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Genetic Testing for Epilepsy

Policy Number: AHS – M2075 – Genetic Testing for Epilepsy	Prior Policy Name and Number, as applicable:
Policy Revision Date: 03/09/2022	

I. Policy Description

Epilepsy is a group of disorders characterized by recurrent, unprovoked seizures due to abnormal, synchronized neuronal firing in the brain that can be distinguished by seizure type, age of onset, developmental status, co-morbid features and etiology (Berg et al., 2010; Myers & Mefford, 2015).

II. Related Policies

Policy Number	Policy Title
AHS-M2145	General Genetic Testing, Germline Disorders
AHS-M2146	General Genetic Testing, Somatic Disorders
AHS-M2085	Genetic Testing of Mitochondrial Disorders

III. Indications and/or Limitations of Coverage

Application of coverage criteria is dependent upon an individual's benefit coverage at the time of the request. Specifications pertaining to Medicare and Medicaid can be found in Section VII of this policy document.

1) Genetic testing for mutations associated with infantile- and early childhood-onset epilepsy syndromes in individuals with infantile- and early-childhood-onset epilepsy syndromes in which epilepsy is the core clinical symptom **MEETS COVERAGE CRITERIA** if positive test results may:

   a) Lead to changes in medication management; AND/OR

   b) Lead to changes in diagnostic testing such that alternative potentially invasive tests are avoided; AND/OR

   c) Lead to changes in reproductive decision making.

2) Current mutation testing **MEETS COVERAGE CRITERIA** in any of the following clinical situations:

   a) Sodium voltage-gated channel alpha subunit 1 *(SCN1A)* testing in assessment for SCN1A-Related Seizure Disorders

   b) Aldehyde dehydrogenase 7 family member A1 *(ALDH7A1)* testing in assessment of Pyridoxine-Related Epilepsy

   c) Solute carrier family 2 member 1 *(SLC2A1)* testing in assessment of Glucose Transporter Type 1 Deficiency Syndrome

   d) Protocadherin 19 *(PCDH19)* testing for evaluation of epilepsy female-restricted with mental retardation (EFMR)

   e) Sodium voltage-gated channel alpha subunit 8 *(SCN8A)* testing in assessment for SCN8A-related epileptic encephalopathy

   f) Potassium voltage-gated channel subfamily Q member 2 *(KCNQ2)* testing in assessment for KCNQ2-related epileptic encephalopathy

   g) Potassium sodium-activated channel subfamily T member 1 *(KCNT1)* testing in assessment for KCNT1-related migrating partial epilepsy of infancy

   h) Glutamate ionotropic receptor NMDA type subunit 2A *(GRIN2A)* testing in assessment for GRIN2A-related epileptic encephalopathy

   i) TSC complex subunit 1 *(TSC1)* and *TSC2* testing for Tuberous sclerosis complex-related epilepsy

   j) Biotinidase *(BTD)* testing in assessment for biotinidase deficiency-related epilepsy

   k) Folate receptor 1 *(FOLR1)* testing in assessment for cerebral folate deficiency-related epilepsy

   l) Solute carrier family 6 member 8 *(SLC6A8)*, glycine amidinotransferase *(GATM)*, and guanidinoacetate N-methyltransferase *(GAMT)* testing for epilepsy due to creatine deficiency syndromes

   m) *P*hosphoglycerate dehydrogenase *(PHGDH)*, phosphoserine aminotransferase 1 *(PSAT1)*, and phosphoserine phosphatase *(PSPH)* testing for epilepsy due to serine biosynthesis defects

The following does not meet coverage criteria due to a lack of available published scientific literature confirming that the test(s) is/are required and beneficial for the diagnosis and treatment of a patient's illness.

3) Genetic testing for epilepsy **DOES NOT MEET COVERAGE CRITERIA** in all other clinical situations not described above and for any other mutations not listed above.

Note: For 5 or more gene tests being run on the same platform, such as multi-gene panel next generation sequencing, please refer to AHS-R2162 Reimbursement Policy.

