Exploration of Neuroprotective Therapy

Open Exploration

Open Access Perspective

Can we find early phase biomarkers for ALS: What are the prospects and challenges?

Christopher A. Shaw[1*], Ceilidh Beck[2], Leal Marakoff[3]

[1]Department of Ophthalmology and Visual Sciences, University of British Columbia, Vancouver, BC V6T 1Z3, Canada
[2]Capilano University, North Vancouver, BC V7J 3H5, Canada
[3]Independent researcher, Vancouver, BC V6M 0B1, Canada

***Correspondence:** Christopher A. Shaw, Department of Ophthalmology and Visual Sciences, 2176 Health Sciences Mall, University of British Columbia, Vancouver, BC V6T 1Z3, Canada. cashawlab@gmail.com
Academic Editor: Yujie Chen, Third Military Medical University, China
Received: November 11, 2025 **Accepted:** December 8, 2025 **Published:** December 26, 2025

Cite this article: Shaw CA, Beck C, Marakoff L. Can we find early phase biomarkers for ALS: What are the prospects and challenges? Explor Neuroprot Ther. 2025;5:1004133. https://doi.org/10.37349/ent.2025.1004133

Abstract

Age-related neurological disorders such as ALS (Lou Gehrig's disease), Parkinson's disease, and Alzheimer's disease have few truly effective treatment options. At best, these may slow the inexorable disease progression without providing a cure. Part of the problem with therapeutic approaches may arise due to the stage at which these diseases are detected, particularly the sporadic forms. In most cases, early signs and symptoms may be insidious, thus hiding the significant damage done to the areas of the nervous system impacted prior to any firm clinical diagnosis. This situation appears to necessitate the development of earlier detection methods for "biomarkers" that might allow for much earlier phase disease state treatments that might serve to significantly slow or even halt disease progression. Currently, most biomarkers in use serve primarily as aids to disease diagnosis, at which point there are no successful treatment options. In contrast, a search for more effective early treatment options would need to identify characteristic and specific molecular signatures of disease onset and progression using methods that are simple, such as blood-based analytical assays, relatively cheap, and crucially minimally invasive.

Keywords

early disease detection, prophylaxis, non-invasive techniques, biomarkers, ALS (Lou Gehrig's disease)

Introduction

Amyotrophic lateral sclerosis (ALS) is a neurological disorder in which motor neurons in the spinal cord and motor cortex degenerate [1, 2], leading eventually to the loss of motor function, including that for the diaphragm. In turn, the loss of innervation to the diaphragm leads inevitably to ventilatory failure; forced ventilation eventually leads to secondary bacterial infections, including pneumonia [3]. Patient death typically occurs within 5 years, although longer survival in some patients occurs [4, 5].

There are currently no "cures" for ALS, despite a multitude of failed attempts [6]. Of the three approved drugs available for treatment of sporadic ALS in North America in 2024, none show more than a modest slowing of disease progression [7–9], with riluzole having the only real efficacy, as modest as that has been [4].

ALS incidence in North America is 2–3/100,000 [10]. Most cases of ALS are sporadic, that is, of unknown origin, with less than 10% of all cases owing to inherited genetic mutations**.** In spite of this, the focus of research over the last 35 years, and even more recently, has been on the genetic "familial" cases, although it remains unclear if the molecular events leading to motor neuron death in familial ALS are identical in all features to the sporadic cases.

Recent work has highlighted the possibility that non-coding regions of the genome may be involved, reinforcing an older notion that ALS arises due to some combination of genetic and environmental interactions of unknown type(s) [11, 12]. It is also becoming apparent that ALS is a multisystem disorder affecting not only motor neurons in the nervous system, but also peripheral tissues such as skin and muscle. The literature on changes in skin structure, particularly collagen, goes back to the observations of Charcot on the absence of bed sores in ALS patients and extends to more recent research from Japanese investigators [13–15].

In ALS, some estimates report the loss of over 60% of motor neurons prior to clinical diagnosis. It remains unclear, however, if the apparent loss of motor neurons represents the actual degeneration of this percentage of motor neurons or may instead reflect a loss of "functional" motor neurons in which some neurons that have not actually degenerated may actually be recoverable. This notion ties in with a view that some neurons are in a state termed "idling neurons" and may still be alive, albeit non-functional [16, 17].

