Amyotrophic Lateral Sclerosis (ALS) Genetic Testing

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Amyotrophic lateral sclerosis (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.

Procedures addressed by this guideline	Procedure codes
ALS gene analysis	81400 81401 81402 81403 81404 81405 81406 81407 81408 81479
ALS known familial mutation analysis	81403
Genetic testing for ALS	S3800
ALS multigene panel	81479

Criteria

Requests for amyotrophic lateral sclerosis (ALS) genetic testing are reviewed using the following criteria.

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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 genetic testing for ALS that would detect the familial mutation, AND
- Diagnostic Testing for Symptomatic or Presymptomatic Individuals:
  - Genetic ALS known familial mutation identified in a 1st, 2nd, or 3rd degree biological relative(s), and
  - Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Sequencing and Deletion/Duplication Analysis of C9orf72, SOD1, FUS, TARDBP

Individual testing of these genes for the purpose of diagnosing ALS is not medically necessary.

Multigene Panel Testing for ALS

When a multi-gene panel is being requested and will be billed with an appropriate CPT panel code, (e.g. 81479), the panel will be considered medically necessary when the following criteria are met:

- Previous Genetic Testing:
  - No previous ALS multi-gene panel testing, and
  - No previous C9orf72 or SOD1 testing performed, and
  - No known ALS-related mutation in the member's family, AND
- Diagnostic Testing for Symptomatic Individuals:
  - Family history of ALS in a first degree relative (i.e., parent, sibling, child), and
  - Evidence of lower motor neuron degeneration (e.g., clinical exam, electrophysiological, muscle or nerve biopsy), and
  - Evidence of upper motor neuron degeneration (e.g., clinical exam, imaging), and
  - Progressive spread of signs within a region or to other regions, and
  - Lower and upper motor neuron disease cannot be explained by another condition, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

For information on ALS genetic testing to determine eligibility for targeted treatment, please refer to the guideline *Pharmacogenomic Testing for Drug Toxicity and Response*, as this testing is not addressed here.

Gene panels that are specific to ALS will be considered for medical necessity according to the criteria outlined in this guideline. Panels must include, at minimum, analysis of all of the following genes: C9orf72, SOD1, FUS, TARDBP.

Billing and Reimbursement

Introduction

This section outlines the billing requirements for tests addressed in this guideline. These requirements will be enforced during the case review process whenever appropriate. Examples of requirements may include specific coding scenarios, limits on allowable test combinations or frequency and/or information that must be provided on a claim for automated processing. Any claims submitted without the necessary information to allow for automated processing (e.g. ICD code, place of service, etc.) will not be reimbursable as billed. Any claim may require submission of medical records for post service review.

- Any individual gene or multi-gene panel is only reimbursable once per lifetime.
- When otherwise reimbursable, the following limitations apply:
  - When a panel is being performed, it is only reimbursable when billed with a single, appropriate panel procedure code (e.g., 81479*).
    - Gene panels that are specific to ALS and include all of the following genes will be eligible for reimbursement according to the criteria outlined in this guideline: C9orf72, SOD1, FUS, TARDBP.
  - When use of a panel code is not possible, each billed component procedure will be assessed independently.
  - In general, only a limited number of panel components that are most likely to explain the member's presentation will be reimbursable. The remaining panel components will not be reimbursable.
  - When an ALS multi-gene panel is billed with multiple stacked codes, only the following genes may be considered for reimbursement:
    - C9orf72
    - SOD1

Note:

*The panel code(s) listed here may not be all-inclusive. For further discussion of what is considered an appropriate panel code, please refer to the guideline *Laboratory Billing and Reimbursement*.

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What is amyotrophic lateral sclerosis?

