Diagnosing ALS: A Challenging Proposition

Gustavo Alameda, MD, FAAN
Medical Director, ALS Multi-disciplinary Clinic
Phil Smith Neuroscience Institute
Holy Cross Health, Ft. Lauderdale

Presentation Goals

- Present and Overview of ALS
- Identify and stress the heterogeneity of clinical presentations of ALS
- Review the diagnostic criteria
- Review reasons for delayed diagnosis
- Discuss urgency in ALS diagnosis!
- Discuss potential solutions to delays in diagnosis and care
- Discuss standards of care and challenges to provide that care

What is ALS?

- ALS is a progressive neurodegenerative disease that leads to death of the motor nerve cells in the brain, brainstem, and spinal cord.
- First described by Charcot in 1869 as a pure motor disorder
- Characterized by progressive loss of control of voluntary muscles, weakness, and muscle atrophy, that eventually affects control speech, swallowing, and breathing
- ***Not limited to motor symptoms!***
  - Presentation is often not straightforward and may vary greatly from patient to patient
  - Respiratory, axial, pseudo-bulbar, cognitive/behavioral

What is ALS?

- Death occurs on average 3 to 5 years *after symptom onset*, ***NOT*** since *time of diagnosis.*
  - The leading cause of death associated with ALS is respiratory failure
- **Delay in diagnosis***:* Worldwide average of 12 months to make the diagnosis of ALS
  - *Let that sink in…..*

Epidemiology

- Incidence: 2-3/100000 (*compared to MS* 2/100000)
- Prevalence: 4-5/100000 (*compared to MS* 36/100000)
- Etiology: No unifying pathophysiology
  - Sporadic 90%
  - Genetic mutations 10%
- Risk factors: no clear risk factors have been established
  - Environmental +/- genetic predisposition, military service, athletes prone to concussive injuries

Clinical Presentation

- **Limb-onset**: 65-70% of ALS presentation; manifests as progressive, painless, distal limb weakness that is not isolated to a single myotome or peripheral nerve distribution; often on dominant side.
  - Most confounding presentation for many clinicians because the differential is so wide.
  - Often leads to needless surgery
- **Bulbar-onset**: 25-30% of ALS presentation; manifests as progressive dysarthria, dysphagia, and dysphonia. Typically progresses rapidly.
- **Axial/spinal onset**: < 10% of ALS presentation that manifests as progressive head drop or respiratory insufficiency.
- **Cognitive/behavioral**: FTD and ALS represent two ends of a spectrum
  - 5-15% of ALS patients have FTD, but about 50% have some cognitive dysfunction
  - 15% of FTD patients eventually develop ALS

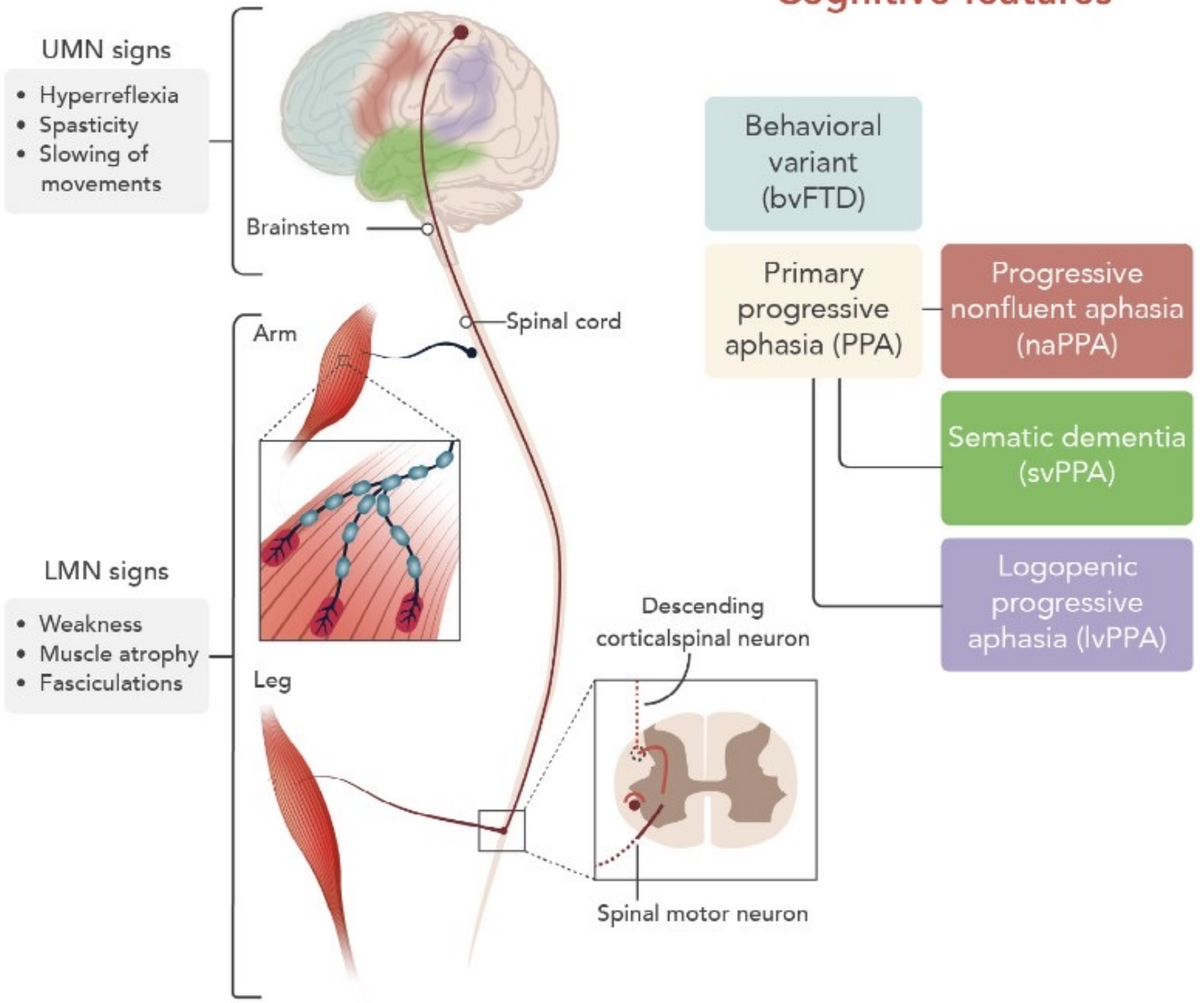
Motor features

Subtypes by regional onset

Classic ALS
- Bulbar ALS
- Spinal ALS

Specific subtypes
- Pseudobulbar palsy
- Progressive bulbar palsy
- Mill's syndrome (hemiplegic)
- Respiratory ALS
- Axial ALS
- Flail arm syndrome
- Flail leg syndrome
- Pseudopolyneuritic ALS

Subtypes by UMN vs LMN involvement
- Primary lateral sclerosis (PLS)
- UMN predominant ALS
- ALS
- LMN predominant ALS
- Progressive muscular atrophy (PMA)



Cognitive features

- Behavioral variant (bvFTD)
- Primary progressive aphasia (PPA)
  - Progressive nonfluent aphasia (naPPA)
  - Sematic dementia (svPPA)
  - Logopenic progressive aphasia (lvPPA)

Masrori, P. and Van Damme, P. (2020), Amyotrophic lateral sclerosis: a clinical review. Eur J Neurol, 27: 1918-1929. https://doi.org/10.1111/ene.14393

Figure 2 Phenotypic presentations of ALS. Motor features of ALS vary in regional distribution and relative UMN versus LMN involvement. Cognitive and behavioural features are detectable in up to 50% of patients.

