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Timothy M. Miller, MD, PhD
RESEARCH PAPER

Defining SOD1 ALS natural history to guide therapeutic clinical trial design

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ABSTRACT

Importance Understanding the natural history of familial amyotrophic lateral sclerosis (ALS) caused by SOD1 mutations (ALS SOD1) will provide key information for optimising clinical trials in this patient population.

Objective To establish an updated natural history of ALS SOD1.

Design, setting and participants Retrospective cohort study from 15 medical centres in North America evaluated records from 175 patients with ALS with genetically confirmed SOD1 mutations, cared for after the year 2000.

Main outcomes and measures Age of onset, survival, ALS Functional Rating Scale (ALS-FRS) scores and respiratory function were analysed. Patients with the A4V (Ala-Val) SOD1 mutation (SOD1 A4V), the largest mutation population in North America with an aggressive disease progression, were distinguished from other SOD1 mutation patients (SOD1 non-A4V) for analysis.

Results Mean age of disease onset was 49.7 ±12.3 years (mean±SD) for all SOD1 patients, with no statistical significance between SOD1A4V and SOD1 non-A4V (p=0.72, Kruskal-Wallis). Total SOD1 patient median survival was 2.7 years. Mean disease duration for all SOD1 was 4.6±6.0 and 1.4±0.7 years for SOD1A4V. SOD1A4V survival probability (median survival 1.2 years) was significantly decreased compared with SOD1 non-A4V (median survival 6.8 years; p<0.0001, log-rank).

A statistically significant increase in ALS-FRS decline in SOD1A4V compared with SOD1 non-A4V participants (p=0.02) was observed, as well as a statistically significant increase in ALS-forced vital capacity decline in SOD1A4V compared with SOD1 non-A4V (p=0.02).

Conclusions and relevance SOD1 A4V is an aggressive, but relatively homogeneous form of ALS. These SOD1-specific ALS natural history data will be important for the design and implementation of clinical trials in the ALS SOD1 patient population.
a central database. Information for all patients was de-identified, and data collection and processing were approved by the local Institutional Review Board (IRB) committees. The following 17 centres sent charts as part of this study: Washington University School of Medicine, Northwestern University Feinberg School of Medicine, University of Washington Medical Center, Neurology Clinical Research Institute at Massachusetts General Hospital, Mayo Clinic Florida, Emory University School of Medicine, Johns Hopkins University, Wake Forest School of Medicine, Perelman School of Medicine at the University of Pennsylvania, Methodist Neurological Institute at The Methodist Hospital, Neurosciences Institute at Albany Medical Center, University of Utah, Sunnybrook Health Sciences Centre, University of California Irvine, University of Michigan, University of Kansas Medical Center and Cedars-Sinai Medical Center.

Data collection and analysis
All sites received a standardised form with the following items requested: gender, genetic mutation, month/year of birth, month/year of symptom onset, month/year of death, month/year of permanent ventilation (if applicable), ALS-Functional Rating Scale (ALS-FRS) at time points where available, and forced vital capacity (FVC) at time points where available. Symptom onset was defined as the first reported loss of function, such as limb weakness or dysarthria.

Genetic testing was performed by individual institutions at the time of diagnosis, and sites were asked to only report the specific SOD1 mutation found. Data were collected and analysed from individual patients or families of index cases with confirmed SOD1 mutations only; mutations recorded as ‘self-reported’ were not included in the analysis. All mutations are reported in this study using the traditional numbering nomenclature, that is, not counting the first (ATG) codon. When time of onset could not be narrowed down to more than a range of several months, for example, ‘fall 2011’, the onset was determined to be the midpoint of that range, for example, ‘October 2011’. Patients still alive at the time of data collection were reported as such, and their last recorded FVC or ALS-FRS, whichever came later, was used for survival analyses. ALS-FRS is understood to be the revised scale (ALSFRS-R), a 12-item questionnaire with the highest, normal score being 48.20 When both sitting and lying FVC readings were available, sitting values were used. Additional clinical features, such as site of onset and presence of non-motor symptoms and signs, were not analysed in this study.

