

Publikationen ALS-Ambulanz

1) RIG-I Mediated Neuron-Specific IFN Type 1 Signaling in FUS-ALS Induces Neurodegeneration and Offers New Biomarker-Driven Individualized Treatment Options for (FUS-)ALS (2026) Naumann, M., Wierschin, T. M., Kretschmer, S., Dash, B. P., Held, A., Salzinger, A., Peikert, K., Karlek, A., Glass, H., Grossmann, D., Gunther, R., Petri, S., Rodiger, A., Brenner, D., Pan-Montojo, F., Aronica, E., Kipp, M., Zimyanin, V., Sternecker, J., Grehl, T., Seebacher, N. D., Bockers, T. M., Catanese, A., Wainger, B. J., Oeckl, P., Lee-Kirsch, M. A. and Hermann, A.

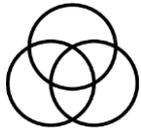
Adv Sci (Weinh) 2026 e17135.

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Abstract: Recent research demonstrated activation of the innate immune system in ALS models. This pathway can be activated by cGAS-STING sensing of cytosolic DNA that accumulates as a result of chronic DNA damage and defective mitochondria, both of which was identified as pathology in FUS-ALS. Therefore, we analyzed innate immune pathways in FUS-ALS, which revealed upregulation of interferon-stimulated genes (ISGs) and activation of the TBK1-IRF3 pathway in FUS(mut) iPSC-derived spinal motor neurons (sMNs). Accumulation of cytosolic dsRNA and its sensor RIG-I, but not MDA5, was found to be significantly upregulated in FUS(mut) sMNs, which was abolished upon siRNA-mediated knockdown of RIG-I. RIG-I was highly expressed in FUS-ALS post-mortem alpha-MNs. IFN treatment of FUS(wt) sMNs phenocopied the axonal degeneration of FUS(mut) sMNs. Mitochondrial transcription, a known source of dsRNA, was found to be upregulated in compartmental axonal RNAseq analysis and its inhibition reduced ISGs in FUS-ALS sMNs. The JAK-STAT inhibitor ruxolitinib alleviated the upregulated ISG expression and reversed the axonal degeneration of sMNs. Finally, we analyzed ISG expression in peripheral blood from 18 FUS-ALS patients, eight of whom had a significantly elevated interferon signature. RIG-I-mediated innate immune activation in sMNs may be an interesting novel individualized biomarker-driven therapeutic target in (FUS-) ALS. A one-sentence summary of your paper: RIG-I-mediated innate immune activation is found in FUS-ALS spinal motor neurons caused by cytosolic dsRNA accumulation due to mitochondrial transcriptional activation and is amenable to JAK-STAT inhibition and might thus be an interesting novel individualized biomarker-driven therapeutic approach in (FUS-) ALS.



2) Minimum important slowing of disease progression as determined by the ALS functional rating scale - a survey of patient expectations toward disease-modifying drugs in

ALS (2026) Meyer, T., Maier, A., Grehl, T., Weyen, U., Rodiger, A., Smesny, U., Steinbach, R., Grosskreutz, J., Goricke, B., Bernsen, S., Weydt, P., Fabian, R., Petri, S., Lumi, R., Bjelica, B., Boentert, M., Lingor, P., Kettemann, D., Norden, J., Walter, B., Riitano, A., Schumann, P., Munch, C. and Spittel, S.

Amyotroph Lateral Scler Frontotemporal Degener 2026 1-12

DOI: 10.1080/21678421.2026.2615117

URL: <https://www.ncbi.nlm.nih.gov/pubmed/41557593>

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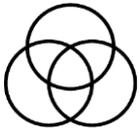
Objective: To define the minimum important slowing (MIS) of ALS progression that patients would expect from disease-modifying drug treatment in ALS. Methods: In a survey of ALS patients, the MIS in ALS progression (change in the ALS Functional Rating Scale-Revised, ALSFRS-R) was assessed by asking: "At what point of slowing of ALS, as determined by the ALSFRS-R, do you consider a drug to be important?" Data were collected during clinic visits or remotely via the ALS App. Participants were differentiated in the prognostic groups of slower (<0.5), intermediate (>/=0.5 and </=1.0), or faster (>1.0) ALS progression (ALSPR; ALSFRS-R/month). Results: Of 522 participants (ALS App, n = 397; clinic, n = 125), 395 (75.7%) completed the survey, while 127 (24.3%) selected the option "cannot estimate". The distribution of MIS was as follows: modest slowing of ALS progression (5% and 10% slowing, n = 146 patients, 36.9%), moderate slowing (20%, 30%, and 40% slowing, n = 135, 34.2%), and major slowing (>/=50% slowing, n = 114, 28.9%). Median MIS was 20% (IQR 10-50%). Patients with faster ALSPR more frequently assessed a major slowing as the MIS (n = 18, 36.0%) compared to those with slower ALSPR (n = 54, 25.2%).

Conclusion: A considerable number of participants viewed a modest slowing in ALS progression as the MIS, followed closely by preferences for moderate and major slowing. Expectations varied according to patients' individual ALS progression. These insights may inform the design of future clinical trials in ALS. Study limitations include potential selection and response biases, as well as the predominantly remote digital assessment.

3) Response to Fortin-Bedard et al. "User expectations and experiences of an assistive robotic arm in amyotrophic lateral sclerosis: a multicenter observational study" (2025) Spittel, S., Meyer, T., Weyen, U., Grehl, T., Weydt, P., Steinbach, R., Petri, S., Baum, P., Metelmann, M., Sperfeld, A. D., Kettemann, D., Norden, J., Rodiger, A., Ilse, B., Grosskreutz, J., Hildebrandt, B., Walter, B., Munch, C. and Maier, A.

Neurol Res Pract 2025 7 (1) 70

DOI: 10.1186/s42466-025-00405-z



URL: <https://www.ncbi.nlm.nih.gov/pubmed/41013833>
<https://link.springer.com/content/pdf/10.1186/s42466-025-00405-z.pdf>

4) Motor phenotypes and neurofilament light chain in genetic amyotrophic lateral sclerosis—results from a multicenter screening program 2025 Schmitt, P., Schumann, P., Koerbs, A., Lin, H. J., Grehl, T., Weyen, U., Petri, S., Rodiger, A., Steinbach, R., Grosskreutz, J., Bernsen, S., Weydt, P., Wolf, J., Gunther, R., Baum, P., Metelmann, M., Weishaupt, J. H., Streubel, B., Kasper, D. C., Koc, Y., Kettemann, D., Norden, J., Walter, B., Munch, C., Spittel, S., Maier, A., Kortvelyessy, P. and Meyer, T.

J Neurol 2025 273 (1) 22

DOI: 10.1007/s00415-025-13555-6

URL: <https://www.ncbi.nlm.nih.gov/pubmed/41388206>

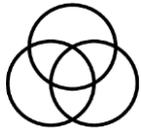
<https://link.springer.com/content/pdf/10.1007/s00415-025-13555-6.pdf>

Objective: In genetic amyotrophic lateral sclerosis (ALS), the clinical phenotypes, disease progression and neurofilament light chain (NfL) levels are incompletely characterized. **METHODS:** In a total cohort of 1988 ALS patients, a subcohort of genetic ALS linked to C9orf72 (n = 137), SOD1 (n = 54), TARDBP (n = 27), and FUS (n = 19) was investigated. The phenotypes of onset region, propagation and motor neuron involvement were analyzed according to the OPM classification. Serum NfL (sNfL) was measured and related to ALS progression (ALSPR, monthly change of ALS Functional Rating Scale-Revised). To quantify NfL elevation relative to ALSPR, the logNfL(index), the log-transformed ratio of sNfL to ALSPR was calculated.

Results: C9orf72-associated ALS showed frequent bulbar onset (n = 42.6%), higher ALSPR (0.95, SD 0.84), highest NfL (116.3, SD 72.7 pg/mL) and logNfL(index) (5.02, SD 0.88). SOD1-ALS had mostly limb onset (n = 96.1%), slower ALSPR (0.57, SD 0.60), high NfL (76.1, SD 61.4 pg/mL) and a comparably high logNfL(index) (4.94, SD 1.03). FUS-ALS exhibited mostly limb onset (82.4%), lower motor neuron dysfunction (70.6%), a wide range of faster (22.2%) to slower ALSPR (55.6%), lower NfL (66.2, SD 32.9) and logNfL(4.65, SD 0.9). TARDBP-ALS displayed the lowest ALSPR (0.53, SD 0.52), the lowest NfL (43.3, SD 31.8 pg/mL) and the lowest logNfL(index) (4.40, SD 0.7).

Conclusion: In C9orf72-ALS, the phenotype and NfL profile are close to typical ALS. The finding of distinct phenotypes and NfL patterns in SOD1-, FUS- and TARDBP-associated ALS underscores the relevance of genetic ALS for prognostic counseling, clinical trial design, treatment expectations and unraveling of pathogenic mechanisms in ALS.

5) Combination of Serum Neurofilament Light Chain and Serum Cardiac Troponin T as Biomarkers Improves Diagnostic Accuracy in Amyotrophic Lateral Sclerosis (2025) Lindenborn, P., Fabian, R., Grehl, T., Nazlican, H., Meyer, T., Bernsen, S. and Weydt, P.



Ann Neurol 2025 DOI: 10.1002/ana.78066

URL: <https://www.ncbi.nlm.nih.gov/pubmed/41133969>

<https://onlinelibrary.wiley.com/doi/pdfdirect/10.1002/ana.78066?download=true>

Objective: We aimed to evaluate the clinical utility of serum neurofilament light chain (sNfL) and cardiac troponin T (cTnT) in amyotrophic lateral sclerosis (ALS) and assess whether their combination improves diagnostic accuracy. **METHODS:** We retrospectively analyzed 293 ALS patients, 85 neurodegenerative disease controls, and 29 healthy controls. A validation cohort of 501 ALS patients was analyzed to confirm reproducibility of the results. Receiver operating characteristic (ROC) curve analysis was performed for sNfL, cTnT, and their combination, and the area under the curve (AUC) was compared across groups. An ALS-specific cTnT cut-off of 8.35ng/L was determined using the Youden index and applied in subgroup analyses, in which "biomarker-negative" ALS patients were compared to "biomarker-positive" patients regarding disease duration and progression.

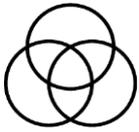
Results: sNfL showed excellent performance in discriminating ALS patients from healthy controls (AUC = 0.94), but only moderate performance in discriminating neurodegenerative disease controls (AUC = 0.82). Combining sNfL and cTnT improved diagnostic accuracy for ALS over neurodegenerative controls, with an AUC of 0.90, whereas cTnT alone showed an AUC of 0.77. The validation cohort showed similar AUCs. "Biomarker-negative" ALS patients had a longer disease duration (73.0 vs 18.0 months, $p = 0.0003$) and a lower progression rate (0.19 vs 0.70 points per months, $p < 0.0001$) than "biomarker-positive" patients.

Interpretation: Although sNfL alone performs well in distinguishing ALS from healthy controls, repurposing cTnT for ALS provides additional value in discriminating ALS from disease controls. The combination of sNfL and cTnT improves diagnostic accuracy and may help identify prognostically distinct ALS subgroups.

6) Dextromethorphan/quinidine (DMQ) for reducing bulbar symptoms in amyotrophic lateral sclerosis - assessment of treatment experience in a multicenter study (2025) Spittel, S., Grehl, T., Weydt, P., Kettemann, D., Fabian, R., Rodiger, A., Smesny, U., Steinbach, R., Ilse, B., Weyen, U., Petri, S., Lumi, R., Bjelica, B., Lingor, P., Grosskreutz, J., Goricke, B. M., Pfeilschifter, W., Schmeja, W., Dorst, J., Mensch, A., Siebert, J., Norden, J., Bernsen, S., Subramanian, S. K., Hildebrandt, B., Walter, B., Munch, C., Maier, A. and Meyer, T.

Amyotroph Lateral Scler Frontotemporal Degener. 2025 Sep 11:1-13. doi: 10.1080/21678421.2025.2557932.

Abstract: In amyotrophic lateral sclerosis (ALS), dextromethorphan/quinidine (DMQ) has been reported to reduce bulbar symptoms, including dysarthria and dysphagia. However, data on patients'



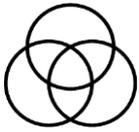
perceptions of DMQ treatment are limited. **METHODS:** Data on DMQ treatment were collected from 1065 ALS patients treated at 13 ALS centers between 10-2015 and 06-2025. Patient-reported outcome measures (PROM) of 179 participants were remotely assessed via the "ALS App". PROM included the self-explanatory version of the ALS Functional Rating Scale (ALSFRS-R-SE), the Net Promoter Score (NPS); and Treatment Satisfaction Questionnaire for Medication (TSQM-9). **RESULTS:** Mean disease duration was 29.3 months (SD 38.1). ALS progression before treatment was 0.82 points/month (ALSFRS-R). Mean DMQ treatment duration was 8.4 months (SD 10.8), including 35.2% (n = 374) of shorter (<3 months), 35.3% (n = 375) of longer (3-9 months), and 29.5% (n = 313) of very long DMQ treatment (>9 months). Patients' recommendation (n = 178) was positive (NPS: +23) with higher scores after very long DMQ treatment (NPS +37) compared to longer (NPS +15) and shorter treatment (NPS +7.5), respectively. TSQM-9 scores (n = 163) demonstrated high satisfaction for effectiveness 60.0 (SD 25.9), convenience 73.8 (SD 18.2), and global satisfaction 63.4 (SD 29.8). **INTERPRETATION:** The positive perception in PROM underscores the value of DMQ as an individualized treatment option for bulbar symptoms in ALS. However, shortage of clinical data, online assessment, and selection biases are among the limitations of this study that need to be addressed in further investigations.