Clinical Presentation

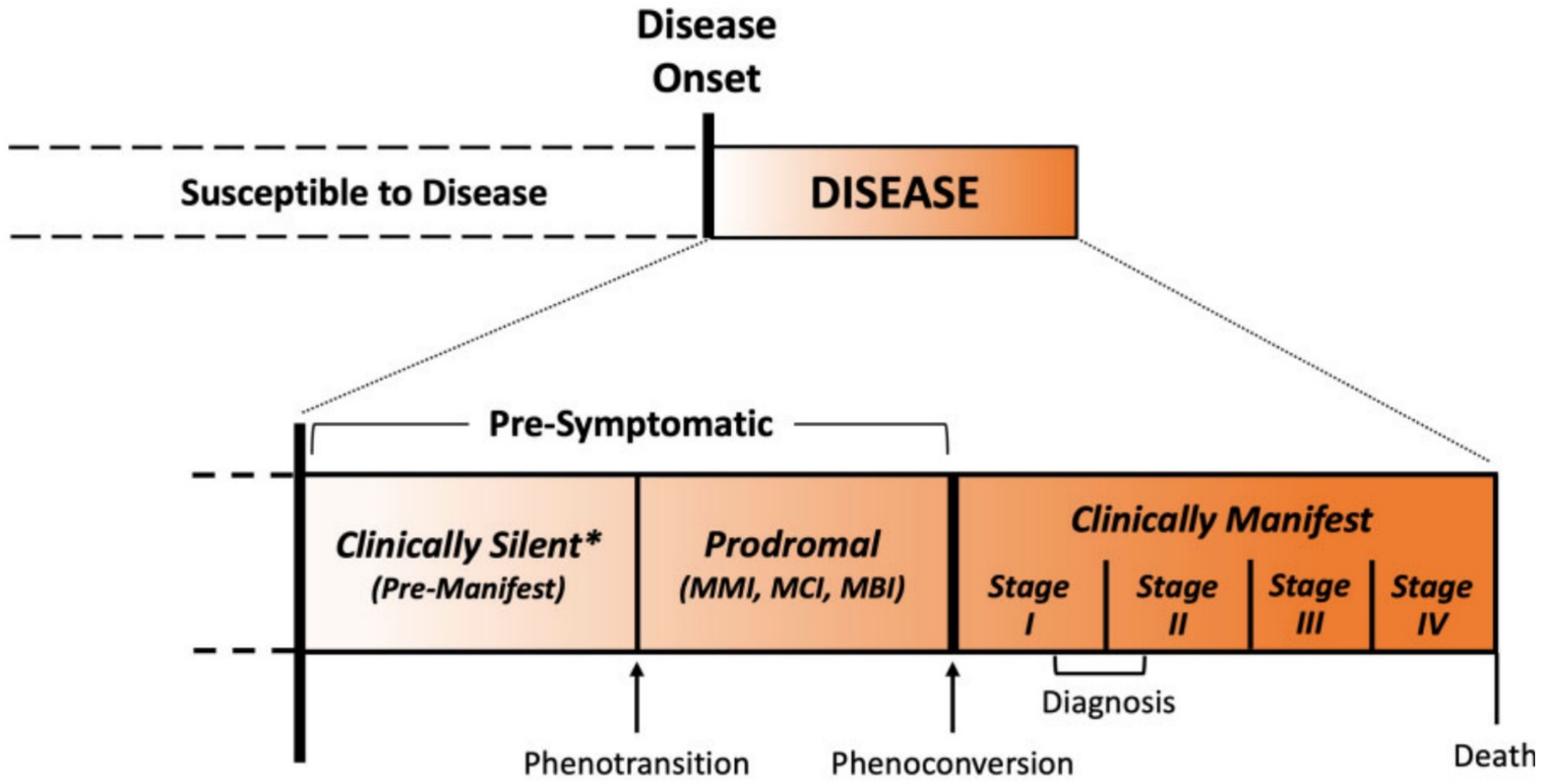
The Pre-Symptomatic Familial ALS Study

- Cohort study of pre-symptomatic gene mutation carriers
- “Offers a unique opportunity to observe what is typically unseen.”
- 20 pre-symptomatic mutation carriers (in SOD1, FUS and C9orf72)
- Pre-symptomatic prodrome
  - EMG changes, asymptomatic LMN dysfunction
- Mild Motor Impairment (MMI)
  - Asymptomatic mild focal weakness, hyperreflexia, scattered ongoing denervation (e.g. fibrillations or positive sharp waves restricted to a single peripheral nerve or nerve root).
- Prospective observation of phenoconversion

Mild motor impairment as prodromal state in amyotrophic lateral sclerosis: a new diagnostic entity; Benatar M, et al; Brain 2022: 145, 3500-3508

Clinical Presentation

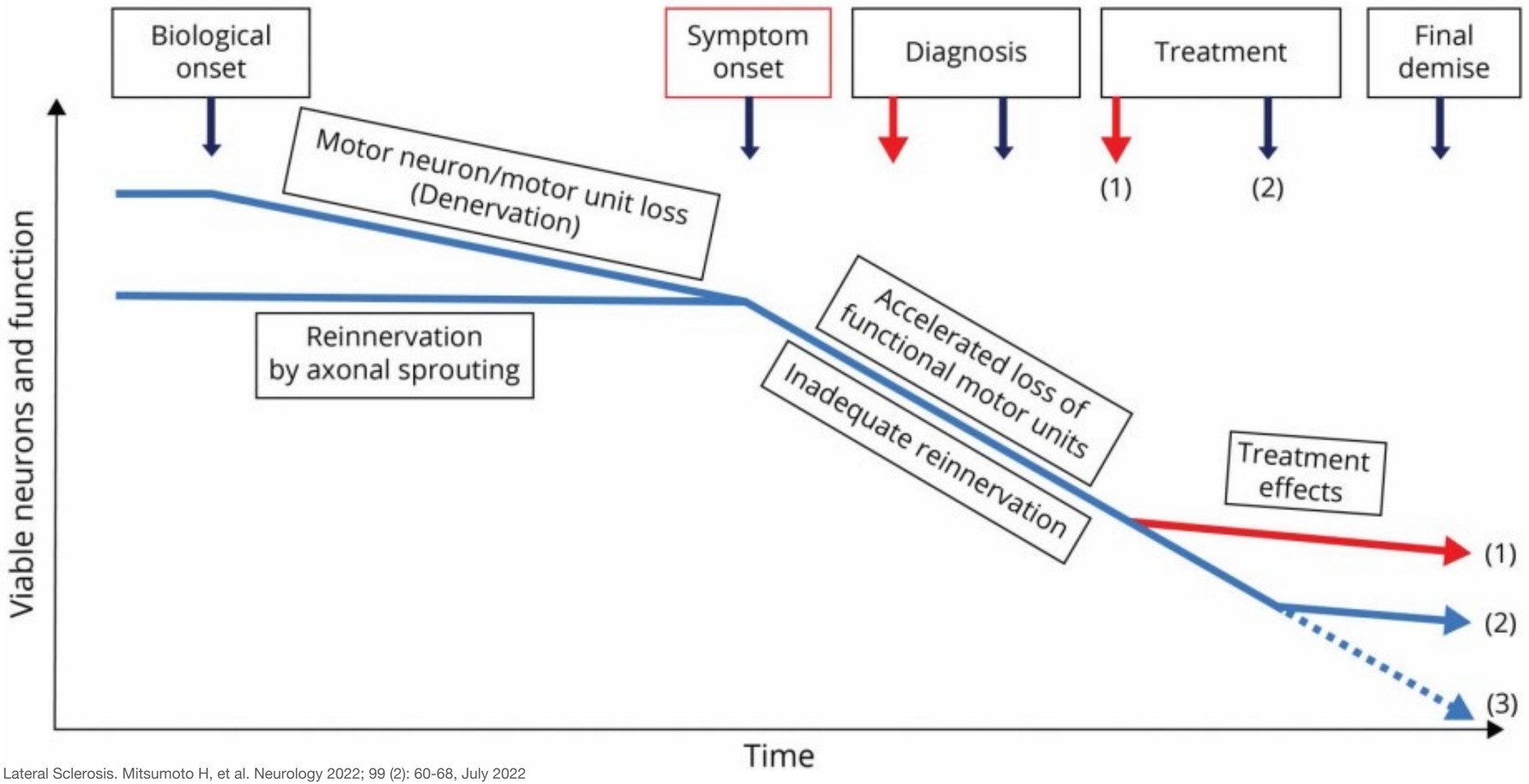
Does ALS begin at the time of symptom onset?