Early phase detection of biomarkers

A second key problem is that the longer the degeneration process has been extant, the number of neural dysfunctions has inevitably increased in a non-linear manner. A disease in which a continuously acting, single insult successively kills motor neurons until reaching the threshold for motor dysfunction would be a simpler situation. However, the progressive nature of motor neuron loss/dysfunction, likely due to a cascade of pathological events, would necessarily involve multiple therapeutic interventions and thus be likely unsuccessful [18, 19]. Given this, it becomes difficult to imagine a successful ALS "cocktail" of molecules capable of halting multiple pathological biochemical pathways without also triggering myriad inevitable side effects.

A potential solution, perhaps the most feasible one, lies in the earliest possible detection of molecular/cellular events that might predispose an individual to the development of ALS (or any neurological disease) in the first place, or those events that occur in the initial stages of the disease prior to clinical detection. Some examples might include various signaling pathways such as those involved in protein phosphorylation or cytokine activation [20].

While such early molecular and cellular events remain largely unknown (save perhaps those traceable to specific, mutant ALS genotypes), early detection of the molecular unpinning of ALS might indeed be crucial to any effective treatment. As noted above, a fundamental problem for any therapeutic strategy for ALS (or any of the other age-related neurological diseases) is the extent of neural damage that occurs prior to clinical detection, for the neural injuries compound and multiply faster than symptom severity grows [11].

In recent years, there has been considerable speculation concerning biomarkers of the disease process [6, 21–23]. Such biomarkers might be molecular or cellular alterations that can be detected by biochemical means or by measurements of neural activity. It is important here to distinguish the various ways biomarkers have or might be used. For example, biomarkers of whatever type can be used as an aid to clinical diagnosis once a preliminary set of signs and symptoms suggests the presence of a particular disease. Or, in disease treatment, biomarkers might be used to evaluate both disease progression and the efficacy of any potential treatment. Most challenging, however, would be the development of biomarkers

detectable prior to clinical diagnosis, when the most effective treatments might be initiated (as described above).

The most common ALS biomarker measures currently are those used to further validate preliminary disease diagnoses [24]. For example, electrophysiological measurements of neural activity, such as axon conduction [25], biochemical analysis of relevant biofluids [26], and magnetic resonance imaging (MRI) or positron emission tomography (PET)-based imaging of CNS tissue [27, 28] have provided reliable assistance in diagnostic confirmation (see Table 1). While valuable information can be obtained in such analyses, the fact that none of the age-related neurological diseases are "curable" post-diagnosis may mean that potential treatment options that might have been successful at earlier disease stages are not deliverable in a timely manner.

Table 1. Selected ALS biomarker candidates, with possible usage.

Biomarker methodology	Intended analyses	Commonly measured tissues	Biomarkers of particular interest	Reference(s)
Imaging biomarkers				
MRI-DTI: FA, MD as proxies of white-matter fiber/axonal integrity	diagnosis, progression	CST, esp. brainstem	+	[27, 44]
[^{18}F]FEDV-PET: high spatial-resolution index of excessive oxidative stress	diagnosis, prediction?	CSF diffuses through the BBB	+	[28]
[^{18}F]FDG-PET: index of reduced oxidative respiration (low ATP)	diagnosis? prognosis?	CSF diffuses through the BBB		[45]
Physiologic biomarkers				
MScanFIT MUNE	progression	various muscles		[25, 45]
MUNIX	progression, prediction?	various muscles		[45, 46]
EIM	progression	various muscles		[45]
Chemical biomarkers				
Protein immunoassay (suggested method)				
(Simoa®): NF-L	prediction, diagnosis, prognosis?	CSF	+	[32, 33]
		blood	+	[32, 33]
(MSD): pNF-H	requires further study	CSF		[32]
		plasma		[33]
(ELISA): PGRN	requires further study	CSF		[33, 47]
		blood		[33, 47, 48]
(nLC-MS): TDP-43	diagnosis, progression	CSF	+	[33, 49]
		PBMC		[33]
		plasma		[33]
nLC-MS: multiprotein expression profiles	diagnosis, progression	PBMC	+	[33]
Cell-based assays: stress granules & associated proteins	requires further study	Cell-based assays		[33]
Immunoassay: cytokines, pro-inflammatory	requires further study	CSF		[32]
		blood		[32, 33]
Hematology exam (photometry): CK	diagnosis, progression	blood	+	[33, 50, 51]
EV NGS: extracellular RNA	diagnosis?	CSF		[33]
		blood		[33]
Structural inspection, cellular-respiratory assays: damaged mitochondria	diagnosis?	all tissues	+	[33]

