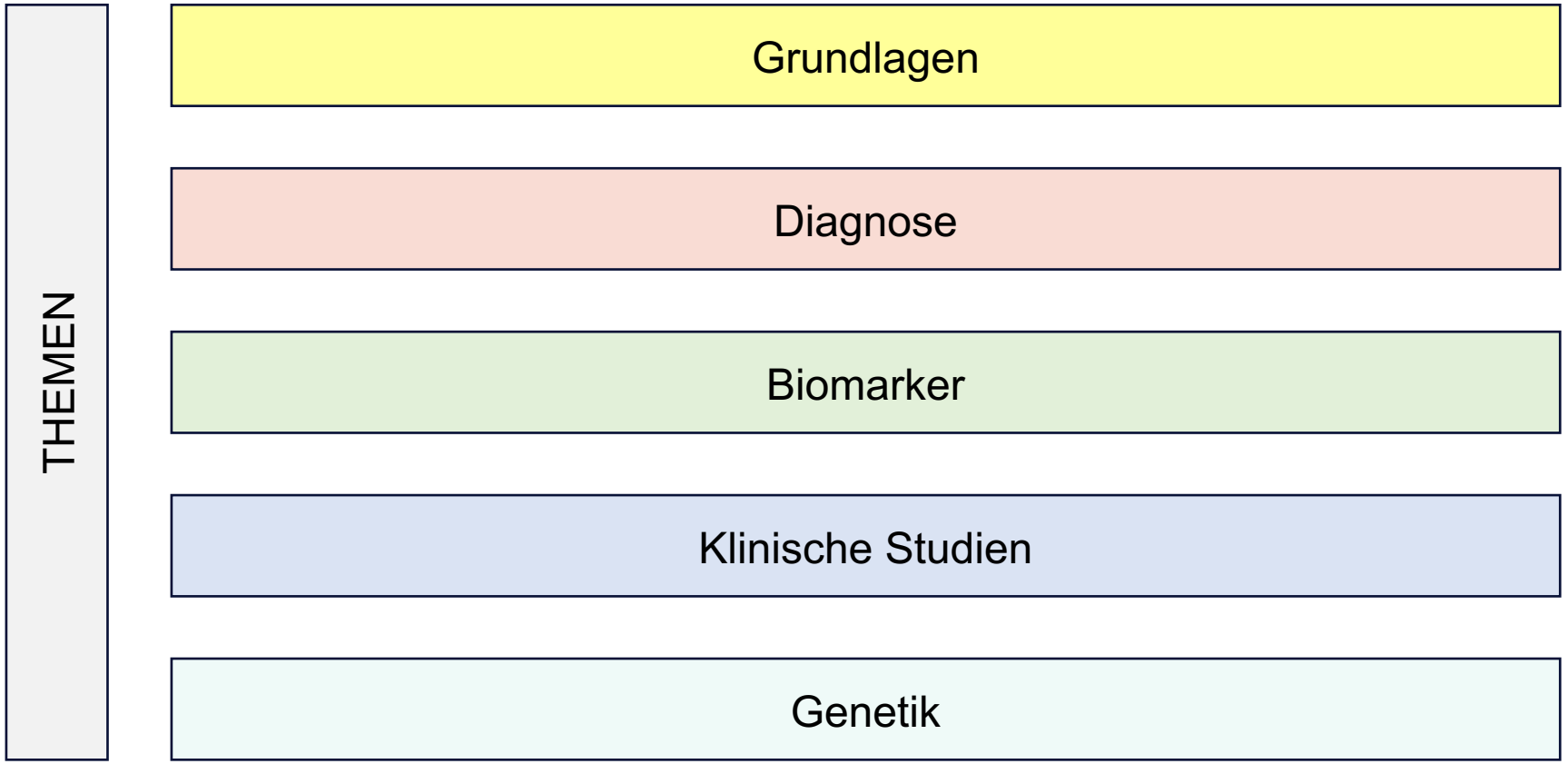
Neues aus der Forschung zur Amyotrophen Lateralsklerose

Ap. Prof. Priv.-Doz. Dr. Hakan Cetin, PhD
Universitätsklinik für Neurologie, Medizinische Universität Wien
Wien, 10.4.2024

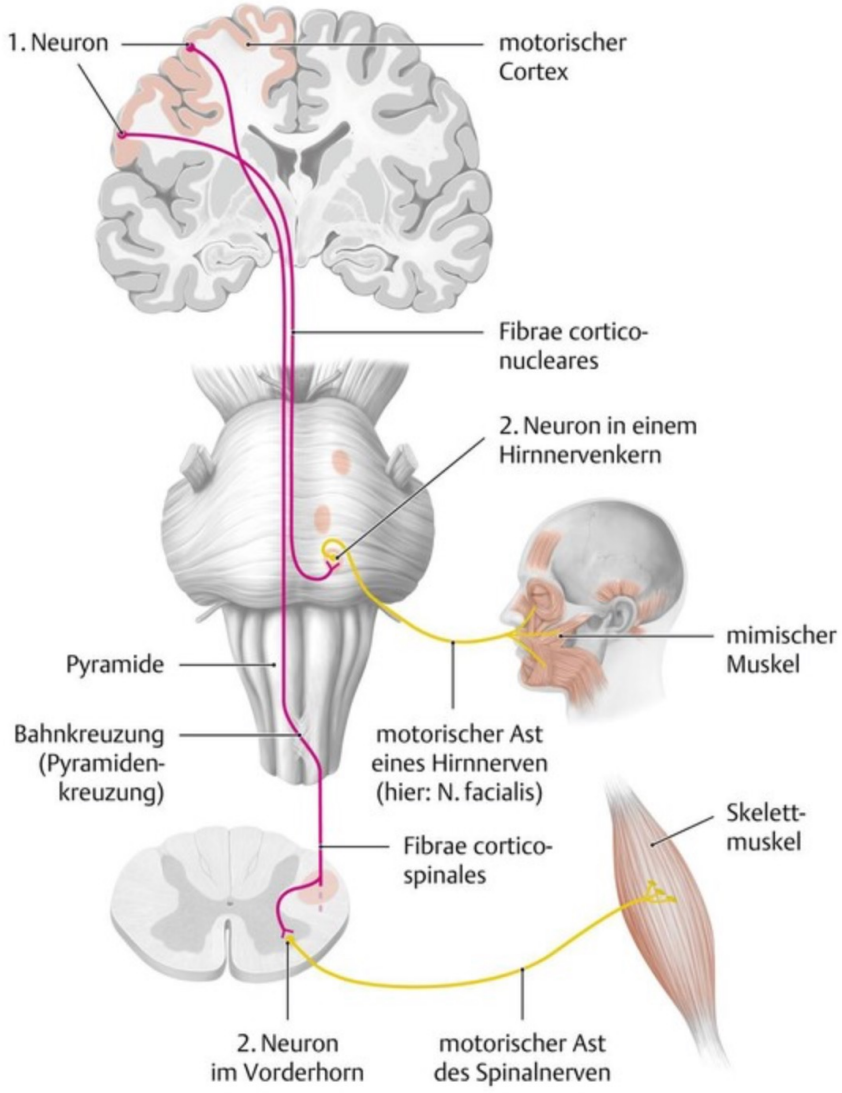
…die nächsten 40 Minuten



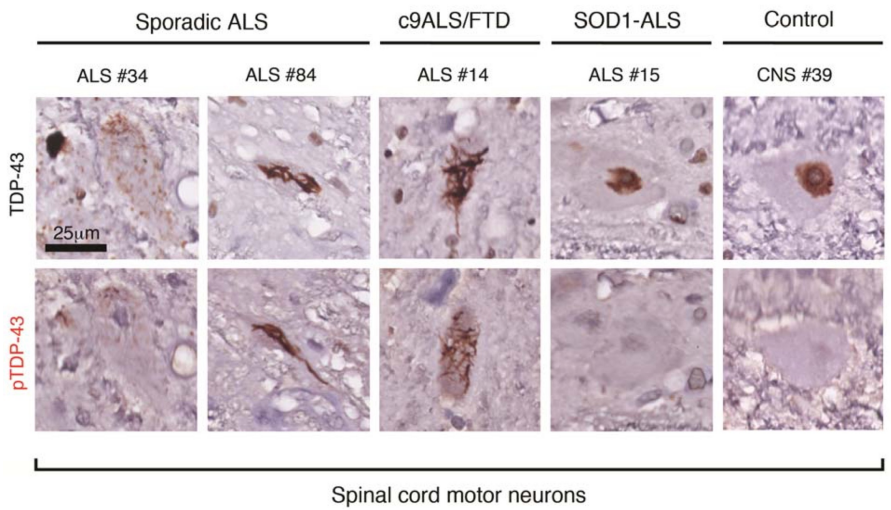
Was ist ALS?

Was sind Motoneuronerkrankungen?

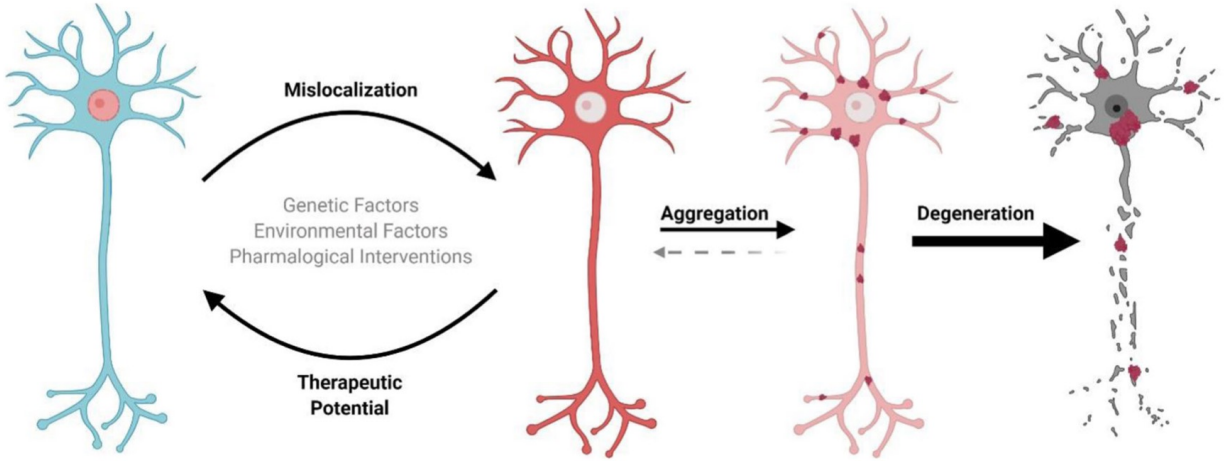
1. und 2. Motoneuron sind primär betroffen



