Overview of Most Commonly Used Genetic Testing Options for People with Epilepsy

Test Name	Region of Genome Analyzed	PROS	CONS
Next Generation Sequencing (NGS) Multi-Gene Panel (MGP)	Specific genes (currently) recognized to be associated with epilepsy (range in 2024: 20 to >1,000 genes depending on panel)	• A curated and focused set of genes, so least likely to get incidental findings • High NGS depth of coverage • Easiest for a neurologist without genetics expertise and/or limited access to medical geneticists to interpret and act upon • Typically, the least expensive and fast turnaround • Easy to order and get covered by insurance	• Causative gene may not be included (yet) • Limited options for reanalysis, so may subsequently undergo repeat WES or WGS testing if high suspicion for genetic etiology • Will likely miss actionable • secondary findings (e.g., BRCA, Lynch syndrome genes) that are unrelated to epilepsy phenotype, but can profoundly affect medical prognosis & treatment • No coverageof non-coding variantsthat have been implicated in generalized genetic epilepsy risk
Whole Exome Sequencing (WES)	Coding regions (exons) and exon/intron boundaries (~1-2% of genome)	• Comprehensive coverage of coding regions and actionable gene findings • Effective for heterogenous neurological conditions & comorbidities • Able to identify mutations in novel genes • Reanalysis is possible	• More likely than MGP to result in incidental or secondaryfindings that require interpretation by medical geneticists and/or clinical action • Depth of coverage is not uniform • Unable to detect non-coding (intronic) variants • Limited abilityto identify CNV or structural variants
Whole Genome Sequencing (WGS)	Entire genome	• Detects coding and noncoding variants (unlike other 2 options) • Uniform coverage • Able to identify mutations in novel genes as well as non- coding (e.g., presumed regulatory) regions • Reanalysis is possible • Allows detection of copy number variants (CNV) and some (smaller) structural variants	• Most expensive and longest turnaround • More challenging to get coveredby insurance • Most likely to result in incidental findings that are more difficult to interpret • Requires medical geneticist for full interpretation
Chromosomal microarray - comparative genomic	Genome-wide copy number variants (CMV) & structural variants (e.g., deletions, translocations)	• Cost effectivein people with epilepsy PLUS comorbid developmental delay (DD), intellectual disability (ID), or birthdefects • Often considered as second line testing if previous testing was unrevealing because it detects structural variants that may be undetectable on other NGS-based tests	• Not cost-effective as first-line genetic testing unless DD/ID or birth defect comorbidities • Cannot detect balanced translocations and certain structural rearrangements, would need chromosome analysis (i.e., karyotype)

Other genetic testing considerations:	• Trio testing can be done with WES vs WGS if both biological parents are available.
	• Quad testing feasible if there is an affected sibling + above
	  ◦ Pros: identifies de novo mutations, Family/pregnancy planning
	  ◦ Cons: risk of unexpected familial implications such as consanguinity or non-paternity		