Amyotrophic Lateral Sclerosis and Genetic Testing: A Perspective from the ALS Community

Thesis

Presented in Partial Fulfillment of the Requirements for the Degree Master of Science in the Graduate School of The Ohio State University

By

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Abstract

**Background:** Although genetic testing for amyotrophic lateral sclerosis (ALS) is widely available, ALS management guidelines do not address the issue of genetic testing and it is unclear how many ALS patients have access to and interest in this technology.

**Hypothesis:** ALS patients have limited access to genetic testing.

**Methods:** We conducted a national survey of ALS patients enrolled in the Agency for Toxic Substances and Disease Registry. The survey consisted of multiple choice questions as well as two 12 item Likert scale series assessing (a) respondents’ individual experience with genetic testing and (b) respondents’ attitude toward genetic testing.

**Results:** The survey was emailed to 5591 registrants; 501 responded (response rate = 9.0%). Family history was reported to be positive for ALS in 8.4% and dementia in 33.7%. Genetic testing was offered to 33.4% and completed in 67.1% of those offered. A minority of respondents (12.3%) saw a genetic counselor, and were much more likely to be offered genetic testing (p=0.0001). Respondents with a family history of ALS were more likely to be offered testing (p=0.0001), but no more likely with a family history of
dementia (p=0.92). Testing was more likely to be completed in those with a positive family history of ALS (p=0.05). The majority of respondents reported a favorable attitude towards genetic testing, and the majority of those who underwent genetic testing reported a favorable experience. Comparison of composite average test experience and attitude scores between groups revealed that respondents with a family history of ALS were no more likely to report a favorable experience with genetic testing (p=0.42), but were more likely to report a favorable attitude towards genetic testing (p=0.0003). No differences in test experience (p=0.73) or attitude (p=0.11) scores were observed between those who tested positive or negative. Respondents who saw a genetic counselor did not have significantly different test experience scores (p=0.14), but had more favorable attitude scores (p=0.02).

**Discussion/Conclusion:** Despite apparently high interest in and satisfaction with ALS genetic testing, survey respondents had limited access to testing. To address this discrepancy, genetic testing and counseling should be offered in the routine management of ALS.
Dedication

Dedicated to my father, who has taught me that a disease never defines a person; rather, it refines a life to be lived in grace and love.
Acknowledgements

A Special Thanks to the ALS community and their families for participating in this study;

Dr. Stephen Kolb and the OSU Neurology team for survey development and implementation, and thesis preparation; Dr. Haikady Nagaraja at OSU Biostatistics for survey development and analysis; Dr. Paul Mehta and the Centers for Disease Control Agency for Toxic Substances and Disease Registry for distribution of this survey to the ALS National Registry Participants; The National Society of Genetic Counselors Neurogenetics Special Interest Group for their generous approval of grant funding for this project; The Ohio State University Genetic Counseling Program directors, faculty, staff and fellow students for their guidance, encouragement and support; my Family for their patience, unwavering love and support.
Vita

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Publications


Fields of Study

Major Field: Genetic Counseling
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Chapter 1: Objectives, Background and Hypothesis

OBJECTIVES

The purpose of this study was to perform a survey of patients with Amyotrophic Lateral Sclerosis (ALS) to assess their understanding, attitude, and experience with genetic testing. Specifically, we hoped to:

1) Assess understanding of concepts of ALS genetics  
2) Identify characteristics which are positively or negatively associated with the decision to seek genetic testing  
3) Identify characteristics which are associated with a favorable attitude towards the genetic testing experience

This information may assist physicians and genetic counselors in providing more effective education and care to patients with ALS. This project is a preliminary step towards developing practice guidelines for genetic counseling and testing in ALS.

BACKGROUND

ALS is an adult-onset neurodegenerative disorder characterized by loss of upper and lower motor neurons, progressive paralysis, and death within an average of 2-5 years after symptom onset. Diagnosis is based on clinical features, electrodiagnostic testing, and exclusion of other diseases with overlapping symptoms (Kinsley and
Siddique 2015). Treatment is supportive and palliative and there are currently no effective medical therapies other than riluzole, which slows progression and prolongs survival by an average of 3 months (Bensimon, Lacomblez et al. 1994). ALS has a prevalence of disease at 1/400 in Europeans (Ingre, Roos et al. 2015) and a mean incidence of 2.8/100,000 in Europeans and 1.8/100,000 North Americans. (Chio, Logroscino et al. 2013). While the majority of ALS cases appear to occur sporadically, approximately 5-10% (Gros-Louis, Gaspar et al. 2006, Gibson, Figueroa et al. 2014) of ALS patients have a family history of the disease. Clinically, familial ALS (fALS) and sporadic ALS (sALS) are similar. However, fALS cases are distinguished by an earlier mean age of onset (46 years) than sALS cases (56 years) (Juneja, Pericak-Vance et al. 1997, Testa, Lovati et al. 2004).

Clinically, ALS is characterized by progressive loss of function of the motor neurons in the nervous system. Loss of the neuron signal leads to atrophy and loss of the muscle it innervates, resulting in the “hallmark” features of ALS which include muscle fasciculation, weakness and wasting, dysarthria and dyspnea leading to respiratory dysfunction (Orsini, Oliveira et al. 2015). The disease mechanisms of ALS are focused on degeneration of the neuron support system (see Figure 1). This neuron support system is provided for by a host of proteins which are formed and regulated by many different genes and genetic factors (Peters OM 2015). The molecular pathways indicated in Figure 1 are neuron support pathways that when altered, lead to motor neuron death. Risk factors for developing ALS include genetic mutations leading to
inhibited protein function as well as environmental and biological factors such as exposures, body mass index, diet, viruses, other medical conditions and ethnicity.

The current understanding of the etiology of motor neuron disease includes the emergence of genetics as a major cause, with complex heterogeneity playing a role in neuron development, maintenance and resilience to these environmental and biological exposures (Calvo, Manzano et al. 2014, Peters OM 2015). With a symptom-based diagnosis paired with a lack of biochemical markers to confirm the diagnosis or mark the progression of disease, genetics is beginning to open the door to understand ALS at a biochemical level (Agrawal and Biswas 2015). Mutations in genes that are closely associated with the molecular pathways which nourish and support the neuron have been identified in fALS and sALS cases (Calvo, Manzano et al. 2014).

Figure 1: Molecular pathways that when altered, lead to motor neuron death causative of ALS; (figure taken from Calvo, Manzano et al. 2014).
Currently, two-thirds of genes associated with a fALS diagnosis have been identified and the remaining one-third of fALS cases is due to unidentified genes. In only 10% of (sALS) diagnoses have genes have been identified and the remaining 90% of sALS cases may have a complex interaction of genes, environmental exposures, lifestyle choices and aging (see Figure 2; Renton et al. 2014).

However, around 23% of sALS may be genetic as suggested by genome-wide data and genes associated with ALS have been classified as limited impact to highly penetrant and causative of disease (Leblond, Kaneb et al. 2014). Today, it is known that some of the genes discovered are highly causative of ALS, whereas others play a minor role and only have a significant impact when paired with other genetic mutations causative of overall motor neuron malnourishment (Boylan 2015, Peters OM 2015) (see Table 1; Appendix A).