Ablagerung von TDP43 in den Zellen

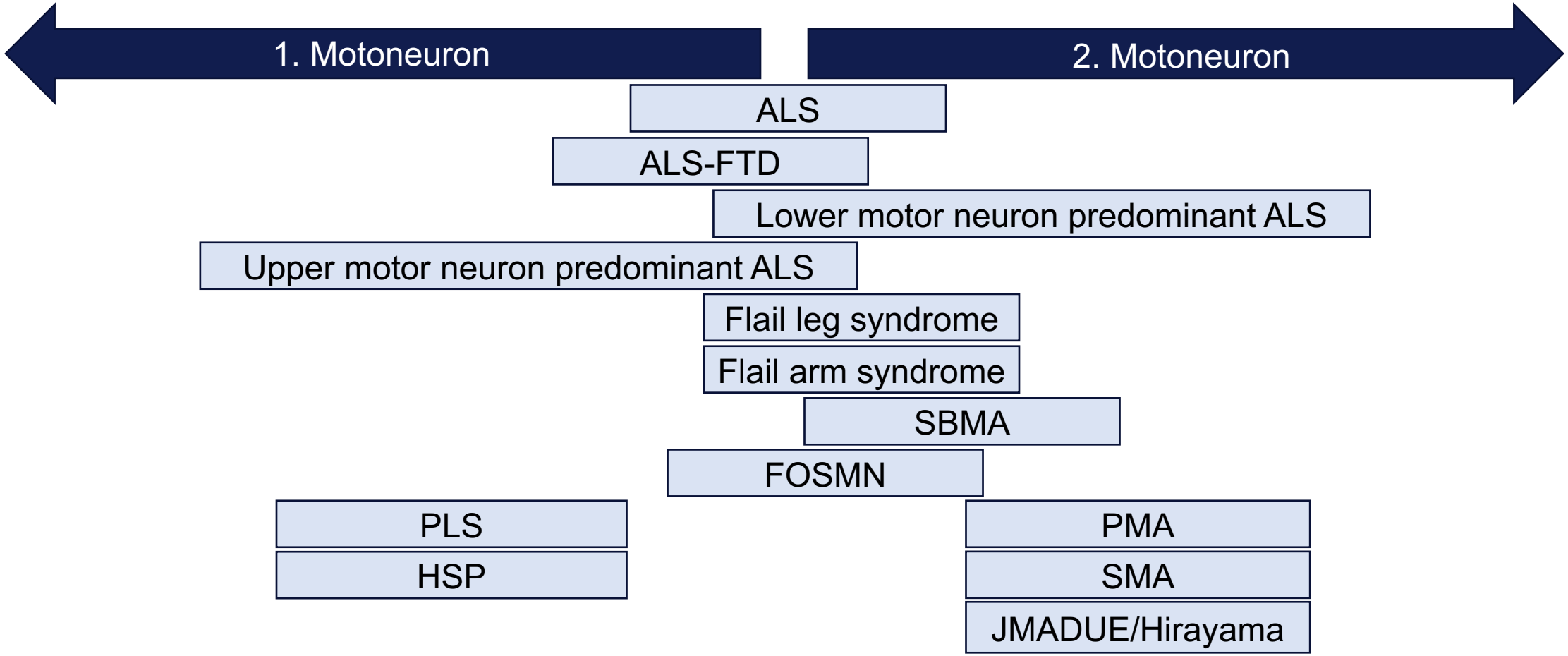


Melamed et al, 2019, Nat Neurosci



Suk et al, 2020, Mol Neurodegeneration

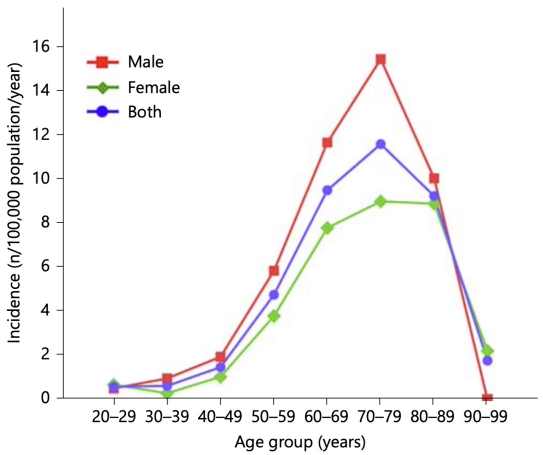
Motoneuronerkrankungen

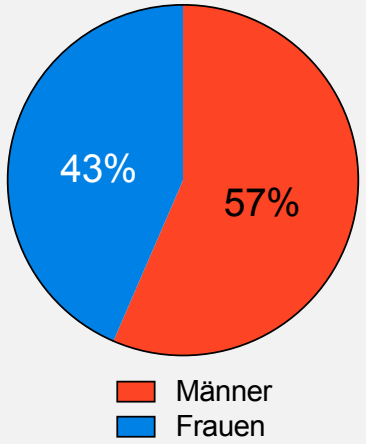


Epidemiologie der ALS

Inzidenz	Punktprävalenz	Lebenszeitprävalenz
~3/100.000/Jahr	~10/100.000	Ca. jede 400. Person erkrankt an ALS

Mediane Alter liegt bei 66 Jahren





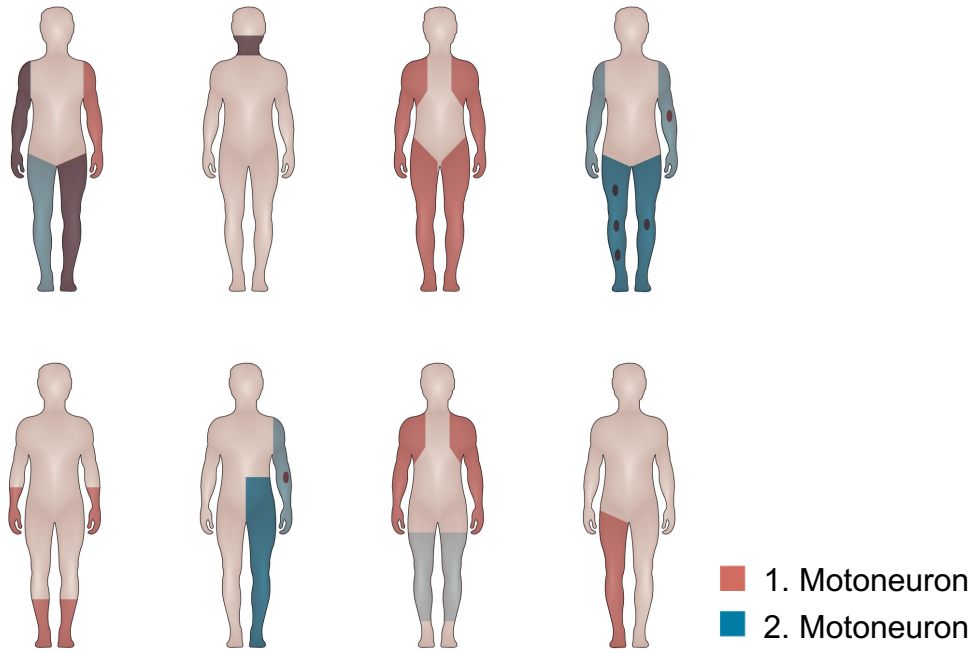
Cetin et al, Neuroepidemiology, 2012

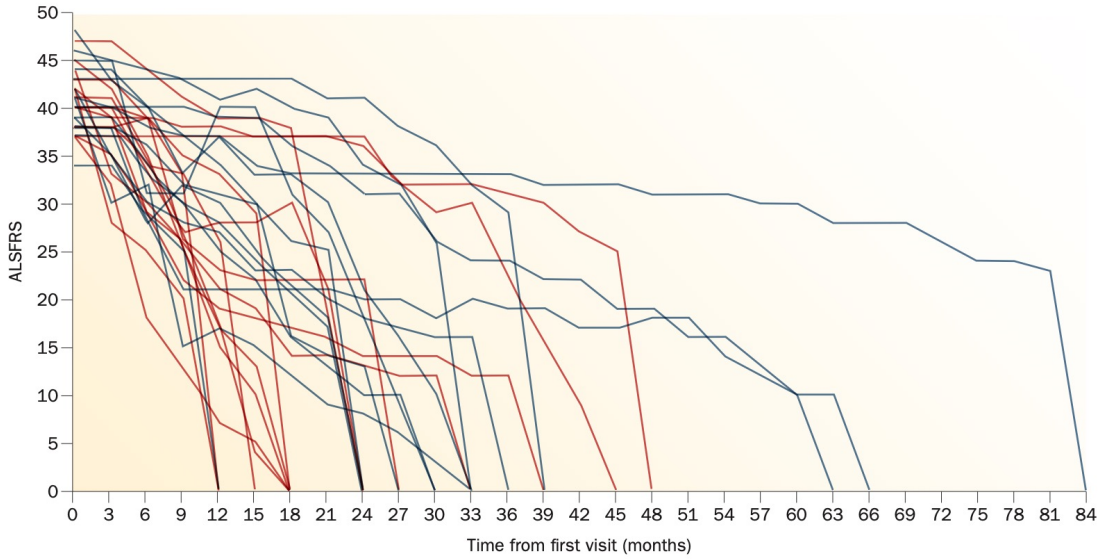
ALS ist eine heterogene Erkrankung

Initial betroffene Region

Defizit des 1./2. Motoneurons

Progressionsrate





Swinnen & Robberecht, 2014, Nat Rev Neurol

Wie wird ALS diagnostiziert?

