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The ALS-FTD-Q
A new screening tool for behavioral disturbances in ALS

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Supplemental data at www.neurology.org

ABSTRACT

Objective: The assessment of behavioral disturbances in amyotrophic lateral sclerosis (ALS) is important because of the overlap with the behavioral variant of frontotemporal dementia (ALS-bvFTD). Motor symptoms and dysarthria are not taken into account in currently used behavioral questionnaires. We examined the clinimetric properties of a new behavioral questionnaire for patients with ALS (Amyotrophic Lateral Sclerosis-Frontotemporal Dementia-Questionnaire [ALS-FTD-Q]).

Methods: In addition to other clinimetric properties, we examined reliability, clinical validity, and construct validity of the ALS-FTD-Q, using data from patients with ALS (n = 103), ALS-bvFTD (n = 10), bvFTD (n = 25), muscle disease control subjects (n = 39), and control subjects (n = 31). Construct validity of the ALS-FTD-Q was assessed using the Frontal Systems Behavior scale (FrSBe), Frontal Behavioral Inventory (FBI), Hospital Anxiety and Depression Scale, ALS Functional Rating Scale—Revised, Frontal Assessment Battery, Mini-Mental State Examination, and a fluency index. In addition, the point prevalence of behavioral disturbances according to the ALS-FTD-Q was compared with those obtained with the FrSBe and FBI.

Results: The internal consistency of the ALS-FTD-Q was good (Cronbach α = 0.92). The ALS-FTD-Q showed construct validity because it correlated highly with other behavioral measures (r = 0.80 and 0.79), moderately with measures of frontal functions and global cognitive functioning (r = 0.37; r = 0.32), and poorly with anxiety/depression and motor impairment (r = 0.18 for both). The ALS-FTD-Q discriminated between patients with ALS-bvFTD, patients with ALS, and control subjects. The point prevalence of behavioral disturbances in patients with ALS measured with the ALS-FTD-Q was lower than that for the FrSBe and FBI.

Conclusion: The ALS-FTD-Q is a feasible and clinimetrically validated instrument for the screening of behavioral disturbances in ALS. Neurology® 2012;79:1377–1383

GLOSSARY

ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale—Revised; ALS-FTD-Q = Amyotrophic Lateral Sclerosis-Frontotemporal Dementia—Questionnaire; bvFTD = behavioral variant of frontotemporal dementia; FAB = Frontal Assessment Battery; FBI = Frontal Behavioral Inventory; FrSBe = Frontal Systems Behavior scale; HADS = Hospital Anxiety and Depression Scale; MMSE = Mini-Mental State Examination.

The frontotemporal brain regions are affected in a proportion of patients with amyotrophic lateral sclerosis (ALS).1–3 Clinically, this may lead to the behavioral variant of frontotemporal dementia (bvFTD) (in 5%–10% of patients with ALS), mild frontotemporal cognitive deficits (in 32%–45% of patients with ALS), or mild behavioral disturbances in patients with ALS.4–8 These nonmotor changes in patients with ALS may negatively influence survival and hinder adherence to therapeutic interventions and relations with caregivers.9–11

The gold standard for behavioral disturbances is a detailed family interview. When this is not feasible, a neuropsychiatric screening instrument is an alternative. Importantly, the scoring

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of items should not be influenced by muscle weakness, dysarthria, or pseudobulbar affect, as these may overestimate behavioral disturbances in patients with ALS.12

The neuropsychiatric instruments currently available for assessing behavior have not been validated in patients with ALS and contain several items that rely on the ability to speak, eat, and move without problems.13–15 To overcome these issues, we investigated the clinimetric properties of a new screening tool, the Amyotrophic Lateral Sclerosis-Frontotemporal Dementia—Questionnaire (ALS-FTD-Q), for the detection of bvFTD and mild behavioral disturbances in ALS.