7) Motor phenotypes of amyotrophic lateral sclerosis - a three-determinant anatomical classification based on the region of onset, propagation of motor symptoms, and the degree of upper and lower motor neuron dysfunction

(2025) Meyer, T., Boentert, M., Grosskreutz, J., Weydt, P., Bernsen, S., Reilich, P., Steinbach, R., Rodiger, A., Wolf, J., Weyen, U., Ludolph, A. C., Weishaupt, J., Petri, S., Lingor, P., Gunther, R., Loscher, W., Weber, M., Munch, C., Maier, A. and Grehl, T.

Neurol Res Pract. 2025 Apr 28;7(1):27. doi: 10.1186/s42466-025-00389-w.

Abstract: **BACKGROUND:** In amyotrophic lateral sclerosis (ALS), heterogeneity of motor phenotypes is a fundamental hallmark of the disease. Distinct ALS phenotypes were associated with a different progression and survival. Despite its relevance for clinical practice and research, there is no broader consensus on the classification of ALS phenotypes. **METHODS:** An expert consensus process for the classification of ALS motor phenotypes was performed from May 2023 to December 2024. A three-determinant anatomical classification was proposed which is based on the (1) region of onset (O), (2) the propagation of motor symptoms (P), and (3) the degree of upper (UMN) and/or lower motor neuron (LMN) dysfunction (M). Accordingly, this classification is referred to as the "OPM classification". **RESULTS:** Onset phenotypes differentiate the site of first motor symptoms: O1) head onset; O2d) distal arm onset; O2p) proximal arm onset; O3r) trunk respiratory onset; O3a) trunk axial onset; O4d)

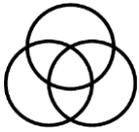


distal leg onset; O4p) proximal leg onset. Propagation phenotypes differentiate the temporal propagation of motor symptoms from the site of onset to another, vertically distant body region: PE) earlier propagation (within 12 months of symptom onset); PL) later propagation (without propagation within 12 months of symptom onset), including the established phenotypes of "progressive bulbar paralysis" (O1, PL), "flail-arm syndrome" (O2p, PL), and "flail-leg syndrome" (O4d, PL); PN) propagation not yet classifiable as time since symptom onset is less than 12 months. Phenotypes of motor neuron dysfunction differentiate the degree of UMN and/or LMN dysfunction: M0) balanced UMN and LMN dysfunction; M1d) dominant UMN dysfunction; M1p) pure UMN dysfunction ("primary lateral sclerosis", PLS); M2d) dominant LMN dysfunction; M2p) pure LMN dysfunction ("progressive muscle atrophy", PMA); M3) dissociated motor neuron dysfunction with dominant LMN and UMN dysfunction of the arms and legs ("brachial amyotrophic spastic paraparesis"), respectively. CONCLUSION: This consensus process aimed to standardize the clinical description of ALS motor phenotypes in clinical practice and research - based on the onset region, propagation pattern, and motor neuron dysfunction. This "OPM classification" contributes to specifying the prognosis, to defining the inclusion or stratification criteria in clinical trials and to correlate phenotypes with the underlying disease mechanisms of ALS.

8) Provision, cough efficacy and treatment satisfaction of mechanical insufflation-exsufflation in a large multicenter cohort of patients with amyotrophic lateral sclerosis (2025) Maier, A., Kettemann, D., Weyen, U., Grehl, T., Schulte, P. C., Steinbach, R., Rodiger, A., Weydt, P., Petri, S., Wolf, J., Grosskreutz, J., Koch, J. C., Weishaupt, J. H., Rosseau, S., Norden, J., Kortvelyessy, P., Koch, B., Holm, T., Hildebrandt, B., Schumann, P., Walter, B., Riitano, A., Munch, C., Meyer, T. and Spittel, S.

Sci Rep. 2025 Mar 1;15(1):7360. doi: 10.1038/s41598-025-91692-8.

Abstract: In patients with amyotrophic lateral sclerosis (ALS), mechanical insufflation-exsufflation (MI-E) addresses cough deficiency to achieve major therapeutic goals: improving costal muscle and joint function, reducing atelectasis through insufflation, and clearing bronchial secretions via exsufflation. Despite its perceived benefits, there is limited systematic research on MI-E provision, symptom alleviation, or patient satisfaction. The research platform Ambulanzpartner coordinated this longitudinal observational study conducted in 12 German ALS centers from July 2018 to September 2023. Patients were enrolled based on ALS-related cough deficiency requiring MI-E therapy. The study recorded provision, reasons for withholding MI-E, clinical parameters, therapy frequency, subjective cough deficiency, and symptomatic relief. Satisfaction with MI-E therapy was determined by the likelihood of recommendation. Out of 694 ALS patients indicated for MI-E, 527 (75.9%) received the therapy. The primary reason for non-provision was that the patient had died before provision (n = 66 of 167; 39.5%). These patients were significantly more affected as represented by higher pro-

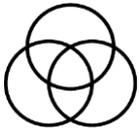


gression rates and lower cough peak flows (CPF) at the time of MI-E indication ($p < 0.05$). Most patients who received MI-E used it daily ($n = 290$ of 370 ; 78.4%). Self-assessed cough deficiency correlated with clinical measurements, especially for patients with higher deficits. At follow-up visits, patients reported reduced cough deficiency ($p < 0.001$). Frequent MI-E use was linked to greater symptom relief and higher likelihood of recommending the therapy. This study highlights the symptomatic and palliative potential of MI-E therapy for ALS patients.

9) Self-assessment of amyotrophic lateral sclerosis functional rating scale on the patient's smartphone proves to be non-inferior to clinic data capture (2025) Steinfurth, L., Grehl, T., Weyen, U., Kettemann, D., Steinbach, R., Rodiger, A., Grosskreutz, J., Petri, S., Boentert, M., Weydt, P., Bernsen, S., Walter, B., Gu, Nther R., Lingor, P., Koch, J. C., Baum, P., Weishaupt, J. H., Dorst, J., Koc, Y., Cordts, I., Vidovic, M., Norden, J., Schumann, P., Kortvelyessy, P., Spittel, S., Munch, C., Maier, A. and Meyer, T.

Amyotroph Lateral Scler Frontotemporal Degener. 2025 Aug;26(5-6):495-506. doi: 10.1080/21678421.2025.2468404. Epub 2025 Feb 22.

Abstract: OBJECTIVE: To investigate self-assessment of the amyotrophic lateral sclerosis functional rating scale-revised (ALSFERS-R) using the patient's smartphone and to analyze non-inferiority to clinic assessment. METHODS: In an observational study, ALSFRS-R data being remotely collected on a mobile application (App-ALSFERS-R) were compared to ALSFRS-R captured during clinic visits (clinic-ALSFERS-R). ALS progression rate (ALSPR)-as calculated by the monthly decline of ALSFRS-R-and its intrasubject variability (ALSPR-ISV) between ratings were used to compare both cohorts. To investigate non-inferiority of App-ALSFERS-R data, a non-inferiority margin was determined. RESULTS: A total of 691 ALS patients using the ALS-App and 1895 patients with clinic assessments were included. Clinical characteristics for the App-ALSFERS-R and clinic-ALSFERS-R cohorts were as follows: Mean age 60.45 (SD 10.43) and 63.69 (SD 11.30) years ($p < 0.001$), disease duration 38.7 (SD 37.68) and 56.75 (SD 54.34) months ($p < 0.001$) and ALSPR 0.72 and 0.59 ($p < 0.001$), respectively. A paired sample analysis of ALSPR-ISV was applicable for 398 patients with clinic as well as app assessments and did not show a significant difference (IQR 0.12 [CI 0.11, 0.14] vs 0.12 [CI 0.11, 0.14], $p = 0.24$; Cohen's $d = 0.06$). CI of IQR for App-ALSFERS-R was below the predefined non-inferiority margin of 0.15 IQR, demonstrating non-inferiority. CONCLUSIONS: Patients using a mobile application for remote digital self-assessment of the ALSFRS-R revealed younger age, earlier disease course, and faster ALS progression. The finding of non-inferiority of App-ALSFERS-R assessments underscores, that data collection using the ALS-App on the patient's smartphone can serve as additional source of ALSFRS-R in ALS research and clinical practice.

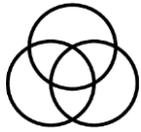


10) Shared prognostic information in amyotrophic lateral sclerosis - systematic assessment of the patients' perception of neurofilament light chain and the ALS functional rating scale (2025) Mohwald, L. M., Maier, A., Grehl, T., Weyen, U., Weydt, P., Gunther, R., Lingor, P., Goricke, B., Petri, S., Grosskreutz, J., Boentert, M., Cordts, I., Weishaupt, J. H., Dorst, J., Munch, C., Meyer, T. and Baum, P.

Neurol Res Pract. 2025 Feb 6;7(1):6. doi: 10.1186/s42466-024-00363-y.

Abstract: **BACKGROUND:** In amyotrophic lateral sclerosis (ALS), neurofilament light chain (NfL) was introduced as a prognostic biomarker. More recently, NfL values can be shared on the patient's ALS app. Also, the ALS functional rating scale (ALSFERS-R) is an established patient-reported assessment of disease progression. The scale can be obtained during clinic visits or remotely. However, few systematic data are available on the patients' perception of prognostic information about NfL and ALSFRS-R and the remote sharing of these data. **METHODS:** In a multicenter study, 149 ALS patients were assessed for their perception of shared information about NfL and ALSFRS-R using an investigator-designed survey and established questionnaires. The recommendation of NfL and ALSFRS-R to fellow patients was assessed using the Net Promoter Score (NPS). Burden by shared information was investigated in two distinct settings: (1) clinic information when receiving results on NfL and/or ALSFRS-R during clinic visits and (2) remote information about NfL values and self-rating of the ALSFRS-R via the ALS app. General anxiety was measured by the Fear of Progression Questionnaire - Short Form (FoP-Q-SF). **RESULTS:** Information about NfL and ALSFRS-R, respectively (n = 149), were regarded as relevant for patients themselves (75.2% and 77.2%) and for research (98% and 96%). The NPS showed a high recommendation rate for NfL (+ 21) and ALSFRS-R (+ 26). Only a minority of patients perceived shared information about NfL as burdensome, with a lower burden in the clinic setting (n = 1, 4.2%) than in the remote setting (n = 8, 12%; p = 0.015). Remote digital assessment of the ALSFRS-R was well received, with a reported burden in 9.8% (n = 9) of the participants. The FoP-Q-SF revealed fear of progression in 40% of the respondents (n = 60). **CONCLUSIONS:** This study underscored the relevance of information about NfL and ALSFRS-R from the patient's perspective. Furthermore, patients proved to appreciate the relevance of this data for ALS research. Sharing information about NfL or ALSFRS-R was rarely perceived as burdensome even in a remote setting using the ALS app. These findings pave the way for further development of the patient-centered approach to sharing prognostic information in ALS.

11) SOD1 gene screening in ALS - frequency of mutations, patients' attitudes to genetic information and transition to tofersen treatment in a multi-center program (2025) Meyer, T., Schumann, P., Grehl, T., Weyen, U., Petri, S., Rodiger, A., Steinbach, R., Grosskreutz, J., Bernsen, S., Weydt, P., Wolf, J., Gunther, R., Vidovic, M., Baum, P., Metelmann, M., Weishaupt, J. H., Streubel, B., Kasper, D. C., Koc, Y., Kettemann, D., Norden, J., Schmitt, P., Walter, B., Munch, C., Spittel, S., Maier, A. and Kortvelyessy, P.



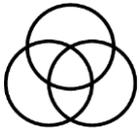
Amyotroph Lateral Scler Frontotemporal Degener. 2025 Feb;26(1-2):162-171. doi: 10.1080/21678421.2024.2401131. Epub 2024 Sep 13.

Abstract: **OBJECTIVE:** To report the frequency of pathogenic SOD1 gene variants in a screening program in amyotrophic lateral sclerosis (ALS), and the clinical practice of transition to an expanded access program (EAP) of tofersen treatment. **METHODS:** From October 2021 to February 2024, at 11 ALS centers in Germany genetic testing for SOD1, FUS, TARDBP, and C9orf72 was performed. Patients were offered to opt for notification either about all genetic variants or SOD1 variants relevant for tofersen therapy. The transition to the EAP with tofersen was assessed. **RESULTS:** 1935 patients were screened (94.7% sporadic ALS). 48.8% (n = 928) opted for notification of treatment-relevant information. Genetic variants were found as follows: SOD1 (likely) pathogenic variants (class 4/5) 1.8% (n = 34), variants of unknown significance (class 3) 0.8% (n = 16), FUS (class 4/5) 0.9% (n = 17), TARDBP (class 4/5) 1.3% (n = 25), C9orf72 hexanucleotide repeat expansion 7.0% (n = 135). In SOD1-ALS (encompassing class 3-5 variants, n = 50), 68.0% (n = 34) reported a negative family history. 74.0% (n = 37) of SOD1-ALS patients - which represent 1.9% of all participants of the screening program - were transitioned to tofersen. Median duration from start of genetic testing to treatment was 94 days (57 to 295 days). Eight patients declined treatment whereas five individuals died before initiation of therapy. **CONCLUSION:** The finding of SOD1 variants in patients with a negative family history underscores the need for a broad genetic screening in ALS. In SOD1-ALS, the treatment option with tofersen was mostly utilized. The wide range in the transition time to tofersen calls for a SOD1-ALS management program.