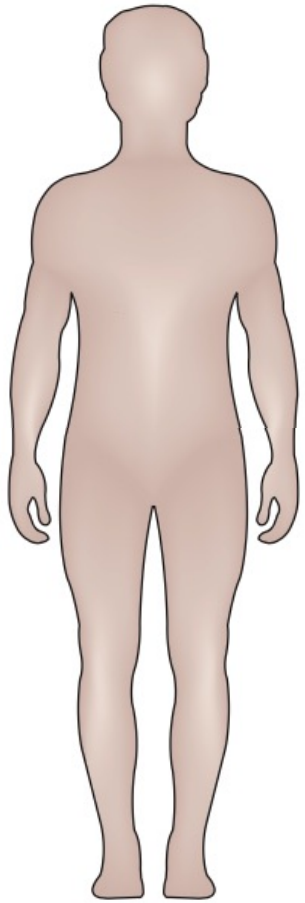
Suche nach Motoneuronzeichen in den 4 Regionen

	1. Motoneuron	2. Motoneuron
HIRNSTAMM Bulbärregion	• Masseterreflex • PMR • Laryngospasmus • Verlangsamte Zungenbewegung	• Reduzierte Mimik • Zungen(rand)atrophie • Zungenfaszikulationen
HWS Arme	• Spastik • Krämpfe • Hyperreflexie • Pathologische Reflexe	• Schlaffe Extremität • Abgeschwächte Sehnenreflexe • Atrophie • Faszikulationen
BWS Brust, Bauch	• Fehlende BHR	• *Dropped head* • *Bent spine* • Hyperlordose • Ausladendes Abdomen • Faszikulationen
LWS Beine	• Spastik • Krämpfe • Hyperreflexie • Pathologische Reflexe	• Schlaffe Extremität • Abgeschwächte Sehnenreflexe • Atrophie • Faszikulationen

Weitere häufige Symptome

- Sialorrhoe
- Mundtrockenheit
- Schmerzen
- Krämpfe
- Obstipation
- Pathologisches Lachen/Weinen
- Depressionen
- Kognitive Defizite
- Schlafstörungen
- Gewichtsverlust

Metabolische Veränderungen bei ALS



Gewichtsverlust

Niedriger BMI

Lipidkonzentration im Serum erniedrigt

Dysphagie

Reduzierte Zufuhr an Kalorien

Hypothalamus

Hormone (Cortisol, Insulin)

Dupuis, 2011, Lancet Neurol

Endpunkte – ALSFRSR

ALS Functional Rating Scale–Revised (ALSFRS-R)[5]

BULBAR

Speech
- **4** Normal
- **3** Detectable speech disturbance
- **2** Intelligible with repeating
- **1** Speech combined with nonvocal communication
- **0** Loss of useful speech

Salivation
- **4** Normal
- **3** Slight but definite excess of saliva in mouth; may have nighttime drooling
- **2** Moderately excessive saliva; may have minimal drooling
- **1** Marked excess of saliva with some drooling
- **0** Marked drooling; requires constant tissue or handkerchief

Swallowing
- **4** Normal
- **3** Early eating problems—occasional choking
- **2** Dietary consistency changes
- **1** Needs supplemental tube feeding
- **0** NPO (exclusively parenteral or enteral feeding)

FINE MOTOR

Handwriting
- **4** Normal
- **3** Slow or sloppy; all words are legible
- **2** Not all words are legible
- **1** Able to grip pen but unable to write
- **0** Unable to grip pen

Cutting Food*
- **4** Normal
- **3** Somewhat slow and clumsy, but no help needed
- **2** Can cut most foods, although clumsy and slow; some help needed
- **1** Food must be cut by someone, but can still feed slowly
- **0** Needs to be fed

Dressing and Hygiene
- **4** Normal
- **3** Independent and complete self-care with effort or decreased efficiency
- **2** Intermittent assistance or substitute methods
- **1** Needs attendant for self-care
- **0** Total dependence

*There are different assessments for cutting food with gastrostomy.

GROSS MOTOR

Turning in Bed
- **4** Normal
- **3** Somewhat slow and clumsy, but no help needed
- **2** Can turn alone or adjust sheets, but with great difficulty
- **1** Can initiate, but not turn or adjust sheets alone
- **0** Helpless

Walking
- **4** Normal
- **3** Early ambulation difficulties
- **2** Walks with assistance
- **1** Non-ambulatory functional movement only
- **0** No purposeful leg movement

Climbing Stairs
- **4** Normal
- **3** Slow
- **2** Mild unsteadiness or fatigue
- **1** Needs assistance
- **0** Cannot do

RESPIRATORY

Dyspnea
- **4** None
- **3** Occurs when walking
- **2** Occurs with one or more of the following: eating, bathing, dressing (ADL)
- **1** Occurs at rest, difficulty breathing when either sitting or lying
- **0** Significant difficulty, considering using mechanical respiratory support

Orthopnea
- **4** None
- **3** Some difficulty sleeping at night due to shortness of breath. Does not routinely use more than two pillows
- **2** Needs extra pillow in order to sleep (more than two)
- **1** Can only sleep sitting up
- **0** Unable to sleep

Respiratory Insufficiency
- **4** None
- **3** Intermittent use of BiPAP
- **2** Continuous use of BiPAP
- **1** Continuous use of BiPAP during the night and day
- **0** Invasive mechanical ventilation by intubation or tracheostomy

Gold Coast Kriterien

Gold Coast Kriterien, 2020
Progredienter Erkrankungsverlauf
1.MN und 2.MN in ≥ 1 Region **ODER** 2.MN in ≥ 2 Regionen
Ausschluss von Differentialdiagnosen

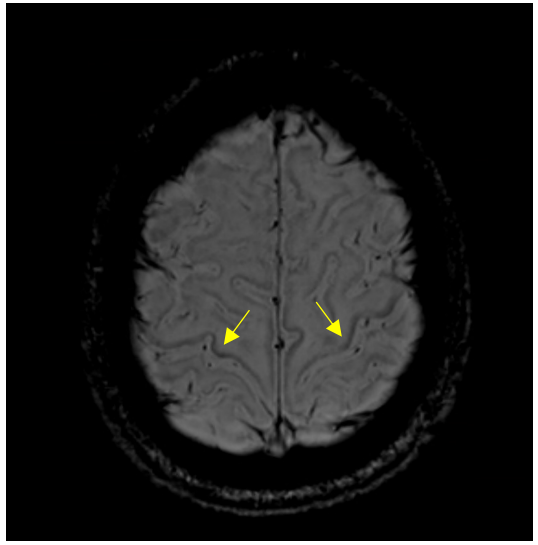
Elektromyographie	Motorisch evozierte Potentiale	MRT
Neurographie	Sonographie	Labor (Serum, Liquor)

Shefner et al, 2020, *Clin Neurophysiol*

Die Suche nach spezifischen Biomarkern?

