 Phenotypic and molecular analyses of primary lateral sclerosis

ABSTRACT

Objective: To understand phenotypic and molecular characteristics of patients with clinically “definite” primary lateral sclerosis (PLS) in a prospective study.

Methods: Six sites enrolled 41 patients who had pure upper motor neuron dysfunction, bulbar symptoms, a normal EMG done within 12 months of enrollment, and onset of symptoms ≥5 years before enrollment. For phenotypic analyses, 27 demographic, clinical, and cognitive variables were analyzed using the k-means clustering method. For molecular studies, 34 available DNA samples were tested for the C9ORF72 expansion, and exome sequencing was performed to exclude other neurologic diseases with known genetic cause.

Results: K-means clustering using the 25 patients with complete datasets suggested that patients with PLS can be classified into 2 groups based on clinical variables, namely dysphagia, objective bulbar signs, and urinary urgency. Secondary analyses performed in all 41 patients and including only variables with complete data corroborated the results from the primary analysis. We found no evidence that neurocognitive variables are important in classifying patients with PLS. Molecular studies identified C9ORF72 expansion in one patient. Well-characterized pathogenic mutations were identified in SPG7, DCTN1, and PARK2. Most cases showed no known relevant mutations.

Conclusions: Cluster analyses based on clinical variables indicated at least 2 subgroups of clinically “definite” PLS. Molecular analyses further identified 4 cases with mutations associated with amyotrophic lateral sclerosis, Parkinson disease, and possibly hereditary spastic paraplegia. Phenotypic and molecular characterization is the first step in investigating biological clues toward the definition of PLS. Further studies with larger numbers of patients are essential. Neurol Genet 2015;1:e3; doi: 10.1212/01.NXG.0000464294.88607.dd

GLOSSARY

ALS = amyotrophic lateral sclerosis; ALS-CBS = Amyotrophic Lateral Sclerosis-Cognitive Behavioral Screen; COWAT = Controlled Oral Word Association Test; HSP = hereditary spastic paraplegia; IRB = Institutional Review Board; LMN = lower motor neuron; LPGM = Laboratory of Personalized Genomic Medicine; MND = motor neuron disease; PD = Parkinson disease; PLS = primary lateral sclerosis; SNP = single nucleotide polymorphism; UMN = upper motor neuron.

Primary lateral sclerosis (PLS) is considered the rarest motor neuron disease (MND). It is clinically characterized by isolated pure upper motor neuron (UMN) dysfunction. Thus, the absence of lower motor neuron (LMN) involvement distinguishes PLS from amyotrophic lateral sclerosis (ALS). The diagnosis of PLS is also based on excluding all definable diseases, such as multiple sclerosis, myelopathy, metabolic diseases, and hereditary spastic paraplegia (HSP). In addition, after a few years of observation, some patients with suspected PLS develop features of LMN...
dysfunction. Consequently, the diagnostic criteria for PLS have been extended from the originally recommended 3 years without UMN involvement to 4 years. Although patients with PLS have markedly impaired motor function, PLS, unlike ALS, is not life-threatening. PLS is suspected to be a heterogeneous disease. Because of its rarity, no prospective studies have analyzed the clinical and molecular characteristics of PLS. However, such investigations are an essential first step to clearly defining PLS and understanding the mechanisms underlying the disease. Here, we report novel analyses of the clinical phenotype and genetic markers of PLS.

METHODS Standard protocol approvals, registrations, and patient consents. The study protocol was approved by the Institutional Review Board (IRB) of Columbia University (Protocol Numbers: AAAE1115 and AAE4850) and the individual IRBs of all participating sites.

Eligible patients were prospectively enrolled in this study, which is a parallel study to ALS Multicenter Cohort Study of Oxidative Stress (ALS COSMOS) (NIEHS, R01ES016348). These 2 studies are nearly identical in structure and methodology, except for eligibility criteria, follow-up visit frequency, and number of participating sites.

