Prior Authorization Review Panel
MCO Policy Submission

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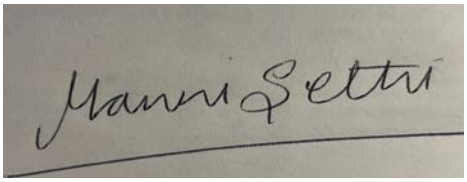
Plan: AmeriHealth Caritas Pennsylvania	**Submission Date**: 1/1/2024
Policy Number: ccp.1475	**Effective Date:** 1/2021 **Revision Date:** December 1, 2023
Policy Name: Genetic testing for epilepsy and seizure disorders	
Type of Submission – Check all that apply: **New Policy** **X Revised Policy*** **Annual Review – No Revisions** **Statewide PDL**	
***All revisions to the policy must be highlighted using track changes throughout the document.** **Please provide any clarifying information for the policy below:** See tracked changes below.	
Name of Authorized Individual (Please type or print): Manni Sethi, MD, MBA, CHCQM	**Signature of Authorized Individual:** 

Genetic testing for epilepsy and seizure disorders

Clinical Policy ID: CCP.1475

Recent review date: 12/2023

Next review date: 4/2025

Policy contains: epilepsy, pharmacogenomics, seizure disorders

AmeriHealth Caritas Pennsylvania has developed clinical policies to assist with making coverage determinations. AmeriHealth Caritas Pennsylvania clinical policies are based on guidelines from established industry sources, such as the Centers for Medicare & Medicaid Services (CMS), state regulatory agencies, the American Medical Association (AMA), medical specialty professional societies, and peer-reviewed professional literature. These clinical policies along with other sources, such as plan benefits and state and federal laws and regulatory requirements, including any state- or plan-specific definition of "medically necessary," and the specific facts of the particular situation are considered by AmeriHealth Caritas Pennsylvania when making coverage determinations. In the event of conflict between this clinical policy and plan benefits and/or state or federal laws and/or regulatory requirements, the plan benefits and/or state and federal laws and/or regulatory requirements shall control. AmeriHealth Caritas Pennsylvania clinical policies are for informational purposes only and not intended as medical advice or to direct treatment. Physicians and other health care providers are solely responsible for the treatment decisions for their patients. AmeriHealth Caritas Pennsylvania clinical policies are reflective of evidence-based medicine at the time of review. As medical science evolves, AmeriHealth Caritas Pennsylvania will update its clinical policies as necessary. AmeriHealth Caritas Pennsylvania clinical policies are not guarantees of payment.

Coverage policy

Genetic testing for epilepsy and seizure disorders is clinically proven and, therefore, may be medically necessary for any of the following indications (Jain, 2019; Smith, 2023):

- Clinical features (age on onset, seizure semiology, electroencephalogram) are consistent with a distinct epilepsy syndrome.
- Prognosis from clinical and electroencephalogram findings is poor or likelihood of lethal outcome is high.
- Epileptic seizures are refractory to medical treatment, with no apparent cause.
- Epilepsy is associated with:
    - Features suggestive of inborn errors of metabolism.
    - Patterns of malformations of cortical development identified on neuroimaging studies.
    - Clinical signs of neurodegeneration.
    - Paroxysmal neurological features such as paroxysmal dyskinesias, episodic ataxia, and hemiplegic migraine.
    - Additional syndromic features such as developmental delay, intellectual disability, multiple congenital anomalies, and dysmorphic features.

- Familial epilepsy, defined as more than one first-degree family members with related epilepsy syndromes, is present — unless the epilepsy syndrome is benign (Jain, 2019).