Figure 2: "Timeline of gene discoveries in familial and sporadic ALS. Values represent the proportion of ALS explained by each gene in populations of European ancestry" (figure taken from Renton et al. 2014).
The landscape of genetic testing and genetic counseling for ALS has been transformed in recent years with the identification of novel genes such as \textit{C9orf72}, the recognition of the link between ALS and frontotemporal dementia (FTD), and the advent of next generation sequencing technology. The 2011 discovery of the hexanucleotide repeat expansion in \textit{C9orf72} led to the identification of pathogenic expansions in a significant percentage of both fALS and sALS, and revealed a common genetic etiology of ALS and FTD. This discovery established the genetic basis for two-thirds of fALS cases and 10\% of sALS cases (Renton, Majounie et al. 2011, Renton, Chio et al. 2014). A relatively short time ago, genetic testing for ALS was limited to one gene (\textit{SOD1}), which accounted for 20\% of fALS diagnoses. Technological advancements and additional gene discoveries have led to the expansion of current testing options to include assays for the \textit{C9orf72} repeat expansion, multigene next-generation panels, and whole exome sequencing. However, these genetic advances have been slow to reach the care of the ALS patient (Talbot 2014).

The high level of genetic heterogeneity and complexity of gene functions has been a barrier to therapy development, availability of clinical genetic testing and interpretation of results for ALS patients (Calvo, Manzano et al. 2014, Peters OM 2015). Genetic testing and confirmation of the molecular mechanism behind a patient's clinical presentation of ALS can aid in guiding diagnosis, care and treatment of ALS. Although diagnosis and disease course of ALS is largely the same as when the disease was first described (Calvo, Manzano et al. 2014), identifying the mechanisms which lead to motor
neuron death may be a gateway into targeted treatment and prevention of ALS. Future
treatments may be targeted toward patient genotype, with current investigations for
patients with SOD1 mutations (Miller, Pestronk et al. 2013), and potentially forthcoming
for patients with C9orf72 expansions (Mendez and Sattler 2015). Despite this impetus,
current management guidelines do not address the issue of genetic testing (Miller,
Jackson et al. 2009).

Although ALS management guidelines (Miller, Jackson et al. 2009) do not discuss
genetic testing or genetic counseling, several publications approach or address this
issue. Fong et al. (2012) state that persons who wish to learn the potential cause of ALS
in their family “should be offered genetic counseling, irrespective of but especially in the
presence of a suggestive family history” but do not suggest specific criteria for testing.
Chio et al. (2014) recommend that genetic testing be offered to those with fALS
(specifically, a first and/or second degree relative also affected). The latter paper
appears to comprise the only published guide for genetic testing in ALS.

Patients with ALS often ask why they developed the disease, what the chance is
that they will pass it on to their children, and how quickly their condition will progress
(Chio, Battistini et al. 2014). Genetic testing has the potential to address each of these
questions. Identification of a specific mutation underlying ALS can identify causality,
allow accurate risk assessment and genetic testing of family members, and, in some
cases, provide prognostic information about disease course (Chio, Battistini et al. 2014).
Genetic testing for an affected ALS patient implicates involvement of the biological family and may result in psychological and emotional effects (Chio, Logroscino et al. 2013; Fanos, Gelinas et al. 2004). Despite this, there are many motivations to pursue genetic testing including to reduce anxiety, plan reproduction, make lifestyle changes (Fanos, Gronka et al. 2011), participate in altruism for research and lend information for the benefit of offspring and relatives (Rahman, Meiser et al. 2012). Some ALS patients may refuse genetic testing based on fear of the results, inability to cope and desire to spare relatives (Fanos, Gronka et al. 2011). It is also important to note that negative or uncertain results can leave an ALS patient feeling ostracized and alone in their disease with no clear explanations (Chio, Battistini et al. 2014). Given these complexities, there is a need for understanding the perspective of the ALS patient towards genetic testing. Fanos et al 2004 investigated patient attitudes towards SOD1 testing in fALS diagnoses which resulted in the recommendations of: (1) physicians refer relatives of newly diagnosed individuals for genetic counseling and possibly psychological counseling; (2) investigators ensure that participants comprehend the purpose of gene identification is for research, not disclosure of individual results; (3) families be helped to understand how to keep abreast of medical and genetic advances; (4) following the model of Huntington disease (HD), consensus guidelines for FALS genetic counseling and testing be developed (Fanos, Gelinas et al. 2004). Our study set out to examine factors associated with access to genetic testing. We also sought to discover if there was an increased interest and positive attitude towards testing, and make suggestions for
clinical practice. To our knowledge, this is the first study directly investigating patient access to genetic testing in the ALS population.

**HYPOTHESIS**

Patients diagnosed with ALS have limited access to genetic testing. This study gathered data directly from the ALS community to assess understanding of ALS genetics, factors associated with the decision to seek genetic testing, and factors associated with positive or negative patient-perceived outcomes. The results of this survey will be a step towards the development of evidence-based practice guidelines for the ALS genetic counseling and testing.
Chapter 2: Research Design, Methodology and Limitations

**RESEARCH DESIGN**

A survey (see Appendix C: Survey Protocol) was designed and edited by the Primary Investigator, Co-Investigators and members of The Ohio State University Neurology Department.

**METHODOLOGY**

Study subjects completed an anonymous online survey using the survey engine SurveyMonkey®. Patients affected with ALS were eligible to participate. Family members and/or caregivers of affected individuals were also eligible to assist ALS patients in survey participation. A $10 incentive to Starbucks was offered to the first fifty participants who completed the survey and supplied their contact information. Consent for participation of this study was implied if survey was completed.

Eligible participants were identified and contacted through the Centers for Disease Control Agency for Toxic Substance and Disease National ALS Registry (CDC; ATSDR) (See Appendix B; Advertisement). The National ALS Registry is a congressionally mandated registry for persons in the U.S. with ALS who are invited to participate after receiving a diagnosis. Patients are notified about the registry through their local treatment team, and are eligible for participation upon giving consent. The CDC’s ATSDR
advertised and distributed the survey link via a one-time email announcement, after approval from the ATSDR committee. All results were tabulated and exported in .xcel, and/or .cvs format for analysis. This survey was conducted with approval from The Ohio State University Institutional Review Board.

The survey included questions about demographic information, disease onset, family history of disease (ALS; FTD, Alzheimer disease, dementia; Parkinson disease) in a first-degree, second-degree or other relative, setting of clinical care, understanding of ALS genetics, and genetic testing and counseling offered, which were available to be answered by all survey participants. Skip logic was utilized to divide the survey into tracks depending on reported access to and outcome of genetic testing. Each track had approximately 20 questions, all of which had to be answered to move forward to the next question, and divided respondents into the following groups: 1) ALS patients who have not had genetic testing; 2) ALS patients who had genetic testing and received a results that was negative or inconclusive; 3) ALS patients who had genetic testing and received a result which was positive.

Two Likert scale items assessed patient experience with (if applicable) and attitudes towards ALS genetic testing. The first Likert scale was completed only by respondents who had genetic testing and assessed personal experience and feelings towards the process and outcome. The second Likert scale was completed by all respondents. Respondents who had participated in the first Likert scale also participated in the second Likert scale after completion of the first. The second Likert scale assessed
general attitudes towards genetic testing and its usefulness for patients, families, the medical community and society. Each Likert item contained a 10 point scale, with response ranging from “strongly agree” to “strongly disagree.” For analysis, responses were collapsed into three categories; agree, neutral and disagree.

