A Guide to Genetic Testing in Pediatric Epilepsy

A review of the latest genetic testing methods utilized for the diagnosis of pediatric epilepsy, with a special emphasis on the timing, value, utility, and accessibility of pediatric genetic testing.

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Pediatric epilepsy presents a complex and multifaceted challenge to neurologists responsible for the diagnosis, treatment, and management of this condition. Whereas epilepsy in children can result from various causes, including structural abnormalities, trauma, or infections, it is increasingly recognized that genetic factors play a pivotal role in the pathogenesis of unexplained pediatric epilepsy. It is estimated that 30% to 40% of unexplained epilepsy has a genetic etiology.[1]

The landscape of pediatric epilepsy diagnosis and management has evolved rapidly, largely because of advances in genetics. The elucidation of genetic etiologies helped reveal the heterogeneity of epileptic conditions and promotes alternative approaches to diagnosis and therapy. General neurologists, who are often the first point of contact for individuals with pediatric epilepsy, must stay abreast of these evolving genetic insights and the implications they hold for clinical practice. This review provides a comprehensive update on the latest evidence and recommendations in genetic testing for pediatric epilepsy.

Importance of Genetic Testing

The timing, utility, and value of genetic testing are critical components of clinical decision-making in pediatric epilepsy, offering both diagnostic clarity and therapeutic guidance at pivotal junctures in a child's medical journey.

Timing

Genetic testing at the onset of recurrent seizures enables clinicians to identify the underlying cause of epilepsy more quickly and accurately. This precision can help distinguish among various epilepsy syndromes and provide insight into the nature and prognosis of the condition, allowing for more targeted interventions. An example of an important effect of early diagnosis on outcome is identification of pyridoxine-dependent epilepsy and initiation of pyridoxine (vitamin B6) to significantly reduce seizure burden and maintain appropriate developmental outcome.[2] For some genetic epilepsies, delays in diagnosis can result in unnecessary medical tests and treatments, such as in the setting of self-limiting or benign infantile seizures. Early genetic testing expedites the diagnostic process, sparing individuals and clinicians from prolonged uncertainty.

Utility

Genetic testing provides valuable prognostic information, helping clinicians predict disease course and anticipate potential comorbidities or complications. This knowledge allows for better long-term planning and management. Test results can inform treatment decisions, which can lead to more effective seizure control and potentially reduce the risk of adverse effects from unnecessary treatments. Some genetic epilepsies are associated with additional health risks, such as cognitive impairment or developmental delays, or even systemic manifestations that may not yet be present. Identification of the risk for these comorbidities can facilitate early intervention, such as supportive rehabilitation therapies, to mitigate these complications.[3]

Value

Not only does early genetic testing improve care, but it contributes to the growing body of genetic data in pediatric epilepsy, which in turn drives research and advancement. Clinicians may use a variety of databases to identify research opportunities tailored to an individual's genomics, such as GeneMatcher.[4] In recent years, targeted therapies or clinical trials for specific genetic conditions have been on the rise.[2] These trials potentially offer novel treatments that may not be available for idiopathic or acquired forms of epilepsy. Early genetic testing also offers critical information for family members. It can identify at-risk relatives and carriers of genetic conditions, allowing for genetic counseling on reproductive risks and informed family planning. Families of children with epilepsy also have identified value in the opportunity to connect with other families for support when a relatively uncommon but shared diagnosis is present.

Genetic Testing

There are a variety of genetic testing technologies that neurologists may consider in their diagnostic workup. The most common include multigene epilepsy panels, whole-exome sequencing (WES) or whole-genome sequencing (WGS), and chromosomal microarray analysis (CMA). The diagnostic yield of each test differs based on clinical indication, and testing strategies should be considered accordingly. Advantages and limitations of these tests are summarized in the Table. Challenges encountered during the genetic testing process are discussed later in this review.

Multigene Epilepsy Panel

Next-generation sequencing (NGS) is a high-throughput genomic technology that allows for rapid DNA sequencing of multiple genes at once. Multigene epilepsy panels are applications of NGS technology designed for targeted analysis of genes specifically associated with epilepsy and related neurologic disorders. These panels, typically composed of 25 or more genes, streamline the identification of known causative variants within epilepsy-related genes, facilitating efficient and targeted genetic testing for the diagnosis, management, and genetic counseling of individuals with epilepsy.

