BACKGROUND
• ALSP is a rapidly progressive and debilitating neurodegenerative disorder that results in diminished quality of life and early demise and remains an unmet medical need with no approved symptomatic or disease-modifying treatments.1,2
• US Prevalence: ~10,000 accounts for ≥10% of idiopathic adult-onset leukodystrophies
• Pathological hallmarks of ALSP are dysfunctional microglia, demyelination of white matter of the brain, swollen axons and pigmentl glial cells
• Brain MRI findings include white matter lesions in a frontal predominant distribution, enlarged ventricles and often thinning of corpus callosum
• ALSP is attributable to loss of function mutations in the CSF1R gene that result in structural abnormalities and pathophysiology of axons and microglia, demyelination of white matter of the brain and accelerated development of neurological symptoms (cognitive impairment, moderate to severe motor dysfunction and neuropsychiatric complications)1,2
• Although accurate clinical diagnosis of ALSP has shown some improvement due to recent publication of diagnostic criteria, the rate of initial misdiagnosis remains problematic.3,4
• ALSP phenotype is associated with cognitive and motor impairment and can be misdiagnosed as MS or other adult-onset leukodystrophies
• Overlapping symptoms with early MS include gait/motor disturbances, cognitive deficits, depression and multiple psychiatric comorbidities5 and trends in MS differential diagnosis include adult-onset leukodystrophies which are recognized as mimics of MS.3,4
• Recent case series of 413 MS patients showed that 19 were diagnosed with an adult-onset leukodystrophy, >10% of which were found to carry CSF1R mutations and classified as ALSP.8

OBJECTIVE
• To characterize the misdiagnosis of ALSP for MS or other adult-onset leukodystrophies

METHODS
• Data for initial misdiagnosis of ALSP were obtained from a comprehensive, systematic literature search identified 90 published case reports with data extracted from 292 patients with ALSP (largest case series to date)
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• MEDLINE search (1/1/1980 - 3/31/2022) of published case reports within MEDLINE using prespecified criteria
• Inclusion: Clinical diagnosis confirmed by genetic testing for CSF1R gene mutation, brain imaging and/or histopathology in adults (18 years of age or older) regardless of gender, male or race, ethnicity or country as well as publications that describe neurologic symptoms, clinical symptoms, brain images and neuropathology from living or deceased patients
• Exclusion: Presence of AARS2 gene mutation confirmed by genetic testing; unconfirmed clinical diagnosis of ALSP and non-English case reports
• Continuous data and categorical data from eligible case reports were extracted, entered and trends in MS differential diagnosis and
evaluated by Specialty Groups using statistical analysis
• The volume and scope of data were prespecified criteria
• INCL: Clinical diagnosis confirmed by genetic testing for CSF1R gene mutation, brain imaging and/or histopathology in adults (18 years of age or older) regardless of gender,

RESULTS
• Medline literature search identified 90 published case reports with data extracted from 292 patients with ALSP (largest case series to date)
• Table 2 summarizes the demographic, commonly reported baseline symptoms and MRI findings from data extracted from the 292 patients with ALSP

<table>
<thead>
<tr>
<th>Initial Symptoms</th>
<th>ALSP [N = 292]</th>
<th>MS [N = 23]</th>
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<tbody>
<tr>
<td>Cognitive Impairment</td>
<td>56 (18.5%)</td>
<td>10 (43.5%)</td>
</tr>
<tr>
<td>Behavioral + Psychiatric</td>
<td>11 (16.9%)</td>
<td>11 (47.8%)</td>
</tr>
<tr>
<td>Pyramidal Motor</td>
<td>12 (13.2%)</td>
<td>6 (26.1%)</td>
</tr>
<tr>
<td>Extrapyramidal Motor</td>
<td>18 (19.8%)</td>
<td>5 (21.7%)</td>
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</tbody>
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- Accurate initial diagnosis of ALSP was achieved in only 31.5% of patients; due to overlap of symptoms with ALSP, patients were often misdiagnosed with a variety of conditions

Table 1. Demographic + Commonly Reported Baseline Symptoms

Figure 1. Most Frequent Initial Misdiagnoses

• Kaplan-Meier (KM) estimates of survival probability (%) and number of patients at risk of death at 30 months after diagnosis were performed with survival time and disease duration related to age of onset of symptoms in patients with ALSP (Figure 2)

CONCLUSIONS
• Literature search identified 90 published case reports with data extracted from 292 patients with ALSP, which represents the largest case study of ALSP patients to date
• Study confirms that ALSP has a diverse phenotype and can be easily misdiagnosed and that both MS and ALSP have heterogeneous clinical and imaging manifestations which challenge accurate diagnostic similarity. There is an overlap of clinical symptoms
• Combination of neurological family history, white matter MRI lesions and early-onset cognitive impairment with behavioral and/or motor dysfunction should trigger suspicion for ALSP and warrant genetic testing for CSF1R mutations
• Increased disease awareness and early genetic testing for CSF1R mutations can improve diagnostic accuracy
• Accurate diagnosis can allow for early intervention with investigational therapies currently in development
• Multidisciplinary approach, including involvement of genetic counselors will have an important role in the accurate diagnosis of ALSP