We defined clinically “definite” PLS when patients had (1) pure UMN dysfunction for at least 5 years following symptom onset based on subjective functional impairment; (2) a normal EMG done within 12 months of enrollment (minimum changes in only one muscle were permitted); and (3) normal brain and spinal cord neuroimaging with allowance for increased signal intensity in the pyramidal tracts at the posterior internal capsules. Exclusion criteria included patients in whom only the legs were affected, patients with HSP, patients with a history of MND in immediate family, or patients with other active neurologic and unstable medical diseases. The known HSP, patients with a history of MND in immediate family, or those with PLS have markedly impaired motor function. However, such investigations are an essential first step to clearly defining PLS and understanding the mechanisms underlying the disease. Here, we report novel analyses of the clinical phenotype and genetic markers of PLS.

Phenotype cluster analyses. We collected data on 27 demographic and clinical variables for all 41 enrolled patients (table e-1 at Neurology.org/ng). Primary analyses were conducted on the 25 patients with complete data; secondary analyses were conducted on all 41 (table 1). Of the 27 potential clinical indicators, 5 (memory impairment, car sickness, stuttering, difficulty spelling, and predominantly unilateral symptoms) were present in no more than 1 patient and therefore excluded from the analysis. Verbal fluency was measured with the Written Verbal Fluency Test or the Controlled Oral Word Association Test (COWAT) with F, A, and S, which consisted of a combination of scores from the 3 subscales. Clinical verbal impairment was defined as either a Fluency Test index score of at least 19 or a COWAT score at least 2 SDs below the mean, adjusted for sex, age, and education level. Finally, before conducting the cluster analysis, we standardized all variables, continuous and binary, to a mean of 0 and an SD of 1 to ensure that they had equal weight in the analysis. A sensitivity analysis in which we scaled only the continuous variables and left the binary variables as 0 or 1 showed no meaningful difference.

In a secondary analysis, we restricted the variables to those with data available from all 41 patients, i.e., age, sex, disease duration, and the 15 binary clinical variables. A cluster analysis was performed following the method described above. Data analyses were conducted using SAS version 9.2 (SAS Institute, Cary, NC) and R version 3.0.1.

K-means clustering. In preliminary analyses, we examined the plot of the within-groups sum of squares over a range of 2–15 possible clusters. Because we did not observe a “bend” in the plot (indicating the optimal number of clusters) and this was an exploratory analysis, we opted for 2 clusters in order to be conservative and for ease of interpretation (figure 1).

We identified the 2 clusters using k-means with Euclidean distance. Variables associated with the clustering were identified in 2 steps. First, a model-building strategy using least absolute shrinkage and selection operator (Lasso) identified potentially important variables. These were included in a logistic regression model. A Wald test for significance of parameters in the logistic model was used to identify important clustering variables.

Genetic analysis. All testing on the available 34 patient samples was performed in the Laboratory of Personalized Genomic Medicine (LPGM) at Columbia University.

C9ORF72 expansion testing. The presence of expanded repeats was determined using the method of Renton et al.

Sequencing and bioinformatics. Sequence capture for high-throughput sequencing was performed using Illumina TruSeq exome capture reagents, and 100-bp paired-end sequencing was performed on an Illumina HiSeq 2500 sequencer. Next-generation sequencing data were mapped and variants were called using NextGENe (SoftGenetics, State College, PA). Variant filtering and comparative analysis were performed using the single nucleotide polymorphism (SNP) catcher software developed by the LPGM. This software relies on allele frequency and functional prediction data from multiple publicly available databases, including ClinVar, 1000 Genomes Project, Exome Variant Server, and MSV3D. Pathogenic mutations were confirmed by Sanger sequencing.

RESULTS All 41 patients had clinically typical PLS. Six patients had no dysarthria or dysphagia, and another 6 had the minimum EMG changes that were permitted for enrollment (table e-1). All patients were alive at the time of report, except 3 who died unexpectedly (patient 7 had a sudden death during sleep, patient 11 had a fall resulting in death, and patient 12 had sepsis resulting in respiratory and cardiac failure). Patient 4 had abnormal CSF (protein of 118 mg/dL and 8 cells) due to a traumatic spinal tap.

Table 1 compares sociodemographic, clinical, and cognitive variables between all patients (n = 41) and those patients with complete data (n = 25). Generally, the data were similar across the 2 datasets, with a slightly lower percentage of women and patients with dysarthria, dysphagia, and objective bulbar signs in patients with complete data.

Using Euclidean distance measures, we constructed a dendrogram to visualize the similarities in
patients with complete data (figure 2). The first branch separated 1 patient (case ID 7), leaving 24. The second branch separated 6 patients, with 18 remaining. The resulting 2 clusters differentiated the 6 patients separated in the second step from the remaining patients (i.e., case ID 7 was grouped with the 18 for a total of 19 patients in that cluster).