[^{18}F]FDG-PET: [^{18}F]fluorodeoxyglucose-positron emission tomography; [^{18}F]FEDV-PET: [^{18}F]fluoroedaravone-positron emission tomography; BBB: blood-brain barrier; CK: creatine kinase; CSF: cerebrospinal fluid; CST: corticospinal tract; EIM: electrical impedance myography; EV: extracellular vesicle; FA: fractional anisotropy; MD: mean diffusivity; MRI-DTI: magnetic resonance imaging-based diffusion tensor imaging; MSD: Meso Scale Discovery; MUNE: motor unit number estimation; MUNIX: motor unit number index; NF-L: neurofilament light chain; NGS: next-generation sequencing; nLC-MS: nano liquid chromatography-mass spectrometry; PBMC: peripheral blood mononuclear cells; PGRN: progranulin; pNF-H: phosphorylated neurofilament heavy chain; Simoa®: single-molecule array immunoassay; TDP-43: transactive response DNA binding protein 43.

A more effective solution would be the development of biomarkers able to detect the earliest stages of dysfunction before the disease has cascaded out of control. In other words, what is urgently needed is a prognostic approach such as that applied to non-neurological disorders, e.g., in spite of specificity issues, the PSA test for prostate cancer [29], or the more robust Framingham criteria for cardiovascular disease [30].

As with any attempt to provide early detection of a future neurological disease state, a series of limiting issues are essential to be addressed. Key amongst these is the requirement for a sufficient number of samples/participants in order to ensure statistical rigor and avoid sampling bias. In this regard, to achieve an appropriate sample size, the methods used must be (a) minimally invasive, (b) easily administered, and (c) low-cost. Further, if data are to be compared and validated between investigators/facilities, standardized protocols must be used. Finally, patient anonymity and informed consent for all procedures are fundamentals that must be fully in place.

A brief review of neurological disease biomarkers currently evaluated

The following summaries provide some studies where biomarkers have been evaluated in neurological diseases. For ALS, Bowser et al. (2011) [31] have considered the use of protein biomarkers in the cerebrospinal fluid (CSF) or in blood. Other biomarkers evaluated are heavy neurofilaments or cytokines, mostly from CSF. One crucial problem with all of these is the invasiveness and potential hazards of lumbar punctures to obtain the CSF for analysis. In addition, it is difficult to imagine that such measures using CSF could ever be used for mass screening. Bowser et al. (2011) [31] also considered electrophysiological and imaging methods, but in the context of an already established ALS state. From the same perspective, Huang et al. (2020) [32] also proposed examining CSF for neurofilament light chain or various increased or decreased cytokines with a focus on the pro-inflammatory ones.

Wilkins et al. (2021) [33] proposed that various molecules in blood or CSF might be used as biomarkers, notably neurofilament proteins, extracellular RNA and stress granules, progranulin, RNAseq, cytokines and metabolites, as well as damaged mitochondria, some of which might be detectable in blood. Included in this list is the presence of creatine kinase.

Insight into the cascade of pathological processes is apparent in "omics" analyses of all types, showing multiple abnormal events. On the one hand, proteomics has enabled the detection of tens if not hundreds of abnormal levels of various proteins (some increased, others decreased) in ALS, discovered through post-diagnosis analysis of CSF [34] or plasma [35] or through post-mortem analysis [36]. Specific protein-protein interactions have been associated with toxicity in neurodegenerative diseases such as ALS [37]. Alternatively, microbiomics, the analysis of microbial (fungal and bacterial) communities and their genetic makeup, is a relevant field of study, as imbalances in the complex microbial relationships within a patient's gut may have neuropathic effects. By decoding the genetic profiles of these microbial groups, researchers might be able to pinpoint specific microbiome signatures linked to particular diseases, offering important markers for diagnosis and prognosis if implicated in ALS [37]. However, isolating a distinct microbiome signature for ALS has not been accomplished to date [38].

As the field of metabolomics expands to collect more data within the ALS patient population, "omics" profiles might be assessed not only for early identification of the ALS disease processes, but also for observation of patient response to therapeutic interventions [37, 38]. Models based on metabolites related to antioxidant defense, polyamine metabolism, amino acid metabolism, platelets, and lipid sub-pathways (i.e., sphingolipids) are showing some correlation to ALSFRS-R status but are currently unusable as diagnostics [39, 40].

