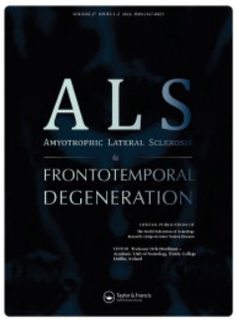

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

ISSN: 2167-8421 (Print) 2167-9223 (Online) Journal homepage: www.tandfonline.com/journals/iafd20

ALS motor phenotypes: a revised 'OPM' classification

Thomas Meyer, Nicola Ticozzi, Markus Weber, John Ravits, Paul Lingor, Magdalena Kuźma-Kozakiewicz, Matthias Boentert, Torsten Grehl, Philippe Corcia, Mónica Povedano Panadés, André Maier, Caroline Ingre, Hakan Cetin, Patrick Weydt, Christian Lunetta, Leonard van den Berg, Albert C. Ludolph, David Brenner, Martin R Turner & Angela Genge

To cite this article: Thomas Meyer, Nicola Ticozzi, Markus Weber, John Ravits, Paul Lingor, Magdalena Kuźma-Kozakiewicz, Matthias Boentert, Torsten Grehl, Philippe Corcia, Mónica Povedano Panadés, André Maier, Caroline Ingre, Hakan Cetin, Patrick Weydt, Christian Lunetta, Leonard van den Berg, Albert C. Ludolph, David Brenner, Martin R Turner & Angela Genge (17 Mar 2026): ALS motor phenotypes: a revised 'OPM' classification, Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, DOI: 10.1080/21678421.2026.2644277

To link to this article: https://doi.org/10.1080/21678421.2026.2644277

Published online: 17 Mar 2026.

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2026; 0: 1–13

RESEARCH ARTICLE

ALS motor phenotypes: a revised 'OPM' classification

THOMAS MEYER[1,2], NICOLA TICOZZI[3,4], MARKUS WEBER[5], JOHN RAVITS[6], PAUL LINGOR[7,8], MAGDALENA KUŹMA-KOZAKIEWICZ[9], MATTHIAS BOENTERT[10], TORSTEN GREHL[11], PHILIPPE CORCIA[12], MÓNICA POVEDANO PANADÉS[13], ANDRÉ MAIER[1], CAROLINE INGRE[14], HAKAN CETIN[15,16], PATRICK WEYDT[17,18], CHRISTIAN LUNETTA[19], LEONARD VAN DEN BERG[20], ALBERT C. LUDOLPH[21], DAVID BRENNER[21], MARTIN R TURNER[22]* & ANGELA GENGE[23]*

[1]*Center for ALS and other Motor Neuron Disorders, Department of Neurology, Charité – Universitätsmedizin Berlin, Corporate Member of Freie Universität Berlin, Humboldt-Universität zu Berlin, and Berlin Institute of Health, Berlin, Germany,* [2]*APST Research, Berlin, Germany,* [3]*Unit of Neurology, IRCCS Istituto Auxologico Italiano, Milan, Italy,* [4]*Department of Pathophysiology and Transplantation, Università degli Studi di Milano, Milan, Italy,* [5]*Neuromuscular Diseases Unit/ALS Clinic, HOCH Health Ostschweiz, St. Gallen, Switzerland,* [6]*Department of Neurosciences, University of CA San Diego, La Jolla, San Diego, USA,* [7]*Department of Neurology, Klinikum rechts der Isar, Technical University of Munich, Munich, Germany,* [8]*DZNE, Deutsches Zentrum für Neurodegenerative Erkrankungen, Research Site Munich, Germany,* [9]*Department of Neurology, Medical University of Warsaw, Warsaw, Poland,* [10]*Neuromedizinisches Zentrum, Klinikum Osnabrück, Osnabrück, Germany,* [11]*Center for ALS and other Motor Neuron Disorders, Department of Neurology, Alfried Krupp Krankenhaus, Essen, Germany,* [12]*Department of Neurology, Center for ALS and other Motor Neuron Disorders, CHU Bretonneau, Tours, France,* [13]*Unidad Funcional de Enfermedad de Motoneurona, Hospital Universitario de Bellvitge, Barcelona, Spain,* [14]*Department of Clinical Neuroscience, Karolinska Institute, Stockholm, Sweden,* [15]*Department of Neurology, Medical University of Vienna, Vienna, Austria,* [16]*Comprehensive Center for Clinical Neurosciences and Mental Health, Medical University of Vienna, Vienna, Austria,* [17]*Department for Neuromuscular Disorders, Bonn University, Bonn, Germany,* [18]*DZNE, Deutsches Zentrum für Neurodegenerative Erkrankungen, Research Site Bonn, Germany,* [19]*Department of Neurorehabilitation of the Milan Institute, Istituti Clinici Scientifici Maugeri IRCCS, Milan, Italy,* [20]*Department of Neurology, UMC Utrecht Brain Centre, Utrecht, Netherlands,* [21]*Department of Neurology, University Hospital Ulm, Ulm, Germany,* [22]*Nuffield Department of Clinical Neurosciences, John Radcliffe Hospital, University of Oxford, UK, and* [23]*The Neuro at Montreal Neurological Institute-Hospital, McGill University, Montreal, Canada*

Abstract

Background: Defining motor phenotypes in amyotrophic lateral sclerosis (ALS) is important for individualized care and optimal therapeutic trial design. The "ALS-OPM" classification is based on the onset region (O), the propagation of motor symptoms (P), and the degree of clinical upper (UMN) and/or lower (LMN) motor neuron dysfunction (M). *Methods*: An international ALS expert focus group was held in September 2025, followed by a consensus process through which revisions of the OPM classification were finalized. *Results*: Onset (O1-4) identifies first motor symptoms as relating to the head (O1), distal/proximal arm (O2d/p), respiratory/axial trunk (O3r/a), or distal/proximal leg (O4d/p). Onset symptoms are defined by weakness or slowed, poorly coordinated voluntary movements in the muscles of the head, arm, trunk, or leg, including dysarthria, dysphagia, dysphonia, dyspnea, and axial instability. Propagation (P1(n)) or absence of propagation (P0(n)) of motor symptoms from the onset region to another body region are designated, where *n* denotes the number of months from onset to propagation or assessment. The degree of UMN dysfunction (slowed, poorly coordinated voluntary movements, hyperreflexia and/or spastic muscle tone, emotional lability) and/or

Correspondence: Thomas Meyer, Charité – Universitätsmedizin Berlin, Center for ALS and other Motor Neuron Disorders, Augustenburger Platz 1, 13353 Berlin, Germany. E-mail: thomas.meyer@charite.de

*Contributed equally

(Received 18 January 2026; revised 25 February 2026; accepted 6 March 2026)

ISSN 2167-8421 print/ISSN 2167-9223 online
DOI: 10.1080/21678421.2026.2644277

LMN dysfunction (weakness with associated muscle atrophy) is classified as follows: balanced UMN and LMN dysfunction (M0); dominant (M1d) or pure UMN dysfunction (M1p); dominant (M2d) or pure LMN dysfunction (M2p); and dissociated UMN/LMN dysfunction (M3), in which the arms and legs predominantly show LMN and UMN involvement, respectively. *Conclusion*: The revised ALS-OPM classification aims to make it routine, practical and feasible to capture phenotype in clinical practice and therapeutic trials.