The Lasso model selected 6 of the 19 variables associated with the cluster groupings: dysarthria, dysphagia, objective bulbar signs, minimum EMG changes, urinary urgency, weight loss, and sensory impairment, the presence of which characterized the smaller cluster of 6 patients. Some of these clinical features were also present in other patients. None of these 6 variables was statistically significant in a joint logistic regression model, which predicted cluster membership. However, in individual logistic regression models, dysphagia ($p = 0.01$), objective bulbar signs ($p = 0.01$), and urinary urgency ($p = 0.002$) were associated with cluster membership. The modeling step was not based on an a priori specification of clustering variables and was exploratory in nature; therefore, the $p$ values should be interpreted cautiously.

**Secondary analyses.** Using all 41 patients, the plot of the within-groups sum of squares by number of clusters was similar to the curve found in the primary analysis, without an obvious bend. We again proceeded with the assumption of 2 clusters for ease of interpretation. Similar to the primary analysis, the Lasso model selected 7 of the 18 variables associated with the grouping: dysarthria, dysphagia, objective bulbar signs, minimum EMG changes, urinary urgency, weight loss, and female sex. Of these 7 variables, none were associated with cluster membership in a joint logistic regression model. However, in individual logistic regression models, dysphagia ($p = 0.004$), objective bulbar signs ($p < 0.001$), urinary urgency ($p < 0.001$), and female sex ($p = 0.02$) were associated with cluster membership. With the exception of sex, the results confirmed the primary analysis. Finally, we tested for cluster differences in all the cognitive variables that were not included in the k-means clustering and none differed across the 2 groups.

We repeated the analyses for the 37 patients with complete data for the Amyotrophic Lateral Sclerosis-Cognitive Behavioral Screen (ALS-CBS) variables. The plot of the within-groups sum of squares by number of clusters was similar to that shown in figure 1. We proceeded assuming 2 clusters. The Lasso model selected 9 of the 18 variables associated with the grouping: age, disease duration at baseline, dysarthria, dysphagia, objective bulbar signs, minimum EMG changes, urinary urgency, weight loss, and female sex. Of these 9 variables, none were associated with cluster membership in a joint logistic regression model. However, in individual logistic regression models, dysphagia ($p = 0.004$), objective bulbar signs ($p < 0.001$), urinary urgency ($p < 0.001$), and female sex ($p = 0.02$) were associated with cluster membership. With the exception of sex, the results confirmed the primary analysis. Finally, we tested for cluster differences in all the cognitive variables that were not included in the k-means clustering and none differed across the 2 groups.

**Exome sequencing.** Table e-1 lists the mutations detected by C9ORF72 expansion testing and exome sequencing in genes associated with HSP, familial

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#### Table 1 Sociodemographic, clinical, and cognitive data for patients with PLS

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients (N = 41)</th>
<th>Patients with complete data (N = 26)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Demographic variables</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age, y</td>
<td>60 (9.1)</td>
<td>60 (8.0)</td>
</tr>
<tr>
<td>Disease duration at baseline, y</td>
<td>7.4 (2.0)</td>
<td>7.1 (2.1)</td>
</tr>
<tr>
<td>Sex, % female</td>
<td>46</td>
<td>40</td>
</tr>
<tr>
<td><strong>Clinical signs and evaluations, %</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Dysarthria</td>
<td>83</td>
<td>76</td>
</tr>
<tr>
<td>Dysphagia</td>
<td>46</td>
<td>36</td>
</tr>
<tr>
<td>Objective bulbar signs</td>
<td>44</td>
<td>36</td>
</tr>
<tr>
<td>Minimum EMG changes</td>
<td>15</td>
<td>16</td>
</tr>
<tr>
<td>Urinary urgency</td>
<td>39</td>
<td>36</td>
</tr>
<tr>
<td>Bowel urgency</td>
<td>5</td>
<td>4</td>
</tr>
<tr>
<td>Weight loss</td>
<td>7</td>
<td>12</td>
</tr>
<tr>
<td>Personality/cognitive changes</td>
<td>10</td>
<td>4</td>
</tr>
<tr>
<td>Sensory impairment</td>
<td>12</td>
<td>16</td>
</tr>
<tr>
<td>No SSEP from legs</td>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td><strong>Cognitive/behavioral test scores</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mini-Mental State Examination</td>
<td>28.8 (1.6)</td>
<td>28.6 (1.8)</td>
</tr>
<tr>
<td>ALS-CBS cognitive</td>
<td>14.4 (2.9)</td>
<td>14.1 (3.1)</td>
</tr>
<tr>
<td>ALS-CBS behavioral</td>
<td>9.6 (8.4)</td>
<td>9.0 (8.0)</td>
</tr>
<tr>
<td>Verbal impairment, %</td>
<td>85</td>
<td>80</td>
</tr>
<tr>
<td>CNS-LS</td>
<td>15.3 (5.3)</td>
<td>14.8 (4.5)</td>
</tr>
<tr>
<td>FBI-ALS</td>
<td>9.7 (9.9)</td>
<td>9.3 (9.1)</td>
</tr>
</tbody>
</table>