METHODS Subjects. Five groups of patients were recruited from tertiary referral centers for ALS and dementia, all in the Netherlands: 103 patients with ALS (possible, probable, or definite ALS according to the El Escorial criteria)16; 10 patients with ALS-bvFTD who had the diagnosis of ALS-bvFTD by the treating clinician before this study, according to the El Escorial and Neary criteria17; 25 patients with bvFTD without ALS that had been diagnosed before the study, according to the Neary criteria18; 39 patients with muscle diseases (muscle controls) (inclu- sion body myositis [n = 10], limb girdle dystrophy 2A [n = 8], oculopharyngeal muscular dystrophy [n = 6], Miyoshi myopathy [n = 9], and ALS mimics [n = 6]); and 31 subjects evaluated at the outpatient neurology clinic for diverging symptoms (e.g., sensory symptoms, tremor, and headache) (other controls). These subjects had no medical history of muscle disease, CNS disorder, or psychiatric disorder. The patients with ALS-bvFTD and bvFTD served as controls (n = 70). Only patients with a proxy were included. A proxy can be a partner, parent, sibling, adult child, or other caregiver who is able to assess the patient’s behavior. In 1.6% of the patients contacted, absence of a proxy was the reason not to participate. Patients and control subjects were excluded if they did not speak Dutch fluently or if they had a history of a psychiatric disorder or a neurologic disease with CNS involvement.

Standard protocol approvals, registrations, and patient consents. The local ethics committees of the participating hospitals approved the study. Written informed consent was obtained from all subjects.

ALS-FTD-Q. The ALS-FTD-Q (appendix e-1 on the Neurology® Web site at www.neurology.org and on www.alsftdq.nl) is an observer report scale aimed at the proxy of a patient with ALS. Items for the ALS-FTD-Q were taken from a systematic review of neurobehavioral symptoms (i.e., behavioral, cognitive, and psychiatric disturbances) in 170 published patients with motor neuron disease and bvFTD,14 and the item selection was mainly based on the pooled prevalence rates of neurobehavioral symptoms in the review. The phrasing of the items was adjusted for motor and speech dysfunction. Face validity of the ALS-FTD-Q is described in appendix e-2. The ALS-FTD-Q has 25 items (including 3 cognitive items: memory, concentration, and orientation in time), with a 4-point rating scale; the maximum score of the ALS-FTD-Q is 100. A higher score indicates more behavioral disturbances. The time required to complete the questionnaire was estimated to be between 5 and 10 minutes.

Procedure. Most patients with ALS were visited at home (n = 97, including 9 patients with ALS-bvFTD). The proxy was requested to fill in the ALS-FTD-Q and 2 other behavioral scales (for instruments, see below) in a separate room while the patient underwent a short battery of tests that assessed cognitive and affective functions and functional motor status. Proxies of 16 consecutive patients with ALS (including 1 patient with ALS-bvFTD) filled in the ALS-FTD-Q during an outpatient clinic visit, separate from the home-visit study.

Proxies of the other patients and control subjects filled in the ALS-FTD-Q at the outpatient clinics during a regular visit, in a room separated from the patient.

Instruments used in the home-visit study. The proxy assessed the behavior of the patient with the ALS-FTD-Q and the Frontal Systems Behavior Scale (FrSBe), a 46-item behavior scale with carer ratings of premorbid and postmorbid behavior in the domains of apathy, executive dysfunction, and disinhibition,14 and the Frontal Behavioral Inventory (FBI), a 24-item scale measuring frontal lobe-mediated behavior.15

The patient was administered the Mini-Mental State Examination (MMSE)15; the Frontal Assessment Battery (FAB), a 6-item instrument measuring frontal lobe functions, e.g., conceptualization and perseveration,20 letter (D, A, T) and category (animals and occupations) fluency, measures of executive function with correction for speech/motor dysfunction by calculating a mean thinking time per word in seconds (fluency index),12,21 (written or spoken versions were used, depending on disability); the Hospital Anxiety and Depression Scale (HADS), a 14-item scale;22 and the ALS Functional Rating Scale—Revised (ALSFRS-R), a 12-item questionnaire for motor dysfunction in ALS.13

Patients in whom impaired manual dexterity precluded performance of the “writing a sentence” item of the MMSE were allowed to say the sentence, provided their speech was intelligible. For other items that require manual dexterity, e.g., “intersecting pentagons” of the MMSE and 5 of the 6 items of the FAB, a note was made when these tasks could not be performed. We recorded the score obtained and the highest obtainable score. The highest obtainable score is the score if all items are done perfectly, leaving out the items missed due to motor impairment.

Extrapolated scores of the MMSE and FAB were used for analyses, according to the formula: extrapolated score = score obtained × maximum scale score/highest obtainable score for this patient. A higher extrapolated score means a better performance.

