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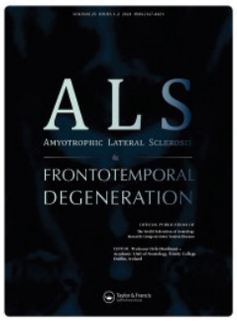

Amyotrophic Lateral Sclerosis and Frontotemporal Degeneration

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**RESEARCH ARTICLE**

# Misdiagnosis of amyotrophic lateral sclerosis in clinical practice in Europe and the USA: a patient chart review and physician survey

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**Abstract**

*Objective*: Delays in amyotrophic lateral sclerosis (ALS) diagnosis can result in compromised disease management and unnecessary costs. We examined the extent of ALS misdiagnosis in the US and Europe. *Methods*: Data were collected via the Adelphi ALS Disease Specific Programme™, a cross-sectional survey of physicians and a medical chart review of their consulting patients with ALS in France, Germany, Italy, Spain, the UK (EU5), and the US. Between July 2020 and March 2021, eligible physicians (primary speciality neurology, active involvement in managing patients with ALS) abstracted data from patients (≥18 years old) with confirmed ALS. *Results*: Overall, 138 physicians completed the survey (EU5 107, US 31), with data reviewed from 795 patient medical charts (EU5 568, US 227); 278 (35.0%) patients (EU5 183 [32.2%], US 95 [41.9%]) had received ≥1 initial misdiagnosis based on symptoms later attributed to ALS. Mean (SD) time from symptom onset to first healthcare professional consultation was 3.8 (5.2) months (EU5 4.3 [4.8] months, US 2.6 [5.8] months). Mean (SD) time from symptom onset to ALS diagnosis was 8.2 (12.5) months (EU5 9.6 [14.0] months, US 5.0 [6.8] months) and increased to 10.4 (17.9) for patients with a misdiagnosis (compared with 6.9 [7.2] for patients with no misdiagnosis). Physician-identified barriers to timely ALS diagnosis included the similarity of symptoms to other conditions and delayed referral to neurologists. *Conclusions*: Misdiagnosis of ALS is frequent, with a protracted diagnostic pathway. Targeted education of patients and physicians about signs and symptoms and benefits of prompt referral to multidisciplinary care are needed.

**Keywords:** *ALS, barriers, diagnosis, real-world data, symptoms*

**Subject Classification Code:** *Epidemiology, neuropathology, pathology*

## 1. Introduction

Amyotrophic lateral sclerosis (ALS) can be fatal within 2–3 years of symptom onset (1,2), which typically occurs when patients are in their mid-to-late fifties (2). Approved disease-modifying therapies are few and have modest effects on disease progression, and disease management focuses on symptom relief and respiratory support (2–4). ALS diagnosis is primarily based on clinical signs and symptoms but may be challenging when clinical presentation overlaps with other neurological disorders such as cervical spondylotic myelopathy (CSM) and cervical and lumbar radiculopathy (5–7). Assessments to aid clinical diagnosis of ALS may include physical examination, electromyography, and neuroimaging (8,9). The use of genetic testing for ALS varies in clinical practice for a variety of reasons, including access to genetic counseling and cost (10,11).

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The rapid progression of ALS means that prompt diagnosis and referral to specialists are essential for access to treatment or enrollment in clinical trials at early stages of the disease when disease-modifying therapies are most effective (12,13). Early diagnosis also provides patients with more time to come to terms with their terminal disease and plan for the future (12,14). In a review of 21 studies published between 1990 and 2020, Richards et al. found that the time from symptom onset to ALS diagnosis generally ranged from 10 to 16 months (12). Factors contributing to the protracted diagnostic timeline included referral time to specialists and misdiagnosis in 13–68% of ALS cases (12). Patients with sporadic ALS and those aged >60 years are more likely to receive a misdiagnosis than those with family history or those aged ≤60 years (13,15). A key challenge to early diagnosis is that initial symptoms may affect only one body region before spreading to other regions (8,16). Compared with bulbar-onset ALS, diagnostic delay may be longer for limb-onset ALS, owing in part to a greater likelihood of misdiagnosis (12,13,17). Misdiagnosis is also associated with advanced disease status at definitive ALS diagnosis, resulting in a reduced quality of life and increased healthcare costs (12,17).

We conducted a review of patient medical charts to examine the extent of misdiagnosis of ALS in the US and Europe and a survey to elicit physician perceptions about the barriers and challenges to timely diagnosis of ALS.

## 2. Materials and methods

Data were collected via the Adelphi ALS Disease Specific Programme™ (DSP), a cross-sectional survey of physicians, and medical chart review of their consulting patients with ALS in France, Germany, Italy, Spain, the United Kingdom (EU5) and the US between 06 July 2020 and 15 March 2021. The DSP survey methods have been previously published and validated (18–20). The survey design ensured that all patient medical charts and physician data were anonymised before receipt. Data collection was undertaken in line with European Pharmaceutical Marketing Research Association guidelines (21) and, as such, did not require ethics committee approval.