Abbreviations: ALS-CBS = Amyotrophic Lateral Sclerosis-Cognitive Behavioral Screen; CNS-LS = Center for Neurologic Study-Lability Scale; COWAT = Controlled Oral Word Association Test; FBI-ALS = Frontal Behavioral Inventory-ALS; PLS = primary lateral sclerosis; SSEP = somatosensory evoked potential.

All data are mean (SD) unless otherwise indicated.

*a* Number of patients with complete cognitive testing data.

*b* Percentages derived from the Written Verbal Fluency Index or the COWAT (consisting of 3 scores)—see the text for further explanation.

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ALS, and other known neurologic diseases. We identified one previously described pathogenic mutation in the \textit{SPG7} gene in heterozygous form (A510V) in patient 121 and one \textit{C9ORF72} expansion in patient 8. Patient 1 and patient 8 belong to the larger cluster (figure 2). Patient 11 had a predicted pathogenic heterozygous mutation in \textit{PARK2},\textsuperscript{22} and patient 41 had a predicted risk allele in \textit{DCTN1}.\textsuperscript{23} Patient 11 also belonged to the larger cluster; patient 41 was not clustered because cognitive testing data were incomplete. A predicted pathogenic mutation in the \textit{SYNE2} gene was identified in patient 6.\textsuperscript{24} However, there was no evidence of myopathy. Several other patients showed SNPs of unknown significance in the \textit{PARK2} (patient 23), \textit{VEGFA} (patient 26), \textit{CLN6} (patient 29), \textit{BTD} (patient 29), and \textit{LRKK2} (patient 32) genes.

From our exome sequencing performed on all patients with PLS, we have identified a combined 4,500 rare (population frequency less than 1%) missense or nonsense variants that occurred in at least 2 patients with PLS. Among these 4,500 variants, one-third mapped to genes with some disease-related annotation in the Online Mendelian Inheritance in Man database, and about one-third were predicted to disrupt protein function based on functional prediction algorithms (SIFT, Provean). We are currently refining our analysis and classification of these variants.

**DISCUSSION** Our overall goal was to take the first step toward determining, through analyzing phenotypes and genotypes, whether PLS is a single entity or a syndrome including multiple neurodegenerative variants. The expanding knowledge of genotypic expression has made it clear that the traditional view of the relationship between phenotypes and genotypes is simplistic. Detailed phenotypic information is now considered essential to understanding new or poorly defined diseases, such as PLS. We accomplished our goal in 2 ways: first, by using k-means clustering of phenotypic characteristics to identify groups of similar patients, and second, by using exome sequencing to identify possible genes associated with these phenotypes.

Our study has several strengths. We prospectively enrolled only those patients with clinically “definite”

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**Figure 1** Within-groups sum of squares vs number of clusters

Within-groups sum of squares vs number of clusters to determine the number needed for k-means cluster analysis. The cluster algorithm assumes a given number of clusters to determine the grouping of patients. Figure 1 shows 15 separate cluster algorithms with 1–15 clusters assumed and the within-groups sum of squares calculated for each. Optimally, one would like to select a small number of clusters for ease of interpretation but with a small within-groups sum of squares. When there is a bend (like an elbow), it provides evidence that the gain is large (i.e., reducing the sum of squares) in identifying a fixed number of clusters with decreased evidence to increase the number of clusters. Our analysis showed no evidence of a bend, so we chose 2 clusters for convenience of interpretation.