Data analysis was performed using JMP Version 11 software (SAS Institute, Cary, NC). Associations between groups and binary characteristics were studied using proportions and Fisher’s exact test. A two-tailed p-value of 0.05 or less was considered significant.
Chapter 3: Results

**ALS PATIENT DEMOGRAPHICS**

The survey was emailed to 5591 registrants and received a response rate of 9.0%. No exclusions were made in this response rate. 501 participants began the survey, with 450 participants completing the entire survey (89.8%). The drop-out rate is represented in reported n’s for each questions (see all tables in results section) and once the survey questions split into the appropriate tracks, the n will vary considerably as not every participant was eligible to answer every question. Patient demographics were reported as 95.15% Caucasian with the majority (87.86%) of respondents over the age of 50 years. Onset of disease symptoms was reported as limb in 76.0%, bulbar in 21.2% and “don’t know/remember” in 2.8%, with a formal diagnosis of ALS most often occurring over the age of 50 years (82.1%). A positive family history of ALS (affected first-degree, second-degree or other relative) was reported in 8.3%. A third of respondents (33.5%) reported a positive family history of fronto-temporal dementia, Alzheimer disease or other dementia, and 16.4% reported a positive family history of Parkinson disease (see Table 1).
<table>
<thead>
<tr>
<th>Onset of ALS</th>
<th>n = 495</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb Onset</td>
<td>376</td>
</tr>
<tr>
<td>Bulbar onset</td>
<td>107</td>
</tr>
<tr>
<td>Not sure</td>
<td>12</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Ethnicity</th>
<th>n = 495</th>
</tr>
</thead>
<tbody>
<tr>
<td>White/Caucasian</td>
<td>471</td>
</tr>
<tr>
<td>Black/African-American</td>
<td>13</td>
</tr>
<tr>
<td>Asian</td>
<td>1</td>
</tr>
<tr>
<td>Multiracial</td>
<td>3</td>
</tr>
<tr>
<td>Other/Prefer not to say</td>
<td>7</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age distribution</th>
<th>n = 494</th>
</tr>
</thead>
<tbody>
<tr>
<td>39 or under</td>
<td>16</td>
</tr>
<tr>
<td>40 - 49</td>
<td>44</td>
</tr>
<tr>
<td>50 - 59</td>
<td>140</td>
</tr>
<tr>
<td>60 - 69</td>
<td>205</td>
</tr>
<tr>
<td>70 or over</td>
<td>89</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Age at diagnosis</th>
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</tr>
</thead>
<tbody>
<tr>
<td>39 or under</td>
<td>26</td>
</tr>
<tr>
<td>40 - 49</td>
<td>62</td>
</tr>
<tr>
<td>50 - 59</td>
<td>158</td>
</tr>
<tr>
<td>60 - 69</td>
<td>187</td>
</tr>
<tr>
<td>70 or over</td>
<td>59</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Family history of ALS</th>
<th>n = 492</th>
</tr>
</thead>
<tbody>
<tr>
<td>Yes</td>
<td>42</td>
</tr>
<tr>
<td>No</td>
<td>387</td>
</tr>
<tr>
<td>Don’t know</td>
<td>63</td>
</tr>
</tbody>
</table>

Table 1: Summary of ALS patient survey respondent demographics

Continued
**Table 1 Continued**

<table>
<thead>
<tr>
<th></th>
<th>n = 489</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of FTD, Alzheimer disease or other dementia</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>165</td>
<td>33.7%</td>
</tr>
<tr>
<td>No</td>
<td>278</td>
<td>56.9%</td>
</tr>
<tr>
<td>Don’t know</td>
<td>46</td>
<td>9.4%</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>n = 488</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Family history of Parkinson disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>80</td>
<td>16.4%</td>
</tr>
<tr>
<td>No</td>
<td>367</td>
<td>75.2%</td>
</tr>
<tr>
<td>Don’t know</td>
<td>41</td>
<td>8.4%</td>
</tr>
</tbody>
</table>

**ALS CLINIC DEMOGRAPHICS**

The majority of respondents (78.8%) indicated care at a Muscular Dystrophy Association (MDA) and/or ALS Association (ALSA) certified center, and reported seeing a physical or occupational therapist, respiratory therapist, speech therapist, genetic counselor, social worker, and/or MDA or ALSA Representative (See Table 2 and Figure 3). Respondents were allowed to choose more than one option and a minority of respondents (12.5%) reported contact with a genetic counselor.

<table>
<thead>
<tr>
<th>Clinics</th>
<th>n= 485</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>MDA</td>
<td>73</td>
<td>15.1%</td>
</tr>
<tr>
<td>ALSA</td>
<td>140</td>
<td>28.9%</td>
</tr>
<tr>
<td>MDA &amp; ALSA</td>
<td>169</td>
<td>34.9%</td>
</tr>
<tr>
<td>Neither</td>
<td>103</td>
<td>21.2%</td>
</tr>
</tbody>
</table>

Table 2: Summary of ALS clinic demographics
In ALS patients who reported a positive family history of ALS, 25% (12/48) reported contact with a genetic counselor, compared to 10.6% (47/442) of ALS patients with a negative family history (p=0.0082).

ALS GENETICS AND HEREDITY DISCUSSION

Genetics and heredity of ALS was discussed with 3 out of 4 (74.7%) of all ALS patients, despite a reported positive or negative family history of ALS (p=0.08).

Respondents who reported a family history of ALS were slightly more likely to also report that genetics was discussed, but this did not reach statistical significance (p=0.08). The chance that an ALS patient’s children could develop ALS was reported as “discussed briefly” with only 19.7% (n=71) of respondents who did not undergo genetic
testing, with the majority of this group (88.7%; n=63) indicating their understanding that the chance their children could develop ALS would be zero to below 25% (Low). The majority (83.4%) of respondents indicated that ALS is “not usually,” “rarely,” or “sometimes” genetic (76.7%; n=369) or familial (96.3%; n=192).

**GENETIC TESTING DEMOGRAPHICS/DATA**

A majority of respondents (77.6% n=367) indicated that genetics was briefly discussed (46.1%; n=218) or explained (31.5%; n=149) to them during the course of their care. 16.7% (n=79) reported genetics was not discussed and 5.7% (n=27) indicated “don’t know/remember.” Almost half of respondents (46.8%) did not know that genetic testing for ALS is available, or indicated it was never or not usually available. Genetic testing was offered to 33.5% of respondents and completed in 67.1% of those offered. Of those who completed testing, 20/501 (4%) tested positive and recalled their genetic mutation status (see Table 3).

<table>
<thead>
<tr>
<th>Genetic testing offered</th>
<th>Genetic testing undertaken</th>
<th>Results</th>
<th>Genes</th>
</tr>
</thead>
<tbody>
<tr>
<td>n</td>
<td>466</td>
<td>156</td>
<td>79</td>
</tr>
<tr>
<td>Yes</td>
<td>156; 33.5%</td>
<td>104; 67.3%</td>
<td>Mutation: 23; 29.1%</td>
</tr>
<tr>
<td>No</td>
<td>268; 57.5%</td>
<td>42; 26.9</td>
<td>Negative: 53; 67.1%</td>
</tr>
<tr>
<td>Don't know/remember</td>
<td>42; 9.0%</td>
<td>9; 5.8%</td>
<td>Inconclusive: 3; 3.8%</td>
</tr>
</tbody>
</table>

Table 3: Summary of responses to genetic testing questions (n,%)

Of all respondents, genetic testing was offered to 33.5% and undertaken by 67.3% of those offered. 22.2% (n=103) of respondents indicated they personally requested information about genetic testing. A clinical genetic test was offered in 47.6%, research in 29.5% and 22.9% indicated “not sure” which type of testing was offered. Of the 156 respondents who reported undergoing genetic testing, 104 were informed of their results, with 79/104 (76.0%) recalling test results (Mutation, Negative or Inconclusive). 85.0% (n=51) of patients who saw a genetic counselor also elected to undergo genetic testing. Of the patients who did not indicate contact with a genetic counselor, 60.9% underwent genetic testing (p=0.006). A minority of respondents (12.5%) saw a genetic counselor, and were much more likely to be offered genetic testing (p=0.00001). Therefore, ALS patients were found to be 36.9 times more likely to undergo genetic testing if they are seen by a genetic counselor.