Fieldwork partners used a non-probabilistic sampling strategy to identify local physicians who were likely to treat patients with ALS. Physicians were eligible to participate if neurology as their primary speciality and they were actively involved in the management of patients with ALS, including consultation with at least two patients with a diagnosis of ALS per month. Physicians provided data, abstracted from medical charts, for a consecutive series of patients seen during the study period. After the consultation with the patient with ALS, the physician used an online patient record form (PRF) to enter data such as patient demographics and clinical characteristics; misdiagnosis history; testing approaches to aid ALS diagnosis; symptoms at disease onset and at the time of ALS diagnosis; and diagnostic timelines. Patients were ≥18 years old with a confirmed diagnosis of ALS and had at least one encounter with their treating physician for ALS during the study period.

Each participating physician also completed an online survey to capture perceptions and attitudes toward the management of ALS. Physicians were asked to select, from a list of options, those that, in their view, were the three key barriers/challenges to identifying and diagnosing ALS as early as possible. No ranking was applied to these barriers. Physician characteristics, including specialization and year of qualification, were also collected.

## 3. Results

### *3.1. Patient demographics and characteristics*

A total of 138 physicians completed PRFs, and medical chart data were abstracted for 795 patients, including 568 (71.4%) from EU5 sites (Table 1). Overall, the mean (SD) age of patients was 61.9 (11.1) years; the majority of patients were male (61.6% [490/795]) and of White/Caucasian ethnicity (89.8% [713/794]), and 51.2% (404/789) were retired (Table 1). The mean (SD) number of concomitant conditions per patient was 1.6 (1.5), and the mean (SD) Charlson Comorbidity Index was 0.3 (0.9). At the time that patient medical chart abstractions were performed, the mean (SD) revised ALS functional rating scale (ALSFRS-R) score was 33.3 (11.5), and the mean (SD) time since ALS diagnosis was 18.0 (18.2) months.

### *3.2. Physician demographics and characteristics*

Over three-quarters of physician respondents had their primary practice in EU5 (77.5% [107/138]); 52.2% (72/138) had qualified as a physician or specialist between 1997 and 2006, and 55.1% (76/138) self-reported as general neurologists (Table 2). Compared with EU5, a higher proportion of physicians in the US self-reported as neuromuscular specialists (45.2% [14/31] versus 28.0% [30/107]). None of the US physicians considered themselves to be ALS specialists, while 16.8% (18/107) of EU5 physicians self-reported as ALS specialists. The mean (SD) percentage of professional time spent managing patients with ALS was 22.9% (22.2%) (Table 2), ranging from 12.4% (14.0%) for those who self-reported as general neurologists ($n = 76$) to 51.0% (19.6%) for those who considered themselves ALS specialists ($n = 18$). The mean (SD) number of ALS diagnoses made in the last 12 months was similar

Table 1. Patient demographics and clinical characteristics from patient medical chart review.

| | Global | EU5 | United States |
|---|---|---|---|
| All patients with ALS, *n* | 795 | 568 | 227 |
| Age, years, mean (SD) | 61.9 (11.1) | 62.7 (11.3) | 60.0 (10.3) |
| Sex, male, *n* (%) | 490 (61.6) | 341 (60.0) | 149 (65.6) |
| BMI, kg/m$^2$, mean (SD) | 24.2 (3.2) | 24.0 (3.0) | 24.8 (3.6) |
| Number of concomitant conditions, mean (SD) | 1.6 (1.5) | 1.4 (1.5) | 1.9 (1.4) |
| Charlson Comorbidity Index, mean (SD) | 0.3 (0.9) | 0.3 (0.9) | 0.3 (0.8) |
| ALSFRS-R score, mean (SD) | 33.3 (11.5) | 33.2 (11.3) | 33.7 (11.9) |
| Time since ALS diagnosis, *n*[a] | 773 | 555 | 218 |
| Time since diagnosis, months, mean (SD) | 18.0 (18.2) | 19.1 (19.4) | 15.0 (14.1) |
| Employment status, *n*[b] | 789 | 562 | 227 |
| Working full-time, *n* (%) | 62 (7.9) | 38 (6.8) | 24 (10.6) |
| Working part-time, *n* (%) | 74 (9.4) | 51 (9.1) | 23 (10.1) |
| On long-term sick leave, *n* (%) | 123 (15.6) | 86 (15.3) | 37 (16.3) |
| Retired, *n* (%) | 404 (51.2) | 308 (54.8) | 96 (42.3) |
| Unemployed, *n* (%) | 49 (6.2) | 27 (4.8) | 22 (9.7) |
| Homemaker or student, *n* (%) | 77 (9.8) | 52 (9.3) | 25 (11.0) |
| Ethnic origin, *n*[c] | 794 | 562 | 227 |
| White/Caucasian, *n* (%) | 713 (89.8) | 531 (93.7) | 182 (80.2) |
| Hispanic/Latino, *n* (%) | 43 (5.4) | 23 (4.0) | 20 (8.8) |
| African American, *n* (%)[d] | 15 (1.9) | NA | 15 (6.6) |
| Afro-Caribbean, *n* (%)[e] | 5 (<1) | 5 (<1) | NA |
| Mixed race, *n* (%) | 8 (1.0) | 3 (<1) | 5 (2.2) |
| Asian (Indian subcontinent), *n* (%) | 4 (<1) | 3 (<1) | 1 (<1) |
| Middle Eastern, *n* (%) | 3 (<1) | 2 (<1) | 1 (<1) |
| Asian (other), *n* (%) | 2 (<1) | 0 | 2 (<1) |
| Native American, *n* (%)[f] | 1 (<1) | NA | 1 (<1) |