Statistical analysis
SAS V9.3 (Cary, North Carolina, USA) was used to perform all statistical analyses. Descriptive statistics were provided for gender, age and disease duration by mutation group (A4V and non-A4V) and total patients, respectively. Additionally, mean, SD of age and disease duration were calculated for each interested mutation. The primary study end points included ALS-FRS and FVC while secondary end point was overall survival (OS). OS was defined as the date of symptom onset to death from any cause or last follow-up. Kaplan-Meier (KM) curves for OS were generated that provide unadjusted survival estimates for total sample and between mutation groups (non-A4V vs A4V), respectively. Difference between mutations groups were determined by log-rank testing.

The study sample includes ALS-FRS and FVC measurements for multiple visits. To account for correlations among repeated measures from the same patient, the longitudinal data were analysed using a generalised estimating equation (GEE) model with log link function to examine the change in ALS-FRS and FVC measurements over the first three time points recorded for a patient. The autoregressive of first order as working correlation structure was used and the patients with missing values at any assessment number were excluded from GEE analysis. The GEE model includes the group indicator, time points, the interaction term between group and time points. The p values of the interaction term from type 3 analysis in the GEE model were estimated to assess whether the measurements across all time points between A4V and non-A4V groups were significantly different. The least square mean and SEM were provided.

RESULTS
Descriptive features
Applicable data were collected from 15 medical centres. A total of 175 participants with confirmed SOD1 mutations were analysed. Of participants collected, 63 had SOD1A4V mutations (36.4%), the most common mutation observed in this cohort. One hundred and twelve participants had SOD1non-A4V mutations (63.6%). There was a slight male dominance in this cohort with a male–female ratio of 1.30:1 in all SOD1 participants, but there was no significant difference in the male–female ratio between SOD1A4V (1.33:1) and SOD1non-A4V (1.29:1) participants (p=0.91, $\chi^2$ testing; table 1).

A total of 36 distinct, missense SOD1 mutations were found in this cohort. The most common SOD1non-A4V mutation was I113T (Ile-Thr) in 32 participants (18.3%), followed by G41D (Gly-Asp; 11 participants; 6.4%), and E40K (Glu-Lys; 10 participants; 5.7%). The frequencies and clinical characteristics of all participants included in this study are shown in table 2.

Age of disease onset
Age of onset data was provided for 162 (92.5%) total participants, with data for 57 SOD1A4V and 105 SOD1non-A4V patients available for analysis. The mean age of onset for all participants was 49.7±12.3 years (mean±SD). The mean age of onset varied across different mutations, with G37R (Gly-Arg) and D133A (Asp-Ala) mutations associated with the youngest and oldest mean ages at onset, respectively (figure 1A). There was no

<table>
<thead>
<tr>
<th>Table 1</th>
<th>Clinical characteristics of SOD1A4V versus SOD1non-A4V mutation populations in familial amyotrophic lateral sclerosis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total SOD1</td>
<td>SOD1A4V</td>
</tr>
<tr>
<td>Number of participants (%)</td>
<td>175 (100)</td>
</tr>
<tr>
<td>Male–female ratio</td>
<td>1.30:1</td>
</tr>
<tr>
<td>Mean age at onset (year)±SD (n)</td>
<td>49.7±12.3 (162)</td>
</tr>
<tr>
<td>Mean disease duration (year)±SD (n)</td>
<td>4.6±6.0 (134)</td>
</tr>
<tr>
<td>Median survival (year)</td>
<td>2.7</td>
</tr>
</tbody>
</table>

* $\chi^2$ Test for categorical variable; Kruskal-Wallis test for continuous variable; log-rank test for overall survival.
significantly different in mean age of onset between SOD1A4V (50.0±12.4 years) and SOD1non-A4V (49.5±12.3 years) participants (p=0.72, Kruskal-Wallis; table 1).

**Disease duration**

Disease duration information was available for 134 (76.6%) of total participants, including 51 SOD1A4V and 83 SOD1non-A4V patients. The mean disease duration was 4.6±6.0 years for all SOD1 participants, 1.4±0.7 years for SOD1A4V participants, and 6.6±7.0 years for SOD1non-A4V (table 1). Disease duration varied between mutation type, ranging from rapidly progressing mutations such as A4T (Ala-Thr; 0.8±0.1 years) to slow progressing mutants such as G41D (Gly-Asp; 23.5±14.0 years; figure 1B).