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**Figure 2** Cluster dendrogram

Cluster dendrogram for similarity between patients with primary lateral sclerosis with complete datasets (N = 25). Each patient is denoted by a corresponding code number.
PLS to narrow clinical diversity and sought to identify any further possible subsets using phenotype cluster analyses. Subsequent \( k \)-means clustering, combined with a final model-building step, suggests that patients with PLS may be classified into 2 groups based on the presence or absence of the following clinical variables: dysarthria, dysphagia, objective bulbar signs, urinary urgency, weight loss, and sensory impairment. One limitation of this approach, however, is that the Lasso method chooses variables randomly from sets of highly correlated variables; thus, the selected variables may represent a subset of the entire group of variables.\(^{25}\) However, the results of sensitivity analyses were essentially similar, and these put fewer restrictions on the number of variables with complete data. Therefore, our results suggest that the diagnosis of PLS may represent at least 2 different groups of patients.

Another important strength is genetic analysis of all patients to test for the presence of known disease-causing mutations associated with other neurodegenerative disorders. Mutations in \( \text{SPG7} \) (A510V) result in autosomal recessive spastic paraplegia. The mutation found in patient 1 is a heterozygous \( \text{SPG7} \) variant, which is reported to predispose individuals to late-onset, complex neurodegenerative disorders.\(^{26}\) A more recent study indicates that this particular heterozygosity can be pathogenic for HSP\(^{27}\) (personal communication with Dr. John Fink, University of Michigan, June 2014). Patient 8 presented with clinically typical PLS but was found to have \( C9ORF72 \) hexanucleotide repeat expansion. A Dutch group previously described a single patient with \( C9ORF72 \) expansion in a PLS cohort of 110 patients.\(^{28}\) Although \( C9ORF72 \) expansion is predominantly found in patients with ALS or ALS plus frontotemporal dementia, it has been described in other neurodegenerative diseases.\(^{28}\) Variable clinical phenotypes may be the result of complex environmental interactions and genetic modifiers.\(^{29}\) Our study and the Dutch study indicate that \( C9ORF72 \) expansion can be expressed phenotypically as typical PLS.

Features of atypical Parkinson disease (PD) have been reported in patients with a diagnosis of PLS.\(^{30,31}\) Although none of our patients had clinical features of PD, we found mutations in the \( \text{PARK2} \) gene (Arg2751rp) previously described as a cause of familial PD. This \( \text{PARK2} \) gene mutation is pathogenic when homozygous, but the heterozygous variants are reported to affect PD onset\(^{32}\) and phenotype.\(^{33,34}\) The \( \text{LRRK2} \) mutation is known to cause autosomal dominant familial PD, although in one study of large families the R1514Q mutation in our patient (patient 32) had not segregated with PD.\(^{35}\) Yet other \( \text{LRRK2} \) mutations are found in sporadic PD cases,\(^{36}\) and typical MND is reported in patients with familial PD resulting from a different \( \text{LRRK2} \) mutation.\(^{37}\) Although the \( \text{LRRK2} \) mutation is interesting, its pathogenic significance in our patient with PLS is at best uncertain, and thus we consider it to be an SNP at this time. Our exome sequencing also identified another important mutation that is a known pathogenic mutation of the \( \text{DCTN1} \) gene;\(^{38}\) although this mutation is rare, it has been reported in an apparent sporadic case of ALS.\(^{32}\)

Therefore, exome sequencing identified 4 potentially pathogenic mutations occurring in 34 patients with PLS (nearly 12%), all associated with neurodegenerative diseases such as ALS, HSP, and PD. With increasing knowledge in the near future, we may need to consider genetic counseling for patients who are found to have known gene mutations. Patients with 2 of these mutations belong to the cluster having the larger number of patients. Five other SNPs of unknown clinical significance were also detected (\( \text{PARK2}, \text{VEGFA}, \text{CNL6}, \text{BTD}, \) and \( \text{LRRK2} \)) as well as a predicted pathogenic mutation in \( \text{SYNE2} \). Based on our experience, we recommend that patients with a diagnosis of PLS, especially those participating in research studies, be screened for pathogenic mutations using partial or complete exome sequencing to determine the prevalence of known pathogenic mutations and the pathogenic significance of variants of unknown significance. Further studies are needed to clarify the significance of these SNPs and the \( \text{SYNE2} \) mutation.