[a]Data missing for 22 patients for whom the time since diagnosis was not known by respondent physician.
[b]Data missing for six patients for whom employment status was not known by respondent physician.
[c]Data missing for one patient for whom ethnicity was not known by the respondent physician. There were no patients identified by respondent physicians as of "South-East Asian" or "Other" ethnicity.
[d]Response options are only available to respondent physicians in the United States.
[e]Response options are only available to respondent physicians in EU5.
ALS, amyotrophic lateral sclerosis; ALSFRS-R, revised ALS functional rating scale; BMI, body mass index; NA, not applicable; SD, standard deviation.

Table 2. Physician demographics from physician survey.

| | Global | EU5 | United States |
|---|---|---|---|
| Year of qualification as a physician, *n*[a] | 138 | 107 | 31 |
| Before 1984, *n* (%) | 5 (3.6) | 3 (2.8) | 2 (6.5) |
| 1984–1996, *n* (%) | 28 (20.3) | 20 (18.7) | 8 (25.8) |
| 1997–2006, *n* (%) | 72 (52.2) | 57 (53.3) | 15 (48.4) |
| 2007–2017, *n* (%) | 33 (23.9) | 27 (25.2) | 6 (19.4) |
| Physician specialty, *n*[a] | 138 | 107 | 31 |
| General neurologist, *n* (%) | 76 (55.1) | 59 (55.1) | 17 (54.8) |
| Neuromuscular specialist, *n* (%) | 44 (31.9) | 30 (28.0) | 14 (45.2) |
| ALS specialist, *n* (%) | 18 (13.0) | 18 (16.8) | 0 |
| Professional time spent managing patients with ALS, n[a] | 138 | 107 | 31 |
| Percentage of professional time spent managing patients with ALS, %, mean (SD) | 22.9 (22.2) | 22.9 (22.1) | 22.9 (23.2) |
| Total number of patients with ALS under current management, mean (SD) | 28.1 (48.5) | 25.5 (44.5) | 37.1 (60.3) |
| Diagnoses of ALS made by the physician, n[a,b] | 132 | 101 | 31 |
| ALS diagnoses made in the last 12 months, mean (SD) | 8.4 (12.5) | 8.4 (13.2) | 8.5 (9.7) |

[a]Number of physician respondents.
[b]Data missing for six physicians.
ALS, amyotrophic lateral sclerosis; SD, standard deviation.

between physicians in EU5 (8.4 [13.2]) and the US (8.5 [9.7]; Table 2).

### *3.3. Misdiagnosis prior to ALS diagnosis*

Overall, at least one initial misdiagnosis based on symptoms later attributed to ALS was reported for 35% (278/795) of patients in the study (Figure 1). The mean (SD) number of prior misdiagnoses per patient was 1.3 (0.6). Misdiagnosis was more common for patients in the US (41.9% [95/227]) than in EU5 (32.2% [183/568]); in the US 24.2% (23/95) of patients with a misdiagnosis received ≥2 misdiagnoses compared with 14.2% (26/183)

