Hereditary Ataxia Multigene Panel Genetic Testing

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Introduction

Hereditary ataxia multigene panel 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
Genomic Unity Ataxia Repeat Expansion and Sequence Analysis	0216U
Genomic Unity Comprehensive Ataxia Repeat Expansion and Sequence Analysis	0217U
Hereditary ataxia multigene panel	81479
Hereditary ataxia multigene panel (including sequencing of at least 15 genes)	81443

Criteria

Introduction

Requests for hereditary ataxia multigene panel testing are reviewed using the following criteria.

Multigene Panel 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 testing of requested genes, and

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  - No known mutation identified by previous analysis, and
  - No known familial mutation in a gene known to cause ataxia, AND

- Diagnostic Testing for Symptomatic Individuals
  - Individual has been diagnosed with cerebellar ataxia, regardless of age of onset, AND
- Documentation from ordering provider indicating how test results will be used to directly impact medical care for the individual (e.g. change in surveillance or treatment plan), AND
- The member does not have a known underlying cause for their ataxia (e.g. alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, tumors, known mutation, etc), AND
- Family and medical history do not point to a specific genetic diagnosis or pattern of inheritance for which a more focused test or panel, such as a nucleotide repeat analysis panel, would be appropriate, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Other Considerations

- For information on spinocerebellar ataxia (SCA) panel testing, please refer to the guideline *Spinocerebellar Ataxia Genetic Testing*, as this testing is not addressed here.
- Gene panels that are specific to hereditary ataxias will be considered for medical necessity according to the criteria outlined in this guideline. Test methodology should be appropriate to the disease-causing mutations that are commonly reported for the disorder in question (e.g., sequencing-only panels will not detect triplet repeat or large deletion/duplication mutations).

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 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., 81443, 81479, 0216U, or 0217U)*.
    - Analysis of individual genes will not be reimbursed separately (i.e. multiple stacked codes are not eligible for reimbursement).

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*.

What are hereditary ataxias?

Definition

The hereditary ataxias are a group of genetic disorders. They are characterized by slowly progressive uncoordinated, unsteady movement and gait, and often poor coordination of hands, abnormal eye movements, and slurred speech. Cerebellar atrophy is also frequently seen via brain imaging.[1]

Prevalence

Prevalence estimates vary. The prevalence is approximately 2.7/100,000 and 3.3/100,000 for autosomal dominant and autosomal recessive hereditary ataxias, respectively.[2] One study in Norway estimated the prevalence of hereditary ataxia at 6.5 per 100,000 people.[3]

Symptoms

Although hereditary ataxias are made up of multiple different conditions, they are characterized by slowly progressive uncoordinated, unsteady movement and gait, and often poor coordination of hands, abnormal eye movements, and slurred speech. Cerebellar atrophy is also frequently seen via brain imaging.[1]

Cause

Hereditary ataxias are caused by pathogenic mutations in one of numerous genes.[1] The following genes are associated with hereditary ataxia; however, this list is not intended to be all inclusive: ATN1, ATXN1, ATXN2, ATXN3, CACNA1A, ATXN7, TBP, FXN, and FMR1. Several of the ataxias are caused by nucleotide repeat expansions. Testing for these conditions is performed by expansion analysis to identify the number of repeats. Expansion analysis can be performed for diagnostic testing, presymptomatic testing, as well as prenatal testing.

Inheritance

Most hereditary ataxias, including the spinocerebellar ataxias (SCA), dentatorubral-pallidoluysian atrophy (DRPLA), and episodic ataxia (EA) types 1 and 2, are inherited in an autosomal dominant manner. A few of the hereditary ataxias, including Friedreich ataxia and ataxia telangiectasia, are inherited in an autosomal recessive manner. Fragile X tremor/ataxia syndrome is an X-linked ataxia.[1]

Diagnosis

The diagnosis of hereditary ataxia is suspected based on clinical and family history, neurological exam, and neuroimaging studies.[1] Acquired causes of ataxia — including alcoholism, vitamin deficiencies, multiple sclerosis, vascular disease, and tumors — should be ruled out.[1]

Molecular genetic testing can be used to establish a specific diagnosis. In the absence of a family history, it can be difficult to differentiate the type or subtype of hereditary ataxia based on clinical features.[1] One study found that in approximately 13% of apparently sporadic ataxias, a causative genetic change was identified.[4]

Management

Treatment of ataxia is largely supportive, and includes the use of canes and walkers for ambulation, speech therapy, and other assistive devices.[1]

Survival

The survival range of the hereditary ataxias varies across the multiple conditions included in this group.