12) End of life perspectives: a systematic survey of patients with amyotrophic lateral sclerosis(2024). C. Eickhoff, B. Schone-Seifert, D. Kettemann, E. Bormann, T. Grehl, M. Boentert, et al.

Nervenarzt 95(12): 1131-1138.

BACKGROUND: Amyotrophic lateral sclerosis (ALS) is a disease that still has to be primarily treated symptomatically or palliatively. It is therefore all the more important, in addition to initiating treatment, such as percutaneous endoscopic gastrostomy (PEG), noninvasive ventilation therapy (NIVT) and invasive ventilation therapy via tracheotomy (IVT), to discuss the possible termination of these measures early on. **QUESTION:** What is the importance of advance directives for those affected and where are possible deficits in therapy planning for the end of life? **MATERIAL AND METHOD:** Between March 2017 and January 2019 patients with a clinically confirmed diagnosis of ALS at six treatment centers were asked to fill out a questionnaire. A total of 328 people returned the completed forms. **RESULTS:** Of the participants 72% had already made an advance directive (AD), 25% planned to fill one out and only 3% refused to do so. In composing the AD most patients (90%) had support, although 56% lacked medical counselling and only 18% had drawn up the will together with the doctor and relatives, with the majority of the rest also wanting support from a doctor. A total of 37% of all patients wanted a contact person to talk about their illness but only 40% of them had such a



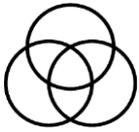
contact person. Of the patients 22% stated that they had considered suicide and of these only 55% stated that they had no contact person for the psychological stress caused by the illness but 31% wished to have such a person. DISCUSSION AND CONCLUSION: A coordinated care of ALS patients, which also takes the psychosocial aspects into account is urgently needed.

13) Cardiac troponin T as a serum biomarker of respiratory impairment in amyotrophic lateral sclerosis (2024), Koch, T., Fabian, R., Weinhold, L., Koch, F. W., Barakat, S., Castro-Gomez, S., Grehl, T., Bernsen, S. and Weydt, P.

Ann Clin Transl Neurol 11(8): 2063-2072.

OBJECTIVE: Informative biomarkers are an urgent need in the management of amyotrophic lateral sclerosis. Serum cardiac troponin T is elevated in the majority of amyotrophic lateral sclerosis patients and increases with disease progression. We sought to establish the informative value of cardiac troponin T with regard to respiratory function, a major prognostic factor in amyotrophic lateral sclerosis. **METHODS:** In this retrospective observation, we analyzed two independent hospital-based cohorts (d = discovery cohort; v = validation cohort) regarding serum cardiac troponin T (n(d) = 298; n(v) = 49), serum neurofilament light chain (n(d) = 117; n(v) = 17), and respiratory tests (n(d) = 93; n(v) = 49). **RESULTS:** Serum cardiac troponin T, in contrast to serum neurofilament levels, was associated with the respiratory domain of the revised amyotrophic lateral sclerosis functional rating scale and with pulmonary function parameters, namely forced vital capacity % (r = -0.45, p = 0.001) and slow vital capacity % (r = -0.50, p = 0.001). Serum cardiac troponin T reliably discriminated benchmarks of slow vital capacity <80% (AUC 0.73, 95% CI 0.62-0.84) and <50% (AUC 0.80, 95% CI 0.68-0.93), forced vital capacity <80% (AUC 0.72, 95% CI 0.61-0.83) and <50% (AUC 0.79, 95% CI 0.67-0.91). **INTERPRETATION:** Our findings position cardiac Troponin T as a valuable serum biomarker in amyotrophic lateral sclerosis, complementing neurofilaments and expanding the understanding of underlying physiological mechanisms. In clinical practice, serum cardiac troponin T can flag benchmarks of compromised respiratory function.

14) Patients' and caregivers' perception of multidimensional and palliative care in amyotrophic lateral sclerosis - protocol of a German multicentre study(2024), Linse, K., Weber, C., Reilich, P., Schoberl, F., Boentert, M., Petri, S., Rodiger, A., Posa, A., Otto, M., Wolf, J., Zeller, D., Brunkhorst, R., Koch, J., Hermann, A., Grosskreutz, J., Schroter, C., Gross, M., Lingor, P., Machetanz, G., Semmler, L., Dorst, J., Lule, D., Ludolph, A., Meyer, T., Maier, A., Metelmann, M., Regensburger, M., Winkler, J., Schrank, B., Kohl, Z., Hagenacker, T., Brakemeier, S., Weyen, U., Weiler, M., Lorenzl, S., Bublitz, S., Weydt, P., Grehl, T., Kotterba, S., Lapp, H. S., Freigang, M., Vidovic, M., Aust, E. and Gunther, R.



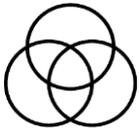
Neurol Res Pract 6(1): 34.

INTRODUCTION: Amyotrophic lateral sclerosis (ALS) is an inevitably fatal condition that leads to a progressive loss of physical functioning, which results in a high psychosocial burden and organizational challenges related to medical care. Multidimensional and multiprofessional care is advised to meet the complex needs of patients and their families. Many healthcare systems, including Germany, may not be able to meet these needs because non-medical services such as psychological support or social counselling are not regularly included in the care of patients with ALS (pwALS). Specialised neuropalliative care is not routinely implemented nor widely available. Caregivers of pwALS are also highly burdened, but there is still a lack of support services for them. **METHODS:** This project aims to assess the perceptions and satisfaction with ALS care in Germany in pwALS and their caregivers. This will be achieved by means of a cross-sectional, multicentre survey. The examination will assess, to which extent the patients' needs in the six domains of physical, psychological, social, spiritual, practical and informational are being met by current care structures. This assessment will be linked to mental well-being, subjective quality of life, attitudes toward life-sustaining measures and physician-assisted suicide, and caregiver burden. The study aims to recruit 500 participants from nationwide ALS centres in order to draw comprehensive conclusions for Germany. A total of 29 centres, mostly acquired via the clinical and scientific German Network for Motor Neuron Diseases (MND-NET), will take part in the project, 25 of which have already started recruitment. **PERSPECTIVE:** It is intended to provide data-based starting points on how current practice of care in Germany is perceived by pwALS and their caregivers and how it can be improved according to their needs. Planning and initiation of the study has been completed. **TRIAL REGISTRATION:** The study is registered at ClinicalTrials.gov; NCT06418646.

15) SOD1 gene screening in ALS - frequency of mutations, patients' attitudes to genetic information and transition to tofersen treatment in a multi-center program (2024). T. Meyer, P. Schumann, T. Grehl, U. Weyen, S. Petri, A. Rodiger, et al.

Amyotroph Lateral Scler Frontotemporal Degener: 1-10.

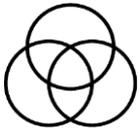
Objective: To report the frequency of pathogenic SOD1 gene variants in a screening program in amyotrophic lateral sclerosis (ALS), and the clinical practice of transition to an expanded access program (EAP) of tofersen treatment. **Methods:** From October 2021 to February 2024, at 11 ALS centers in Germany genetic testing for SOD1, FUS, TARDBP, and C9orf72 was performed. Patients were offered to opt for notification either about all genetic variants or SOD1 variants relevant for tofersen therapy. The transition to the EAP with tofersen was assessed. **Results:** 1935 patients were screened (94.7% sporadic ALS). 48.8% (n = 928) opted for notification of treatment-relevant information. Ge-



netic variants were found as follows: SOD1 (likely) pathogenic variants (class 4/5) 1.8% (n = 34), variants of unknown significance (class 3) 0.8% (n = 16), FUS (class 4/5) 0.9% (n = 17), TARDBP (class 4/5) 1.3% (n = 25), C9orf72 hexanucleotide repeat expansion 7.0% (n = 135). In SOD1-ALS (encompassing class 3-5 variants, n = 50), 68.0% (n = 34) reported a negative family history. 74.0% (n = 37) of SOD1-ALS patients - which represent 1.9% of all participants of the screening program - were transitioned to tofersen. Median duration from start of genetic testing to treatment was 94 days (57 to 295 days). Eight patients declined treatment whereas five individuals died before initiation of therapy. Conclusion: The finding of SOD1 variants in patients with a negative family history underscores the need for a broad genetic screening in ALS. In SOD1-ALS, the treatment option with tofersen was mostly utilized. The wide range in the transition time to tofersen calls for a SOD1-ALS management program.

16) Serum neurofilament light chain in distinct phenotypes of amyotrophic lateral sclerosis: A longitudinal, multicenter study (2024) T. Meyer, M. Dreger, T. Grehl, U. Weyen, D. Kettemann, P. Weydt, et al. *Eur J Neurol* 31(9): e16379.

OBJECTIVE: To assess the performance of serum neurofilament light chain (sNfL) in clinical phenotypes of amyotrophic lateral sclerosis (ALS). **METHODS:** In 2949 ALS patients at 16 ALS centers in Germany and Austria, clinical characteristics and sNfL were assessed. Phenotypes were differentiated for two anatomical determinants: (1) upper and/or lower motor involvement (typical, typMN; upper/lower motor neuron predominant, UMNp/LMNp; primary lateral sclerosis, PLS) and (2) region of onset and propagation of motor neuron dysfunction (bulbar, limb, flail-arm, flail-leg, thoracic onset). Phenotypes were correlated to sNfL, progression, and survival. **RESULTS:** Mean sNfL was - compared to typMN (75.7 pg/mL, n = 1791) - significantly lower in LMNp (45.1 pg/mL, n = 413), UMNp (58.7 pg/mL, n = 206), and PLS (37.6 pg/mL, n = 84). Also, sNfL significantly differed in the bulbar (92.7 pg/mL, n = 669), limb (64.1 pg/mL, n = 1305), flail-arm (46.4 pg/mL, n = 283), flail-leg (53.6 pg/mL, n = 141), and thoracic (74.5 pg/mL, n = 96) phenotypes. Binary logistic regression analysis showed highest contribution to sNfL elevation for faster progression (odds ratio [OR] 3.24) and for the bulbar onset phenotype (OR 1.94). In contrast, PLS (OR 0.20), LMNp (OR 0.45), and thoracic onset (OR 0.43) showed reduced contributions to sNfL. Longitudinal sNfL (median 12 months, n = 2862) showed minor monthly changes (<0.2%) across all phenotypes. Correlation of sNfL with survival was confirmed ($p < 0.001$). **CONCLUSIONS:** This study underscored the correlation of ALS phenotypes - differentiated for motor neuron involvement and region of onset/propagation - with sNfL, progression, and survival. These phenotypes demonstrated a significant effect on sNfL and should be recognized as independent confounders of sNfL analyses in ALS trials and clinical practice.



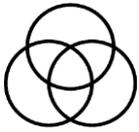
17) In-depth analysis of data from the RAS-ALS study reveals new insights in rasagiline treatment for amyotrophic lateral sclerosis (2024), Schuster, J., Dreyhaupt, J., Monkemoller, K., Dupuis, L., Dieterle, S., Weishaupt, J. H., Kassubek, J., Petri, S., Meyer, T., Grosskreutz, J., Schrank, B., Boentert, M., Emmer, A., Hermann, A., Zeller, D., Prudlo, J., Winkler, A. S., Grehl, T., Heneka, M. T., Johannesen, S., Goricke, B., Witzel, S., Dorst, J., Ludolph, A. C. and Group, Ras-Als Study.

Eur J Neurol 31(4): e16204.

BACKGROUND AND PURPOSE: In 2016, we concluded a randomized controlled trial testing 1 mg rasagiline per day add-on to standard therapy in 252 amyotrophic lateral sclerosis (ALS) patients. This article aims at better characterizing ALS patients who could possibly benefit from rasagiline by reporting new subgroup analysis and genetic data. **METHODS:** We performed further exploratory in-depth analyses of the study population and investigated the relevance of single nucleotide polymorphisms (SNPs) related to the dopaminergic system. **RESULTS:** Placebo-treated patients with very slow disease progression (loss of Amyotrophic Lateral Sclerosis Functional Rating Scale-Revised [ALSFRS-R] per month before randomization of ≤ 0.328 points) showed a per se survival probability after 24 months of 0.85 (95% confidence interval = 0.65-0.94). The large group of intermediate to fast progressing ALS patients showed a prolonged survival in the rasagiline group compared to placebo after 6 and 12 months ($p = 0.02$, $p = 0.04$), and a reduced decline of ALSFRS-R after 18 months ($p = 0.049$). SNP genotypes in the MAOB gene and DRD2 gene did not show clear associations with rasagiline treatment effects. **CONCLUSIONS:** These results underline the need to consider individual disease progression at baseline in future ALS studies. Very slow disease progressors compromise the statistical power of studies with treatment durations of 12-18 months using clinical endpoints. Analysis of MAOB and DRD2 SNPs revealed no clear relationship to any outcome parameter. More insights are expected from future studies elucidating whether patients with DRD2(CC) genotype (Rs2283265) show a pronounced benefit from treatment with rasagiline, pointing to the opportunities precision medicine could open up for ALS patients in the future.

18) User expectations and experiences of an assistive robotic arm in amyotrophic lateral sclerosis: a multicenter observational study (2024) S. Spittel, T. Meyer, U. Weyen, T. Grehl, P. Weydt, R. Steinbach, et al.. Neurol Res Pract 6(1): 42.