Clinical Indications. The age at seizure onset and age at presentation for genetic testing should not prevent a clinician from considering genetic testing. An epilepsy panel may be considered for all individuals with epilepsy.[5] When a child presents with early-onset epilepsy or refractory seizures, such as developmental epileptic encephalopathies, genetic testing has a higher likelihood of identifying underlying genetic causes that may inform treatment decisions.[1] For children with clinical features consistent with an epilepsy syndrome, such as genetic epilepsy with febrile seizures plus, a multigene epilepsy panel is recommended for accurate diagnosis and prognosis in a timely manner.[6] In the referenced review,[6] Pickrell and Fry characterize genetic epilepsies and their clinical features to aid clinicians in identifying appropriate epilepsy panels.

Diagnostic Yield. The diagnostic yield of a multigene epilepsy panel varies depending on the number of genes in the curated panel, indications for testing, and population. Most standard commercial epilepsy panels include commonly implicated epilepsy genes and preliminary genes associated with epilepsy. Recent studies have highlighted the effectiveness of epilepsy panels, quoting diagnostic yields between 20% and 25%.[5,7] The yield is highest in cohorts with distinct features of epileptic syndromes, children with epilepsy and intellectual disability, and infantile-onset seizures.[8]

WES/WGS

WES technology selectively sequences the protein-coding regions of an individual's genome, known as exons. WGS is the most comprehensive genomic analysis technique that sequences coding and noncoding regions of an individual's DNA. Both tests use NGS technology and allow for continual reanalysis of data over time. WGS enables the identification of coding variants, structural variations, regulatory elements, and potential novel genetic variants. The burden of interpreting such data in a clinical setting is complex and resource-intensive, so WGS has not been introduced in outpatient clinical practice at most institutions.[5,6] Both tests use NGS technology and allow for continual reanalysis of genomic data over time, which is particularly valuable in the diagnosis of rare disorders or identifying candidate genes potentially associated with epilepsy.

Clinical Indications. WES and WGS are typically indicated for pediatric epilepsy when the underlying cause of the condition remains elusive after initial clinical evaluation and targeted genetic tests. In 2023, the National Society of Genetic Counselors issued a practice guideline for genetic testing and counseling for unexplained epilepsy, recommending that WES/WGS should be considered as a first-tier genetic test for unexplained epilepsy.[5] This recommendation has not been fully implemented, as pretest and posttest genetic counseling are strongly recommended and often required to pursue WES/WGS. Other considerations including turnaround time to obtain test results, cost of testing, and insurance coverage limit pursuing these tests at the onset of an individual's seizures.[5,9]

WES/WGS may be indicated as a first-tier test when a child presents with early-onset, drug-resistant epilepsy or seizure semiology evolves over time and there is no clear differential diagnosis based on clinical assessment; the child has extraneurologic features, neurodevelopmental delays, or intellectual disability; or a new genetic etiology is suspected. WES and WGS are especially useful when a family history of epilepsy or related neurologic disorders may indicate a hereditary component and first-degree relatives are available to participate in testing to improve analysis and interpretation of results. WES/WGS can reveal novel genetic pathways and mutations, contributing to research efforts aimed at developing targeted therapies.[9]

Diagnostic Yield. The diagnostic yield of WES and WGS for pediatric epilepsy is approximately 24% to 48%, with WGS

TABLE. ADVANTAGES AND LIMITATIONS OF GENETIC DIAGNOSTIC TESTS

	Multigene epilepsy panel	WES	WGS	CMA
Single nucleotide variants	Coding region	Coding region	Coding and noncoding regions	–
Indels	+	+	+	–
Copy number variants	Exon, single gene	Exon, single gene, multigene	Exon, single gene, multi-gene	Exon, single gene, multigene
Trinucleotide repeat expansion	–	–	+	–
Deep intronic variants	–	–	+	–
Structural rearrangements	–	–	Balanced and unbalanced	Unbalanced
Incidental findings	–	+	+	–
Candidate or novel genes	–	+	+	–
Faster turnaround time[a]	+	–[b]	–[b]	+
Cost of testing	+	++	+++	+
Diagnostic yield	++	++	+++	+

Abbreviations: WES, whole-exome sequencing; WGS, whole-genome sequencing; CMA, chromosomal microarray.
This is not a comprehensive summary of the technical advantages and limitations of a multigene epilepsy panel, WES, WGS, or CMA, as there are specific laboratory and bioinformatics platform advantages and limitations. Indels are insertions or deletions smaller than 1 kb. + through +++ indicate lowest to highest cost of testing and diagnostic yield.
[a]Defined as return of results within weeks (rather than months).
[b]Rapid WES and WGS options are available under certain circumstances and could result more quickly than other testing modalities.

on the high end of the range.[5,8,9] When comparing targeted versus comprehensive analysis, WES and WGS are expected to yield a higher diagnostic rate than multigene panels, especially in the setting of more complex clinical history.[8,10] The diagnostic yield is optimized when incorporating genetic data from family members to aid in identification of de novo variants or suspicious variants of uncertain significance (VUS). Diagnostic yield should be interpreted in the context of specific individual and clinical scenarios.[8]