IV. Table of Terminology

Term	Definition
AAN	American Academy of Neurology
ALDH7A1	*Aldehyde dehydrogenase 7 family member A1*
AMA	Antiseizure medication
ANK2	*Ankyrin 2*
ASD	Autism Spectrum Disorders
BTD	*Biotinidase*
CACNA1A	*Calcium voltage-gated channel subunit alpha 1A*
CACNA1AE	*Calcium voltage-gated channel subunit alpha 1AE*
CACNA1D	*Calcium voltage-gated channel subunit alpha 1D*
CACNA1H	*Calcium voltage-gated channel subunit alpha 1H*
CACNA2D3	*Calcium voltage-gated channel subunit alpha 1A*
CDKL5	Calcium voltage-gated channel subunit alpha2delta3
CGH	Comparative genomic hybridization
CHD2	*Chromodomain helicase DNA binding protein 2*
CLIA ’88	Clinical Laboratory Improvement Amendments of 1988
CMA	Chromosomal Microarray Analysis
CMS	Centers for Medicare and Medicaid
CNS	Child Neurology Society
CNV	Copy number variant
DEE	Developmental and epileptic encephalopathy
DLG4	*Discs large homolog 4*
DS	Dravet syndrome
EE	Epileptic encephalopathy
EEG	Electroencephalography
EFMR	Epilepsy Female-Restricted with Mental Retardation
EFNS	European Federation of Neurological Societies
EP	Epileptic panels
FGF12	*Fibroblast growth factor 12*
FOLR1	*Folate receptor 1*
GABRA1	*Gamma-aminobutyric acid type A receptor alpha1*
GABRG2	*Gamma-aminobutyric acid type A receptor gamma2*
GAMT	*Guanidinoacetate n-methyltransferase*
GATM	*Glycine amidinotransferase*
GGE	Genetic generalized epilepsy
Glut1DS	Glucose transporter 1 deficiency syndrome
GRIA2	*Glutamate ionotropic receptor AMPA type subunit 2*
GRIN2A	*Glutamate ionotropic receptor NMDA type subunit 2a*
GRIN2B	*Glutamate ionotropic receptor NMDA type subunit 2b*
GS	Genome sequencing

GTAC	Genetic Testing Advisory Committee
HNRNPU	*Heterogeneous nuclear ribonucleoprotein U*
IC-CODE	International Classification of Cognitive Disorders in Epilepsy
ID	Intellectual disability
ILAE	International League Against Epilepsy
KANSL1	*KAT8 regulatory NSL complex subunit 1*
KB	Kilo-base pair
KCNC1	*Potassium voltage-gated channel subfamily C member 1*
KCNQ2	*Potassium voltage-gated channel subfamily Q member 2*
KCNT1	*Potassium sodium-activated channel subfamily T member 1*
KD	Ketogenic diet
LDTs	Laboratory-developed tests
MECP2	*Methyl-CpG binding protein 2*
MGP	Multigene panel
mTOR	Mammalian target of rapamycin
NDD	Neurodevelopmental disorders
NGS	Next generation sequencing
NICE	National Institute for Health and Care Excellence
PCDH19	*Protocadherin 19*
PHGDH	*Phosphoglycerate dehydrogenase*
PNPO	*Pyridoxamine 5'-phosphate oxidase*
PRRT2	Proline-rich transmembrane protein 2
PSAT1	*Phosphoserine aminotransferase 1*
PSPH	*Phosphoserine phosphatase*
PURA	*Pur-alpha*
SCN1A	*Sodium voltage-gated channel alpha subunit 1*
SCN2A	*Sodium voltage-gated channel type 2 alpha subunit*
SCN8A	*Sodium voltage-gated channel type 8 alpha subunit*
SE	Status epilepticus
SIGN	Scottish Intercollegiate Guidelines Network
SLC2A1	*Solute carrier family 2 member 1*
SLC6A1	*Solute carrier family 6 member 1*
SLC6A8	*Solute carrier family 6 member 8*
SMEI	Severe myoclonic epilepsy of infancy
STX1B	*Syntaxin 1B*
STXBP1	Syntaxin-binding protein 1
TCF4	Transcription factor 4
TSC	Tuberous sclerosis complex
TSC1	Tuberous sclerosis complex 1
TSC2	Tuberous sclerosis complex 2

UBE3A	*Ubiquitin protein ligase E3A*
WES	Whole exome sequencing
WGS	Whole genome sequencing
YWHAG	*Tyrosine 3-monooxygenase/tryptophan 5-monooxygenase activation protein gamma*

V. Scientific Background

Epilepsy, defined as having two or more unprovoked seizures, is a common neurologic disorder, affecting an estimated 3.4 million people in the United States (England, Liverman, Schultz, & Strawbridge, 2012; Zack & Kobau, 2017). The biological and genetic mechanisms that disturb the balance between excitatory and inhibitory neuronal circuits to result in epilepsy are extremely heterogeneous (Ottman et al., 2010; Williams & Battaglia, 2013). Approximately 20–30% of epilepsy diagnoses can be attributed to other primary conditions, such as stroke, tumor or head injury, but the remaining 70–80% of cases are believed to be due to one or more genetic factors (Hildebrand et al., 2013; Myers & Mefford, 2015).

The epilepsies can be classified by multiple approaches. Clinically, they can be broadly grouped into three classes: genetic generalized epilepsy (GGE), focal epilepsy, and epileptic encephalopathy (EE). GGE is characterized by generalized seizures that involve both sides of the brain, start in childhood or adolescence, are usually associated with normal development and intellect, and include juvenile myoclonic epilepsy and childhood absence epilepsy, among others. Focal seizures originate in one hemisphere of the brain and include temporal lobe epilepsy and autosomal dominant nocturnal frontal lobe epilepsy. EE are severe, early onset conditions characterized by refractory seizures, developmental delay or regression associated with ongoing epileptic activity, and generally poor prognosis such as Dravet, Ohtahara and West syndromes. Epilepsy is often a comorbid condition with intellectual disability (ID), autism, or schizophrenia, and may be a feature of many metabolic conditions and genetic syndromes (Myers & Mefford, 2015).