Disease onset was defined as the month when the first sign of muscle weakness (ALS) or behavioral changes (bvFTD) was noted. Bulbar involvement was defined as a score ≤11 on the 3 bulbar items of the ALSFRS-R.

Clinimetric evaluation of ALS-FTD-Q. The following clinimetric properties of the ALS-FTD-Q were studied: reliability (both internal consistency and test-retest reliability), construct validity, clinical validity, and the presence of a floor and ceiling effect.

Internal consistency refers to the statistical coherence of the scale items and can be measured by the Cronbach α coefficient, which is based on the weighted average correlation of items within a scale. Internal consistency is considered to be good if α ≥ 0.80. We calculated item-total correlations, which represent...
the correlation of a single item with the sum of all other scale items. Correlations ≥0.30 were considered to be sufficient. Test-retest reliability was investigated in a pilot study on the proxies of 17 patients with ALS, including 4 patients with ALS-bvFTD (appendix e-2).

Construct validity was assessed in the group of 97 patients with ALS (including 9 patients with ALS-bvFTD) who underwent multiple tests at home. We measured the extent to which the ALS-FTD-Q correlates with measures that address the same concept (i.e., frontal behavior) and measures that address different concepts. We assumed that for the ALS-FTD-Q to be valid, the ALS-FTD-Q scores had to show high correlations with the other frontal behavior scale scores (FrSBe and FBI), moderate correlations with frontal lobe functions (FAB and fluency) and global cognitive functions (MMSE), and low correlations with affective functions (HADS) and motor functions (ALSFRS-R).

A scale demonstrates clinical validity if it discriminates between groups of patients with known differences in clinical status (i.e., ALS without bvFTD vs bvFTD with or without ALS). Floor and ceiling effects of the ALS-FTD-Q were analyzed (percentage of patients with a minimum and maximum score).

**ALS-FTD-Q vs comparable scales.** To explore whether the results of the ALS-FTD-Q differ from scales that are currently used in patients with ALS, we compared point prevalences of abnormal behavior assessed with the ALS-FTD-Q (using tentative cutoff scores derived from our negative and positive control groups) with those from the FrSBe and the FBI (using published cutoff scores). We aimed to compare the ALS-FTD-Q scores with scores for the other scales for both mildly and severely ab

### Table 1: Demographic and clinical characteristics of the patients with ALS and positive and negative control subjects assessed with the ALS-FTD-Q

<table>
<thead>
<tr>
<th>Age, y, mean (SD)</th>
<th>Positive control subjects</th>
<th>Negative control subjects</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS (n = 103)</td>
<td>ALS-bvFTD (n = 10)</td>
<td>bvFTD (n = 25)</td>
</tr>
<tr>
<td>61.4 (11.9)</td>
<td>60.2 (10.4)</td>
<td>63.4 (6.4)</td>
</tr>
<tr>
<td>Sex, M/F</td>
<td></td>
<td></td>
</tr>
<tr>
<td>73/30</td>
<td>7/3</td>
<td>17/8</td>
</tr>
<tr>
<td>Limb/bulbar onset, n</td>
<td>89/14</td>
<td>4/6</td>
</tr>
<tr>
<td>Bulbar involvement, %a</td>
<td>60.2</td>
<td>100</td>
</tr>
<tr>
<td>Disease duration, mo, median (range)</td>
<td>33.5 (4 – 328)</td>
<td>35.5 (0 – 80)</td>
</tr>
<tr>
<td>ALSFRS-Rb</td>
<td>31.5 (9.2)</td>
<td>32.9 (6.1)</td>
</tr>
</tbody>
</table>

**Abbreviations:** ALS – amyotrophic lateral sclerosis; ALSFRS-R – ALS Functional Rating Scale – Revised; ALS-FTD-Q – Amyotrophic Lateral Sclerosis-Frontotemporal Dementia – Questionnaire; bvFTD – behavioral variant of frontotemporal dementia.

The maximum score of the ALSFRS-R is 48 and indicates no motor dysfunction.

### Statistical analysis.
**Internal consistency of the ALS-FTD-Q** scores was expressed as Cronbach α coefficient. Item-total correlations and test-retest correlations were expressed as Pearson correlation coefficients (r) and intraclass correlation coefficients, respectively. Associations between the ALS-FTD-Q scores and the other measures were expressed as Spearman rank correlation coefficients (r). Differences between ALS-FTD-Q scores and patient characteristics in relation to the various subgroups were analyzed using the Mann-Whitney U test, Kruskal-Wallis test, or χ² test. Statistical significance level was set at p = 0.05. Analyses were performed in PASW statistics, version 18 (SPSS).

