Epilepsy Genetic Testing

Effective Date: March 2025

Executive Summary:

This health insurance policy describes genetic testing recommendations for people with recurrent, unprovoked seizures. This condition, known as epilepsy, affects about 1.2% of people in the United States, which includes roughly 3 million adults and 470,000 children. Although the exact cause of epilepsy is unknown in about half of these patients, it can result from various factors such as genetic variants, head injuries, brain abnormalities, strokes, infections, autoimmune conditions, metabolic disorders, tumors, or prenatal injuries.

Genetic factors are believed to play a role in about 30% of epilepsy cases. This means that some people with epilepsy might have a genetic variant that contributes to their condition. For patients who have epilepsy without a clear cause, genetic testing is recommended. Finding a genetic variant can help healthcare providers decide the best treatments, like which anti-seizure medicine to use, if a special diet is needed, or if surgery might be effective.

Genome sequencing is considered the best initial test for identifying genetic causes of epilepsy. If genome sequencing is not available, other tests like exome sequencing or multi-gene panels can also be useful. Single-gene testing is not typically recommended unless there is a known genetic variant in the family or specific clinical features suggest a particular genetic condition. This is because there is a lot of genetic variation and overlap in epilepsy symptoms, making broader tests more reliable.

This policy summarizes current evidence and guidelines for epilepsy genetic testing and emphasizes the importance of genetic counseling before and after testing.

Criteria:

Genetic testing for epilepsy by genome sequencing, exome sequencing, or multi-gene panel is considered medically necessary when ALL of the following criteria are met:

1. The patient has epilepsy with onset at any age, AND
2. Alternate etiologies have been considered and ruled out when possible (e.g., head trauma, toxic exposures, stroke, infections, autoimmune conditions, metabolic conditions, tumors, prenatal injury), AND
3. Clinical presentation does not fit a well-described syndrome for which more targeted testing is available.

Background:

Epilepsy is a neurological disorder that causes recurrent, unprovoked seizures. Epilepsy is one of the most common neurological conditions, affecting 1.2% of the United States population - approximately 3 million adults and 470,000 children.[1] While the cause of epilepsy is unknown in approximately 50% of cases, it can be caused by genetic factors, head trauma, structural brain abnormalities, stroke, infections, autoimmune conditions, metabolic conditions, tumors, or prenatal injury.[2] It is estimated that 30% of all epilepsies have a genetic cause.[3] Patients with unexplained epilepsy with onset at any age should receive genetic testing.

Treatment

- Treatment for epilepsy differs based on the patient's diagnosis, underlying causes, and treatment response. Treatment may include antiepileptic medications, brain surgery, radiosurgery, neurostimulation, laser interstitial thermal therapy, and/or a ketogenic diet.

Etiology and Diagnosis

- Causes of epilepsy can be assessed by electroencephalogram (EEG), magnetic resonance imaging (MRI), laboratory testing (for infection, autoimmune conditions, metabolic conditions, and toxic exposures), clinical evaluation, and genetic testing.[4]
- Genetic causes of epilepsy can be assessed by chromosomal microarrays, multi-gene panels, exome sequencing, and genome sequencing. A genetic diagnosis is made in 12% to 49% of epilepsy cases across several studies.[5–10]
- Hundreds of genes have been associated with epilepsy across the lifespan of individuals (ranging from early-onset infantile epilepsy to adult-onset epilepsy). Relatively common genes that have actionable results include *ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2,* and *ZEB2*.[11]
- Epilepsy has high genetic heterogeneity and considerable phenotypic overlap between epilepsy conditions. It is not uncommon for a patient with clinical features fitting a certain epilepsy condition to have a genetic diagnosis in a gene not traditionally associated with that condition.