OBJECTIVE: Robotic arms are innovative assistive devices for ALS patients with progressive motor deficits of arms and hands. The objective was to explore the patients expectations towards a robotic arm system and to assess the actual experiences after the provision of the device. **METHODS:** A prospective observational study was conducted at 9 ALS centers in Germany. ALS-related functional deficits were assessed using the ALS-Functional Rating Scale-revised (ALSFRS-R). Motor deficit of the upper limbs was determined using a subscore of three arm-related items of the ALSFRS-R (items 4-6;

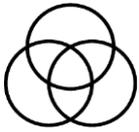


range 0–12 points). User expectations before provision (expectation group, $n = 85$) and user experiences after provision (experience group, $n = 14$) with the device (JACO Assistive Robotic Device, Kinova, Boisbriand, QC, Canada) were assessed. RESULTS: In the total cohort, mean ALSFRS-R subscore for arm function was 1.7 (SD: 2.0, 0–9) demonstrating a severe functional deficit of the upper limbs. In the expectation group ($n = 85$), the following use cases of the robotic arm have been prioritized: handling objects (89%), close-body movements (88%), pressing buttons (87%), serving drinks (86%), and opening cabinets and doors (85%). In the experience group ($n = 14$), handling objects (79%), serving drinks (79%), near-body movements (71%), pushing buttons (71%), serving food (64%), and opening doors (64%) were the most frequent used cases. Most patients used the device daily (71.4%, $n = 10$), and 28.6% ($n = 4$) several times a week. All patients of the experience group found the device helpful, felt safe while using the device, and were satisfied with its reliability. NPS of the assistive robotic arm revealed 64% "promoters" (strong recommendation), 29% "indifferents" (uncertain recommendation) and 7% "detractors" (no recommendation). Total NPS was + 57 demonstrating strong patient satisfaction. CONCLUSIONS: Initiation of procurement with a robotic assistive arm was confined to patients with severe functional deficit of the upper limbs. User experience underlined the wide spectrum of use cases of assistive robotic arms in ALS. The positive user experience together with high satisfaction underscore that robotic arm systems serve as a valuable treatment option in ALS patients with severe motor deficits of the arms.

19) Clinical and genetic features of amyotrophic lateral sclerosis patients with C9orf72 mutations (2023) Maximilian Wiesenfarth, Kornelia Günther, Kathrin Müller, Simon Witzel, Ulrike Weiland, Kristina Mayer, Christine Herrmann, David Brenner, Joachim Schuster, Axel Freischmidt, Dorothée Lulé, Thomas Meyer, Martin Regensburger, Torsten Grehl, Alexander Emmer, Susanne Petri, Julian Großkreutz, Annkathrin Rödiger, Robert Steinbach, Thomas Klopstock, Peter Reilich, Florian Schöberl, Joachim Wolf, Tim Hagenacker, Ute Weyen, Daniel Zeller, Albert C Ludolph, Johannes Dorst

Brain Communications 2023 <https://dx.doi.org/10.1093/braincomms/fcad087>

An expansion of the GGGGCC hexanucleotide in the non-coding region of C9orf72 represents the most common cause of familial amyotrophic lateral sclerosis. The objective was to describe and analyse the clinical and genetic features of amyotrophic lateral sclerosis patients with C9orf72 mutations in a large population. Between November 2011 and December 2020, clinical and genetic characteristics of $n = 248$ patients with amyotrophic lateral sclerosis carrying C9orf72 mutations were collected from the clinical and scientific network of German motoneuron disease centres. Clinical parameters included age of onset, diagnostic delay, family history, neuropsychological examination, progression rate, phosphorylated neurofilament heavy chain levels in CSF and survival. The number of repeats was correlated with the clinical phenotype. The clinical phenotype was compared to $n = 84$ patients with SOD1 mutations and $n = 2178$ sporadic patients without any known disease-related

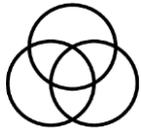


mutations. Patients with C9orf72 featured an almost balanced sex ratio with 48.4% (n = 120) women and 51.6% (n = 128) men. The rate of 33.9% patients (n = 63) with bulbar onset was significantly higher compared to sporadic (23.4%, P = 0.002) and SOD1 patients (3.1%, P < 0.001). Of note, 56.3% (n = 138) of C9orf72, but only 16.1% of SOD1 patients reported a negative family history (P < 0.001). The GGGGCC hexanucleotide repeat length did not influence the clinical phenotypes. Age of onset (58.0, interquartile range 52.0–63.8) was later compared to SOD1 (50.0, interquartile range 41.0–58.0; P < 0.001), but earlier compared to sporadic patients (61.0, interquartile range 52.0–69.0; P = 0.01). Median survival was shorter (38.0 months) compared to SOD1 (198.0 months, hazard ratio 1.97, 95% confidence interval 1.34–2.88; P < 0.001) and sporadic patients (76.0 months, hazard ratio 2.34, 95% confidence interval 1.64–3.34; P < 0.001). Phosphorylated neurofilament heavy chain levels in CSF (2880, interquartile range 1632–4638 pg/ml) were higher compared to sporadic patients (1382, interquartile range 458–2839 pg/ml; P < 0.001). In neuropsychological screening, C9orf72 patients displayed abnormal results in memory, verbal fluency and executive functions, showing generally worse performances compared to SOD1 and sporadic patients and a higher share with suspected frontotemporal dementia. In summary, clinical features of patients with C9orf72 mutations differ significantly from SOD1 and sporadic patients. Specifically, they feature a more frequent bulbar onset, a higher share of female patients and shorter survival. Interestingly, we found a high proportion of patients with negative family history and no evidence of a relationship between repeat lengths and disease severity.

20) Frequency of C9orf72 and SOD1 mutations in 302 sporadic ALS patients from three German ALS centers (2023) Rüstem Yilmaz, Torsten Grehl, Lukas Eckrich, Ines Marschalkowski, Kanchi Weishaupt, Ivan Valkadinov, Melita Simic, David Brenner, Peter M. Andersen, Joachim Wolf, Jochen H. Weishaupt

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2023
<https://dx.doi.org/10.1080/21678421.2023.2165946>

Background: ALS patients with a negative family history (sporadic ALS, SALS) represent more than 90% of all ALS cases. In light of the gene-specific therapies that are currently in development for ALS, knowledge about the genetic landscape of SALS in Germany is urgently needed. Objectives: We aimed to determine the frequency of C9orf72 hexanucleotide repeat expansion (HRE) and SOD1 mutations among patients in Germany with a diagnosis of sporadic or idiopathic ALS. Methods: We genotyped SALS patients from three German ALS centers. Sanger sequencing, fragment length analysis, and repeat-primed PCR technologies were used to detect mutations in SOD1 and C9orf72 HRE. Pathological C9orf72 HRE results were confirmed in an independent laboratory. Results: In 302 patients with SALS, 27 (8.9%) patients with a C9orf72 HRE mutation were detected. Moreover, we identified two patients with a pathogenic SOD1 mutation, one patient with a heterozygous p.D91A mutation in SOD1, and three additional patients with rare SOD1 variants not predicted to change the amino acid



sequence. Conclusions: According to our data, the proportion of SALS patients with SOD1 mutations is in the expected range, whereas that with C9orf72 HRE is higher, suggesting a reduced penetrance. A considerable number of SALS patients can be amenable to gene-specific therapies.

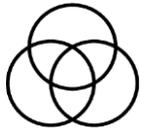
21) Guideline "Motor neuron diseases" of the German Society of Neurology (Deutsche Gesellschaft für Neurologie) (2023) Susanne Petri, Torsten Grehl, Julian Grosskreutz, Martin Hecht, Andreas Hermann, Sarah Jesse, Paul Lingor, Wolfgang Löscher, André Maier, Benedikt Schoser, Marcus Weber, Albert C Ludolph

Neurological Research and Practice 2023 <https://dx.doi.org/10.1186/s42466-023-00251-x>

Abstract Introduction In 2021, the Deutsche Gesellschaft für Neurology published a new guideline on diagnosis and therapy of motor neuron disorders. Motor neuron disorders affect upper motor neurons in the primary motor cortex and/or lower motor neurons in the brain stem and spinal cord. The most frequent motor neuron disease amyotrophic lateral sclerosis (ALS) is a rapidly progressive disease with an average life expectancy of 2–4 years with a yearly incidence of 3.1/100,000 in Central Europe (Rosenbohm et al. in *J Neurol* 264(4):749–757, 2017. <https://doi.org/10.1007/s00415-017-8413-3>). It is considered a rare disease mainly due to its low prevalence as a consequence of short disease duration. **Recommendations** These guidelines comprise recommendations regarding differential diagnosis, neuroprotective therapies and multidisciplinary palliative care including management of respiration and nutrition as well as provision of assistive devices and end-of-life situations. **Conclusion** Diagnostic and therapeutic guidelines are necessary due the comparatively high number of cases and the aggressive disease course. Given the low prevalence and the severe impairment of patients, it is often impossible to generate evidence-based data so that ALS guidelines are partially dependent on expert opinion.

22) Performance of serum neurofilament light chain in a wide spectrum of clinical courses of amyotrophic lateral sclerosis—a cross-sectional multicenter study (2023) Thomas Meyer, Erma Salkic, Torsten Grehl, Ute Weyen, Dagmar Kettemann, Patrick Weydt, René Günther, Paul Lingor, Jan Christoph Koch, Susanne Petri, Andreas Hermann, Johannes Prudlo, Julian Großkreutz, Petra Baum, Matthias Boentert, Moritz Metelmann, Jenny Norden, Isabell Cordts, Jochen H Weishaupt, Johannes Dorst, Albert Ludolph, Yasemin Koc, Bertram Walter, Christoph Münch, Susanne Spittel, Marie Dreger, André Maier, Péter Körtvélyessy

European Journal of Neurology 2023 <https://dx.doi.org/10.1111/ene.15773>



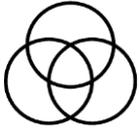
Abstract Background and purpose The objective was to assess the performance of serum neurofilament light chain (sNfL) in amyotrophic lateral sclerosis (ALS) in a wide range of disease courses, in terms of progression, duration and tracheostomy invasive ventilation (TIV). **Methods** A prospective cross-sectional study at 12 ALS centers in Germany was performed. sNfL concentrations were age adjusted using sNfL Z scores expressing the number of standard deviations from the mean of a control reference database and correlated to ALS duration and ALS progression rate (ALS-PR), defined by the decline of the ALS Functional Rating Scale. **Results** In the total ALS cohort (n = 1378) the sNfL Z score was elevated (3.04; 2.46–3.43; 99.88th percentile). There was a strong correlation of sNfL Z score with ALS-PR (p < 0.001). In patients with long (5–10 years, n = 167) or very long ALS duration (>10 years, n = 94) the sNfL Z score was significantly lower compared to the typical ALS duration of <5 years (n = 1059) (p < 0.001). Furthermore, in patients with TIV, decreasing sNfL Z scores were found in correlation with TIV duration and ALS-PR (p = 0.002; p < 0.001). **Conclusions** The finding of moderate sNfL elevation in patients with long ALS duration underlined the favorable prognosis of low sNfL. The strong correlation of sNfL Z score with ALS-PR strengthened its value as progression marker in clinical management and research. The lowering of sNfL in correlation with long TIV duration could reflect a reduction either in disease activity or in the neuroaxonal substrate of biomarker formation during the protracted course of ALS.

23) Remote digital assessment of amyotrophic lateral sclerosis functional rating scale – a multicenter observational study (2023) Thomas Meyer, Susanne Spittel, Torsten Grehl, Ute Weyen, Robert Steinbach, Dagmar Kettemann, Susanne Petri, Patrick Weydt, René Günther, Petra Baum, Elena Schlapakow, Jan Christoph Koch, Matthias Boentert, Joachim Wolf, Julian Grosskreutz, Annekathrin Rödigger, Benjamin Ilse, Moritz Metelmann, Jenny Norden, Ruhan Yasemin Koc, Péter Körtvélyessy, Alessio Riitano, Bertram Walter, Barbara Hildebrandt, Friedrich Schaudinn, Christoph Münch, André Maier

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2023

<https://dx.doi.org/10.1080/21678421.2022.2104649>

Remote self-assessment of the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R) using digital data capture was investigated for its feasibility as an add-on to ALSFRS-R assessments during multidisciplinary clinic visits. From August 2017 to December 2021, at 12 ALS centers in Germany, an observational study on remote assessment of the ALSFRS-R was performed. In addition to the assessment of ALSFRS-R during clinic visits, patients were offered a digital self-assessment of the ALSFRS-R – either on a computer or on a mobile application (“ALS-App”). An estimated multicenter cohort of 4,670 ALS patients received care at participating ALS centers. Of these patients, 971 remotely submitted the ALSFRS-R, representing 21% of the multicenter cohort. Of those who opted for remote assessment, 53.7% (n = 521) completed a minimum of 4 ALSFRS-R per year with a

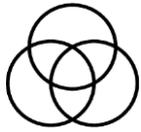


mean number of 10.9 assessments per year. Different assessment frequencies were found for patients using a computer (7.9 per year, n = 857) and mobile app (14.6 per year, n = 234). Patients doing remote assessments were more likely to be male and less functionally impaired but many patients with severe disability managed to complete it themselves or with a caregiver (35% of remote ALSFRS-R cohort in King's Stage 4). In a dedicated ALS center setting remote digital self-assessment of ALSFRS-R can provide substantial data which is complementary and potentially an alternative to clinic assessments and could be used for research purposes and person-level patient management. Addressing barriers relating to patient uptake and adherence are key to its success.

