3° Convegno SLA/ALS

Formazione e informazione

SEMPRE AVANTI !!

FabiOnlus

#NeverGiveUp vs SLA

Aggiornamenti in ambito clinico: dalla diagnosi alla prognosi

Andrea Calvo
CRESLA di Torino – CSST Torino e Dipartimento di Neuroscienze 'Rita Levi Montalcini' Università di Torino

AZIENDA OSPEDALIERO - UNIVERSITARIA
Città della Salute e della Scienza di Torino

C.R.E.SLA
Torino

No disclosure

Un ringraziamento a Adriano Chiò, Jessica Mandrioli e Markus Weber per la cortesia nel fornire alcune slides

Cos'è la SLA?

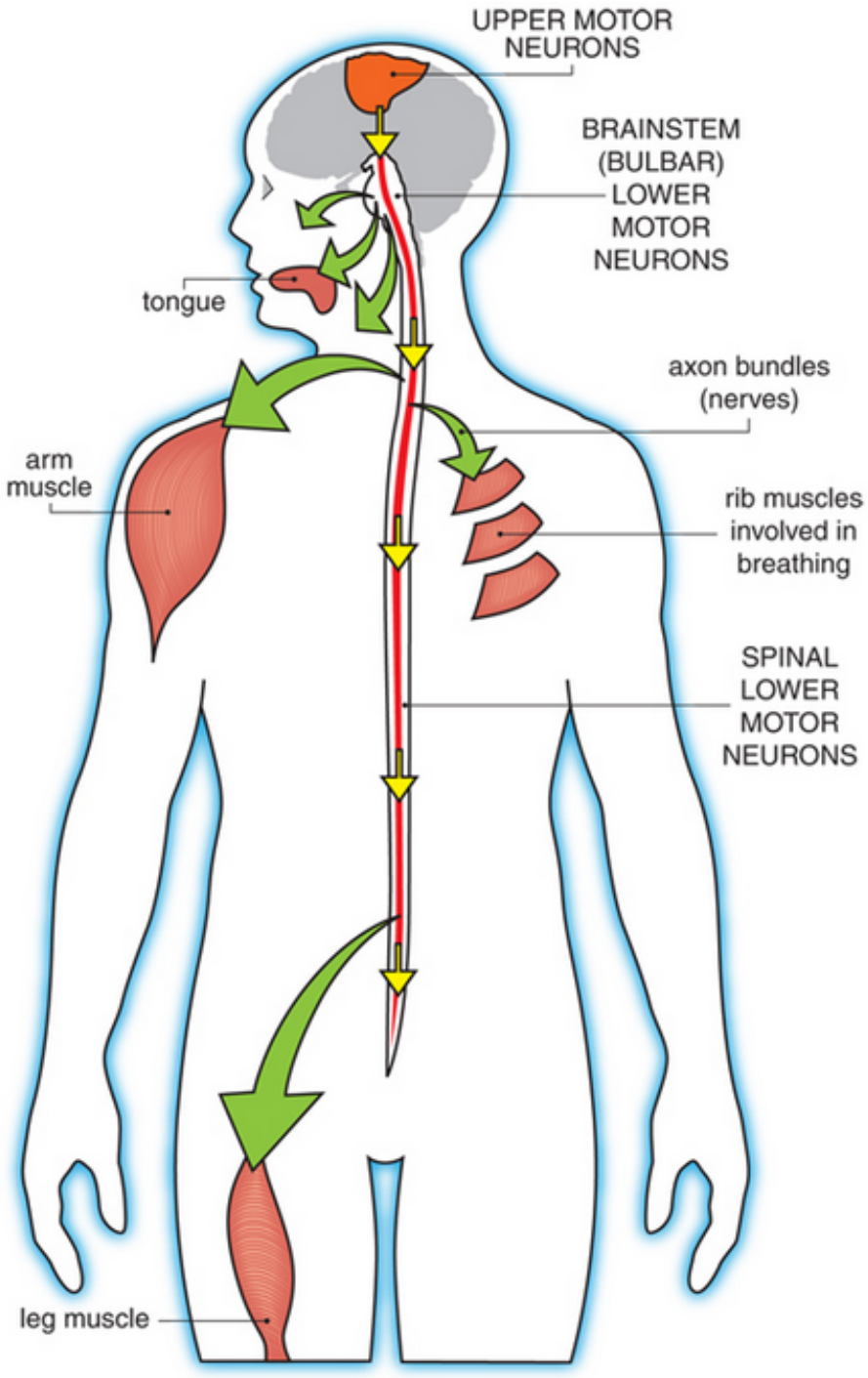
Taylor & Francis
Taylor & Francis Group

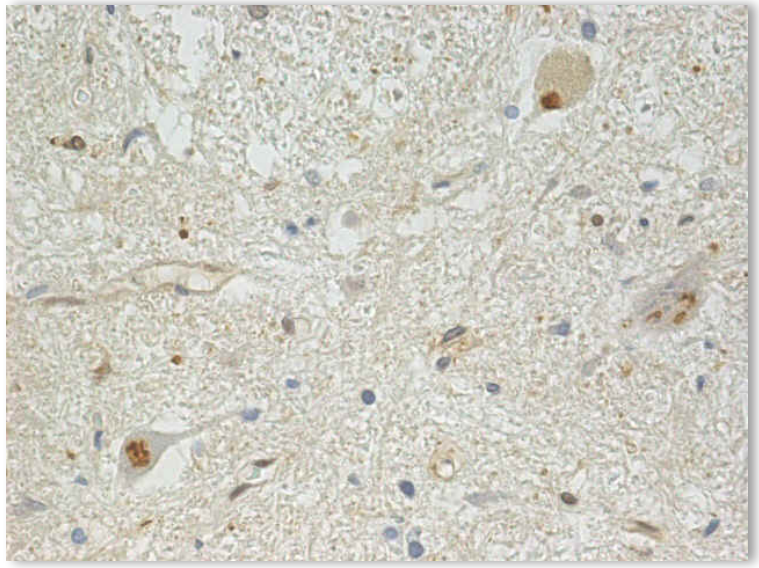
Expert Review of Neurotherapeutics

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/iern20

Is it accurate to classify ALS as a neuromuscular disorder?

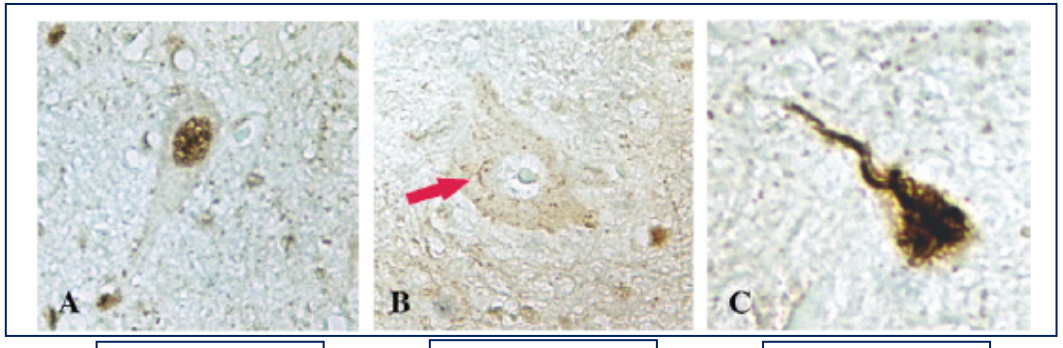
Michael A. van Es , H. Stephan Goedee , Henk-Jan Westeneng , Tanja C.W. Nijboer & Leonard H. van den Berg





From Maria Teresa Giordana – Neuropathology Turin Lab

Strong et al, *Mol Cell Neurosci* 2007



Control | ALS | ALS

JAMA Neurology | Original Investigation

Secular Trends of Amyotrophic Lateral Sclerosis
The Piemonte and Valle d'Aosta Register

Adriano Chiò, MD; Gabriele Mora, MD; Cristina Moglia, MD, PhD; Umberto Manera, MD; Antonio Canosa, MD, PhD; Stefania Cammarosano, MD, PhD; Antonio Ilardi, MD; Davide Bertuzzo, MD; Enrica Bersano, MD; Paolo Cugnasco; Maurizio Grassano, MD; Fabrizio Pisano, MD; Letizia Mazzini, MD; Andrea Calvo, MD, PhD; for the Piemonte and Valle d'Aosta Register for ALS (PARALS)

JAMA Neurology September 2017 Volume 74, Number 9

Table 1. Demographic and Clinical Characteristics of Patients With ALS in the Two 10-Year Periods[a]

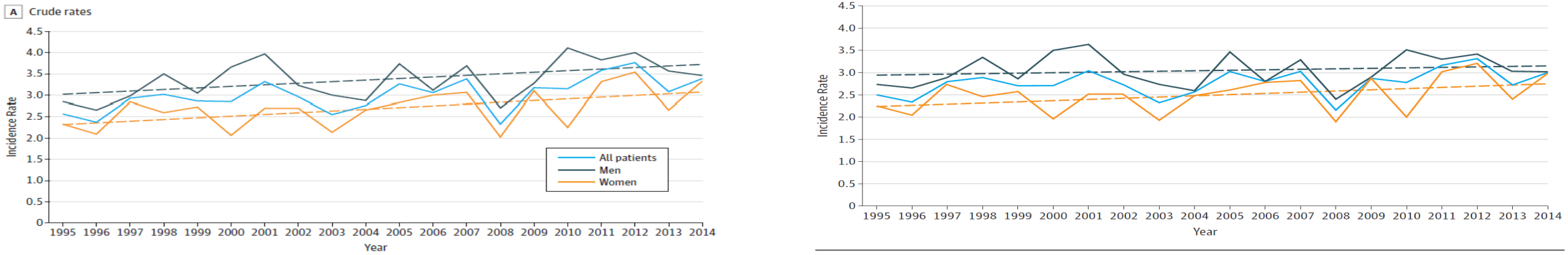
Characteristic	1995-2004 (n = 1243)	2005-2014 (n = 1459)	*P* Value
Male	678 (54.5)	778 (53.3)	.54
Age at onset, mean (SD), y	65.0 (11.1)	66.3 (11.1)	.002
Diagnostic delay, mean (SD), mo	11.3 (9.6)	10.9 (10.3)	.01
Bulbar onset	465 (37.4)	508 (34.8)	.17
Familial ALS	53 (4.3)	110 (7.5)	<.001
Followed by an ALS multidisciplinary center	601 (48.4)	1154 (79.1)	<.001