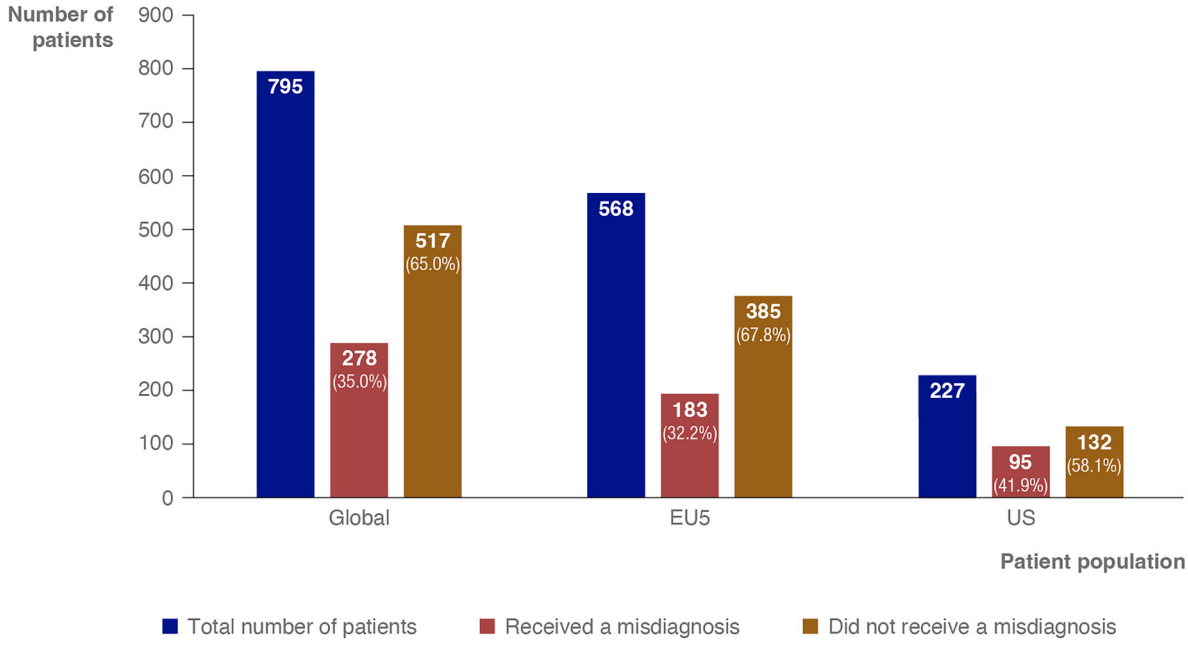


Figure 1. Misdiagnosis of ALS based on data from patient medical chart review.
ALS, amyotrophic lateral sclerosis.

in EU5. Within EU5, misdiagnosis was less common in Germany at 12.9% (15/116) than in the other countries, which were between 36.7% and 38.5%.

Globally, when asked about all the patients with ALS whom they currently manage (not only those included in this study), physicians estimated that around one-third (mean [SD] 32.2% [21.4%]) of patients initially received a misdiagnosis, or were suspected to have another condition, prior to receiving an ALS diagnosis. Compared with physicians in EU5 ($n = 107$), physicians in the US ($n = 31$) reported a higher proportion of patients who may have received an incorrect diagnosis prior to an ALS diagnosis (mean [SD] 36.5% [25.3%] versus 31.0% [20.0%]).

### *3.4. Time to ALS diagnosis*

Overall, the mean (SD) time from symptom onset to first consultation with a healthcare professional (HCP) was 3.8 (5.2) months (Table 3) and was similar for patients who went on to receive a misdiagnosis (3.7 [5.8] months) and for those who did not (3.8 [4.8] months). A longer mean (SD) time from symptom onset to first consultation with an HCP was reported in EU5 (4.3 [4.8] months) than in the US (2.6 [5.8] months; Table 3). In the US, the mean (SD) time from symptom onset to first consultation with an HCP was longer for patients who went on to receive a misdiagnosis than for those who did not (3.4 [8.2] months versus 1.8 [2.5] months).

Overall, the mean (SD) time from symptom onset to ALS diagnosis was 8.2 (12.5) months. Misdiagnosis resulted in a mean (SD) time from onset to ALS diagnosis of 10.4 (17.9) months compared with 6.9 (7.2) for patients who did not receive a misdiagnosis (Table 3). Compared with patients in the US, patients in EU5 waited almost twice as long from symptom onset to ALS diagnosis (9.6 [14.0] months versus 5.0 [6.8] months; Table 3). In both the US and EU5, misdiagnosis extended the average time from symptom onset to ALS diagnosis by around 3–4 months (Table 3).

### *3.5. ALS symptoms*

At symptom onset, 51.3% (407/793) and 19.7% (156/793) of patients experienced only limb symptoms and only bulbar symptoms, respectively, with both limb and bulbar symptoms experienced by 28.0% (222/793) of patients (Table 4). By the time of diagnosis, the proportion of patients with both limb and bulbar symptoms had increased to 40.0% (317/793; Table 4).

ALS symptoms at onset differed between patients who did and did not go on to receive a misdiagnosis (Table 4). Patients who went on to receive a misdiagnosis were more likely than those without a misdiagnosis to have experienced only limb symptoms at onset (61.0% [169/277] versus 46.1% [238/516]), while only having bulbar symptoms at onset was more common among patients who did not go on to receive a misdiagnosis than for patients who did (23.6% [122/516] versus 12.3% [34/277]). Proportions of patients with both limb and bulbar symptoms at onset were similar among those with or without a misdiagnosis. Similar observations were apparent for symptoms at diagnosis and were consistent for both EU5 and the US (Table 4). Proportions of patients with cognition/behavior symptoms at onset

Table 3. Time to first consultation with a healthcare professional and to definitive ALS diagnosis by misdiagnosis status, from patient medical charts.

