AMERICAN EPILEPSY SOCIETY

Genetic Testing in the Epilepsy Clinic

Created by the AES Practice Management Committee | June 2025

WHY (do it), **WHO** (needs it), **WHEN** (to order), **WHERE** (to obtain), **HOW** (to interpret) and **WHAT** (test)

WHY: The Value of Genetic Testing in Epilepsy

Many individuals with epilepsy do not have an identified cause. In these cases, **genetic testing can be a valuable tool**. It helps differentiate between epilepsy syndromes and provides a more precise diagnosis, improving our understanding of the underlying biological mechanisms and informing the development and use of targeted therapies. Genetic insights enable **personalized treatment plans**, reducing the risk of adverse drug reactions and improving medication choices. Testing also provides important information for families, including the identification of at-risk family members and the determination of whether offspring will be affected. Genetic testing can reveal a cause **in 20–30% of epilepsy cases**. While challenges remain — including limited understanding of some variants and barriers related to cost and access — expanding access and advancing genetic knowledge are essential to realizing the full benefits of testing. The utility of genetic testing in epilepsy is formally supported by both the National Society of Genetic Counselors and the American Epilepsy Society.

WHO AND WHEN: Epilepsy That Is Unexplained

Patients with one of the following:

- Syndromic disorder
- Malformations of cortical development
- Suspected channelopathies
- Suspected metabolic disorders
- Childhood onset epilepsy including severe forms of childhood epilepsy
- Drug-resistant epilepsy, especially of unknown cause
- Neurodegeneration
- Family history of epilepsy in two first-degree family members
- Other neurologic findings
- Unexplained epilepsy

Certain patient populations have historically faced limited access to genetic testing and lower referral rates. Some individuals from within these groups are more likely to receive uncertain results (variants of undetermined significance).

WHERE: Practicalities of Testing

1. **Identify** which test is right for your patient, their insurance, and financial status.
2. **Consent** your patient. This requires understanding of the range of risks which includes inability to obtain life insurance, revelation of non-paternity status, the emotional toll of a positive OR negative result, among others.
3. **Choose** a testing company/organization.
4. **Ordering/Billing.** Company/organization-specific requisition paperwork must be submitted by ordering providers. Most tests require a prior authorization if insurance is used.
   There are often restrictions on inpatient ordering; be familiar with your hospital systems.
5. **Results follow-up.** Testing may include options that allow for patients to view results in real time. Please consider this when ordering. Follow up to review if testing should be offered. If more complex or uncertain results return, refer to a genetic counselor/geneticist.

https://findageneticcounselor.nsgc.org/

https://clinics.acmg.net/

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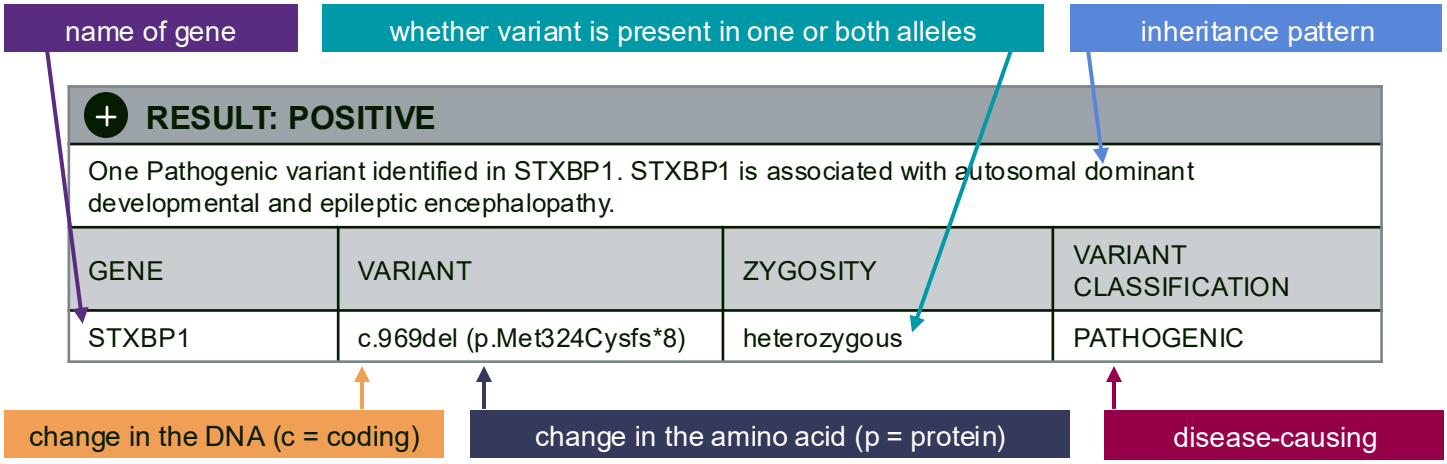
HOW: Interpretation of an Example Test Report



WHAT: Descriptions of Test Types

Name	NGS MGP	WES	WGS	CGH/CMA
Region	Epilepsy-associated genes	Exons, exon/intron boundaries	Entire genome	Copy number and structural variants
Pros	• Less incidental findings • Easiest to interpret • Most cost-effective/fastest • Often covered by insurance	• Comprehensive coverage • Good for heterogenous conditions • May ID novel genes/variants	• Also detects noncoding variants • May ID novel genes/variants • Able to ID CNV variants, some structural variants	• Cost effective in epilepsy + comorbidities • May find structural variants not found on other tests
Cons	• Causative gene may not be included • Limited options for reanalysis • Misses actionable secondary findings	• Possible identification of incidental findings • Depth of coverage is not uniform • Unable to detect non-coding and structural variants and limited ability to detect CNVs	• Most expensive, longest turnaround • Challenging for insurance coverage • Possible identification of incidental findings	• Not cost-effective as first-line test if comorbidities not present • Cannot detect balanced translocations, may still need chromosome analysis
		May require input from geneticist and/or genetic counselor.		

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NGS=Next Generation Sequencing. MGP=Multigene Panel. WES=Whole Exome Sequencing. WGS=Whole Genome Sequencing. CGH/CMA=Comparative Genomic Hybridization/Chromosomal Microarray. CNV=Copy Number Variant.

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