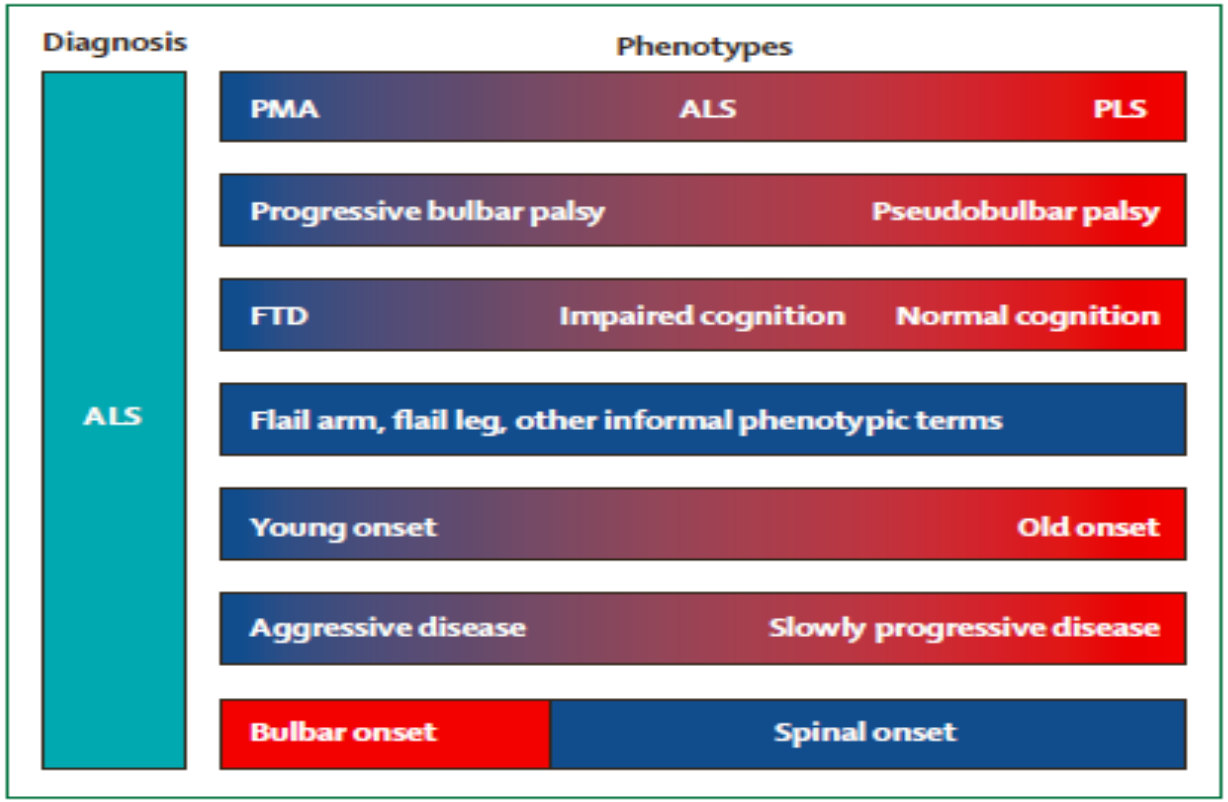
Incidence: **3.2/100,000**

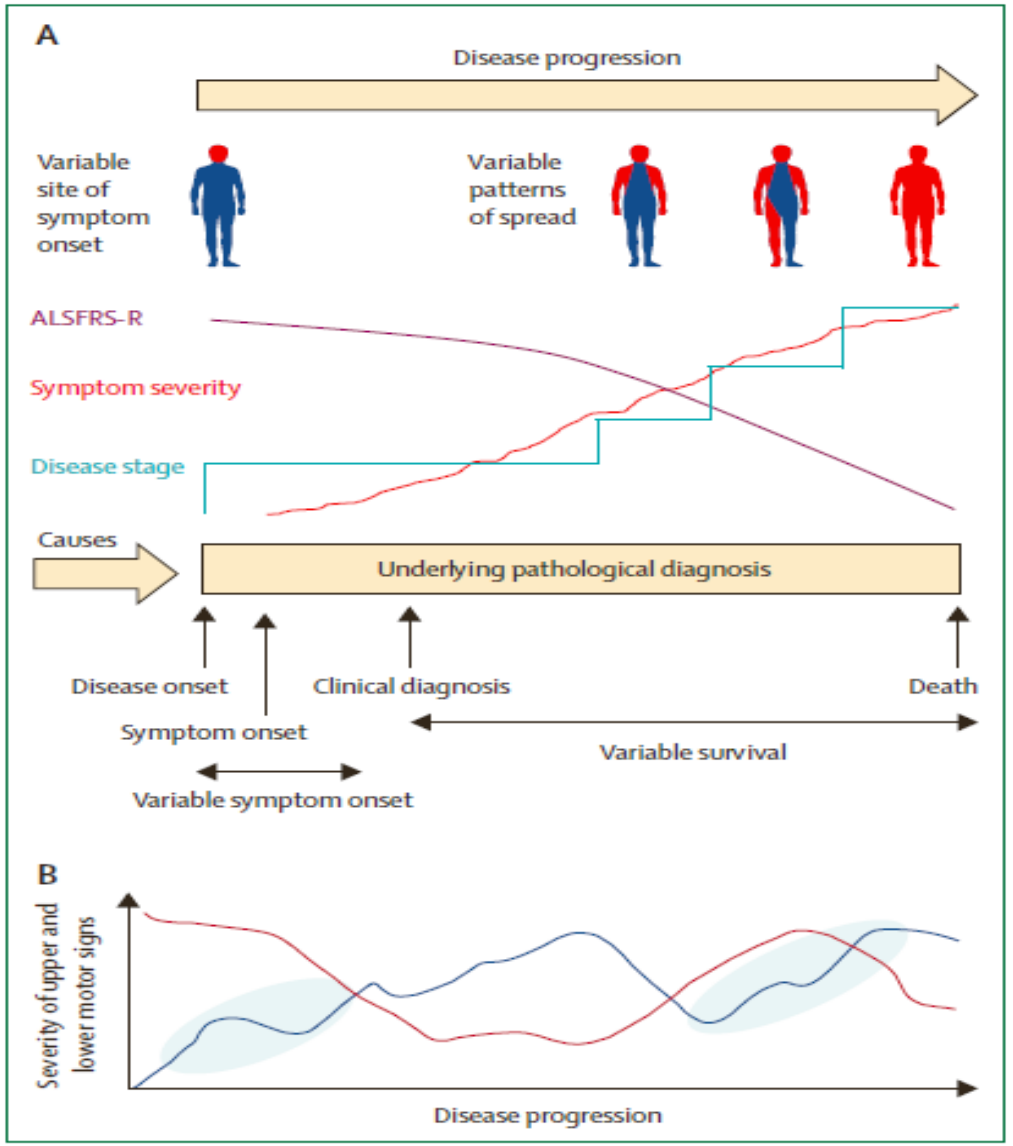
Prevalence **10.5/100,000**

Prevalence including tracheostomized patients: **12.3/100,000**

Figure 1. Incidence Rates During the 20-Year Study







Al-Chalabi et al, Lancet Neurol 2016

Panel 1: Potential reasons for negative results from amyotrophic lateral sclerosis randomised controlled trials*

1 Rationale

- Relevance of SOD
- Interpretation of
- Overall rationale i

2 Pharmacology

- Interaction with r
- Dose too low[23,26,33]
- Broad pharmacol
- Pharmacokinetic i
- ~~Pharmacodynami~~
- Poor CSF penetrat
- Biomarker relevance[26]

3 Design and methodological issues

- Expected effect sizes were too high[24–26]
- Disease at enrolment was already too advanced[30]
- Two primary endpoints caused confounding[22]
- Study period was too short[30]
- Disease diversity or heterogeneity[23]
- Imbalance of enrolled patients[27]
- Need for different phase 2 study[23,25]
- Patient population differed from phase 2 study[45]
- Patient diagnostic changed during enrolment[46]
- Off-label drugs are easily available to anyone (placebo)[24]

ARTICLE OPEN ACCESS

Revised Airlie House consensus guidelines for design and implementation of ALS clinical trials

Leonard H. van den Berg, MD, PhD, Eric Sorenson, MD, Gary Gronseth, MD, Eric A. Macklin, PhD, Jinsy Andrews, MD, Robert H. Baloh, MD, PhD, Michael Benatar, MD, PhD, James D. Berry, MD, Adriano Chio, MD, Philippe Corcia, MD, PhD, Angela Genge, MD, Amelie K. Gubitz, PhD, Catherine Lomen-Hoerth, MD, PhD, Christopher J. McDermott, MD, Erik P. Pioro, MD, PhD, Jeffrey Rosenfeld, MD, PhD, Vincenzo Silani, MD, Martin R. Turner, MBBS, PhD, Markus Weber, MD, Benjamin Rix Brooks, MD, Robert G. Miller, MD, and Hiroshi Mitsumoto, MD, DSc, for the Airlie House ALS Clinical Trials Guidelines Group

