Genetic Testing for Epilepsy

Policy Number: PG0467
Last Review: 03/01/2021

PARAMOUNT

ADVANTAGE | ELITE | HMO
INDIVIDUAL MARKETPLACE |
PROMEDICA MEDICARE
PLAN | PPO

GUIDELINES

This policy does not certify benefits or authorization of benefits, which is designated by each individual policyholder terms, conditions, exclusions and limitations contract. It does not constitute a contract or guarantee regarding coverage or reimbursement/payment. Self-Insured group specific policy will supersede this general policy when group supplementary plan document or individual plan decision directs otherwise.
Paramount applies coding edits to all medical claims through coding logic software to evaluate the accuracy and adherence to accepted national standards.
This medical policy is solely for guiding medical necessity and explaining correct procedure reporting used to assist in making coverage decisions and administering benefits.

SCOPE

X Professional
X Facility

DESCRIPTION

Epilepsy is a neurological (central nervous system) disorder marked by sudden recurrent episodes of sensory disturbance, loss of consciousness, or convulsions, associated with abnormal electrical activity in the brain. Epilepsy is characterized by unpredictable seizures and can cause other health problems. Epilepsy is defined as the occurrence of two or more unprovoked seizures more than 24 hours apart or after one seizure with a high risk for more.

Treatment with medications or sometimes surgery can control seizures for the majority of people with epilepsy. Some people require lifelong treatment to control seizures, but for others, the seizures eventually go away. Some children with epilepsy may outgrow the condition with age.

There are numerous rare epileptic syndromes associated with global developmental delay and/or cognitive impairment that occur in infancy or early childhood and that may be caused by single-gene pathogenic variants. Infantile- and early childhood-onset epilepsy syndromes include but are not limited to the following:
• Early myoclonic encephalopathy
• Ohtahara syndrome
• West syndrome
• Dravet syndrome (severe myoclonic epilepsy in infancy)
• Lennox–Gastaut syndrome
• Landau–Kleffner syndrome
• Epilepsy with continuous spike-and-waves during slow-wave sleep (other than Landau Kleffner syndrome)
• Myoclonic status in non-progressive encephalopathies

Some types of epilepsy, which are categorized by the type of seizure experienced or the part of the brain that is affected, run in families and are inherited. In these cases, it is likely that there is a genetic influence. Not all epilepsies that are due to genetic causes are inherited. Certain types of epilepsy are associated with specific genetic changes, including changes in an individual gene or changes in a chromosome. However, for most people, genes are only part of the cause of epilepsy. Certain genes may make a person more sensitive to environmental conditions that trigger seizures.
There are various methods used to test for mutations in genes that can cause epilepsy.

- Chromosomal microarray analysis

- Single gene analysis
- Multi-gene panels
- Exome sequencing

Genes Most Commonly Associated With Genetic Epilepsy, not all inclusive;	
Genes	Physiologic Function
KCNQ2	Potassium channel
KCNQ3	Potassium channel
SCN1A	Sodium channel α-subunit
SCN2A	Sodium channel α-subunit
SCN1B	Sodium channel β-subunit
GABRG2	γ-aminobutyrate A-type subunit
GABRRA1	γ-aminobutyrate A-type subunit
GABRD	γ-aminobutyrate subunit
CHRNA2	Acetylcholine receptor α2 subunit
CHRNA4	Acetylcholine receptor α4 subunit
CHRNB2	Acetylcholine receptor β2 subunit
STXBP1	Synaptic vesicle release
ARX	Homeobox gene
PCDH19	Protocadherin cell-cell adhesion
EFHC1	Calcium homeostasis
CACNB4	Calcium channel subunit
CLCN2	Chloride channel
LGI1	G-protein component

Single Genes Associated with Epileptic Syndromes, not all inclusive;	
Syndrome	Associated Genes
Dravet syndrome	SCN1A, SCN9A, GABRA1, STXBP1, PCDH19, SCN1B, CHD2, HCN1
Epilepsy limited to females with mental retardation	PCDH19
Epileptic encephalopathy with continuous spike-and-wave during sleep	GRIN2A
Genetic epilepsy with febrile seizures plus	SCN1A, SCN9A
Early infantile epileptic encephalopathy with suppression burst (Ohtahara syndrome)	KCNQ2, SLC25A22, STXBP1, CDKL5, ARX
Landau-Kleffner syndrome	GRIN2A
West syndrome	ARX, TSC1, TSC2, CDKL5, ALG13, MAGI2, STXBP1, SCN1A, SCN2A, GABA, GABRB3, DNM1
Glucose transporter type 1 deficiency syndrome	SLC2A1

POLICY

HMO, PPO, Individual Marketplace, Elite/ProMedica Medicare Plan, Advantage
Genetic Testing for Epilepsy requires Prior Authorization for all product lines.

Procedure codes 81188, 81189, 81190, 81401, 81403, 81404, 81405, 41406, 81407, 81419, and 81479.

If multi-gene panel testing is being pursued, more targeted panels are preferred. If clinical findings dictate that a more targeted panel is appropriate, a broader multi-gene panel may not be considered medically necessary.

If the servicing laboratory elects to use multiple CPT codes (i.e. unbundled or stacked version) for billing purposes, and the medical necessity criteria are met below for a panel, the laboratory will be strongly encouraged to use an applicable panel CPT code.