Specific mutation testing is medically necessary for the following clinical situations:

- SCN1A testing in assessment for SCN1A-related seizure disorders.
- ALDH7A1 testing in assessment of Pyridoxine-related epilepsy.
- SLC2A1 testing in assessment of Glucose transporter type 1 deficiency syndrome.
- PCDH19 testing for evaluation of epilepsy female-restricted with mental retardation.
- SCN8A testing in assessment for SCN8A-related epileptic encephalopathy.
- KCNQ2 testing in assessment for KCNQ2-related epileptic encephalopathy.
- KCNT1 testing in assessment for KCNT1-related migrating partial epilepsy of infancy.
- GRIN2A testing in assessment for GRIN2A-related epileptic encephalopathy.
- TSC1 and TSC2 testing for tuberous sclerosis complex-related epilepsy.
- BTD testing in assessment for biotinidase deficiency-related epilepsy.
- FOLR1 testing in assessment for cerebral folate deficiency-related epilepsy.
- SLC6A8, GATM, and GAMT testing for epilepsy due to creatine deficiency syndromes.
- PHGDH, PSAT1, and PSPH testing for epilepsy due to serine biosynthesis defects (Moller, 2016).

Limitations

All other uses of genetic testing for epilepsy and seizure disorder are investigational/not clinically proven and, therefore, not medically necessary. Testing is not recommended in drug-responsive epilepsy, at epilepsy onset, in a recognizable seizure syndrome with benign course, for childhood epilepsy with centro-temporal spikes (previously known as benign rolandic epilepsy), and in isolated mesial temporal lobe epilepsy with hippocampal sclerosis (Jain, 2019).

Alternative covered services

No alternative covered services were identified during the writing of this policy.

Background

Epilepsy is a brain disease which predisposes people to unprovoked and recurrent seizures. The terms epilepsy and seizure disorder are used interchangeably.

An estimated 3.4 million Americans have active epilepsy, and 5.1 million have a history of the disorder (U.S. Centers for Disease Control and Prevention, 2022). The highest incidence rates of the condition occur in infants and in people over age 85, with rates slightly higher for males. In high-income nations, about 50% of cases lack a known cause (Beghi, 2020).

Approximately half of epilepsy cases achieve prolonged seizure remission, indicating a need for effective treatments. Anti-seizure medications are most commonly used (Vossler, 2018). However, about 30% of people with epilepsy are drug-refractory (Jain, 2019). Surgery can be considered in cases refractory to medications; options such as dietary therapy, vagus nerve stimulation, and responsive neurostimulation may also be used (Epilepsy Foundation, 2023).

Selecting the drug most likely to successfully treat a patient with epilepsy poses a challenge for clinicians. With the development of the human genome, research identified genes with a major effect on susceptibility to idiopathic epilepsies (Wang, 2017).

The number of patients with known genetic abnormalities causing both severe and mild epilepsies is rising. Identification of the causative mutation in a large number of epilepsy genes, most frequently arising *de novo*, occurs in 30% to 50% of infants with severe developmental and epileptic encephalopathies. In Dravet syndrome, for example, more than 80% of patients have a pathogenic variant of *SCN1A* (Scheffer, 2017). A meta-analysis (n = 1,308) found drug resistance to be 6.5 times greater in epilepsy patients with genetic defects (Lin, 2021).

The *de novo* mutations indicate epilepsy that is not inherited or related to a family history of epilepsy, but rather a new mutation developed in the patient due to environmental factors such as sleep disorders, stress, and illness. Thus, the terms “genetic” and “inherited” are not interchangeable in describing mutations in epilepsy (Scheffer, 2017).

Diagnosing epilepsy-associated genes has the potential to:

- Focus treatments on medicines known to be effective for particular epilepsy syndromes.
- Prognosticate and limit additional tests, which may have risks and costs.
- Identify or anticipate potential comorbidities, which can improve treatment (Jain, 2019).

Genetic factors account for 70% of epilepsy cases as a single genetic variant in rare epilepsies or multiple genetic variants combined with environmental factors in common epilepsies. Genetic testing and precision treatment is employed more in rare epilepsies; precision medicine in common epilepsies require non-genetic factors like microbiome, diet, age at onset, optimal treatment time, and lifestyle factors. Types of genetic tests used for epilepsy include karotype, genomic microarray, targeted gene sequencing, next-generation sequencing panel, whole-exome sequencing, and whole-genome sequencing (Thakran, 2020).