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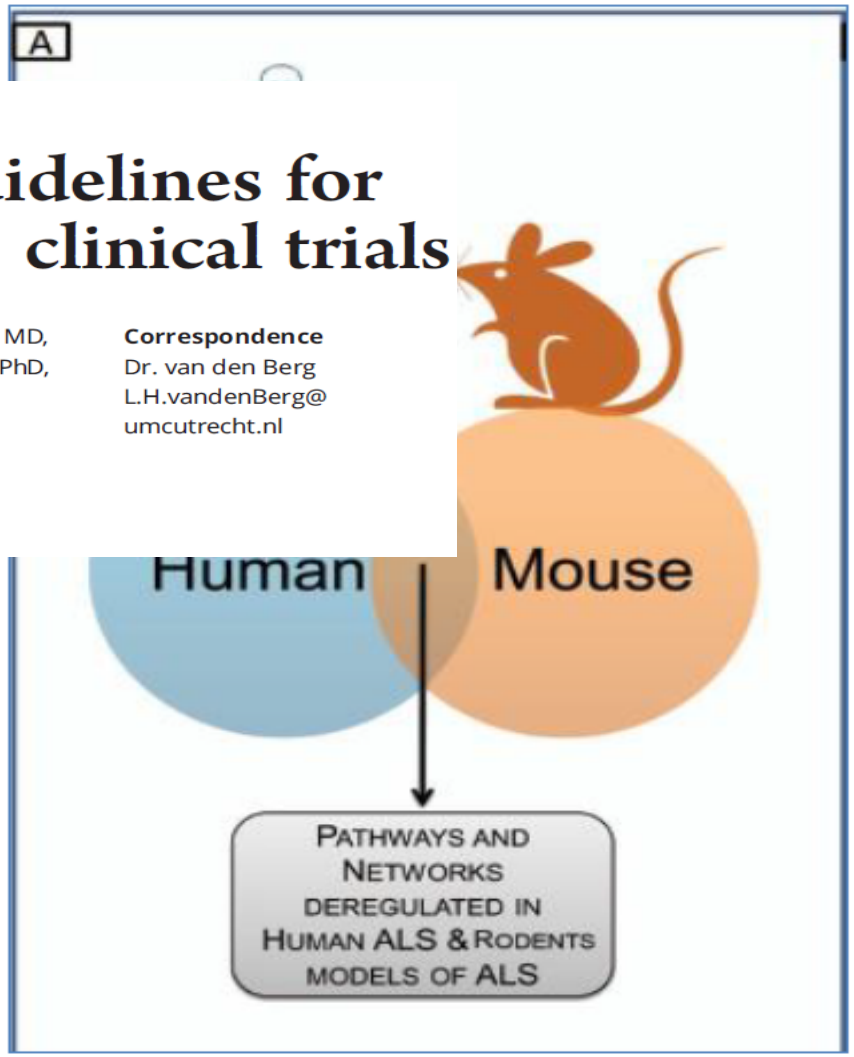
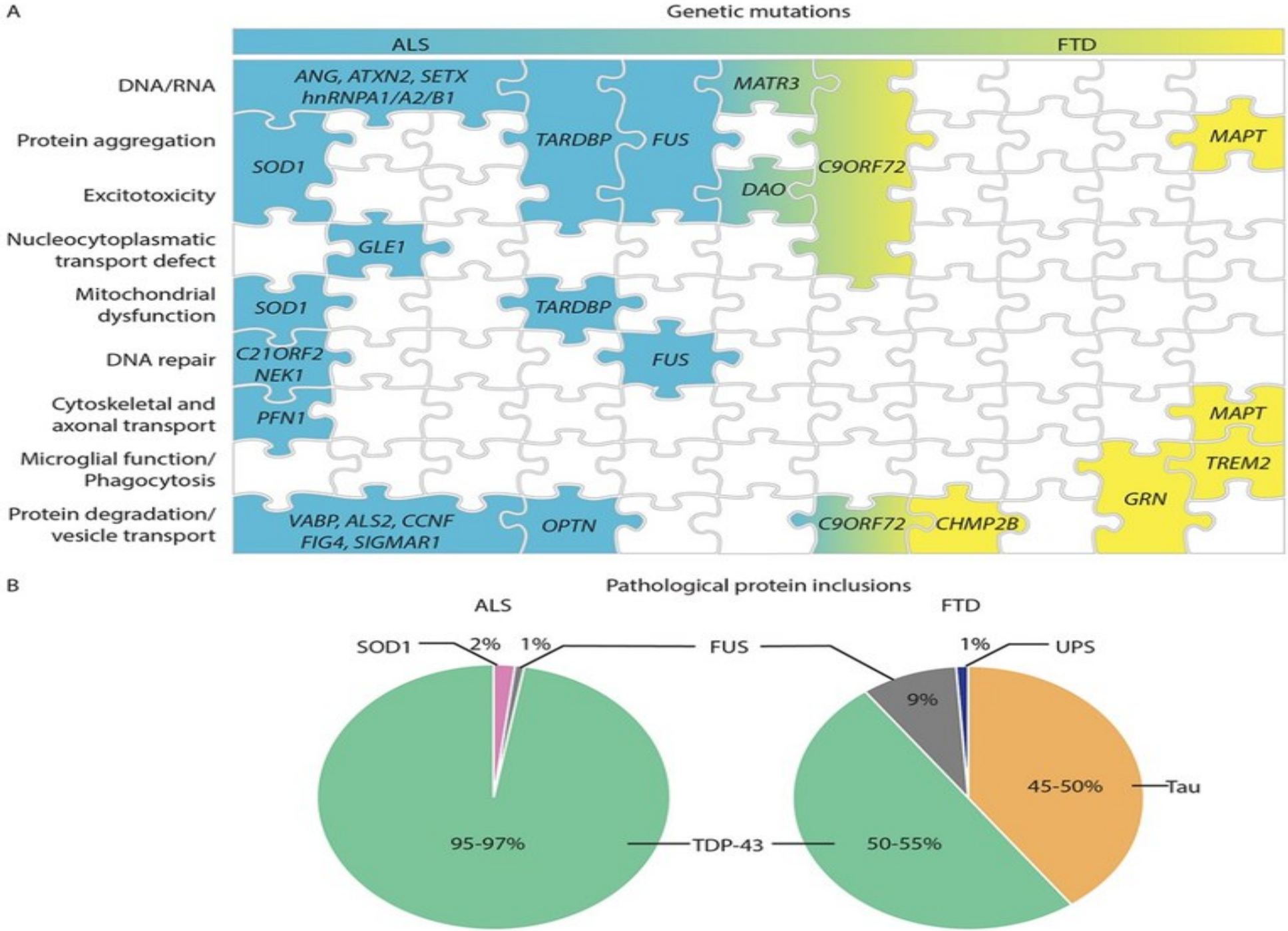
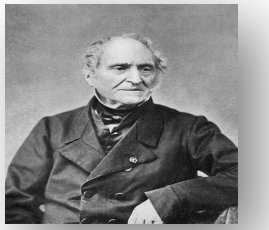
Neurology® 2019;92:e1-e14. doi:10.1212/WNL.0000000000007242



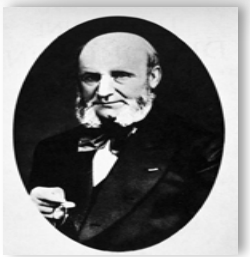
Mitsumoto et al., Lancet Neurol 2014


A
Genetic mutations
ALS
FTD
DNA/RNA
Protein aggregation
Excitotoxicity
Nucleocytoplasmatic transport defect
Mitochondrial dysfunction
DNA repair
Cytoskeletal and axonal transport
Microglial function/ Phagocytosis
Protein degradation/ vesicle transport
ANG, ATXN2, SETX
hnRNPA1/A2/B1
MATR3
TARDBP
FUS
SOD1
C9ORF72
DAO
MAPT
GLE1
SOD1
TARDBP
C21ORF2
NEK1
FUS
PFN1
MAPT
TREM2
GRN
VABP, ALS2, CCNF
FIG4, SIGMAR1
OPTN
C9ORF72
CHMP2B
B
Pathological protein inclusions
ALS
FTD
SOD1
2%
1%
FUS
1%
UPS
9%
45-50%
Tau
95-97%
TDP-43
50-55%