Early disease detection in Alzheimer's disease as well as Parkinson's disease is developing through proteomics and metabolomics, with metabolomics "...hold greater potential for facilitating early diagnosis and developing effective therapies..." [41]. In the case of Alzheimer's disease, Hunter et al. (2025) [42] noted the absence of effective blood-based tests for molecules involved in the disease, observing that the field was largely focused on CSF analyses of amyloid beta 40/4 and p-tau 181 or their metabolites, or

extracellular vesicles from degenerating neurons. Broader capture of alterations in metabolic processes as well as protein abnormalities through blood analysis could lead researchers to the cause of the disease, earlier stages of disease progression, and patient response to treatment, rather than having to rely on higher-risk CSF sampling. Acknowledged by Franco et al. (2024) [41] is the need for "…combined application of both proteomics and metabolomics…for early disease diagnosis" in Alzheimer's and Parkinson's disease.

The following multiple, recurring problems continue to impede the discovery of early diagnostic approaches: 1) the late-stage of disease progression at the time of analyses, 2) the invasiveness of the procedures, 3) underpowered studies, 4) poor replication, 5) incomplete patient characterization, and 6) substantial differences in data collection and analyses [43].

What would an ideal early ALS biomarker look like?

As detailed above, the most effective biomarker would be one that allows the earliest possible detection of the onset of the processes leading to neuron loss and thus the greatest likelihood of effective treatment. If the goal is the earliest possible detection, the biomarker hunt would necessarily require the least invasive procedures possible. For example, if the underlying pathology begins early in life, then it would be almost impossible to get those who do not yet show any signs or symptoms of neurological disease to submit to invasive procedures such as lumbar punctures, particularly if such procedures need to be repeated multiple times. Not least, even assuming that various imaging techniques could be applied in pre-clinical disease, there is the problem of cost: Any such screening offered to the population at large would have to be cost-effective, and given prohibitive costs and logistics, a solution is difficult to imagine.

Conclusions

A plausible approach to early ALS, or other neurological disease onset, would likely entail all of the following tests: screening of easily accessible and minimally invasive fluids/tissues, e.g., blood, urine, saliva, and hair; and screening using somewhat more invasive techniques, such as muscle or skin biopsies. Any of these would need to be part of a routine medical checkup.

Failing the future availability of such tests, preventing disease onset or progression is unlikely to be successful.

Abbreviations

ALS: amyotrophic lateral sclerosis

CSF: cerebrospinal fluid

Declarations

Author contributions

CAS: Conceptualization, Writing—original draft, Writing—review & editing, Project administration, Investigation. CB: Writing—review & editing, Investigation. LM: Writing—review & editing, Investigation, Visualization. All authors read and approved the submitted version.

Conflicts of interest

The first author, Christopher A. Shaw, holds founder shares in Neurodyn Corp and its subsidiary, Alpha Cognition, biotechnology companies that are developing treatments for neurological disorders but are not involved in biomarker studies. Christopher A. Shaw, who is the Associate Editor of Exploration of Neuroprotective Therapy, had no involvement in the decision-making or the review process of this manuscript. The other authors declare no conflicts of interest.

Ethical approval

Not applicable.

Consent to participate

Not applicable.

Consent to publication

Not applicable.

Availability of data and materials

Not applicable.

Funding

Not applicable.

