the majority of those with ALS and provides a mere 3–6-month window for eligibility for many trials. However, improving diagnostic delay is challenging. Increasing public awareness of ALS and education of primary care practitioners of “red flags” such as tongue fasciculations can trigger early referrals to specialist clinics. But this risks “false positive” presentations, limiting the availability of expensive specialist services for those with definite diagnoses and increasing waiting lists in public clinics. Conversely, failure to recognize the variability of presentation of ALS, including cognitive/behavioural change, and excessive reliance on neuropsychologic evidence, particularly in bulbar onset disease, can delay referrals from general to specialist clinics. Reluctance by non-specialist neurologist to disclose a terminal diagnosis, nihilistic perspectives about clinical trials, and excessive and inappropriate investigations or treatments to exclude rare mimic syndromes can also delay definitive diagnosis. How can we do better? Diagnostic biomarkers based in biochemical, imaging and neurophysiology will be helpful. But whether current technologies reduce diagnostic delay remains to be determined. In the meantime, there is limited evidence that increasing awareness among general practitioners reduces diagnostic delay. Increased referrals from primary care will require that clinics accept higher rates of “non-ALS” for diagnostic exclusion. This will likely require an expansion of ALS clinics. Additional, expedited diagnosis will require a recognition of the heterogeneity of ALS, the inclusion of cognitive and behavioural change as part of the clinical phenotype, and the identification of “at risk” groups (e.g., members of kindreds with familial ALS). There is scope for educating secondary and tertiary care clinicians in appropriate investigations including the judicious use of emerging biomarkers, and the value of early referral to specialist clinics. Ultimately, expedited referral to specialist neurologists of those with suspected ALS remains the best ways to reduce diagnostic delays and improve access for patients to clinical trials.

C25 Patterns of genetic testing among patients with amyotrophic lateral sclerosis (ALS): Real-world results from the United States and Europe

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Background: Amyotrophic lateral sclerosis (ALS) is a rare, neurodegenerative disease, leading to progressive muscle function loss, and ultimately death. Historically, ALS has been classified as familial (those with a known family history) or sporadic (those with no known family history) but genetic mutations causative of ALS occur in both groups.

Methods: Data were drawn from the Adelphi ALS Disease Specific Programme (DSP14), a point-in-time survey of neurologists and their ALS patients in France, Germany, Italy, Spain, the UK and the USA, collected between July 2020–March 2021. Neurologists (general neurologists, neuromuscular specialists, ALS specialists [EUS only]) were asked to complete a questionnaire reporting recently consulted patients’ demographics and clinical characteristics, including family history of ALS, and genetic testing status.

Results: 142 neurologists completed questionnaires for 880 ALS patients, with genetic testing history being reported for 838 patients (US =244, EUS = 594). 92% of patients tested had no known family history of ALS (US: 91%, EUS: 92%). Globally it was reported that 51% of patients had been offered a genetic test (US: 56%, EUS: 49%) and 34% had accepted and undergone testing (US: 27%, EUS: 37%), with an acceptance rate of 68% (US: 49%, EUS: 77%). 99% of familial patients had been offered a genetic test (US: 100%, EUS: 98%) and 94% accepted (US: 86%, EUS: 98%) a genetic test, compared to 47% of sporadic patients being offered a genetic test (US: 52%, EUS: 45%) and 63% accepting (US: 42%, EUS: 72%). Among those patients who had received genetic testing (US: 27%, EUS: 37%), 88% had been tested for mutations at the SOD1 locus (US: 78%, EUS: 91%), 81% at C9orf72 (US: 63%, EUS: 86%), and 78% at ATXN-2 (US: 73%, EUS: 80%). 22% of patients had returned a positive result for SOD1 (US: 25%, EUS: 21%), 11% for C9orf72 (US: 10%, EUS: 12%), and 10% for ATXN-2 (US: 20%, EUS: 7%). In the case of SOD1, 32 (52%) familial ALS patients returned a positive test (US: 65%, EUS: 47%) compared to 25 (12%) sporadic ALS patients (US: 9%, EUS: 13%). Of those who tested positive for SOD1, 44% were sporadic ALS patients (US: 27%, EUS: 50%).

Discussion: Only approximately one-third of patients with ALS were offered and underwent genetic testing. While the proportion of positive results is higher in familial than sporadic patients, these results show the importance of testing all patients, regardless of family history. Although testing was more frequently offered to familial patients, SOD1 variants of ALS were almost equally identified within sporadic and familial patients and similar results were seen for other genetic variants of ALS. Genetic testing while available, is not being
conducted and accepted widely. Barriers to genetic testing must be identified and addressed in advance of gene therapy approval in ALS.

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C26 Reliability and feasibility of unsupervised vital capacity testing at home in patients with MND

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Background: Home-based monitoring of spirometry allows for more frequent assessments of respiratory function in patients with motor neuron disease (MND) and saves travel and clinic burden, compared to regular MND care. However, use of home-based spirometry in MND care is still lacking.

Objective: Therefore, we aim to assess the reliability and feasibility of unsupervised home-based vital capacity (VC) testing in patients with MND.

Methods: We included 33 patients with MND who had access to a smartphone, and did not use non-invasive or invasive ventilation during daytime. Patients completed a 12-week home monitoring protocol, consisting of 4-weekly unsupervised home assessments of the upright VC with a full-face mask, functional impairment (ALSFRS-R) and dyspnea-related symptoms (MND Dyspnea Scale). In total 9 patients were assisted with home-monitoring by a caregiver. At baseline, during a home visit, patients and caregivers were trained in performing a VC test, and the investigator performed a supervised VC test, which was repeated at final follow-up during a second home visit. Reminders were sent at each follow-up through text message or email. Inter-rater reliability was determined through the 95% limits of agreement and the intraclass correlation coefficient (ICC) between the unsupervised and supervised VC tests. Sensitivity and specificity were assessed to determine whether the unsupervised VC could detect a supervised VC <80%, and feasibility was assessed through a survey on user-experiences, including items on user-friendliness, burden of monitoring and complexity of measuring.