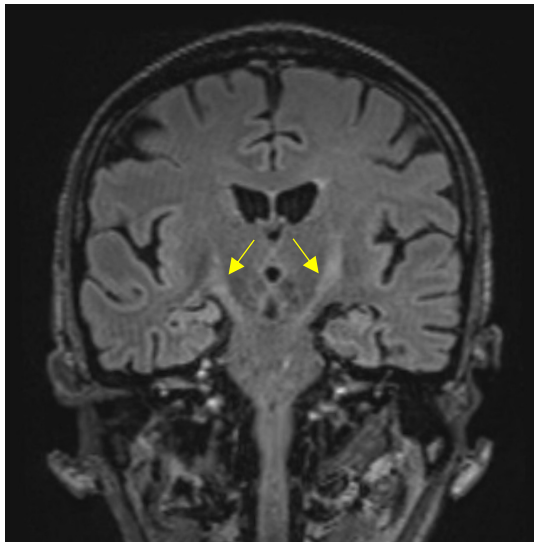
Radiologische Biomarker: MRT

Motor band sign

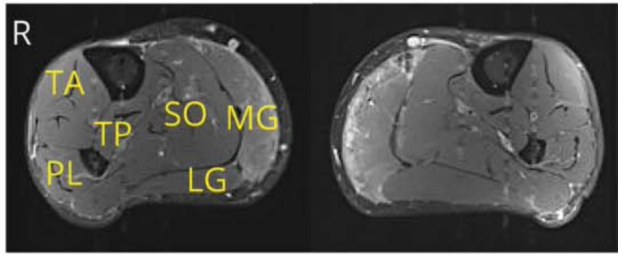


ALS Patient aus dem AKH

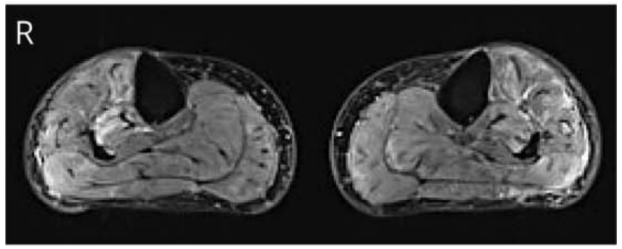
Pyramidenbahn



CTR



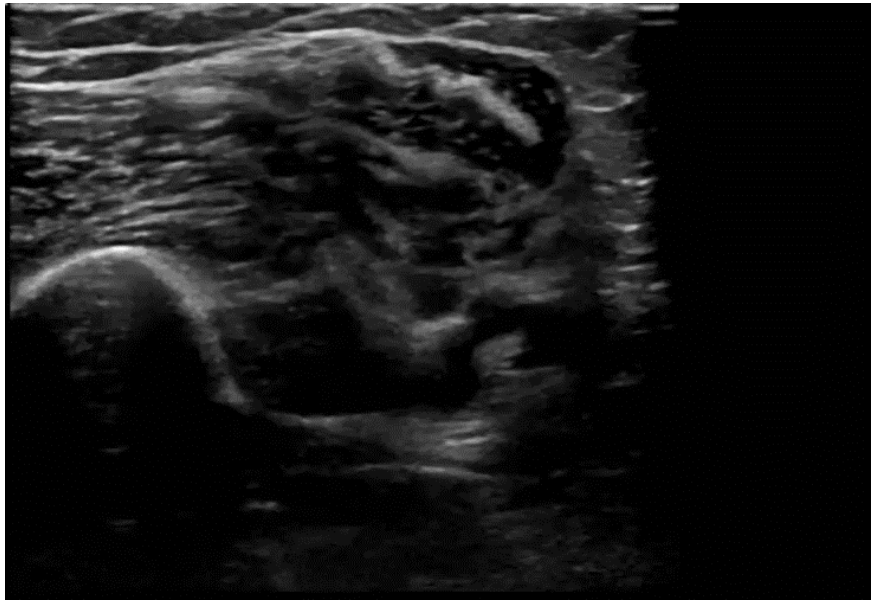
ALS



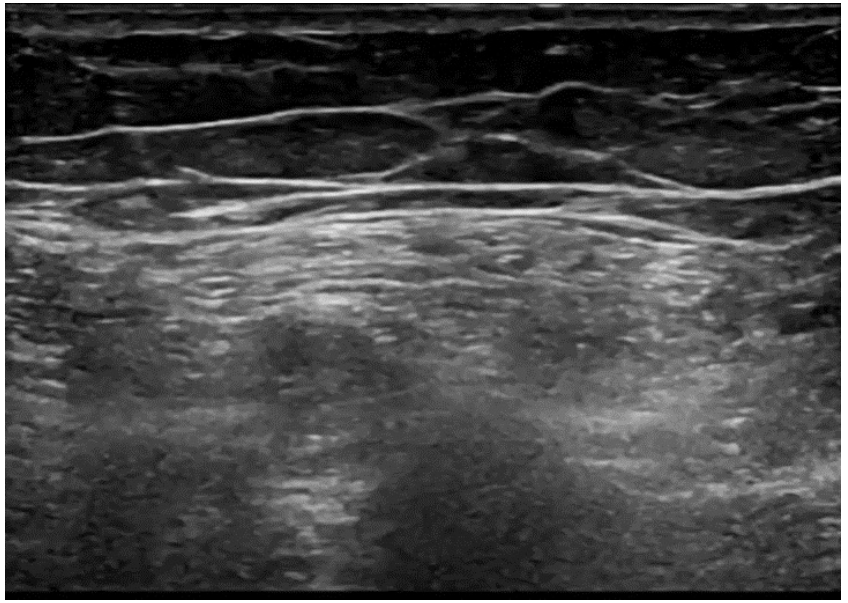
Klickovic et al, 2019, *Neurology*

Faszikulationen in der Sonographie

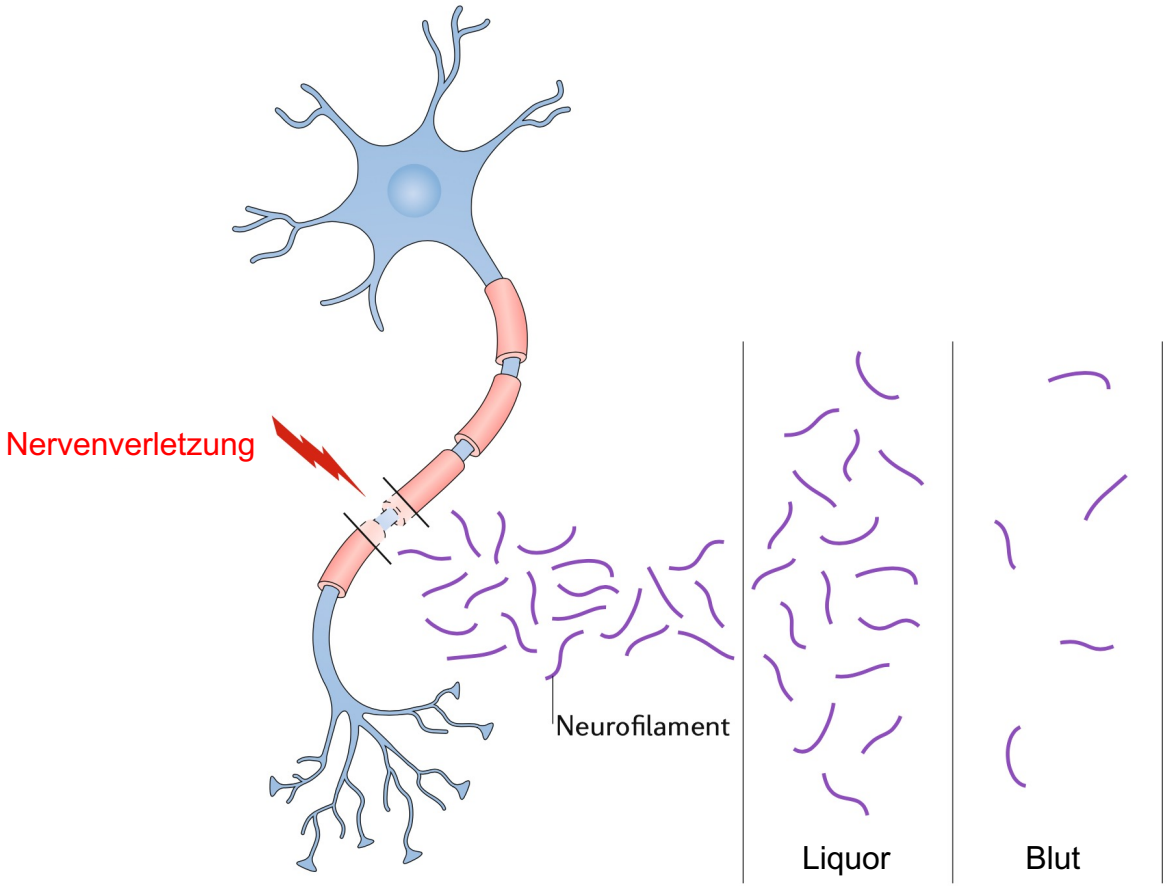
M. biceps brachii



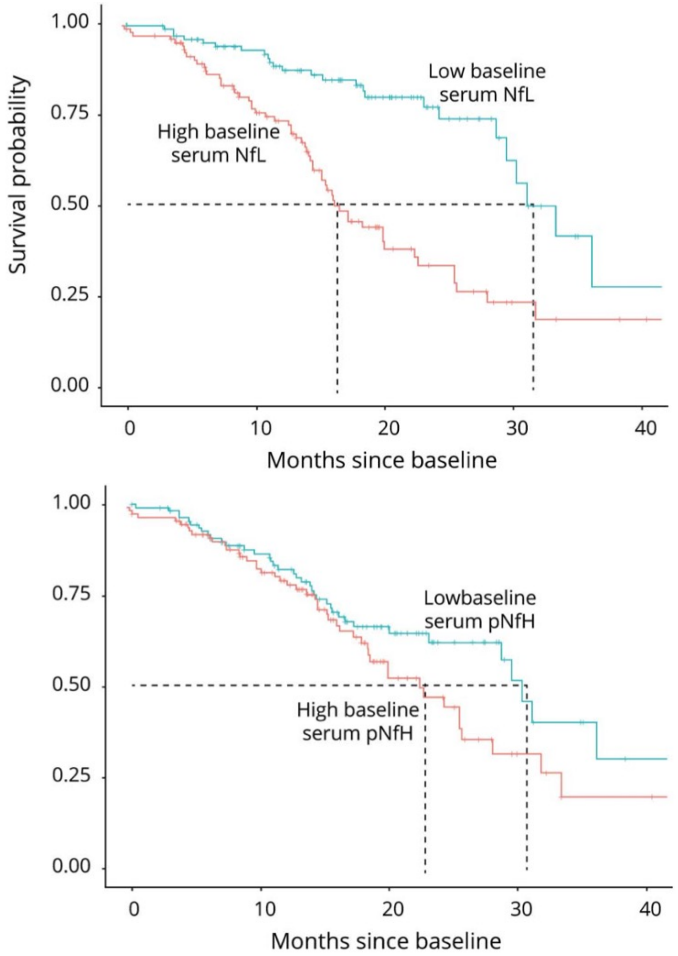
M. gastrocnemius (atroph und fettig umgewandelt)



Biomarker in Körperflüssigkeiten: Neurofilamente



Khalil et al, 2018, *Nature Rev Neurol*



Benatar et al, 2020, Neurology

Aktuelle klinische Studien

Zahl der klinischen Studien nimmt zu: Reviews


frontiers in Aging Neuroscience

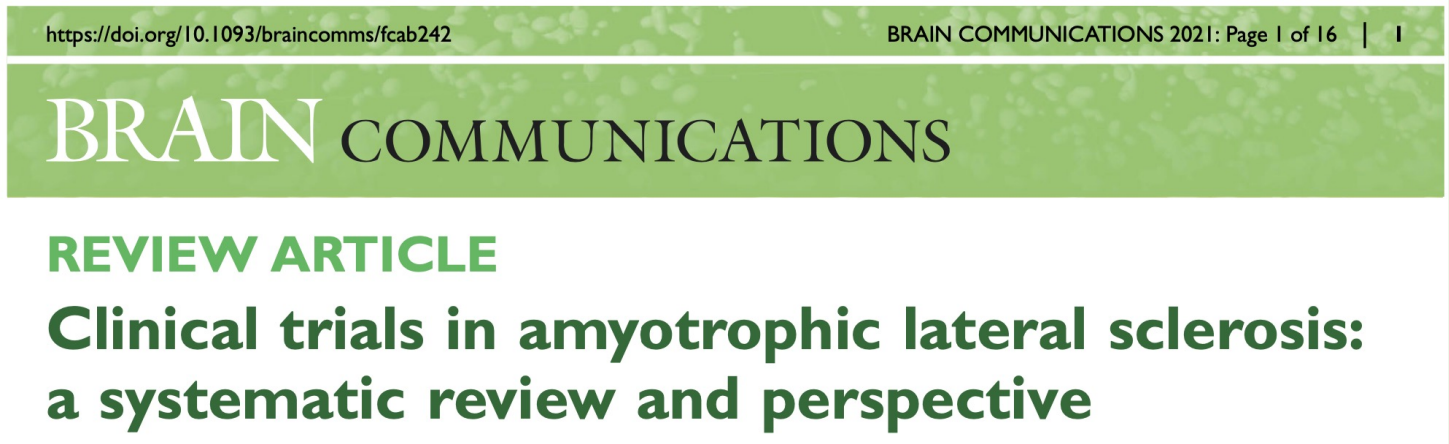
REVIEW
published: 22 March 2017
doi: 10.3389/fnagi.2017.00068

ALS Clinical Trials Review: 20 Years of Failure. Are We Any Closer to Registering a New Treatment?

*Dmitry Petrov[1], Colin Mansfield[1], Alain Moussy[1] and Olivier Hermine[1,2,3,4,5,6,7,8]**

1995-2016
25 Moleküle
51 CTs
>13.000 Patient:innen

2008-2019
76 Moleküle
125 CTs
>15.000 Patient:innen


https://doi.org/10.1093/braincomms/fcab242 BRAIN COMMUNICATIONS 2021: Page 1 of 16 | 1

BRAIN COMMUNICATIONS

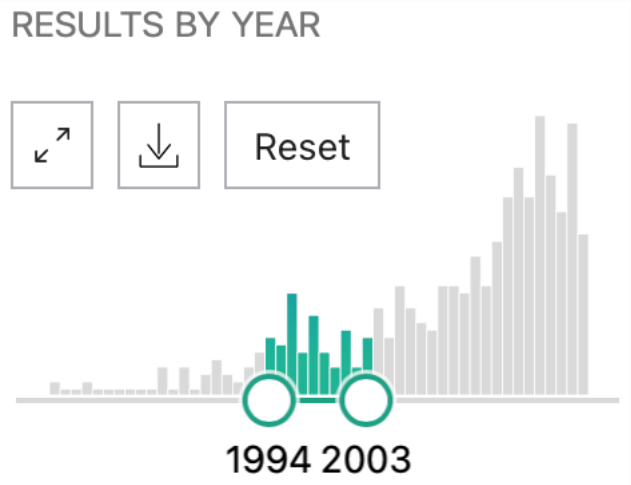
REVIEW ARTICLE

Clinical trials in amyotrophic lateral sclerosis: a systematic review and perspective

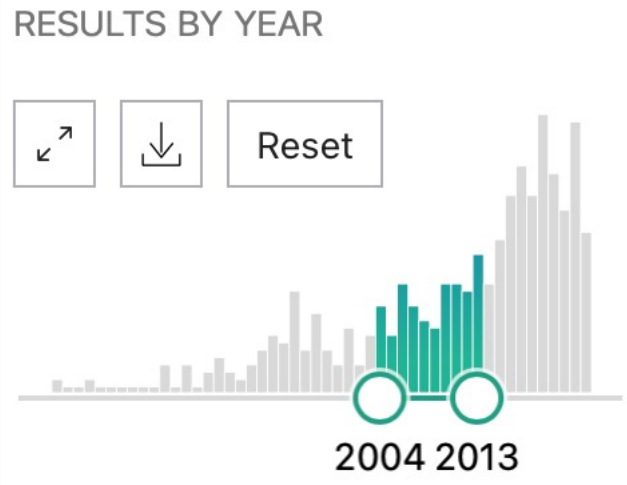
Petrov et al, 2017, Front Aging Neurosci; Wong et al, 2021, Brain Commun