KEYWORDS: *Amyotrophic lateral sclerosis, ALS motor phenotypes, classification, OPM, revision*

Background

In amyotrophic lateral sclerosis (ALS), distinct motor phenotypes are a fundamental hallmark of the disease and have been associated with differences in disease progression, neurofilament levels, and survival (1–9). From a clinical perspective, phenotype classification supports prognostic assessment and may guide symptomatic management and care (7,9,10). Furthermore, ALS phenotypes have important implications for inclusion and stratification criteria in clinical trials, based on the assumption that distinct ALS variants progress differently and may impact the response to investigational therapies (10–12). Only recently, a classification of ALS motor phenotypes was introduced that is based on three anatomical determinants: the region of onset, the pattern of propagation of motor symptoms, and the degree of upper (UMN) and/or lower motor neuron (LMN) dysfunction (ALS-OPM classification)(13). Based on the results of an international expert meeting held in Berlin in September 2025, as well as practical experience from a large, ongoing multicenter phenotype and biomarker study, a revision of this classification has been proposed. The objectives of the revised ALS-OPM classification were to (i) incorporate key perspectives on ALS phenotypes from a broader group of international ALS experts, (ii) integrate structured feedback from the implementation of the classification in an ongoing multicenter phenotype study, (iii) introduce new items to the ALS-OPM classification, and (iv) adapt and expand the accompanying guideline, commentary, and glossary for standardized ALS-OPM phenotyping.

Methods

Setting

An ALS expert consensus process was conducted between September and December 2025. The initiative was led by the focus group of the ALS Motor Phenotype Symposium, an international ALS expert meeting held in Berlin, September 3 to 5, 2025. The objectives of the symposium were to consolidate current knowledge on ALS motor phenotypes, to delineate the strengths and limitations of the published OPM classification (ALS-OPM 3.1), and to contextualize the OPM framework within clinical practice and trial design. Following the initial in-person meeting, three virtual meetings were conducted to allow for further discussion and refinement of the ALS-OPM classification. In addition, written input, recommendations, and comments were provided by all participating experts and shared using a structured version-controlled document management process. Practical experience with the published ALS-OPM classification, derived from its implementation in an observational study in Germany and Austria, was contributed by representatives from these countries (9). The writing group comprised 20 international ALS experts, each with specific expertise in ALS motor phenotyping.

Design

A focus-group approach was applied to the revision of the ALS-OPM phenotype classification (ALS-OPM 3.3). The design combined an initial in-person expert meeting with subsequent iterative discussions and written feedback to support systematic refinement of the classification (Table 1).

Scope of classification

The ALS-OPM classification is restricted to clinical symptoms and signs of motor neuron dysfunction (Table 2). Assessment is confined to the patient history and neurological examination and deliberately excludes electrophysiologic, laboratory, and imaging studies. Non-motor features, including cognitive, behavioral, and metabolic manifestations, fall outside the scope of this framework and were not addressed in the revision process.

Results

Onset region of motor symptoms

Classification. Phenotypes of onset differentiate the body region of first motor neuron symptoms. Four regions are distinguished: head (O1), arm (O2), trunk (O3), and leg (O4) (Table 1, Figure 1). Onset is defined by symptoms of UMN/LMN dysfunction, whereas motor neuron signs such as fasciculations, muscle wasting, or pathological reflexes are not classified as onset (Table 2).

Assessment. The assessment is based on the patient history (Figure 2).

Revisions. Dysphonia was newly included as a potential first symptom of head onset (O1). As

Table 1. ALS motor phenotypes – classification according to the onset region, propagation of motor neuron symptoms, and the degree of upper and/or lower motor neuron dysfunction ("ALS-OPM phenotype classification"): guidance and commentary for the use in clinical practice and research.

Short name	Code	Guidance	commentary	Examples
Onset	**O**	**Onset region**		
head onset	O1	Onset with dysarthria, dysphonia or dysphagia.	Synonymous to bulbar or pseudobulbar onset; for hypophonia see O3r. Dysphonia should only be classified as O1 when O3r is excluded.	#1: History of progressive dysarthria; classify as O1. #2: History of dysarthria and dysphagia; classify as O1. #3: History of dysphonia (without dysarthria and dysphagia), along with hypophonia, dyspnea or other symptoms of hypoventilation; classify not as O1, but as O3r.
arm onset, distal	O2d	Onset with weakness or slowed, poorly coordinated voluntary movements of the distal arm (hand and forearm).	History of fasciculations or muscle atrophy in the arm is *not* classified as onset.	#1: History of progressive weakness of the left hand; classify as O2d. #2: History of muscle fasciculations in the legs prior to progressive weakness of the left hand; classify as O2d. #3: History of progressive "stiffness" of right hand, without reported weakness or atrophy; classify as O2d.
arm onset, proximal	O2p	Onset with weakness or slowed, poorly coordinated voluntary movements of the proximal arm (shoulder and upper arm).	History of fasciculations or muscle atrophy in the arm is *not* classified as onset.	#1: History of progressive weakness of the right shoulder; classify as O2p. #2: History of progressive weakness in both shoulders, with uncertainty about which side was first affected; classify as O2p. #3: History of progressive "stiffness" of right shoulder and arm muscles, without reported weakness or atrophy of the hand; classify as O2p.
arm onset, not otherwise classifiable	O2x	Onset with weakness or slowed, poorly coordinated voluntary movement of the arm; however, the distinction between distal or proximal onset cannot be made.	History of fasciculations or muscle atrophy in the arm is *not* classified as onset.	#1: History of weakness "somewhere" in the left arm, classify as O2x. #2: History of progressive "stiffness" of left arm, and hand, reported as occurring "at the same time"; classify as O2x.
trunk respiratory onset	O3r	Onset with weakness of the respiratory trunk muscles presenting as dyspnea or hypophonia.	Hypophonia should only be classified as O3r when O1 is excluded.	#1: History of progressive dyspnea, followed by weakness of the arms; classify as O3r. #2: History of progressive dyspnea and instability of the trunk; classify as O3r.
trunk axial onset	O3a	Onset with weakness of the axial trunk muscles presenting as dropped head syndrome, camptocormia, or truncal postural instability due to axial muscle weakness.	In the presence of dyspnea or hypophonia, O3a should be classified as O3r. Axial instability should only be classified as O3a when O4 is excluded.	#1: History of progressive weakness/instability of the neck and trunk; classify as O3a. #2: History of progressive instability of the trunk, followed by dyspnea; classify as O3a. #3: History of progressive instability of the trunk and of weakness in the hip muscles; classify not as O3a, but as O4p.
leg onset, distal	O4d	Onset with weakness or slowed, poorly coordinated voluntary movements of the distal leg (foot and calf).	History of fasciculations or muscle atrophy in the leg is *not* classified as onset.	#1: History of progressive weakness of right foot; classify as O4d. #2: History of progressive "stiffness", and slowed, poorly coordinated voluntary movement of left foot; classify as O4d.
leg onset, proximal	O4p	Onset with weakness or slowed, poorly coordinated		#1: History of progressive weakness of left hip and leg muscles;

(*Continued*)

Table 1. (*Continued*).