| | Global | | | EU5 | | | United States | | |
|---|---|---|---|---|---|---|---|---|---|
| | All patients | Patients who received a misdiagnosis | Patients who did not receive a misdiagnosis | All patients | Patients who received a misdiagnosis | Patients who did not receive a misdiagnosis | All patients | Patients who received a misdiagnosis | Patients who did not receive a misdiagnosis |
| Time from symptom onset to first HCP consultation, *n*[a] | 652 | 243 | 409 | 460 | 156 | 304 | 192 | 87 | 105 |
| Months, mean (SD) | 3.8 (5.2) | 3.7 (5.8) | 3.8 (4.8) | 4.3 (4.8) | 3.8 (3.8) | 4.5 (5.3) | 2.6 (5.8) | 3.4 (8.2) | 1.8 (2.5) |
| Time from symptom onset to ALS diagnosis, *n*[b] | 686 | 259 | 427 | 480 | 167 | 313 | 206 | 92 | 114 |
| Months, mean (SD) | 8.2 (12.5) | 10.4 (17.9) | 6.9 (7.2) | 9.6 (14.0) | 12.5 (21.0) | 8.1 (7.7) | 5.0 (6.8) | 6.7 (8.9) | 3.7 (4.0) |

[a]Data missing for 143 patients for whom the date of symptom onset and/or date of first consultation was not known by a respondent physician.
[b]Data missing for 109 patients for whom the date of symptom onset and/or date of ALS diagnosis was not known by a respondent physician.
ALS, amyotrophic lateral sclerosis; HCP, healthcare professional; SD, standard deviation.

Table 4. Symptoms at onset and at ALS diagnosis by misdiagnosis status, from patient medical charts.

| | Global | | | EU5 | | | United States | | |
|---|---|---|---|---|---|---|---|---|---|
| | All patients | Patients who received a misdiagnosis | Patients who did not receive a misdiagnosis | All patients | Patients who received a misdiagnosis | Patients who did not receive a misdiagnosis | All patients | Patients who received a misdiagnosis | Patients who did not receive a misdiagnosis |
| *n*[a] | 793 | 277 | 516 | 566 | 182 | 384 | 227 | 95 | 132 |
| Symptoms at onset, *n* (%) | | | | | | | | | |
| Limb only | 407 (51.3) | 169 (61.0) | 238 (46.1) | 285 (50.4) | 109 (59.9) | 176 (45.8) | 122 (53.7) | 60 (63.2) | 62 (47.0) |
| Bulbar only[b] | 156 (19.7) | 34 (12.3) | 122 (23.6) | 106 (18.7) | 21 (11.5) | 85 (22.1) | 50 (22.0) | 13 (13.7) | 37 (28.0) |
| Limb and bulbar[b] | 222 (28.0) | 71 (25.6) | 151 (29.3) | 167 (29.5) | 49 (26.9) | 118 (30.7) | 55 (24.2) | 22 (23.2) | 33 (25.0) |
| Other only | 8 (1.0) | 3 (1.1) | 5 (1.0) | 8 (1.4) | 3 (1.6) | 5 (1.3) | 0 | 0 | 0 |
| Symptoms at diagnosis, *n* (%) | | | | | | | | | |
| Limb only | 360 (45.4) | 142 (51.3) | 218 (42.2) | 245 (43.3) | 87 (47.8) | 158 (41.1) | 115 (50.7) | 55 (57.9) | 60 (45.5) |
| Bulbar[b] only | 111 (14.0) | 24 (8.7) | 87 (16.9) | 69 (12.2) | 13 (7.1) | 56 (14.6) | 42 (18.5) | 11 (11.6) | 31 (23.5) |
| Limb and bulbar[b] | 317 (40.0) | 110 (39.7) | 207 (40.1) | 247 (43.6) | 81 (44.5) | 166 (43.2) | 70 (30.8) | 29 (30.5) | 41 (31.1) |
| Other only | 5 (<1) | 1 (<1) | 4 (<1) | 5 (<1) | 1 (<1) | 4 (1.1) | 0 | 0 | 0 |

[a]Data missing for two patients for whom symptoms at onset/diagnosis were not known by respondent physician.
[b]Separate categories for bulbar, speech and swallowing responses were combined into a "bulbar" category during analysis.

Table 5. Conditions previously diagnosed or suspected before ALS diagnosis, from patient medical charts[a].

| | Global | EU5 | United States |
|---|---|---|---|
| Patients who received a misdiagnosis, *n*[b] | 278 | 184 | 94 |
| Any spinal condition(s)[c], *n* (%) | 145 (52.2) | 96 (52.2) | 49 (52.1) |
| Chronic inflammatory demyelinating polyneuropathy, *n* (%) | 25 (9.0) | 14 (7.6) | 11 (11.7) |
| Guillain-Barré syndrome, *n* (%) | 16 (5.8) | 9 (4.9) | 7 (7.4) |
| Hereditary spastic paraplegia, *n* (%) | 2 (<1) | 2 (1.1) | 0 |
| Huntington's disease, *n* (%) | 2 (<1) | 1 (<1) | 1 (1.1) |
| Kennedy's disease, *n* (%) | 1 (<1) | 0 | 1 (1.1) |
| Multifocal motor neuropathy, *n* (%) | 7 (2.5) | 5 (2.7) | 2 (2.1) |
| Multiple sclerosis, *n* (%) | 26 (9.4) | 13 (7.1) | 13 (13.8) |
| Myasthenia gravis, *n* (%) | 18 (6.5) | 10 (5.4) | 8 (8.5) |
| Parkinson's disease, *n* (%) | 14 (5.0) | 9 (4.9) | 5 (5.3) |
| Primary lateral sclerosis, *n* (%) | 1 (<1) | 1 (<1) | 0 |
| Progressive muscular atrophy, *n* (%) | 3 (1.1) | 3 (1.6) | 0 |
| Progressive supranuclear palsy, *n* (%) | 3 (1.1) | 2 (1.1) | 1 (1.1) |
| Spinal muscular atrophy, *n* (%) | 1 (<1) | 1 (<1) | 0 |
| Other, *n* (%) | 51 (18.3) | 35 (19.0) | 16 (17.0) |