Utility of Genetic Diagnoses

- A precise diagnosis can lead to more effective treatments and help identify, treat, and/or prevent co-occurring medical conditions. [5,22]

- A genetic diagnosis changed treatment in 12-80% of epilepsy patients including avoiding, stopping, or initiating specific anti-seizure medication, dietary treatment, epilepsy surgical decisions, and initiation of palliative care in several studies.[5,10,12,13]
- The most common treatment changes include the addition of a new medication (21.7%), initiating taking medication (14.2%), referral to an appropriate specialist (13.4%), monitoring for subclinical or extra-neurological features (12.6%), and medication cessation (11.7%)[12]
- A genetic diagnosis informs recurrence risk estimations used in family planning.[5,12–14]
- A genetic diagnosis ends diagnostic odysseys that burden families, providers, and payers.[15]A diagnosis was reached 1-8 years earlier in patients who received genetic testing by multi-gene panels or exome sequencing.[8,15]

Characteristics of Genetic Epilepsy

- Both focal and generalized epilepsy can have a genetic cause. Focal epilepsy involves abnormal activity in one area of the brain and can cause impaired awareness or loss of consciousness. Generalized epilepsy involves all areas of the brain and includes absence seizures, tonic seizures, atonic seizures, clonic seizures, myoclonic seizures, and tonic-clonic seizures.[2] A genetic cause was identified in 15.8% of patients with focal epilepsy, in 24.3% of patients with generalized epilepsy, and in 24.7% of patients with both generalized and focal epilepsy.[6]
- Earlier age of seizure onset increases the likelihood of a genetic cause.
    - The diagnostic yield of exome sequencing was 42.9% in patients with seizure onset within the first month of life, 36.3% in patients with seizure onset within the first year of life, 38.5% for onset between 1-10 years, 18.2% for onset between 10-18 years, and 20% with onset after 18 years.[17]
    - While the patient's age at seizure onset affects the likelihood of a genetic cause, the patient's age at the time of testing does not.[17]
- Comorbidities including intellectual disability, developmental delay, autism spectrum disorder, and/or encephalopathy increase the likelihood of a genetic cause for epilepsy.[5,6,9,10,15,17]
- Drug-resistant epilepsy is more likely to have a genetic cause.[15]
- A family history of epilepsy increases the chance of identifying a genetic cause, however, a lack of family history does not rule out a genetic cause. De novo variants were identified in 33.7% of patients with epileptic encephalopathies[17], and both de novo and recessive variants have been noted as significant causes of epilepsy.[15,17]

- Some of the most common genetic causes of epilepsy are summarized below. This is not an exhaustive list due to the significant genetic and phenotypic heterogeneity in epilepsy. There is also considerable genetic and phenotypic overlap between conditions.
    - **Benign Familial Epilepsy**
        - Characterized by cluster seizures and focal motor seizures that evolve to grand mal seizures. EEG is normal. Age of onset is within the first few months of life with remission by age 3.
        - Caused by variants in *PRRT2, SCN2A*, and *SCN8A* (Benign Familial Infantile Epilepsy), *KCNQ2* and *KCNQ3* (Benign Familial Neonatal Epilepsy), *SCN2A* (Benign Familial Neonatal-Infantile Epilepsy). Inheritance pattern is autosomal dominant.
    - **Genetic Epilepsy with Febrile Seizures Plus (GEFS+)**
        - A spectrum of conditions with a combination of febrile, absence, myoclonic, and atonic seizures. EEG shows a normal background with generalized discharges. Age of onset is after 6 months of life with remission by age 5 or early adolescence.
        - Caused by variants in *SCN1A, SCN1B, GABRG2, STX1B* and *SCN9A*. Inheritance patterns include autosomal dominant and autosomal recessive.
    - **Early Infantile Epileptic Encephalopathy,** also known as **Ohtahara Syndrome**
        - Characterized by a wide spectrum of seizure types, most commonly focal or generalized tonic seizures or clustered tonic spasms (as many as hundreds per day). EEG shows a burst-suppression pattern. Most individuals have intellectual disability, hypotonia, or spastic quadriplegia. Age of onset is within the first 3 months of life and is lethal in infancy or severely progressive to West Syndrome or Lennox-Gastaut Syndrome in childhood.
        - Caused by variants in *STXBP1* (30%), *KCNQ2* (20%), *SCN2A* (10%), and at least 12 other genes including *SLC25A22*, *CDKL5*, and *ARX*. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
    - **Early Myoclonic Encephalopathy**
        - Characterized by focal myoclonic seizures, and isolated or clustered tonic spasms. EEG shows a burst-suppression pattern that can be more distinct during sleep. Prognosis is