Short name	Code	Guidance	commentary	Examples
		voluntary movements of the proximal leg (hip and thigh).		classify as O4p. #2: History of "stiffness", and slowed, poorly coordinated voluntary movement of left hip and leg muscles; classify as O4p.
leg onset, not otherwise classifiable	O4x	Onset with weakness or slowed, poorly coordinated voluntary movements of the leg; however, the distinction between distal or proximal onset cannot be made.	History of fasciculations or muscle atrophy in the arm is *not* classified as onset.	#1: History of weakness "somewhere" in the right leg; classify as O4x. #2: History of progressive "stiffness" of left hip, leg and foot, reported as occurring "at the same time"; classify as O4x.
Propagation	**P**	**Propagation ("vertical spreading")**		
No propagation (number of months)	P0(n)	Absence of propagation of motor neuron *symptoms* from the region of onset to another, vertically distant body region: Neurological examination or history taking shows no evidence of weakness or slowed, poorly coordinated voluntary movements in the muscles of the head, arm, trunk, or leg, including dysarthria, dysphagia, dysphonia, dyspnea, dropped head syndrome, axial instability, or camptocormia. The temporal qualifier of the absence of propagation denotes the number of months (n) from symptom onset to the date of assessment.	Horizontal spreading from one arm or leg to the other is *not* classified as propagation. Motor neuron *signs* such as fasciculations, muscle atrophy, increased or pathological reflexes are *not* classified as propagation.	#1: Neurological examination 14 months after onset does not show motor neuron symptoms outside the onset region; classify as P0(14). #2: A remote assessment 14 months after onset provides no anamnestic indication of motor neuron symptoms outside the onset region; classify as P0(14).
Propagation (number of months)	P1(n)	Propagation of motor neuron *symptoms* from the region of onset to another, vertically distant body region has occurred: Neurological examination or history taking provides evidence of weakness or slowed, poorly coordinated voluntary movements in the muscles of the head, arm, trunk, or leg, including dysarthria, dysphagia, dysphonia, dyspnea, dropped head syndrome, axial instability, or camptocormia. The temporal qualifier denotes the time between symptom onset and the involvement of the next vertically distant body region. It is expressed as the number of months (n) from symptom onset to the date of assessment or to the date in the patient's history when propagation occurred.	Motor neuron *signs* such as fasciculations, muscle atrophy, increased or pathological reflexes are *not* classified as propagation.	#1: Neurological examination 10 months after onset shows a motor neuron symptom outside the onset region; classify as P1(10). #2: Neurological examination 10 months after onset shows a motor neuron symptom outside the onset region, and the patient's history indicates such symptom occurred 8 months after onset; classify as P1(8). #3: A remote assessment 14 months after onset provides anamnestic evidence of motor neuron symptoms outside the onset region at 10 months after onset; classify as P1(10).
Propagation (uncertain number of months)	P1(x)	Propagation of motor neuron *symptoms* from the region of onset to another, vertically distant body region has	Motor neuron *signs* such as fasciculations, muscle atrophy, increased or	#1: Neurological examination 14 months after onset shows a motor neuron symptom outside the onset region, and the

(*Continued*)

Table 1. (*Continued*).

Short name	Code	Guidance	commentary	Examples
		occurred: Neurological examination or history taking provides evidence of weakness or slowed, poorly coordinated voluntary movements in the muscles of the head, arm, trunk, or leg, including dysarthria, dysphagia, dysphonia, dyspnea, dropped head syndrome, axial instability, or camptocormia. The temporal qualifier denotes the time between symptom onset and the involvement of the next vertically distant body region. However, there is no date (x) in the patient's history when propagation occurred. Also, the date of assessment is more than 12 months from onset or from the last neurological examination.	pathological reflexes are *not* classified as propagation.	patient's history provides no indication when such symptom occurred; classify as P1(x). #2: Neurological examination 10 months after onset shows a motor neuron symptom outside the onset region, and the patient's history provides no indication of when this symptom first occurred; classify not as P1(x), but as P1(10).
Motor neuron dysfunction	**M**	**Degree of upper and/or lower motor neuron dysfunction (UMN/LMN)**		
balanced upper and lower motor neuron dysfunction	M0	Balanced combined UMN (slowed, poorly coordinated voluntary movements, increased deep tendon reflexes and/or spastic muscle tone, emotional lability) and LMN dysfunction (weakness and associated atrophy).	Synonymous to "classic ALS", "Charcot ALS" or "typical ALS".	#1: Dysarthria, and slowed, poorly coordinated voluntary movement of the tongue; weakness and atrophy of right arm; classify M0 #2: Dysarthria, atrophy, weakness and slowed, poorly coordinated voluntary movement of the tongue; classify M0 #3: Weakness and hyperreflexia of right arm; classify M0 #4: Low-grade weakness and atrophy of left arm; hyperreflexia of left leg; classify M0 #5: Discretely impaired, poorly coordinated voluntary movements of both legs; wasting and asymmetric weakness of the hands; classify as M0.
dominant upper motor neuron (UMN) dysfunction	M1d	Dominant UMN dysfunction (slowed, poorly coordinated voluntary movements, increased deep tendon reflexes and/or spastic muscle tone, emotional lability) with only discrete LMN dysfunction (weakness and associated atrophy) relative to the UMN dysfunction.	During disease, weakness may also progress; however, it must be associated with increased spastic muscle tone and remain substantially less pronounced than slowed, poorly coordinated voluntary movements; otherwise, classify M0.	#1: Spasticity, and markedly impaired, slowed, poorly coordinated voluntary movement and hyperreflexia of the left arm and both legs; discrete atrophy of both hand muscles; classify M1d. #2: Dysarthria and spasticity of the tongue; spasticity and markedly impaired, poorly coordinated voluntary movements of the arms and legs; discrete wasting and asymmetric weakness of the hand and hip muscles; classify as M1d.
pure UMN dysfunction	M1p	Pure UMN dysfunction (slowed, poorly coordinated voluntary movements, increased deep tendon reflexes and/or spastic muscle tone, emotional	Weakness related to LMN dysfunction must not fall below MRC grade 5 in any body region; otherwise, classify as	#1: High-grade spasticity and asymmetric, markedly slowed, poorly coordinated voluntary movements with hyperreflexia in all limbs; no LMN symptoms; classify as M1p.

(*Continued*)

Table 1. (*Continued*).