From splitt to lump



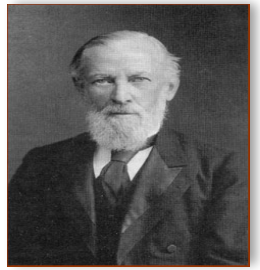
Aran 1850:
PMA



Duchenne 1860: PBP

Charcot 1869: ALS

Erb 1875: PLS



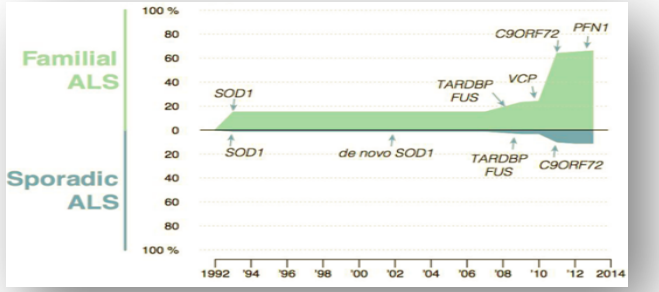
Gowers 1892:
Motor system
degeneration

Brain 1933:
Motor neuron disease

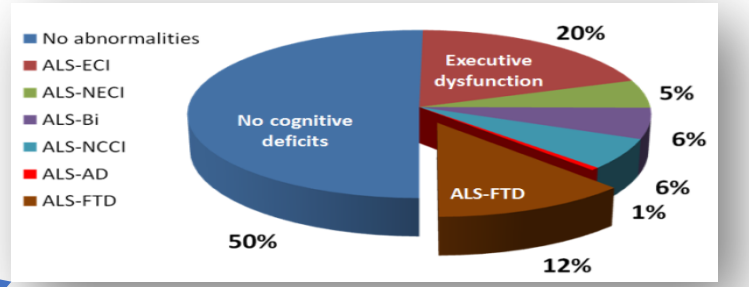
From lump to splitt

Brain 1933:
Motor neuron disease

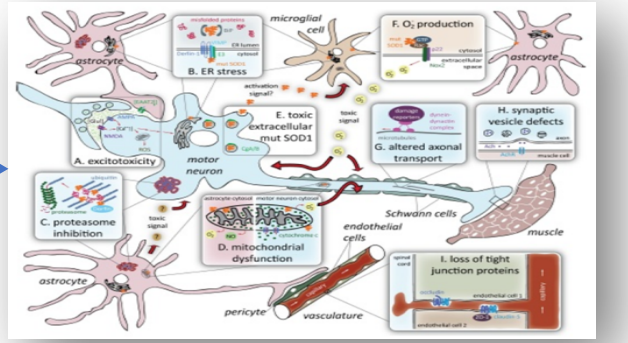
Genetic heterogeneity



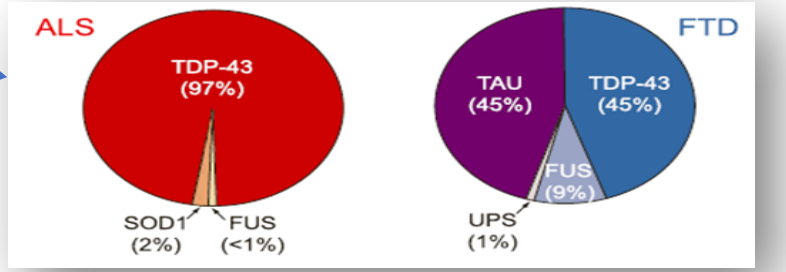
Cognitive heterogeneity



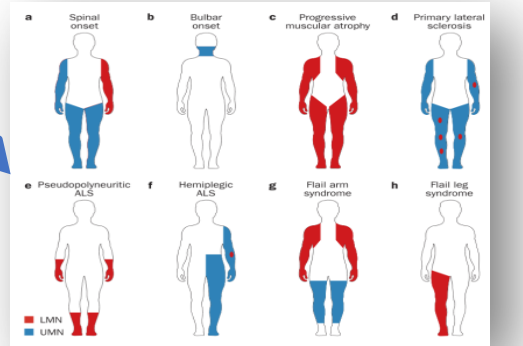
Pathogenic heterogeneity



Pathologic heterogeneity



Phenotypic heterogeneity

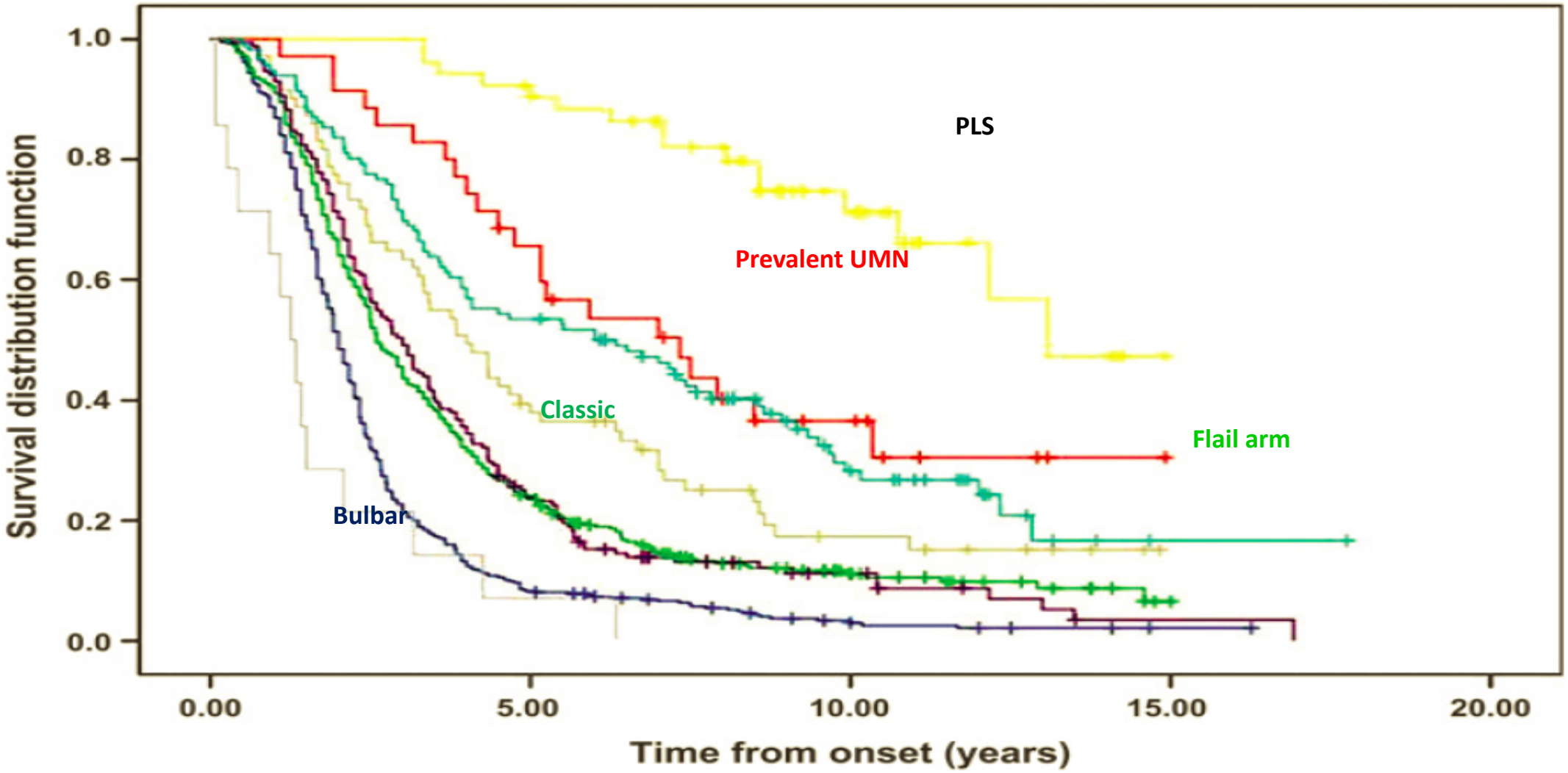


Research paper

Phenotypic heterogeneity of amyotrophic lateral sclerosis: a population based study

Adriano Chiò,[1,2] Andrea Calvo,[1] Cristina Moglia,[1] Letizia Mazzini,[3] Gabriele Mora,[4] PARALS study group*

J Neurol Neurosurg Psychiatry 2011;**82**:740—746.



Caratteristiche cliniche della compromissione cognitivo-comportamentale nella SLA

- Fluenza verbale
- Flessibilità
- Attenzione
- Working memory

- Linguaggio
- Funzione visuopercettiva

- Disturbo del comportamento (soprattutto apatia)

	Patients (n)	Neuropsychological test performance that showed impairment	Neuropsychological test performance in the normal range
Gallassi, 1985[38]	22	Verbal fluency (COWA), verbal reasoning, visual attention (Barrage test), short-term verbal memory (Rey's), short-term visual recall	Long-term verbal memory (Rey's), memory spans (verbal and spatial)
David, 1986[43]	14	Set shifting (WCST), episodic memory (VPAL), picture recall	Attention (digit span), visual recall (RCFT), prose recall
Neary, 1990[44]	4	Verbal fluency (letter and category), set shifting (WCST and WBT), intelligence (WAIS-R), interpretation of proverbs, episodic memory (VPAL)	Visuoperception (Money road map), intelligence (KBF), memory (Warrington memory test), delayed verbal recall
Kew, 1993[36] Kew, 1993[35]	12 16	Verbal fluency (written), free picture recall, recall memory (KOLT)	Cognitive inhibition (Stroop), recognition memory, visuoperceptual battery, set shifting (WCST), episodic memory (VPAL)
Ludolph, 1992[33]	18	Verbal fluency	Set shifting (WCST), cognitive inhibition (Stroop), visual recall (RCFT), attention (digit span), naming (modified test), visual concentration (d2 test)
Massman, 1996[45]	146	Verbal fluency (COWA), immediate free recall (CVLT), continuous recognition memory (CRMT, major deficiency in some patients), attention (VSAT), set shifting (WCST)	Delayed verbal recognition memory (CVLT), visuoperception (Benton JLO), confrontation naming (BNT)
Abrahams, 1997[46]	52	Verbal fluency (written), executive function and intrinsic generation (RMJT; noted in pseudobulbar palsy only), planning and working memory (CTH), set shifting (WCST), word recognition memory test, Stroop negative priming (trend towards significance)	Episodic memory (VPAL), recall memory (KOLT)
Rakowicz, 1998[47]	18	Verbal fluency, attention (reverse digit span), conceptual semantic processing (pyramids and palm trees test), syntactic comprehension (TROG), MMSE, confrontation naming (graded naming test)	Attention (forward digit span), picture naming, word-picture matching
Moretti, 2002[48]	14	Verbal fluency (letter), set shifting (WCST), cognitive inhibition (Stroop), attention (PASAT), interpretation of proverbs, bilingual, aphasia test–B, MMSE	Intellectual ability (RSPM, WAIS-R, KBF), attention (digit span), story retrieval, past events retrieval, visuoperception (JLO)
Abrahams, 2005[49]	20	Verbal fluency (written and spoken), computerised sentence-completion task	Confrontation naming (graded naming test), fluency (category and design), attention (PASAT, letter span), set shifting (WCST), episodic memory (VPAL), recognition memory test, recall memory (KOLT), visuoperception (Benton JLO), object decision, position discrimination
Ringholz, 2005[50]	279	Verbal fluency, VSAT, visual recall, logical memory (verbal recall), confrontation naming (BNT)	Visuoperceptual ability (Benton facial recognition test), MMSE (except severely impaired patients), cognitive inhibition (Stroop)

COWA=controlled oral word association test. WCST=Wisconsin card-sorting test. VPAL=verbal paired associate learning. RCFT=Rey complex figure test. WBT=Weigl's block task. KBF=Koh's block figures. WAIS-R=Weschler adult intelligence scale. KOLT=Kendrick object learning task. CVLT=California verbal learning test. CRMT=continuous recognition memory test. VSAT=verbal series attention test. JLO=judgment of line orientation. BNT=Boston naming test. RMJT=random movement joystick test. CTH=computerised Tower of Hanoi test. TROG=test for the reception of grammar. MMSE=mini mental state examination. PASAT=paced auditory serial addition test. RSPM=Raven's standard progressive matrices.

Table 3: **Neuropsychological test performance in ALS**

Pukhan et al, Lancet Neurology 2007

I criteri per la diagnosi dei disturbi cognitivo-comportamentali nella SLA

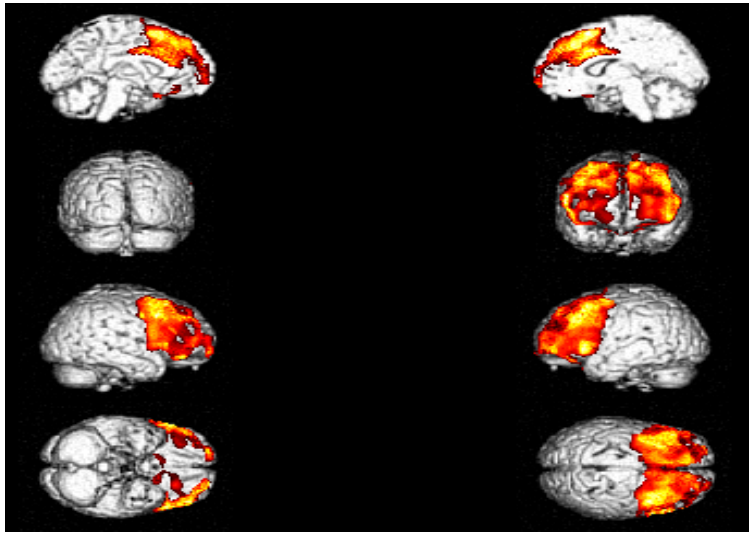
ALS-Bi	Apatia *OPPURE* almeno due fra i sintomi elencati fra i criteri di Raskovsky et al (Brain 2011)
ALS-Ci	Disturbo disesecutivo *OPPURE* disturbo del linguaggio
ALS-CBi	Presenza dei criteri sia di ALS-Bi sia di ALS-Ci
ALS-FTD	Evidenza di deterioramento progressivo del comportamento o della cognizione mediante osservazione o storia clinica *E* 1. Almeno 3 fra i sintomi cognitivi elencati fra i criteri di Raskovski et al (Brain 2011) *OPPURE* 2. Sintomi cognitivi/comportamentali, associati a perdita di insight e/o sintomi psicotici *OPPURE* 3. Sintomi compatibili con demenza semantica/variante semantica di PPA o variante non fluente di PPA
ALS-demenza	SLA associata ad AD o a demenza vascolare

Strong et al, ALS 2017

Original research

Metabolic brain changes across different levels of cognitive impairment in ALS: a ^{18}F-FDG-PET study

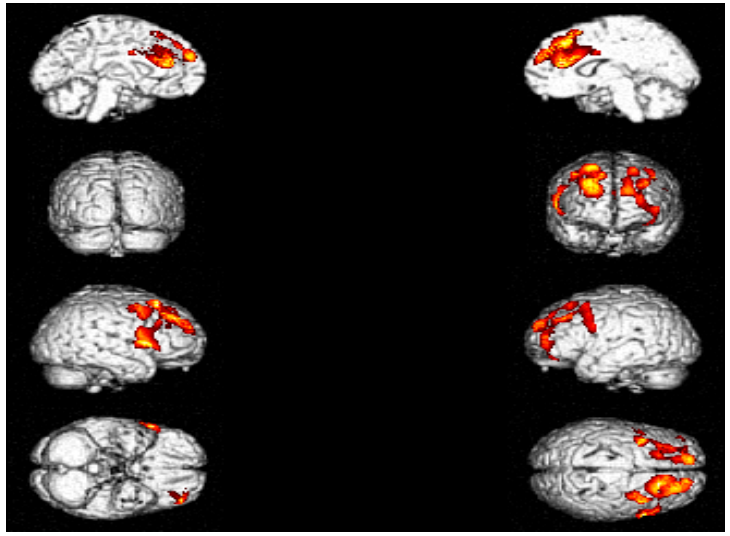
Antonio Canosa ,[1,2] Cristina Moglia,[1,2] Umberto Manera,[1] Rosario Vasta ,[1] Maria Claudia Torrieri,[1] Vincenzo Arena,[3] Fabrizio D'Ovidio ,[1] Francesca Palumbo,[1] Jean Pierre Zucchetti,[1] Barbara Iazzolino,[1] Laura Peotta,[1] Andrea Calvo ,[1,2,4] Marco Pagani,[5,6] Adriano Chiò[1,2,4,5]



ALS-FTD

(P<0.001 uncorrected

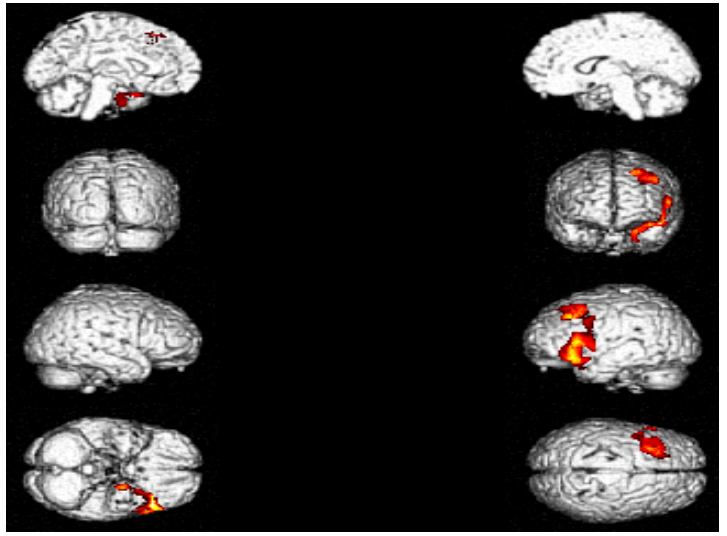
P<0.05 FWE-corrected)



