Amyotrophic Lateral Sclerosis (ALS)
Genetic Testing

Introduction

ALS genetic testing is addressed by this guideline.

Procedures addressed

The inclusion of any procedure code in this table does not imply that the code is under management or requires prior authorization. Refer to the specific Health Plan’s procedure code list for management requirements.

<table>
<thead>
<tr>
<th>Procedures addressed by this guideline</th>
<th>Procedure codes</th>
</tr>
</thead>
<tbody>
<tr>
<td>ALS Known Familial Mutation Analysis</td>
<td>81403</td>
</tr>
<tr>
<td>Genetic Testing for ALS</td>
<td>S3800</td>
</tr>
<tr>
<td>ALS Gene Analysis</td>
<td>81400-81408</td>
</tr>
<tr>
<td>ALS Gene Analysis</td>
<td>81479</td>
</tr>
</tbody>
</table>

What is amyotrophic lateral sclerosis

Definition

Amyotrophic lateral sclerosis (ALS) is a disease caused by the progressive degradation of motor neurons (nerve cells that control muscle movement).\(^1\) ALS may initially present with muscle weakness, twitching, cramping, or slurred speech.\(^1\) Symptoms worsen over time and include muscle atrophy and difficulty swallowing.\(^1\)

Diagnosis

Most cases of suspected ALS are diagnosed based on a unique combination of symptoms and the exclusion of similar disorders. The Escorial Criteria were developed in 2000 to standardize the clinical diagnosis of ALS.\(^2\) These criteria include:

- the presence of upper and lower motor neuron deterioration
- the progressive spread of symptoms, and
- no clinical evidence of other diseases with similar symptoms.
Causes of ALS

There are more than 25 genes known to cause familial Amyotrophic Lateral Sclerosis (FALS), and the condition demonstrates genetic overlap with frontotemporal dementia (FTD). Genetic testing for many of the genes is clinically available.\textsuperscript{1,3-6} FALS subtypes are named based on the causative gene. For example, ALS1 subtype is caused by SOD1 gene mutations.

A pathogenic mutation can be identified in 60-70\% of cases of FALS. Mutations in SOD1, TARDBP, FUS, VCP, C9orf72, and TBK1 account for the greatest number of cases, while the remaining genes are relatively rare causes of the disorder.\textsuperscript{1,3-8} The majority of combined ALS/FTD cases with a family history of either disorder are caused by C9orf72 repeat expansions, particularly in Caucasian populations, while the percentage of cases attributed to this gene is somewhat lower in China.\textsuperscript{4,8} Many other candidate genes have been identified and are still pending further validation studies.\textsuperscript{6}

Genes commonly associated with familial ALS

Some of the most common genetic causes of ALS are summarized below. The remaining genes are relatively rare causes of the disorder. Genetic testing for many of the genes is available clinically.\textsuperscript{1,3-7}

<table>
<thead>
<tr>
<th>Gene symbol</th>
<th>FALS subtype</th>
<th>% of individuals with FALS</th>
<th>Inheritance</th>
</tr>
</thead>
<tbody>
<tr>
<td>SOD1</td>
<td>ALS1</td>
<td>20%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>C9orf72</td>
<td>ALS/FTD</td>
<td>23%-30%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>FUS/TLS</td>
<td>ALS6</td>
<td>~4%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>TARDBP</td>
<td>ALS10</td>
<td>1%-4%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>VCP</td>
<td>ALS14</td>
<td>1%-2%</td>
<td>Autosomal dominant</td>
</tr>
<tr>
<td>TBK1</td>
<td>ALS/FTD</td>
<td>1%-3%</td>
<td>Autosomal dominant</td>
</tr>
</tbody>
</table>

Inheritance

Most people with FALS have an autosomal dominant form, meaning only one mutation is required to cause disease. In this case, children of an affected person have a 50\% chance of inheriting the disease-causing mutation.

There are rare autosomal recessive forms of ALS as well as one X-linked form. Two mutations are required to cause autosomal recessive types, usually only siblings are affected, and there is no parent-to-child transmission.