Short name	Code	Guidance	commentary	Examples
		lability) and no presence of LMN dysfunction (weakness and associated atrophy).	M1d or M0. Weakness clearly associated with increased spastic muscle tone does not preclude classification as M1p. It can only be classified as M1p if weakness is absent or, if present, is not accompanied by signs of LMN involvement (such as muscle atrophy or fasciculations). This phenotype, when persisting for 48 months, is also known as "primary lateral sclerosis (PLS)".	#2: Severe dysarthria; hyperreflexia of the mandibular reflex; palatal spasticity; high-grade spasticity and asymmetric, markedly impaired, slowed, poorly coordinated voluntary movements with hyperreflexia in all limbs; no LMN symptoms; classify as M1p.
dominant lower motor neuron (LMN) dysfunction	M2d	Dominant LMN dysfunction (weakness and associated atrophy) with only discrete UMN dysfunction (preserved deep tendon reflexes) relative to LMN dysfunction.	UMN dysfunction must be discrete and exclude slowed, poorly coordinated voluntary movements, increased reflexes and/or spastic muscle tone in any of the body regions; otherwise, classify as M0. Absent reflexes indicate M2p.	#1: Weakness (MRC 2) and atrophy of bilateral legs; preserved reflexes in wasted muscle of the left leg; classify M2d. #2: Weakness (MRC 3) and severe atrophy of bilateral legs and left arm; preserved reflexes in wasted muscle of the left hand; classify M2d.
pure LMN dysfunction	M2p	Pure LMN dysfunction (weakness and associated atrophy) and no presence of UMN dysfunction (slowed, poorly coordinated voluntary movements, preserved or increased deep tendon reflexes and/or spastic muscle tone).	This phenotype, when persisting for 48 months, is also known as "progressive muscle atrophy (PMA)".	#1: Asymmetric weakness (MRC 1) and wasting of the foot, leg, hip, hand, arm, and shoulder muscles; absent reflexes; no UMN symptoms; classify as M2p. #2: Weakness (MRC 3) and wasting of the left hand, arm, and shoulder muscles; absent reflexes; no UMN symptoms; classify as M2p. #3: Asymmetric weakness and wasting of both leg muscles; absent reflexes; no UMN symptoms; classify as M2p.
dissociated upper and lower motor neuron dysfunction	M3	Dominant LMN dysfunction (weakness and associated atrophy) with only discrete UMN dysfunction (preserved deep tendon reflexes) relative to LMN dysfunction in the arms, and dominant UMN dysfunction (slowed, poorly coordinated voluntary movements, increased deep tendon reflexes and/or spastic muscle tone) with only discrete LMN dysfunction (weakness and associated atrophy) relative	Synonymous to "brachial atrophic paraspastic variant" of ALS.	#1: Discrete dysarthria with atrophy and weakness of the tongue; severe asymmetric weakness (MRC 1) and wasting of the hands and arms; no UMN symptoms in the arms; high-grade spasticity and asymmetric, markedly slowed, poorly coordinated voluntary movements with hyperreflexia in both legs; discrete atrophy in the lower limbs relative to the degree of UMN dysfunction; classify as M3. #2: Asymmetric weakness (MRC 3) and wasting of the hands and arms; preserved deep tendon

(*Continued*)

Table 1. (*Continued*).

Short name	Code	Guidance	commentary	Examples
		to the UMN dysfunction in the legs.		reflexes, high-grade spasticity, and asymmetric, markedly slowed, poorly coordinated voluntary movements with hyperreflexia in both legs; no LMN symptoms in the lower limbs; classify as M3.

Glossary

- Body region – the body is classified into four anatomical regions: head, arm, trunk and leg.
- Increased deep tendon reflex – exaggerated or brisk reflex response
- Hyperreflexia – abnormally exaggerated deep tendon reflex, often associated with increased reflex spread beyond the stimulated territory.
- Lower motor neuron signs – muscle atrophy of the muscles in the head, arm, trunk, and/or leg; absent reflexes; fasciculations of the tongue; persistent fasciculations in muscles with atrophy and/or weakness
- Lower motor neuron symptoms – weakness with associated muscle atrophy of the muscles in the head, arm, trunk, and/or leg.
- Motor neuron dysfunction – clinical signs and symptoms of upper and/or lower motor neuron involvement.
- Onset region – body region presenting with first motor neuron symptoms. The body is differentiated in four regions: head, arm, trunk and leg.
- Onset criteria – motor neuron *symptoms* of weakness and/or slowed, poorly coordinated voluntary movements in the muscles of the head, arm, trunk, or leg, including dysarthria, dysphagia, dysphonia, dyspnea, dropped head syndrome, axial instability, or camptocormia. Motor neuron *signs* such as fasciculations, muscle atrophy, increased or pathological reflexes are not classified as onset.
- Preserved deep tendon reflex – minimal yet clearly elicitable reflex response in a muscle group that is weak and atrophic.
- Propagation – spreading of motor neuron *symptoms* from the onset region to another, vertically located body region. Horizontal spreading from one arm or leg to the other is *not* considered as propagation.
- Propagation criteria – motor neuron *symptoms* of weakness or slowed, poorly coordinated voluntary movements in the muscles of the head, arm, trunk, or leg, including dysarthria, dysphagia, dysphonia, dyspnea, dropped head syndrome, axial instability, or camptocormia. Motor neuron *signs* such as fasciculations, muscle atrophy, increased or pathological reflexes are not classified as propagation.
- Upper motor neuron signs – emotional lability; preserved reflexes in wasted or weak muscles, increased reflexes, hyperreflexia, and increased velocity-dependent tone (spasticity); pathological abdominal reflexes; Babinski sign; Hoffman sign.
- Upper motor neuron symptoms – slowed, poorly coordinated voluntary movements of the muscles in the head, arm, trunk, and/or leg.
- Weakness – reduction in the ability of a muscle or muscle group to generate voluntary force.

differentiation from hypophonia due to hypoventilation may be difficult, dysphonia is classified as head onset (O1) only when respiratory trunk onset (O3r) is excluded. In the absence of dysarthria or dysphagia, dysphonia accompanied by hypophonia, dyspnea, or other signs of respiratory muscle weakness is classified as O3r. Arm and leg onset "not otherwise classifiable" (O2x and O4x) were newly included to capture first symptoms in the arm or leg when a distinction between distal and proximal onset cannot be made. Axial instability, defined by weakness or instability of the neck and/or trunk, should only be classified as trunk axial onset (O3a) when onset in the lower limbs (O4) has been excluded. This newly introduced commentary reflects the difficulty of distinguishing true axial instability from gait disturbance related to proximal leg weakness.

Propagation of motor symptoms

Classification. Propagation (P1) or the absence (P0) of propagation of motor neuron symptoms from the region of onset (for example, head) to another, vertically distant body region (for example, arm, trunk or leg) are distinguished (Table 1, Figure 1). Motor neuron signs such as fasciculations, muscle atrophy, or reflex abnormalities (defined as preserved reflexes in wasted or weak muscles, increased reflexes, hyperreflexia) are not classified as propagation (Table 2). A temporal qualifier denotes the number of months (n) from symptom onset to the date of assessment or to the date in the patient's history when propagation occurred (P1(n)) or was still absent (P0(n)). Propagation (P1(x)) is used if there is no date (x) in the patient's history indicating when propagation occurred, and the date of assessment is more than 12 months from symptom onset or from the last neurological examination.

Assessment. The assessment is based on patient history or the presence of motor symptoms on neurological examination (Figure 2).

Revisions. The previous differentiation between earlier (PE) and later (PL) propagation (ALS-OPM 3.1) was replaced by propagation (P1) or absence of propagation (P0), supplemented by the number of months (n) from symptom onset to the occurrence or absence of propagation. In addition, a classification option for uncertainty regarding the date of propagation was introduced (P1(x)).

Table 2. ALS motor phenotypes – motor neuron symptoms and signs: guidance for the use in clinical practice and research.