poor with high mortality and morbidity. Age of onset is within the first 3 months of life.
    - Caused by variants in *SETBP, SIK1, SLC25A22, PIGA*, and *ERBB4*. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Infantile Spasms Syndrome, including West Syndrome**
    - Characterized by infantile spasms, developmental delay, and regression. EEG shows hypsarrhythmia. May progress to Lennox-Gastaut Syndrome or other seizure types. Age of onset is 2-12 months, usually around 6 months.
    - Caused by variants in *CDKL5* (10%), *STXBP1* (2%), and at least 46 other genes. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Dravet Syndrome and Dravet-like Phenotypes**
    - Characterized by prolonged hemiconvulsive or generalized febrile seizures for the first year, followed by intractable afebrile seizures, frequent status epilepticus, developmental delay, and possible regression. EEG is normal for the first 1-2 years, then shows generalized and multiform epileptiform abnormalities. Age of onset is 5-16 months, usually around 5-8 months.
    - Caused by variants in *SCN1A* (90%) and at least 12 other genes including *SCN1B, SCN9A, STXBP1, PCDH19, HCN1, GABRA1,* and *CHD2*. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)**
    - Characterized by focal seizures that migrate between cerebral hemispheres, severe-to-profound developmental delay, and often regression. EEG can be normal, show multifocal spikes with slow background activity, or show a burst-suppression pattern. Age of onset is within the first 6 months of life.
    - Caused by variants in *KCNT1* (27%), *SCN2A* (7-25%), and at least 21 other genes. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Lennox-Gastaut Syndrome**
    - Characterized by focal, tonic, atonic, myoclonic, absence, or generalized tonic-clonic seizures, spasms, or nonconvulsive status epilepticus, developmental delay, and cognitive impairment. EEG shows a slow spike-and-wave pattern. Age of onset is 1-8 years, usually between 3-5 years, with rare adult onset.

- Caused by variants in *ALG13, CACNA1A, CDKL5, CHD2, DNM1, FLNA, GABRB3, GRIN2B, HNPRNU, HNRNPH1, IQSEC1, IQSEC2, KCNQ3, MTOR, SCN1A, SCN2A, SCN8A*, and *STXBP1*. While most variants are de novo, the inheritance pattern is autosomal dominant.

- **Epilepsy-Aphasia Spectrum,** including **Landau-Kleffner Syndrome, Epileptic Encephalopathy with Continuous Spike-Wave Discharges in Slow Wave Sleep,** and **Atypical Benign Rolandic Epilepsy**
  - Characterized by language impairment, rolandic seizures, focal seizures, atonic seizures, epileptic encephalopathy, mild to severe intellectual disability, and normal to severe developmental delay often with regression. EEG shows a continuous spike-and-wave during slow-wave sleep pattern or centrotemporal spikes that synchronize and increase during sleep. Age of onset is 3-7 years with remission by mid-adolescence.
  - Caused by variants in *GRIN2A* (10-20%). Inheritance pattern is autosomal dominant.
- **Childhood Absence Epilepsy**
  - Characterized by brief, frequent absence seizures. EEG shows an asynchronous, bilateral spike-and-wave pattern. Age of onset is 3-8 years, usually between 5-7 years.
  - Caused by variants in *GABRA1, GABRB3, GABRG2, JRK,* and *CACNA1H*. Inheritance patterns include autosomal dominant and multifactorial.
- **Juvenile Myoclonic Epilepsy**
  - Characterized by myoclonic jerks or seizures, generalized tonic-clonic seizures, and absence seizures. EEG shows a 3-6 Hz generalized polyspike and wave discharge. Age of onset is 12-18 years.
  - Caused by *CACNB4, EFHC1, GABRA1,* and *CILK1*. Inheritance patterns include autosomal dominant, autosomal recessive, and multifactorial.
- **Familial Temporal Lobe Epilepsy**
  - Characterized by seizures involving one or both temporal lobes, including focal aware seizures, focal impaired awareness seizures, tonic-clonic jerking, and rarely, status epilepticus. EEG shows spikes or sharp waves in the front of the temporal lobe. Age of onset is adolescence or early adulthood.