Onset

The average age of ALS onset is 56 years if the affected individual has no family history, and 46 years old if there is a family history of ALS.\textsuperscript{1,2} However, there are...
infantile and juvenile onset forms that should also prompt consideration of a genetic etiology.¹

Survival
ALS is fatal. The average survival after diagnosis is 3 years, but can vary widely. Treatment focuses on slowing progression with medication and therapy.¹

Prevalence
Between 4 and 8 out every 100,000 people develop ALS. About 90% of ALS cases are sporadic, and the remaining 10% of individuals have familial ALS (FALS).¹

Test information
Introduction
Testing for Familial Amyotrophic Lateral Sclerosis (FALS) may include targeted expansion analysis of C9orf72, gene sequencing, or known familial mutation analysis.

Targeted expansion analysis of C9orf72
Expansions of the hexanucleotide repeat non-coding region of the open reading frame C9orf72 (a protein as yet uncharacterized) are assessed through targeted analysis.¹ Although estimation of the repeat size is typically accurate, there is disagreement as to the normal and pathogenic repeat size ranges.⁹

Sequence analysis
Genetic testing of other genes associated with FALS is usually done by gene sequencing because mutations are diverse. Sequencing is generally >99% accurate for identifying mutations in the coding region of a gene.

Laboratories may offer individual gene sequencing or multi-gene panels for FALS.

Sequential genetic testing approach
An expert-authored review makes the following suggestions when pursuing a sequential individual gene approach:¹

- "SOD1 testing is appropriate in any individual with ALS who has another affected family member or an incomplete family history, including the early death of a close relative from any cause. Approximately 20% of individuals with FALS have ALS1 with an identified disease-causing mutation in SOD1. Interpretation of the significance of a SOD1 mutation regarding disease severity and progression depends on the specific mutation identified because of wide variability in genotype/phenotype correlations. Failure to detect a SOD1 mutation does not rule out FALS. Up to 3% of individuals with ALS with no family history of ALS have
SOD1 mutations. Because data on penetrance of many mutations are limited, establishing the risk to other family members of developing clinical symptoms can be difficult.

- "SETX testing is appropriate in kindreds with adolescent-onset spinal muscular atrophy with pyramidal features."
- "VAPB testing should be pursued in the context of clinical symptoms of primarily adult-onset spinal muscular atrophy."
- "FUS/TLS, TARDBP, and ANG testing should be considered for SOD1-negative individuals with FALS."
- "ALS2 testing is appropriate for those with childhood-onset UMN-predominant ALS."
- "VCP testing should be considered for individuals with a family history of ALS with or without symptoms of inclusion body myopathy, Paget disease and/or frontotemporal dementia."
- "OPTN testing may be considered for individuals with a family history consistent with autosomal dominant or autosomal recessive inheritance, including simplex cases who do not have a mutation in more common ALS-related genes."

Known familial mutation analysis

Known familial mutation analysis can provide predictive information about the risk to develop ALS. It can also be used to diagnose ALS when the patient does not yet meet the full ALS diagnostic criteria.\(^\text{10}\)

Once a mutation has been identified through sequencing in an affected family member, it is straightforward to test at-risk relatives for that one mutation. The involved gene and precise mutation name/location must be known.

The detection rate for a known familial mutation is greater than 99%.

Guidelines and evidence

Introduction

This section includes relevant guidelines and evidence pertaining to ALS genetic testing.

World Federation of Neurology Research Group on Motor Neuron Diseases

The World Federation of Neurology Research Group on Motor Neuron Diseases (2015) revised the El Escorial criteria:\(^\text{11}\)

- These revised criteria still do not specify when genetic testing should be done, but they do state "If a pathogenic mutation in a disease-causing gene is found in the
patient and segregates with the disease the term hereditary or primary genetic ALS (HALS/GALS) should be used. The finding of a pathogenic mutation in a known gene can substitute for either lower or upper motor neuron signs, so that diagnosis of ALS can be made on the basis of UMN or LMN signs in one body region, associated with a positive genetic test."

- “ALS can be defined as Mendelian in inheritance if a disease-causing gene variant can be shown to segregate within a family. In such cases the genetic variant can serve as a substitute for upper motor neuron deficits or a second limb or region (rule of two).”