Region	Upper motor neuron (UMN)	Lower motor neuron (LMN)
Head	*Clinical symptoms* • slowed, poorly coordinated voluntary movements of the tongue leading to dysarthria, dysphonia and/or dysphagia *Clinical signs* • hyperreflexia of mandibular reflex • emotional lability • snout reflex exaggerated gag reflex	*Clinical symptoms* • weakness with associated muscle atrophy of the tongue leading to dysarthria, dysphonia and/or dysphagia *Clinical signs* • muscle atrophy of the tongue • fasciculations of the tongue
Arm	*Clinical symptoms* • slowed, poorly coordinated voluntary movements in hand, arm or shoulder *Clinical signs* • preserved reflexes in wasted or weak muscles • increased reflexes • hyperreflexia • Hoffman sign • increased velocity-dependent tone (spasticity) in hand and arm	*Clinical symptoms* • weakness with associated muscle atrophy of hand, arm or shoulder muscles *Clinical signs* • muscle atrophy of hand, arm or shoulder muscles • persistent fasciculations in muscles with atrophy and/or weakness • absent reflexes
Trunk	*Clinical symptoms* • slowed, poorly coordinated voluntary movements of paraspinal, costal and abdominal muscles *Clinical signs* • pathological abdominal reflexes	*Clinical symptoms* • weakness with associated muscle atrophy of paraspinal, costal and abdominal muscles *Clinical signs* • muscle atrophy of paraspinal, costal and abdominal muscles • persistent fasciculations in muscles with atrophy and/or weakness
Leg	*Clinical symptoms* • slowed, poorly coordinated voluntary movements of foot, leg or hip *Clinical signs* • preserved reflexes in wasted or weak muscles • increased reflexes • hyperreflexia • increased velocity-dependent tone (spasticity) in foot, leg or hip • Babinski sign (mostly absent) • crossed adductor reflex	*Clinical symptoms* • weakness with associated muscle atrophy of foot, leg or hip muscles *Clinical signs* • muscle atrophy of foot, leg or hip muscles • persistent fasciculations in muscles with atrophy and/or weakness • absent reflexes

Motor neuron dysfunction

Classification. The degree of UMN and/or LMN dysfunction is differentiated into balanced (M0), dominant LMN (M2d), pure LMN (M2p), dominant UMN (M1d), pure UMN (M1p), and dissociated LMN/UMN symptoms and signs (M3) (Table 1, Figure 1).

Assessment. The assessment is based on neurological examination and/or on existing data from a detailed neurological investigation (Figure 2).

Revisions. Guidance for the assessment of UMN dysfunction was expanded to include signs of increased deep tendon reflexes, spastic muscle tone, and/or emotional lability. For the assessment of LMN dysfunction, it was emphasized that weakness must be accompanied by muscle atrophy. A commentary was provided to guide the classification of clinical findings (Table 1). For dominant UMN dysfunction (M1d), a limited degree of weakness was accepted, provided it is associated with increased spastic muscle tone and remains substantially less pronounced than UMN symptoms. For pure UMN dysfunction (M1p), the acceptable degree of weakness was defined and must not fall below MRC grade 5. It was further clarified that weakness clearly associated with increased spastic muscle tone does not preclude classification as M1p. Overall, pure UMN dysfunction (M1p) can only be classified if weakness is absent or, if present, is not accompanied by signs of LMN involvement (such as muscle atrophy or fasciculations). For dominant LMN dysfunction (M2d), it was emphasized that UMN dysfunction must be discrete and must exclude slowed, poorly coordinated voluntary movements, increased reflexes, and/or spastic muscle tone in any body region. M2d is defined by weakness with associated muscle atrophy and preserved deep tendon reflexes; absent reflexes indicate M2p, whereas increased reflexes (or other UMN symptoms or signs) indicate M0.

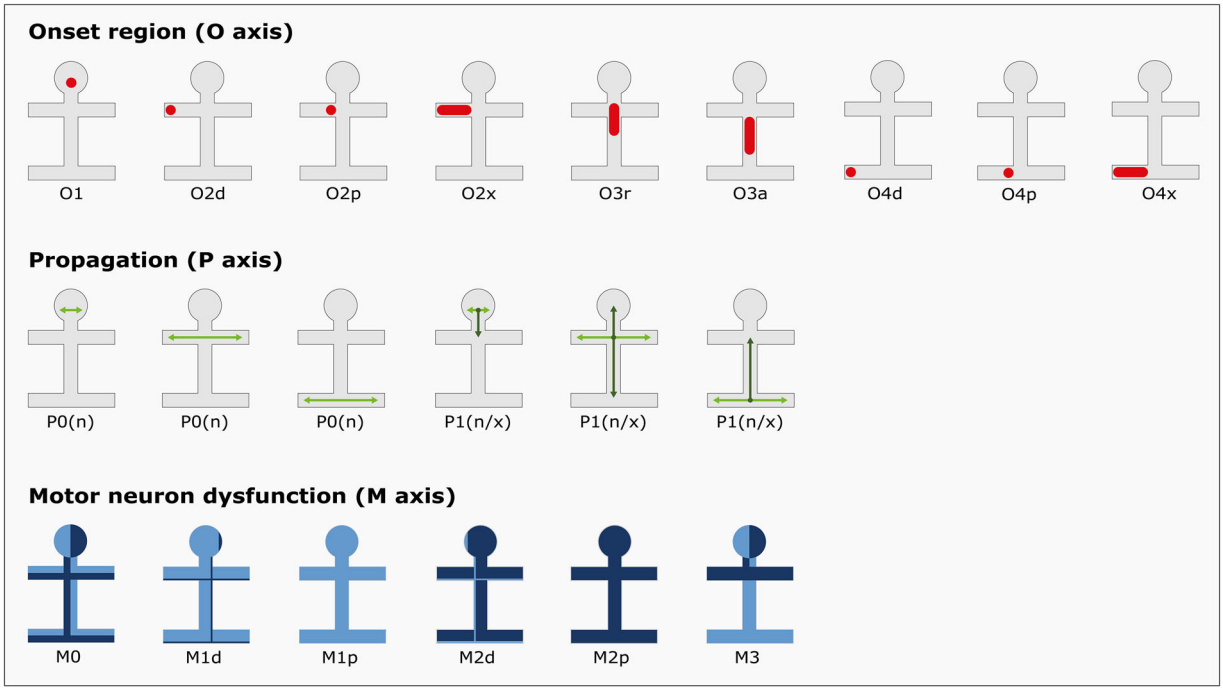

Figure 1. ALS motor phenotypes – classification according to the onset region, propagation of motor neuron symptoms, and the degree of upper and/or lower motor neuron dysfunction ("ALS-OPM Phenotype Classification"). Phenotypes of the onset region (O) differentiate the site of first symptoms including the head (O1), distal/proximal/uncertain (O2d/p/x) arm, respiratory/axial trunk (O3r/a), or distal/proximal/uncertain (O4d/p/x) leg. Phenotypes of propagation (P) differentiate propagation (P1) or the absence (P0) of propagation of motor neuron symptoms from the region of onset to another, vertically distant body region. A temporal qualifier denotes the number of months (n) from symptom onset to the date of assessment or to the date in the patient's history when propagation occurred (P1(n)) or was still absent (P0(n)). Propagation (P1(x)) is used if there is no date (x) in the patient's history indicating when propagation occurred. Phenotypes of motor neuron dysfunction (M) differentiate the degree of upper (UMN) and/or lower motor neuron (LMN) dysfunction into balanced UMN and LMN (M0), dominant LMN (M2d), pure LMN (M2p), dominant UMN (M1d), pure UMN (M1p), and dissociated LMN/UMN involvement (M3).

