BRAINWEEKEND

**A Shifting Paradigm:
Translating Research Into Treatment Approaches for ALS**

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Disclosures Dr. Li

- Nothing to disclose

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Disclosures Dr. Bedlack

- Consulting Fee (eg, Advisory Board):
  AB Science, Alexion, ALSA, Amylyx, Apellis, Biogen, Black Swan, Brainstorm Cell, Corcept, Cytokinetics, GenieUs, Guidepoint, ITF Pharma, Mallinkrodt, New Biotic, Orphazyme, Shinkei, Woolsey Pharma
- Contracted Research (Principal Investigators must provide information, even if received by the institution):
  Orion, MediciNova
- Speakers Bureau: Amylyx

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Learning Objectives

- Outline the disease progression and impact that amyotrophic lateral sclerosis (ALS) has on the lives of patients
- Describe the challenges pertaining to and the need for timely diagnosis of ALS
- Review the current treatment landscape for ALS, including safety and efficacy
- Summarize the pipeline drugs and emerging treatment options for ALS
- Identify the importance of utilizing collaborations to optimize patient outcomes for those struggling with ALS

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BRAINWEEKEND

Outline the disease progression and impact that ALS has on the lives of patients

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Overview

- Amyotrophic lateral sclerosis (ALS, or Lou Gehrig's disease) is a degenerative disease most obviously affecting upper and lower motor neurons
- Affected patients become disconnected from their muscles, typically leading to rapidly progressive weakness, disability, and dramatically shortened survival

Lancet Neurol 2022;21:480-493.
Mayo Clin Proc. 2018;93Z:1617-1628

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Variability

- Causes
  (ex. “familial” or “sporadic”)
- Site of onset
  (ex. limb, bulbar, respiratory)
- Degree of upper vs lower motor neuron involvement
- Comorbidities
  (ex. pseudobulbar affect, cognitive and behavioral changes)

ALS phenotypes based on anatomical region of neuropathology

	Anatomical region of involvement			
	Neuronal region		Somatic region	
Phenotypic variant	UMN	LMN	Bulbar muscles	Limb muscles
Based on neuronal level of involvement				
Typical ALS	+	+	+	+
PLS	++	–	+	+
PMA	–	++	+/–	++
Based on somatic region of involvement				
Bulbar ALS	–	++	++	–
Pseudobulbar ALS	++	–	++	–
Limb ALS	+	+	–	++
Limb variants	+/–	++	–	++
Mill’s variant	++	–	–	++

Supplement to *Neurol Rev*. 2020;March:38-45.
Cold Spring Harb Perspect Med. 2017 Aug;7(8):a024117.

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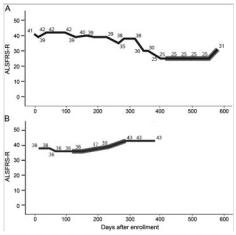
Variability

- Progression pattern
- Progression speed, between patients and even within individuals at different times over the course of the disease



Supplement to *Neurol Rev*. 2020;March:38-45.
Cold Spring Harb Perspect Med. 2017 Aug;7(8):a024117. *Neurology*. 2016 Mar 1; 86(9):808-812.

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Epidemiology

- Age of onset usually 50s-60s, but wide range possible[1]
- Males affected 1.5-2X more than females[1]
- Incidence 2-3 per 100,000 per year[1]
  - More common in certain places (such as Guam)
- Prevalence[1]
  - Now 4-8 per 100,000
  - Projected increase of 69% by 2040[2]
- Lifetime risk for an individual is 1 in 400[3]

1. *Curr Op Neurol*. 2019;32:771-776.
2. *Nat Commun*. 2016;7:12408.
3. *JAMA Neurol*. 2019;76:1387-1374.387-1374

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Burdens

- Physical, mental strain on patient, caregiver[1,2]
  - Some but not all studies show a decline in quality of life with loss of motor function, especially in older patients
  - Patient description from our clinic
- Financial burden to family[3]
  - $10,000-$100,000
- Financial burden to society[3]