**Expert-authored review**

A 2015 expert-authored review states: “Presymptomatic testing for a TARDBP mutation is complicated because the penetrance is unknown, the age of onset is not predictable, and preventative measures do not exist. Because of the individualized nature of predictive testing, consultation with a genetic counselor and a psychologist to obtain informed consent is recommended. At this time, no established testing protocol (e.g., as in Huntington disease) exists, although establishment of such protocols has been suggested. However, to err on the side of caution, testing centers often follow a similar protocol.”

Identifying a SOD1 mutation in a pre-symptomatic individual can impact future management and overall prognosis of ALS. However, it is considered controversial because of reduced penetrance, which means that not everyone with a mutation will necessarily develop symptoms. It also lacks overall intervention or prevention strategies and has an inability to predict the age of onset.1,3

**European Federation of Neurological Societies**

A European Federation of Neurological Societies Task Force (EFNS, 2012) addressed presymptomatic testing in its diagnosis and management guidelines:4 “Presymptomatic genetic testing should only be performed in first-degree adult blood relatives of patients with a known gene mutation. Testing should only be performed on a strictly voluntary basis as outlined (see Table 7 in the original guideline document) and should follow accepted ethical principles.”

**European Federation of Neurological Societies**

Guidelines from the European Federation of Neurological Societies (EFNS, 2012) address molecular testing of ALS: 13

“Clinical deoxyribonucleic acid (DNA) analysis for gene mutations should only be performed in cases with a known family history of ALS, and in sporadic ALS cases with the characteristic phenotype of the recessive D90A mutation.”

“Clinical DNA analysis for gene mutations should not be performed in cases with sporadic ALS with a typical classical ALS phenotype.”
“In familial or sporadic cases where the diagnosis is uncertain, SMN, androgen receptor, or TARDBP, FUS, ANG, or SOD1 DNA analysis may accelerate the diagnostic process.”

“Before blood is drawn for DNA analysis, the patient should receive genetic counselling. Give the patient time for consideration. DNA analysis should be performed only with the patient’s informed consent.”

**European Federation of Neurological Societies**

Guidelines from the European Federation of Neurological Societies (EFNS, 2011) address the molecular diagnosis of ALS and other neurogenetic disorders. They state:  

“Currently, molecular diagnosis mainly has implications for genetic counseling rather than for therapy. However, when more directed causal therapies become available in the future, establishing a correct genetic diagnosis in a given patient will be essential. Despite the rather low prevalence sequencing of the small SOD1 gene should be considered in patients with ALS with dominant inheritance to offer presymptomatic or prenatal diagnosis, if this is requested by the family (Level B).”

**World Federation of Neurology Research Group on Motor Neuron Diseases**


This group doesn’t specify when genetic testing should be done, but they do state “The demonstration of the presence of a pathogenetically relevant gene mutation can assist in the diagnosis of ALS (such as SOD1).”

These criteria set a lower threshold for diagnosis when an ALS-causing mutation is known in the family. For example, a patient may be diagnosed as “Clinically Definite Familial ALS — Laboratory-supported” with evidence of only upper or lower motor neuron disease in one region; whereas a definite diagnosis without genetic test results requires upper and lower motor neuron disease in three regions.

**Criteria**

**Introduction**

Requests for ALS genetic testing are reviewed using these criteria.

**Known familial mutation testing**

- Genetic Counseling
- Pre- and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND

- Previous Genetic Testing:
  - No previous targeted expansion analysis, full gene sequencing and/or large rearrangement testing of the gene with the known familial mutation, AND
  - Known familial mutation in a gene that causes amyotrophic lateral sclerosis (e.g., SOD1, C9orf72, FUS, TARDBP) identified in a 1st, 2nd, or 3rd degree relative(s), AND
  - Age 18 years or older, AND
  - Rendering laboratory is a qualified provider of service per the Health Plan policy.

**Targeted expansion analysis, full sequence analysis, and deletion/duplication analysis**

- Targeted expansion analysis, full gene sequencing, and deletion/duplication analysis for ALS are considered investigational and experimental and, therefore, not eligible for reimbursement.

**References**

**Introduction**

These references are cited in this guideline.