ALS-Cbi

(P<0.001 uncorrected

P<0.05 FWE-corrected)



ALS-Ci

(P<0.005 uncorrected

P<0.05 FWE-corrected)

J Neurol Neurosurg Psychiatry 2021;**92**:357–363. doi:10.1136/jnnp-2020-323876

ARTICLE

Cognitive impairment across ALS clinical stages in a population-based cohort

Adriano Chiò, MD, FAAN, Cristina Moglia, MD, PhD, Antonio Canosa, MD, PhD, Umberto Manera, MD, Rosario Vasta, MD, Maura Brunetti, BSc, Marco Barberis, BSc, Lucia Corrado, PhD, Sandra D'Alfonso, PhD, Enrica Bersano, MD, Maria Francesca Sarnelli, PsyD, Valentina Solara, PsyD, Jean Pierre Zucchetti, MS, Laura Peotta, PsyD, Barbara Iazzolino, PsyD, Letizia Mazzini, MD,* Gabriele Mora, MD,* and Andrea Calvo, MD, PhD*

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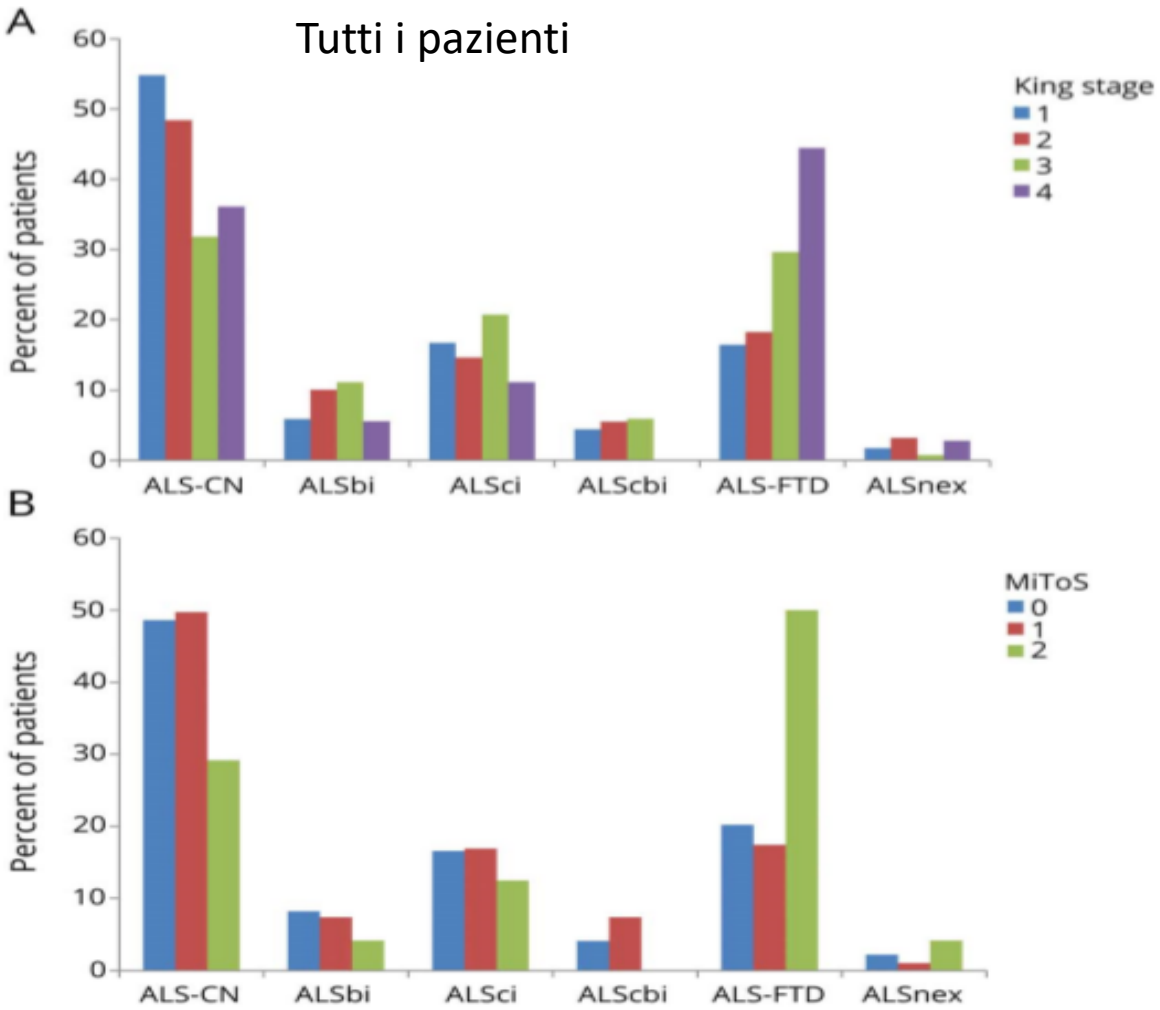
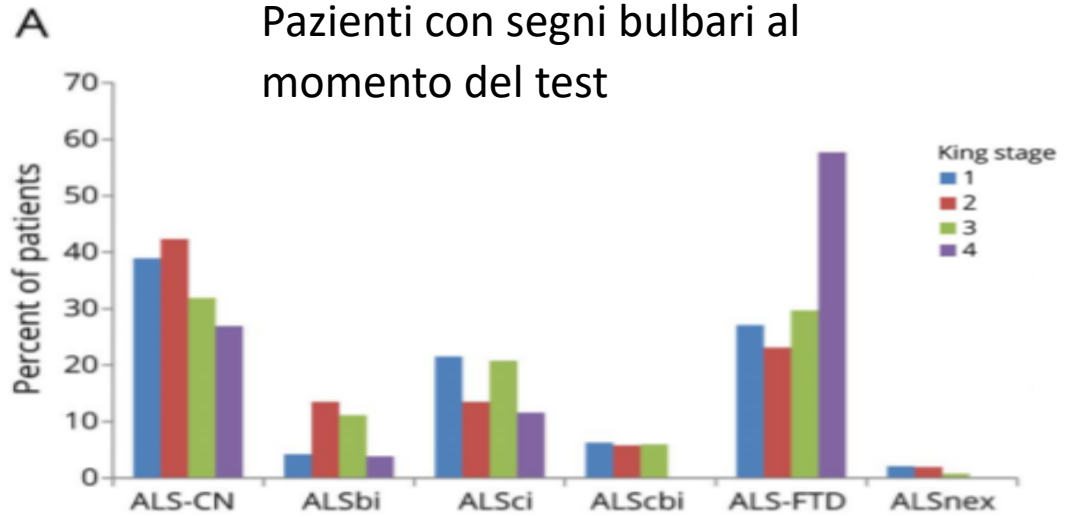
Neurology® 2019;93:e984-e994. doi:10.1212/WNL.0000000000008063