Amyotrophic lateral sclerosis (ALS) is a progressive, fatal neurodegenerative disease that involves the brain and spinal cord.[1]

Prevalence

Between 4 and 8 out every 100,000 people develop ALS.[2] About 10% of individuals with ALS have at least one other family member affected with ALS.[1] About 85% of ALS occurs in individuals with no family history of ALS.[1]

Symptoms

While ALS historically has been described as primarily affecting motor neurons, additional areas within the frontal and temporal lobes are involved to varying degrees in a subset of individuals.[1] Systems outside the nervous system may also be involved, such as bone (Paget disease of the bone) and muscle (inclusion body myopathy). The clinical picture includes motor decline, and may also include cognitive and behavioral symptoms, based on the location and extent of the degeneration in an individual.[1]

The average age of ALS onset is 55 years in males, and mid 60s in females.[1] Earlier onset of symptoms is seen in individuals with genetic forms of ALS.[1] There are infantile and juvenile onset forms that should also prompt consideration of a genetic etiology.[1]

Cause

Traditionally, a diagnosis of "familial ALS" indicated that two or more close relatives were known to be affected with ALS and "sporadic ALS" indicated that no other relatives are known to have ALS. However, evolving genetic research in ALS and an increase in the clinical use of genetic testing has resulted in new terminology. "Genetic ALS" refers to ALS caused by a pathogenic mutation in a known ALS gene, regardless of family history and "ALS of unknown cause" refers to ALS in which a pathogenic mutation in a known ALS gene has not been identified, also regardless of family history.[1]

Thirty genes have been implicated with varying degrees of certainty to cause genetic ALS and the condition demonstrates genetic overlap with frontotemporal dementia (FTD). Genetic testing for many of the genes is clinically available.[1,4-7]

A pathogenic mutation can be identified in 50-60% of cases of ALS when there is a family history of ALS or dementia, and in approximately 10% of simplex cases (no family history).[8-10] Mutations in SOD1, C9orf72 (39-45%)[1], TARDBP (TDP-43), and FUS account for the greatest number of cases, while the remaining genes are relatively rare causes of the disorder.[1,4-13] 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

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somewhat lower in China.[5,11] Many other candidate genes have been identified and are still pending further validation studies.[7]

Inheritance

Genetic ALS can be inherited in an autosomal dominant, autosomal recessive, or X-linked manner although autosomal dominant is the most common inheritance mode.[1] The mode of inheritance is based on family history and molecular genetic testing.

Genes commonly associated with genetic ALS

Some of the most common genetic causes of genetic ALS are summarized below. The remaining genes are relatively rare causes of the disorder. Genetic testing for many of the genes is available clinically.[1,4-13]

Gene symbol	% of ALS with family history	% of simplex ALS	Inheritance
C9orf72	39%-45%	3%-7%	Autosomal dominant
SOD1	15%-20%	3%	Autosomal dominant, Autosomal recessive
FUS	~4%-8%	Very Rare	Autosomal dominant
TARDBP/TDP43	1%-4%	Unknown	Autosomal dominant

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.[3] 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.

Management

Treatment for individuals with ALS is palliative. There are three FDA-approved drugs available, including a gene-specific treatment for individuals with ALS due to a SOD1 mutation.[1] "Many individuals benefit from care by a multidisciplinary team that includes a neurologist, specially trained nurses, pulmonologist, speech therapist, physical therapist, occupational therapist, respiratory therapist, nutritionist, psychologist, social worker, and genetic counselor."[1]

Survival

ALS is fatal. Disease duration is variable and can range from months to several decades. Approximately half of affected individuals die within five years of symptom onset.[1] Treatment focuses on slowing progression with medication and therapy, and optimizing quality of life.[1]

Test information

Testing for genetic forms of ALS may include known familial mutation testing, targeted expansion analysis of C9orf72, or next generation sequencing of a single gene or in multigene panel testing.

Known Familial Mutation (KFM) Testing

Known familial mutations analysis is performed when a causative mutation has been identified in a close biological relative of the individual requesting testing. Analysis for known familial mutations typically includes only the single mutation. However, if available, a targeted mutation panel that includes the familial mutation may be performed.

Known familial mutation analysis can provide predictive information about the risk to develop genetic ALS. It can also be used to diagnose ALS when the individual does not yet meet the full ALS diagnostic criteria.[14]

Targeted Mutation Analysis

Targeted mutation analysis uses hybridization, single nucleotide extension, select exon sequencing, or similar methodologies to assess a set of disease-causing mutations. This analysis identifies common and/or recurring mutations. Targeted mutation panels or select exon sequencing may have differing clinical sensitivities dependent upon ethnicity, phenotypic presentation, or other case-specific characteristics.