COVERAGE CRITERIA

HMO, PPO, Individual Marketplace, Elite/ProMedica Medicare Plan, Advantage

Single gene testing and mutli-gene panel testing comprised entirely of genes related to infantile- and early-childhood onset epilepsy syndromes, in which epilepsy is the core clinical symptom, may be considered medically necessary for either of the following:

A. In individuals with infantile- and early-childhood-onset epilepsy syndromes when all of the following are met:
    1. Onset of seizures before the age of five years; and
    2. Clinically severe seizures that affect daily functioning and/or interictal EEG abnormalities; and
    3. No other clinical syndrome, associated metabolic, or brain structural abnormalities would potentially better explain the patient's clinical features(such as Tuberous Sclerosis or Rett syndrome); and
    4. Testing will result in:
        a. Medication management
        b. Diagnostic testing such that alternative potentially invasive tests are avoided
        c. C. Dietary changes (such as a ketogenic diet)

There is clinical and genetic overlap for many of the electro clinical syndromes previously discussed. If there is suspicion for a specific syndrome based on history, EEG findings, and other test results, testing should begin with single gene testing for the candidate gene most likely to be involved, followed by sequential testing for other candidate genes. In particular, if an SCN1A-associated syndrome is suspected (Dravet syndrome, GEFS+), molecular genetic testing of SCN1A with sequence analysis of the SCN1A coding region, followed by deletion and duplication analysis if a pathogenic variant is not identified, should be obtained. Given the genetic heterogeneity of early-onset epilepsy syndromes, a testing strategy that uses a multigene panel may be considered reasonable.

Exclusions:

- Genetic testing for all other epilepsy conditions not related to infantile or early childhood-onset epilepsy.
- Coverage is not available for investigational medical treatments or procedures, drugs, devices or biological products.

This policy does not address testing for genetic syndromes that have a wider range of symptomatology, of which seizures may be one, such as the neurocutaneous disorders (e.g., Rett syndrome, neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders.

Experts recommend formal genetic counseling for patients who are at risk for inherited disorders and who wish to undergo genetic testing. Paramount covers pre- and post-test genetic counseling as medically necessary for EITHER of the following:

- an individual undergoing genetic testing
- an individual who is a potential candidate for genetic **testing**

CPT CODES		HMO, PPO, Individual Marketplace	Elite/ProMedica Medicare Plan	Advantage
81188	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; evaluation to detect abnormal (eg, expanded) alleles	**Prior Authorization required**	**Prior Authorization required**	**Prior Authorization required**
81189	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; full gene sequence	**Prior Authorization required**	**Prior Authorization required**	**Prior Authorization required**
81190	CSTB (cystatin B) (eg, Unverricht-Lundborg disease) gene analysis; known familial variant(s)	**Prior Authorization required**	**Prior Authorization required**	**Prior Authorization required**
81401	Molecular pathology procedure, Level 2 (e.g., 2-10 SNPs, 1 methylated variant, or 1 somatic variant [typically using nonsequencing target variant analysis], or detection of a dynamic mutation disorder/triplet repeat)	**Prior Authorization required for all product lines**		
81402	Molecular pathology procedure, Level 3 (eg, >10 SNPs, 2-10 methylated variants, or 2-10 somatic variants [typically using non-sequencing target variant analysis], immunoglobulin and T-cell receptor gene rearrangements, duplication/deletion variants of 1 exon, loss of heterozygosity [LOH], uniparental disomy [UPD])	**Prior Authorization required for all product lines**		
81403	Molecular pathology procedure, Level 4 (eg, analysis of single exon by DNA sequence analysis, analysis of >10 amplicons using multiplex PCR in 2 or more independent reactions, mutation scanning or duplication/deletion variants of 2-5 exons)	**Prior Authorization required for all product lines**		
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)	**Prior Authorization required for all product lines**		
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)	**Prior Authorization required for all product lines**		
81406	Molecular pathology procedure, Level 7 (e.g., analysis of 11-25 exons by DNA sequence analysis, mutation scanning or duplication/deletion variants of 26-50 exons, cytogenomic array analysis for neoplasia)	**Prior Authorization required for all product lines**		
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,	**Prior Authorization required for all product lines**		

	sequence analysis of multiple genes on the 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	**Prior Authorization required**	**Prior Authorization required**	**Prior Authorization required**
		PG0453 Germline Multi-Gene Panel Testing/PG0467 Genetic Testing for Epilepsy		
81479	Unlisted molecular pathology procedure	**Prior Authorization required for all product lines**		

Paramount reserves the right to review and revise our policies periodically when necessary. When there is an update, we will publish the most current policy to https://www.paramounthealthcare.com/services/providers/medical-policies/ .

Additional Medical Policy Reference: PG0041 Genetic Testing

REVISION HISTORY EXPLANATION
ORIGINAL DATE: 04/01/2020

Date	Explanation & Changes
12/08/2020	• Medical Policy placed on the new Paramount Medical Policy Format
03/01/2021	• New 2021 procedure code 81419 added

REFERENCES/RESOURCES

Centers for Medicare and Medicaid Services, CMS Manual System and other CMS publications and services

Ohio Department of Medicaid

American Medical Association, *Current Procedural Terminology (CPT®)* and associated publications and services

Centers for Medicare and Medicaid Services, Healthcare Common Procedure Coding System, HCPCS Release and Code Sets

Hayes, Inc.

Industry Standard Review

Epilepsy Foundation