**KM survival analysis** was performed comparing the survival probabilities from time of disease onset to death between SOD1A4V and SOD1non-A4V (figure 2). Of 120 participants analysed, 35 were SOD1A4V and 85 were SOD1non-A4V. The median survival for all participants was 2.7 years, 1.2 years for SOD1A4V and 6.8 for SOD1non-A4V. SOD1A4V median survival was significantly shorter than SOD1non-A4V by log-rank test (p<0.0001). No SOD1A4V participants survived to 4 years (figure 2B).

**FRS and FVC**

Only three data points were considered for FRS and FVC. Thirty SOD1A4V and 75 SOD1non-A4V participants were used for ALS-FRS and FVC analysis. The least mean and SE of ALS-FRS for SOD1A4V were 37.8±1.4, 30.0±2.0 and 22.3±3.7; while

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Table 2 Disease characteristics by mutation type in SOD1 familial ALS

<table>
<thead>
<tr>
<th>Mutation*</th>
<th>Mean age (year)±SD (n)</th>
<th>Mean duration† (year)±SD (n)</th>
<th>Median duration (year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1 4 Ala-Val</td>
<td>49.9±12.3 (57)</td>
<td>1.4±0.7 (51)</td>
<td>1.2</td>
</tr>
<tr>
<td>4 113 Ile-Thr</td>
<td>54.2±10.7 (29)</td>
<td>5.3±4.8 (22)</td>
<td>3.3</td>
</tr>
<tr>
<td>2 41 Gly-Asp</td>
<td>34.2±7.8 (8)</td>
<td>23.5±14 (4)</td>
<td>21</td>
</tr>
<tr>
<td>4 100 Gly-Lys</td>
<td>39.6±5.9 (10)</td>
<td>8.9±5.2 (8)</td>
<td>9.1</td>
</tr>
<tr>
<td>4 100 Gly-Gly</td>
<td>42.6±9.1 (5)</td>
<td>9.6±2 (4)</td>
<td>7.2</td>
</tr>
<tr>
<td>4 89 Ala-Val</td>
<td>56±10.4 (4)</td>
<td>8±1.6 (2)</td>
<td>8</td>
</tr>
<tr>
<td>1 4 Ala-Thr</td>
<td>50±10.1 (3)</td>
<td>0.8±0.05 (2)</td>
<td>0.8</td>
</tr>
<tr>
<td>4 90 Asp-Ala</td>
<td>57.7±9.6 (3)</td>
<td>9.7±5.4 (2)</td>
<td>9.7</td>
</tr>
<tr>
<td>4 93 Gly-Asp</td>
<td>49±12.5 (3)</td>
<td>2.2±0.6 (2)</td>
<td>2.2</td>
</tr>
<tr>
<td>5 137 Thr-Thr</td>
<td>38.3±9.2 (3)</td>
<td>9.6±7 (3)</td>
<td>6.4</td>
</tr>
<tr>
<td>1 14 Val-Gly</td>
<td>50.3±21.0 (3)</td>
<td>2.6±1 (2)</td>
<td>2.6</td>
</tr>
<tr>
<td>6 6 Cys-Ser</td>
<td>54±16.9 (2)</td>
<td>4.1±0.5 (2)</td>
<td>4.1</td>
</tr>
<tr>
<td>5 133 Gly-Ala</td>
<td>62±2.8 (2)</td>
<td>0.9±0.6 (2)</td>
<td>0.9</td>
</tr>
<tr>
<td>2 49 Gly-Lys</td>
<td>59±19.8 (2)</td>
<td>6.8±1.9 (2)</td>
<td>6.8</td>
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<tr>
<td>5 141 Gly-Arg</td>
<td>42.5±2.1 (2)</td>
<td>1.1±0.7 (2)</td>
<td>1.1</td>
</tr>
<tr>
<td>2 37 Gly-Arg</td>
<td>26.5±6.4 (2)</td>
<td>7.8</td>
<td></td>
</tr>
<tr>
<td>2 41 Gly-Ala</td>
<td>44.5±10.6 (2)</td>
<td>17.3±0 (2)</td>
<td>17.3</td>
</tr>
<tr>
<td>2 41 Gly-Gly</td>
<td>51±2.8 (2)</td>
<td>1.5±0.7 (2)</td>
<td>18.5</td>
</tr>
<tr>
<td>1 41 Gly-Thr</td>
<td>49.5±0.7 (2)</td>
<td>0.7±0.4 (2)</td>
<td>0.7</td>
</tr>
<tr>
<td>5 148 Val-Gly</td>
<td>37 (1.2)</td>
<td>50</td>
<td></td>
</tr>
<tr>
<td>5 125 Asp-Ala</td>
<td>63</td>
<td>1.1</td>
<td></td>
</tr>
<tr>
<td>3 76 Asp-Tyr</td>
<td>75</td>
<td>3.7</td>
<td></td>
</tr>
<tr>
<td>4 108 Gly-Arg</td>
<td>67</td>
<td>1.7</td>
<td></td>
</tr>
<tr>
<td>1 101 Gly-Ala</td>
<td>59</td>
<td>4.8</td>
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</tr>
<tr>
<td>5 141 Gly-Ala</td>
<td>43</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>2 37 Gly-Ala</td>
<td>36</td>
<td>4.6</td>
<td></td>
</tr>
<tr>
<td>2 41 Gly-Ser</td>
<td>67</td>
<td>0.4</td>
<td></td>
</tr>
<tr>
<td>4 93 Gly-Ser</td>
<td>45</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>2 43 His-Arg</td>
<td>56</td>
<td>0.3</td>
<td></td>
</tr>
<tr>
<td>2 46 His-Arg</td>
<td>47</td>
<td>23.4</td>
<td></td>
</tr>
<tr>
<td>5 144 Leu-Phe</td>
<td>66</td>
<td>6.2</td>
<td></td>
</tr>
<tr>
<td>5 144 Leu-Ser</td>
<td>56</td>
<td>7.8</td>
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</tr>
<tr>
<td>1 14 Val-Met</td>
<td>54</td>
<td>4.1</td>
<td></td>
</tr>
<tr>
<td>4 87 Val-Met</td>
<td>39</td>
<td>8.8</td>
<td></td>
</tr>
<tr>
<td>5 134 Thr-Cys</td>
<td>55</td>
<td>13</td>
<td></td>
</tr>
</tbody>
</table>