Expansions of the hexanucleotide repeat non-coding region of the open reading frame C9orf72 (a protein as yet uncharacterized) are the most frequent cause of genetic ALS and can be assessed through targeted analysis.[1,8] Although estimation of the repeat size is typically accurate, there is disagreement as to the normal and pathogenic repeat size ranges.[15] In general, more than 30 hexanucleotide repeats are considered pathogenic and Southern blot is considered the gold standard for clinical testing.[9]

Next Generation Sequencing Assay

Next generation sequencing (NGS), which is also sometimes called massively parallel sequencing, was developed in 2005 to allow larger scale and more efficient gene sequencing. NGS relies on sequencing many copies of small pieces of DNA

simultaneously and using bioinformatics to assemble the sequence. Sequence analysis detects single nucleotide substitutions and small (several nucleotide) deletions and insertions. Regions analyzed typically include the coding sequence and intron/exon boundaries. Promoter regions and intronic sequences may also be sequenced if disease-causing mutations are known to occur in these regions of a gene.

Multi-Gene Testing Panels

The efficiency of NGS has led to an increasing number of large, multi-gene testing panels. NGS panels that test several genes at once are particularly well-suited to conditions caused by more than one gene or where there is considerable clinical overlap between conditions making it difficult to reliably narrow down likely causes. Additionally, tests should be chosen to maximize the likelihood of identifying mutations in the genes of interest, contribute to alterations in management for an individual, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and evidence

European Federation of Neurological Societies

A European Federation of Neurological Societies Task Force (EFNS, 2012) addressed presymptomatic testing in its diagnosis and management guidelines: "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."[16]

The EFNS (2012) stated the following regarding molecular testing for ALS:[16]

- "Clinical 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."
- "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 counseling. Give the patient time for consideration. DNA analysis should be performed only with the patient's informed consent."

The EFNS (2011) addressed the molecular diagnosis of ALS and other neurogenetic disorders:[17]

- "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

The World Federation of Neurology Research Group on Motor Neuron Diseases (WFNALS, 2015) revised the El Escorial criteria:[18]

- These revised criteria did not specify when genetic testing should be done, but stated "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)."

Consensus guidelines from the WFNALS (2000) revised the El Escorial criteria to improve ALS diagnostic sensitivity.[3] This group didn't specify when genetic testing should be done, but stated, "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, an individual 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.

Selected Relevant Publications

An ALS Expert Panel (2023) developed evidence-based, consensus guidelines for care of individuals with ALS that stated:[19]

- "...all persons with ALS should be offered single-step genetic testing, consisting of a C9orf72 assay, along with sequencing of SOD1, FUS, and TARDBP at a minimum."
- In addition, gene panels should include "Any gene for which the Food and Drug Administration (FDA) approves a targeted therapy" and "Genes rated as 'strong' or 'definitively' associated with ALS by ClinGen".
- The guideline stated that pretest genetic counseling should be provided. This should include pedigree analysis, risk assessment, discussion of genetic heterogeneity, penetrance, and inheritance patterns, and a review of the possible test results such as positive, negative, and variant of uncertain significance. Furthermore,

pretest genetic counseling should also "prepare individuals for possible personal, psychological, and economic impacts of testing on themselves and their family members."

- "All persons with ALS who have genetic testing should receive posttest counseling." The points to review in the posttest counseling sessions are outlined in the consensus guideline.
- The consensus guideline also provided information for commercial laboratories on testing methods and reporting of the C9orf72 mutation and other genes.

An expert recommendation (2016) for predictive genetic counseling and testing for genetic ALS stated: [20]

- Testing should be voluntary and include informed consent.
- Psychosocial readiness to undergo presymptomatic testing should be assessed.
- Genetic counseling should be provided and at least two counseling sessions should be performed. "These may include predecision counseling as well as pretest and posttest counseling." Specific points to review during each of these sessions were discussed in detail.
- Individuals have the option "not to take the test at all, to undergo testing but not to learn the results, or simply to provide a DNA sample for future research."
- The rendering laboratory should be a Clinical Laboratory Improvement Amendments (CLIA)-certified laboratory.

Note: This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the guidelines and evidence provided in the clinical policy, following EviCore's criteria for Amyotrophic Lateral Sclerosis (ALS) testing will ensure that testing will be available to those members most likely to benefit from a genetic diagnosis. For those not meeting criteria, it ensures alternate diagnostic strategies are considered. However, it is possible that some members who have the condition, but have non-standard features, will not receive an immediate approval for testing.

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