**OVERALL UNDERSTANDING OF GENETICS AND TESTING SERVICES**

A significant proportion of respondents (41.4%; n=198) did not know that genetic testing for ALS is available, or indicated it was never available. Half of respondents (49.9%) did not know whether genetic testing is available for family members of ALS patients, or indicated it was never available (see Table 4).
Respondents diagnosed with ALS before age 50 years (n=88) were equally likely to report a positive family history (11.4%; n=10) as those diagnosed after age 50 years (n=402; fALS reported in 9.45% n=38) (p=0.5563). Genetics and heredity was also equally likely to be discussed with patients diagnosed before age 50 years (81%) and after age 50 years (73%; p=0.104). However, genetic testing was more likely to be offered to patients diagnosed with ALS before age 50 years (44.6%) than to those diagnosed after age 50 years (31.0%) (p=0.02).

Respondents with a family history of ALS were more likely to be offered genetic testing (p=0.0001), but no more likely with a family history of dementia (p=0.92). Genetic testing was more likely to be completed in those who reported a family history of ALS (p=0.05). Among those who declined genetic testing, various reasons were given with 52.00% indicating “cost” was a major factor in this decision (see Figure 4).
Concerned about ability to obtain insurance coverage
Do not wish to know if ALS is running in the family
Concerned about burdening my family members
Do not believe ALS is running in the family
Cost

14.0% 16.0% 22.0% 40.0% 52.0%

*Concerned about ability to obtain insurance coverage, Do not wish to know if ALS is running in the family, Concerned about burdening my family members, Do not believe ALS is running in the family, Cost

Figure 4: Respondents indications for deciding against pursuing genetic testing; respondents were allowed to choose more than one specialty

GENETIC TESTING RESULTS & RESULTS DISCUSSION

Genetic testing results were disclosed most often by a doctor (69.4%; n=59) and also disclosed by a nurse practitioner (4.7%; n=4), nurse (5.9%; n=5), genetic counselor (25.9%; n=22) and other (8.2%; n=7). Test results were most likely to be disclosed during an office visit (65.1%; n=54) or by letter (37.4%; n=31). 16.9% (n=14) reported results disclosure via telephone.

Of the 156 respondents who reported undergoing genetic testing, 85 were informed of their results. Test results were reported as negative in 53 (67.1%), positive in 23 (29.1%), and inconclusive in 3 (3.8%). Fifteen respondents recalled testing positive for C9orf72, five for SOD1, while three could not recall which gene they tested positive for (see Figure 5).
In ALS patients who reported a pathogenic C9orf72 mutation, 10/15 (66.7%) also reported a positive family history. In ALS patients who reported a pathogenic SOD1 mutation, 100% (5/5) also reported a positive family history. Out of the ALS patients who reported a negative test result, 14.0% (8/57) also reported a positive family history of ALS. Therefore, ALS patients who reported positive test results were more likely to also report a positive family history of ALS (p=<0.0001).

ALS patients who reported a positive family history were 2.9 times more likely to undergo genetic testing than those who had an apparently sporadic ALS diagnosis. 83.3% of respondents who reported a familial ALS diagnosis underwent genetic testing. 63.2% of respondents who reported a sporadic ALS diagnosis underwent genetic testing (p=0.05). Among the six respondents who reported that family members were offered
pre-symptomatic testing, three indicated that family members underwent testing. Only one of these also indicated contact with a genetic counselor.

Among respondents who underwent genetic testing, about half (55.6%) indicated an understanding of the typical autosomal dominant inheritance of ALS mutations. About half (49.1%) recalled discussing the chance that their children could also develop ALS. A minority of those completing testing (25.0%) recalled that a doctor/team member discussed the likelihood of a gene carrier developing ALS (i.e. the concept of variable penetrance).

LIKERT SCALE RESPONSES AND ANALYSIS

Data collected from the two Likert scale items assessing a) personal experience with and b) attitude towards genetic testing indicated that most respondents who underwent testing had a favorable experience, and that most respondents had a favorable attitude towards genetic testing. The majority of respondents agreed with each of 12 positive statements indicating understanding, autonomy, and emotional support during the testing process and utility of the test outcome. Specifically, respondents who underwent genetic testing indicated that genetic testing results were useful to them (70.8%) and their families (62.5%) with 83.3% agreeing that other persons with ALS should consider genetic testing (see Table 5).
<table>
<thead>
<tr>
<th>Question</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Does Not Apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>The genetics of ALS was explained in a way that I could understand</td>
<td>88.5%</td>
<td>7.3%</td>
<td>4.2%</td>
<td>0.0%</td>
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<td>I received the information I needed to make an informed decision about genetic testing</td>
<td>89.6%</td>
<td>6.2%</td>
<td>4.2%</td>
<td>0.0%</td>
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<td>It was my decision to have genetic testing</td>
<td>90.7%</td>
<td>5.2%</td>
<td>3.1%</td>
<td>1.0%</td>
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<tr>
<td>I was satisfied with the way my test result was told/disclosed to me</td>
<td>75.0%</td>
<td>5.2%</td>
<td>8.3%</td>
<td>11.5%</td>
</tr>
<tr>
<td>My test result was explained to me in a way that I could understand</td>
<td>77.1%</td>
<td>7.3%</td>
<td>4.2%</td>
<td>11.5%</td>
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<tr>
<td>My doctor/care team was emotionally supportive during the testing process</td>
<td>70.8%</td>
<td>17.7%</td>
<td>4.2%</td>
<td>7.3%</td>
</tr>
<tr>
<td>My doctor/care team explained what my result means for my children/family members</td>
<td>59.0%</td>
<td>15.8%</td>
<td>8.4%</td>
<td>16.8%</td>
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<tr>
<td>The results of my genetic testing were useful to me</td>
<td>70.8%</td>
<td>10.4%</td>
<td>7.3%</td>
<td>11.5%</td>
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<tr>
<td>The results of my genetic testing were useful to my family members</td>
<td>62.5%</td>
<td>18.8%</td>
<td>5.2%</td>
<td>13.5%</td>
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<tr>
<td>If I could “do it all over again,” I would choose to have genetic testing</td>
<td>80.1%</td>
<td>5.3%</td>
<td>4.2%</td>
<td>10.5%</td>
</tr>
<tr>
<td>I would recommend that other persons with ALS consider genetic testing</td>
<td>83.3%</td>
<td>12.5%</td>
<td>1.1%</td>
<td>3.1%</td>
</tr>
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</table>

Table 5: Respondent attitudes toward genetic testing for ALS completed by participants who underwent genetic testing (n=97)
Comparison of composite average test experience and attitude scores between groups revealed that respondents with a family history of ALS were more likely to report a favorable attitude towards genetic testing ($p=0.0003$), as were respondents who saw a genetic counselor ($p=0.02$). No significant difference in test attitude scores were observed between those who tested positive or negative ($p=0.11$). Among those who tested positive, 20/20 (100%) indicated ‘agree/strongly agree’ in response to the items “For me, the pros of genetic testing for ALS outweigh the cons” and “For society, the pros of genetic testing for ALS outweigh the cons.”