Test Information

Introduction

Testing for hereditary ataxias may include known familial mutation analysis, single gene testing, nucleotide repeat expansion analysis, or multigene panel testing. This guideline only addresses multigene panel testing via next generation sequencing (NGS).

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 Sciences

The European Federation of Neurological Sciences (EFNS, 2014) stated the following regarding testing for hereditary ataxias:[5]

- "In the case of a family history that is compatible with an autosomal dominant cerebellar ataxia, screening for SCA1, SCA2, SCA3, SCA6, SCA7, and SCA17 is recommended (Level B). In Asian patients, DRPLA should also be tested for."
- "If mutation analysis is negative, we recommend contact with or referral to a specialized clinic for reviewing the phenotype and further genetic testing (good practice point)."
- "In the case of sporadic ataxia and independent from onset age, we recommend routine testing for SCA1, SCA2, SCA3, SCA6, and DRPLA (in Asian patients) (level B), the step one panel of the recessive ataxia workup, i.e. mutation analysis of the FRDA gene (level B), and biochemical testing that includes cholestanol, vitamin E, cholesterol, albumin, CK, and alpha-fetoprotein."

Selected Relevant Publications

The diagnostic evaluations for ataxia may include assessments for acquired, other nongenetic, and genetic etiologies.[6,7] Establishing the diagnosis of a hereditary ataxia may include demonstration of typical clinical signs on neurological examination and exclusion of acquired or other nongenetic causes. Additionally, a positive family history, documentation of a hereditary ataxia disease causing mutation, and/or the presence of a characteristic clinical phenotype of a specific hereditary ataxia may solidify the diagnosis.[7]

The results of additional evaluations, such as brain imaging, may increase the suspicion of a hereditary etiology. These additional studies may indicate that an ataxia is slowly progressive and long standing which may signify early onset.[4] Furthermore, findings on MR spectroscopy may indicate a hereditary etiology is more likely compared to an immune-mediated ataxia.[4]

The likelihood of a hereditary etiology is higher in those with early age of onset (81%) compared to late onset (55%) idiopathic ataxia.[4] The presence of other clinical features also increases the likelihood of detecting a mutation.[4] In those with a family history consistent with autosomal dominant inheritance, a mutation was detected in 50-60% with testing for SCA1, 2, 3, 6, 7, 8, 10, 12, 17 and dentatorubral-pallidoluysian atrophy (DRPLA).[7] In a simplex case with no known acquired cause, according to one study, the likelihood an individual has SCA1, 2, 3, 6, 8, 17, or Friedrich ataxia (FRDA) is approximately 13% and the likelihood of a mutation in a different hereditary ataxia gene

is more rare.[7] In another study utilizing targeted exome analysis of 441 genes in individuals with ataxia of unknown etiology, a positive result was detected in 52% of individuals. Forty percent of the positive cases were due to mutations in SPG7, SYNE1, ADCK3, CACNA1A, ATP1A3, and SPTBN2.[8] Even in those with an unremarkable family history, genetic testing may aid in their medical evaluation and in genetic counseling.[7]

It was suggested that genetic testing for progressive ataxias should include evaluation of the genes for FRDA, SCA 1, 2, 3, 6, 7 (12, 17) and fragile X-associated tremor/ataxia syndrome.[6] Testing may proceed in a sequential fashion. For those with a family history suggestive of autosomal dominant inheritance, first round testing for the most common hereditary ataxias (SCA1, SCA2, SCA3, SCA6, and SCA7) may be completed followed by testing for less common hereditary etiologies which may be guided by ethnic background and/or specific clinical features.[7] In those with a family history suggestive of autosomal recessive inheritance, the following may be tested due to "frequency and/or treatment potential": FRDA, ataxia telangiectasia, ataxia with oculomotor apraxia type 1, ataxia with oculomotor apraxia type 2, ataxia with vitamin E deficiency, and metabolic or lipid storage disorders.[7] Single-gene testing may be pursued if the clinical examination is consistent with a specific diagnosis or if a specific type is known in the family.[7]

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 hereditary ataxia multigene panel 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 would benefit from the testing, but do not meet clinical criteria, will not receive an immediate approval for testing.

References

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