[a]Frontotemporal dementia and progressive bulbar palsy were listed as conditions in the patient medical charts but were removed during analysis, as frontotemporal dementia and progressive bulbar palsy are considered to be on a spectrum with ALS (22,23).
[b]Data missing for five patients for whom specific conditions(s) were not known by respondent physician.
[c]Cervical spondylotic myelopathy, lumbar myelopathy, radiculopathy and spinal stenosis were combined into an 'any spinal condition category' during analysis.
ALS, amyotrophic lateral sclerosis.

and at diagnosis were similar among those with and without a misdiagnosis.

### *3.6. Conditions misdiagnosed prior to ALS diagnosis*

Of patients who received a misdiagnosis, 52.2% (145/278) received a diagnosis of a spinal condition (Table 5), while other frequently diagnosed conditions included multiple sclerosis (MS, 9.4% [26/278]), chronic inflammatory demyelinating polyneuropathy (CIDP, 9.0% [25/278]) and myasthenia gravis (6.5% [18/278]). Misdiagnoses that were more common for patients in the US than in EU5 included CIDP (11.7% [11/94] versus 7.6% [14/184]) and MS (13.8% [13/94] versus 7.1% [13/184]). Conditions misdiagnosed were fairly consistent among individual EU5 countries with the exception of Germany; spinal conditions were the most common misdiagnoses in France (58.5%; 24/41), Italy (66.7%; 28/42), Spain (52.7%; 29/55) and the UK (37.9%; 11/29), but only accounted for 23.5% (4/17) of misdiagnoses in Germany. Multiple sclerosis was the most common misdiagnosed condition in Germany (35.3%, 6/17) and accounted for 2–10% in the other EU5 countries.

Globally, the percentage of patients who received surgical intervention for a misdiagnosed condition was 13.5% (37/275), with more patients in the US receiving surgical intervention (21.5%; 20/93) than in EU5 (9.3%; 17/182).

### *3.7. Physicians' perception of barriers to ALS diagnosis*

The most frequently selected barriers/challenges were 'ALS symptoms have similarities with other conditions'; 'Patients are not referred to neurologists quickly enough'; and 'Takes time to rule out other potential causes of symptoms' (Table 6). 'Low awareness of ALS among the general population' and 'Low awareness of ALS among healthcare professionals' were both selected by a greater proportion of physicians in EU5 (29.9% and 34.6%, respectively) than in the US (19.4% and 9.7%, respectively).

### *3.8. Tests to aid ALS diagnosis or rule out other conditions*

To aid diagnosis, 96.1% of patients (764/795) received a neurological examination (Table 7). Review of medical history, electromyography, and magnetic resonance imaging (MRI) were conducted for 76.5% (608/795), 87.8% (698/795) and 68.1% (541/795) of patients, respectively. Compared with the US, the diagnostic approach for patients in EU5 more commonly included any type of scan (87.9% [499/568] versus 59.0% [134/227] of patients) and genetic testing (32.4% [184/568] versus 13.7% [31/227]). Compared with EU5, patients in the US were more likely to undergo muscle biopsy (20.3% [46/227] versus 14.4% [82/568]) and nerve conduction tests (72.2%, [164/227] versus 62.1% [353/568]). Genetic testing after the onset of ALS symptoms was reported for 32.7% (251/768) of patients and was more frequent in EU5 (36.0% [198/550]) than in the US (24.3% [53/218]). Genetic testing was reported as a diagnostic test for 27.0% (215/795) of patients (Table 7).