Table 4 Costs of national studies

References	Country	Population	Currency year	Source of prevalence	Estimated prevalence	Total costs	Direct costs	Indirect costs
Canadian Institute for Health Information [49]	Canada	N/A	NA	ALS Society of Ontario (2006) [50]	2000	148,537,987	11,230,050	137,299,897
Deloitte Access Economics [47]	Australia	23,050,000	2015	N/A	2094	239,944,648	87,918,248	152,027,520
Larkindale et al. [37]	USA	308,745,538	2010	Wagner et al. (2012) [51]	4104	213,377,253	179,264,504	51,392,563
					6792	394,546,661	303,329,610	91,968,911
				Orphanet (2012) [52]	16,033	932,197,774	717,683,677	214,790,874
Mountain Dysautonomia Association [34]	USA	308,745,538	2010	Alcot (1996) [37]	3596	197,730,922	152,147,558	45,434,456
				Orphanet (2011) [50]	16,053	914,020,252	719,295,949	214,796,874
				Weems (2011) [50]	22,047	1,329,490,895	1,071,591,065	305,665,786

All costs are presented in $ per year. NA: Not Available

1. *Arq Neuropsiquiatr*. 2022;80:255-261.
2. *Brain Sci*. 2021;11:748-778.
3. *Eur J Health Econ*. 2021;22:1151-1166.

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Describe the challenges pertaining to and the need for timely diagnosis of ALS

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Diagnosing ALS

- Clinical diagnosis:
  no one test can rule in or rule out an ALS diagnosis[1]
  - History of gradual painless onset progressive weakness
  - Exam with upper and lower motor neuron signs
  - EMG showing motor axonopathy
  - Imaging, blood tests to exclude mimics

en.wikipedia.org/wiki/Amyotrophic_lateral_sclerosis#Diagnosis.

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Diagnostic "Criteria"

- Older: El Escorial Criteria, Revised El Escorial Criteria, Awaji Criteria[1]
  - Used terminology that was confusing in clinic "Definite, Probable, Possible…"
  - Designed to stratify research patients
  - Not sensitive
- Newer: Gold Coast Criteria[1,2]
  - Can be used for research and clinic
  - More sensitive[3]

Table 1. Diagnostic criteria for amyotrophic lateral sclerosis

Revised El Escorial diagnostic criteria for ALS (2000)	
Diagnostic certainty	**Definition**
Definite ALS	Upper and lower motor neuron signs in 3 regions
Probable ALS	Upper and lower motor neuron signs in 2 regions
Laboratory-supported probable ALS	Upper and lower motor neuron sings in one region or upper motor neuron signs in one or more regions with electromyography demonstrating acute denervation in 2 or more limbs
Possible ALS	Upper and lower motor neuron signs in 1 region
Suspected ALS	Lower motor neuron sings only in one or more region or upper motor neuron signs only in one or more region

Gold coast criteria (2019)

1. Progressive motor impairment documented by history or repeated clinical assessment, preceded by normal motor function, and
2. Presence of upper and lower motor neuron dysfunction in at least 1 body region (with upper and lower motor neuron dysfunction noted in the same body region if only one body region is involved) or lower motor neuron dysfunction in at least 2 body regions, and
3. Investigations excluding other disease processes

1. *Curr Opin Neurol.* 2020;33:641-648.
2. *Pract Neurol.* 2022;0:1-3.
3. *Ann Neurol.* 2021;89:979-986.

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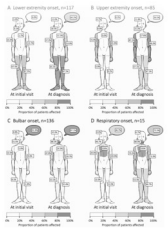
Diagnostic Delay in ALS

- Interval from symptom onset to a diagnosis of ALS is about 12 months
- Has consequences
  - Anxiety, lost income for patient and family
  - Unnecessary tests and treatments (including surgeries)
  - Delay in starting ALS treatments that can slow progression, improve quality of life, prevent complications
  - Progression where patient no longer qualifies for clinical trials



Amyotroph Lateral Scler Frontotemporal Degener. 2014;15:453-456.
Amyotroph Lateral Scler Frontotemporal Degener. 2022;Mar 27:1-9.
J Neurol Sci. 2020;417:117054.

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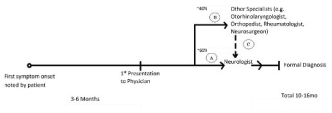
Improving Diagnostic Delay in ALS?