The International League Against Epilepsy (ILAE) classifies epilepsies at three levels: seizure types, epilepsy types, and epilepsy syndromes. The classification starts with seizure type as the least specific, epilepsy type as more specific, and epilepsy syndromes as the most specific classification. Seizure type is based on onset, of which there are three categories: focal, generalized, and unknown. The second category, epilepsy type, is divided into four categories; focal, generalized, combined generalized & focal, and unknown. This level of classification typically requires electroencephalography (EEG) data. The "combined generalized & focal" group is new to the 2017 edition of the ILAE classification, and it was created to include patients with both types of seizures, such as patients with Dravet Syndrome. Finally, the "Unknown" category refers to a case where there is not enough information to determine the epilepsy type. This can occur for numerous reasons, such as the unavailability of an EEG. The third level of classification is "epilepsy syndromes". A syndrome refers to a cluster of features incorporating items such as seizure types, EEG results, and imaging results that tend to occur together. Other distinctive features, such as intellectual disability, may be a part of a syndrome (Scheffer et al., 2017).

Epilepsy is genetically heterogeneous, and extensive phenotypic heterogeneity has been observed even in many monogenic epilepsies. This heterogeneity makes testing each gene individually through Sanger sequencing impractical despite its status as the gold standard (Lemke et al., 2012). Mutations in ion channels, chromatin remodeling, transcriptional regulation, and regulation of the mammalian target of rapamycin (mTOR) protein have been implicated in the etiology of epilepsy (Moller et al., 2016).

Clinical Utility and Validity

The DNA sequencing methods have high analytic validity; the methods are well-established in laboratories. Sequencing bi-directionally has been evaluated at over 98% sensitivity (Stenhouse, Ellis, & Zuberi, 2013). Next generation sequencing (NGS) allows for parallel sequencing of any number of genes, thereby allowing for far superior testing of heterogenous conditions such as epilepsy. Since the number of new epilepsy genes continues to grow and the phenotypes associated with mutations in each gene are so variable, NGS is a desirable option to diagnose epilepsy patients (Mefford, 2015).

New test options have an increased yield of molecular diagnosis, particularly in patients with severe, early-onset epilepsies. For example, a study by Lemke et al. (2012) focused on targeted resequencing of 265 candidate genes, which identified mutations that were presumed to be pathogenic in 16 of 33 patients. Many of these patients had severe epilepsies associated with intellectual disability. This NGS method detected mutations that had been missed by the previous gold standard of Sanger sequencing (with at least one mutation missed due to artifacts from Sanger sequencing). Furthermore, the authors concluded that a patient with more than one possible gene responsible for their phenotype would benefit from this sequencing method compared to Sanger. The authors noted that NGS is only suited for conditions with at least one major gene effect and that whole exome sequencing (WES) would be a better option for more complex genetic conditions (Lemke et al., 2012).

In 2016, a gene panel targeting 46 epilepsy genes was used on 216 patients representing a wide spectrum of epilepsies with age of onset spanning from the neonatal period to adulthood. A presumed pathogenic variant was identified in 49 (23%) patients. The variants were found in 19 different genes including *SCN1A, STXBP1,* and *CDKL5.* Patients with neonatal-onset epilepsies had the highest rate of positive findings (57%). The overall yield for patients with EEs was 32%, compared to 17% among patients with generalized epilepsies and 16% in patients with focal or multifocal (Moller et al., 2016). Another study focusing on the diagnostic use of microarray was performed by Hrabik et al. (2015). Approximately 17.7% (26/147) of participants between the ages of birth to 23 years who were diagnosed with epilepsy and had a SNP microarray performed had an abnormal microarray as defined by laboratory guidelines (Hrabik et al., 2015). Gene panels and exome sequencing for clinical diagnostics provide better and less expensive options for testing and could be implemented early in the diagnostic process. Chromosome microarrays may be considered in severe cases and in GGE with co-morbid features (Myers & Mefford, 2015). Overall, sequencing of many genes at once may provide major benefits to those with epilepsy as epilepsy's genetic profile is widespread.

Copy number abnormalities also play an important role in patients with epilepsy. Of 973 patients who had chromosomal microarray (CMA) and ICD-9 codes for epilepsy or seizures, 805 patients

satisfied criteria for epilepsy. 437 copy number variants (CNVs) in 323 patients (1-4 per patient), including 185 (42%) deletions and 252 (58%) duplications were observed. Forty (9%) were confirmed de novo, 186 (43%) were inherited, and parental data were unavailable for 211 (48%). Because the diagnostic yield of CMA for epilepsy patients is similar to the yield in autism spectrum disorders (ASD) and in prenatal diagnosis (which published guidelines recommending testing with CMA), the authors recommended implementation of CMA in the evaluation of unexplained epilepsy (Olson et al., 2014).