*The mutations are ordered by decreasing number of affected patients. Nomenclature corresponds to amino acid sequence excluding ATG start codon.
†Censored data are included in determination of mean or median duration.
‡Mutations that are not listed in the ALSoD Database as of 5/5/15.
§Total number of participants with available data.
ALS, amyotrophic lateral sclerosis.


KM survival analysis was performed comparing the survival probabilities from time of disease onset to death between SOD1A4V and SOD1non-A4V (figure 2). Of 120 participants analysed, 35 were SOD1A4V and 85 were SOD1non-A4V. The median survival for all participants was 2.7 years, 1.2 years for SOD1A4V and 6.8 for SOD1non-A4V. SOD1A4V median survival was significantly shorter than SOD1non-A4V by log-rank test (p<0.0001). No SOD1A4V participants survived to 4 years (figure 2B).

FRS and FVC

Only three data points were considered for FRS and FVC. Thirty SOD1A4V and 75 SOD1non-A4V participants were used for ALS-FRS and FVC analysis. The least mean and SE of ALS-FRS for SOD1A4V were 37.8±1.4, 30.0±2.0 and 22.3±3.7; while
those of SOD1non-A4V were 35.9±0.9, 32.9±1.1 and 29.9±1.3 at time points 1, 2 and 3, respectively. A statistically significant difference was seen in ALS-FRS across three time points in SOD1A4V compared with SOD1non-A4V participants (p=0.02, figure 3A). Additionally, 37 SOD1A4V and 81 SOD1non-A4V participants were used for FVC analysis. Dates of permanent ventilation were rarely available (<5% of total participants), most likely due to death without receiving tracheal ventilation, and so were not included in final analysis. Similarly, a statistically significant increase in ALS-FVC decline was observed in SOD1A4V compared with SOD1non-A4V (p=0.02, figure 3B). The least mean and SE of FVC for SOD1A4V were 86.2±4.1, 58.8±5.1 and 50.7±9.8; while those of SOD1non-A4V were 73.2±2.8, 62.2±3.2 and 54.7±4.0 at time points 1, 2 and 3, respectively.