** Clinically silent, but biomarker evidence of disease may be present*

Mild motor impairment as prodromal state in amyotrophic lateral sclerosis: a new diagnostic entity; Benatar M, et al; Brain 2022: 145, 3500-3508

Figure 1 Hypothetical Illustration of ALS Disease Progression and Intervention



Hastening the Diagnosis of Amyotrophic Lateral Sclerosis. Mitsumoto H, et al. Neurology 2022; 99 (2): 60-68, July 2022

The biological process in ALS (loss of motor neurons) precedes symptom onset.[3] When intrinsic compensatory muscle reinnervation by axonal sprouting is no longer possible because of relentless motor neuron loss, symptoms begin to appear and loss of functional motor units may be accelerated. Currently, it takes approximately 11–12 months after symptom onset to reach a diagnosis of ALS, at which time appropriate disease-modifying drug therapy can be initiated to slow disease progression. Three possible trajectories are indicated: (1) The greatest slowing of disease progression is achieved with early diagnosis after symptom onset and early initiation of treatment, as indicated by the red arrows. (2) More modest slowing of disease progression results from the conventional timeframe for diagnosis and treatment, indicated by the dark blue arrows. (3) Disease trajectory is most rapid in the absence of any disease-modifying therapy, indicated by the blue dotted arrow. Blue arrows demonstrate several critical time points. ALS = amyotrophic lateral sclerosis.

ALS Physical Exam Findings

- **Upper Motor Neuron**: Spastic dysarthria, spasticity, hyperreflexia, long tract signs, gait imbalance, and weakness (but not profound atrophy)
- **Lower Motor Neuron**: Weakness with more profound atrophy (including the tongue), fasciculations, flaccid tone, hypo/areflexia
- **Pseudobulbar**: laughing/crying/yawning spells with inappropriate affect, facial weakness, primitive reflexes
- **Cognitive**: Behavioral and personality changes; not an amnestic disorder

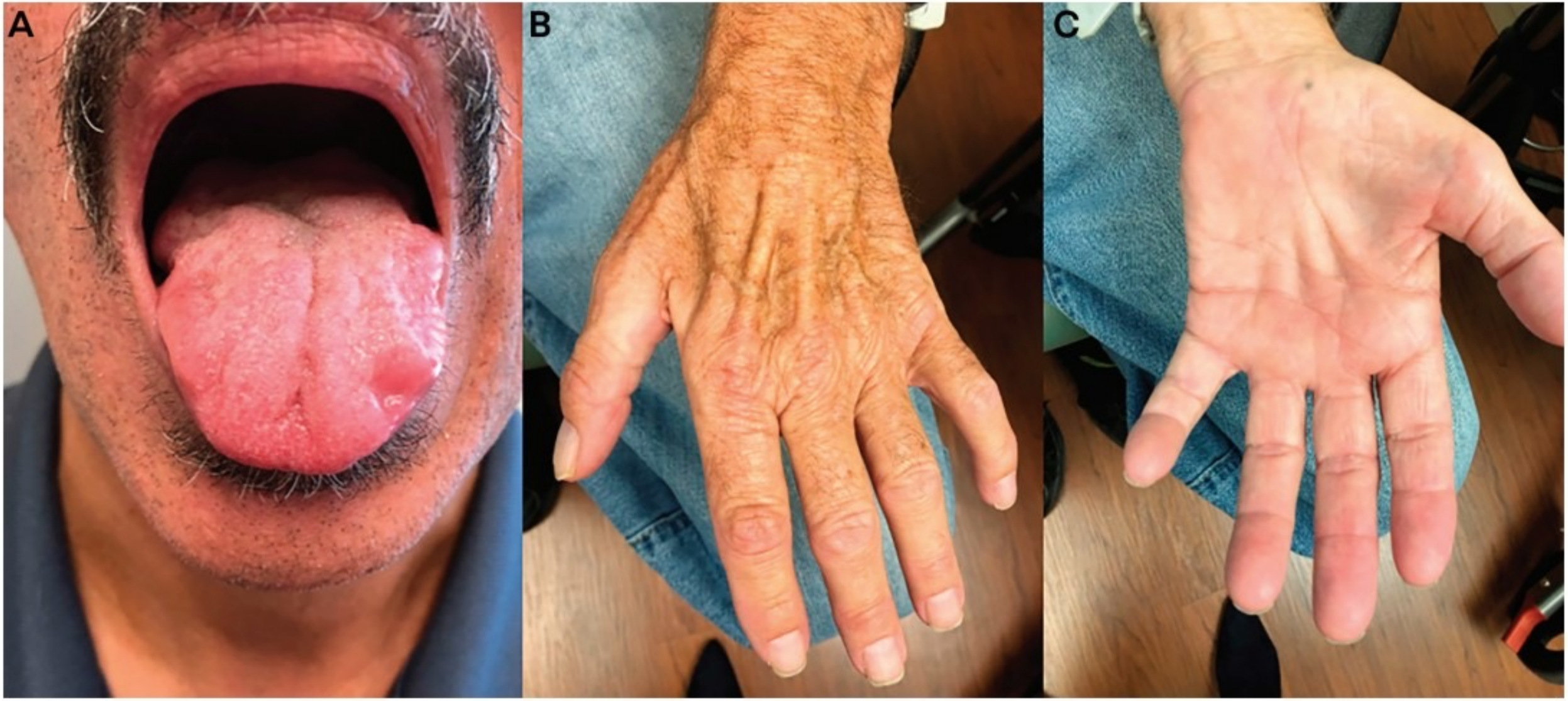


FIGURE 9-1

Photographs of the patient in CASE 9-1 with amyotrophic lateral sclerosis. *A*, Atrophy of the tongue. Atrophy of the hand is worst in the lateral ulnar (*B*, first dorsal interosseous) and median (*C*, abductor pollicis brevis) innervated muscles, commonly referred to as split hand syndrome.

Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

Quinn, Colin; Elman, Lauren
CONTINUUM: Lifelong Learning in Neurology26(5):1323-1347, October 2020.
doi: 10.1212/CON.0000000000000911

The ALS Work-Up

- MRI of the neuraxis
- EMG/NCS
  - Often may need to be repeated several times
    - EMG findings are likely to become more obvious over time
    - Not all studies are high quality studies
- Labs: ACh-R antibodies (to include MuSK and LRP4), ANA, comprehensive panel, Lyme, HIV, HTLV 1/2, GM1 antibody panel, GAD antibody, serum heavy metals
  - Bio markers: neurofilament light chain (NfL), phosphorylated neurofilament heavy chain (pNfH)
- Lumbar puncture of increasing importance
  - CSF biomarkers
- Genetic testing: oral-buccal swab, many testing options at no-cost to the patient

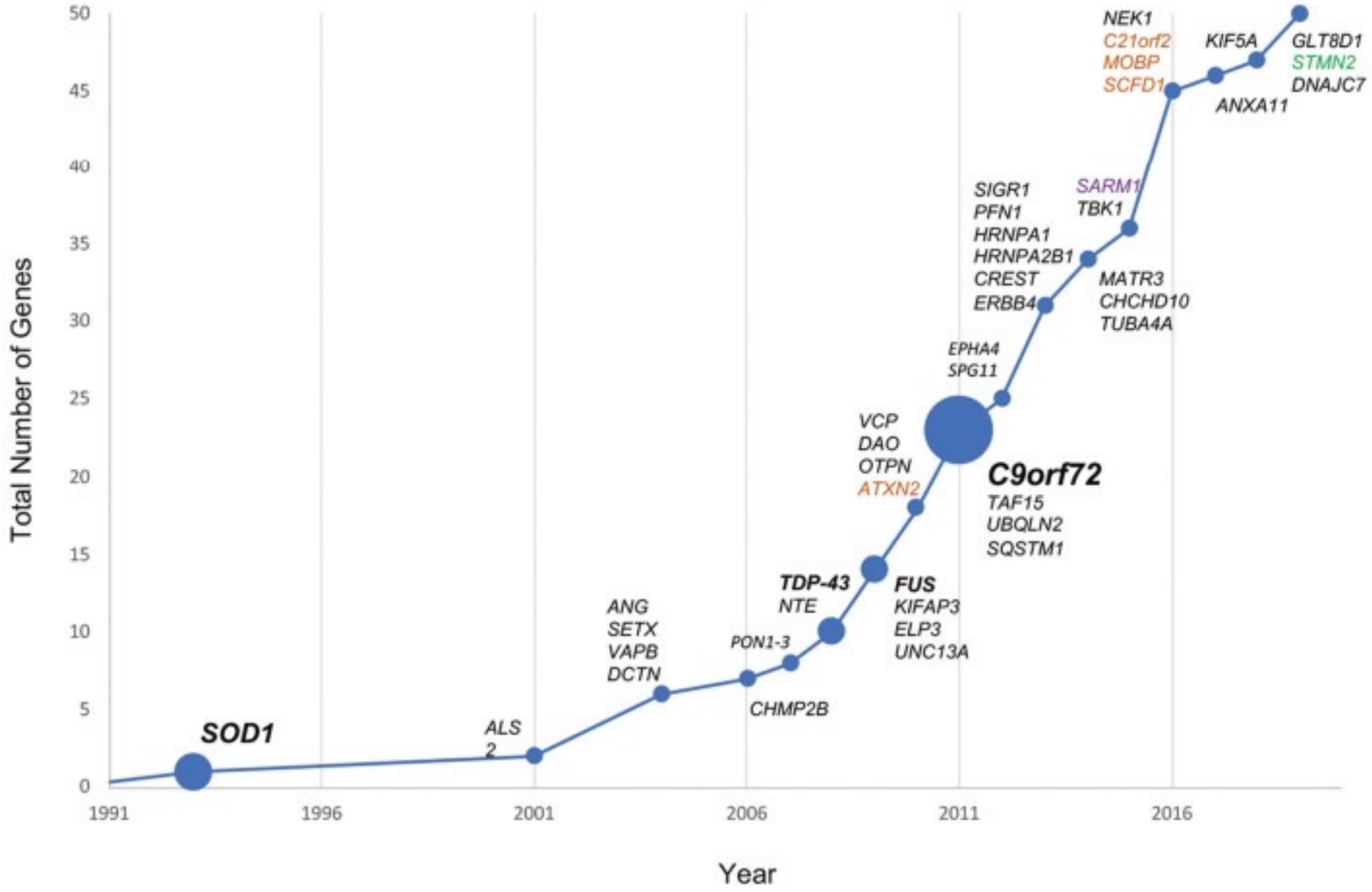


FIGURE 9-5

Timeline of amyotrophic lateral sclerosis (ALS) gene discovery. The discovery of genes associated with familial and sporadic ALS has rapidly increased over the past 20 years. Most of the genes identified are associated with familial ALS, with *C9orf72* representing the largest proportion, followed by *SOD1* and then *TDP-43* and *FUS*. Some genes listed are ALS risk factors (*ATXN2*, *C21orf2*, *MOBP*, and *SCFD1)* or possible disease modifiers (*SARM1*). *STMN2* mutations have not been found in familial ALS, but missplicing of *STMN2* RNA appears to be important in ALS pathophysiology. The size of the circles is proportionate to the contribution of each gene to the overall population of familial ALS.

Data courtesy of Robert H. Brown Jr, DPhil, MD.

teral Sclerosis and Other Motor Neuron Diseases

Quinn, Colin; Elman, Lauren
CONTINUUM: Lifelong Learning in Neurology26(5):1323-1347, October 2020.
doi: 10.1212/CON.0000000000000911

Diagnosis	Diagnostic Clue	Confirmatory Testing
Lower motor neuron predominant/weakness		
Benign fasciculations	Acute onset, widespread, no weakness	EMG does not demonstrate denervation or chronic reinnervation (and often does not show fasciculations)
Inclusion body myopathy	Weakness of deep finger flexors and quadriceps	Myopathic EMG, plus NT5C1A antibody (helpful when present), muscle biopsy findings
Multifocal motor neuropathy (MMN) with conduction block	Nerve (rather than myotome) pattern with asymmetric upper extremity predominance	Partial motor conduction block on nerve conduction studies, positive anti-GM1 antibodies
Neuralgic amyotrophy	Pain at onset, involvement of named nerves, self-limited course	Nerve conduction studies and EMG findings, MRI with and without contrast of the involved plexus
Monomelic amyotrophy (Hirayama disease)	Young male with asymmetric hand and distal forearm weakness and atrophy, self-limited course	MRI findings
Spinal bulbar muscular atrophy (Kennedy disease)	Slow progression, facial twitching, tremor, sensory neuropathy, evidence of androgen insensitivity (eg, gynecomastia, testicular atrophy)	Absent sural sensory responses, CAG repeat expansion in the androgen receptor gene
Motor-predominant Charcot-Marie-Tooth disease (CMT)/distal spinal muscular atrophy	Symmetric and distal onset, young age of onset, slow progression	Nerve conduction studies demonstrating abnormal sensory nerve action potential (SNAP) amplitudes and (in CMT type 1) evidence of demyelination; positive genetic testing for CMT
Post-severe denervation (postpolio) syndrome	History of distant polio or other severe nerve injury with recovery followed by slow progression of weakness in the distribution of prior polio symptoms; muscle pain is common	Giant motor unit action potentials on EMG