Berg et al. (2017) conducted a prospective cohort study of 775 children with newly diagnosed epilepsy with an onset at less than 3 years of age to determine the role of genetic testing in the initial evaluation of early life epilepsies. 95 children had brain injury, and of the other 680, 327 underwent genetic testing, such as microarrays, WES, and gene panels. 132 (40.4%) children were found to have pathogenic variants. A total of 446 children were deemed to have an unknown etiology without genetic testing, and 180 of these children were tested. Pathogenic variants were found in 48 or 26.7% of the children, However, epilepsy gene-sequencing panels and whole-exome sequencing (WES) had substantially greater diagnostic yields than CMA. 28 of 96 or 29.2% were detected by epilepsy panels, 5 of 18 or 27.8% for WES, and 8 for 101 or 7.9% for CMA. Without a clinically identified cause, testing yields were greater than 15% and as high as 47% depending on patient subgroups. The authors concluded that broad genetic sequencing methods have high diagnostic yields in diagnosing early-life epilepsies regardless of clinical features. Sequencing tests should be incorporated into the initial evaluation of newly presenting early-life epilepsies and not just reserved for those with severe presentations (Berg et al., 2017). Gene panels including the most commonly mutated genes have a 10%-50% diagnostic rate (depending on the panel used and the population) although it is possible that a greater number of genes in the panel does not necessarily equate to a higher diagnostic rate. A 67 gene panel and a 265 gene panel were found to have nearly equivalent diagnostic rates; however, the study using the 67 gene panel only included nineteen patients (Dunn et al., 2018; Mefford, 2015). Exome sequencing has been evaluated at a 25% diagnostic rate (without a prior diagnosis), and whole-genome sequencing (WGS) has been evaluated at as high as 60% with smaller studies and known phenotypes. The weaker sequencing depth contributes to the difficulty of locating copy number variants, which are a significant cause of epilepsy-related conditions. Nonetheless, the authors conclude that WES and WGS will become part of the regularly used tools for clinicians once their cost decreases (Dunn et al., 2018).

Stosser et al. (2017) conducted a retrospective analysis of "893 probands with epilepsy who had an epilepsy panel or WES performed and were positive for a pathogenic or likely pathogenic variant in one of nine genes (*CDKL5*, *GABRA1*, *GABRG2*, *GRIN2B*, *KCNQ2*, *MECP2*, *PCDH19*, *SCN1A*, or *SCN2A*)," which found "mosaic pathogenic variants… at an overall frequency of 3.5% (95% CI, 2.4%-4.9%) in nine genes associated with epilepsy-related disorders…. Mosaicism was most common in the *CDKL5*, *PCDH19*, *SCN2A*, and *SCN1A* genes. Mosaicism was observed in *GABRA1*, *GABRG2*, and *GRIN2B*, which were not reported to have mosaicism prior to this study, and in *KCNQ2* and *MECP2*. Parental mosaicism was observed for pathogenic variants in multiple genes including *KCNQ2*, *MECP2*, *SCN1A*, and *SCN2A*." The authors concluded that patients with epilepsy who previously tested negative for pathogenic variants may benefit from an NGS test, which is superior at detecting mosaic variants. The authors also noted that targeted testing of parents of probands may use NGS to better assess risk and mosaicism (Stosser et al., 2017).

Some conditions have well-known mutations caused by a singular gene. For example, in Dravet syndrome, (DS, previously known as severe myoclonic epilepsy of infancy - SMEI) the occurrence of *SCN1A* mutations is 70%-80%. About 90% of these mutations are *de novo*. Truncating mutations have found to be more severe (earlier onset of symptoms, faster cognitive decline) compared to missense mutations. *PCDH19*-related epilepsy is a rare syndrome characterized by focal and/or generalized seizures, which are commonly fever-induced and in clusters. Previously referred to as epilepsy female-restricted with mental retardation (EFMR), *PCDH19*-related epilepsy occurs primarily in females and has an early onset. A mutation in *PCDH19* can cause both DS and *PCDH19*-related epilepsy as *PCDH19* is thought to account for 5% of patients with DS (Andrade & Nascimento, 2020). Another example is tuberous sclerosis complex (TSC); as many as 89% of cases have mutations in either the *TSC1* or *TSC2* gene (Randle, 2020). Other mutations include *KCNQ2* with EE, *SLC2A1* with glucose transporter deficiency syndrome, *PRRT2* with general infantile convulsions, and *ALDH7A1* and *PNPO* with severe early-onset epilepsy (Poduri, Sheidley, Shostak, & Ottman, 2014). Missense variants in *SLC32A1* can cause genetic epilepsy with febrile seizures plus (GEFS+) and idiopathic generalizes epilepsy (IGE) (Heron et al., 2021).

"Epilepsy-plus" patients tend to have highest yield for diagnostic testing; that is, patients with other symptoms such as autism in addition to their epilepsy. Still, even the diagnostic yield of these individuals only reached 50% with panel or exome sequencing (Poduri, 2017). The potential clinical utility of genetic testing for these syndromes is in avoiding further diagnostic testing, directing medication management, and assisting in reproductive decision making. Establishing the genetic basis of epilepsy in a given patient will help in making treatment decisions, genetic counseling, and more (Poduri et al., 2014). For instance, mutations in *ALDH7A1* or in the *PNPO* gene may lead to seizures not treated with typical antiepileptic drugs, but with pyridoxine (Falsaperla & Corsello, 2017). On the other hand, sodium channel agents may be avoided in patients with an *SCNA1* mutation. Genetic counseling revolving around topics such as recurrence or heritability risk for pregnancies or testing of relatives is also helpful, and proper care must be taken to ensure that the information is clearly explained to the patient and their family (Poduri et al., 2014).