Likert scale responses from all survey participants indicated that a majority of respondents agreed that genetic testing should be offered to any patient with ALS (82.7%) and to patients with a family history of ALS (94.0%), with 77.5% of respondents indicating they would have genetic testing if offered (see Table 6).
<table>
<thead>
<tr>
<th>Question</th>
<th>Agree</th>
<th>Neutral</th>
<th>Disagree</th>
<th>Does Not Apply</th>
</tr>
</thead>
<tbody>
<tr>
<td>Genetic testing should be offered to patients with ALS</td>
<td>82.7%</td>
<td>14.4%</td>
<td>2.2%</td>
<td>0.7%</td>
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<tr>
<td>Genetic testing should be offered to patients with ALS who have a family history of ALS</td>
<td>94.0%</td>
<td>4.9%</td>
<td>0.7%</td>
<td>0.4%</td>
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<tr>
<td>Genetic testing can provide useful information to patients with ALS</td>
<td>80.2%</td>
<td>17.1%</td>
<td>2.0%</td>
<td>0.7%</td>
</tr>
<tr>
<td>Genetic testing should be offered to family members of persons with ALS</td>
<td>82.1%</td>
<td>15.3%</td>
<td>2.2%</td>
<td>0.4%</td>
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<tr>
<td>Genetic testing should be offered to family members of persons with ALS who have a gene mutation</td>
<td>87.8%</td>
<td>10.0%</td>
<td>1.3%</td>
<td>0.9%</td>
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<tr>
<td>Genetic testing can provide useful information to family members of persons with ALS</td>
<td>81.7%</td>
<td>16.3%</td>
<td>1.3%</td>
<td>0.7%</td>
</tr>
<tr>
<td>If I were offered genetic testing for ALS, I would have genetic testing</td>
<td>77.5%</td>
<td>14.3%</td>
<td>5.3%</td>
<td>2.9%</td>
</tr>
<tr>
<td>If my adult children wanted genetic testing for ALS, I would support them</td>
<td>85.6%</td>
<td>5.6%</td>
<td>0.7%</td>
<td>8.2%</td>
</tr>
<tr>
<td>Genetic testing can help doctors understand my condition</td>
<td>77.6%</td>
<td>19.0%</td>
<td>2.7%</td>
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</tr>
<tr>
<td>In the future, genetic testing may help doctors treat ALS</td>
<td>86.0%</td>
<td>12.2%</td>
<td>1.1%</td>
<td>0.7%</td>
</tr>
<tr>
<td>For me, the pros of genetic testing for ALS outweigh the cons</td>
<td>75.9%</td>
<td>20.3%</td>
<td>3.1%</td>
<td>0.7%</td>
</tr>
<tr>
<td>For society, the pros of genetic testing for ALS outweigh the cons</td>
<td>77.1%</td>
<td>19.5%</td>
<td>2.7%</td>
<td>0.7%</td>
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</tbody>
</table>

Table 6: Combined Likert Scale responses completed by all survey respondents
These data suggest that the majority of ALS patients have a favorable attitude towards genetic testing, and feel that genetic testing should be available to all patients. Although the majority of respondents indicated that the genetics of ALS was discussed with them, only one-third reported being offered genetic testing. Factors positively associated with access to testing include family history of ALS ($p = 0.0001$), young age at onset ($p=0.02$), and seeing a genetic counselor ($p = 0.0001$). Interestingly, family history of dementia was not associated with the offer of testing ($p = 0.92$), suggesting that clinicians may not recognize the presence of dementia in the family (specifically, frontotemporal dementia) as a risk factor for hereditary ALS. Only 12.5% reported seeing a genetic counselor. Among those with a positive family history, this proportion was somewhat higher (25.0%) indicating clinician’s potential understanding that a fALS case warrants a referral to genetic counseling to discuss family history and genetic testing options.

The majority of respondents reported that the genetics of ALS had been discussed with them during the course of their care, and most indicated understanding that ALS is only sometimes genetic or familial. However, only 19.7% reported that the risk children could develop ALS was discussed, and 41.4% did not know genetic testing was available. Among those who underwent testing, roughly half indicated
understanding of dominant transmission, and 25% recalled discussing the issue of variable penetrance. Patients with ALS are often concerned about the risk to their children and family members to also develop the disease and from this data, it appears that most ALS patients have a basic understanding of the hereditary component of ALS, but opportunities for improvement in education are apparent. The concepts of a patient’s understanding of genes associated with ALS, their inheritance pattern and risk factors for patients and their families can be improved upon and facilitated by the expertise of a genetic counselor. Genetic counselors are trained clinicians who have been found to educate and inform patients of their condition, provide support to patients and their families in coping and to facilitate informed decision making. Genetic counselors have also been found to increase genetic knowledge in patients, especially in cases of complex heterogeneous disorders (Wang, Gonzalez et al. 2004).

Survey respondents indicated a favorable attitude towards genetic testing and perceived benefits to ALS patients, families, the medical community, and society. This was most pronounced in respondents who reported a positive family history of ALS, and in those who saw a genetic counselor. The majority of respondents who did undergo genetic testing had a positive experience, and indicated satisfaction with understanding, autonomy, and emotional support during the testing process and utility of the test outcome. Interestingly, there was no difference in test attitude scores in those who tested positive (mutation found) compared to those who tested negative (no mutation found and inconclusive). This finding indicates that despite a positive genetic test, there
may not be significant psychological distress or harms in the genetic testing process for patients and may also apply to respondents who indicated a “negative” or “inconclusive” test result. However, it is important to note that this finding only represents approximately 19% of all respondents and we did not explore the potential for psychological distress or harm in this study. All respondents (100%) who tested positive chose “agree” or “strongly agree” to the Likert items stating “for me/society, the pros of genetic testing outweigh the cons.” The lowest test satisfaction scores were observed in items related to implications for children. This study shows that more thorough discussion of the implications of test results for family members would be beneficial for ALS patients and their families. Genetic testing for an affected ALS patient implicates involvement of the biological family and may result in psychological and emotional effects, all of which can be explored through consultation with a genetic counselor (Chio, Logroscino et al. 2013). In a survey of patients with Parkinson disease, Falcone et al. (2011) similarly found a high level of interest in genetic testing, with 86% indicating that genetic testing is useful, and 59% indicating interest in genetic testing. Although most respondents were found to have a low level of genetic knowledge and poor awareness of genetic testing, most perceived benefits from genetic testing including development of better treatments. The authors concluded that there is ‘considerable need for genetics education and counseling in the PD population.’ This survey was a hypothetical scenario asking patients with Parkinson disease if they would pursue genetic testing, as was our survey asking the same question of patients with ALS.
Similar findings of a positive response to the offer of genetic services and testing have been explored in Huntington’s disease (Craufurd, Dodge et al. 1989). However, once testing became available for this condition, actual uptake of predictive genetic services and testing was routinely reported as low in the 50% at-risk population with the majority of patients not undergoing testing until symptomatic (Morrison, Harding-Lester et al. 2011; Crauford, Dodge et al. 1989). Our results of overall positive response to genetic testing and its benefits suggest a similar scenario in the ALS population with the discovery of 82.7% of respondents agreeing to the statement “genetic testing should be offered to patient with ALS,” 80.2% agreeing that “genetic testing can provide useful information to patients with ALS,” and 75.9% agreeing to the statement “for me, the pros of genetic testing for ALS outweigh the cons.”

In light of the demonstrated patient interest in and satisfaction with ALS genetic testing, and the prevalence of ALS mutations (found in 2/3 of fALS and ~11% of sALS), genetic counseling and testing should be offered in the routine management of ALS. Although our data show that positive family history of ALS is very strongly correlated with access to testing, the majority (80.0%) of those offered testing did not have a family history. Of all respondents, 33.5% were offered genetic testing, but only 9% overall reported a positive family history. As such, this data suggests that the clinical approach genetic testing may be inconsistent in its offer. These inconsistencies consist of timing of the testing offer and lack of education about the complex heterogeneity of ALS genetics. It was also apparent that there is a lack of discussion with ALS patients
about heredity of the genes being tested for, their inheritance pattern, variable penetrance of the genes and potential impact for family members. These inconsistencies have resulted in a lack of education about the testing process among the clinicians offering the service causing a disparity of access to genetic testing for an ALS diagnosis.