Zahl der klinischen Studien nimmt zu: Pubmed

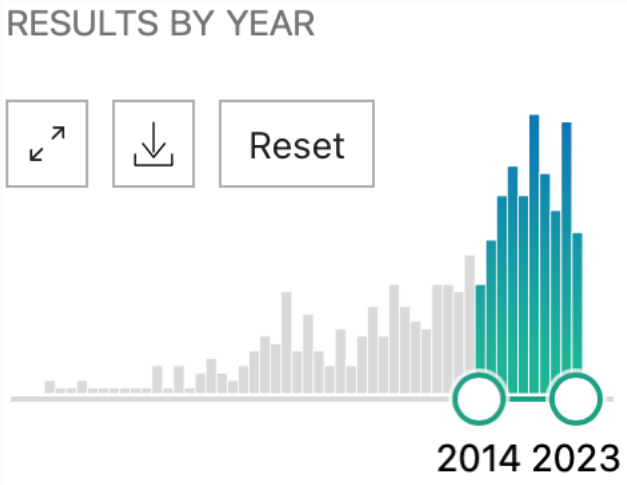
Suchbegriff: „controlled trial“ AND „amyotrophic lateral sclerosis“



67 Treffer

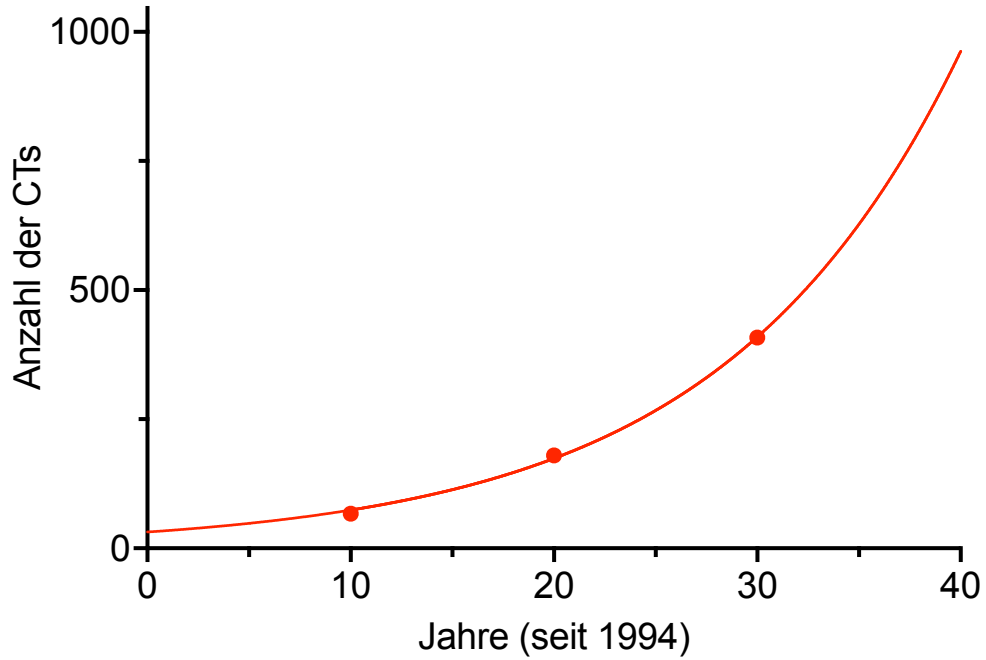


113 Treffer



228 Treffer

Zahl der klinischen Studien nimmt exponentiell zu



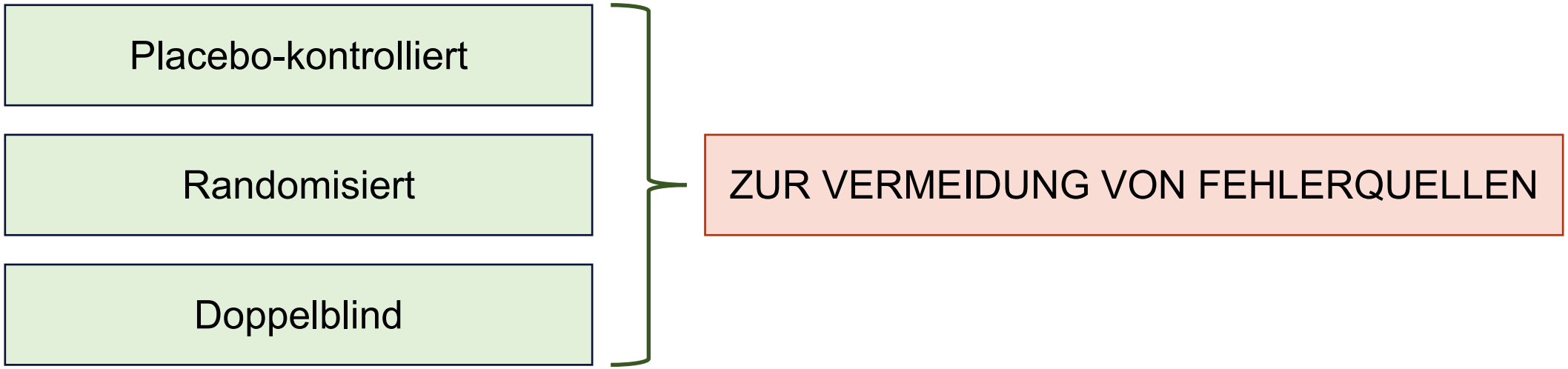
VERDOPPLUNGSZEIT:
8.1 Jahre (95CI 4.0-17.1)

PROGNOSE:
2023-2034 - 555 Klinische Studien

Klinische Studien und ihre Phasen

	Wer wird getestet?	Was soll herausgefunden werden?	Placebo	Fallzahl
Phase I	Kleine Zahl gesunder Freiwilliger	Verträglichkeit & Sicherheit	–	10-50
Phase II	Kleine Zahl von Patient*innen	Dosierung & Hinweise auf Wirkung	–/+	100-500
Phase III	Große Zahl von selektionierten Patient*innen und Kontrollen	Wirkung & Verträglichkeit	+	>1000
Phase IV	Nach Zulassung an Gesamtzahl der (nicht selektionierten) Patient*innen	Wirkung & sehr seltene Nebenwirkungen	–	>10.000

Wie läuft eine Studie ab?



Aktuelle klinische Studien

- Edaravone
- AMX0035
- Ernährung/Kalorien
- Tofersen
- Jacifusen

Edaravone

Wirkungsweise unbekannt

Monatliche intravenöse Gabe über 2 Wochen

Täglich orale Einnahme

AMX0035

Natriumphenylbutyrat + Taurursodiol

Neuroprotektiv – Reduktion der Abbauvorgänge in der Zelle

CENTAUR Phase 2 Studie wurde 2020 publiziert

Laufende PHOENIX Phase 3 Studie

Beide Studien sind negativ

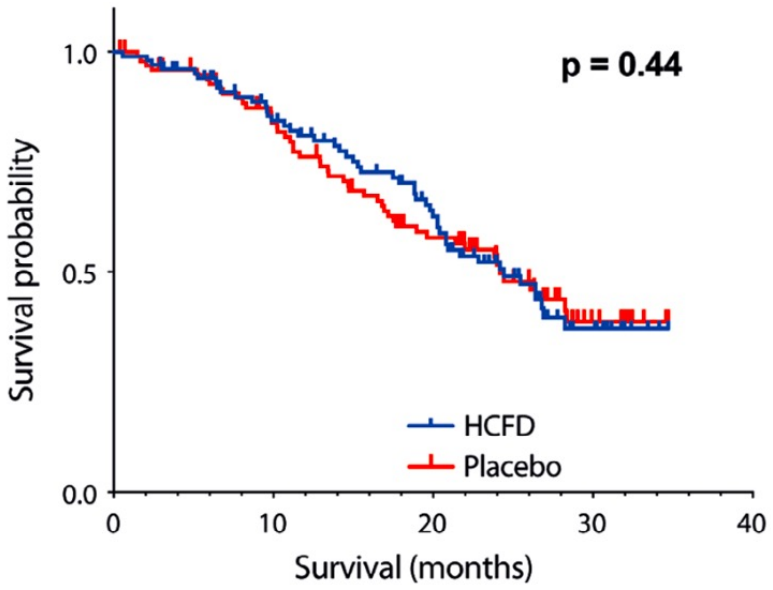
Edaravone

AMX0035

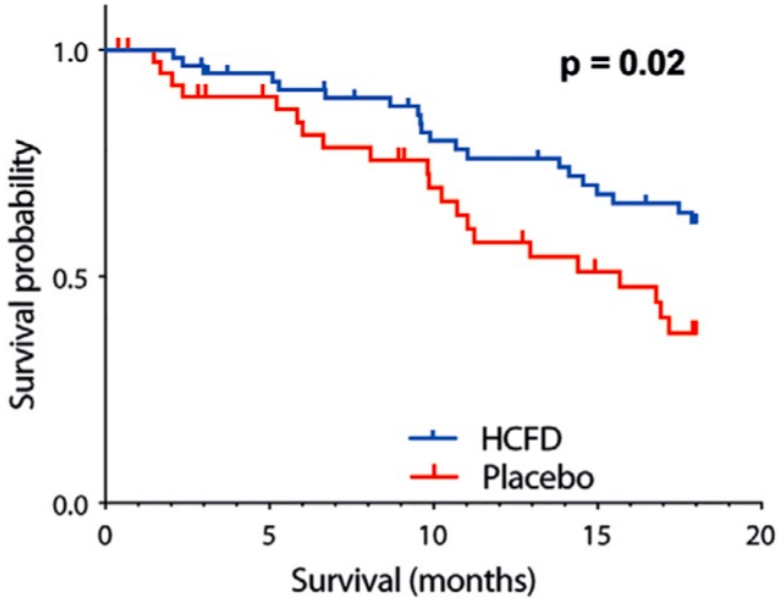
NEGATIV

Ernährung – Kalorien

Effekt einer hochkalorischen Ernährung auf das ALS-Überleben (405kcal/d)