### RESULTS
We included 113 patients with ALS (80 male [70.8%]), 10 of whom were diagnosed with ALS-bvFTD before the study. The mean age at examination was 61.3 years (SD 11.7), and the median disease duration was 2.8 years (34 months, range 4–328 months) (table 1). Ninety-three patients (82.3%) had limb-onset ALS. Bulbar involvement was present in 72 patients (63.7%). Gender and age were not different among any of the groups.

### Clinimetrics.
The ALS-FTD-Q scores showed substantial internal consistency (Cronbach α = 0.92), and 23 of the 25 items showed an item-total score correlation ranging between 0.31 and 0.78. Two items (hypersexuality and euphoria) had an item-total score correlation of 0.20 and 0.26. The test-retest intraclass correlation of the ALS-FTD-Q total score was 0.89 (n = 17; mean time between 2 assessments 65 days [SD 26.7]) (additional data for the test-retest group are given in appendix e-2).

Construct validity was shown by high correlations between the ALS-FTD-Q and the FrSBe and FBI, moderate correlations with the FAB, fluency, and MMSE, and low correlations with the HADS and...
Extrapolated scores of the MMSE and FAB were used, corrected for missed items due to motor impairment. Negative as higher scores on the FAB, MMSE, and ALSFRS-R indicate better performance. Correlation values are expressed as Spearman correlation coefficients. Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; ALS-FTD-Q = Amyotrophic Lateral Sclerosis-Frontotemporal Dementia–Questionnaire; FAB = Frontal Assessment Battery; FBI = Frontal Behavioral Inventory; FrSBe = Frontal Systems Behavior scale; HADS = Hospital Anxiety and Depression Scale; MMSE = Mini-Mental State Examination.

Table 2: Test scores and correlations of the ALS-FTD-Q with other measures of behavioral, cognitive, affective, and motor functions in patients with ALS

<table>
<thead>
<tr>
<th></th>
<th>No.</th>
<th>Test score, median (range)</th>
<th>Correlation with ALS-FTD-Q*</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS-FTD-Q</td>
<td>97</td>
<td>11 (0–56)</td>
<td></td>
</tr>
<tr>
<td>Frontal behavioral symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FrSBe</td>
<td>95</td>
<td>56 (34–129)</td>
<td>0.80</td>
</tr>
<tr>
<td>FBI</td>
<td>92</td>
<td>14 (0–39)</td>
<td>0.79</td>
</tr>
<tr>
<td>Frontal/executive functions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>FAB</td>
<td>92</td>
<td>16 (3–18)</td>
<td>–0.37b,c</td>
</tr>
<tr>
<td>Fluencya</td>
<td>92</td>
<td>5.6 (1.9–24.3)</td>
<td>0.30</td>
</tr>
<tr>
<td>Cognitive functions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MMSE</td>
<td>97</td>
<td>26.8 (9–30)</td>
<td>–0.32b,c</td>
</tr>
<tr>
<td>Affective functions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HADS</td>
<td>85</td>
<td>6 (0–24)</td>
<td>0.18</td>
</tr>
<tr>
<td>Motor functions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ALSFRS-R</td>
<td>97</td>
<td>33.0 (8–47)</td>
<td>–0.18b</td>
</tr>
</tbody>
</table>

Abbreviations: ALS = amyotrophic lateral sclerosis; ALSFRS-R = ALS Functional Rating Scale–Revised; ALS-FTD-Q = Amyotrophic Lateral Sclerosis-Frontotemporal Dementia–Questionnaire; FAB = Frontal Assessment Battery; FBI = Frontal Behavioral Inventory; FrSBe = Frontal Systems Behavior scale; HADS = Hospital Anxiety and Depression Scale; MMSE = Mini-Mental State Examination.

With regard to clinical validity, the median ALS-FTD-Q score of patients with ALS without bvFTD (9, range 0–46) was lower than those for either patients with ALS-bvFTD (42, range 30–56) or patients with bvFTD (50, range 29–68) and higher than those for the muscle disease control group (6, range 0–24) and the other control subjects (5, range 0–20) (figure 2).