- Studies have delineated specific parts of the delay[1]
- Reasons may include rarity, variability, lack of single diagnostic test, lack of time to explain diagnosis, nihilism about ALS[1-3]
- Despite multiple attempts to improve, unchanged over many years of study[1-3]



1. *Amyotroph Lateral Scler Frontotemporal Degener.* 2014;15:453-456.
2. *Amyotroph Lateral Scler Frontotemporal Degener.* 2022;Mar 27:1-9.
3. *J Neurol Sci.* 2020;417:117054.

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BRAINWEEKEND

Review the current treatment landscape for ALS, including safety and efficacy

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Then

- Dr. Bedlack's first encounter with ALS was 23 years ago (resident at Duke)
- Amazed by the person's story, physical findings
- Horrified when attending said, "We know what this is called, but we don't know why it happens and there is nothing we can do about it. Go home and get your affairs in order."
- Decided to stay at Duke and build a new clinic to offer options and hope

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Now

- Many evidence- and experience-based treatment options
  - Entire books describing these[1]
  - AAN has 11 "ALS Quality Measures"[2]

1. Multidisciplinary Care Plan Developed or Updated
2. Disease Modifying Pharmacotherapy Discussed
3. Cognitive and Behavioral Impairment Screening
4. Symptomatic Treatment Offered
5. Respiratory Insufficiency Querying and Referral for PFT
6. NIV Treatment for Respiratory Insufficiency Discussed
7. Screening for Dysphagia, Weight Loss, and Impaired Nutrition
8. Nutritional Support Offered
9. Communication Support Offered
10. End of Life Planning Assistance
11. Falls Querying

1. ALS: A Care Guide for Clinicians; Demos Publishing 2013.
2. *Neurology*. 2013;10:2136-2140.

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Multidisciplinary Team Care

- ALS affects so many functions so quickly, it is difficult for 1 clinician to keep up
- Multidisciplinary teams are defined as having an ALS neurologist, and at least 2 of the following specialists: pulmonologist, gastroenterologist, physiatrist, psychiatrist, social worker, occupational therapist, physical therapist, speech therapist, psychologist, respiratory therapist, genetic counselor, palliative care specialist, specialized nurse, dietician, or dentist[1]
- Attendance in these is associated with better QOL scores, reduced hospitalizations, significantly longer survival[1,2]

1. *Neurology.* 2013;10:2136-2140.
2. *J Multidiscipln Healthc.* 2017;10:205-215.

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Multidisciplinary Team Care: Challenges

- Resource and time intensive
- No special billing code for this
  - Each provider bills separately
  - Some providers cannot bill (NT)
  - Insurance has limits on PT, OT, ST
  - Outside funding to supplement clinical losses is essential
- Too few of these
  - Half of all patients live more than 50 miles from a multidisciplinary care team[1]
  - Travel becomes difficult
    - Telemedicine can help

Amyotroph Lateral Scler Frontotemporal Degen. 2018;19:126-133.

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Riluzole

- Benzothiazole, given orally, blocks release of glutamate and modulates sodium channels
- FDA approved for ALS in 1995
  - Multiple randomized, double-blind, placebo-controlled trials showed it increased tracheostomy-free survival by a few months
- Many subsequent "real world" studies: most showed survival benefits, range 6-19 months[1]
- Can work even in late-stage patients[2]
- Now available in pill, film, and liquid forms
- Most patients in US take this throughout their disease

1. *Amyotroph Lateral Scler Frontotemporal Degen.* 2020;21:509-518.
2. *Lancet Neurol.* 2018;17(5):416-422.

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Riluzole: Challenges

- Overcoming nihilism of previous providers, Internet chat rooms
- Some patients will have side effects[1]
  - Usually minor (asthenia, nausea, oral numbness, change in taste)
  - Transaminase elevations of 3X ULN in 2%-10%; monitoring required
- Most hospice groups will not cover
  - But can be obtained inexpensively or free using Good.RX and HealthWell websites

Expert Opin Drug Safety. 2004;8:525-534.