Publisher's note

References

1. van Es MA, Hardiman O, Chio A, Al-Chalabi A, Pasterkamp RJ, Veldink JH, et al. Amyotrophic lateral sclerosis. Lancet. 2017;390:2084–98. [DOI] [PubMed]
2. Feldman EL, Goutman SA, Petri S, Mazzini L, Savelieff MG, Shaw PJ, et al. Amyotrophic lateral sclerosis. Lancet. 2022;400:1363–80. [DOI] [PubMed] [PMC]
3. Elman L, McCluskey L, Quinn C. Clinical features of amyotrophic lateral sclerosis and other forms of motor neuron disease [Internet]. UpToDate; c2025 [cited 2025 Apr 3]. Available from: https://www.uptodate.com/contents/clinical-features-of-amyotrophic-lateral-sclerosis-and-other-forms-of-motor-neuron-disease
4. Riva N, Domi T, Pozzi L, Lunetta C, Schito P, Spinelli EG, et al. Update on recent advances in amyotrophic lateral sclerosis. J Neurol. 2024;271:4693–723. [DOI] [PubMed] [PMC]
5. 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. [DOI] [PubMed]
6. Genge A, Wainwright S, Vande Velde C. Amyotrophic lateral sclerosis: exploring pathophysiology in the context of treatment. Amyotroph Lateral Scler Frontotemporal Degener. 2024;25:225–36. [DOI] [PubMed]
7. Miller RG, Mitchell JD, Moore DH. Riluzole for amyotrophic lateral sclerosis (ALS)/motor neuron disease (MND). Cochrane Database Syst Rev. 2002;2:CD001447. [DOI] [PubMed]
8. Writing Group}; {Edaravone (MCI-186) ALS 19 Study Group. Safety and efficacy of edaravone in well defined patients with amyotrophic lateral sclerosis: a randomised, double-blind, placebo-controlled trial. Lancet Neurol. 2017;16:505–12. [DOI] [PubMed]
9. Paganoni S, Macklin EA, Hendrix S, Berry JD, Elliott MA, Maiser S, et al. Trial of Sodium Phenylbutyrate-Taurursodiol for Amyotrophic Lateral Sclerosis. N Engl J Med. 2020;383:919–30. [DOI] [PubMed] [PMC]

10. Xu L, Liu T, Liu L, Yao X, Chen L, Fan D, et al. Global variation in prevalence and incidence of amyotrophic lateral sclerosis: a systematic review and meta-analysis. J Neurol. 2020;267:944–53. [DOI] [PubMed]
11. Shaw CA, Morrice JR, editors. Spectrums of Amyotrophic Lateral Sclerosis: Heterogeneity, Pathogenesis and Therapeutic Directions. Boston: John Wiley and Sons; 2021.
12. Duan QQ, Jiang Z, Su WM, Gu XJ, Wang H, Cheng YF, et al. Risk factors of amyotrophic lateral sclerosis: a global meta-summary. Front Neurosci. 2023;17:1177431. [DOI] [PubMed] [PMC]
13. Paré B, Gros-Louis F. Potential skin involvement in ALS: revisiting Charcot's observation—a review of skin abnormalities in ALS. Rev Neurosci. 2017;28:551–72. [DOI] [PubMed]
14. FULLMER HM, SIEDLER HD, KROOTH RS, KURLAND LT. A cutaneous disorder of connective tissue in amyotrophic lateral sclerosis. A histochemical study. Neurology. 1960;10:717–24. [DOI] [PubMed]
15. Ono S. The skin in amyotrophic lateral sclerosis. Amyotroph Lateral Scler Other Motor Neuron Disord. 2000;1:191–9. [DOI] [PubMed]
16. James PB, editor. Oxygen and the Brain: The Journey of Our Lifetime. North Palm Beach: Best Publishing Company; 2014.
17. Neubauer RA, James P. Cerebral oxygenation and the recoverable brain. Neurol Res. 1998;20:S33–6. [DOI] [PubMed]
18. Richards D, Morren JA, Pioro EP. Time to diagnosis and factors affecting diagnostic delay in amyotrophic lateral sclerosis. J Neurol Sci. 2020;417:117054. [DOI] [PubMed]
19. Gwathmey KG, Corcia P, McDermott CJ, Genge A, Sennfält S, de Carvalho M, et al. Diagnostic delay in amyotrophic lateral sclerosis. Eur J Neurol. 2023;30:2595–601. [DOI] [PubMed]
20. Martínez HR, Escamilla-Ocañas CE, Tenorio-Pedraza JM, Gómez-Almaguer D, Jaime-Perez JC, Olguín-Ramírez LA, et al. Altered CSF cytokine network in amyotrophic lateral sclerosis patients: A pathway-based statistical analysis. Cytokine. 2017;90:1–5. [DOI] [PubMed]
21. Jia R, Chen Q, Zhou Q, Zhang R, Jin J, Hu F, et al. Characteristics of serum metabolites in sporadic amyotrophic lateral sclerosis patients based on gas chromatography-mass spectrometry. Sci Rep. 2021;11:20786. [DOI] [PubMed] [PMC]
22. McMackin R, Bede P, Ingre C, Malaspina A, Hardiman O. Biomarkers in amyotrophic lateral sclerosis: current status and future prospects. Nat Rev Neurol. 2023;19:754–68. [DOI] [PubMed]
23. Katzeff JS, Bright F, Phan K, Kril JJ, Ittner LM, Kassiou M, et al. Biomarker discovery and development for frontotemporal dementia and amyotrophic lateral sclerosis. Brain. 2022;145:1598–609. [DOI] [PubMed] [PMC]
24. Bede P, Hardiman O. Lessons of ALS imaging: Pitfalls and future directions—A critical review. Neuroimage Clin. 2014;4:436–43. [DOI] [PubMed] [PMC]
25. de Carvalho M, Scotto M, Lopes A, Swash M. Quantitating progression in ALS. Neurology. 2005;64: 1783–5. [DOI] [PubMed]
26. Irwin KE, Sheth U, Wong PC, Gendron TF. Fluid biomarkers for amyotrophic lateral sclerosis: a review. Mol Neurodegener. 2024;19:9. [DOI] [PubMed] [PMC]
27. Baek SH, Park J, Kim YH, Seok HY, Oh KW, Kim HJ, et al. Usefulness of diffusion tensor imaging findings as biomarkers for amyotrophic lateral sclerosis. Sci Rep. 2020;10:5199. [DOI] [PubMed] [PMC]
28. Wilde JH, Sun YY, Simpson SR, Hill ER, Fu Z, Bian EJ, et al. A positron emission tomography tracer for the imaging of oxidative stress in the central nervous system. Nat Biomed Eng. 2025;9:716–29. [DOI] [PubMed] [PMC]
29. Canadian Cancer Society. Prostate-specific antigen (PSA) test [Internet]. Canadian Cancer Society; c2025 [cited 2025 Apr 7]. Available from: https://cancer.ca/en/treatments/tests-and-procedures/prostate-specific-antigen-psa-test
30. Framingham Heart Study (FHS) [Internet]. [cited 2025 Apr 7]. Available from: https://www.nhlbi.nih.gov/science/framingham-heart-study-fhs