24) Spectrum and frequency of genetic variants in sporadic amyotrophic lateral sclerosis (2023)
Wolfgang P Ruf, Matej Boros, Axel Freischmidt, David Brenner, Veselin Grozdanov, Joao de Meirelles, Thomas Meyer, Torsten Grehl, Susanne Petri, Julian Grosskreutz, Ute Weyen, Rene Guenther, Martin Regensburger, Tim Hagenacker, Jan C Koch, Alexander Emmer, Annekathrin Roediger, Robert Steinbach, Joachim Wolf, Jochen H Weishaupt, Paul Lingor, Marcus Deschauer, Isabell Cordts, Thomas Klopstock, Peter Reilich, Florian Schoeberl, Berthold Schrank, Daniel Zeller, Andreas Hermann, Antje Knehr, Kornelia Günther, Johannes Dorst, Joachim Schuster, Reiner Siebert, Albert C Ludolph,

Brain Communications 2023 <https://dx.doi.org/10.1093/braincomms/fcad152>

Kathrin Müller Therapy of motoneuron diseases entered a new phase with the use of intrathecal antisense oligonucleotide therapies treating patients with specific gene mutations predominantly in the context of familial amyotrophic lateral sclerosis. With the majority of cases being sporadic, we conducted a cohort study to describe the mutational landscape of sporadic amyotrophic lateral sclerosis. We analysed genetic variants in amyotrophic lateral sclerosis-associated genes to assess and potentially increase the number of patients eligible for gene-specific therapies. We screened 2340 sporadic amyotrophic lateral sclerosis patients from the German Network for motor neuron diseases for variants in 36 amyotrophic lateral sclerosis-associated genes using targeted next-generation sequencing and for the C9orf72 hexanucleotide repeat expansion. The genetic analysis could be completed on 2267 patients. Clinical data included age at onset, disease progression rate and survival. In this study, we found 79 likely pathogenic Class 4 variants and 10 pathogenic Class 5 variants (without the C9orf72 hexanucleotide repeat expansion) according to the American College of Medical Genetics and Genomics guidelines, of which 31 variants are novel. Thus, including C9orf72 hexanucleotide repeat expansion, Class 4, and Class 5 variants, 296 patients, corresponding to ~13% of our cohort, could be genetically resolved. We detected 437 variants of unknown significance of which 103 are novel. Corroborating the theory of oligogenic causation in amyotrophic lateral sclerosis, we found a co-occurrence of pathogenic variants in 10 patients (0.4%) with 7 being C9orf72 hexanucleotide repeat expansion carriers. In a gene-wise survival analysis, we found a higher hazard ratio of



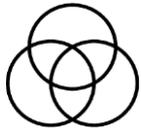
1.47 (95% confidence interval 1.02–2.1) for death from any cause for patients with the C9orf72 hexanucleotide repeat expansion and a lower hazard ratio of 0.33 (95% confidence interval 0.12–0.9) for patients with pathogenic SOD1 variants than for patients without a causal gene mutation. In summary, the high yield of 296 patients (~13%) harbouring a pathogenic variant and oncoming gene-specific therapies for SOD1/FUS/C9orf72, which would apply to 227 patients (~10%) in this cohort, corroborates that genetic testing should be made available to all sporadic amyotrophic lateral sclerosis patients after respective counselling. In a study of 2267 sporadic amyotrophic lateral sclerosis patients, Ruf et al. report that ~13% could be genetically resolved with ~10% being eligible for one of the oncoming gene-specific therapies (SOD1/FUS/C9orf72). They conclude that genetic testing should be made available to all amyotrophic lateral sclerosis patients after respective counselling.

Graphical Abstract

25) ALSFRS-R-SE: an adapted, annotated, and self-explanatory version of the revised amyotrophic lateral sclerosis functional rating scale (2022) André Maier, Matthias Boentert, Peter Reilich, Simon Witzel, Susanne Petri, Julian Großkreutz, Moritz Metelmann, Paul Lingor, Isabell Cordts, Johannes Dorst, Daniel Zeller, René Günther, Tim Hagenacker, Torsten Grehl, Susanne Spittel, Joachim Schuster, Albert Ludolph, Thomas Meyer, MND-NET consensus group

Neurological Research and Practice 2022 <https://dx.doi.org/10.1186/s42466-022-00224-6>

Abstract Background The ALS Functional Rating Scale in its revised version (ALSFRS-R) is a disease-specific severity score that reflects motor impairment and functional deterioration in people with amyotrophic lateral sclerosis (ALS). It has been widely applied in both clinical practice and ALS research. However, in Germany, several variants of the scale, each differing slightly from the others, have developed over time and are currently in circulation. This lack of uniformity potentially hampers data interpretation and may decrease item validity. Furthermore, shortcomings within the standard ALSFRS-R questions and answer options can limit the quality and conclusiveness of collected data. **Methods** In a multistage consensus-building process, 18 clinical ALS experts from the German ALS/MND network analyzed the ALSFRS-R in its current form and created an adapted, annotated, and revised scale that closely adheres to the well-established standardized English version. **Results** Ten German-language variants of the ALSFRS-R were collected, three of which contained instructions for self-assessment. All of these variants were compiled and a comprehensive linguistic revision was undertaken. A short introduction was added to the resulting scale, comprising general instructions for use and explanations for each of the five reply options per item. This adapted version of the scale, named ALSFRS-R-SE (with the "SE" referring to "self-explanatory"), was carefully reviewed for language and comprehensibility, in both German and English. **Conclusion** An adapted and annotated version of the ALSFRS-R scale was developed through a multistage consensus process. The decision to include brief explanations of specific scale items and reply options was intended to facilitate

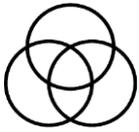


ALSFRS-R-SE assessments by both healthcare professionals and patients. Further studies are required to investigate the accuracy and utility of the ALSFRS-R-SE in controlled trials and clinical real-world settings.

26) Use and subjective experience of the impact of motor-assisted movement exercisers in people with amyotrophic lateral sclerosis: a multicenter observational study (2022). André Maier, Marcel Gaudlitz, Torsten Grehl, Ute Weyen, Robert Steinbach, Julian Grosskreutz, Annkathrin Rödiger, Jan Christoph Koch, Teresa Lengenfeld, Patrick Weydt, René Günther, Joachim Wolf, Petra Baum, Moritz Metelmann, Johannes Dorst, Albert C Ludolph, Dagmar Kettemann, Jenny Norden, Ruhan Yasemin Koc, Bertram Walter, Barbara Hildebrandt, Christoph Münch, Thomas Meyer, Susanne Spittel

Scientific reports 2022 <https://dx.doi.org/10.1038/s41598-022-13761-6>

Motor-assisted movement exercisers (MME) are devices that assist with physical therapy in domestic settings for people living with ALS. This observational cross-sectional study assesses the subjective experience of the therapy and analyzes users' likelihood of recommending treatment with MME. The study was implemented in ten ALS centers between February 2019 and October 2020, and was coordinated by the research platform Ambulanzpartner. Participants assessed symptom severity, documented frequency of MME use and rated the subjective benefits of therapy on a numerical scale (NRS, 0 to 10 points, with 10 being the highest). The Net Promotor Score (NPS) determined the likelihood of a participant recommending MME. Data for 144 participants were analyzed. Weekly MME use ranged from 1 to 4 times for 41% of participants, 5 to 7 times for 42%, and over 7 times for 17%. Particularly positive results were recorded in the following domains: amplification of a sense of achievement (67%), diminution of the feeling of having rigid limbs (63%), diminution of the feeling of being immobile (61%), improvement of general wellbeing (55%) and reduction of muscle stiffness (52%). Participants with more pronounced self-reported muscle weakness were more likely to note a beneficial effect on the preservation and improvement of muscle strength during MME treatment ($p < 0.05$). Overall, the NPS for MME was high (+ 61). High-frequency MME-assisted treatment (defined as a minimum of five sessions a week) was administered in the majority of participants (59%) in addition to physical therapy. Most patients reported having achieved their individual therapeutic objectives, as evidenced by a high level of satisfaction with MME therapy. The results bolster the justification for extended MME treatment as part of a holistic approach to ALS care.



27) Amyotrophe Lateralsklerose (ALS) (2021) Torsten Grehl

Neurologie up2date 2021 <https://dx.doi.org/10.1055/a-1495-1862>

Chronisch fortschreitende, letal verlaufende und in der Regel sporadische, neurodegenerative Erkrankung, die durch einen klinisch (fast) ausschließlichen Befall der Motoneurone charakterisiert ist. Die klassische amyotrophe Lateralsklerose (ALS) stellt dabei die häufigste Form einer Motoneurondegeneration dar. Die Ursache der ALS ist weiterhin unbekannt, auch wenn eine Proteinopathie vermutet wird und auch etliche genetische Defekte bekannt sind, die mit der ALS in Verbindung gebracht werden. Eine kausale Therapie ist jedoch weiterhin nicht möglich.

28) Clinical Determinants of Disease Progression in Amyotrophic Lateral Sclerosis—A Retrospective Cohort Study (2021) Maria Viktoria Requardt, Dennis Görlich, Torsten Grehl, Matthias Boentert

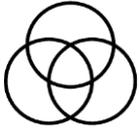
Journal of Clinical Medicine 2021 <https://dx.doi.org/10.3390/jcm10081623>

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease that is ultimately fatal but characterized by substantial phenotypic heterogeneity, which is known to impact long-term course and survival. This study investigated clinical determinants of disease progression and outcome in a large cohort of patients with ALS. Methods: Retrospective analysis included comprehensive data from 625 patients who attended a tertiary ALS centre at least twice. Patients were stratified according to five distinct clinical phenotypes: classical ALS; bulbar ALS; ALS with frontotemporal dementia (ALS-FTD); upper motor neuron predominant (UMNP); and lower motor neuron predominant (LMNP). Results: This study confirmed higher age at symptom onset, shorter latency to diagnosis and more rapid decline in the revised ALS Functional Rating Scale sum score as predictors of poor prognosis. Hazard ratios for shorter survival were higher in patients with ALS-FTD versus classical ALS, and in patients with versus without chronic obstructive pulmonary disease (COPD). Mean survival was longest in the UMNP phenotype group. Conclusions: This study confirmed established predictors of shorter survival in ALS and showed that concomitant COPD in particular relates to poor outcome.

29) Cortical Thinning of Motor and Non-Motor Brain Regions Enables Diagnosis of Amyotrophic Lateral Sclerosis and Supports Distinction between Upper- and Lower-Motoneuron Phenotypes (2021) Stefano Ferrea, Frederick Junker, Mira Korth, Kai Gruhn, Torsten Grehl, Tobias Schmidt-Wilcke

Biomedicines 2021 <https://dx.doi.org/10.3390/biomedicines9091195>

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder clinically characterized by muscle atrophy and progressive paralysis. In addition to the classical ALS affecting both



the upper and lower motoneurons (UMN and LMN), other subtypes with the predominant (or even exclusive) affection of the UMN or LMN have been identified. This work sought to detect specific patterns of cortical brain atrophy in the UMN and LMN phenotypes to distinguish these two forms from the healthy state. Methods: Using high-resolution structural MRI and cortical thickness analysis, 38 patients with a diagnosis of ALS and predominance of either the UMN (n = 20) or the LMN (n = 18) phenotype were investigated. Results: Significant cortical thinning in the temporal lobe was found in both the ALS groups. Additionally, UMN patients displayed a significant thinning of the cortical thickness in the pre- and postcentral gyrus, as well as the paracentral lobule. By applying multivariate analyses based on the cortical thicknesses of 34 brain regions, ALS patients with either a predominant UMN or LMN phenotype were distinguished from healthy controls with an accuracy of 94% and UMN from LMN patients with an accuracy of 75%. Conclusions: These findings support previous hypothesis that neural degeneration in ALS is not confined to the sole motor regions. In addition, the amount of cortical thinning in the temporal lobe helps to distinguish ALS patients from healthy controls, that is, to support or discourage the diagnosis of ALS, while the cortical thickness of the precentral gyrus specifically helps to distinguish the UMN from the LMN phenotype.