Findings

The National Society of Genetic Counselors published an evidence-based guideline on genetic testing and counseling for the unexplained epilepsies. The Society defined epilepsy as unexplained when, after standard evaluations, the cause of seizures cannot be attributed to a structural, metabolic, infectious, immunological, or other acquired etiology. The Scheidley (2022) systematic review served as the evidence basis for the guideline. Key recommendations are as follows (Smith, 2023):

- Individuals with unexplained epilepsy should be offered genetic testing, without limitation of age, using comprehensive, multi-gene testing, such as exome sequencing, genome sequencing, or multigene panels as a first-tier test (strong recommendation). The Society conditionally recommended exome sequencing or genome sequencing over multigene panels as the first tier test. The multi-gene panel should have a minimum of 25 genes and include copy number analysis.
- Genetic tests should be selected, ordered, and interpreted by a qualified healthcare provider in the setting of appropriate pre- test and post- test genetic counseling (strong recommendation). The Society defined a “qualified healthcare provider” as “an individual with specialized training or knowledge in genetics who can adequately discuss the scope, benefits, limitations, and psychological implications of genetic testing and has the ability to evaluate and interpret genetic test results in the context of an individual's presenting phenotype.”

A 2014 American Academy of Neurology quality measurement stated that the diagnosis of epilepsy in children should feature laboratory findings, including genetic testing (American Academy of Neurology, 2014).

A summary of a presentation at the 2015 American Epilepsy Society Annual Meeting supported triaging those with epilepsy who could most benefit from genetic testing and choosing the appropriate test, both done by neurologists. It also suggested neurologists can partner with specialists in genetics (Poduri, 2017).

A guideline from the Genetic Testing Advisory Committee in Ontario, Canada, lists “potentially treatable” genetic/metabolic epilepsies, and provides specific mutations and treatments for each mutation. These mutations are listed in the Coverage section of this policy (Jain, 2019).

The International League Against Epilepsies 2017 position paper on epilepsy classification notes the growing number of patients with known genetic abnormalities causing epilepsy, along with the increased understanding of treatments specific to individual genetic mutations (Scheffer, 2017).

A review of 216 patients with epilepsy identified presumed disease-causing variants for 19 genes, listed in the coverage section of this policy (Moller, 2016).

A survey of 293 patients in specialty epilepsy centers, nearly half of whom are children, with genetic epilepsies revealed treatment was altered due to genetic findings in 94 (32%). Precision medicine treatments existed for 56 patients (19%), but the treatment was tried in only 33 (59%) and successful for just 10 of the 33 patients. Authors recognize that precision medicine in epilepsy has much room for improvement (Balestrini, 2021).

A meta-analysis of 1,504 people from Hong Kong and Malaysia taking anti-epileptic drugs reviewed 39 polymorphisms in the SCN1A, SCN2A, and SCN3A genes. No significant allele, genotype, and haplotype association of polymorphisms in the three genes with drug response to epilepsy was documented. Authors concluded these three genes do not play major roles in response to anti-epileptics (Haerian, 2013).

A meta-analysis of 12 studies (n = 34,853), included 8,696 cases and 26,157 controls. Studies identified the rs6732655 polymorphism of the SCN1A gene to be associated with the presence of epilepsy (highly significant at $P = 8.71 \times 10^{-10}$), as was the 4p15.1 polymorphism of the PCDH7 gene (significant at $P = 5.44 \times 10^{-9}$) (International League, 2014).

A meta-analysis of six studies (n = 5,036), randomized to 2,719 cases and 2,317 controls, resulted in a significant association between SCN1A polymorphism IVS5N+5G>A and epilepsy with febrile seizures in both recessive and dominant models. The association was especially strong among Caucasians, but not among Indians and Chinese (Tang, 2014).

A meta-analysis of eight studies included patients with epilepsy taking sodium channel blocking anti-epileptic drugs. Results showed the SCN1A rs2298771 polymorphism was significantly associated with drug resistance ($P = .02$), with no observed association for the SCN1A rs3812718 polymorphism (Bao, 2018).