        - Caused by variants in *GAL, CPA6, RELN, LGI1, DEPDC5*, and *MICAL1*. Inheritance patterns include autosomal dominant and multifactorial.
    - **Syndromes with epilepsy in addition to other clinical features**
        - The following conditions have clinical features in addition to unexplained epilepsy, and should be included in panel, exome, and genome testing for epilepsy. Targeted testing may be more appropriate for these conditions if there is strong clinical suspicion due to the presence of characteristic clinical features.
            - Glucose Transporter Type 1 Deficiency Syndrome (*SLC2A1*)
            - Angelman Syndrome (*UBE3A*, 15q11-q13 deletion, or uniparental disomy of chromosome 15)
            - Chromosome 1p36 Deletion Syndrome (1p36 deletion)
            - Miller-Dieker Syndrome (17p13.3 deletion)
            - Rett Syndrome (*MECP2*)
            - Ring chromosome 20 (breakage of fusion of chromosome 20)
            - Tuberous Sclerosis Complex (*TSC1, TSC2*)
            - Smith Kingsmore Syndrome (*MTOR*)
            - Focal cortical dysplasia (*MTOR, PIK3CA, PTEN, DEPDC5, NPRL2, NPRL3*)

Technical Information:

Genome sequencing is the most effective first-line test for diagnosing genetic epilepsy. If genome sequencing is not available, exome sequencing and multi-gene panels are also appropriate first-line tests. Due to significant genetic heterogeneity and large phenotypic overlap, single-gene testing is not recommended unless there is a known familial variant, or the patient has additional clinical features distinctive of a particular genetic condition.

- The investigation and diagnosis of patients with epilepsy necessitates a combination of analyses, including EEG, imaging techniques (e.g., MRI, CT), laboratory testing (for infection, autoimmune conditions, metabolic conditions, and toxic exposures), genetic testing, and clinical evaluation.[4]
- Genetic testing is not indicated for patients with epilepsy that can be explained by known etiologies such as trauma, toxic exposures, infection, or other underlying conditions.

- Exome/genome sequencing
  - Next-generation sequencing (NGS) is used to assess (1) the coding DNA sequence of all genes, also known as the exome, or (2) both coding and non-coding DNA sequences, also known as the genome.
  - Exome/genome sequencing has higher diagnostic yield and efficiency compared to multi-gene panel sequencing.[5,18] Exome/genome sequencing can identify variants that may be missed by multi-gene panel testing due to increased coverage of the genome.
  - Genome sequencing has higher diagnostic yield and efficiency compared to exome sequencing.[19] Genome sequencing has more uniform coverage and can identify variants that may be missed by exome sequencing, including deep intronic SNVs, small CNVs, and SNVs in noncoding RNA.[20]
  - A meta-analysis of 40 studies utilizing genetic testing in cohorts ascertained for epilepsy showed that the diagnostic yield of genome sequencing was 48%, exome sequencing was 24%, gene panels was 19%, and chromosomal microarray was 9%.[5]
  - Exome/genome sequencing may identify secondary findings that are variants associated with diseases other than epilepsy. The American College of Medical Genetics (ACMG) has identified a list of genes with clinically actionable findings that are recommended to report as secondary findings and is updated periodically.[21]
- Multi-gene panel testing
  - NGS is used to assess the coding DNA sequence of a select number of genes.
  - The diagnostic yield of multi-gene panels increases as the number of genes included on the panel increases.[5]
  - Multi-gene panel testing for epilepsy should include but not be limited to at least the following genes: *ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2,* and *ZEB2*.[11]
  - Multi-gene panel tests vary in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).
  - Under certain circumstances, technologies used in multi-gene panel testing may fail to identify variants that might be identifiable through single-gene testing. If high clinical suspicion remains for a particular syndrome after negative multi-gene

panel test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted. Ideal sample type may also be considered due to the occurrence of brain tissue-specific mosaicism in epilepsy.

- Single-gene testing
    - Due to significant genetic heterogeneity and large phenotypic overlap, single-gene testing is not recommended for epilepsy unless there is a known familial variant, or the patient has additional clinical features distinctive of a particular genetic condition.

Guidelines and Evidence:

There are several relevant guidelines that support genetic testing for epilepsy by genome/exome sequencing, or multi-gene panel conducted by qualified healthcare providers, including test selection, ordering, interpretation, and pre- and post-test counseling.