Diagnosis	Diagnostic Clue	Confirmatory Testing
Upper motor neuron predominant		
Nutritional myeloneuropathies	Sensory (predominantly dorsal column) deficits, sensory neuropathy	Abnormal sensory nerve conduction studies, vitamin B_{12} or copper deficiency, dorsal column abnormalities on MRI
Hereditary spastic paraparesis	Young onset, family history, slow progression, predominantly leg involvement	Positive hereditary spastic paresis genetic screen
Adrenomyeloneuropathy	Sensory neuropathy, with or without adrenal insufficiency, X-linked (females may still be affected)	Abnormal sensory nerve conduction studies, *ABCD1* mutation
Late-onset Tay-Sachs disease	Cerebellar ataxia/atrophy, psychiatric features, Ashkenazi descent (recessive)	*HEXA* mutations
Polyglucosan body disease	Distal sensory loss, neurogenic bladder, cerebellar ataxia, cognitive deficits	White matter changes on MRI, *GBE1* mutations
Human immunodeficiency virus (HIV) myelopathy	Extended history of HIV; MRI may be unremarkable	HIV positive
Multiple sclerosis	Sensory and sphincter involvement, relapsing-remitting course (some)	MRI findings, CSF findings
Mixed lower motor neuron/upper motor neuron		
Cervical radiculomyelopathy	Sphincter involvement, pain, sensory symptoms/level	Foraminal and canal stenosis on MRI (should be rostral to highest upper motor neuron examination findings)

Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

Quinn, Colin; Elman, Lauren
CONTINUUM: Lifelong Learning in Neurology26(5):1323-1347, October 2020.
doi: 10.1212/CON.0000000000000911

The ALS Work-Up

Does completion of the extensive work-up always yield a definitive diagnosis?

NOPE

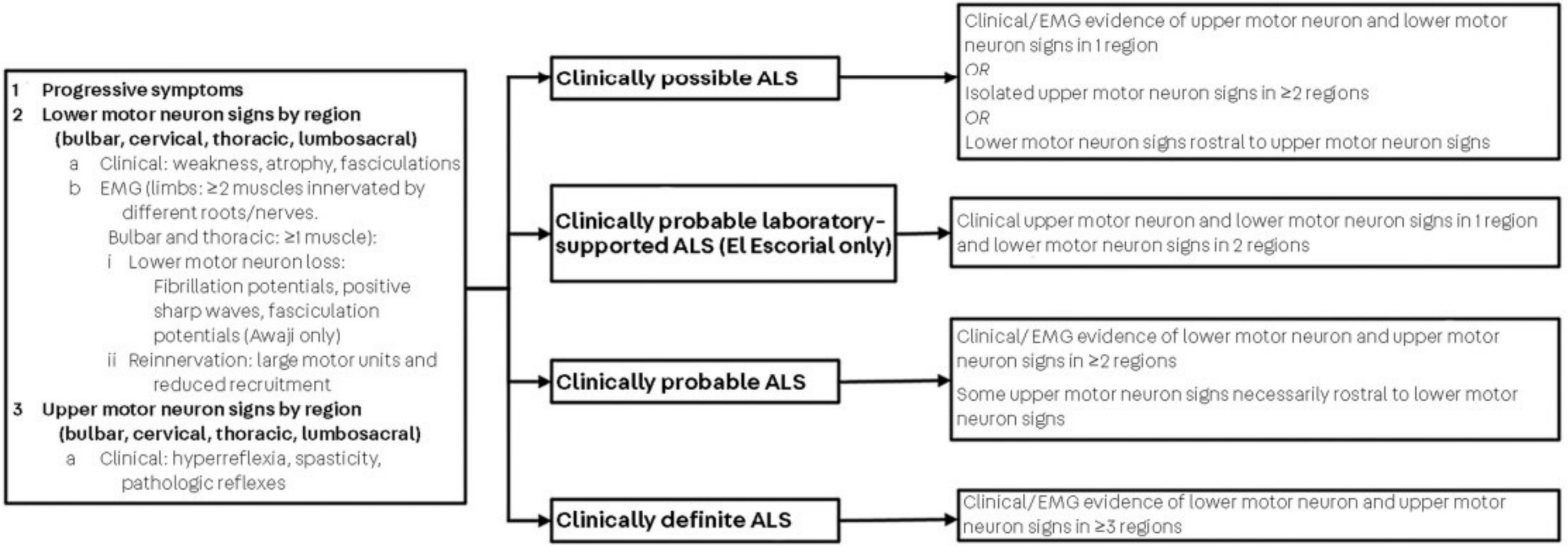


FIGURE 9-2

Revised El Escorial and Awaji diagnostic criteria for amyotrophic lateral sclerosis (ALS).

EMG = electromyography.

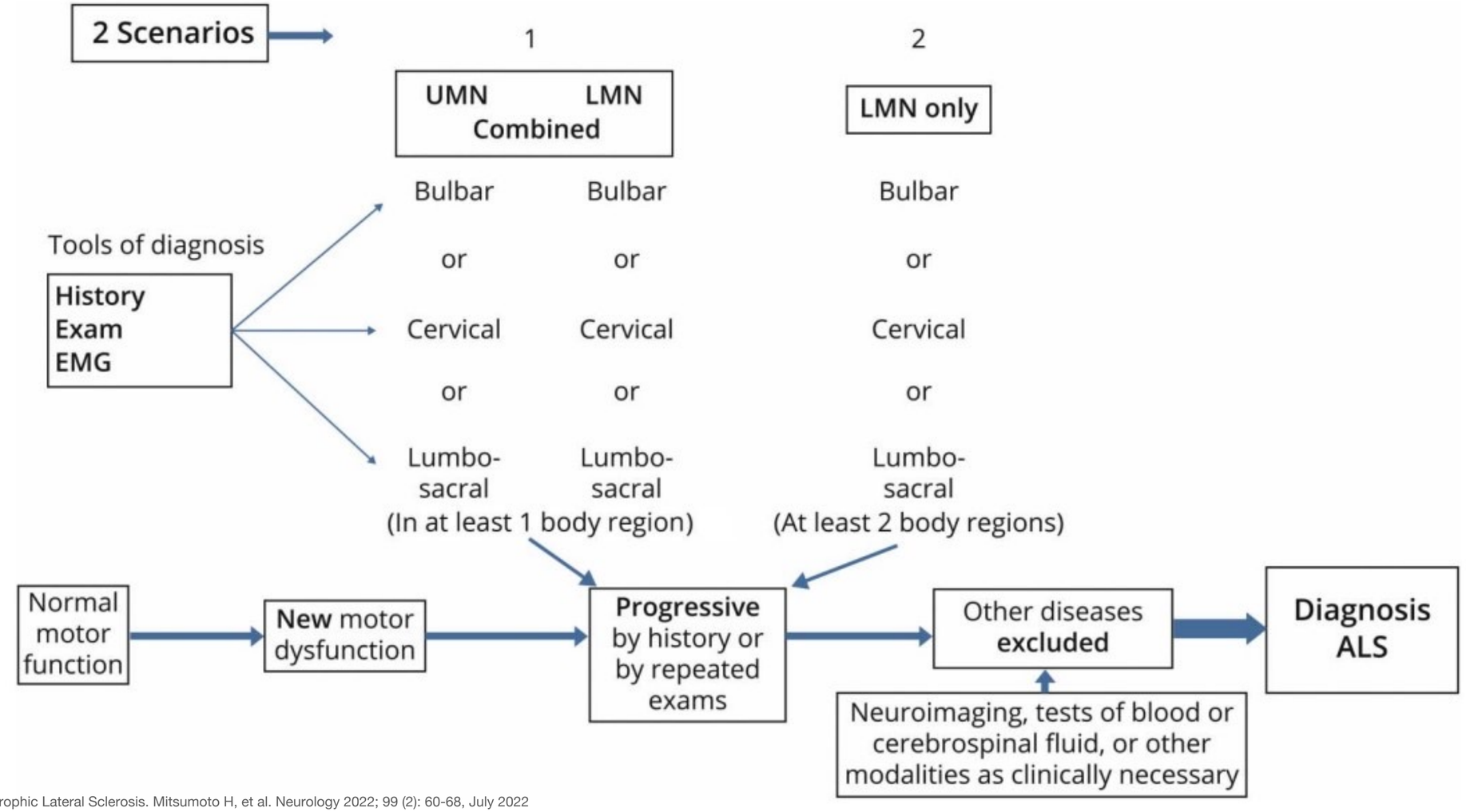
Data from Ludolph A, et al, Amyotroph Lateral Scler Frontotemporal Degener[40] and Nodera H, et al, Brain Nerve.[41]

Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases

Quinn, Colin; Elman, Lauren
CONTINUUM: Lifelong Learning in Neurology26(5):1323-1347, October 2020.
doi: 10.1212/CON.0000000000000911

Revised El Escorial and Awaji diagnostic criteria for amyotrophic lateral sclerosis (ALS).EMG = electromyography. Data from Ludolph A, et al, Amyotroph Lateral Scler Frontotemporal Degener40 and Nodera H, et al, Brain Nerve.41

Figure 3 Crucial Components for Reaching the Diagnosis of ALS Based on Gold Coast ALS Diagnostic Criteria



Hastening the Diagnosis of Amyotrophic Lateral Sclerosis. Mitsumoto H, et al. Neurology 2022; 99 (2): 60-68, July 2022

The disease must be progressive by history or repeated examinations, and other diseases should be excluded by investigations.[37] There are 2 scenarios for identifying UMN and LMN signs to make the correct diagnosis. The presence of LMN dysfunction in at least 2 body regions is diagnosed as ALS. This is based on the fact that UMN signs are often not apparent in these cases and ancillary tests can identify UMN involvement. Furthermore, LMN disease, such as PMA, is considered to be ALS. ALS = amyotrophic lateral sclerosis; Exam = neurologic examinations; EMG = electromyogram including nerve conduction studies; LMN = lower motor neuron; PMA = progressive muscular atrophy; UMN = upper motor neuron.

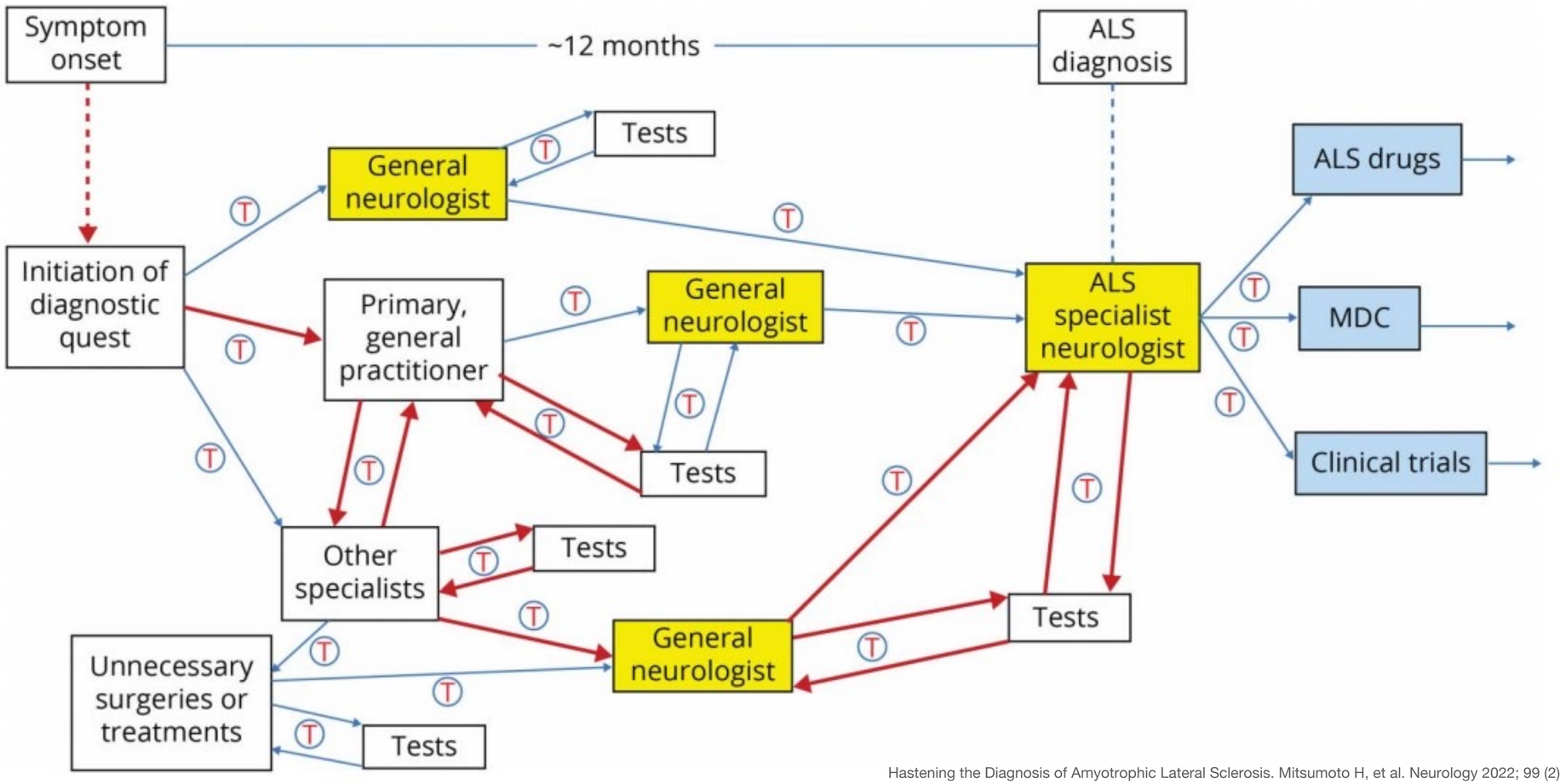
Table 1 Duration From Symptom Onset to the Diagnosis of ALS

Authors	Years of the study	Country and study population	No. of patients studied	Months from symptom onset to diagnosis (median)	Bulbar-onset (%)
Household & Swash[11]	After 1996 before 2000	UK, London	57	16.2 (mean[a])	25
Miller et al.[12]	1996 to 1998	USA, ALS Care Data Base	1,857	14.4 (mean[a])	—
Paganoni et al.[13]	2000–2011	USA, Hospital-based	304	11.5 (combined) 9 (bulbar) 12 (limb)	28
Williams et al.[14]	2005–2009	USA, Medicare Data Set	272[b]	15 (bulbar) 30 (limb)	26
Talman et al.[15]	2005–2015	Australia, MND Registry	1,677	10 (bulbar) 11.5 (limb) mo	26
Palese et al.[16]	2010–2014	Italy, Hospital-based	134	11.5	35
Martinez-Molina et al.[17]	2013–2017	Spain, Hospital-based	166	8.6 (ALS referral); 12.1 (general clinic)	29
Galvin et al.[18]	2013 (6 mo study)	Ireland, Hospital-based	35	13	23
Falcão De Campos et al.[19]	2015–2018	Lisbon, Portugal	580	10	22

Abbreviation: ALS = amyotrophic lateral sclerosis.
[a] Median data were not available for this study.
[b] Patients were 65 years and older. Cases for whom the diagnosis of ALS (*International Classification of Diseases, Ninth Revision*, Clinical Modification code 335.20) was claimed twice were included in this study.