A meta-analysis of nine studies (n = 4,710), mostly performed in China, showed that SCN1A polymorphism rs3812718 was associated with resistance to valproic acid, used in treating epilepsy, for Asians ($P = .016$) but not for Caucasians ($P = .906$) (Wang, 2018).

A meta-analysis of eight studies (n = 7,184) randomized subjects into 3,595 cases and 3,589 controls. A significant association between SCN1A rs3812718 polymorphism and the risk of epilepsy was detected in the homozygote comparison ($P = .001$), dominant model ($P < .001$), and heterozygote comparison ($P = .003$), but not recessive model ($P = .104$) (Zhi, 2018).

A systematic review of 12 studies identified a significant negative association between the SCN1A IVS5N+5 G>A polymorphism and febrile seizures/epilepsy. Authors note that SCN1A IVS5N+5 G>A polymorphism is a protective factor of febrile seizures and epilepsy, and testing for this mutation can play a role in determining the risk of febrile seizure/epilepsy in symptomatic children (Hao, 2020).

A systematic review of 49 studies identified 27 genes associated with neonatal onset epilepsy. Authors state that while precision medicine is now possible for mutations in a few genes (KCNQ2, SCN2A, SCN8A), enhanced knowledge of early onset epilepsy will improve practice and outcomes (Spagnoli, 2021).

A systematic review/meta-analysis of 103 studies determined the most reported genetic predictor of drug-resistant epilepsy was the ABCB1 gene polymorphism (Sultana, 2021).

A meta-analysis of 14 studies concluded there was no significant association between the rs17183814 polymorphism in SCN2A and the risk of epilepsy. Moreover, it found no link between the rs17183814 or the rs2304016 polymorphisms with response to antiepileptic drugs, despite mixed previous findings (Yang, 2021).

A study of 1,529 epilepsy patients and 1,935 controls from Hong Kong and Malaysia genotyped 43 polymorphisms. The strongest association with epilepsy was rs3812718, or SCN1A IVS5N+5G>A for allele G (*P* = .0009) and for genotype GG versus AA (*P* = .003). SCN2A rs12467383 also had a strong association with epilepsy (*P* = .01) (Baum, 2014).

In 2022, we added one systematic review of 154 studies comparing the diagnostic yields of genetic tests used for patients with epilepsy. The overall diagnostic yield across all test modalities was 17%. The highest yield was for genome sequencing (48%) followed by exome sequencing (24%), multigene panels (19%), and genome-wide comparative genomic hybridization/chromosomal microarray (9%). The presence of developmental and epileptic encephalopathy and of neurodevelopmental comorbidities were the only phenotypic factors significantly associated with increased diagnostic yield (Sheidley, 2022).

According to the American Academy of Pediatrics (2022), the clinical utility of genetic testing is highest where epilepsy is associated with developmental delays, but genetic causes of epilepsy have also been identified in generalized epilepsies or focal epilepsies. Genetic testing can assist in diagnosing, guiding treatment, providing prognostic information and risk assessment, reducing the need for additional or repeated studies, and supporting families and research efforts. No policy changes are warranted.

In 2023, we added a new guideline by the National Society of Genetic Counselors on genetic testing and counseling for the unexplained epilepsies (Smith, 2023). No policy changes are warranted.

References

On October 2, 2023, we searched PubMed and the databases of the Cochrane Library, the U.K. National Health Services Centre for Reviews and Dissemination, the Agency for Healthcare Research and Quality, and the Centers for Medicare & Medicaid Services. Search terms were “epilepsy (MeSH),” “seizures (MeSH),” “genetic testing (MeSH),” “epilepsy,” “pharmacogenomic,” and “seizure disorders.” We included the best available evidence according to established evidence hierarchies (typically systematic reviews, meta-analyses, and full economic analyses, where available) and professional guidelines based on such evidence and clinical expertise.

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Policy updates

12/2020: initial review date and clinical policy effective date: 1/2021.

12/2021: Policy references updated.

12/2022: Policy references updated.

12/2023: Policy references updated.