Genetic Testing for Variants of Uncertain Clinical Significance

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Introduction

Genetic testing for variants of uncertain clinical significance is addressed by this guideline.

Description

Genetic testing of an affected individual by gene sequencing or multi-gene panel testing can reveal genetic variants that have an unknown effect. These variants of uncertain clinical significance (VUS) may or may not cause disease in the individual; there is simply not enough known at the time of the report to call the variant disease-causing or benign.[1]

The accumulation of sufficient data to reclassify a VUS may take many years and require identification of the variant in multiple individuals. Pathogenicity of a variant is determined by labs through assessing:

- Disease-specific or gene-specific mutation databases
- Large population variant frequency databases
- In silico prediction tools
- Multi-species conservation assessment
- Peer reviewed literature
- Functional studies
- Family assortment studies

Family studies may be offered by the laboratory at no charge to the family, as the result may assist the lab in future classification of the variant. Testing relatives for a VUS may not always lead to reclassification of a variant to either disease-causing or benign, but it can be helpful in certain clinical scenarios, potentially contributing evidence that it is more or less likely to be disease-causing.

Targeted VUS Testing

Testing the parents of an affected child who has a VUS may be helpful in determining the clinical significance of that variant in some situations. For instance, if the condition is dominant and the VUS is not inherited from either parent (de novo), it is more likely to be disease-causing. If it is inherited from a healthy parent, it may be more likely to be benign.

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Similarly, for an autosomal recessive condition, one or both of two potential disease-causing variants in a child may be called VUS. Testing parents should confirm whether one of the variants was inherited from each parent, and therefore fits the recessive pattern of inheritance.

If a VUS is identified in apparent homozygosity (2 copies), testing parents should determine copy number. A VUS that is inherited in two copies, one from each parent, would be consistent with the expected pattern of inheritance for recessive disease. If the VUS is only inherited from one parent, other mechanisms for pathogenicity (such as gene deletion or uniparental disomy) should be investigated.

Simply testing a relative for a VUS will not determine if that variant is disease causing or benign. This is especially true for adult onset conditions (e.g.: hereditary cancer syndromes) or conditions for which there is reduced or non-penetrance or highly variable expressivity. After targeted testing for a VUS, careful clinical and family history evaluation and correlation with the result are essential.

Genes of Uncertain Clinical Significance

Broader tests, such as whole exome sequencing or whole genome sequencing, may identify variants in genes that have an unknown effect. That is, for a gene of uncertain clinical significance (GUS) there is not enough known about the gene and its function to say whether it can cause the disease in question.[1]

Potential Outcomes of Targeted VUS testing

Results of testing and possible significance of testing.

Result of VUS testing	Possible significance
VUS is not inherited (de novo)	Increased likelihood of causing disease
VUS is inherited from affected parent	Increased likelihood of causing disease
VUS is inherited from unaffected parent	Decreased likelihood of causing disease
VUS is inherited with a disease-causing variant or VUS from the same parent	Decreased likelihood of causing disease
VUS that is apparently homozygous is not inherited from both parents	Alternate mechanisms should be investigated

Note This benefit/harm statement only applies to those jurisdictions that do not have Medicare guidance. Based upon the clinical policy, following EviCore's criteria for genetic testing for variants of uncertain clinical significance 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/management strategies are considered. However, it is possible that some members who would benefit from the testing, but do not meet criteria, will not receive an immediate approval for testing.

Criteria

Introduction

Requests for genetic testing for variants of uncertain clinical significance are reviewed using these criteria.

Criteria: General Coverage Guidance

- Pre and post-test genetic counseling by an appropriate provider (as deemed by the Health Plan policy), AND
- No previous genetic testing of the requested gene that would detect the VUS, AND
- No known alternate genetic cause for the diagnosis in the family, AND
- Member is the biological parent of a child in whom a VUS was identified, AND
- VUS is in a gene that is
    - Known to be disease-associated, and
    - Consistent with the child's clinical diagnosis, AND
- Purpose of testing is to determine
    - Whether the VUS is inherited or de novo, or
    - Whether the VUS is present in homozygosity, AND
- Determination of the inheritance or copy number of the VUS will lead to treatment changes for the member or the member's child, AND
- Rendering laboratory is a qualified provider of service per the Health Plan policy

Limitations and Exclusions

- Testing of multiple affected and unaffected relatives to determine if a VUS assorts with symptoms in the family is not considered medically necessary; therefore, it is not reimbursable.
- Testing for variants in genes of uncertain clinical significance (GUS) is not considered medically necessary; therefore, it is not reimbursable.
- Each test request for VUS testing should be reviewed based on the medical information available for the member and the clinical utility and technical and clinical validity of the service requested.

Criteria: Test-specific Guidelines

Test-specific guidelines may be available for tests that could target a VUS. For tests without a specific guideline, use the General Coverage Guidance above.

References

Introduction

This guideline cites the following references.

1. Richards S, Aziz N, Bale S, et al. Standards and guidelines for the interpretation of sequence variants: a joint consensus recommendation of the American College of Medical Genetics and Genomics and the Association for Molecular Pathology. *Genet Med*. 2015; 17(5):405-24. doi: 10.1038/gim.2015.30.

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