31. Bowser R, Turner MR, Shefner J. Biomarkers in amyotrophic lateral sclerosis: opportunities and limitations. Nat Rev Neurol. 2011;7:631–8. [DOI] [PubMed]
32. Huang F, Zhu Y, Hsiao-Nakamoto J, Tang X, Dugas JC, Moscovitch-Lopatin M, et al. Longitudinal biomarkers in amyotrophic lateral sclerosis. Ann Clin Transl Neurol. 2020;7:1103–16. [DOI] [PubMed] [PMC]
33. Wilkins HM, Dimachkie MM, Agbas A. Blood-based Biomarkers for Amyotrophic Lateral Sclerosis. In: Araki T, editor. Amyotrophic Lateral Sclerosis. Brisbane: Exon Publications; 2021. [DOI] [PubMed]
34. Katzeff JS, Bright F, Lo K, Kril JJ, Connolly A, Crossett B, et al. Altered serum protein levels in frontotemporal dementia and amyotrophic lateral sclerosis indicate calcium and immunity dysregulation. Sci Rep. 2020;10:13741. [DOI] [PubMed] [PMC]
35. Xu Z, Lee A, Nouwens A, Henderson RD, McCombe PA. Mass spectrometry analysis of plasma from amyotrophic lateral sclerosis and control subjects. Amyotroph Lateral Scler Frontotemporal Degener. 2018;19:362–76. [DOI] [PubMed]
36. Sohn AL, Ping L, Glass JD, Seyfried NT, Hector EC, Muddiman DC. Interrogating the Metabolomic Profile of Amyotrophic Lateral Sclerosis in the Post-Mortem Human Brain by Infrared Matrix-Assisted Laser Desorption Electrospray Ionization (IR-MALDESI) Mass Spectrometry Imaging (MSI). Metabolites. 2022;12:1096. [DOI] [PubMed] [PMC]
37. Scarcella S, Brambilla L, Quetti L, Rizzuti M, Melzi V, Galli N, et al. Unveiling amyotrophic lateral sclerosis complexity: insights from proteomics, metabolomics and microbiomics. Brain Commun. 2025;7:fcaf114. [DOI] [PubMed] [PMC]
38. Di Minno A, Gelzo M, Caterino M, Costanzo M, Ruoppolo M, Castaldo G. Challenges in Metabolomics-Based Tests, Biomarkers Revealed by Metabolomic Analysis, and the Promise of the Application of Metabolomics in Precision Medicine. Int J Mol Sci. 2022;23:5213. [DOI] [PubMed] [PMC]
39. Torres P, Pradas I, Fernàndez-Bernal A, Povedano M, Dominguez R, Jové M, et al. Exploring platelet metabolomics and fatty acid profiles for ALS prognosis and diagnosis. Sci Rep. 2025;15:34236. [DOI] [PubMed] [PMC]
40. Goutman SA, Guo K, Savelieff MG, Patterson A, Sakowski SA, Habra H, et al. Metabolomics identifies shared lipid pathways in independent amyotrophic lateral sclerosis cohorts. Brain. 2022;145: 4425–39. [DOI] [PubMed] [PMC]
41. Franco R, Garrigós C, Lillo J, Rivas-Santisteban R. The Potential of Metabolomics to Find Proper Biomarkers for Addressing the Neuroprotective Efficacy of Drugs Aimed at Delaying Parkinson's and Alzheimer's Disease Progression. Cells. 2024;13:1288. [DOI] [PubMed] [PMC]
42. Hunter TR, Santos LE, Tovar-Moll F, De Felice FG. Alzheimer's disease biomarkers and their current use in clinical research and practice. Mol Psychiatry. 2025;30:272–84. [DOI] [PubMed]
43. Steinbach R, Gaur N, Stubendorff B, Witte OW, Grosskreutz J. Developing a Neuroimaging Biomarker for Amyotrophic Lateral Sclerosis: Multi-Center Data Sharing and the Road to a "Global Cohort". Front Neurol. 2018;9:1055. [DOI] [PubMed] [PMC]
44. Qin J, Wang X, Fan G, Zhang W, Wu X, Wang B, et al. Identifying amyotrophic lateral sclerosis using diffusion tensor imaging, and correlation with neurofilament markers. Sci Rep. 2024;14:28110. [DOI] [PubMed] [PMC]
45. Verber NS, Shepheard SR, Sassani M, McDonough HE, Moore SA, Alix JJP, et al. Biomarkers in Motor Neuron Disease: A State of the Art Review. Front Neurol. 2019;10:291. [DOI] [PubMed] [PMC]
46. Neuwirth C, Barkhaus PE, Burkhardt C, Castro J, Czell D, de Carvalho M, et al. Motor Unit Number Index (MUNIX) detects motor neuron loss in pre-symptomatic muscles in Amyotrophic Lateral Sclerosis. Clin Neurophysiol. 2017;128:495–500. [DOI] [PubMed]
47. Wilke C, Gillardon F, Deuschle C, Dubois E, Hobert MA, Müller vom Hagen J, et al. Serum Levels of Progranulin Do Not Reflect Cerebrospinal Fluid Levels in Neurodegenerative Disease. Curr Alzheimer Res. 2016;13:654–62. [DOI] [PubMed]