Table 6. Perception of barriers to diagnosing ALS from physician survey[a].

| | Global | EU5 | United States |
|---|---|---|---|
| Physician respondents | 138 | 107 | 31 |
| ALS symptoms have similarities with other conditions, *n* (%) | 87 (63.0) | 70 (65.4) | 17 (54.8) |
| Patients are not referred to neurologists quickly enough, *n* (%) | 66 (47.8) | 50 (46.7) | 16 (51.6) |
| Takes time to rule out other potential causes of symptoms, *n* (%) | 65 (47.1) | 50 (46.7) | 15 (48.4) |
| Patients are not referred to ALS specialists quickly enough, *n* (%) | 41 (29.7) | 32 (29.9) | 9 (29.0) |
| Low awareness of ALS among healthcare professionals, *n* (%) | 40 (29.0) | 37 (34.6) | 3 (9.7) |
| Low awareness of ALS among the general population, *n* (%) | 38 (27.5) | 32 (29.9) | 6 (19.4) |
| Lack of distinct test/diagnostic criteria for confirming the presence of ALS, *n* (%) | 33 (23.9) | 23 (21.5) | 10 (32.3) |
| Lack of education available for identifying and diagnosing ALS, *n* (%) | 28 (20.3) | 21 (19.6) | 7 (22.6) |
| No barriers, *n* (%) | 5 (3.6) | 2 (1.9) | 3 (9.7) |
| Other, *n* (%) | 1 (<1) | 0 | 1 (3.2) |

[a]Physicians were asked "What do you consider to be the three key barriers/challenges that clinicians face in terms of identifying and. diagnosing ALS patients as early as possible?".
ALS, amyotrophic lateral sclerosis.

Table 7. Summary of testing approaches used to aid diagnosis of ALS, from patient medical charts.

| Diagnostic testing of patients | Global (*N* = 795) | EU5 (*n* = 568) | United States (*n* = 227) |
|---|---|---|---|
| Neurological examination, *n* (%) | 764 (96.1) | 549 (96.7) | 215 (94.7) |
| Review of medical history, *n* (%) | 608 (76.5) | 434 (76.4) | 174 (76.7) |
| Electromyography, *n* (%) | 698 (87.8) | 507 (89.3) | 191 (84.1) |
| Muscle biopsy, *n* (%) | 128 (16.1) | 82 (14.4) | 46 (20.3) |
| Any scan, *n* (%)[a] | 633 (79.6) | 499 (87.9) | 134 (59.0) |
| Bone scan | 22 (2.8) | 19 (3.3) | 3 (1.3) |
| CT scan | 201 (25.3) | 177 (31.2) | 24 (10.6) |
| MRI scan | 541 (68.1) | 411 (72.4) | 130 (57.3) |
| PET scan | 50 (6.3) | 43 (7.6) | 7 (3.1) |
| SPECT scan | 34 (4.3) | 33 (5.8) | 1 (<1) |
| X-ray | 95 (11.9) | 86 (15.1) | 9 (4.0) |
| Genetic test, *n* (%)[b] | 215 (27.0) | 184 (32.4) | 31 (13.7) |
| Urine test, *n* (%) | 110 (13.8) | 91 (16.0) | 19 (8.4) |
| Any blood test, *n* (%)[c] | 629 (79.1) | 463 (81.5) | 166 (73.1) |
| Any CSF test, *n* (%)[c] | 294 (37.0) | 241 (42.4) | 53 (23.3) |
| Any respiratory assessment, *n* (%)[c] | 499 (62.8) | 391 (68.8) | 108 (47.6) |

[a]Body region of scan not specified in the question.
[b]In a separate question on genetic testing, physicians reported the use of genetic testing after the onset of ALS symptoms for 251/768 (32.7%) patients: 198/550 (36.0%) in EU5 and 53/218 (24.3%) in the United States.
[c]Further details of individual tests performed are provided in Supplemental materials, Table 1.
ALS, amyotrophic lateral sclerosis; CSF, cerebrospinal fluid; CT, computed tomography; MRI, magnetic resonance imaging; PET, positron emission tomography; SPECT, single-photon emission computed tomography.

## 4. Discussion

In this study, we used real-world data to assess the extent of diagnostic delay and misdiagnosis of ALS in EU5 and the US. The demographic and clinical characteristics of the EU5 and US patient populations were similar and reflect the known epidemiology of ALS, including a higher prevalence of the disease in males in their late fifties or older, and in White/Caucasian populations (2,24). The mean time of 8.2 months from symptom onset to ALS diagnosis in our study was shorter than estimates (10–16 months) from studies published between 1990 and 2020 (12). This may reflect regional variation in diagnostic delays, as we observed a shorter time for ALS diagnosis in the US than in the EU5. A recent analysis of diagnostic trends in Turkey, Germany, Poland, and Portugal reported a mean ALS diagnostic delay of 11 months from symptom onset (25). A 2016–2021 study in Sweden found time from onset to diagnosis ranged from 8.3 months to 16 months depending on onset phenotype (26). Regional variations in diagnostic pathways can include differences in referral systems, delays in the assessment of younger patients, and whether the first assessment was conducted by a neurologist or non-neurologist specialist (25). The shorter diagnostic timeline in our study may also reflect the DSP study design in which all patients involved were actively consulting with a neurologist at the time of the survey. Collectively,

these studies demonstrate a significant diagnostic delay for a disease with a prognosis of 2–3 years and do not represent much, if any, improvement since the 1990s (12).