Tutti i pazienti

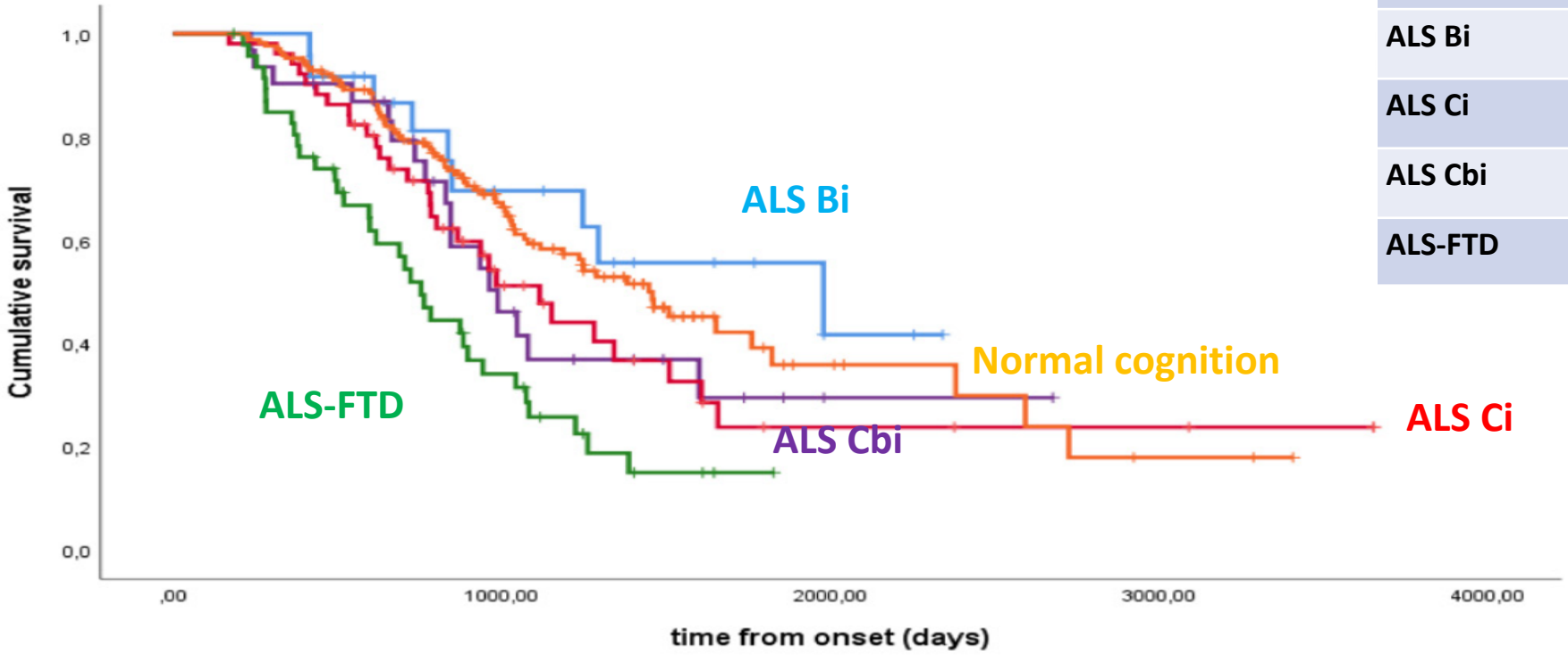


Pazienti con segni bulbari al momento del test



Pazienti senza segni bulbari al momento del test

Influenza dei disturbi cognitivo- comportamentali sulla prognosi della SLA



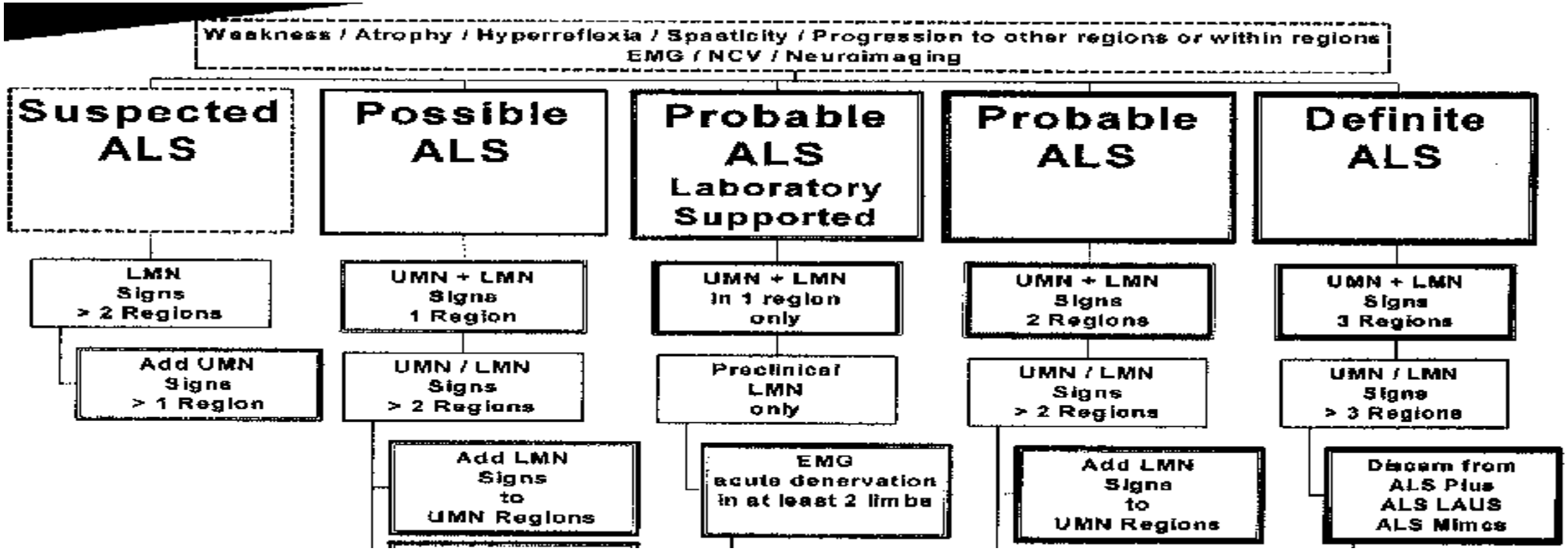
Fenotipo	Sopravvivenza mediana (anni)
CN	**4.0** (3.2-4.8)
ALS Bi	**5.4** (1.4-9.4)
ALS Ci	**3.1** (2.3-3.8)
ALS Cbi	**2.7** (2.1-3.3)
ALS-FTD	**2.1** (1.7-2.4)

Iazzolino et al, J Neurol Neurosurg Psychiatry 2019

ALS diagnosis: facts

- In the absence of a diagnostic biomarker, diagnostic criteria have been established based on the identification of UMN and LMN signs found in the neurological examination and the progressive nature of the disease.
- The El Escorial criteria were established in 1990 and revised in Airlie House in 1999 to allow classification of patients into categories of diagnostic certainty. They have proven to be specific for the diagnosis of ALS.
- Diagnosis is usually easy in advanced stages , whereas in the early phase, misdiagnosis of ALS remains a common clinical problem due to ALS clinically heterogeneity. The site of onset varies greatly and neurological signs can be limited to focal regions or be the result of a UMN or LMN lesion only.
- An alternative diagnosis can be found in up to 10% of patients who are initially diagnosed with ALS. The failure of symptoms to progress is the most common reason for diagnostic revision.

Revised El Escorial criteria (Brooks et al. ALS 2000)



Lower Motor Neuron and Upper Motor Neuron Signs in Four CNS Regions

Revised El Escorial criteria , Brooks 2000;

	Brainstem	**Cervical**	**Thoracic**	**Lumbosacral**
Lower motor neuron signs weakness, atrophy, fasciculations	jaw, face, palate, tongue, larynx	neck, arm, hand, diaphragm	back, abdomen	back, abdomen, leg, foot
Upper motor neuron signs pathologic spread of reflexes, clonus, etc.	clonic jaw gag reflex exaggerated snout reflex pseudobulbar features forced yawning pathologic DTR's spastic tone	clonic DTR's Hoffman reflex pathologic DTR's spastic tone preserved reflex in weak wasted limb	loss of superficial abdominal reflexes pathologic DTR's spastic tone	clonic DTR's - extensor plantar response pathologic DTR's spastic tone preserved reflex in weak wasted limb

El Escorial - R (1998) for neurophysiological diagnosis

- Conventional EMG study: Needle EMG signs of active or chronic denervation including fasciculations and fibrillations. Nerve conduction studies are also needed to rule out motor neuropathy.
  - ***Signs of active denervation: fibrillation potentials; positive waves***
  - ***Signs of chronic denervation: motor unit potentials of great amplitude, with increased duration and increased percentage of polyphasic potentials; reduced interference pattern with discharge frequency greater than 10 Hz, except in the presence of unstable PUMs, in which case the discharge frequency may be less than 10 Hz; unstable motor unit potentials.***
- Presence of EMG signs of LMN involvement in at least 2 regions of the CNS among the following 4: trunk, cervical, thoracic or lumbosacral. For the trunk it is sufficient to demonstrate the damage in a muscle. For the thoracic region it is sufficient to demonstrate damage in the paraspinal muscles or in the abdominal muscles. For the cervical and lumbosacral regions, at least two muscles innervated by different roots and peripheral nerves are sufficient.

Neuropysiological Criteria

El Escorial criteria revised, 1998:

1. Signs of active denervation
2. Signs of chronic denervation

Electrophysiological features that ***support*** the identification of ***possible*** primary LMN degeneration include one or more of the following:

(1) either reduced recruitment, large motor unit potentials, fibrillation potentials or unstable motor unit potentials alone,

(2) polyphasic motor unit potentials or increased single fiber density alone,

(3) low amplitude motor unit potentials if the disease duration is over 5 years or if there is associated atrophy,

(4) low amplitude compound muscle action potentials,

(5) compound muscle action potential change between proximal and distal sites of stimulation that is uniform along the length of the nerve,

(6) up to 30% decrement in motor conduction velocity below established normal values if a low amplitude compound muscle action potential greater than 10 percent of normal is present,

(7) up to 50% decrement in motor conduction velocity below established normal values if the compound muscle action potential is below 10% of normal,

(8) up to 20% decrement of the compound muscle action potential on 2 Hz repetitive stimulation,

(9) up to 10% decrement in sensory nerve conduction velocity and action potential amplitude from established normal values,

(10) complex repetitive discharges,

(11) absence of fasciculations.

Exclusion Criteria

Criteri di El Escorial rivisti, 1998

Electrophysiological features suggesting other disease processes include:

1. Evidence of motor conduction block.
2. Motor conduction velocities lower than 70%, and distal motor latencies over 30%, of the lower and upper limit of normal values, respectively.
3. Sensory nerve conduction studies that are abnormal. Entrapment syndromes, peripheral neuropathies and advanced age may render sensory nerve action potentials difficult to elicit in the lower extremities.
4. F-wave or H-wave latencies more than 30% above established normal values.
5. Decrements greater than 20% on repetitive stimulation.
6. Somatosensory evoked response latency greater than 20% above established normal values.

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Review

Electrodiagnostic criteria for diagnosis of ALS ☆

Mamede de Carvalho [a], Reinhard Dengler [b], Andrew Eisen [c], John D. England [d], Ryuji Kaji [e], Jun Kimura [f], Kerry Mills [g], Hiroshi Mitsumoto [h], Hiroyuki Nodera [i], Jeremy Shefner [j], Michael Swash [k,*]

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[i] *Department of Neurology, Tokushima University, Tokushima-city, Japan*
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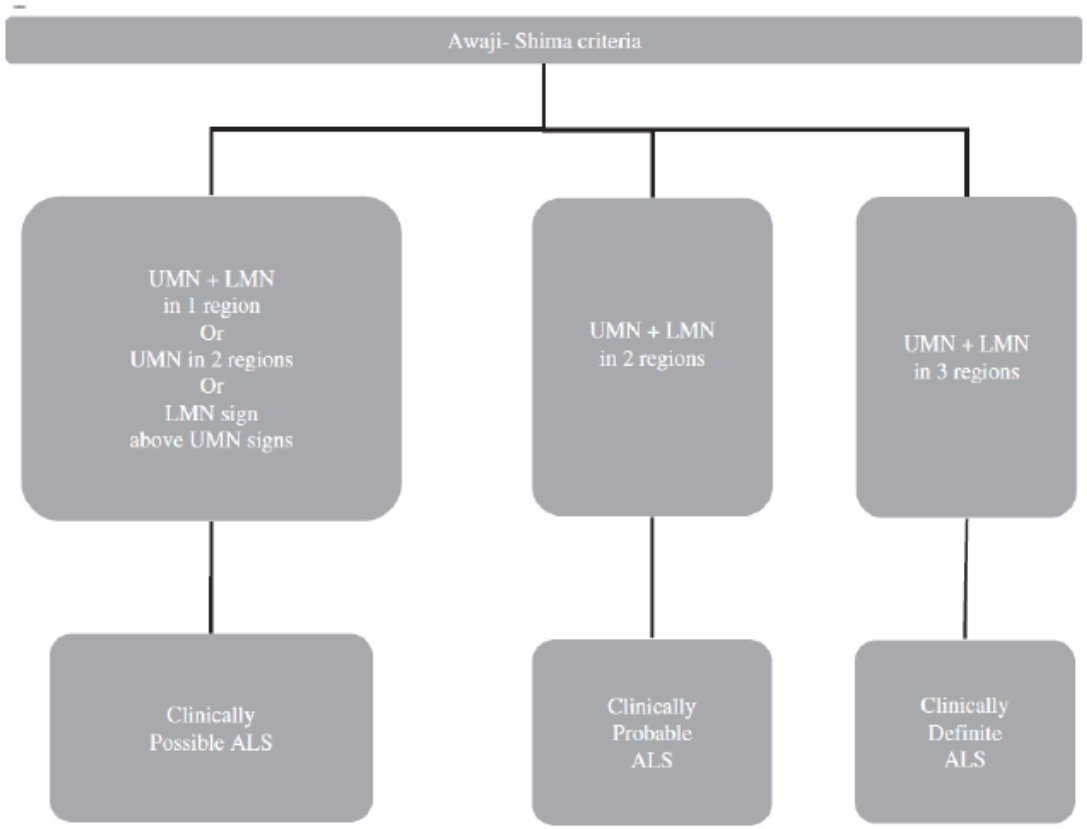
Revised El Escorial vs Awaji-Shima Criteria



The assessment of UMN dysfunction, however, remains clinically based.