- The National Society of Genetic Counselors published a 2022 practice guideline[22] that was endorsed by the American Epilepsy Society and provides the following two recommendations:
    - "Genetic testing is strongly recommended for all individuals with unexplained epilepsy, without limitation of age, with exome/genome sequencing and/or a multi-gene panel (>25 genes) as first-tier testing followed by chromosomal microarray, with exome/genome sequencing conditionally recommended over multi-gene panel."
    - "It is strongly recommended that genetic tests be selected, ordered, and interpreted by a qualified healthcare provider in the setting of appropriate pre-test and post-test genetic counseling."
- The International League Against Epilepsy published "Current practice in diagnostic genetic testing of the epilepsies" in 2022[23], updated from their 2015 recommendations for the management of infantile seizures.[24]
    - "Epilepsies with a monogenic cause, especially severe epilepsies with early onset, are currently the primary target for diagnostic genetic testing.
    - "For most genetic epilepsy disorders, genetic heterogeneity has been described, i.e., variants in different genes can cause the same disorder."
    - "Genetic testing, as well as genetic counseling before and after testing, should be performed by appropriately qualified and trained professionals."

  - "In most cases, ES or GS (including CNV analysis) is currently recommended as first-line testing."
  - "Periodical genetic re-evaluation should be undertaken for individuals with suspected genetic epilepsy without a molecular genetic diagnosis. This includes re-analysis of previously acquired sequencing data and consideration of further testing based on new or evolving clinical information and availability of novel testing strategies."
  - "We recommend genetic testing in the following conditions (provided no other clear cause has been identified):
    - Severe childhood-onset epilepsies, particularly DEEs.
    - Epilepsy with intellectual disability, autism, and/or other comorbidities.
    - Progressive myoclonus epilepsies and progressive phenotypes generally.
    - Non-acquired focal epilepsies in specific familial syndromes."
  - "Genetic testing can be considered (rather than recommended) in the following conditions:
    - Non-acquired focal, pharmacoresistant epilepsies in the setting of presurgical evaluation.
    - Epilepsy in the setting of malformations of cortical development (which may require DNA from brain tissue to be tested in parallel with DNA from another tissue source, e.g., blood or saliva)."
- The National Association of Epilepsy Centers published a guideline for specialized epilepsy centers in 2024[25] covering many services including genetic testing:
  - "Recommendation: All epilepsy centers should use genetic testing as part of the diagnostic workup for patients with intractable epilepsy of unknown etiology"
  - "Recommendation: All epilepsy centers should have an established protocol to identify those patients who would most likely benefit from genetic testing, even if their seizures are well controlled."
  - "Recommendation: All epilepsy centers should offer genetic counseling from a certified genetic counselor either within the program or by referral."
  - "No consensus exists currently on the optimal genetic testing strategy."

- Karlin *et al.* published a 2024 practice guideline[26] for testing and referrals to specialized epilepsy genetics centers in *Current Problems in Pediatric and Adolescent Health Care*:
    - "Given the rapid advancements in the field of epilepsy genetics, the challenge in interpreting genetic testing results, and the potential for impact with early diagnosis and treatment, we propose that individuals with unexplained epilepsy and with congenital lesional epilepsy be referred to one of several specialized epilepsy genetics centers across the United States."
    - "For patients who are admitted with refractory seizures, whether neonatal or later onset, we recommend early consultation with an Epilepsy Genetics team (if available) or with Genetics to facilitate genetic testing as soon as possible. This should be done in conjunction with other diagnostic tests such as neuroimaging, electroencephalogram, and laboratory testing as indicated. Certain laboratories can send rapid WES, which can yield the quickest results possible, which may significantly alter the course of treatment."
    - "In the outpatient setting, selection of the most appropriate genetic testing strategy is important for improving diagnostic clarity and maximizing the psychosocial benefit of testing for the patient and family. Within community neurology practices, this is most frequently in the form of gene panels, with the opportunity to refer to a specialized center in more complex cases."

Exclusions and Other Considerations:

Exclusions:

- Genetic testing for epilepsy is considered not medically necessary in individuals who do not meet the above criteria.
- Comprehensive genetic testing for epilepsy is not appropriate for individuals with a known familial variant unless targeted genetic testing has been performed and is negative.
- Genetic testing is considered experimental/investigational for screening for genetic epilepsy in asymptomatic individuals.