ALS diagnosis can be challenging due to similarities of some initial symptoms with those of other conditions and may be particularly challenging for physicians who are not ALS specialists. Previous studies have associated misdiagnosis with diagnostic delays and with more advanced disease at the time of ALS diagnosis (12,13,15,17). As a consequence, misdiagnosis of ALS may result in delays in receiving appropriate treatment, missed opportunities to participate in clinical trials, unnecessary surgeries, and the potential for patients to receive inappropriate interventions (12,13,17,27). Overall, misdiagnosis occurred for over a third of patients (35.0%) in our study and extended the time from symptom onset to ALS diagnosis by 3–4 months. While the time from symptom onset to first consultation with an HCP was similar between patients who did and did not go on to receive a misdiagnosis, symptoms at disease onset differed between these patients. Consistent with previous studies showing that patients with limb-onset ALS are more likely to receive a misdiagnosis than patients with bulbar-onset ALS (12,13,17), we observed a higher prevalence of limb symptoms without bulbar symptoms among those who went on to receive a misdiagnosis than among those who did not. Conversely, bulbar symptoms without limb symptoms (which were more common among patients without a misdiagnosis) may lead to earlier suspicion of ALS by physicians. The observed increase in the proportion of patients with both limb and bulbar symptoms between symptom onset and diagnosis is consistent with disease progression (28,29). Increased awareness in the medical community is needed to recognize the salient features of ALS (such as lack of sensory involvement and rate of progression of symptoms) and to distinguish spinal conditions from ALS in a timely manner. Diagnostic delay could be reduced if general practitioners initiate patient assessments that aid ALS diagnosis (30). Additionally, limited access to healthcare and health insurance, factors that disproportionately affect African Americans in the US and ethnic minorities in Europe, may increase diagnosis delay (31).

In our study, neurological examination and electromyography were consistently used in the diagnosis of ALS. This is generally in line with current approaches to diagnose ALS, in which MRI, blood tests and electromyography are mainly used to rule out other conditions (9,16). We still lack biomarkers that can be used to definitively diagnose ALS, and the low sensitivity and poor test-retest reliability of diagnostic criteria developed for ALS research limit their use in clinical practice (5). Genetic testing is useful to confirm a diagnosis in patients with a genetic form of ALS, but in clinical practice, it may not be offered to up to half of patients with suspected ALS if they have no family history of the disease (11). Genetic testing after symptom onset was performed for 32.7% of our study population; the lower proportion of patients who received genetic testing in the US may reflect that ALS diagnostic testing became available at no charge in 2021 (32). A multicenter study conducted for the ALS Genetic Access Program found that genetic testing was more likely to identify patients with ALS who experienced disease onset at a younger age than the typical age of ALS onset (10). In addition, ALS onset at a younger age is known to be more prevalent in males and patients who do not have bulbar-onset disease (8,33). Therefore, genetic testing could be expanded based on the likelihood of a positive result in a subset of younger individuals. The use of genetic testing to categorize ALS variants is recommended for all patients with ALS, irrespective of age or family history (34). Further education about genetic testing and genetic counseling for ALS is recommended for healthcare professionals and the general population.

In terms of limitations, the physician survey may be subject to selection bias such as responder bias; the phrasing of survey questions could have impacted the answers provided. The DSP methodology provides only a practical sample of physicians and a medical chart review of ALS patients taken at a particular timepoint.

In conclusion, this study shows that misdiagnosis remains a widespread and significant issue in ALS, both in terms of the frequency of misdiagnosis and time lost between symptom onset and obtaining an ALS diagnosis, in the US and EU5. Improvement of the diagnostic pathway for ALS may improve patient quality of life and reduce healthcare costs associated with misdiagnosis of ALS. Strategies for reducing the time to diagnosis could include increasing the awareness of ALS among the general population to encourage individuals to seek medical support without delay after symptom onset. There is a need for the general medical community to better understand the symptoms associated with ALS, such as unexplained painless progressive weakness, muscle atrophy and loss of dexterity in the limbs. Greater awareness is needed of the symptom profile most commonly associated with misdiagnosis of ALS, such as the higher prevalence of limb symptoms compared with bulbar symptoms. Prompt referral of patients with suspected ALS for specialist assessment should promote timely diagnosis of ALS and differentiation from other conditions that show similar clinical presentation.

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## Consent

The Disease Specific Programme was conducted in accordance with the European Pharmaceutical Market Research Association (EphMRA) Code of Conduct. The study protocol (reference number AG8802) was submitted to the Western Institutional Review Board, which provided an ethics waiver, as it was determined that ethics approval was not required for this study. All data were collected following procedures with ethics committee approval, and data were fully de-identified prior to receipt by Adelphi Real World. The respondents provided informed consent for the use of their anonymized and aggregated data for research and publication in scientific journals. All data, i.e., methodology, materials, data and data analysis, that support the findings of this survey are the intellectual property of Adelphi Real World. As such no administrative permissions were required to access and use the data.

## Disclosure of interest

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## Data availability statement

All data, i.e., methodology, materials, data and data analysis, that support the findings of this survey are the intellectual property of Adelphi Real World. All requests for access should be addressed directly to Jennifer Mellor at jennifer.mellor@adelphigroup.com.

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