1. electrophysiological and clinical signs of LMN degeneration have equal weight in the decision as to which diagnostic category the patient is assigned.
2. R-EEC do not allow EMG and clinical abnormalities to be combined in a single limb. The AC, by accepting neurogenic EMG abnormality as equal to clinical abnormality, allow a currently strong limb to be classified as abnormal earlier than if the decision was based on EMG or clinical signs alone.
3. Laboratory supported probable ALS category is redundant
4. EMG evidence of LMN involvement = signs of both active and chronic denervation (in 2 muscles of C and LS regions and in 1 muscles in T and B regions):
   - Chronic denervation: long-duration, large-amplitude, polyphasic, unstable MUP and decreased MU recruitment.
   - Active denervation: PSW and Fib potentials. Unstable, complex fasciculation potentials in the presence of unstable MUP in the context of suspected ALS are an evidence of acute denervation, equivalent to Fib and PSW

Awaji consensus

1. *Electrodiagnostic (Edx) and clinical data* are of equal and interchangeable value in diagnosing ALS
2. *In the presence of signs of partial denervation*, Fasciculation potentials (preferably of complex morphology) are equivalent to fibs-psw, indicating ongoing denervation.
3. *Unstable MUPs & FPs* are especially relevant

Amyotrophic Lateral Sclerosis. 2009; 10: 53–57

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ORIGINAL ARTICLE

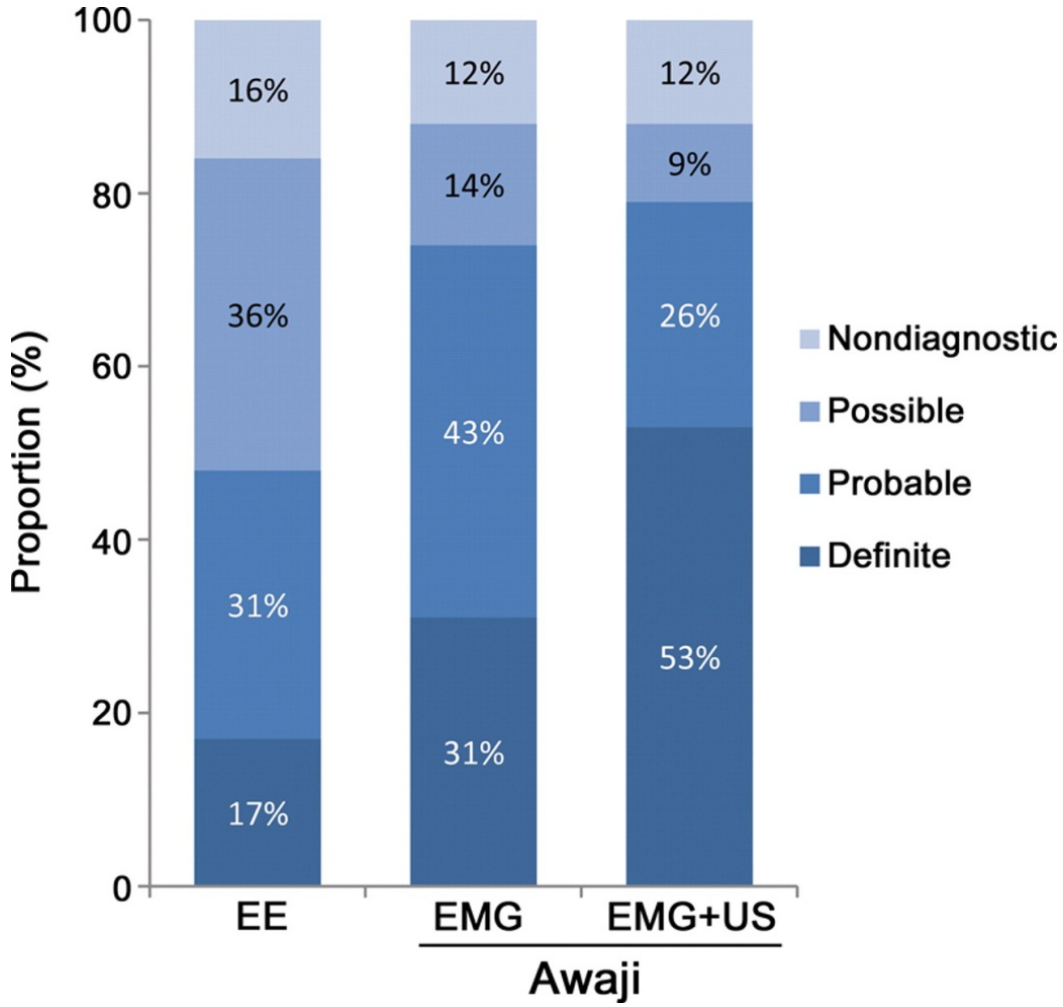
Awaji diagnostic algorithm increases sensitivity of El Escorial criteria for ALS diagnosis

MAMEDE DE CARVALHO[1] & MICHAEL SWASH[1,2]

[1]*Hospital of Santa Maria and Instituto de Medicina Molecular -Faculty of Medicine, University of Lisbon, Lisbon, Portugal, and* [2]*The Royal London Hospital and Queen Mary School of Medicine, University of London, London, UK*

Abstract
We have tested the sensitivity of a recently published approach to combining clinical and EMG data in the 'research diagnosis' of ALS, in 55 consecutive patients clinically diagnosed with ALS. The application of this 'Awaji algorithm' to the revised El Escorial diagnostic criteria for diagnosis of ALS achieved a diagnostic sensitivity of 95% for definite ALS compared with 18% using the clinical El Escorial criteria and 53% when the EMG criteria as defined in the El Escorial criteria, were applied to the same dataset. This increased sensitivity was particularly relevant for bulbar onset patients (sensitivity improved from 38% to 87%) and for patients with El Escorial clinically possible ALS (from 50% to 86%). We suggest that, in future, investigators and triallists should use the Awaji algorithm superimposed onto the El Escorial criteria, in selecting patients for research studies.

Awaji effect on diagnostic level



Awaji-Shima vs Revised El Escorial Criteria

An evaluation of neurophysiological criteria used in the diagnosis of motor neuron disease

C P Douglass,[1] R H Kandler,[2] P J Shaw,[3] C J McDermott[3]

J Neurol Neurosurg Psychiatry 2010;**81**:646–649. doi:10.1136/jnnp.2009.197434

Table 2 Sensitivity and specificity of the diagnostic criteria

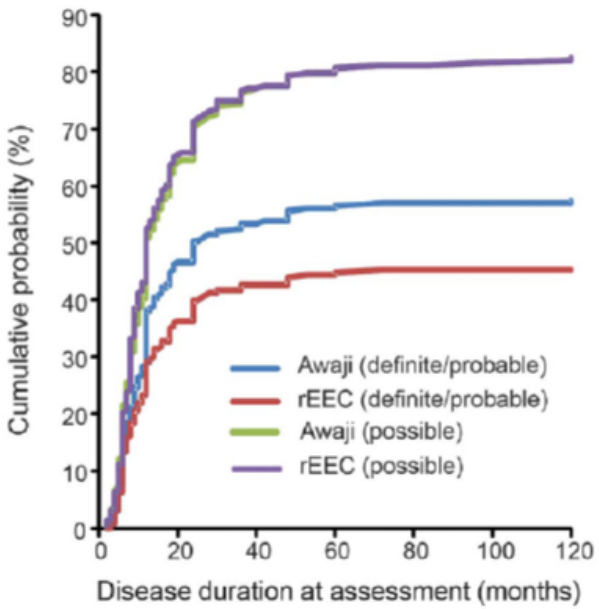
	Sensitivity	Specificity
Pre-EMG diagnosis	27.1%	95.9%
El Escorial criteria	28.0%	95.9%
Awaji Shima criteria	60.7%	95.9%

The increase in sensitivity was evident in patients with bulbar and limb-onset ALS, as well as those with milder functional impairment and shorter disease duration, suggesting a greater role for the Awaji criteria in recruitment of patients with ALS into treatment trials at an early stage in the disease process.

Diagnostic criteria in amyotrophic lateral sclerosis

A multicenter prospective study

Cumulative probability of amyotrophic lateral sclerosis (ALS) diagnosis



12% gain of sensitivity

Nimeshan Geevasinga, Parvathi Menon, Daniel B. Scherman, et al.
Neurology published online July 20, 2016

El Escorial-R and Awaji-Shima Criteria: pros and cons

Usefullness in the clinic

- They emerged to facilitate inclusion of patients into large RCT. Accordingly, they had a greater impact in clinical research than within clinical practice.
- The goal: to standardize steps of the diagnosis, clarification of the complexity of the various clinical features, and to ensure diagnostic certainty.
- With time the need to simplify the criteria (from 5 to 3 classes) arouse without a clear gain regarding either the accuracy of the diagnosis (false-negative: 37% before, 30% after), or diagnostic delay (12 months before, 11 months after)
- The heterogeneity of ALS based on clinical phenotyping is not addressed by these criteria

Clinical trials: early diagnosis and the El Escorial criteria

- Prior to 2010, RCT restricted enrollment to definite, probable, or laboratory-supported probable ALS .
- More recently some trials allowed inclusion of possible ALS. Erroneous diagnosis does not seem to be increased in these trials; only 5/952 enrolled subjects for the study of dexpramipexole were subsequently found to have alternative diagnoses, within the range of previously published trials
- The addition of possible ALS as an inclusion criterion means that subjects with clinical signs limited to one body region are eligible for clinical trials. It is difficult to conceive of a less stringent criterion that would still ensure that patients were appropriately diagnosed. ALS trials prioritize patients with early disease, and given the low diagnostic error rate, it appears that the current criteria meet the needs of clinical trials now
- Exception: genetic ALS

Revised criteria should facilitate the inclusion of specific phenotypes that ultimately reflect the widespread neuro-pathological process.

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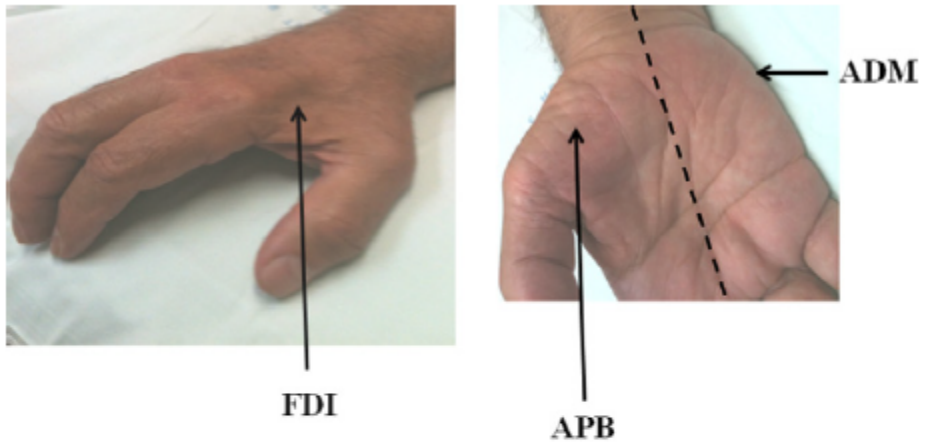
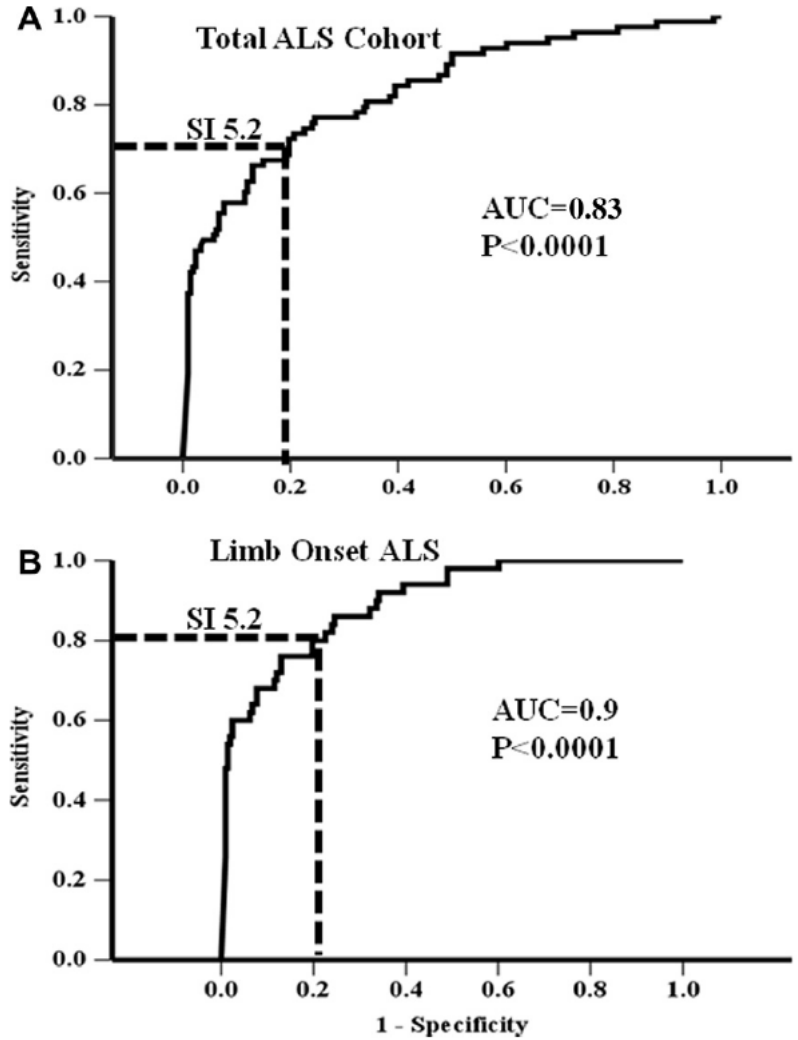
Split-hand index for the diagnosis of amyotrophic lateral sclerosis