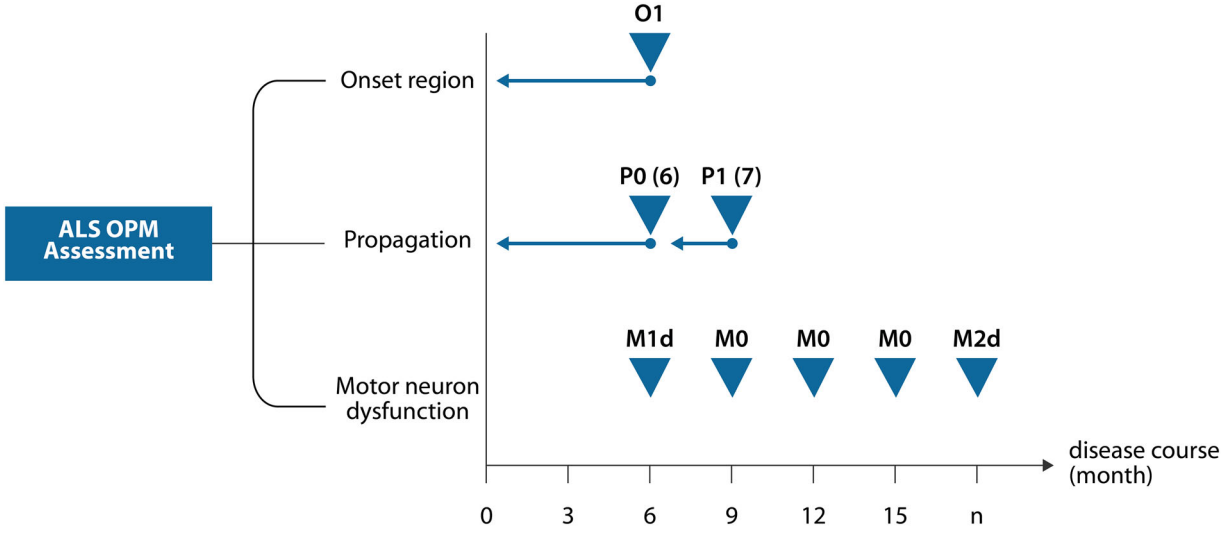

Figure 2. Assessment of ALS motor phenotypes according to the onset region, propagation of motor neuron symptoms, and the degree of upper and/or lower motor neuron dysfunction. Phenotypes of the onset region are assessed by patient history (illustrated example: head onset, O1). Propagation of motor neuron symptoms from the region of onset to another, vertically distant body region is assessed by patient history and/or neurological examination (illustrated examples: absence of propagation at 6 months after onset, P0(6); reported propagation occurring 7 months after onset and assessed at 9 months after onset, P1(7)). Phenotypes of motor neuron dysfunction are determined by neurological examination assessing the degree of upper motor neuron (UMN) and/or lower motor neuron (LMN) symptoms and signs. Motor neuron dysfunction may evolve over the disease course and therefore requires reevaluation at follow-up assessments (illustrated example: dominant UMN dysfunction, M1d, at 6 months; balanced UMN and LMN dysfunction, M0, at 9, 12, and 15 months; dominant LMN dysfunction, M2d, at 18 months after onset). Arrows indicate patient-reported history; triangles indicate time points of assessment.

Definition of symptoms and signs of UMN/LMN

In Table 2, symptoms and signs of UMN and LMN dysfunction are presented separately, as onset and propagation are determined solely by symptoms, whereas the degree of motor neuron involvement is assessed based on both signs and symptoms of motor neuron dysfunction. In the head region, UMN signs (emotional lability, snout reflex, exaggerated gag reflex) and LMN symptoms (weakness with associated muscle atrophy of the tongue leading to dysarthria, dysphonia, and/or dysphagia) were defined in greater detail. In the arms, trunk, and legs, weakness was defined as an LMN symptom only when associated with muscle atrophy of the respective muscle group (14).

Glossary

An alphabetically organized glossary was included to provide standardized definitions supporting ALS phenotyping in accordance with the ALS-OPM classification (Table 1).

Discussion

A standardized classification of ALS phenotype has been a long-standing need (15–19). In July 2020, a two-determinant phenotype classification (ALS-OPM 2.1) was introduced as part of a multicenter study on ALS phenotypes and neurofilament light chain (NfL), with initial results published in 2024 (9). In parallel, a structured consensus process involving 20 ALS experts from ALS centers in Germany was initiated. The outcome of this process was published in April 2025 and introduced a three-determinant anatomical phenotype classification based on the region of onset, the propagation of motor symptoms, and the degree of motor neuron involvement (ALS-OPM 3.1) (14). Fundamentally, the implementation of any phenotype classification requires consensus beyond the national level. In line with this principle, an international meeting of invited ALS experts – predominantly from Europe and with established expertise in ALS phenotyping – was convened. Within this meeting, a focus group was formed to further refine the classification, resulting in the current version (ALS-OPM 3.3). The authors acknowledge that this focus group did not encompass all relevant key opinion leaders and that further expansion of the consensus process is required. In particular, broader inclusion of experts and stakeholders representing diverse geographic regions, clinical perspectives, and healthcare settings will be essential. Accordingly, the revised OPM classification should be viewed as part of a dynamic, iterative process, with future updates incorporating advances in research and clinical development.

Onset region of motor symptoms. The assessment of the region of onset is based primarily on patient history and is therefore inherently associated with a degree of uncertainty. Symptoms such as dysarthria in head-onset phenotypes or frank weakness in extremity-onset phenotypes are generally salient to patients and thus more likely to be reliably self-reported. In contrast, other forms of onset may be less readily recognized by patients and are more prone to alternative explanations from the patient's perspective. In particular, discrete motor dysfunction resulting predominantly from UMN involvement – such as slowed, poorly coordinated voluntary movements or subtle gait abnormalities – may be reported later than overt weakness associated with muscle atrophy. Similarly, distal arm or leg onset may be detected earlier than proximal onset, as distal functions are more closely related to fine motor control and dexterity. Proximal arm weakness can initially have limited impact on activities of daily living, while proximal leg weakness can lead to less pronounced gait disturbances compared with distal leg weakness presenting as foot drop. However, these remain assumptions that have not yet been substantiated. The distal–proximal distinction in the ALS-OPM classification may support further studies on diagnostic delay in patients with proximal disease onset. The assessment of proximal onset is further complicated by prevalent differential diagnoses. Conditions such as shoulder elevator muscle injuries, rotator cuff pathology, or hip joint arthrosis may distract from the recognition of ALS onset. These factors may systematically bias the perceived onset region and contribute to variability in onset classification. Rare forms of onset, including dysphonia or dysphagia preceding dysarthria, have not been systematically investigated to date, and data on their frequency, clinical relevance, and prognostic implications remain scarce. Whether such distinctions meaningfully contribute to phenotype stratification remains an open question and warrants dedicated investigation. Likewise, the predictive value of differentiating distal versus proximal onset with respect to ALS progression and survival is currently uncertain and awaits validation in longitudinal analyses. In principle, if future analyses demonstrate limited clinical or predictive relevance of specific onset phenotypes, subsequent revisions of the ALS-OPM classification may discontinue their distinction. Importantly, decisions regarding further refinement of onset regions should be guided by empirical data derived from real-world application of the ALS-OPM 3.3 classification. Further standardization of history-taking procedures may improve reliability and reproducibility of onset classification across centers and healthcare settings.