102 Verum vs. 99 Placebo

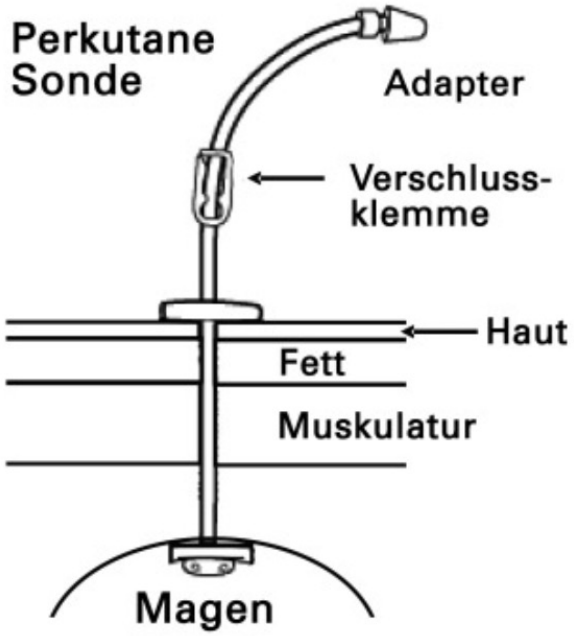


Rasch verlaufend (>0,62/Monat)

59 Verum vs. 41 Placebo

Ludolph et al, 2019, Ann Neurol

Ernährung – PEG-Sonde



INDIKATION

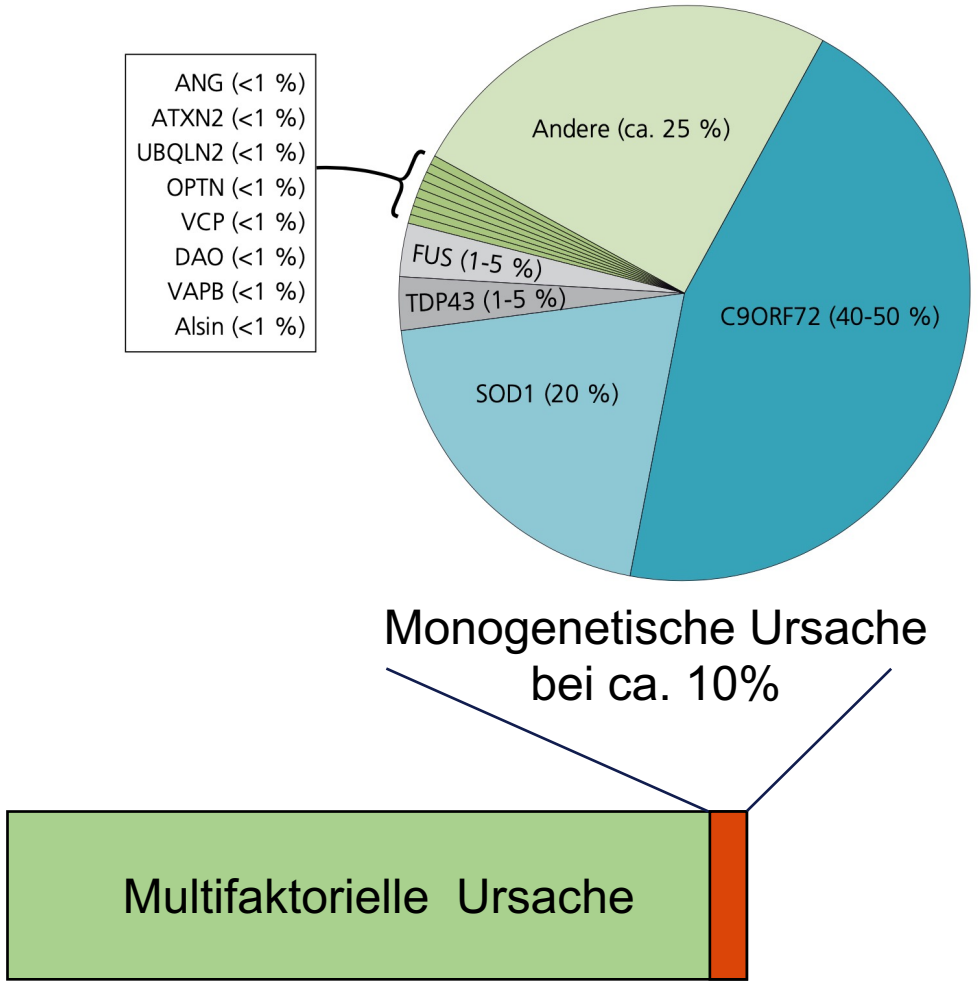
- Leidensdruck
- Gewichtsabnahme (~10%)
- Dehydratation
- Aspirationsgefahr

AUFKLÄRUNG

Castanheira et al, 2022, ALS & FTD

Genetische Therapien

Sod1-assoziierte ALS

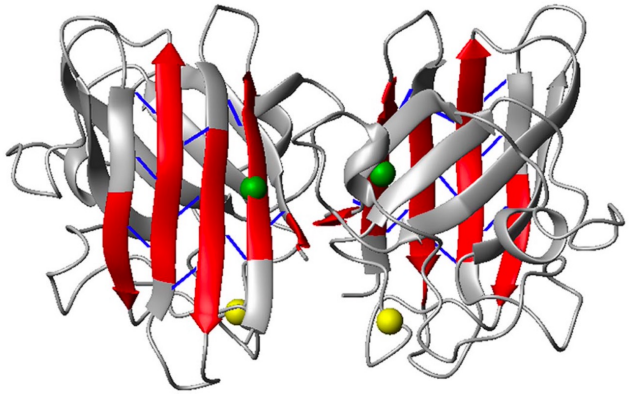


SOD1

Homodimer mit Disulfidbrücke

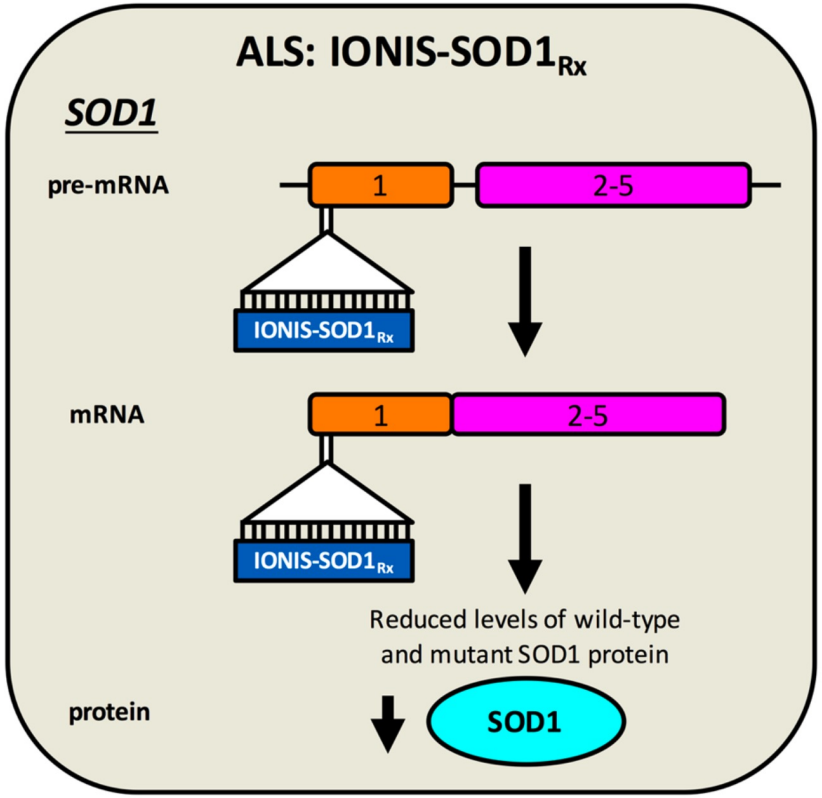
Elimination von O_2-Radikalen im Zytosol

„prion-like“ Ausbreitung (transzellulär über Exosome)



Banci et al, 2009, PNAS; Münch et al, 2011, PNAS

Tofersen ist ein ASO gegen *SOD1*-(pre)mRNA

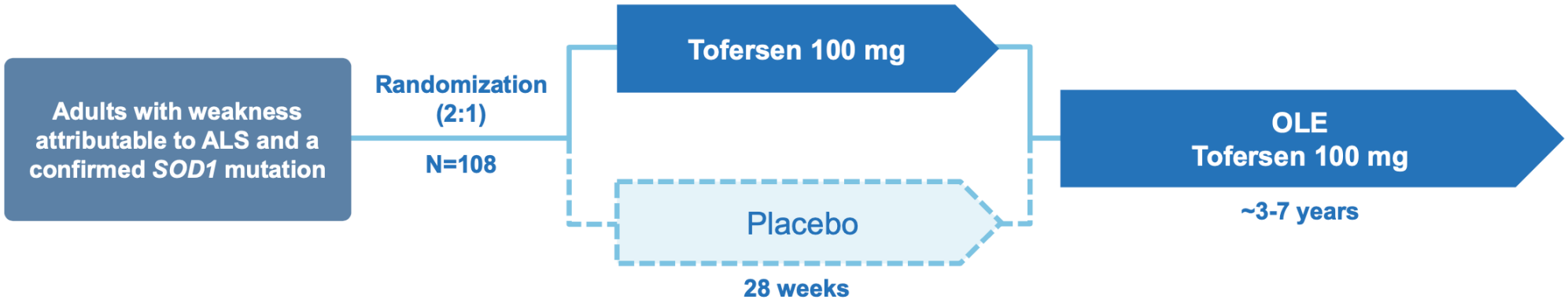


Reduktion von $SOD1_{WT}$ und $SOD1_{Mutant}$

Loss-of-function Mutationen weniger relevant

Tosolini & Sleigh, 2017, Front Mol Neurosci

Tofersen gegen *SOD1*-ALS: Phase 3 Studie (VALOR)



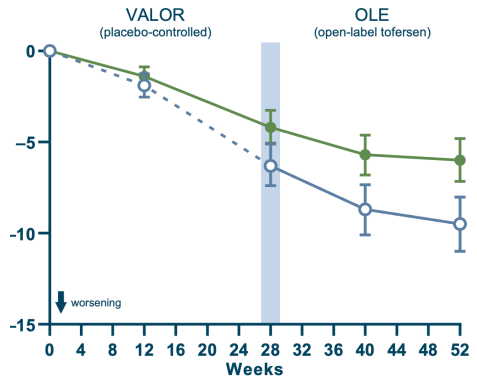
ENDPOINTS

	Primary	Key Secondary	Key Exploratory
Clinical	ALSFRS-R total score	% predicted SVC HHD megascore Time to death or PV Time to death	
Fluid Biomarker		Total CSF SOD1 Plasma NfL	
Quality-of-life			ALSAQ-5