Parvathi Menon [a,b], Matthew C. Kiernan [c,d], Con Yiannikas [e,f], Jill Stroud [e], Steve Vucic [a,b,d,*]



$$\textit{Split hand index (SI)} = \frac{CMAP_{APB} * CMAP_{FDI}}{CMAP_{ADM}}$$

Fig. 1. An illustration of the split-hand sign in a patient with amyotrophic lateral sclerosis. Specifically, the split hand sign refers to preferential wasting of the abductor pollicis brevis (APB) and first dorsal interosseous (FDI) muscles in comparison to the abductor digit minimi (ADM). The novel split-hand index is calculated by multiplying the compound muscle action potential (CMAP) amplitude recorded over the APB by that recorded over the FDI and dividing the product by the CMAP amplitude recorded over the ADM.



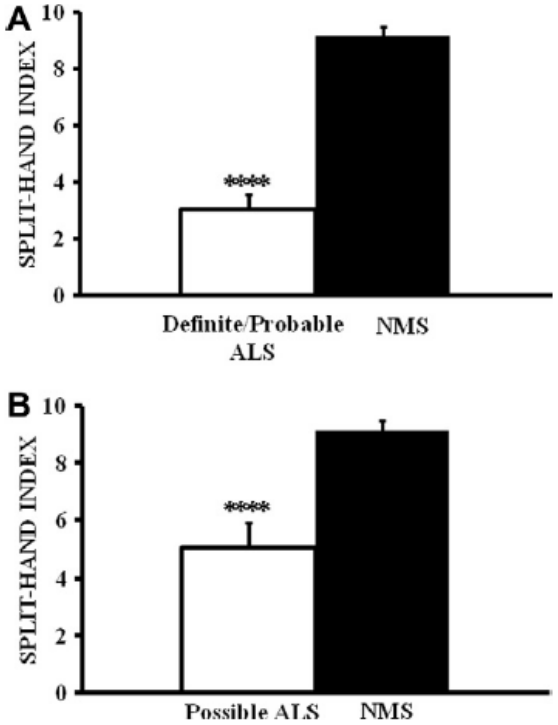
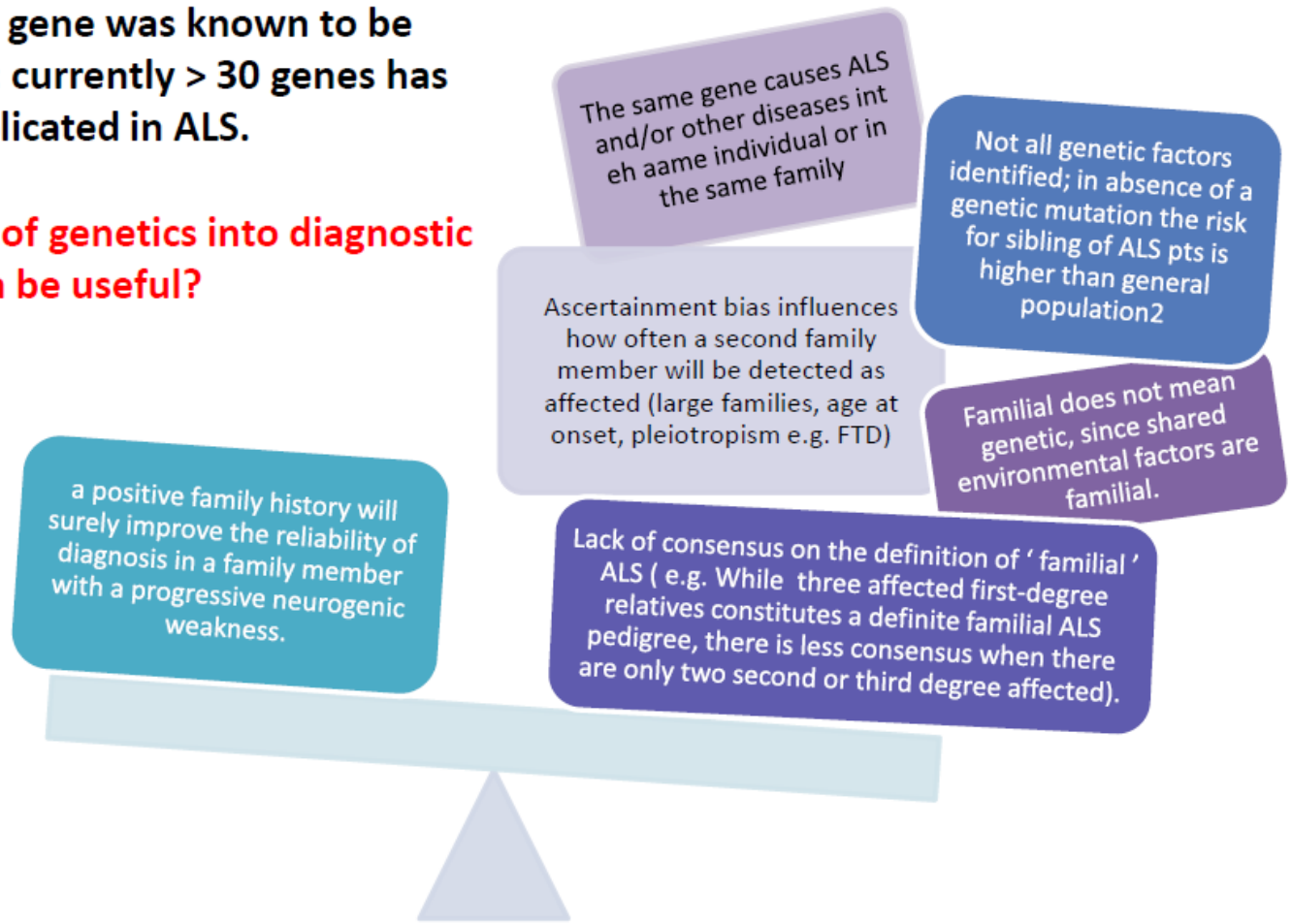


Fig. 5. (A) The split-hand index (SI) was significantly reduced in patients with amyotrophic lateral sclerosis (ALS) classified as 'definite/probable' according to the Awaji criteria when compared to patients classified as other neuromuscular disorders (NMS) ($P < 0.0001$). (B) There was a significant reduction of SI in patients classified as 'possible' ALS when compared to patients with other neuromuscular disorders (NMS), thereby suggesting that the SI may aid in the earlier diagnosis of ALS ****P< 0.0001.

fALS, genetics and EEC-R/AC

In 1999 only SOD1 gene was known to be associated with ALS; currently > 30 genes has been implicated in ALS.

Would incorporation of genetics into diagnostic criteria be useful?



Change the term 'familial' with 'genetic' ALS;

The existing familial ALS classification should be overhauled with international agreement to reflect the phenotypes generated by different ALS genes

El Escorial revision in 2015

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration, 2015; Early Online: 1–2

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A revision of the El Escorial criteria - 2015

ALBERT LUDOLPH[1], VIVIAN DRORY[2], ORLA HARDIMAN[3], IMAHARU NAKANO[4], JOHN RAVITS[5], WIM ROBBERECHT[6] & JEREMY SHEFNER[7] FOR THE WFN RESEARCH GROUP ON ALS/MND

Genetics

Familial ALS is not the same as hereditary ALS. Accordingly, the term hereditary ALS should be considered if a first- or second-degree relative suffers from ALS or FTD. ALS can be defined as Mendelian in inheritance if a disease-causing gene variant can be shown to segregate within a family. In such cases the genetic variant gene can serve as a substitute for upper motor neuron deficits or a second limb or region ('rule of two').

Phenotypes

Restricted phenotypes of ALS currently recognized include:

1. Progressive bulbar palsy (PBP)
2. Flail arm (Vulpian Bernhard) syndrome and Flail leg syndrome
3. Progressive muscular atrophy (PMA)
4. Primary lateral sclerosis (PLS)

Need LMN signs

Concomitant signs

Deficits in sensory, oculomotor systems and sphincter disturbances can be features of ALS.

(FTD, AD) does not exclude the diagnosis of ALS. Any new staging system should include a cognitive domain.

Diagnostic criteria

The diagnosis of ALS requires:

- Clinical, electrophysical, or neuropathologic evidence of lower motor neuron degeneration
- Clinical, electrophysical, or neuropathologic evidence of upper motor neuron degeneration
- Evidence of progressive spread of symptoms or signs within a region or to other regions

Combined with the absence of:

- Electrophysiologic or pathologic evidence of other disease processes that might explain the patient's motor neuron degeneration
- Neuroimaging evidence of other diseases that might explain the observed clinical and electrophysiologic signs

TABLE 1-5 Diagnostic Certainty Based on Revised El Escorial Criteria[a,b,c]

Level of Certainty	Degree of Involvement
Suspected ALS	UMN signs only in one or more regions, or LMN signs only in one or more regions
Possible ALS	UMN and LMN signs in one region, or UMN signs in at least two regions, or UMN and LMN signs in two regions without UMN signs rostral to the LMN signs
Probable ALS	UMN and LMN signs in two regions with some UMN signs rostral to the LMN signs
Laboratory-supported probable ALS	UMN signs in one or more regions with LMN involvement by EMG in at least two regions
Definite ALS	UMN and LMN signs in three regions
Laboratory-supported familial ALS	UMN and LMN signs in one region and confirmatory genetic testing

ALS = amyotrophic lateral sclerosis; UMN = upper motor neuron; LMN = lower motor neuron; EMG = electromyography.
[a] Data from Caravalho M, et al, Clin Neurophysiol.[17] *www.clinph-journal.com/article/S1388-2457(07)00643-8/abstract.*
[b] Cervical and lumbar region requires involvement of two muscles innervated by different nerve roots.
[c] Bulbar and thoracic region requires involvement of only one muscle per region.

Revision in 2000