Hastening the Diagnosis of Amyotrophic Lateral Sclerosis. Mitsumoto H, et al. Neurology 2022; 99 (2): 60-68, July 2022

Figure 2 Arduous Journey to Reach a Diagnosis of ALS



Hastening the Diagnosis of Amyotrophic Lateral Sclerosis. Mitsumoto H, et al. Neurology 2022; 99 (2): 60-68, July 2022

Patients with ALS symptoms usually consult their primary physician first. A few may consult neurologists and other specialists, such as otolaryngologists, orthopedic surgeons, or neurosurgeons. Arrows indicate many different paths to reach the diagnosis of ALS. Red thick arrows denote less common paths that often derail the expected paths to diagnosis. Every physician during this process may order tests, including multiple neuroimaging procedures and electrodiagnostic studies (nerve conduction studies and EMGs), which require time. Some patients might undergo inappropriate operations, resulting in a long delay to a correct diagnosis. Scheduling and general logistics of obtaining appointments take time as well. These waiting periods sum up to create the observed long duration from symptom onset to the diagnosis of ALS. T in a blue circle indicates that time is required to obtain necessary appointments or test procedures. ALS = amyotrophic lateral sclerosis; MDC = multidisciplinary clinic.

You've Made the ALS Diagnosis: *Now what?*

ALS Multidisciplinary Clinics

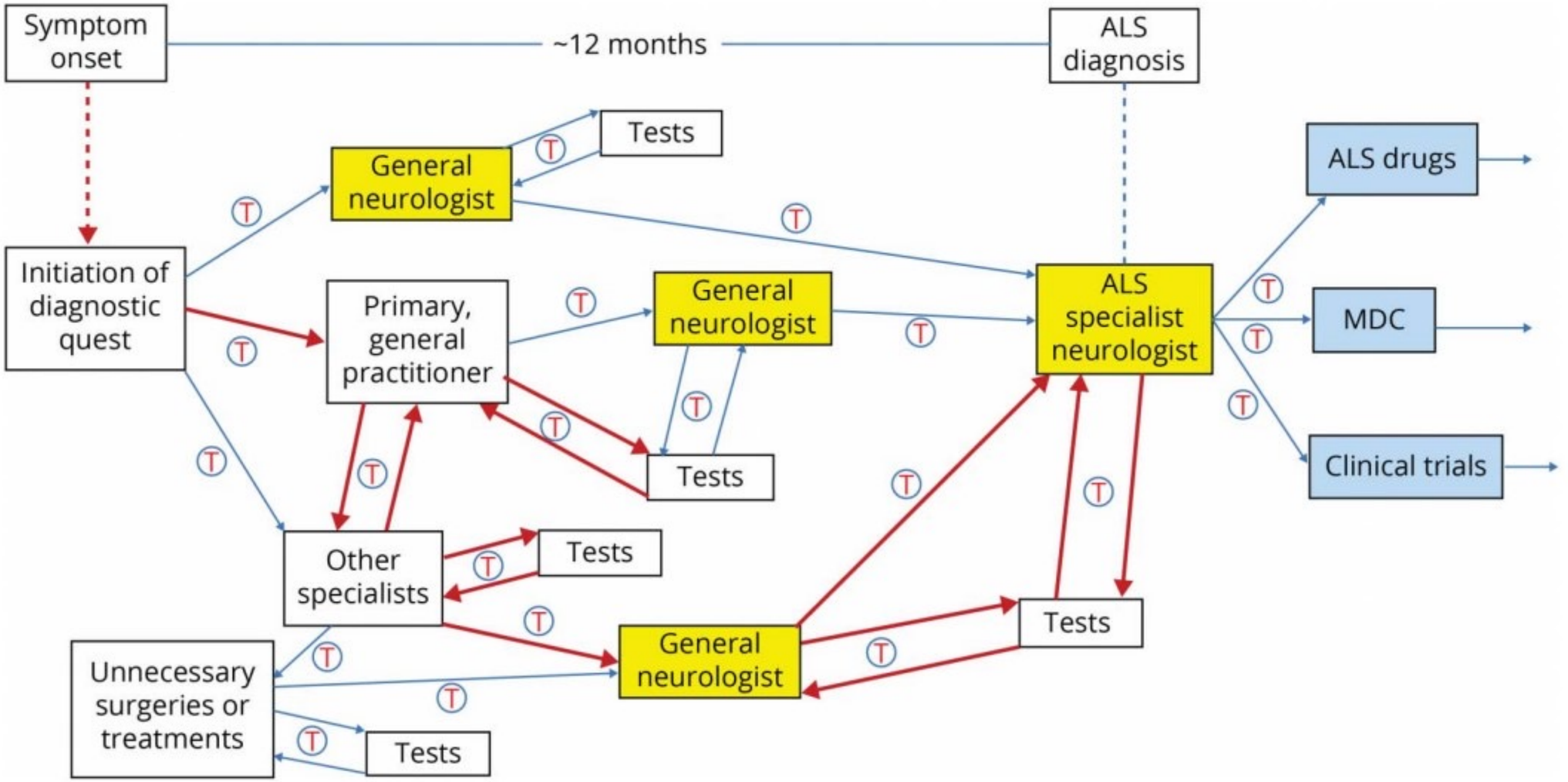
- **MDC Team:** MD/NP/PA, Nurse, Speech Language Pathologist, Registered Dietician, Physical and Occupational Therapists, Palliative Care, Neuropsychologist, ALSA Liaison, Social Worker, Research, Respiratory Therapists, DME.
- Multidisciplinary clinic care has been shown to improve quality of life and survival
  - symptom management: sialorrhea, spasticity, pseudobulbar palsy, depression, muscle cramping, communication, dysphagia
- Initiation of FDA approved medications ("The Three R's"): riluzole, edaravone, sodium phenylbutyrate/TUDCA
  - many community neurologists do not start any therapy
- Initiation of off-label use of high dose parenteral methylcobalamin (50 mg twice weekly)
- Access to clinical trials
- Early adoption of noninvasive volume ventilation
  - repeatedly shown to prolong survival and respiratory function
- Nutrition optimization (pre- and post-PEG)

ALS is an Expensive Endeavor

- For ALS patients in the U.S., medical costs are substantial and increase rapidly with each disability milestone
- The ALS Association sponsored study in 2014 (“Financial cost of amyotrophic lateral sclerosis”)
  - total disease-duration costs were $1,433,992 (85% paid by insurance, 9% paid by family, 6% paid by charities)
  - The highest costs were for in-home caregivers ($669,150), ventilation ($212,430), and hospital care ($114,558)
- This is likely significantly higher today
  - edaravone and sodium phenylbutyrate/TUDCA each cost over $150K/year
  - Insurance restricts coverage: criteria for use, prior authorizations, appeals, peer-to-peer
- Disparities in standards of care due to patients’ financial status
  - Being under-insured is likely as bad as being uninsured
  - Off-label use of compounded medications

Consequences of Delayed Diagnosis

- Disease modifying therapies are likely started too late to provide benefit
  - Ad-hoc analyses of studies of all three FDA approved drugs show an outsized benefit of starting therapy early in the disease course
  - Ad-hoc analysis of high-dose parenteral methylcobalamin study showed the same pattern; follow-up study limited to early disease (<12 months) showed benefit
- MDC recommendations and protocols are likely less impactful



Remember this mess?

