Test Specific Guidelines

Amyotrophic Lateral Sclerosis (ALS) Genetic Testing

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Introduction

Amyotrophic lateral sclerosis genetic testing is addressed by this guideline.

Procedures Addressed

The inclusion of any procedure code in this table is provided for informational purposes and is not a guarantee of coverage nor an indication that prior authorization is required.

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

What Is Amyotrophic Lateral Sclerosis?

Definition

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 70% of cases of ALS when there is a family history of the disease.[8] Mutations in SOD1, C9orf72, TARDBP (TDP-43), and FUS account for the greatest number of cases, while the remaining genes are relatively rare causes of the disorder.[1,4-10] 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.[5,10] 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.[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.[1,4-9]

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 is palliative. 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.[1]

Test Information

Introduction

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 multi-gene panels.

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.[11]

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 patient 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.[12]

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 patient management, and/or minimize the chance of finding variants of uncertain clinical significance.

Guidelines and Evidence

Introduction

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

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." [13]

The EFNS (2012) stated the following regarding molecular testing for ALS:[13]

- **"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."**

- **"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 s 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:[14]

- **"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:[15]

- **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.

Criteria

Introduction

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 relative(s), and
  - Age 18 years or older, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy.

Other Considerations

- Genetic testing for ALS, in the absence of a known familial mutation, is considered investigational and experimental and, therefore, not eligible for reimbursement

References

Introduction

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