The diagnosis of PLS is still problematic because of the time required to wait before making a diagnosis and how strictly pure UMN involvement is defined. We decided to use very strict criteria (5 years after symptom onset before enrollment) so we could investigate clinically well-defined PLS cases. Yet waiting for such an extended time to make the diagnosis is neither practical nor helpful because physicians need to make a diagnosis at the earliest opportunity. Investigators also want to start PLS research at earlier stages of the disease, when active biological changes can be more readily found. We made every effort to select patients who had a “definite” diagnosis of PLS, short of autopsy proof. Therefore, disease diagnosed using our clinical criteria as described above (pure UMN dysfunction with normal EMG along with bulbar symptom(s), normal neuroimaging, and all definable diseases excluded) with negative exome sequencing and a negative \( C9ORF72 \) expansion test can be considered clinically “definite” PLS for research purposes currently. PLS with a shorter disease duration (3–4 years) could be considered clinically “probable” or clinically “possible.” These clinically probable or possible cases could be elevated to definitive PLS if the exome sequence and \( C9ORF72 \) expansion tests detect no known molecular abnormalities. Until we have improved biological or genetic markers, such criteria may be suitable for research investigation of PLS. We need an updated international consensus for PLS diagnosis.
Study limitations. Although the number of patients we studied is not small in comparison to other studies in PLS, a larger number of patients is required to achieve definitive results for both clinical clustering and exome sequencing analyses. We need to include more centers, preferably with long-term funding to allow adequate time for recruitment and to overcome the limitations involved with studying such a rare disease. Another limitation is the selection of patients with clinically “definite” PLS, which included patients who are in more advanced stages of the disease. Waiting a long period of time to diagnose PLS is a major drawback. Ideally, we should study PLS much earlier in the disease course, when biomarkers that can identify early PLS are most essential. To find such biomarkers, studying patients with clinically “definite” PLS is a necessary step.

We identified 2 phenotypic groups and a small number of patients with gene mutations known to be pathogenic for various neurodegenerative diseases. Further studies are needed. Our study is only the beginning of such investigations in PLS, providing a foundation that will hopefully stimulate other investigators to examine and expand our phenotypic and genetic studies in order to more fully understand PLS.

AUTHOR CONTRIBUTIONS

Dr. Mitsumoto served as the primary investigator for this study. He was involved in all stages of this project, including data collection, analyses, and preparing the draft of the manuscript. Dr. Nagy assisted in analyses of biomarkers in addition to reviewing the manuscript. Dr. Gennings assisted in statistical analyses, specifically cluster analyses, in addition to reviewing the manuscript. Dr. Murphy assisted in cognitive analyses in addition to reviewing the manuscript. Dr. Andrews assisted in data management for the entire study in addition to reviewing the manuscript.

Dr. Goetz assisted in general statistical analyses in addition to reviewing the manuscript. Dr. Floeter served as a site investigator for National Institute of Neurological Diseases and Stroke and was involved in planning the study, data collection, and reviewing the manuscript. Mr. Hupf assisted in planning and coordination of the study, data collection, and reviewing the manuscript. Ms. Singleton assisted in coordination of the study, data collection, and reviewing the manuscript. Dr. Barohn served as site investigator for the University of Kansas and was involved with planning of the study, data collection, and reviewing the manuscript. Dr. Nations served as site investigator for University of Kentucky and was involved with planning of the study, data collection, and reviewing the manuscript. Dr. Shoesmith served as site investigator for Western University, London, Ontario, Canada, and was involved with planning of the study, data collection, and reviewing the manuscript. Dr. Shoemich served as site investigator for the University of Texas Southwestern Medical Center and was involved with planning of the study, data collection, and reviewing the manuscript. Dr. Factor-Litvak served as site investigator for Western University, London, Ontario, Canada, and was involved with planning of the study, data collection, and reviewing the manuscript. Dr. Factor-Litvak served as the co-PI and was involved with the planning and statistical analyses as well as analyses of biomarkers, exposures, and cognition. She also reviewed the manuscript. All PLS COSMOS Study Group members assisted in data collection and reviewing the manuscript.

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DISCLOSURE

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