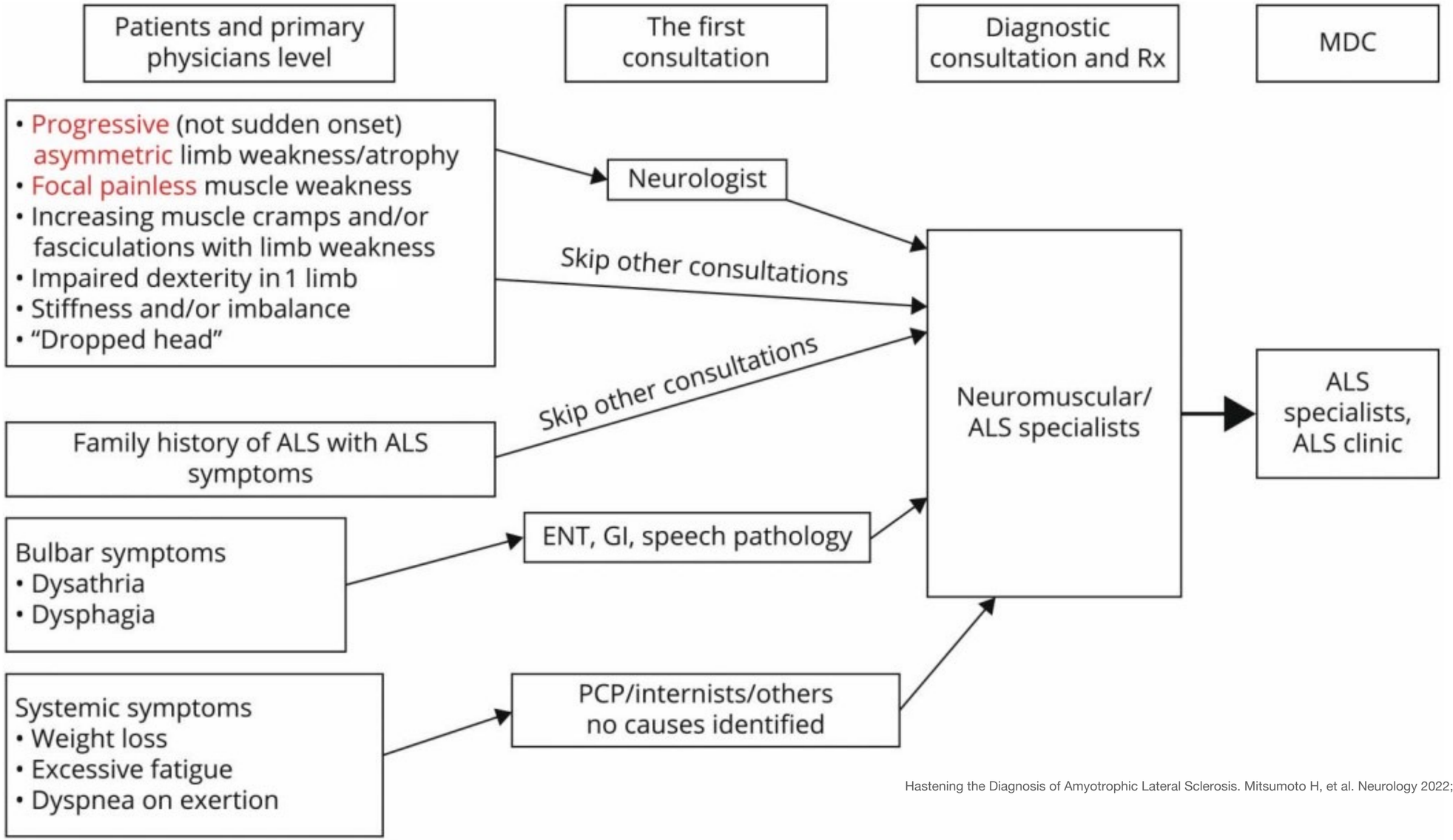
Delays in Diagnosis are *BUILT INTO* the System

- Patients are often not referred to neurologists as the first evaluation: neurosurgeons and orthopedic surgeons see a large percentage of ALS patients in the initial months
  - MANY unnecessary surgeries
  - Accelerated clinical decline following each surgery
- Few specialists (neurologists) with long waits to see new patients
- Fewer sub-specialists (also neurologists!) with even longer wait times
- Each referral adds to a further delay
- General *lack of urgency* (by neurologists!) to make the diagnosis
  - lack of robust treatments
  - inevitability of the disease course

Delays in Diagnosis are *BUILT INTO* the Disease

- Heterogeneity of presentation
  - presents in any number of motor distributions
  - age
  - wide differential
- Most patients and clinicians think of ALS only in terms of a motor syndrome

Figure 4 Idealized and Simplified Process to Hasten the Diagnostic Process in ALS



Hastening the Diagnosis of Amyotrophic Lateral Sclerosis. Mitsumoto H, et al. Neurology 2022; 99 (2): 60-68, July 2022

Table 2 Challenges and Recommendations for Hastening the Diagnosis of ALS

1. Education of general physicians and surgeons
a. Core characteristic features of ALS b. Acceptable aging process
2. Role of neurologists
a. Developing a sense of urgency to save motor neurons in ALS b. Prioritize patients with a potential diagnosis of ALS for an appointment, EMG testing, and other studies c. Patient education whenever possible regarding the importance of initiating early treatment
3. Diagnostic process
a. Use the Gold Coast ALS Diagnostic Criteria as a supplement to clinical judgment b. Use Nf measurements when making a diagnosis of ALS c. Promote the use of Nf diagnostic testing by hospital and commercial laboratories d. Use genetic testing as a supplementary diagnostic tool when clinically appropriate
4. Disseminating the proposal
a. Include all practicing neurologists through communications from professional neurologic organizations, if possible b. Incorporate a need for hastening the diagnosis into the ALS Practice Guidelines and Quality Measures c. Neuromuscular/ALS disease organizations should join this effort and make it one of their top priorities
5. Proposal for new research projects
a. Recommend more prospective validity and reliability investigations of the Gold Coast Criteria b. Encourage more research in developing novel, measurable diagnostic markers c. Use an approach that tests the validity of these concepts and accelerates ALS therapeutics, particularly in patients with bulbar-onset ALS

Hastening the Diagnosis of Amyotrophic Lateral Sclerosis. Mitsumoto H, et al. Neurology 2022; 99 (2): 60-68, July 2022

References

Benatar M, et al; Mild motor impairment as prodromal state in amyotrophic lateral sclerosis: a new diagnostic entity; *Brain* 2022: 145, 3500-3508

Hanyu N, et al, Degeneration and regeneratin of ventral motor fibers in amyotrophic lateral sclerosis. Morphometric studies of cervical ventral roots. *J Neurol Sci*; 1982 Jul; 55 (1): 99-115.

Masrori, P, Van Damme P; Amyotrophic Lateral Sclerosis: a clinical review. *European J Neurology* 2020, 27; 1918-1921.

Meng, L., et al (2018). Profile of medical care costs in patients with amyotrophic lateral sclerosis in the Medicare program and under commercial insurance. *Amyotrophic lateral sclerosis & frontotemporal degeneration*, 19(1-2), 134–142.

Mitsumoto H, et al. Hastening the Diagnosis of Amyotrophic Lateral Sclerosis. *Neurology* 2022; 99 (2): 60-68, July 2022

Quinn, C; Elman, L; Amyotrophic Lateral Sclerosis and Other Motor Neuron Diseases; *CONTINUUM: Lifelong Learning in Neurology* 26 (5):1323-1347, October 2020.