**DISCUSSION**

We collected data from 15 North American centres, studying 175 participants with confirmed SOD1 mutations, cared for from the year 2000 to present. The number of patients available for this study represent the largest effort to study ALSSOD1 natural history in almost 20 years. Combining data from multiple studies suggests mean disease duration for all SOD1 is 3.9±5.5 years and SOD1A4V is 1.4±0.9 years. Three of these studies represent 92% of the 199 reported patients and use data collected more than 20 years ago and published in the 1990s. Our calculated disease duration for all SOD1 of 4.6±6.0 and SOD1A4V of 1.4±0.7 years indicates no significant change in the natural history of the disease since these historical data were collected. Our results provide updated...
survival data that could serve in the design and interpretation of future clinical trials specific for patients with ALS\textsuperscript{SOD1}.

A total of 36 missense SOD1 mutations were captured, with the four most common (SOD1\textsuperscript{A4V}, SOD1\textsuperscript{T113I}, SOD1\textsuperscript{G41D} and SOD1\textsuperscript{E100K}) accounting for two-thirds of all participants. Our data show a smaller percentage (36.4\%) of SOD1\textsuperscript{A4V} among all ALS\textsuperscript{SOD1} participants than previously reported (50\%). This may reflect the recent expansion in genetic testing and improvement of ALS care, leading to increased detection of SOD1 mutations with less aggressive or typical presentations. Interestingly, male predominance was present, although mild, in ALS\textsuperscript{SOD1} participants as a whole (M:F of 1.3). These findings may reflect potential bias in the data set, as they are in contrast to a recent literature review.\textsuperscript{28} However, ALS\textsuperscript{SOD1} cohorts published earlier report similar male predominance.\textsuperscript{18} Age of onset for all SOD1 patients (49.7±12.3 years) was not statistically different from SOD1\textsuperscript{A4V} age of onset (50.0±12.4 years), which might be unexpected due to the aggressive nature of SOD1\textsuperscript{A4V}. However, these findings are consistent with previous reports,\textsuperscript{18} in which onset is similar between SOD1\textsuperscript{A4V} and all SOD1 patients, while progression is more rapid in the SOD1\textsuperscript{A4V} population.

Our results are limited by the design of this study as retrospective. As with all retrospective studies, inherent biases exist based on the availability of data collected. Of the original 37 NEALS medical centres which we corresponded, 17 participated in this study. No obvious variables such as geographic location or size of centre were linked to the 20 medical centres that did not respond. Correspondingly, data included in the study have come from clinical centres spanning wide geographical regions and likely capture a significant portion of the ALS\textsuperscript{SOD1} population in North America. However, assumptions must be made when compiling survival data from multiple centres, including consistency of standard of care. Also, given that our data were drawn from large ALS referral centres, survival and progression rate numbers may be different than outcomes in the community.

Natural history data are optimally collected prospectively, and in fact a portion of our data from 2013 to 2014 was collected as such. Efforts to collect prospective natural history data on ALS\textsuperscript{SOD1} and FALS in general, should be considered in the future and will be better able to capture real-time clinical information, such as site of onset and presence of extramotor findings, in addition to more closely documenting paraclinical end points such as ALS-FRS, FVC and time-to-permanent-ventilation. Despite these limitations, the rarity of ALS\textsuperscript{SOD1} coupled with the urgent need for enabling new clinical trials helps justify the use of a retrospective study design.