Propagation of motor symptoms. A major change introduced with this revision of the ALS-OPM classification concerns the operationalization of propagation phenotypes. In the previous version (ALS-OPM 3.1), propagation was categorized as earlier (PE) or later (PL), based on an a priori temporal threshold of 12 months (14,20). In the revised framework, this dichotomous approach has been replaced by a more granular temporal qualifier that specifies the exact number of months (n) from symptom onset to the occurrence of propagation. The former 12-month threshold separating early and late propagation was, to some extent, arbitrary, and derived from the diagnostic criteria used to define flail limb syndromes, which represent prototypical phenotypes of protracted vertical propagation. By replacing PE and PL with a continuous temporal descriptor, the revised classification allows to identify data-driven inflection points at which trajectories of earlier and later propagation begin to diverge and prognostic curves separate. Identifying patients with protracted propagation is critical when aiming to reduce clinical heterogeneity in clinical trials. The proportion of patients classified as P1(x) is likely influenced by the interview skills and experience of the investigator, and patient-related factors such as symptom awareness, and the ability to recall the temporal sequence of symptom spread. Propagation status can be assessed through two modalities: neurological examination or patient history. Neurological examination is considered the most reliable method for identifying the presence or absence of propagation. Importantly, examination findings can often be extracted from medical records, enabling retrospective ALS-OPM classification in existing datasets. However, patient history plays a crucial role in assessing the temporal qualifier of propagation, especially given the typically long intervals of three to four months between follow-up visits in clinical practice. Motor symptoms affecting proximal arm or leg muscles are less likely to be self-detected and may be assessed predominantly by neurological examination and can appear later than propagation inferred from history. These considerations underscore that allowing both, history and examination, is necessary to balance feasibility and accuracy in the assessment of propagation. The factors that determine propagation of motor neuron symptoms—or, even more importantly, the sustained absence of propagation—remain poorly understood. Only recently, an analysis of ALS phenotypes using the ALS-OPM 3.1 classification demonstrated distinct propagation patterns in genetic ALS associated with *C9orf72*, *SOD1*, *TARDBP*, and *FUS* (21). These findings support the notion that vertical propagation dynamics differ across genetically defined subtypes of ALS. In future studies, temporal propagation data are expected to contribute to a more refined understanding of ALS spreading mechanisms and to the identification of biologically distinct propagation trajectories (1,8,22,23).

Motor neuron dysfunction. Motor neuron involvement in the ALS-OPM classification is based on neurological examination and integrates both symptoms and signs of UMN/LMN dysfunction. Inevitably, this assessment is subject to a degree of clinical subjectivity. From a practical perspective, distinguishing balanced involvement (M0) from dominant phenotypes (M1d or M2d) represents the most difficult and subjective aspect of phenotyping. Also, the distinction between pure (M1p) and dominant UMN (M1d) phenotypes may be challenging in cases of disuse atrophy. To address these challenges in the practical application of phenotyping, a detailed commentary and case vignettes were developed to guide clinicians in assigning patients to the respective ALS-OPM phenotype (Table 1). The extent of interrater variability in assessing motor neuron involvement is currently unknown. It is likely influenced by factors such as neurological training and depth of experience with ALS. Systematic evaluation of this variability is therefore an important next step and will be addressed in future natural history studies incorporating the ALS-OPM classification. As ALS progresses, the relative composition of UMN and LMN symptoms may change. Patients initially classified as having dominant UMN or LMN dysfunction (M1d/M2d) may later develop combined UMN and LMN features, resulting in reclassification as a balanced phenotype (M0). In advanced disease stages, LMN symptoms often dominate and may mask UMN involvement (24). Despite longstanding clinical experience suggesting a temporal shift toward LMN predominance, the prognostic relevance of LMN predominance remains incompletely understood. Thus, it is unclear whether a clinical tipping point exists at which a shift toward LMN dysfunction acquires predictive value. Similar considerations apply in the context of clinical trials, where effective disease-modifying treatments may alter the relative degree of UMN and LMN involvement over time. Addressing these open questions will require longitudinal application of the OPM framework in clinical trials in which ALS-OPM phenotypes are used as exploratory endpoints.

ALS-OPM classification in clinical trials. Stratification by motor neuron involvement may facilitate assessment of target engagement, particularly for therapies directed at UMN or LMN pathology, as well as for symptomatic treatments of UMN-related symptoms. Use of ALS-OPM phenotypes may also reduce clinical heterogeneity, for example by excluding axial trunk onset (O3a) or prolonged no-propagation (P0) phenotypes. Incorporation of ALS-OPM variables into

prediction models may improve prognostic stratification in ALS (11,12,25,26).

Outlook for implementing the ALS-OPM classification. Implementation of the ALS-OPM classification is expected to proceed in a stepwise manner. At present, ALS-OPM 3.1 is in use, and data from ongoing natural history cohorts applying this version are anticipated (9,14). These data will provide an important reference for subsequent analyses using the revised ALS-OPM 3.3 classification, including correlations with ALSFRS-R trajectories and biomarkers such as NfL and troponin T (9,27–29). The ALS-OPM framework is conceived as an "operating system" for phenotyping, allowing for continuous refinement as empirical evidence accumulates. Version management and public availability of past and current ALS-OPM versions will be maintained via the dedicated platform (https://als-opm.org/). Notably, an alternative ALS phenotype classification was recently proposed (11). In principle, parallel use of different classification systems is likely, each with distinct strengths and limitations. Ultimately, practical applicability in clinical practice and trials will determine which phenotype classifications are adopted and sustained.

Scope of ALS-OPM classification. The authors acknowledge that the ALS-OPM classification is restricted to motor phenotypes, with non-motor manifestations remaining outside its scope (30). This deliberate focus on motor symptoms was instrumental in mitigating the complexity inherent in developing and implementing a novel phenotypic framework. The omission of cognitive, behavioral, metabolic and other non-motor dimensions of the disease spectrum should therefore be understood as an operational decision, intended to enhance feasibility, consistency, and acceptance of the classification in clinical practice and research. This also applies to electrophysiological features of ALS, including electromyography findings and quantitative measures such as the motor unit number index (MUNIX) and compound muscle action potential (CMAP). In future iterations of ALS phenotype classification, integration of non-motor phenotypes will need to be addressed.

Authors' contributions

TM, NT, MW, JR, PL, MK, MB, TG, AM, PW, LVB, AL, DB, MRT, and AG made substantial contributions to the conception of the work; TM, NT, MW, PL, MK, MB, TG, PC, MP, CI, HC, CL, MRT, and AG have drafted the work or substantively revised it.

Disclosure statement

No potential conflict of interest was reported by the author(s).

Funding

This work was supported by the Boris Canessa ALS Stiftung (Düsseldorf, Germany). NT acknowledges the support of the Italian Ministry of Health (Hub Life Science – Diagnostica Avanzata (HLS-DA), PNC-E3-2022-23683266) and of the Italian Ministry of Education and Research ("Dipartimenti di Eccellenza" Program 2023–2027 – Department of Pathophysiology and Transplantation, Università degli Studi di Milano).