ALS-FTD-Q and comparable scales. Based on our scoring algorithm (Methods section), the ALS-FTD-Q cutoff indicating mild disturbances was set at ≥22; the cutoff indicating severe disturbances (in the bvFTD range) was set at ≥29. In patients without a prior diagnosis of bvFTD who had complete data for the 3 behavioral scales (n = 86), mild and severe behavioral disturbances were shown in 11 (10.7%) and 7 patients (6.8%), respectively, with the ALS-FTD-Q. In comparison, according to the FrSBe and FBI, 16 patients (18.6%) had mild behavioral disturbances and 12 patients (14%) had severe behavioral changes. Of the 103 patients who were assessed with the ALS-FTD-Q, 27 (26.2%) were assessed within 1 year of the diagnosis (patients with incident disease), of whom 4 (14.8%) scored in the mild range and 1 in the severe range on the ALS-FTD-Q. The proportion of those with mild behavioral disturbances of the patients with incident disease was not significantly different from that of patients with prevalent disease (χ² test; not analyzed for severe behavioral disturbances).

DISCUSSION This study shows the clinimetric properties of a new screening instrument for behavioral disturbances, which was constructed to avoid bias due to motor and speech impairment in patients with ALS. The ALS-FTD-Q showed substantial internal consistency and test-retest reliability and both construct and clinical validity. Construct validity was shown by high correlations of the ALS-FTD-Q with frontal behavioral scales (same construct), intermediate correlations with frontal cognitive functions (related construct), and low correlations with anxiety/depression and motor function (not related constructs). The intermediate correlation between fluency and the ALS-FTD-Q in our study is comparable to findings by others and shows that the questionnaire measures a construct (frontal-mediated behavior) that is related to fluency, supporting the construct validity of the ALS-FTD-Q. In addition, clinical validity was shown because the ALS-FTD-Q discriminated between patients with a known difference in the presence of frontal behavioral disturbances. These good clinimetric properties and the easy way of administering the ALS-FTD-Q make it a feasible screening instrument in clinical practice as well as for research projects.

The assessment of behavioral changes and especially bvFTD in patients with ALS is important in clinical practice because bvFTD hinders adherence to therapeutic interventions and may negatively influence survival. In addition, bvFTD has a great impact on the relation of patients with ALS with their caregivers.

To our knowledge, 3 screening instruments for nonmotor involvement (focusing on cognitive functions) have been investigated in patients with ALS. One screen contains 15 questions about behavior; 2 other screens included the FBI. Compared with these screening instruments, the ALS-FTD-Q has 4 unique advantages. First, behavioral items were selected from a systematic review of case descriptions of 170 patients with ALS-bvFTD. Second, the phrasing of items was adjusted to take motor and speech dysfunction into account. This was done to minimize overestimation of behavioral disturbances due to motor impairment. Third, the ALS-FTD-Q has good clinimetric properties includ-
ing internal consistency, construct validity, and clinical validity. Fourth, test scores were compared with both negative and positive control groups.

The point prevalence of severe and mild behavioral disturbances according to the ALS-FTD-Q in our patients with ALS without a prior diagnosis of bvFTD is lower compared with the FBI (severe) and the FrSBe (mild behavioral changes). Our data may suggest that the FrSBe and FBI could overestimate behavioral disturbances in patients with ALS (because of bias due to motor symptoms and dysarthria). The alternative explanation, i.e., a low sensitivity of the ALS-FTD-Q, is less likely for 3 reasons. First, we carefully selected items based on a systematic review to capture the full range of neuropsychiatric changes known to occur in ALS, including delusions (paranoia), hallucinations, apathy, and eating disturbances, which were recently found to be prominent in patients with bvFTD with ALS.18,30,31 Second, our cutoff included all the patients with a prior diagnosis of bvFTD and ALS-bvFTD, which implies high sensitivity of the ALS-FTD-Q. Third, the point prevalence of 7% severe behavioral disturbances in patients with ALS (without a prior diagnosis of bvFTD) in our cohort is in agreement with a pooled prevalence of 8% bvFTD in 570 patients with ALS in a systematic review of population-based or outpatient clinic-based studies using family interviews or clinical questionnaires.5,6,18