Our data further suggest that providing ALS patients with the opportunity to see a genetic counselor will increase access to genetic testing. Current ALS management guidelines (Miller, Jackson et al. 2009) advocate the multidisciplinary management of the ALS patient, and specify the disciplines of “physician, physical therapist, occupational therapist, speech pathologist, dietitian, social worker, respiratory therapist, and nurse case manager.” The importance of genetic counseling for patients and families affected by ALS has been emphasized, irrespective of family history or testing status (Fong, Karydas et al. 2012, Chio, Battistini et al. 2014). This data shows that more appropriate genetic testing was done when a patient was seen by a genetic counselor. Therefore, inclusion of genetic counselors as part of the multidisciplinary team may be one way to provide broader access to genetic counseling and appropriate testing recommendations for ALS patients and their families.

Further study is needed to study the impact of genetic testing in ALS. Our data suggests that ALS patients generally have a favorable attitude towards testing, but further exploration of specific subgroups may inform genetic testing and counseling in challenging cases, such as those patients who receive inconclusive results, those with a
positive family history who test negative, and those who with a negative family history who test positive. As the genetics of ALS continues to be elucidated, there will be an increasing need to integrate this knowledge into clinical care.

**LIMITATIONS**

This survey was sent to registrants as a one-time announcement per CDC; ATSDR protocol. A previous publication utilizing the registry for survey distribution also received a similar response rate of 11.5% (Kullman, Hayes et al. 2015). The low response rate could bias study data if respondents were not representative of the general ALS patient population. However, respondent demographic and disease characteristics mirror those reported in ALS population as a whole (Mehta, Antao et al. 2014). All data was analyzed on the assumption that the survey responses were collected from ALS patients or family members acting on behalf of the patient and no methods were set up to differentiate between these two groups.

This survey was distributed electronically to only those ALS patients registered with the CDC; ATSDR registry, which is introduced to patients receiving care at a certified MDA or ALSA treatment center, which is a minority of all ALS patients (Mehta, Antao et al. 2014). Our results could reflect an ascertainment bias of a skewed population of ALS patients who are actively engaged with research participation and potentially more receptive to new technologies such as genetic testing. If our survey reached a broader spectrum of ALS patients in all care settings, patient attitudes toward genetic testing may have been less positive.
CONCLUSION

These data suggest that majority of ALS patients have a favorable attitude towards genetic testing, and feel that it should be available to all patients. However, only 1/3 of survey respondents reported being offered testing. To address this discrepancy, the inclusion of genetic professionals in the care of ALS patients to facilitate genetic counseling and testing could be helpful. In addition, genetic testing and counseling should be offered in the routine management of ALS. The publication of ALS genetic counseling and testing practice guidelines, similar to those for Alzheimer disease (Goldman, Hahn et al. 2011), would be significant step towards broader and more equitable access to genetic counseling and testing in ALS.


Talbot, K. (2014). "Should all patients with ALS have genetic testing?". J Neurol Neurosurg Psychiatry 85(5).


Appendix A: Table of ALS Genes

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Table 7: ALS genes which are listed as causative or modifying based on review papers Peters et al 2015 (green column titles and indicators), Boylan et al 2015 (red column titles and indicators) and Gene Reviews (black column title and indicators). Rows which are shaded indicate proven causative with pathogenic mutations in fALS and sALS cases.

Continued
Table 7 Continued

| Gene  | FUS | GRN | HFE | hnRNP A1 | hnRNP A2/B1 | ITPR2 | KIFAP3 | LUM | MAOB | MAPT | MATR3 | NEFH | NTE | OPTN | PFN1 | PON1-3 | PPARGC1A | PRPH | PRPH2 | SETX | SIGMAR1 | SMN | SOD1 | SOD2 | SPAST | SPG11 | SPG20 | SQSTM1 | S581L1 | TAF15 | TARDBP | Tbk1 | TMEM106B | TREM2 | TUBA4A | UBQLN2 | UNC13A | VAPB | VCP | VEGFA | ZNFS12B |
|-------|-----|-----|-----|---------|------------|-------|--------|-----|------|------|-------|------|-----|------|------|--------|--------|------|-------|------|---------|-----|-------|-----|--------|-------|------|-----------|------|-------|--------|--------|-------|------|-------|-------|--------|
The Ohio State University Medical Center
Division of Human Genetics
Invites you to participate in a research survey for ALS The survey results will be used to improve ALS care and education

- This survey will only take about 10 minutes of your time
- Any person(s) affected with ALS is eligible
- It is completely anonymous
- To participate in this survey please follow this link: [https://www.surveymonkey.com/r/ALS_preview](https://www.surveymonkey.com/r/ALS_preview)
- The first 50 participants will receive a $10 Starbucks gift card
- You may terminate the survey at any time
Appendix C: Survey Protocol

TITLE: Amyotrophic Lateral Sclerosis and Genetic Testing: A Perspective from the ALS Community
PRIMARY INVESTIGATOR: Jennifer Roggenbuck, MS LGC
(Please note: all italicized are for skip logic and/or notes for survey track)

Thank you for participating in this research survey. We hope that the result of this study will help us provide improved care and education for persons with ALS.

If you are unable to complete the survey on your own, a family member and/or caregiver may answer on your behalf. Participation in this research survey is voluntary and a refusal to participate will involve no penalty or loss of benefits to which you are otherwise entitled.

The survey will take about 20 minutes to complete. Please answer carefully because you may not go back to previous questions. The survey is not saved until it is completed.

You may terminate the survey at any time by closing your browser window. You may return to the survey later, but if you do so you will retake the survey from the beginning.

Once completed, the first 50 participants are eligible to enter a drawing to receive a $10 gift card to Starbucks (instructions for entry will be given upon survey completion) as compensation for your time and participation.

We will work to make sure that no one sees your survey responses without approval. But, because we are using the Internet, there is a chance that someone could access your online responses without permission. In some cases, this information could be used to identify you.

If you have any questions or concerns regarding this research study and/or your rights as a participant, please contact us at alssurveyosu@gmail.com or contact OSU ALS survey personnel (614) 688-7838.

1. Are you affected with ALS (amyotrophic lateral sclerosis; aka “Lou Gehrig’s Disease”)?
   a. Yes, limb onset (started in arm or leg)
   b. Yes, bulbar onset (started with trouble speaking/swallowing)
   c. Yes, not sure which type
d. No (end survey)

2. What best describes your race?
   a. White/Caucasian
   b. Black/African-American
   c. Asian
   d. Multiracial
   e. Other
   f. Prefer not to say

3. What is your age now?
   a. 39 or under
   b. 40 - 49
   c. 50 - 59
   d. 60 - 69
   e. 70 or over

4. What was your age at the time of your diagnosis?
   a. 39 or under
   b. 40 - 49
   c. 50 - 59
   d. 60 - 69
   e. 70 or over

5. When did you receive your diagnosis?
   a. 0 – 6 months ago
   b. 7 – 12 months ago
   c. 13 – 18 months ago
   d. 19 – 24 months ago
   e. 25 – 30 months ago
   f. 31 – 36 months ago
   g. More than 3 years ago

6. Do you have a family history of ALS? (choose all that apply)
   a. Yes, in my mother
   b. Yes, in my father
   c. Yes, in my child
   d. Yes, in my aunt or uncle
   e. Yes, in my grandparent
   f. Yes, in another relative(s)
   g. I do not know if I have a positive family history of ALS
   h. No

7. Do you have a family history of fronto-temporal dementia, Alzheimer disease, or other dementia? (choose all that apply)
   a. Yes, in my mother
   b. Yes, in my father
   c. Yes, in my child
d. Yes, in my aunt or uncle  
e. Yes, in my grandparent  
f. Yes, in another relative(s)  
g. I do not know if I have a family history of these conditions  
h. No  