Genetic testing for epilepsy could also be useful in diagnosing ASD. Peng, Zhou, and Wang (2021) discussed, in their research on developing a multiplex gene and phenotype network to identify shared genes between epilepsy and autism, that mutations in genes for subunits of ion channels were related to epilepsy, and that general ion channel dysfunctions "are also linked to susceptibility to autism, as well as bipolar disorder, schizophrenia, and other neuropsychiatric disorders." The researchers "prioritize *ANK2, CACNA1AE, CACNA2D3, GRIA2,* and *DLG4*… as candidate epilepsy genes because of their overlap with the epilepsy-focused module 2 of the WES [whole-exome sequencing] network;" these genes originated as having association only with autism prior to this study (Peng et al., 2021). A study with similar intention done on co-occurring epilepsy and ASD in Chinese children found *SCN1A* and *MECP2* gene mutations to be the most common; *SCN1A* was more associated with epilepsy, while *MECP2* was more associated with Rett Syndrome. Mutations in *SCN2A, CACNA1A, CACNA1H, CACNA1D,* and *KCNQ2* were also identified, although individual cases for each gene were small in the latter set of genes (Long et al., 2019). Both studies contribute to the understanding of the beneficial utility for genetic testing of epilepsy in the context of other comorbidities, such as ASD.

Sanchez Fernandez, Loddenkemper, Gainza-Lein, Sheidley, and Poduri (2019) evaluated the cost-effectiveness of genetic testing in patients with epilepsy of unknown etiology. 20 studies were included, with 8 evaluating chromosomal microarray (CMA), 9 evaluating epileptic panels (EP) with deletion/duplication testing, and 6 evaluating whole exome sequencing (WES). The authors found WES to have the highest diagnostic yield at 0.45, followed by EP at 0.23 and then CMA at 0.08. EP was found to be the most cost-effective, at $15,848 per diagnosis. Although cost-effectiveness of strategies overlapped, the authors found CMA to be consistently less cost-effective than WES and EP (Sanchez Fernandez et al., 2019).

Borlot et al. (2019) analyzed the results of epilepsy gene panels from 64 patients. Up to 185 genes were tested. 14 probands were found to have "pathogenic or likely pathogenic" variants in the following genes: "*SCN1A, GABRB3, UBE3A, KANSL1, SLC2A1, KCNQ2, SLC6A1, HNRNPU, STX1B, SCN2A, PURA, and CHD2*". The authors also identified 6 mutations arising *de novo*, with unknown inheritance for 8 mutations. Overall, the authors concluded that a commercial gene panel for epilepsy may be useful, as it detected etiology in 22% of patients with epilepsy and intellectual disability (Borlot et al., 2019).

Kim et al. (2020) analyzed the clinical utility of whole-exome sequencing (WES) for patients with infantile-onset epilepsy that had tested negative on gene panel tests for epilepsy. The study included 59 patients. Following WES, 55.4% of the participants received genetic conformation of epilepsy, indicating that WES increased diagnostic yield by 8%. Three epilepsy-causing genes (that were not included on the original gene panel) were identified: *YWHAG, KCNC1,* and *FGF12*. The authors conclude that WES could be an important way to reanalyze novel epilepsy-linked genes without updated gene panels (Kim et al., 2021).

Willimsky et al. (2021) studied the use of next generation sequencing (NGS) by comping the diagnostic yield of small and large gene panels. The authors completed a retrospective study of 190 patients under the age of 18 years who were diagnosed with epilepsy of unknown etiology. Small gene panels were defined as those under 25 kilo-base pair (kb), and large gene panels were defined as those over 25 kb. Diagnostic yield was defined as detection of pathogenic or likely pathogenic variants. The authors found that the diagnostic yield of large panels (29%) was significantly larger than small panels (13%). The authors then analyzed the differences in diagnostic yield in developmental and epileptic encephalography (DEE) and non-DEE. The authors found that the significant increase of diagnostic yield in large panels was only significant for non-DEE patients, and not for DEE patients. The authors conclude that large epilepsy gene panels have significantly higher diagnostic yield for non-DEE patients but note that small gene panels (a maximum of 10 genes) is sufficient for DEE patients (Willimsky et al., 2021).