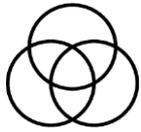
30) Effect of high-caloric nutrition on serum neurofilament light chain levels in amyotrophic lateral sclerosis (2020) Johannes Dorst, Joachim Schuster, Jens Dreyhaupt, Simon Witzel, Jochen H Weishaupt, Jan Kassubek, Ulrike Weiland, Susanne Petri, Thomas Meyer, Torsten Grehl, Andreas Hermann, Berit Jordan, Julian Grosskreutz, Daniel Zeller, Matthias Boentert, Bertold Schrank, Johannes Prudlo, Andrea S Winkler, Stanislav Gorbulev, Franceso Roselli, Luc Dupuis, Markus Otto, Albert C Ludolph

Journal of Neurology, Neurosurgery & Psychiatry 2020 <https://dx.doi.org/10.1136/jnnp-2020-323372>

31) Symptomatic pharmacotherapy in ALS: data analysis from a platform-based medication management programme (2020) Thomas Meyer, Dagmar Kettemann, André Maier, Torsten Grehl, Ute Weyen, Julian Grosskreutz, Robert Steinbach, Jenny Norden, Annette George, Andreas Hermann, René Guenther, Susanne Petri, Olivia Schreiber-Katz, Johannes Dorst, Albert C Ludolph, Bertram Walter, Christoph Münch, Susanne Spittel

Journal of Neurology, Neurosurgery, and Psychiatry 2020 <https://dx.doi.org/10.1136/jnnp-2020-322938>

32) Effect of High-Caloric Nutrition on Survival in Amyotrophic Lateral Sclerosis (2020) Albert C. Ludolph, Johannes Dorst, Jens Dreyhaupt, Jochen H. Weishaupt, Jan Kassubek, Ulrike Weiland, Thomas



Meyer, Susanne Petri, Andreas Hermann, Alexander Emmer, Julian Grosskreutz, Torsten Grehl, Daniel Zeller, Matthias Boentert, Bertold Schrank, Johannes Prudlo, Andrea S. Winkler, Stanislav Gorbulev, Francesco Roselli, Joachim Schuster, Luc Dupuis, for the LIPCAL-ALS Study Group

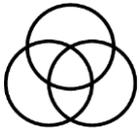
Annals of Neurology 2020 <https://dx.doi.org/10.1002/ana.25661>

Objective Weight loss has been identified as a negative prognostic factor in amyotrophic lateral sclerosis, but there is no evidence regarding whether a high-caloric diet increases survival. Therefore, we sought to evaluate the efficacy of a high-caloric fatty diet (HCFD) for increasing survival. Methods A 1:1 randomized, placebo-controlled, parallel-group, double-blinded trial (LIPCAL-ALS study) was conducted between February 2015 and September 2018. Patients were followed up at 3, 6, 9, 12, 15, and 18 months after randomization. The study was performed at 12 sites of the clinical and scientific network of German motor neuron disease centers (ALS/MND-NET). Eligible patients were randomly assigned (1:1) to receive either HCFD (405kcal/day, 100% fat) or placebo in addition to riluzole (100mg/day). The primary endpoint was survival time, defined as time to death or time to study cutoff date. Results Two hundred one patients (80 female, 121 male, age = 62.4 ± 10.8 years) were included. The confirmatory analysis of the primary outcome survival showed a survival probability of 0.39 (95% confidence interval [CI] = 0.27–0.51) in the placebo group and 0.37 (95% CI = 0.25–0.49) in the HCFD group, both after 28 months (point in time of the last event). The hazard ratio was 0.97, 1-sided 97.5% CI = $-\infty$ to 1.44, $p = 0.44$. Interpretation The results provide no evidence for a life-prolonging effect of HCFD for the whole amyotrophic lateral sclerosis population. However, post hoc analysis revealed a significant survival benefit for the subgroup of fast-progressing patients. ANN NEUROL 2020;87:206–216

33) Excitability in somatosensory cortex correlates with motoric impairment in amyotrophic lateral sclerosis. (2019) Oliver Höffken, Alena Schmelz, Melanie Lenz, Kai Gruhn, Torsten Grehl, Martin Tegenhoff, Matthias Sczesny-Kaiser

Amyotrophic lateral sclerosis & frontotemporal degeneration 2019
<https://dx.doi.org/10.1080/21678421.2019.1570270>

Objective: Amyotrophic lateral sclerosis (ALS) is a progressive neurodegenerative motoneuron disease. As previous studies reported alterations in motor cortex excitability, we evaluate excitability changes in somatosensory system. Methods: We examined 15 ALS patients and 15 healthy controls. Cortical excitability was assessed using paired somatosensory evoked potentials of median nerves. To determine disease severity and functional impairment, we assessed muscle strength and revised ALS-Functional Rating Scale (ALSFRS-R). Results: We found significantly reduced bilateral paired-stimulation inhibition in the ALS-group (both $p < 0.05$). Additionally, paired-stimulation ratios significantly correlated with ALSFRS-R (left somatosensory cortex: $r = -0.47$; right somatosensory cortex: $r = -0.44$;



both $p < 0.05$) and contralateral muscle strength (left somatosensory cortex: $r = -0.37$, $p = 0.007$; right somatosensory cortex: $r = -0.37$, $p = 0.003$). Conclusions: The results indicate disinhibition of the somatosensory cortex in ALS. It remains open if central somatosensory disinhibition is a primary characteristic of ALS as one element of a multisystem neurodegenerative disorder or a compensatory up-regulation due to functional motoric impairment. Longitudinal studies are necessary to categorize these findings.

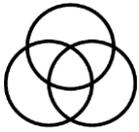
34) Eine hochkalorische, fettreiche Nahrungsergänzung für ALS-Patienten: Ergebnisse einer multi-zentrischen, randomisierten, placebo-kontrollierten Studie im Deutschen Netzwerk für Motoneuronenerkrankungen (LIPCAL-ALS-Studie) (2019) J Dorst, J Schuster, L Dupuis, J Dreyhaupt, J Kassubek, T Meyer, T Grehl, A Hermann, S Zierz, S Petri, J Großkreutz, M Deschauer, M Boentert, A Storch, B Schrank, D Zeller, AC Ludolph 24.

Kongress des Medizinisch-Wissenschaftlichen Beirates der Deutschen Gesellschaft für Muskelkranke (DGM) e.V. 2019 <https://dx.doi.org/10.1055/s-0039-1685045>

35) Prognostic factors in ALS: a comparison between Germany and China (2019) Johannes Dorst, Lu Chen, Angela Rosenbohm, Jens Dreyhaupt, Annemarie Hübers, Joachim Schuster, Jochen H Weishaupt, Jan Kassubek, Burkhard Gess, Thomas Meyer, Ute Weyen, Andreas Hermann, Jürgen Winkler, Torsten Grehl, Tim Hagenacker, Paul Lingor, Jan C Koch, Anne Sperfeld, Susanne Petri, Julian Großkreutz, Moritz Metelmann, Joachim Wolf, Andrea S Winkler, Thomas Klopstock, Matthias Boentert, Siw Johannesen, Alexander Storch, Bertold Schrank, Daniel Zeller, Xiao-lu Liu, Lu Tang, Dong-Sheng Fan, Albert C Ludolph

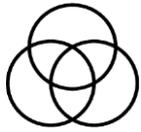
Journal of Neurology 2019 <https://dx.doi.org/10.1007/s00415-019-09290-4>

Several independent prognostic factors, such as age of onset, type of onset, body mass index (BMI), and progression rate have been identified for amyotrophic lateral sclerosis (ALS) in Caucasians. The aim of this study was to identify such factors in Chinese patients and to compare their impact with German patients. Comparison of prognostic factors was based on two hospital-based registries. The registry of the German Network for Motor Neuron Diseases contains 3100 patients with ALS. The Chinese registry comprises 2101 patients who were collected between 2003 and 2015 in the metropolitan area of Beijing. Disease progression was slower in China [median loss of 0.50 points (IQR 0.26–0.87 points) versus 0.55 points (IQR 0.28–1.00 points) of ALS functional rating scale revised (ALS-FRS-R) score per month; $p < 0.0001$]. Survival of patients with ALS was similar in Germany and China ($p > 0.05$). We found that younger age of onset ($p < 0.0001$), spinal onset ($p < 0.0001$), high BMI ($p < 0.0001$) and low progression rate ($p < 0.0001$) were positive prognostic factors in China as



well as in Germany. Prognostic factors, which are known to modify the course of disease in Caucasians, apply to Chinese patients as well. The results indicate that despite the apparent differences regarding genotype and clinical phenotype, findings from interventional studies in Caucasians aiming at disease-modifying prognostic factors (such as body weight) may be transferred to Chinese patients.

36) ROCK-ALS: Protocol for a Randomized, Placebo-Controlled, Double-Blind Phase IIa Trial of Safety, Tolerability and Efficacy of the Rho Kinase (ROCK) Inhibitor Fasudil in Amyotrophic Lateral Sclerosis (2019) Paul Lingor, Markus Weber, William Camu, Tim Friede, Reinhard Hilgers, Andreas Leha, Christoph Neuwirth, René Günther, Michael Benatar, Magdalena Kuzma-Kozakiewicz, Helen Bidner, Christiane Blankenstein, Roberto Frontini, Albert Ludolph, Jan C. Koch, Shahram Attarian, Mathias Bähr, Matthias Boentert, Nathalie Braun, Philippe Corcia, Isabell Cordts, Marcus Deschauer, Torsten Grehl, Julian Grosskreutz, Andreas Hermann, Josua Kuttler, Teresa Lengenfeldt, Fabian Maass, Thomas Meyer, Susanne Petri, Yvonne Remane, Jens Schmidt, Joachim Schuster, Marie-Hélène Soriani, Jeffrey Statland, Jochen Weishaupt, Daniel Zeller, Eirini Zielke Objectives: Disease-modifying therapies for amyotrophic lateral sclerosis (ALS) are still not satisfactory. The Rho kinase (ROCK) inhibitor fasudil has demonstrated beneficial effects in cell culture and animal models of ALS. For many years, fasudil has been approved in Japan for the treatment of vasospasm in patients with subarachnoid hemorrhage with a favorable safety profile. Here we describe a clinical trial protocol to repurpose fasudil as a disease-modifying therapy for ALS patients. Methods: ROCK-ALS is a multicenter, double-blind, randomized, placebo-controlled phase IIa trial of fasudil in ALS patients (EudraCT: 2017-003676-31, NCT: 03792490). Safety and tolerability are the primary endpoints. Efficacy is a secondary endpoint and will be assessed by the change in ALSFRS-R, ALSAQ-5, slow vital capacity (SVC), ECAS, and the motor unit number index (MUNIX), as well as survival. Efficacy measures will be assessed before (baseline) and immediately after the infusion therapy as well as on days 90 and 180. Patients will receive a daily dose of either 30 or 60 mg fasudil, or placebo in two intravenous applications for a total of 20 days. Regular assessments of safety will be performed throughout the treatment period, and in the follow-up period until day 180. Additionally, we will collect biological fluids to assess target engagement and evaluate potential biomarkers for disease progression. A total of 120 patients with probable or definite ALS (revised El Escorial criteria) and within 6–18 months of the onset of weakness shall be included in 16 centers in Germany, Switzerland and France. Results and conclusions: The ROCK-ALS trial is a phase IIa trial to evaluate the ROCK-inhibitor fasudil in early-stage ALS-patients that started patient recruitment in 2019. *Frontiers in Neurology* 2019 <https://dx.doi.org/10.3389/fneur.2019.00293>



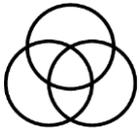
37) Reply: Adult-onset distal spinal muscular atrophy: a new phenotype associated with KIF5A mutations. (2019) David Brenner, Angela Rosenbohm, Rüstem Yilmaz, Kathrin Müller, Torsten Grehl, Susanne Petri, Thomas Meyer, Julian Grosskreutz, Patrick Weydt, Wolfgang Ruf, Christoph Neuwirth, Markus Weber, Susana Pinto, Kristl G Claeys, Berthold Schrank, Berit Jordan, Antje Knehr, Kornelia Günther, Annemarie Hübers, Daniel Zeller, Christian Kubisch, Sibylle Jablonka, Michael Sendtner, Thomas Klopstock, Mamede de Carvalho, Anne Sperfeld, Guntram Borck, Alexander E Volk, Johannes Dorst, Joachim Weis, Markus Otto, Joachim Schuster, Kelly Del Tredici, Heiko Braak, Karin M Danzer, Axel Freischmidt, Thomas Meitinger, Albert C Ludolph, Peter M Andersen, Jochen H Weishaupt, German ALS network MND-NET, Ute Weyen, Andreas Hermann, Jürgen Winkler, Tim Hagenacker, Jan Christoph Koch, Paul Lingor, Bettina Göricke, Stephan Zierz, Petra Baum, Joachim Wolf, Andrea Winkler, Peter Young, Ulrich Bogdahn, Johannes Prudlo, Jan Kassubek

Brain : a journal of neurology 2019 <https://dx.doi.org/10.1093/brain/awz306>

38) Provision of assistive technology devices among people with ALS in Germany: a platform-case management approach (2018) Andreas Funke, Susanne Spittel, Torsten Grehl, Julian Grosskreutz, Dagmar Kettemann, Susanne Petri, Ute Weyen, Patrick Weydt, Johannes Dorst, Albert C. Ludolph, Petra Baum, Moritz Oberstadt, Berit Jordan, Andreas Hermann, Joachim Wolf, Matthias Boentert, Bertram Walter, Nadine Gajewski, André Maier, Christoph Münch, Thomas Meyer

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration 2018
<https://dx.doi.org/10.1080/21678421.2018.1431786>

Objective: The procurement of assistive technology devices (ATD) is an essential component of managed care in ALS. The objective was to analyze the standards of care for ATD and to identify challenges in the provision process. Methods: A cohort study design was used. We investigated the provision of 11,364 ATD in 1494 patients with ALS at 12 ALS centers in Germany over four years. Participants were patients that entered a case management program for ATD including systematic assessment of ATD on a digital management platform. Results: Wheelchairs (requested in 65% of patients), orthoses (52%), bathroom adaptations (49%), and communication devices (46%) were the most needed ATD. There was a wide range in the number of indicated ATD per patient: 1 to 4 ATD per patient in 45% of patients, 5 to 20 ATD in 48%, and >20 ATD in 7% of patients. Seventy percent of all requested ATD were effectively delivered. However, an alarming failure rate during procurement was found in ATD that are crucial for ALS patients such as powered wheelchairs (52%), communication devices (39%), or orthoses (21%). Leading causes for not providing ATD were the refusal by health insurances, the decision by patients, and the death of the patient before delivery of the device. Conclusions: The need for ATD was highly prevalent among ALS patients. Failed or protracted provision posed substan-



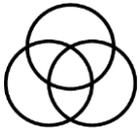
tial barriers to ATD procurement. Targeted national strategies and the incorporation of ATD indication criteria in international ALS treatment guidelines are urgently needed to overcome these barriers.