8. Do you have a family history of Parkinson disease? (choose all that apply)  
a. Yes, in my mother  
b. Yes, in my father  
c. Yes, in my child  
d. Yes, in my aunt or uncle  
e. Yes, in my grandparent  
f. Yes, in another relative(s)  
g. I do not know if I have a family history of this condition  
h. No  

9. Is your ALS doctor part of an ALS clinic?  
a. Yes, MDA - affiliated  
b. Yes, ALSA - affiliated  
c. Yes, both MDA and ALSA - affiliated  
d. Not sure  
e. No  

10. Which specialists have you seen in your ALS clinic? (choose all that apply)  
a. Physical or Occupational Therapist  
b. Respiratory therapist  
c. Speech therapist  
d. Genetic Counselor  
e. Social Worker  
f. MDA or ALSA representative  

11. Based on your knowledge or opinion, is ALS genetic (does it run in families)?  
a. Never  
b. Not usually  
c. Sometimes  
d. Most of the time  
e. Always  
f. Don’t know  

12. Based on your knowledge or opinion, is genetic testing for ALS available?  
a. Never  
b. Not usually  
c. Sometimes  
d. Most of the time  
e. Always  
f. Don’t know
13. Based on your knowledge or opinion, is genetic testing available for family members of persons with ALS?
   a. Never
   b. Not usually
   c. Sometimes
   d. Most of the time
   e. Always
   f. Don’t know

14. At your clinic, was the genetics or heredity of ALS discussed with you?
   a. No, this was not mentioned or discussed
   b. Yes, this was mentioned briefly
   c. Yes, this was explained and discussed with me
   d. Don’t remember

15. Did your doctor, or other care team member, tell you how often ALS is familial (runs in families)?
   a. No (skip to question 17)
   b. Yes
   c. Don’t know/don’t remember (skip to question 17)

16. Based on what your doctor/team member told you, how often is ALS familial (runs in the family)?
   a. Never
   b. Not usually
   c. Rarely
   d. Sometimes
   e. Often
   f. Always

17. Did you personally request information about genetic testing for ALS?
   a. Yes
   b. No
   c. Don’t know/Don’t remember

18. Was genetic testing for ALS offered to you?
   a. No (skip to question 21)
   b. Yes, only clinical testing was offered
   c. Yes, only research testing was offered
   d. Yes, clinical and research testing were offered
   e. Yes, I don’t remember which type was offered
   f. Don’t know/don’t remember (skip to question 21)

19. If genetic testing was offered, did you have genetic testing?
   a. No
   b. Yes (skip to question 24)
   c. Not sure

20. Why did you decide against genetic testing? (choose all that apply)
a. Cost
b. Did not believe that ALS is running in the family
c. Do not wish to know if something is wrong
d. Concerns about ability to obtain insurance
e. Concerns about burdening my family members

21. Did your doctor/team member tell you what the chance is that your children could develop ALS?
   a. Yes, the chance was described as a percent (skip to question 22)
   b. Yes, the chance was described in words (skip to question 23)
   c. No (skip to question 43)
   d. Don’t know/don’t remember (skip to question 43)

22. Based on what your doctor/team member told you, what is the chance that your children could develop ALS? (please choose the range that includes the percent chance that was mentioned) (skip to question 43 – Likert scale)
   a. 0%
   b. 1 - 4%
   c. 5 - 9%
   d. 10 - 24%
   e. 25 - 49%
   f. 50 - 74%
   g. 75% or higher

23. Based on what your doctor/team member told you, what is the chance your children could develop ALS? (skip to question 43 – Likert scale)
   a. Zero
   b. Very Low
   c. Low
   d. Moderate
   e. High
   f. Very High

24. Was your genetic testing done as a clinical test, or part of a research project?
   a. Clinical
   b. Research
   c. Not sure

25. Were you informed of the result of your genetic testing?
   a. No (skip to question 35)
   b. Yes
   c. Don’t know/Don’t remember (skip to question 35)

26. Who discussed your result with you? (choose all that apply)
   a. Doctor
   b. Nurse practitioner
   c. Nurse
   d. Genetic counselor
27. How were the results of genetic testing disclosed and explained to you (choose all that apply)?
   a. Telephone
   b. Office visit
   c. Letter
   d. Results were not given to me (skip to question 34)
28. What was the result of your genetic test?
   a. No gene or mutation was found (skip to question 36)
   b. The test was inconclusive (skip to question 36)
   c. Yes, a mutation or gene for ALS was found
   d. Don’t know/don’t remember (skip to question 34)
29. My test result identified a mutation in the following gene:
   a. C9orf72
   b. SOD1
   c. FUS
   d. TARDP
   e. Other
   f. Don’t know/Don’t remember
30. Did your doctor/team member tell you what the chance is that your children could inherit this gene?
   a. No
   b. Yes, the chance was described in words (skip to question 32)
   c. Yes, the chance was described as a percent (skip to question 33)
   d. Don’t know/Don’t remember
31. Based on your knowledge or opinion, what is the chance that your children would inherit the gene? (skip to question 34)
   a. 0%
   b. 25%
   c. 50%
   d. 75%
   e. 100%
   f. Other chance
   g. Don’t know/Don’t remember
32. Based on what your doctor/team member told you, what is the chance that your children would inherit this gene? (skip to question 34)
   a. Zero
   b. Low
   c. Moderate
   d. Very High
   e. Other
   f. Don’t know/Don’t remember
33. Based on what your doctor/team member told you, what is the chance that your children would inherit the gene?
   a. 0%
   b. 25%
   c. 50%
   d. 75%
   e. 100%
   f. Other chance
   g. Don’t know/Don’t remember

34. Did your doctor/team member discuss the chance that a gene carrier will actually develop ALS?
   a. No, this was not discussed
   b. Yes, they said that gene carriers always develop ALS (skip to question 40)
   c. Yes, they said that gene carriers usually develop ALS (skip to question 40)
   d. Yes, they said that gene carriers sometimes develop ALS (skip to question 40)
   e. Don’t know/don’t remember if this was discussed (skip to question 40)

35. Based on your knowledge or opinion, what is the chance that a carrier of an ALS gene will develop ALS? (skip to question 39)
   a. Gene carriers always develop ALS
   b. Gene carriers usually develop ALS
   c. Gene carriers sometimes develop ALS
   d. Gene carriers rarely develop ALS
   e. Don’t know

36. Did you doctor/team member discuss the chance that your children could develop ALS?
   a. No (skip to question 39)
   b. Yes, the chance was described in words (skip to question 38)
   c. Yes, the chance was described as a percent
   d. Don’t know/don’t remember (skip to question 39)

37. Based on what your doctor/team member told you, what is the chance that your children could develop ALS? (skip to question 42)
   a. 0%
   b. 1 - 4%
   c. 5 - 9%
   d. 10 - 24%
   e. 25 - 49%
   f. 50 - 74%
   g. 75% or higher

38. Based on what your doctor/team member told you, what is the chance your children could develop ALS? (skip to question 42)
   a. Zero
b. Very Low

c. Low

d. Moderate

e. High

f. Very High

39. Based on your knowledge or opinion, what is the chance your children could develop ALS? *(skip to question 42)*

a. Zero
b. Very Low
c. Low
d. Moderate
e. High
f. Very High

40. Did your doctor/team member say that genetic testing could be offered for your unaffected family members?

a. No
b. Yes
c. Don’t know/Don’t remember

41. Did any of your family members have genetic testing for ALS? *(choose all that apply)*

a. No
b. Yes, family member(s) with ALS
c. Yes, family member(s) who do not have ALS
d. Don’t know

42. Based on YOUR EXPERIENCE with genetic testing for ALS, please indicate whether you agree with the following statements: *(Likert scale)*