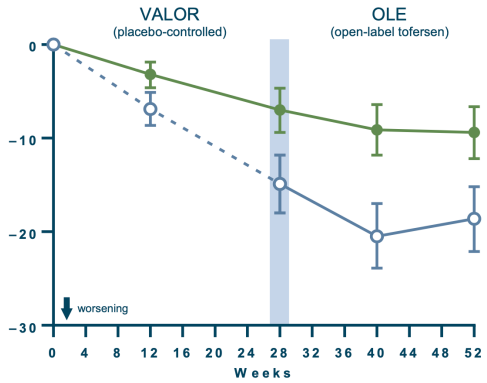
Miller et al, 2022, NEJM

Ergebnisse II

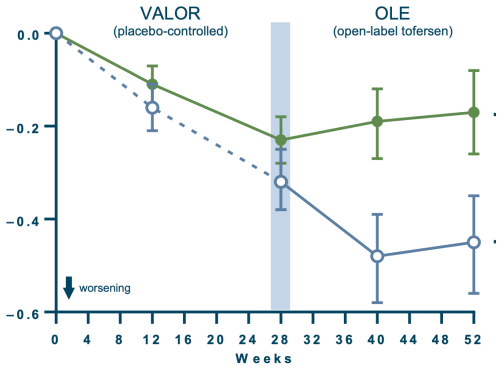
1 ALSFRSr



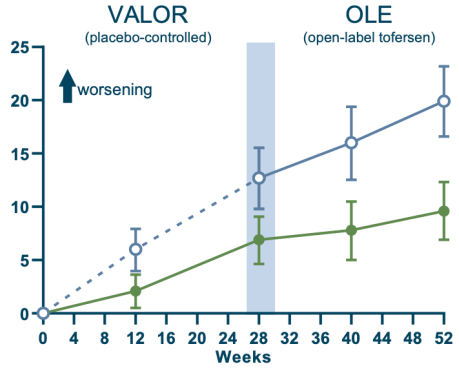
2 Slow vital capacity



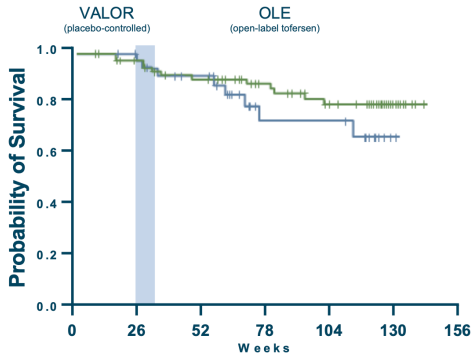
3 Handkraft



4 ALSAQ-5



5 (Ventilationsfreies) Überleben

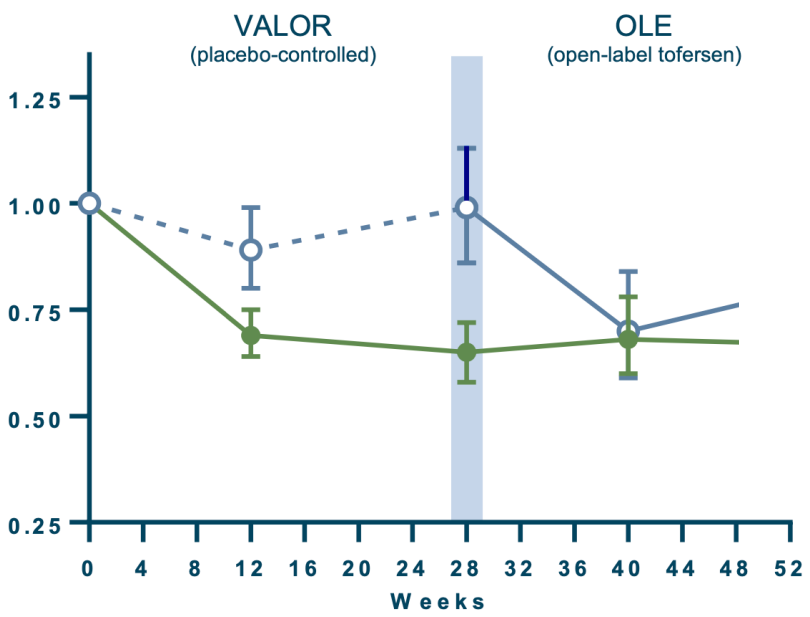


Events	Early-start tofersen	Placebo → delayed-start tofersen	Hazard ratio
Death or Permanent Ventilation	12/72 (16.7%)	8/36 (22.2%)	**0.36** 95% CI, 0.137–0.941

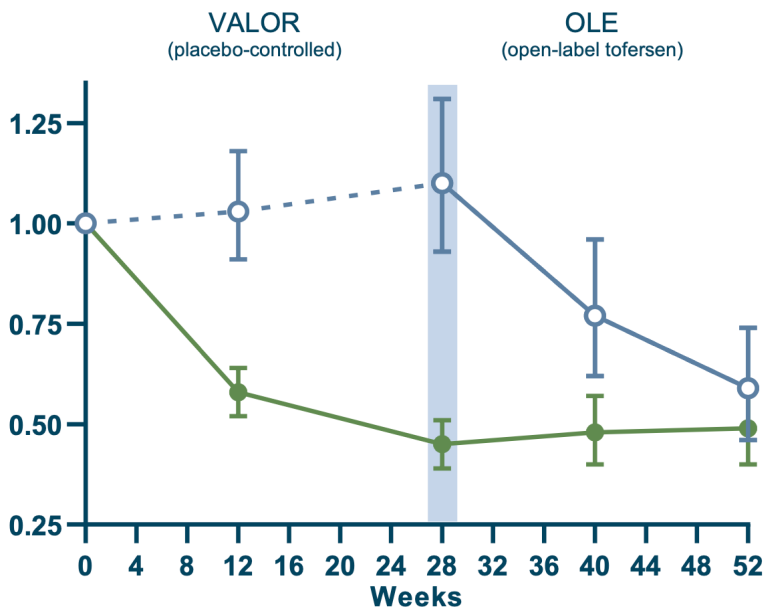
Miller et al, 2022, NEJM

Ergebnisse I

Sod1 Konzentration



Plasma NfL



Miller et al, 2022, NEJM

Sod1-assoziierte ALS

Tang *et al. Transl Neurodegener* (2021) 10:42
https://doi.org/10.1186/s40035-021-00266-x

Translational Neurodegeneration

LETTER Open Access

A natural history comparison of *SOD1*-mutant patients with amyotrophic lateral sclerosis between Chinese and German populations

Lu Tang[1,2†], Johannes Dorst[3,4†], Lu Chen[1,2], Xiaolu Liu[1,2], Yan Ma[1,2], Kornelia Günther[3], Sebastian Michels[3], Kathrin Müller[3], Axel Freischmidt[3], Jochen H. Weishaupt[3], Dongsheng Fan[1,2*] and Albert C. Ludolph[3,4*]

Table 1 Clinical characteristics of Chinese and German ALS patients with *SOD1* mutations

	Total (data available)	China	Germany	*P*
Nominal variables, n (%)				
Numbers of subjects	150	66	84	
Sex, male	80 (55.6%) (144)	35 (53.8%)	45 (57.0%)	0.70
Young-onset ALS (25–45 years)	63 (47.5%) (139)	40 (62.5%)	23 (30.7%)	**< 0.001**
Site of onset, spinal	116 (94.3%) (123)	57 (91.9%)	59 (96.7%)	0.25
Pure LMN	16 (20.0%) (80)	9 (17.3%)	7 (25.0%)	0.41
Riluzole prescription	54 (53.5%) (101)	15 (28.3%)	39 (81.3%)	**< 0.001**
Continuous variables, median (IQR)				
Age of onset (years)	46.0 (40.0–54.0) (139)	43.0 (38.3–50.0)	50.0 (41.0–58.0)	**0.002**
BMI at diagnosis	23.5 (21.6–26.3) (91)	22.6 (20.9–24.9)	25.9 (23.1–28.7)	**< 0.001**
Diagnostic delay (months)	12.0 (6.0–35.0) (107)	14.5 (6.0–36.5)	11.0 (6.0–32.0)	0.59
ALSFRS-R at diagnosis	41.0 (35.0–45.0) (116)	42.0 (35.5–46.0)	40.0 (31.0–44.0)	**0.04**
Early progression rate	0.42 (0.14–0.90) (116)	0.33 (0.15–0.90)	0.46 (0.13–0.93)	0.79
Late progression rate	0.26 (0.09–0.79) (69)	0.28 (0.08–0.80)	0.17 (0.11–0.77)	0.89
Survival (months)	141.0 (21.0–364.0) (140)	NA	198.0 (22.0–364.0)	0.90
Follow-up period	24.0 (7.3–40.8) (88)	30.0 (10.0–42.0)	15.0 (6.0–40.0)	0.06

Spinaler Onset

Jünger

Längeres Überleben

Tofersen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New treatment for rare motor neurone disease recommended for approval
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23 February 2024
EMA has recommended granting a marketing authorisation in the European Union for a new therapy for the treatment of adult patients with amyotrophic lateral sclerosis (ALS), a rare and often fatal disease that causes muscles to become weak and leads to paralysis. Qalsody (tofersen) is indicated for the treatment of adults with ALS, who have a mutation in the superoxide dismutase 1 (SOD1) gene.
News
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Jacifusen gegen FUS-ALS

KURIER

ABO ANMELDEN

FORSCHUNG

30.08.2022

Muskellähmung gestoppt: Hoffnung für ALS-Patienten

Ein neues Medikament zeigt bei einer Patientin, dass sich die genetisch bedingte Form der unheilbaren Nervenkrankheit aufhalten lässt.