Results: The 95% limits of agreement were −13.5 and 14.7 %predicted VC, showing that there was no systematic bias towards the unsupervised or supervised VC, and the ICC was excellent (ICC =0.981, p < 0.001). The unsupervised VC had high sensitivity (97.1%) and specificity (93.3%) for detecting supervised VC <80% of predicted. Patients who showed a decrease in VC reported an increase in severity of dyspnea-related symptoms. Adherence to the home-based VC testing was 100%, and most patients perceived unsupervised VC testing as not burdensome (88%), were confident in their ability to perform a VC test (73%) and would like home monitoring of VC in MND care (91%). Seven out of nine caregivers believed they were able to correctly (help) perform a VC test, while four out of nine did not think that the unsupervised VC test was performed just as well as a supervised in-clinic VC test.

Conclusion: Home-based VC testing, with prior face-to-face training and reminders during follow-up, is a viable method for the remote monitoring of respiratory function, and well-accepted by patients with MND and their caregivers in our cohort. Future studies may evaluate the long-term unsupervised home-monitoring of VC in patients with MND.

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SESSION 10 CLOSING SESSION

C27 Gene therapy for ALS: opportunities and pitfalls

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With the recent approval of Zolgensma for the childhood motor neuron disorder Spinal Muscular Atrophy (SMA) and the exponential growth in companies committed to gene therapy development for rare and neurological disorders, there is much excitement and anticipation for this therapeutic modality for adult motor neuron disease/amyotrophic lateral sclerosis (ALS). Whilst SMA is a monogenic disorder, multiple genes contribute to the demise of neurons in ALS. Mutations in the gene encoding Cu/Zn superoxide dismutase (SOD1) account for 2% of ALS. Pre-clinical studies in SOD1 mouse models provide the preliminary rationale to block production of SOD1 protein and hence the gain of a toxic function, an approach now in phase III clinical trials using antisense technology. The discovery of hexanucleotide expansions C9orf72 accounts for 10% of ALS and is potentially amenable to a gene therapy approach. Gene therapy provides a one-time therapeutic approach directly to the root cause of the disease, as opposed to multiple ongoing administration of small molecules or antisense oligonucleotides. With growing evidence that neurofilaments provide a strong early predictor of disease several years before clinical onset one could envision treatment over an extended period, favoring the gene therapy approach.

Whilst the field has learned numerous lessons from the development of gene therapy for a childhood disease, SMA, and we can leverage these learnings for ALS, there are significant considerations when comparing a childhood disorder to an adult disorder. The route of administration and an understanding of the cells types transduced is critical. In addition to challenges in delivery, immunogenicity remains a concern and various approaches are in consideration to circumvent these challenges. Furthermore, with advances in capsid technology, the hope is that we will eventually be able to regulate gene expression and have the ability to switch the expression of a gene product on and off as needed.

The significant investment into gene therapy development demands rigorous trial design and biomarker development. A clear correlation between target engagement and a change in a clinically meaningful endpoint is important for the approval of this therapeutic modality. Whilst there is progress in the development of biomarkers for ALS, there are limited data in the field showing a correlation between these promising biomarkers (soluble and imaging biomarkers) and clinical outcome measures.

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C28 Technology to empower living with ALS/MND

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When Lou Gehrig was diagnosed with ALS in the 1930s and when I was diagnosed with in 2011, there were no effective medical treatments available. However, during the same time period technological advancements for ALS patients have been, like the technology industry, exponential. Despite the lack of medical intervention available for people living with ALS, we do now have ventilation and innovative leading edge technology. Those technologies are empowering me and others to live and remain productive and purposeful for years and perhaps decades. In a sense, while there is no medical cure or treatments for ALS, technology can act as a cure. Stated another way, some of what ALS takes away, technology can give back.

Technology, for people with ALS and other disabilities, in many ways is the absolute cutting edge of the technology industry. Technology for disabled people is a training ground, which will eventually impact all others. Investing in these technologies is not only important because it is for the right reasons, but because of this ‘collision’ it is valuable in the global marketplace.

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Biomedical Research Grants 2022

The vision of the MND Association is a world free from MND. We fund and promote research that leads to new understanding and treatments, and brings us closer to a cure for MND.

Non-Clinical Fellowship Awards
Deadline*: 29 April 2022

The aim of these awards is to foster and nurture post-doctoral scientists to become leaders of the future in MND research. The length and value of a grant will depend on the applicant’s experience. The awards may be held at recognised research institutes and universities in the UK or Ireland. They are not open to practising clinicians.

Biomedical Project Grants
Deadline*: 28 October 2022

Awards are provided for a period of between one and three years. Although most grants are awarded in the UK, applicants can be based at any recognised research institute worldwide, provided no similar research is being conducted in the UK and Ireland and the project involves significant collaboration with a UK or Irish Institute.

PhD Studentship Awards
Deadline*: 29 April 2022

Awards for three years are intended to attract promising science and healthcare graduates to develop a career in MND-related research. Applicants must be established researchers based at recognised research institutes and universities in the UK or Ireland.

For further information, terms and conditions, application process and research governance, please visit www.mndassociation.org/for-researchers/apply-for-funding or email research.grants@mndassociation.org.

*Summary applications will only be accepted via our online summary application form available during submission periods.
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