Other Considerations:

- Ideal sample type should be considered based on the clinical presentation (e.g., if mosaicism is suspected, consider testing brain tissue after focal resection).
- While exome and genome sequencing are similar diagnostic tools in the evaluation of individuals with epilepsy, there are clear technical

advantages of genome sequencing that support increased diagnostic yield and efficiencies. As such, if given a choice, genome sequencing is the preferred diagnostic test in individuals who meet the above criteria. Criteria for genome sequencing can be found in the Genomic Sequencing for Rare Disease policy.

- Exome/genome sequencing is preferred over multi-gene panel testing due to increased diagnostic yield. If multi-gene panels are used, larger panels are preferred due to increased diagnostic yield. Panels should include at least 24 genes: *ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2,* and *ZEB2*.[11]
- Pre- and post-test counseling by an appropriate provider, such as an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor, is strongly recommended.
- Trio samples are preferred for exome/genome sequencing. Use of family trio samples in genomic sequencing analysis helps reduce the time to diagnosis and the rate of uncertain findings, improves the clinical sensitivity and efficiency with regard to the interpretation of clinically novel genes, and increases the diagnostic yield of exome/genome sequencing.
- Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. Re-analysis could be considered prior to additional genomic sequencing, particularly if there have been additional clinical manifestations that broaden the clinical phenotype assessed during the original exome/genome sequencing analysis, and/or there has been a change in the family history that expands the clinical picture, such as the birth or diagnosis of a similarly affected first-degree relative.
- Targeted variant testing is the most appropriate test for a known familial variant in pre-symptomatic individuals.
- Genetic testing has rapidly advanced over the last 20 years. Exceptions to once per lifetime testing may be considered if an individual has previously had negative genetic testing, but technical advances in testing demonstrate significant advantages that would support a medical need to retest or re-analyze data from previous testing.
- Genetic testing for epilepsy in the setting of prenatal genetic diagnosis or screening is not addressed in this policy.

- Rapid genome sequencing, defined as return of preliminary positive results in <7 days and final report in <14 days, may be indicated for critically ill individuals.
- Criteria for rapid genome sequencing can be found in the Rapid Genome Sequencing policy.

CPT Codes:

Procedure(s) addressed by this policy:	Procedure Code(s)
Epilepsy genomic sequence analysis panel	81419
Unlisted molecular pathology procedure	81479
Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81415
Sequence analysis, each comparator exome (e.g., parent(s), sibling(s))	81416
Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81425
Sequence analysis, each comparator genome (e.g., parent(s), sibling(s))	81426
Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis (e.g., RCIGM Rapid Whole Genome Sequencing; Rady Children's Institute for Genomic Medicine)	0094U
Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	0212U
Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (e.g., parent, sibling)	0213U
Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence	0214U

analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	
Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (e.g., parent, sibling)	0215U

References:

1. Epilepsy data and statistics. *CDC* (2024).
2. Epilepsy - symptoms and causes. *Mayo Clinic* https://www.mayoclinic.org/diseases-conditions/epilepsy/symptoms-causes/syc 20350093 (2023).
3. International League Against Epilepsy Consortium on Complex Epilepsies. Electronic address: epilepsy-austin@unimelb.edu.au. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. *Lancet Neurol* 13, 893–903 (2014).
4. Barcia Aguilar, C., Sánchez Fernández, I. & Loddenkemper, T. Status Epilepticus-Work-Up and Management in Children. *Semin Neurol* 40, 661–674 (2020).
5. Sheidley, B. R. *et al.* Genetic testing for the epilepsies: A systematic review. *Epilepsia* 63, 375–387 (2022).
6. Stefanski, A. *et al.* Clinical sequencing yield in epilepsy, autism spectrum disorder, and intellectual disability: A systematic review and meta-analysis. *Epilepsia* 62, 143–151 (2021).
7. Sánchez Fernández, I., Loddenkemper, T., Gaínza-Lein, M., Sheidley, B. R. & Poduri, A. Diagnostic yield of genetic tests in epilepsy: A meta-analysis and cost-effectiveness study. *Neurology* 92, e418–e428 (2019).
8. Swartwood, S. M. *et al.* Early genetic testing in pediatric epilepsy: Diagnostic and cost implications. *Epilepsia Open* 9, 439–444 (2024).
9. Burk, K. C. *et al.* Diagnostic Yield of Epilepsy-Genes Sequencing and Chromosomal Microarray in Pediatric Epilepsy. *Pediatr Neurol* 150, 50–56 (2024).