The proportion of patients with mild behavioral changes as assessed with the ALS-FTD-Q (11%) is lower than that in other studies (17%–50%).8,27,32,33 Earlier studies used instruments that have not been validated for the assessment of behavioral changes in ALS and contain items that have not been corrected for motor impairment.5,11 In particular, apathy has
been shown to be present in up to 50% of patients with ALS.\textsuperscript{11,26,34} However, apathy was studied with the 14-item FrSBe apathy subscale, of which 7 items are directly related to speaking and moving, which may have led to overestimating motor-related mild behavioral changes, e.g., apathy.\textsuperscript{11,26,34}

The mild and severe behavioral changes in ALS in the present study have to be interpreted in relation to the cutoffs, which have to be further validated, and in relation to the study population. We did not perform a receiver operating characteristic analysis to define the cutoffs of the ALS-FTD-Q because, for mild behavioral disturbances, a gold standard in ALS does not exist (the FrSBe could not be used for this purpose as it contains motor- and speech-related items). For severe behavioral disturbances, we could not use the clinical diagnosis of bvFTD as a gold standard because the bvFTD diagnoses were made before the study (time between bvFTD diagnosis and assessment ranged from 3 to 18 months).

Our study population was largely a prevalence cohort with a relatively long disease duration, and 18% of patients had bulbar-onset ALS (compared with 30% in incidence cohorts).\textsuperscript{35} The design of this study with more patients with prevalent than with incident disease was chosen to examine our questionnaire in patients with different disease durations, because previous studies described the development of bvFTD in the course of ALS.\textsuperscript{36,37}

In terms of further validation of the ALS-FTD-Q, the high test-retest correlation should be replicated, and the responsiveness (detection of changes over time) of the ALS-FTD-Q should be explored in depth in a larger sample of patients with incident disease. When sufficient data are collected, a factor analysis may generate insight into subscales and a subset of items that would suffice, which would make the scale even more usable. Compared with a self-report instrument, a potential drawback of the ALS-FTD-Q is that it is limited to patients with a proxy. However, less than 2% of the patients we contacted did not participate because of the absence of a proxy. An important reason to choose an observer-report scale in this study is that frontal lobe dysfunction may interfere with the patient’s ability to assess his or her own behavior. The ALS-FTD-Q is a unique and novel instrument to be used in the clinic for the screening of behavioral disturbances in patients with ALS. It is a user-friendly tool with validated clinimetric characteristics.

**AUTHOR CONTRIBUTIONS**

Dr. Raaphorst: drafting/revising the manuscript for content, study concept, analysis and interpretation of the data, acquisition of the data, statistical analysis, and study coordination. E. Beeldman: drafting/revising the manuscript for content, study concept, analysis and interpretation of the data, acquisition of the data, and statistical analysis. Dr. Schmand: drafting/revising the manuscript for content and interpretation of the data, and study supervision. J. Berkhout: drafting/revising the manuscript for content and acquisition of the data., Dr. Linssen, Dr. van den Berg, Dr. Pijnenburg, Dr. Grupstra, J. Weikamp, Dr. Schelhaas, Dr. Papma, Dr. van Swieten: drafting/revising the manuscript for content and acquisition of the data. Dr. de Visser: drafting/revising the manuscript for content, study concept, interpretation of the data, and study supervision. Dr. de Haan: drafting/revising the manuscript for content, study concept, analysis and interpretation of the data, statistical analysis, and study supervision.

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**DISCLOSURE**

J. Raaphorst., E. Beeldman, B. Schmand, J. Berkhout, and W. Linssen report no disclosures. L. van den Berg received travel grants and consultancy fees from Baxter; serves on scientific advisory boards for ARISLA (the Italian ALS Association), Primes Beatrix Fonds, Theirry Latran Foundation, and Biogen Idec; serves as a consultant for and has received funding for travel from Baxter International Inc.; serves on the editorial board of Amyotrophic Lateral Sclerosis; and receives research support from the Primes Beatrix Fonds, Netherlands ALS Foundation, VSB Fonds, Adesium Foundation, and the European Union. Y. Pijnenburg, H. Grupstra, J. Weikamp, and H. Schelhaas report no disclosures. J.M. Papma receives financial support by a grant from Alzheimer Nederland (Dutch Alzheimer’s Society). J.C. van Swieten received research support from AFTD (Association for Frontotemporal Dementias), Dioraphte Foundation, Hersenstichting, and Nuts Ohra Foundation. M. de Visser and R.J. de Haan report no disclosures. Go to Neurology.org for full disclosures.

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