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Radicava

- Intravenous antioxidant
- FDA approved for ALS in 2017, based on 2 randomized, double-blind, placebo-controlled trials in Japanese PALS
  - First trial showed no benefit over placebo[1]
  - Second trial of very early, rapidly progressive patients with well-preserved function showed 30% slowing in ALSFRS-R vs placebo over 6m[2]
  - Trials suggest good tolerability and safety
    - 10%-15% minor side effects, most commonly bruising, gait disturbance, headache
    - Rare hypersensitivity reactions, avoid with sulfite allergy

1. *Amyotroph Lateral Scler Frontotemporal Degener.* 2014;15:610-617.
2. *Lancet Neurol.* 2017;16:505-512.

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Radicava: Challenges

- Re-analysis of pivotal trial data raised questions about efficacy and safety[1]
- "Real world" studies often fail to confirm benefits[2,3]
- Infusion schedule is onerous
  - 60mg IV over 60min 14d in a row first month, 10d every month thereafter
  - Challenge to find infusion centers open on weekends
- Route of administration, infusion schedule warrant central access (ex. port)
- Medication cost: $12,000 per month
  - Most insurance companies will cover with PA (physician must certify patient meets certain criteria similar to single positive trial)
  - Health Well Foundation can help with cost

1. *Amyotroph Lateral Scler Frontotemporal Degener.* 2018;19:477-482.
2. *Amyotroph Lateral Scler Frontotemporal Degener.* 2019;20:260-263.
3. *JAMA Neurol.* 2022 Feb 1;79(2):121-130.

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Symptomatic Therapies

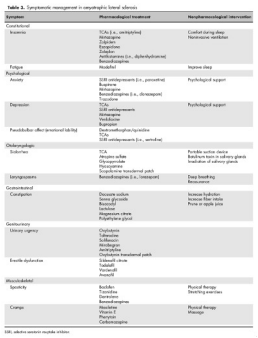

Table 2. Symptomatic management in amyotrophic lateral sclerosis

Symptom	Pharmacological treatment	Non-pharmacological intervention
Constitutional		
Insomnia	TCAs (i.e., amitriptyline) Mirtazapine SSRI Eszopiclone Zolpidem Antihistamines (i.e., diphenhydramine) Benzodiazepines	Comfort during sleep Noninvasive ventilation
Fatigue	Modafinil	Improve sleep
Psychological		
Anxiety	SSRI serotonin reuptake (i.e., paroxetine) TCAs Mirtazapine Benzodiazepines (i.e., clonazepam) Buspirone	Psychological support
Depression	TCAs SSRI serotonin reuptake Mirtazapine Venlafaxine Bupropion	Psychological support
Pseudobulbar affect (emotional lability)	Dextromethorphan/quinidine TCAs SSRI serotonin reuptake (i.e., sertraline)	
Oropharyngeal		
Sialorrhea	TCA Botulinum toxins Glycopyrrolate Hyoscyamine Scopolamine transdermal patch	Portable suction device Radiation therapy to salivary glands Excision of salivary glands
Laryngospasms	Benzodiazepines (i.e., lorazepam)	Deep breathing Relaxation
Gastrointestinal		
Constipation	Docusate sodium Polyethylene glycols Bisacodyl Lactulose Magnesium citrate Polyethylene glycol	Increase hydration Increase fiber intake Prune or apple juice
Genitourinary		
Urinary urgency	Oxybutynin Tolterodine Solifenacin Hyoscyamus Amitriptyline Scopolamine transdermal patch	
Erectile dysfunction	Sildenafil citrate Tadalafil Vardenafil Avanafil	
Musculoskeletal		
Spasticity	Baclofen Tizanidine Diazepam Benzodiazepines	Physical therapy Stretching exercises
Cramps	Mexiletine Vitamin E Quinine Carbamazepine	Physical therapy Massage

SSRI, selective serotonin reuptake inhibitor.

Curr Opin Neurol. 2020;33:641-648.

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Dextromethorphan/Quinidine

- An oral combination of dextromethorphan and quinidine
- FDA approved in 2010 for pseudobulbar affect (PBA) based on 2 randomized, double-blind, placebo-controlled trials[1]
- Can also improve bulbar function (speech, swallowing, sialorrhea)[2]
  - Even in patients without PBA (but difficult to get coverage in this setting)
- Generally safe, well-tolerated, but watch for QT prolongation

1. *CNS Drugs.* 2011;25:435-441.
2. *Neurotherapeutics.* 2017;14:762–772.