Stefanski et al. (2021) completed a meta-analysis and systematic review on the success rate of genetic testing of neurodevelopmental disorders (NDD). The study measured the diagnostic yield, defined as the "percent of pathogenic variant carriers identified in a cohort." The study included 103 clinical sequencing studies that used NGS in a total of 32,331 people with epilepsy, ASD, or ID. The diagnostic yield for epilepsy was 24%. The epilepsy subtypes with the highest diagnostic yield were epilepsy with ID (27.9%) and early onset seizures (36.9%). The authors then studied the diagnostic yield of each sequencing technology and found a diagnostic yield of 27.2% for exome sequencing and a diagnostic yield of 22.6% for target gene sequencing panels (Stefanski et al., 2021). Sheidly et al (2021) completed a similar meta-analysis and systematic

review on 5985 studies on genetic testing of patients with epilepsy. "The overall diagnostic yield across all test modalities was 17%, with the highest yield for GS [genome sequencing] (48%), followed by ES [exome sequencing] (24%), MGP [multigene panel] (19%), and [genome-wide comparative genomic hybridization/chromosomal microarray] CGH/CMA (9%)." The authors also studied non-yield outcomes. 24 studies reported on changes in treatment based on genetic testing; "treatment changes were reported in 12-18% of patients with a genetic diagnosis, including avoiding, stopping, or initiating specific antiseizure medications (AMAs) or ketogenic diet (KD) and halting a plan for surgery in the presence of a specific genetic diagnosis" (Sheidley et al., 2021).

Beyond developing panels to identify genetic variants among epileptic patients, recent advancements in the study of epigenetics could potentially be of use with epilepsy symptoms but not a clear-cut genetic basis. In the patients with neurodevelopmental disorders an epilepsy phenotype, 23% of cases had rare differential methylations (Barbosa et al., 2018). "When the parents were able to be tested, ~40% of the methylation variants were *de novo*, suggesting that methylation abnormalities may be causative in 5-10% of their cohort. When identified, the underlying causes of the methylation changes were varied and included CNVs (copy number variants), sequence variants in regularly elements, or repeat expansions, each of which is easily missed by conventional (even next-generation) sequencing methods" (Hebbar & Mefford, 2020). Genetic and epigenetic testing could further help shape precision medicine in the best types of pharmaceutical drugs used to treat specific epilepsies, such as by understanding individual responses to antiepileptic drug treatment and alterations in drug pharmacokinetics and pharmacodynamics that could guide safer and more effective treatment strategies (Balestrini & Sisodiya, 2018).

VI. Guidelines and Recommendations

International League Against Epilepsy (ILAE)

In 2015, the ILAE Commission of Pediatrics issued a task force report which included the following related to genetic testing in epilepsy.

- "Genetic screening should not be undertaken at a primary or secondary level of care."
- "Standard care should permit genetic counseling by trained personnel to be undertaken at all levels of care (primary to quaternary)."
- "Genetic evaluation for Dravet syndrome and other infantile-onset epileptic encephalopathies should be available at tertiary and quaternary levels of care (optimal intervention would permit an extended genetic evaluation)."
- "Early diagnosis of some mitochondrial conditions may alter long-term outcome, but whether screening at quaternary level is beneficial is unknown." (Wilmshurst et al., 2015)

In 2017, the ILAE released a position paper containing a stance on the genetic etiologies of epilepsies. The ILAE states that "the epilepsies in which a genetic etiology has been implicated are quite diverse and, in most cases, the underlying genes are not yet known". The ILAE also notes that genetic is not equivalent to inherited; de novo mutations are being identified with increasing frequency, thereby making an epileptic syndrome not inherited. Furthermore, the

ILAE states that environmental contributions to an epileptic syndrome should not be minimized and that a genetic etiology should be of significant effect in causing epilepsy (Scheffer et al., 2017).

In the 2021 report, the ILAE and the International Neuropsychological Society address the lack of an international taxonomy for cognitive disorders in epilepsy and proposes the International Classification of Cognitive Disorders in Epilepsy (IC-CODE), stating that "a taxonomy built on the alignment of genetic, neuroimaging, and cognitive processes promises high precision for the diagnosis of cognitive disorders in epilepsy and their treatment" (Norman et al., 2021).

European Federation of Neurological Societies

In 2010, EFNS issued the following recommendations pertaining to epilepsy. The EFNS noted that molecular investigations may be useful for diagnosis but cannot be considered routine with the large amount of mutations present and state that clinical or physiological methods are generally superior. However, they note severe myoclonic epilepsy of infancy (SMEI) has a mutation in the gene *SCN1A* in 80% of patients. Since 2010, this organization has been renamed to the European Academy of Neurology, but no new updates on epilepsy have been released (Burgunder et al., 2010).

American Academy of Neurology (AAN) and Child Neurology Society (CNS)

The AAN and CNS issued guidelines for clinicians on diagnostic assessment of the child with status epilepticus (SE) in 2006, reaffirmed 2019. The recommendations provided guidance for the assessment of laboratory studies, metabolic and genetic studies, electroencephalography, and neuroimaging in children with SE. The expert panel concluded that "there are insufficient data to support or refute whether genetic testing (chromosomal or molecular studies) should be done routinely in children with SE" (Riviello et al., 2006).