1 - Strongly Agree
2 - Agree
3 - Somewhat agree
4 - Maybe agree
5 - Neutral
6 - Maybe disagree
7 - Somewhat disagree
8 - Disagree
9 - Strongly disagree
0 - Does not apply

a. The genetics of ALS was explained in a way that I could understand
b. I received the information I needed to make an informed decision about genetic testing
c. It was my decision to have genetic testing
d. I was satisfied with the way my test result was told/disclosed to me
e. My test result was explained to me in a way I could understand

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f. My questions about my test result were answered
g. My doctor/care team was emotionally supportive during the testing process
h. My doctor/care team explained what my result means for my children/family members
i. The results of my genetic testing were useful to me
j. The results of my genetic testing were useful to my family members
k. If I could ‘do it over again’ I would choose to have genetic testing for ALS
l. I would recommend that other persons with ALS consider genetic testing

43. Based on your knowledge or opinion, please indicate whether you agree or disagree with the following statements: (Likert scale)
1 - Strongly Agree
2 - Agree
3 - Somewhat agree
4 - Maybe agree
5 - Neutral
6 - Maybe disagree
7 - Somewhat disagree
8 - Disagree
9 - Strongly disagree
0 - Does not apply

a. Genetic Testing should be offered to patients with ALS
b. Genetic Testing should be offered to patients with ALS who have a family history of ALS
c. Genetic testing can provide useful information to patients with ALS
d. Genetic testing should be offered to family members of persons with ALS
e. Genetic testing should be offered to family members of persons with ALS who have a gene/mutation
f. Genetic testing can provide useful information to family members of persons with ALS
g. If I were offered genetic testing for ALS, I would have genetic testing
h. If my adult children wanted genetic testing for ALS, I would support them
i. Genetic testing can help doctors understand my condition
j. In the future, genetic testing may help doctors treat ALS
k. For me, the pros of genetic testing for ALS outweigh the cons
l. For society, the pros of genetic testing for ALS outweigh the cons
Thank-you for completing this survey.

If you would like more information about genetic testing options for ALS, please talk to your doctor and/or visit these resources:
Amyotrophic Lateral Sclerosis Association at ALSA.org
Muscular Dystrophy Association at MDA.org
National Society of Genetic Counseling at www.nsgc.org (click "find a counselor")

To enter for the $10 gift card to Starbucks, please send your email address to: ALSsurveyOSU@gmail.com. The first 50 email submissions will be selected for the gift card and you will be contacted by research personnel for a mailing address to distribute your winnings. You may withdraw your information at any time. No personal emails, addresses or other identifiers will be published and all participation for this drawing is voluntary. Once winnings are distributed, all personal information provided will be eliminated from the study, and the ALSsurveyOSU@gmail.com account deactivated from further use.
Appendix D: ABSTRACT – JOURNAL OF GENETIC COUNSELING

ABSTRACT

Purpose: Although commercial genetic testing for amyotrophic lateral sclerosis (ALS) is widely available, it is unknown how many patients have access to genetic testing and counseling, and patient attitudes towards ALS genetic testing have not been studied.

Methods: We conducted a national survey of ALS patients enrolled in the Agency for Toxic Substances and Disease Registry, which consisted of multiple choice questions and two 12 item Likert scale series assessing respondents’ experience with and attitude toward genetic testing.

Results: The survey received a response rate of 9.0%. Genetic testing was offered to 33.4% and completed in 67.1% of those offered. A minority of respondents (12.3%) saw a genetic counselor, and were much more likely to be offered genetic testing (p=0.0001). Respondents with a family history of ALS (8.4%) were more likely to be offered testing (p=0.0001) and complete testing (p=0.05). Respondents with a family history of ALS were more likely to report a favorable attitude towards genetic testing (p=0.0003), as were respondents who saw a genetic counselor (p=0.02). The majority of respondents (82.7%) felt that genetic testing should be offered to all patients with ALS.

Conclusions: Our results indicate that ALS patients may have limited access to genetic testing, but perceive benefit from this service. To address this discrepancy, genetic testing and counseling should be offered as part of the routine management of ALS.

Keywords: Amyotrophic Lateral Sclerosis, Genetic Testing, ALS Genetics, Access to care
ABSTRACT

Purpose: Although genetic testing for amyotrophic lateral sclerosis (ALS) is widely available at commercial testing laboratories, it is unclear how many patients with ALS have access to genetic testing. Current ALS management guidelines do not address the issue of genetic testing. Methods: We conducted a national survey of ALS patients enrolled in the Agency for Toxic Substances and Disease Registry. The survey consisted of multiple choice questions, as well as two 12 item Likert scale series, assessing respondents’ individual experience with and attitude toward genetic testing. Results: The survey was emailed to 5591 registrants; 501 responded (response rate = 9.0%). Genetic testing was offered to 33.4% and completed in 67.1% of those offered. Respondents with a family history of ALS were more likely to be offered testing (p=0.0001), but no more likely with a family history of dementia (p=0.92). A minority of respondents (12.3%) saw a genetic counselor, and were much more likely to be offered genetic testing (p = 0.0001). Most respondents who underwent genetic testing indicated that test results were useful to them (70.5%) and their families (62.5%). A majority of respondents (79.5%) indicated that they would have genetic testing if offered, with 83.3% indicating that other persons with ALS should consider genetic testing.

Conclusions: Despite apparently high interest and satisfaction with ALS genetic testing, survey respondents had limited access to testing. To address this discrepancy, genetic counseling and genetic testing should be offered in the routine management of ALS.

Keywords: Genetic Testing, ALS Genetics, Patient Attitudes, Access to Care, Genetic Counseling
Appendix F: NEALS Poster

Poster submitted and presented to the Northeast Consortium of ALS Researchers (NEALS) November 2015 and awarded as “Best Clinical Abstract”

**Genetic Testing in Amyotrophic Lateral Sclerosis**

A Perspective from the ALS Community

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**BACKGROUND**

Although genetic testing for amyotrophic lateral sclerosis (ALS) is widely available, ALS management guidelines do not address the issue of genetic testing. It is unclear how many ALS patients have access to and interest in this technology.

**HYPOTHESIS**

ALS patients have limited access to genetic testing.

**METHODS**

We conducted a national survey of ALS patients enrolled in the Agency for Toxic Substances and Disease Registry (ATSDR). Survey Instrument: The survey consisted of multiple choice questions as well as two 12 item Likert scale series addressing (a) respondents' individual experience with genetic testing and (b) respondents' attitude toward genetic testing.

**RESULTS**

- The survey was emailed to 5591 registrants; 501 responded (response rate = 9.0%).
- Almost half of respondents (46.8%) did not know that genetic testing for ALS is available, or indicated that it was never or not usually available (see Figure 1).
- Family history was reported to be positive for ALS in 8.4% and dementia in 33.7% (see Figure 2). Respondents with familial ALS (ALS) were more likely to be offered testing (p<0.0001), but no more likely with a family history of dementia (p=0.92). Testing was more likely to be completed in those with ALS (p=0.05).
- Genetic testing was offered to 33% of respondents and completed in 67.1% of those offered, 20/501 (4%) tested positive and recalled their genetic mutation status (see Figure 3). A minority of respondents (12.3%) saw a genetic counselor, and were much more likely to be offered genetic testing (p<0.0001).

**LIMITATIONS**

This survey was sent to registrants as a one-time announcement per ATSDR protocol. The low response rate could bias study data if respondents were not representative of the general ALS patient population.

**REFERENCE**


**ACKNOWLEDGEMENTS**

- The ALS community and their families for participating in this survey
- The Centers for Disease Control Agency for Toxic Substances and Disease Registry for distribution of this survey to the ALS National Registry participants.
- This work was funded by the National Society of Genetic Counselors Oncogenetics Special Interest Group
- This project is part of Kari Wagner’s Master’s Thesis work for The Ohio State University Genetic Counseling Program