ORCID

Thomas Meyer http://orcid.org/0000-0002-2736-7350
Nicola Ticozzi http://orcid.org/0000-0001-5963-7426
Paul Lingor http://orcid.org/0000-0001-9362-7096
Magdalena Kuźma-Kozakiewicz http://orcid.org/0000-0002-9676-1263
Caroline Ingre http://orcid.org/0000-0001-5327-7204
Leonard van den Berg http://orcid.org/0000-0002-5203-9674

References

1. Ravits JM, La Spada AR. ALS motor phenotype heterogeneity, focality, and spread: deconstructing motor neuron degeneration. Neurology. 2009;73:805–11.
2. Turner MR, Parton MJ, Shaw CE, Leigh PN, Al-Chalabi A. Prolonged survival in motor neuron disease: a descriptive study of the King's database 1990-2002. J Neurol Neurosurg Psychiatry. 2003;74:995–7.
3. Talman P, Forbes A, Mathers S. Clinical phenotypes and natural progression for motor neuron disease: analysis from an Australian database. Amyotroph Lateral Scler. 2009;10:79–84.
4. Talman P, Duong T, Vucic S, Mathers S, Venkatesh S, Henderson R, et al. Identification and outcomes of clinical phenotypes in amyotrophic lateral sclerosis/motor neuron disease: Australian National Motor Neuron Disease observational cohort. BMJ Open. 2016;6:e012054.
5. Chiò A, Calvo A, Moglia C, Mazzini L, Mora G. Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study. J Neurol Neurosurg Psychiatry. 2011;82:740–6.
6. Chiò A, Moglia C, Canosa A, Manera U, D'Ovidio F, Vasta R, et al. ALS phenotype is influenced by age, sex, and genetics: A population-based study. Neurology. 2020;94:e802–e810.
7. Ganesalingam J, Stahl D, Wijesekera L, Galtrey C, Shaw CE, Leigh PN, et al. Latent cluster analysis of ALS phenotypes identifies prognostically differing groups. PLoS One. 2009;4:e7107.
8. Maranzano A, Verde F, Colombo E, Poletti B, Doretti A, Bonetti R, et al. Regional spreading pattern is associated

with clinical phenotype in amyotrophic lateral sclerosis. Brain. 2023;146:4105–16.
9. Meyer T, Dreger M, Grehl T, Weyen U, Kettemann D, Weydt P, et al. Serum neurofilament light chain in distinct phenotypes of amyotrophic lateral sclerosis: A longitudinal, multicenter study. Eur J Neurol. 2024;31:e16379.
10. Feldman EL, Goutman SA, Petri S, Mazzini L, Savelieff MG, Shaw PJ, et al. Amyotrophic lateral sclerosis. Lancet. 2022;400:1363–80.
11. Rosenfeld J, Abrahams S, McHutchinson C, Ajroud-Driss S, Weber M, Paganoni S, et al. Utility of patient subgrouping in ALS clinical trials: a World Federation of Neurology white paper. Amyotroph Lateral Scler Frontotemporal Degener. 2025;2025:1–8.
12. Al-Chalabi A, Hardiman O, Kiernan MC, Chiò A, Rix-Brooks B, van den Berg LH. Amyotrophic lateral sclerosis: moving towards a new classification system. Lancet Neurol. 2016;15:1182–94.
13. Goutman SA, Hardiman O, Al-Chalabi A, Chió A, Savelieff MG, Kiernan MC, et al. Recent advances in the diagnosis and prognosis of amyotrophic lateral sclerosis. Lancet Neurol. 2022;21:480–93.
14. Meyer T, Boentert M, Großkreutz J, Weydt P, Bernsen S, Reilich P, et al. 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. Neurol Res Pract. 2025;7:27.
15. Swash M, Desai J. Motor neuron disease: classification and nomenclature. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:105–12.
16. Turner MR, Swash M. The expanding syndrome of amyotrophic lateral sclerosis: a clinical and molecular odyssey. J Neurol Neurosurg Psychiatry. 2015;86:667–73.
17. Turner MR. The reunification of amyotrophic lateral sclerosis. J Neurol Neurosurg Psychiatry. 2019;90:122–3.
18. Rutter-Locher Z, Turner MR, Leigh PN, Al-Chalabi A. Analysis of terms used for the diagnosis and classification of amyotrophic lateral sclerosis and motor neuron disease. Amyotroph Lateral Scler Frontotemporal Degener. 2016; 17:600–4.
19. Rosenfeld J, Swash M. What's in a name? Lumping or splitting ALS, PLS, PMA, and the other motor neuron diseases. Neurology. 2006;66:624–5.
20. Wijesekera LC, Mathers S, Talman P, Galtrey C, Parkinson MH, Ganesalingam J, et al. Natural history and clinical features of the flail arm and flail leg ALS variants. Neurology. 2009;72:1087–94.
21. Schmitt P, Schumann P, Koerbs A, Lin HJ, Grehl T, Weyen U, et al. Motor phenotypes and neurofilament light chain in genetic amyotrophic lateral sclerosis-results from a multicenter screening program. J Neurol. 2025;273:22.
22. Eisen A, Vucic S, Kiernan MC. Amyotrophic lateral sclerosis represents corticomotoneuronal system failure. Muscle Nerve. 2025;71:499–511.
23. Ludolph AC, Dietrich J, Dreyhaupt J, Kassubek J, Del Tredici K, Rosenbohm A. Clinical spreading of muscle weakness in amyotrophic lateral sclerosis (ALS): a study in 910 patients. J Neurol. 2024;271:5357–67.
24. Gromicho M, Figueiral M, Uysal H, Grosskreutz J, Kuzma-Kozakiewicz M, Pinto S, et al. Spreading in ALS: The relative impact of upper and lower motor neuron involvement. Ann Clin Transl Neurol. 2020;7:1181–92.
25. Westeneng HJ, Debray TPA, Visser AE, van Eijk RPA, Rooney JPK, Calvo A, et al. Prognosis for patients with amyotrophic lateral sclerosis: development and validation of a personalised prediction model. Lancet Neurol. 2018; 17:423–33.
26. van Eijk RPA, Nikolakopoulos S, Roes KCB, Kendall L, Han SS, Lavrov A, et al. Innovating clinical trials for amyotrophic lateral sclerosis: challenging the established order. Neurology. 2021;97:528–36.
27. Lindenborn P, Fabian R, Grehl T, Nazlican H, Meyer T, Bernsen S, et al. Combination of serum neurofilament light chain and serum cardiac troponin t as biomarkers improves diagnostic accuracy in amyotrophic lateral sclerosis. Ann Neurol. 2026;99:408–17.
28. Koch T, Fabian R, Weinhold L, Koch FW, Barakat S, Castro-Gomez S, et al. Cardiac troponin T as a serum biomarker of respiratory impairment in amyotrophic lateral sclerosis. Ann Clin Transl Neurol. 2024;11:2063–72.
29. Chamoun S, Imrell S, Upate Z, Kläppe U, Öijerstedt L, Yazdani S, et al. Plasma troponin T reflects lower motor neuron involvement on electromyography in amyotrophic lateral sclerosis. Brain Commun. 2025;7:fcaf177.
30. Strong MJ, Abrahams S, Goldstein LH, Woolley S, Mclaughlin P, Snowden J, et al. Amyotrophic lateral sclerosis – frontotemporal spectrum disorder (ALS-FTSD): Revised diagnostic criteria. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18:153–74.