American Epilepsy Society Annual Meeting

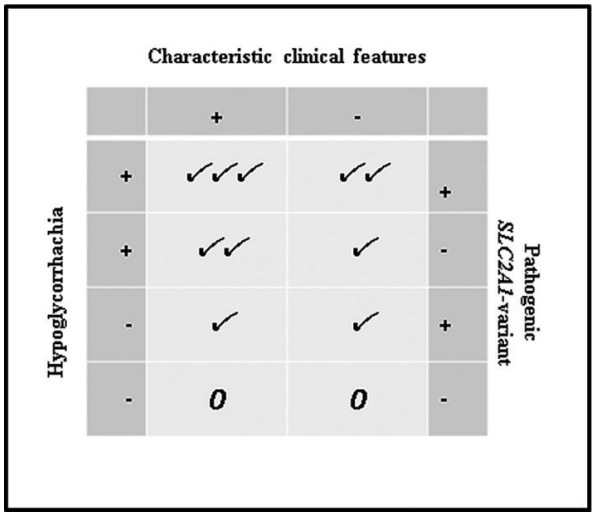
In 2015, a talk presented at the American Epilepsy Society Annual Meeting focused on reviewing the genetics of epilepsy, which groups were likely to benefit from genetic testing, and how to approach genetic testing in the current evolution of medicine. With regards to who would benefit most, "it would make sense to focus testing at this time on those in whom there is a high likelihood of a diagnostic finding and on those whose refractory epilepsy may be influenced by a precise genetic diagnosis that can guide treatment." This study concluded that genetic testing is needed to determine if treatment regimens will be affected, especially in younger children and infants.

With regards to the proper way to approach genetic testing, "we should start with a clinical approach, defining a specific epilepsy syndrome when relevant, to guide the nature and sequence of genetic testing. Pre- and post- testing counseling, whether provided by a physician or genetic counselor, is critical to maintaining clear communication with patients about the implications and limitations of their genetic testing." The types of testing include chromosomal microarray analysis (CMA), complete genome sequencing, and exome sequencing (Poduri, 2017).

International Glut1DS Study Group

The International Glut1DS (glucose transporter 1 deficiency syndrome) put forth recommendations on the diagnosis and treatment of Glut1DS in 2020, which involves "characteristic clinical features, definite hypoglycorrhachia, and pathogenic *SLC2A1* variants." Hypoglycorrhachia is defined as a low glucose level in cerebrospinal fluid in the setting normal glucose levels in blood, or normoglycemia. Their strength of support for a combination of the three features is shown below.

Symbol	diagnosis of Glut1DS	start KDT
✓✓✓	confirmed	yes
✓✓	probable	yes
✓	possible	consider
0	negative	not required



On genetic testing, the International Glut1DS group also stated that "the absence of *SLC2A1* pathogenic variants does not always exclude Glut1DS…*SLC2A1*-negative patients can be diagnosed on the basis of hypoglycorrhachia and distinctive clinical features, especially when responsive to KDT [ketogenic diet therapies]" (Klepper et al., 2020).

North American Consensus Panel on Dravet Syndrome

This panel was convened to establish standards for evaluation of Dravet Syndrome. The panel recommended that genetic testing be performed in patients whose symptoms indicated Dravet syndrome; the panel noted that either specific *SCN1A* sequencing or a larger gene panel may be performed, and a chromosomal microarray was not necessary.

The panel also notes that genetic testing should be pursued in a child <12 months and with ≥2 febrile seizures >15 minutes as well as a child 12-35 months old with at least 1 febrile seizure over 15 minutes. However, genetic testing should not be performed for a child <12 months with only one focal or generalized febrile seizure.

Genetic counseling should be provided, particularly information about heritability and risk of epilepsy in siblings. Other information about *SCN1A* mutations may also be provided (Wirrell et al., 2017).

Scottish Intercollegiate Guidelines Network (SIGN)

SIGN lists features suggesting genetic generalized epilepsies, which are as follows:

- childhood or teenage onset
- triggered by sleep deprivation and alcohol
- early morning tonic-clonic seizures or myoclonic jerks
- short absence seizures
- photoparoxysmal response on electroencephalography (EEG)
- generalized 3 per second spike and wave or polyspike and wave on EEG.

Genetics services are recommended for patients with a "very strong" family history of epilepsy, or with "a clinical phenotype suggestive of a monogenic epilepsy syndrome" (SIGN, 2018).

National Institute for Health and Care Excellence (NICE)
The NICE clinical guideline on epilepsy diagnosis and management does not mention genetic testing.

United Kingdom Expert Group on Tuberous Sclerosis Complex

The expert group recommended, with consensus, to offer a genetic test at baseline to patients with definite or probable TSC. The group noted that a genetic test may clarify the diagnosis of TSC for patients that do not fulfill clinical criteria for the condition (Amin et al., 2018).

Genetic Testing Advisory Committee (GTAC) for Ontario, Canada

These guidelines recommend the following as indications for genetic testing:

- "When the clinical features (age of onset, seizure semiology and EEG features) are consistent with a distinct epilepsy syndrome as defined by the International League Against Epilepsy (ILAE), with the exception of syndromes outlined in the following section."
- "When the prognosis based on clinical and EEG findings is poor or the likelihood of lethal outcome is high."
- "When epileptic seizures are refractory to medical treatment as defined by the ILAE12 (with no apparent acquired cause)."
- "When epilepsy is associated with features suggestive of inborn errors of metabolism."
- "When epilepsy is associated with distinctive patterns of malformations of cortical development identified on neuroimaging studies."
- "When epilepsy is associated with clinical signs of neurodegeneration."
- "When epilepsy is associated with paroxysmal neurological features such as paroxysmal dyskinesias, episodic ataxias and hemiplegic migraine."
- "When epilepsy is associated with additional syndromic features such as developmental delay/intellectual disability, multiple congenital anomalies and dysmorphic features."
- "When familial epilepsy is present, defined as at least two first- degree family members with related epilepsy syndromes, unless the epilepsy syndrome is benign."