Jacifusen gegen FUS-ALS

Jacifusen in den Spinalkanal, 77 Patient*innen

Teil 1 für 61 Wochen

Teil 2 für 85 Wochen (OLE)

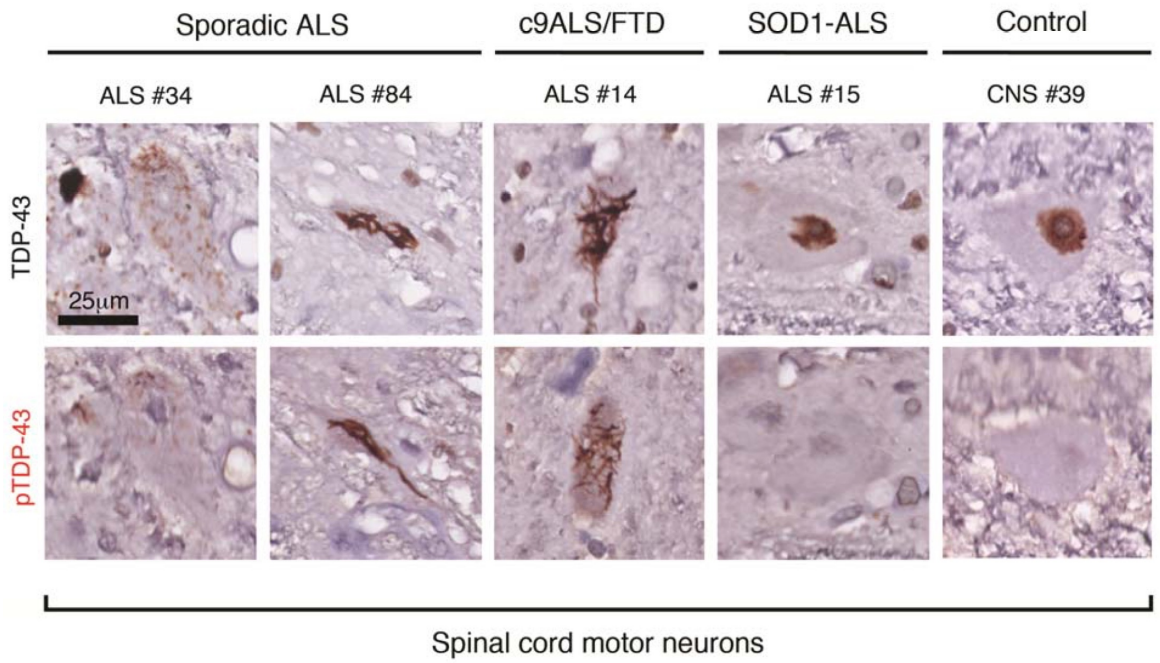
Endpunkt: ALSFRSR, Lungenfunktion, Überleben, Neurofilamente

Ergebnisse 2025 erwartet

Stathmin-2

TDP-43 reguliert andere Gene

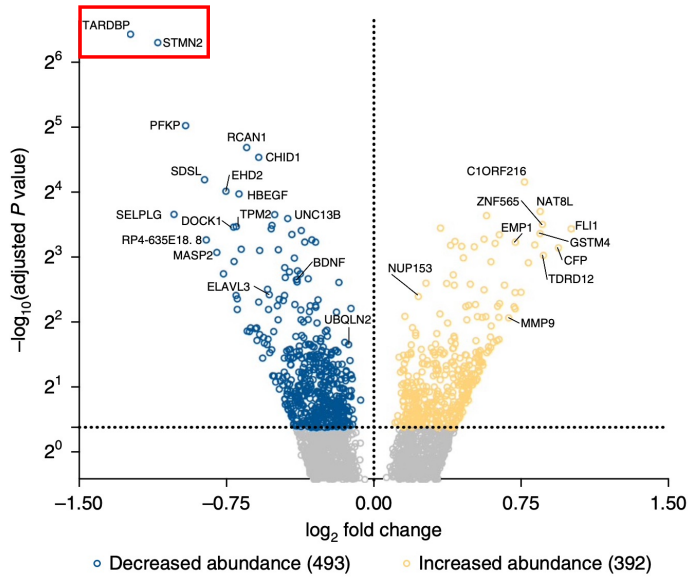
TDP-43 ist ein Protein, das andere Gene reguliert

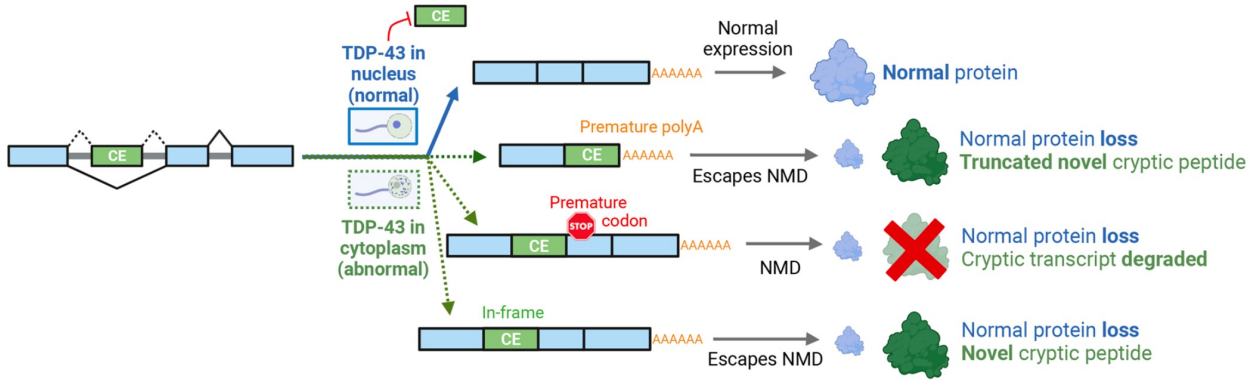


Melamed et al, 2019, Nat Neurosci

TDP-43 reguliert andere Gene

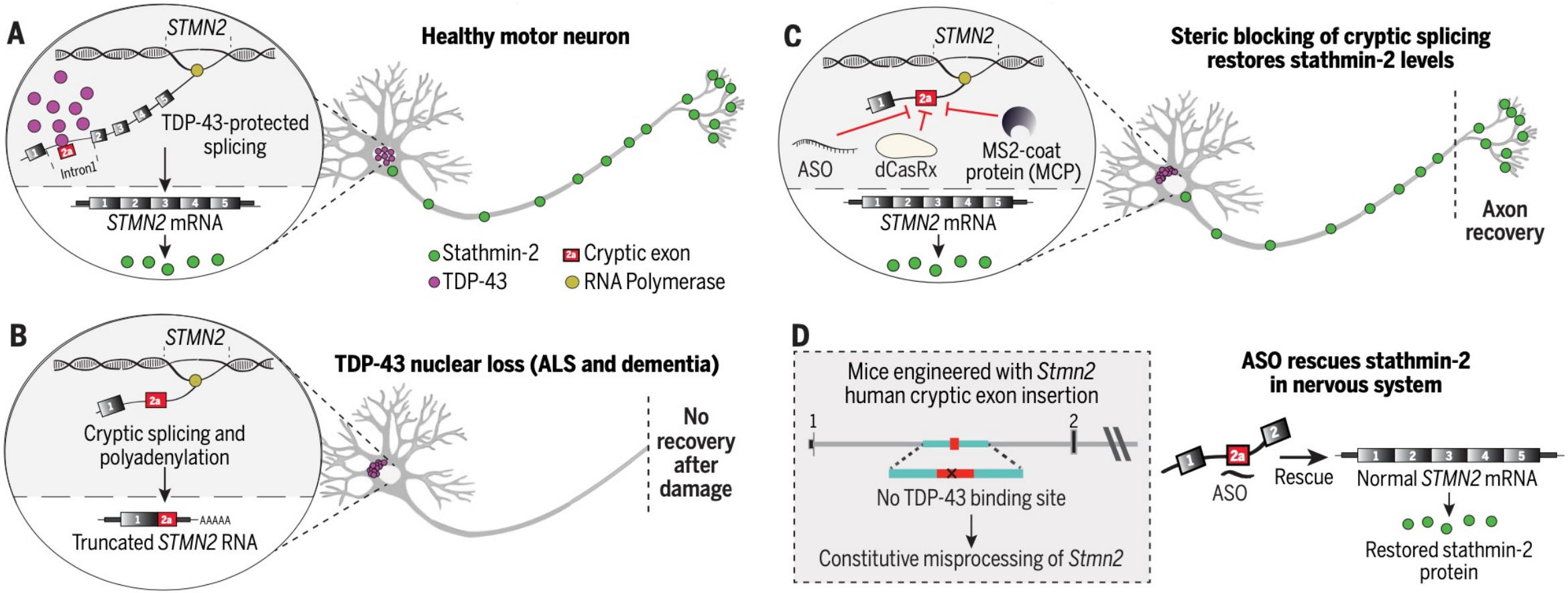
TDP-43 reguliert **Stathmin-2**





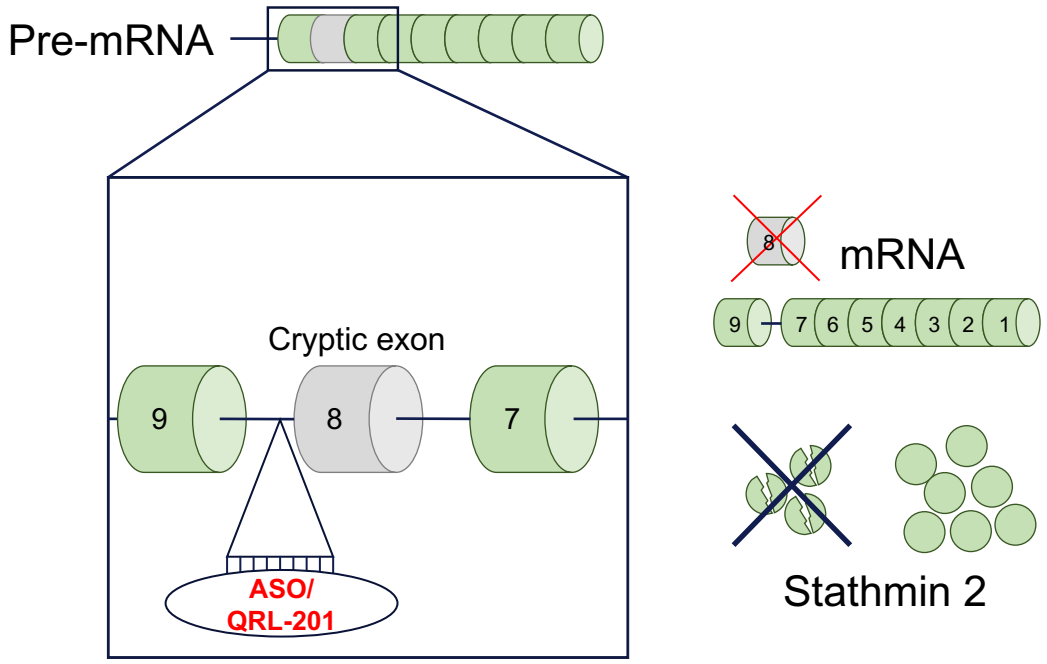
Klim et al, 2019, Nat Neurosci; Mehta et al, 2023, Mol Neurodegener

Alternatives STMN2-Splicing führt zur Motoneuronopathie



Baughn et al, 2023, Science

QurAlis (QRL-201) stellt Stathmin-2 Protein wieder her



Beginn der klinischen Phase

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Dosing begins in Phase 1 trial of QRL-201 in promoting neuronal repair

Study in ALS patients testing safety of therapy to raise stathmin-2 protein levels

Mai 2022

Gentherapie für sporadische ALS

Danke für die Aufmerksamkeit!

Neuromuskuläre Arbeitsgruppe im AKH

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About ALS

ALS overview

Last updated March 20, 2023, by Marisa Wexler, MS
Fact-checked by Ines Martins, PhD

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