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Summarize the pipeline drugs and emerging treatment options for ALS

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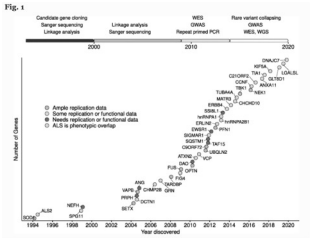
ALS Pathophysiology: Genetics

- 10% of patients with ALS have a family history of the disease ("familial ALS"), and 5%-10% of those with "sporadic ALS" have an identifiable ALS-causing gene
  - More than 30 different ALS-causing genes have been discovered



Curr Genetic Med Rep. 2020;8:121-131.

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SOD1 Mutations (Case 2%-3% of all ALS)

- Believed to cause disease via a "toxic gain of function"[1]
- Pharmacodynamic goal: reduce the amount of mSOD1 protein
- Tofersen (Biogen's ASO) reduced mSOD1 protein by 35%, failed to produce convincing clinical benefits in a 6-month, phase 3 trial[2]
  - Too late in the disease, too little mSD1 reduction, or too short a f/u interval?
- A trial of Tofersen in "presymptomatic" patients now enrolling[3]
- Other ways to reduce mSOD1 now in development[2,4]
  - RNA interference, antibodies

1. *Mol Ther.* 2021;29:3365-3376.
2. *Nature Rev Drug Discovery.* 2021;20:883-885.
3. NCT04856982.
4. *N Engl J Med.* 2020;383:151-158.

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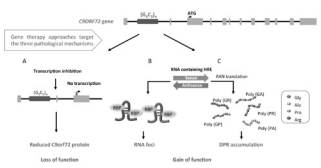
C9ORF72 Repeats (Cause 5%-7% of All ALS)

- Controversy in how they cause disease (loss vs gain of function)
- Biogen's ASO targeting C9ORF72 failed in recent trial[2]
- Other ways to reduce C9-associated RNA foci, DPR accumulation, now underway[3,4]



1. *Int J Mol Sci.* 2019;20:1-21
2. alsnewstoday.com/news-posts/2022/04/11/biogen-ionis-discontinuing-bib078-development-c9orf72-associated-als.
3. ir.wavelifesciences.com/news-releases/news-release-details/wave-life-sciences-announces-positive-update-ongoing-phase-1b2a.
4. NCT04220021.

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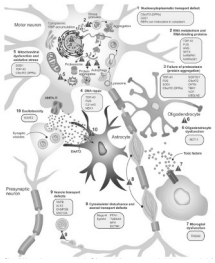
ALS Pathophysiology: Downstream Events

- While we do not understand the cause of most ALS, we have evidence that several specific "downstream events" contribute to the death of motor neurons
  - These are targets for many current trials



Dis Model Mech. 2017;10:537-549.

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Transcriptional Dysregulation and Mitochondrial Dysfunction

- Amylyx's AMX0035, oral combination of TUDCA and NaPB
- In 6-month trial, slowed ALSFRS-R progression by 30% vs placebo[1]
- In an OLE, those initially receiving AMX0035 had 6m longer survival[2]
- Currently under FDA review; replication trial also underway[3]

1. *N Engl J Med.* 2020;383:919-930.
2. *Muscle & Nerve.* 2021;63:51-39.
3. NCT05021536.

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Targeting Neuroinflammation

Phase 3

- Tyrosine kinase: AB Science's Mastinib[1,2]
- Phosphodiesterase: Medicinova's Ibudilast[3,4]

Phase 2

- Tregs: RAPA-501[5]
- C3 compliment: Pegcetacoplan[6]
- RIP1K: SAR4438207[7]
- Microglia: Verdiperstat[8]
- Microbiome: Fecal Transplants[9], Theracurmin[10]

1. *Amyotroph Lateral Scler.* 2010;21:5-14.
2. NCT03127267.
3. *Neurodegen Dis Manag.* 2021;11:431-443.
4. NCT04057898.
5. NCT04220190.
6. NCT04579664.
7. NCT05237284.
8. NCT04436510.
9. NCT03766321.
10. NCT04899963.