10. Koh, H. Y. *et al.* Utility of Exome Sequencing for Diagnosis in Unexplained Pediatric-Onset Epilepsy. *JAMA Netw Open* 6, e2324380 (2023).
11. American Medical Association. *CPT Professional 2024*.
12. McKnight, D. *et al.* Genetic Testing to Inform Epilepsy Treatment Management From an International Study of Clinical Practice. *JAMA Neurol* 79, 1267–1276 (2022).
13. D'Gama, A. M. *et al.* Evaluation of the feasibility, diagnostic yield, and clinical utility of rapid genome sequencing in infantile epilepsy (Gene-STEPS): an international, multicentre, pilot cohort study. *Lancet Neurol* 22, 812–825 (2023).
14. Lindy, A. S. *et al.* Diagnostic outcomes for genetic testing of 70 genes in 8565 patients with epilepsy and neurodevelopmental disorders. *Epilepsia* 59, 1062–1071 (2018).
15. Symonds, J. D. & McTague, A. Epilepsy and developmental disorders: Next generation sequencing in the clinic. *Eur J Paediatr Neurol* 24, 15–23 (2020).
16. McKnight, D. *et al.* Multigene Panel Testing in a Large Cohort of Adults With Epilepsy: Diagnostic Yield and Clinically Actionable Genetic Findings. *Neurol Genet* 8, e650 (2022).
17. Helbig, K. L. *et al.* Diagnostic exome sequencing provides a molecular diagnosis for a significant proportion of patients with epilepsy. *Genet Med* 18, 898–905 (2016).
18. Regier, D. A. *et al.* Real-world diagnostic outcomes and cost-effectiveness of genome-wide sequencing for developmental and seizure disorders: Evidence from Canada. *Genet Med* 26, 101069 (2024).
19. Marwaha, S., Knowles, J. W. & Ashley, E. A. A guide for the diagnosis of rare and undiagnosed disease: beyond the exome. *Genome Med* 14, 23 (2022).
20. Wang, H. *et al.* Optimized trio genome sequencing (OTGS) as a first-tier genetic test in critically ill infants: practice in China. *Hum Genet* 139, 473–482 (2020).
21. Miller, D. T. *et al.* ACMG SF v3.1 list for reporting of secondary findings in clinical exome and genome sequencing: A policy statement of the American College of Medical Genetics and Genomics (ACMG). *Genet Med* 24, 1407–1414 (2022).
22. Smith, L. *et al.* Genetic testing and counseling for the unexplained epilepsies: An evidence-based practice guideline of the National Society of Genetic Counselors. *J Genet Couns* 32, 266–280 (2023).
23. Krey, I. *et al.* Current practice in diagnostic genetic testing of the epilepsies. *Epileptic Disord* 24, 765–786 (2022).

24. Wilmshurst, J. M. *et al.* Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. *Epilepsia* 56, 1185–97 (2015).
25. Lado, F. A. *et al.* Guidelines for Specialized Epilepsy Centers: Executive Summary of the Report of the National Association of Epilepsy Centers Guideline Panel. *Neurology* 102, e208087 (2024).
26. Karlin, A., Ruggiero, S. & Fitzgerald, M. Genetic testing for unexplained epilepsy: A review of diagnostic approach, benefits, and referral algorithm. *Curr Probl Pediatr Adolesc Health Care* 54, 101579 (2024).

Update details:

- Added Executive Summary section
- Added most common treatment changes to the Utility of Genetic Diagnoses in the Background section
- Edited the Guidelines and Evidence section
    - Added guidelines from The National Association of Epilepsy Centers, 2024 and Karlin *et al*., 2024
    - Replaced the 2015 International League Against Epilepsy guidelines with updated 2022 guidelines
    - Removed published criteria created by a Genetic Testing Advisory Committee in Ontario, Canada, 2018
- Added References after updated literature search
    - Reiger *et al.* 2024
    - Swartwood *et al.* 2024
    - Burk *et al.* 2024
    - D'Gama *et al.* 2023
    - Koh *et al.* 2023
    - McKnight *et al.* 2022