The guidelines also recommend against genetic testing in the following situations:

- "Recognizable seizure syndrome with benign course."
- "Childhood epilepsy with centro-temporal spikes (previously termed benign rolandic epilepsy)."
- "Isolated mesial temporal lobe epilepsy with hippocampal sclerosis."
- "Typical childhood Absence epilepsy (although if it is early-onset or medically refractory epilepsy, one should consider and test for GLUT1 deficiency)."
- "Juvenile myoclonic epilepsy, which is well controlled on medications and without intellectual disability or any signs of neurodegeneration."
- "Acquired epilepsy."

The guideline also provides a list of "potentially treatable" genetic/metabolic epilepsies, shown below

Table 3: Potentially treatable genetic/metabolic epilepsies

Effect on ion channels
Dravet syndrome (*SCN1A*)—avoidance of sodium-channel blockers
SCN8A-related epileptic encephalopathy—carbamazepine, phenytoin [sodium-channel blockers]
KCNQ2-related epileptic encephalopathy—retigabine [potassium-channel openers] or carbamazepine [sodium-channel blockers]
KCNT1-related migrating partial epilepsy of infancy—quinidine [gain-of-function mutations being treated by partial channel antagonist]
GRIN2A-related epileptic encephalopathy—memantine [NMDA (N-methyl-d-aspartate) receptor antagonists]
Alternative energy source
GLUT-1 deficiency syndrome (*SLC2A1* gene)—ketogenic diet
Modulate epileptogenesis
Tuberous sclerosis complex (*TSC1/2*)—mTOR inhibitors (Rapamycin/analogs)
Modulating biochemical pathways
Pyridoxine dependency (*ALDH7A1*)—B6 vitamin
Biotinidase deficiency (*BTD*)—biotin
Cerebral folate deficiency (*FOLR1*)—folinic acid
Creatine deficiency syndromes (*SLC6A8, GATM, GAMT*)—creatine, other amino acid supplementation (glycine, arginine, ornithine) or restriction (arginine)
Serine biosynthesis defects (*PHGDH, PSAT1, PSPH*)—serine, glycine

Finally, the guideline also makes recommendations for panel testing. Some situations in which a gene panel may be considered are if:

- epilepsy phenotyping is broad and does not easily classify the patient into a distinct group.
- "if the clinical diagnosis is clear and genetic heterogeneity is high, but clinical diagnosis is not indicative of a treatable condition."
- "if clinical diagnosis is unclear and genetic heterogeneity is unknown."

The guidelines further list examples of these situations, such as seizures with fever as a major trigger and idiopathic generalized epilepsy refractory to treatment (Jain et al., 2019).

VII. Applicable State and Federal Regulations

DISCLAIMER: If there is a conflict between this Policy and any relevant, applicable government policy for a particular member [e.g., Local Coverage Determinations (LCDs) or National Coverage Determinations (NCDs) for Medicare and/or state coverage for Medicaid], then the government policy will be used to make the determination. For the most up-to-date Medicare policies and coverage, please visit the Medicare search website: http://www.cms.gov/medicare-coverage-database/overview-and-quick-search.aspx. For the most up-to-date Medicaid policies and coverage, visit the applicable state Medicaid website.

A. Food and Drug Administration (FDA)

Many labs have developed specific tests that they must validate and perform in house. These laboratory-developed tests (LDTs) are regulated by the Centers for Medicare and Medicaid (CMS) as high-complexity tests under the Clinical Laboratory Improvement Amendments of 1988 (CLIA '88). LDTs are not approved or cleared by the U. S. Food and Drug Administration; however, FDA clearance or approval is not currently required for clinical use.

B. Centers for Medicare & Medicaid Services (CMS)

- N/A

VIII. Applicable CPT/HCPCS Procedure Codes

CPT	Code Description
81404	Molecular pathology procedure, Level 5 (eg, analysis of 2-5 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 6-10 exons, or characterization of a dynamic mutation disorder/triplet repeat by Southern blot analysis)
81405	Molecular pathology procedure, Level 6 (eg, analysis of 6-10 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 11-25 exons, regionally targeted cytogenomic array analysis)
81406	Molecular pathology procedure, Level 7 (eg, analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)
81407	Molecular pathology procedure, Level 8 (eg, analysis of 26-50 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of >50 exons, sequence analysis of multiple genes on one platform)
81419	Epilepsy genomic sequence analysis panel, must include analyses for 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
81479	Unlisted molecular pathology procedure

IX. Evidence-based Scientific References

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