48. Steinacker P, Huss A, Mayer B, Grehl T, Grosskreutz J, Borck G, et al. Diagnostic and prognostic significance of neurofilament light chain NF-L, but not progranulin and S100B, in the course of amyotrophic lateral sclerosis: Data from the German MND-net. Amyotroph Lateral Scler Frontotemporal Degener. 2017;18:112–9. [DOI] [PubMed]
49. Noto Y, Shibuya K, Sato Y, Kanai K, Misawa S, Sawai S, et al. Elevated CSF TDP-43 levels in amyotrophic lateral sclerosis: specificity, sensitivity, and a possible prognostic value. Amyotroph Lateral Scler. 2011;12:140–3. [DOI] [PubMed]
50. Patin F, Corcia P, Madji Hounoum B, Veyrat-Durebex C, Respaud E, Piver E, et al. Biological follow-up in amyotrophic lateral sclerosis: decrease in creatinine levels and increase in ferritin levels predict poor prognosis. Eur J Neurol. 2015;22:1385–90. [DOI] [PubMed]
51. Chiò A, Calvo A, Bovio G, Canosa A, Bertuzzo D, Galmozzi F, et al.; Piemonte and Valle d'Aosta Register for Amyotrophic Lateral Sclerosis. Amyotrophic lateral sclerosis outcome measures and the role of albumin and creatinine: a population-based study. JAMA Neurol. 2014;71:1134–42. [DOI] [PubMed]