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Targeting Muscle

- Cytokinetics: Reldesemtiv
  - Troponin-activator, increases muscle force
  - Phase 2 trial showed promising trends toward slowing SVC, ALSFRS-R, muscle strength progression[1]
  - Phase 3 trial now underway[2]
- Duke: Clenbuterol
  - Beta2-adrenergic receptor agonist, stimulates protein synthesis which can lead to increases in muscle size, power
  - Previous animal study[3], case series[4] promising
  - Our very small, open label study suggested 70% slowing in ALSFRS-R and FVC progression on drug[5]

1. *Amyotroph Lateral Scler.* 2021;22:287-299.
2. NCT04944784.
3. *Neurosci Lett.* 2006;397:155-158.
4. *Amyotroph Lateral Scler.* 2006;7:246-248.
5. *Amyotroph Lateral Scler.* 2021;2152):150-173.

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Many Other Treatments In Development

- As of 4/27/22, there are 66 ALS trials listed on www.clinialtrials.gov as active or recruiting/enrolling
- In 21 years, Dr. Bedlack has never seen this many trials underway at one time

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Identify the importance of utilizing collaborations to optimize patient outcomes for those struggling with ALS

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ALS Collaborations

- Patient care
  - As we previously discussed, multidisciplinary team care can improve quality of life, reduce hospitalizations, lengthen life
- Research
- Advocacy

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ALS Research Collaborations

- Across different institutions
  - ALS trial consortia have formed (ex. NEALS), facilitate training, standardization of outcomes, conduct of multicenter trials[1]
- Between clinical researchers in ALS and other fields
  - Ideas for more efficient ways to conduct trials (ex. Registries[2], Platform Trials[3])

1. *Amyotroph Lateral Scler.* 2013;14(S1):53-61.
2. *J Med Internet Res.* 2021;23:e28021.
3. *Ann Neurol.* 2022;91:161-175.

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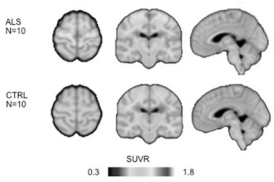
ALS Research Collaborations

- Between basic and clinical researchers
  - New models for the disease (ex. IPSC-derived motor neurons) which we hope will be more predictive[1]
  - Biomarkers that can potentially help select most promising patients for new treatments, shorten duration of trials[2,3]



1. *Brain Res.* 2017;1:88-97.
2. *Front Neurol.* 2019;10:291.
3. *Neuroimage Clin.* 2015;7:409-414.

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ALS Research Collaborations

- Between researchers and patients
  - "Better together"
  - We started hosting ALS Clinical Research Learning Institutes to empower patients to understand research better[1]
  - The 500 graduates of these (called Research Ambassadors) are now connecting regularly with sponsors, researchers, other patients to improve trial design, efficiency[2]

1. *Amyotroph Lateral Scler.* 2020;21:216-221.
2. *Amyotroph Lateral Scler.* 2021;22:147-150.

45

ALS Advocacy Collaborations

- Between patients, patient advocacy groups (ALSA, IAMALS), clinicians and researchers
  - Laws, policies being changed to improve benefits[1], increase federal funding for research[2], speed FDA approvals[3], expand access to experimental treaments[4]

1. secure.ssa.gov/poms.nsf/lnx/0423580001.
2. cdmrp.army.mil/alsrp/default.
3. www.fda.gov/regulatory-information/search-fda-guidance-documents/amyotrophic-lateral-sclerosis-developing-drugs-treatment-guidance-industry.
4. iamals.org/updates/act-for-als/.

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Conclusions

- ALS is a degenerative disease most obviously affecting motor neurons, which has devastating effects on individual patients and families, and on societies
- Diagnosis is often delayed, which can lead to unnecessary tests and surgeries, can delay important treatments, and can reduce trial enrollment
- There are currently several therapies that can improve quality of life and some that may slow disease progression slightly
- Improved understanding of the disease has led to many promising current trials; better treatments are coming
- Collaborations are key in terms of optimizing patient care, research, and advocacy: We are better together

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Thanks

- Patients and families living with ALS for inspiring us, believing in us, participating in our clinics and our research
- Collaborators around the world
- Sponsors of this program

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