39) Comprehensive analysis of the mutation spectrum in 301 German ALS families (2018) Kathrin Müller, David Brenner, Patrick Weydt, Thomas Meyer, Torsten Grehl, Susanne Petri, Julian Grosskreutz, Joachim Schuster, Alexander E Volk, Guntram Borck, Christian Kubisch, Thomas Klopstock, Daniel Zeller, Sibylle Jablonka, Michael Sendtner, Stephan Klebe, Antje Knehr, Kornelia Günther, Joachim Weis, Kristl G Claeys, Berthold Schrank, Anne-Dorte Sperfeld, Annemarie Hübers, Markus Otto, Johannes Dorst, Thomas Meitinger, Tim M Strom, Peter M Andersen, Albert C Ludolph, Jochen H Weishaupt, German ALS network MND-NET

Journal of Neurology, Neurosurgery & Psychiatry 2018 <https://dx.doi.org/10.1136/jnnp-2017-317611>

Objectives Recent advances in amyotrophic lateral sclerosis (ALS) genetics have revealed that mutations in any of more than 25 genes can cause ALS, mostly as an autosomal-dominant Mendelian trait. Detailed knowledge about the genetic architecture of ALS in a specific population will be important for genetic counselling but also for genotype-specific therapeutic interventions. **Methods** Here we combined fragment length analysis, repeat-primed PCR, Southern blotting, Sanger sequencing and whole exome sequencing to obtain a comprehensive profile of genetic variants in ALS disease genes in 301 German pedigrees with familial ALS. We report C9orf72 mutations as well as variants in consensus splice sites and non-synonymous variants in protein-coding regions of ALS genes. We furthermore estimate their pathogenicity by taking into account type and frequency of the respective variant as well as segregation within the families. **Results** 49% of our German ALS families carried a likely pathogenic variant in at least one of the earlier identified ALS genes. In 45% of the ALS families, likely pathogenic variants were detected in C9orf72, SOD1, FUS, TARDBP or TBK1, whereas the relative contribution of the other ALS genes in this familial ALS cohort was 4%. We identified several previously unreported rare variants and demonstrated the absence of likely pathogenic variants in some of the recently described ALS disease genes. **Conclusions** We here present a comprehensive genetic characterisation of German familial ALS. The present findings are of importance for genetic counselling in clinical practice, for molecular research and for the design of diagnostic gene panels or genotype-specific therapeutic interventions in Europe.

40) Hot-spot KIF5A mutations cause familial ALS (2018) David Brenner, Rüstem Yilmaz, Kathrin Müller, Torsten Grehl, Susanne Petri, Thomas Meyer, Julian Grosskreutz, Patrick Weydt, Wolfgang Ruf, Christoph Neuwirth, Markus Weber, Susana Pinto, Kristl G Claeys, Berthold Schrank, Berit Jordan, Antje Knehr, Kornelia Günther, Annemarie Hübers, Daniel Zeller, Christian Kubisch, Sibylle Jablonka,

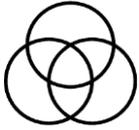


Michael Sendtner, Thomas Klopstock, Mamede de Carvalho, Anne Sperfeld, Guntram Borck, Alexander E Volk, Johannes Dorst, Joachim Weis, Markus Otto, Joachim Schuster, Kelly Del Tredici, Heiko Braak, Karin M Danzer, Axel Freischmidt, Thomas Meitinger, Tim M Strom, Albert C Ludolph, Peter M Andersen, Jochen H Weishaupt, The German ALS network MND-NET, Ute Weyen, Andreas Hermann, Tim Hagenacker, Jan Christoph Koch, Paul Lingor, Bettina Göricke, Stephan Zierz, Petra Baum, Joachim Wolf, Andrea Winkler, Peter Young, Ulrich Bogdahn, Johannes Prudlo, Jan Kassubek

Brain 2018 <https://dx.doi.org/10.1093/brain/awx370>

Heterozygous missense mutations in the N-terminal motor or coiled-coil domains of the kinesin family member 5A (KIF5A) gene cause monogenic spastic paraplegia (HSP10) and Charcot-Marie-Tooth disease type 2 (CMT2). Moreover, heterozygous de novo frame-shift mutations in the C-terminal domain of KIF5A are associated with neonatal intractable myoclonus, a neurodevelopmental syndrome. These findings, together with the observation that many of the disease genes associated with amyotrophic lateral sclerosis disrupt cytoskeletal function and intracellular transport, led us to hypothesize that mutations in KIF5A are also a cause of amyotrophic lateral sclerosis. Using whole exome sequencing followed by rare variant analysis of 426 patients with familial amyotrophic lateral sclerosis and 6137 control subjects, we detected an enrichment of KIF5A splice-site mutations in amyotrophic lateral sclerosis (2/426 compared to 0/6137 in controls; $P = 4.2 \times 10^{-3}$), both located in a hot-spot in the C-terminus of the protein and predicted to affect splicing exon 27. We additionally show co-segregation with amyotrophic lateral sclerosis of two canonical splice-site mutations in two families. Investigation of lymphoblast cell lines from patients with KIF5A splice-site mutations revealed the loss of mutant RNA expression and suggested haploinsufficiency as the most probable underlying molecular mechanism. Furthermore, mRNA sequencing of a rare non-synonymous missense mutation (predicting p.Arg1007Gly) located in the C-terminus of the protein shortly upstream of the splice donor of exon 27 revealed defective KIF5A pre-mRNA splicing in respective patient-derived cell lines owing to abrogation of the donor site. Finally, the non-synonymous single nucleotide variant rs113247976 (minor allele frequency = 1.00% in controls, $n = 6137$), also located in the C-terminal region [p.(Pro986Leu) in exon 26], was significantly enriched in familial amyotrophic lateral sclerosis patients (minor allele frequency = 3.40%; $P = 1.28 \times 10^{-7}$). Our study demonstrates that mutations located specifically in a C-terminal hotspot of KIF5A can cause a classical amyotrophic lateral sclerosis phenotype, and underline the involvement of intracellular transport processes in amyotrophic lateral sclerosis pathogenesis.

41) Safety and efficacy of rasagiline as an add-on therapy to riluzole in patients with amyotrophic lateral sclerosis: a randomised, double-blind, parallel-group, placebo-controlled, phase 2 trial.(2018) Albert C Ludolph, Joachim Schuster, Johannes Dorst, Luc Dupuis, Jens Dreyhaupt, Jochen H Weishaupt, Jan Kassubek, Ulrike Weiland, Susanne Petri, Thomas Meyer, Julian Grosskreutz, Berthold



Schrank, Matthias Boentert, Alexander Emmer, Andreas Hermann, Daniel Zeller, Johannes Prudlo, Andrea S Winkler, Torsten Grehl, Michael T Heneka, Siw Wollebæk Johannesen, Bettina Göricke

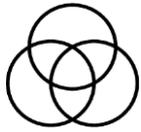
The Lancet. Neurology 2018 [https://dx.doi.org/10.1016/s1474-4422\(18\)30176-5](https://dx.doi.org/10.1016/s1474-4422(18)30176-5)

RAS-ALS Study Group Rasagiline, a monoamine oxidase B inhibitor with neuroprotective potential in Parkinson's disease, has shown a disease-modifying effect in the SOD1-Gly93Ala low-expressing mouse model of amyotrophic lateral sclerosis, both alone and in combination with riluzole. We sought to test whether or not rasagiline 1 mg/day can prolong survival in patients with amyotrophic lateral sclerosis also receiving riluzole.

42) The metabolic and endocrine characteristics in spinal and bulbar muscular atrophy (2018) Rosenbohm, A., Hirsch, S., Volk, A. E., Grehl, T., Grosskreutz, J., Hanisch, F., Herrmann, A., Kollwe, K., Kress, W., Meyer, T., Petri, S., Prudlo, J., Wessig, C., Müller, H. P., Dreyhaupt, J., Weishaupt, J., Kubisch, C., Kas-subek, J., Weydt, P. and Ludolph, A. C.

J Neurol 265(5): 1026-1036.

OBJECTIVE: Spinal and bulbar muscular atrophy (SBMA) is caused by an abnormal expansion of the CAG repeat in the androgen receptor gene. This study aimed to systematically phenotype a German SBMA cohort (n = 80) based on laboratory markers for neuromuscular, metabolic, and endocrine status, and thus provide a basis for the selection of biomarkers for future therapeutic trials. **METHODS:** We assessed a panel of 28 laboratory parameters. The clinical course and blood biomarkers were correlated with disease duration and CAG repeat length. A subset of 11 patients was evaluated with body fat MRI. **RESULTS:** Almost all patients reported muscle weakness (99%), followed by dysphagia (77%), tremor (76%), and gynecomastia (75%) as major complaints. Creatine kinase was the most consistently elevated (94%) serum marker, which, however, did not relate with either the disease duration or the CAG repeat length. Paresis duration and CAG repeat length correlated with dehydroepiandrosterone sulfate after correction for body mass index and age. The androgen insensitivity index was elevated in nearly half of the participants (48%). **CONCLUSIONS:** Metabolic alterations in glucose homeostasis (diabetes) and fat metabolism (combined hyperlipidemia), and sex hormone abnormalities (androgen insensitivity) could be observed among SBMA patients without association with the neuromuscular phenotype. Dehydroepiandrosterone sulfate was the only biomarker that correlated strongly with both weakness duration and the CAG repeat length after adjusting for age and BMI, indicating its potential as a biomarker for both disease severity and duration and, therefore, its possible use as a reliable outcome measure in future therapeutic studies.

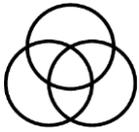


43) Diagnostic and prognostic significance of neurofilament light chain NF-L, but not progranulin and S100B, in the course of amyotrophic lateral sclerosis: Data from the German MND-net (2017) Petra Steinacker, André Huss, Benjamin Mayer, Torsten Grehl, Julian Grosskreutz, Guntram Borck, Jens Kuhle, Dorothee Lulé, Thomas Meyer, Patrick Oeckl, Susanne Petri, Jochen Weishaupt, Albert C. Ludolph, Markus Otto

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There is a need for diagnostic, prognostic, and monitoring blood biomarkers for ALS. We aimed to analyse and compare proposed candidate markers for disease progression in the course of ALS. Blood samples were taken from 125 ALS patients, including nine patients with C9orf72 or SOD1 mutation, at regular intervals of six months. ALS patients were characterized by the ALS functional rating scale (ALSFRS-R) and the Edinburgh Cognitive and Behavioural ALS Screen (ECAS). We quantified neurofilament light chain (NF-L), S100B, and progranulin (PGRN) and analysed it in relation to disease progression. Results showed that, at baseline, serum concentrations of NF-L but not PGRN or S100B discriminated significantly between ALS and controls. Within 24 months follow-up the marker concentrations remained stable. Baseline serum NF-L levels correlated with survival time, which was confirmed in subgroups with fast, intermediate, and slow disease progression and there was a weak association with disease duration. For S100B and PGRN we found an association with ALSFRS-R score changes and a trend for decreased levels in the fast progressor subgroup. In conclusion, serum NF-L in any ALS disease stage is a promising marker to support diagnosis and predict outcome, while serum PGRN and S100B are only of minor prognostic value.

44) July 2017 ENCALS statement on edaravone.(2017) Ammar Al-Chalabi, Peter M Andersen, Siddharthan Chandran, Adriano Chio, Philippe Corcia, Philippe Couratier, Olof Danielsson, Mamede de Carvalho, Claude Desnuelle, Torsten Grehl, Julian Grosskreutz, Trygve Holmøy, Caroline Ingre, Merete Karlsborg, Grethe Kleveland, Jan Christoph Koch, Blaz Koritnik, Magdalena KuzmaKozakiewicz, Hannu Laaksovirta, Albert Ludolph, Christopher McDermott, Thomas Meyer, Bernardo Mitre Roperio, Jesus Mora Pardina, Ingela Nygren, Susanne Petri, Mónica Povedano Panades, Francois Salachas, Pamela Shaw, Vincenzo Silani, Gert Staaf, Kirsten Svenstrup, Kevin Talbot, Ole-Bjørn Tysnes, Philip Van Damme, Anneke van der Kooi, Markus Weber, Patrick Weydt, Joachim Wolf, Orla Hardiman, Leonard H van den Berg Amyotrophic lateral sclerosis & frontotemporal degeneration 2017
<https://dx.doi.org/10.1080/21678421.2017.1369125>

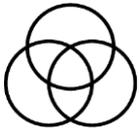


45) P 48 The time of the ALSFRS-R to decrease to 50% (D50) in a sigmoidal decay model sufficiently describes the complete disease course of amyotrophic lateral sclerosis (2017) B. Stubendorff, T. Grehl, C. Neuwirth, A. Rödiger, A. Gunkel, M. Radscheidt, B. Ilse, T. Prell, O.W. Witte, M. Weber, J. Grosskreutz

Clinical Neurophysiology 2017 <https://dx.doi.org/10.1016/j.clinph.2017.06.127>

IntroductionThe progression of ALSFRS-R is not linear (Gordon et al., 2010; Proudfoot et al., 2016); the often used calculated progression rate using $PR = ((48 - \text{ALSFRS-R}) / \text{disease duration})$ presents the progression at a certain time point rather than reflecting the entire disease course. A model describing the disease progression at different time points would facilitate the stratification of ALS patients according to disease severity and progression type and will in combination with other biomarkers enable identification of effective drugs in clinical trials.**Objectives**The aim of our study was to develop a model that describes the disease course mathematically for each individual ALS patient which can be estimated from regularly ascertained ALSFRS-R scores.**Methods**The model is based on the observation that after symptom onset the ALSFRS-R does not drop immediately but decays slowly first followed by a period of uniform progression which is captured in most clinical trials due to a relatively late inclusion requiring at least laboratory supported ALS according to EL Escorial/A-waji criteria. With increasing disability, ALSFRS-R seems to reach a plateau again. Thus we used a function which describes the transition between two states, i.e. full health to maximum disease. The model results in two parameters describing the ALS disease course: D50=time point when ALSFRS-R drops to 24 and dx=slope of ALSFRS-R decrease.**Results**Based on the ALSFRS-R scores and the disease duration from onset to ALSFRS-R date from a cohort of 339 patients in our database, we have been able to determine D50 and dx in 90% of patients using the Microsoft® Excel Add-In Solver tool with dynamic presets derived from the conventional estimation of ALSFRS-R progression. Mean age at symptom onset was 59.4years. ALSFRS-R at the first visit was 36.6+/-7.9 and 28.2+/-10.7 at the last recorded visit. The relationship between D50 and dx was highly linear ($R^2=0.993$), so that using modeling the whole disease course can be described using only one of these two parameters, i.e. D50.**Conclusion**D50 is more accessible to the end user as the number of months passed to reach an ALSFRS-R of 24 along the model based trajectory. In addition, any sampling taken at any given time point can be correlated to any one parameter which allows the exploration of early prognostic markers and possibly improve the readout in clinical trials.**Acknowledgment**This research is supported by BMBF (Bundesministerium für Bildung and Forschung) in the framework of the E-RARE programme (PYRAMID) and JPND (OnWebDUALS).