In clinical trials with a rare disease population, such as ALS\textsuperscript{SOD1}, historical controls may be implemented to assess outcomes. As recruitment of patients to a trial in a rare disease population is challenging, the use of historical controls would be valuable to design an adequately powered trial. However, it is important to validate if historical data have changed over time. In contrast to our results focusing on ALS\textsuperscript{SOD1}, previous natural history studies\textsuperscript{29, 30} of the ALS population suggest an increase in survival and conclude this may reflect improvement in respiratory, nutritional and supportive clinical care. These findings may suggest that, although overall ALS survival has improved over time, ALS\textsuperscript{SOD1} may represent a unique ALS subpopulation. Although our data suggest the ALS\textsuperscript{SOD1} has not changed over time, the use of historical controls in clinical trials is challenging, and key limitations exist in our data for direct implementation as historical controls. To properly match patients in trials with historical controls, additional data such as standard of care (riluzole use, non-invasive ventilation), cognitive status and site of disease onset must be collected, leading to enhanced comparisons with a future cohort. Future prospective studies will focus on these missing data in future prospective natural history studies in ALS\textsuperscript{SOD1} or other ALS disease populations. Nevertheless, the data reported regarding updated survival statistics for this population are one important consideration in the use of historical controls.

The first reported cause of FALS was a mutation in SOD1, and it is now widely accepted that the pathogenesis of mutations in SOD1 is related to a gain of toxic function of the SOD1 protein. Therefore, global reduction of toxic SOD1 in ALS has been recognised as a possible therapeutic intervention. Our work with SOD1 antisense oligonucleotides\textsuperscript{6–10} and others (ClinicalTrials.gov NCT00706147)\textsuperscript{11–17} have focused on targeted SOD1-lowering therapeutics approaches for ALS\textsuperscript{SOD1}. Given the heterogeneity of disease progression in different mutation carriers, one may envision the design of a trial that...
stratifies results from patients with rapidly progressing disease as defined by unchanged natural history data. For example, our analysis of the SOD1A4V patient population in this study suggests that SOD1A4V disease characteristics are homogeneous, and natural history has remained unchanged over time with a median survival of 1.2 years. As SOD1A4V is the most common mutation found in North America, recruitment for a SOD1A4V-focused trial for therapeutic efficacy may be feasible. Assuming an accrual interval of 1 year and additional follow-up interval of 2 years, 52 SOD1A4V participants per group (new treatment and placebo) are needed to achieve at least 80% power at a 0.05 significance level to detect the statistical difference when the median survival in the treatment group is 2.4 years using two-sided log-rank test, where HR of new treatment to control is 0.5. In contrast, our findings suggest that the median survival in all SOD1 participants is 2.7 years, and thus 88 SOD1 participants per group (new treatment and placebo) are needed when the median survival probability in the treatment group is 5.4 years, where HR of new treatment to control is 0.5.

Overall, the data presented here will help guide clinical trial design and may serve as a historical control database for ALS SOD1 interventional trials, with the hope of demonstrating that one of the upcoming therapies extends survival.

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Contributors TMM, AP, JJ-B, PA, MEC, TB designed the study. TMM, TB, WS, JJ-B, JL, ER performed the analyses. TMM, TKY, JS, JW, JJ-B, JL, ER analyzed the data. TMM, MB, JK, PA, MEC, TKY, TL, KS, BC, ALM, PA, GL, AP, MEC, TMM contributed clinical data to the study. TMM had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

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Competing interests TB, WS, JL, JS, LH, ER, NA, KBB, IDG, NJM, JBC, LFM, SHA, JPN, SG, LZ, ALM, JJ-B, PA, ER, GL, AP report no disclosures. TDB receives licensing fees from Athena Diagnostics, Inc. TM served on a medical advisory board for Biogen Idec. BC receives research support from Impeto Medical Inc and performs medical consultations for Advance Medical and consults for a PCORI grant. MEC is a consultant for Denali Inc, Cytokinetics Inc, Astrazeneca, Biogen Idec, and Voyager Therapeutics. TMM receives research support from Biogen Idec, Ionis Pharmaceuticals and research reagents from Regulus Therapeutics. Washington University, with TMM as a co-inventor, has submitted the US non-provisional patent application ‘Metabolism of SOD1 in CSF’ (Docket #011873-PC1-T1). CZN Diagnostics has licensed IP associated with this patent. TMM served on a medical advisory board for Biogen Idec, and for Ionis Pharmaceuticals.

Ethics approval Institutional Review Board.

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Defining SOD1 ALS natural history to guide therapeutic clinical trial design


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