CMA

CMA technology is a high-resolution genomic analysis method that enables the detection of submicroscopic chromosomal imbalances, such as deletion, duplications, and copy number variations, across an individual's genome. CMA allows for the identification of smaller genetic alterations that may be associated with various developmental and neurologic disorders where epilepsy is a secondary feature of the condition.[10]

Clinical Indications. CMA should be considered in cases of pediatric epilepsy associated with neurodevelopmental delays, autism spectrum disorder, intellectual disability, or multiple congenital anomalies, as these features may indicate the presence of chromosomal abnormalities or copy number variations.[10] Generalized genetic epilepsy (GGE) is more commonly associated with deletions and duplications than single-gene changes. Examples of copy number deletions associated with GGE include 15q11.2, 15q13.3, and 16p13.11.[3] Other copy number variations reported in children with epilepsy include 1q21.1, 15q12.2, and 16p11.2.[11] NGS panels may reveal a single gene deletion or duplication that suggests a larger multigene imbalance, in which case a CMA should be pursued as a secondary genetic test. For example, a deletion of *PRRT2* identified on an epilepsy panel indicates that the child likely has a larger recurrent deletion of 16p11.2. This more detailed diagnosis reveals a child's risk to have developmental delay, behavioral concerns, autism, and cardiac concerns, which should be evaluated promptly.[12] Overall, CMA is recommended in cases where a genetic etiology is suspected but not confirmed through other means, as it has the capability to uncover genomic imbalances that NGS panels and WES/WGS are unable to detect.[3,5,6]

Diagnostic Yield. Studies have reported diagnostic yield of CMA ranging from around 5% to 10% in pediatric epilepsy cohorts.[10,13] Higher diagnostic yields are often observed in individuals with comorbid neurodevelopmental disorders or intellectual disability alongside epilepsy, and when these neurologic deficits preceded seizure onset.[5]

Challenges in Genetic Testing

Accessibility

Genetic testing, although increasingly essential for accurate diagnosis and treatment of pediatric epilepsy, faces significant challenges in terms of accessibility to testing and resources. Many individuals, particularly those from underserved populations or regions with limited health care resources, encounter difficulties in accessing genetic testing because of geographic and financial constraints.[14] Furthermore, insurance coverage for genetic testing can be inconsistent and insufficient, leaving families with the burden of high costs or facing denials of coverage for tests deemed medically necessary by their health care providers.[5] These barriers can result in disparities in health care, leaving some individuals without opportunity to benefit from the value provided by genetic testing, hindering the full potential to improve care and management.

Results Interpretation

VUS are common results in every genetic test. A VUS is a genetic variant detected that does not have well-established clinical significance or known association with a human disease. VUS are not definitively categorized as pathogenic variants or benign variants and are challenging for health care providers to interpret and for families to understand in terms of effects on their child's health. Whereas advanced genomic technologies have expanded the capacity to identify genetic variants, a substantial portion of these variants lack clear clinical significance or are novel. The uncertainty may lead to ambiguity in diagnosis and treatment decisions, causing anxiety for individuals and their health care providers.[6,13] The dynamic nature of genetic databases and evolving understanding of genetic variants mean that the significance of a variant may change over time. Genetic counselors and clinicians must navigate this uncertainty carefully, emphasizing the importance of ongoing communication and the need for periodic reevaluation as new information emerges to ensure the most accurate and updated interpretation of genetic test results.[7]

When genetic counselors are available to assist ordering clinicians, we strongly encourage collaboration. Genetic counselors are trained to identify appropriate genetic testing strategies based on an individual's clinical history, coordinate testing and navigate potential barriers that arise with testing, and interpret and communicate results to individuals, families, and clinicians to improve care.[5]

Conclusion

The timing, value, and usefulness of genetic testing are essential considerations in the diagnostic and therapeutic course of children with epilepsy. Multigene epilepsy panels, CMA, and WES/WGS are important tools in the diagnostic workup. The application of these genetic tests, each prioritized in specific clinical scenarios, offers the potential for timely, accurate diagnoses, resulting in personalized care that can improve outcomes and enhance quality of life. The dynamic landscape of genetic research continues to uncover novel genes and variants associated with pediatric epilepsy, further expanding our diagnostic capabilities. As we navigate the challenges of accessibility, insurance coverage, and variant interpretation, collaboration among clinicians, genetic counselors, and researchers is critical to ensure equitable access and use of genetic diagnostic tools. Genomics will continue to influence pediatric epilepsy, enhancing our ability to provide tailored management and improve the prognosis of genetic epilepsy disorders. ■

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Disclosure

The author reports no disclosures.