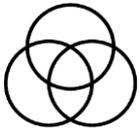
46) Safety and efficacy of ozanezumab in patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled, phase 2 trial (2017) Vincent Meininger, Angela Genge, Leonard H van den Berg, Wim Robberecht, Albert Ludolph, Adriano Chio, Seung H Kim, P Nigel Leigh, Matthew C Kiernan, Jeremy M Shefner, Claude Desnuelle, Karen E Morrison, Susanne Petri, Diane Boswell, Jane



Temple, Rajat Mohindra, Matt Davies, Jonathan Bullman, Paul Rees, Arseniy Lavrov, NOG112264 Study Group, Susanne Abdulla, Cathy Alsop, Francesca Barbieri, Stewart Bates, James D Berry, Stephan A Botez, Gaelle Bruneteau, Andrea Calvo, Rodrigo Refoios Camejo, William Camu, Deven Chauhan, Veronique Danel-Brunaud, Jerzy Daniluk, Annelot Dekker, Alain Destee, Matthew Devine, Stephen DeWall, Johannes Dorst, Giuseppe Fuda, Harutoshi Fujimura, Andreas Funke, Torsten Grehl, Julian Grosskreutz, Usha Gungabissoon, Robert Henderson, Peggy Ho, William Huynh, Saiju Jacob, Raul Juntas-Morales, Byung-Jo Kim, Xenia Kobeleva, Sonja Koerner, Stephen Kolb, Katja Kollwe, Lawrence Korngut, Geraldine Lautrette, Amy Lee, Anthony Lynch, Rami Massie, Genevieve Matte, Darryl Menezes, Stefano Milleri, Linda Nichols, Kazutoshi Nishiyama, Mieko Ogino, Chris Parkinson, Pierre-François Pradat, Tino Prell, Jeffrey Price, Eleanor Ramsey, Thomas M Ringer, Kristiana Salmon, Christen Shoesmith, Marie Helene Soriani, Marloes Stam, Erik Steinberg, Rob Stubbs, Herman Sullivan, Philip Van Damme, Michael van Es, Anne Visser, Mary Lou Watson, Andrea Sylvia Winkler, Lorne Zinman, Margie

The Lancet Neurology 2017 [https://dx.doi.org/10.1016/S1474-4422\(16\)30399-4](https://dx.doi.org/10.1016/S1474-4422(16)30399-4)

Zoing Background Neurite outgrowth inhibitor A (Nogo-A) is thought to have a role in the pathophysiology of amyotrophic lateral sclerosis (ALS). A monoclonal antibody against Nogo-A showed a positive effect in the SOD1 G93A mouse model of ALS, and a humanised form of this antibody (ozanezumab) was well tolerated in a first-in-human trial. Therefore, we aimed to assess the safety and efficacy of ozanezumab in patients with ALS. **Methods** This randomised, double-blind, placebo-controlled, phase 2 trial was done in 34 centres in 11 countries. Patients aged 18–80 years with a diagnosis of familial or sporadic ALS were randomly assigned (1:1), centrally according to a computer-generated allocation schedule, to receive ozanezumab (15 mg/kg) or placebo as intravenous infusions over 1 h every 2 weeks for 46 weeks, followed by assessments at week 48 and week 60. Patients and study personnel were masked to treatment assignment. The primary outcome was a joint-rank analysis of function (ALS Functional Rating Scale–Revised) and overall survival, analysed at 48 weeks in all patients who received at least one dose of study drug. This study is registered with ClinicalTrials.gov, number NCT01753076, and with GSK-ClinicalStudyRegister.com, NOG112264, and is completed. **Findings** Between Dec 20, 2012, and Nov 1, 2013, we recruited 307 patients, of whom 303 were randomly assigned to receive placebo (n=151) or ozanezumab (n=152). The adjusted mean of the joint-rank score was –14·9 (SE 13·5) for the ozanezumab group and 15·0 (13·6) for the placebo group, with a least squares mean difference of –30·0 (95% CI –67·9 to 7·9; p=0·12). Overall, reported adverse events, serious adverse events, and adverse events leading to permanent discontinuation of study drug or withdrawal from study were similar between the treatment groups, except for dyspepsia (ten [7%] in the ozanezumab group vs four [3%] in the placebo group), depression (11 [7%] vs five [3%]), and diarrhoea (25 [16%] vs 12 [8%]). Respiratory failure was the most common serious adverse event (12 [8%] vs seven [5%]). At week 60, the number of deaths was higher in the ozanezumab group (20 [13%]) than in the placebo group (16 [11%]), mainly as a result of respiratory failure



(ten [7%] vs five [3%]). Two deaths were considered related to the study drug (bladder transitional cell carcinoma in the ozanezumab group and cerebrovascular accident in the placebo group). Interpretation Ozanezumab did not show efficacy compared with placebo in patients with ALS. Therefore, Nogo-A does not seem to be an effective therapeutic target in ALS. Funding GlaxoSmithKline.

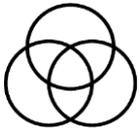
47) Sequence variations in C9orf72 downstream of the hexanucleotide repeat region and its effect on repeat-primed PCR interpretation: a large multinational screening study (2017) Angelica Nordin, Chizuru Akimoto, Anna Wuolikainen, Helena Alstermark, Karin Forsberg, Peter Baumann, Susana Pinto, Mamede de Carvalho, Annemarie Hübers, Frida Nordin, Albert C. Ludolph, Jochen H. Weishaupt, Thomas Meyer, Torsten Grehl, Kathi Schweikert, Markus Weber, Christian Burkhardt, Christoph Neuwirth, Trygve Holmøy, Mitsuya Morita, Ole-Bjørn Tysnes, Michael Benatar, Joanne Wu, Dale J. Lange, Carsten Bisgård, Nasrin Asgari, Ilkka Tarvainen, Thomas Brännström, Peter M. Andersen

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A large GGGGCC-repeat expansion mutation (HREM) in C9orf72 is the most common known cause of ALS and FTD in European populations. Sequence variations immediately downstream of the HREM region have previously been observed and have been suggested to be one reason for difficulties in interpreting RP-PCR data. Our objective was to determine the properties of these sequence variations with regard to prevalence, the range of variation, and effect on disease prognosis. We screened a multi-national cohort (n = 6981) for the HREM and samples with deviant RP-PCR curves were identified. The deviant samples were subsequently sequenced to determine sequence alteration. Our results show that in the USA and European cohorts (n = 6508) 10.7% carried the HREM and 3% had a sequence variant, while no HREM or sequence variants were observed in the Japanese cohort (n = 473). Sequence variations were more common on HREM alleles; however, certain population specific variants were associated with a non-expanded allele. In conclusion, we identified 38 different sequence variants, most located within the first 50 bp downstream of the HREM region. Furthermore, the presence of an HREM was found to be coupled to a lower age of onset and a shorter disease survival, while sequence variation did not have any correlation with these parameters.

48) Rare Variants in Neurodegeneration Associated Genes Revealed by Targeted Panel Sequencing in a German ALS Cohort. (2016) Stefanie Krüger, Florian Battke, Andrea Sprecher, Marita Munz, Matthis Synofzik, Ludger Schöls, Thomas Gasser, Torsten Grehl, Johannes Prudlo, Saskia Biskup

Frontiers in molecular neuroscience 2016 <https://dx.doi.org/10.3389/fnmol.2016.00092>

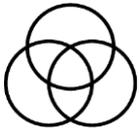


Amyotrophic lateral sclerosis (ALS) is a progressive fatal multisystemic neurodegenerative disorder caused by preferential degeneration of upper and lower motor neurons. To further delineate the genetic architecture of the disease, we used comprehensive panel sequencing in a cohort of 80 German ALS patients. The panel covered 39 confirmed ALS genes and candidate genes, as well as 238 genes associated with other entities of the neurodegenerative disease spectrum. In addition, we performed repeat length analysis for C9orf72. Our aim was to (1) identify potentially disease-causing variants, to (2) assess a proposed model of polygenic inheritance in ALS and to (3) connect ALS with other neurodegenerative entities. We identified 79 rare potentially pathogenic variants in 27 ALS associated genes in familial and sporadic cases. Five patients had pathogenic C9orf72 repeat expansions, a further four patients harbored intermediate length repeat expansions. Our findings demonstrate that a genetic background of the disease can actually be found in a large proportion of seemingly sporadic cases and that it is not limited to putative most frequently affected genes such as C9orf72 or SOD1. Assessing the polygenic nature of ALS, we identified 15 patients carrying at least two rare potentially pathogenic variants in ALS associated genes including pathogenic or intermediate C9orf72 repeat expansions. Multiple variants might influence severity or duration of disease or could account for intrafamilial phenotypic variability or reduced penetrance. However, we could not observe a correlation with age of onset in this study. We further detected potentially pathogenic variants in other neurodegeneration associated genes in 12 patients, supporting the hypothesis of common pathways in neurodegenerative diseases and linking ALS to other entities of the neurodegenerative spectrum. Most interestingly we found variants in GBE1 and SPG7 which might represent differential diagnoses. Based on our findings, we recommend two-staged genetic testing for ALS in Germany in patients with familial and sporadic ALS, comprising C9orf72 repeat analysis followed by comprehensive panel sequencing including differential diagnoses that impair motor neuron function to meet the complexity of ALS genetics.

49) Alterations in the hypothalamic melanocortin pathway in amyotrophic lateral sclerosis (2016)
Pauline Vercruyssen, Jérôme Sinniger, Hajer El Oussini, Jelena Scekcic-Zahirovic, Stéphane Dieterlé, Reinhard Dengler, Thomas Meyer, Stephan Zierz, Jan Kassubek, Wilhelm Fischer, Jens Dreyhaupt, Torsten Grehl, Andreas Hermann, Julian Grosskreutz, Anke Witting, Ludo Van Den Bosch, Odile Spreux-Varoquaux, GERP ALS Study Group, Albert C Ludolph, Luc Dupuis

Brain 2016 <https://dx.doi.org/10.1093/brain/aww004>

Amyotrophic lateral sclerosis, the most common adult-onset motor neuron disease, leads to death within 3 to 5 years after onset. Beyond progressive motor impairment, patients with amyotrophic lateral sclerosis suffer from major defects in energy metabolism, such as weight loss, which are well correlated with survival. Indeed, nutritional intervention targeting weight loss might improve survival of patients. However, the neural mechanisms underlying metabolic impairment in patients with



amyotrophic lateral sclerosis remain elusive, in particular due to the lack of longitudinal studies. Here we took advantage of samples collected during the clinical trial of pioglitazone (GERP-ALS), and characterized longitudinally energy metabolism of patients with amyotrophic lateral sclerosis in response to pioglitazone, a drug with well-characterized metabolic effects. As expected, pioglitazone decreased glycaemia, decreased liver enzymes and increased circulating adiponectin in patients with amyotrophic lateral sclerosis, showing its efficacy in the periphery. However, pioglitazone did not increase body weight of patients with amyotrophic lateral sclerosis independently of bulbar involvement. As pioglitazone increases body weight through a direct inhibition of the hypothalamic melanocortin system, we studied hypothalamic neurons producing proopiomelanocortin (POMC) and the endogenous melanocortin inhibitor agouti-related peptide (AGRP), in mice expressing amyotrophic lateral sclerosis-linked mutant SOD1(G86R). We observed lower Pomc but higher Agrp mRNA levels in the hypothalamus of presymptomatic SOD1(G86R) mice. Consistently, numbers of POMC-positive neurons were decreased, whereas AGRP fibre density was elevated in the hypothalamic arcuate nucleus of SOD1(G86R) mice. Consistent with a defect in the hypothalamic melanocortin system, food intake after short term fasting was increased in SOD1(G86R) mice. Importantly, these findings were replicated in two other amyotrophic lateral sclerosis mouse models based on TDP-43 (Tardbp) and FUS mutations. Finally, we demonstrate that the melanocortin defect is primarily caused by serotonin loss in mutant SOD1(G86R) mice. Altogether, the current study combined clinical evidence and experimental studies in rodents to provide a mechanistic explanation for abnormalities in food intake and weight control observed in patients with amyotrophic lateral sclerosis. Importantly, these results also show that amyotrophic lateral sclerosis progression impairs responsiveness to classical drugs leading to weight gain. This has important implications for pharmacological management of weight loss in amyotrophic lateral sclerosis.