Protocol	Genetic Testing for Epilepsy

(204109)

Medical Benefit		Effective Date: 04/01/16	Next Review Date: 11/18
Preauthorization	Yes	Review Dates: 01/16, 11/16, 11/17	

Preauthorization is required.

The following protocol contains medical necessity criteria that apply for this service. The criteria are also applicable to services provided in the local Medicare Advantage operating area for those members, unless separate Medicare Advantage criteria are indicated. If the criteria are not met, reimbursement will be denied and the patient cannot be billed. Please note that payment for covered services is subject to eligibility and the limitations noted in the patient's contract at the time the services are rendered.

Populations	Interventions	Comparators	Outcomes
Individuals: • With infantile- or early-childhood-onset epileptic encephalopathy	Interventions of interest are: • Testing for genes associated with epileptic encephalopathies	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Changes in reproductive decision making • Symptoms • Quality of life • Medication use • Resource utilization • Treatment related morbidity
Individuals: • With presumed genetic epilepsy	Interventions of interest are: • Testing for genes associated with genetic epilepsies	Comparators of interest are: • Standard management without genetic testing	Relevant outcomes include: • Test accuracy • Test validity • Changes in reproductive decision making • Symptoms • Quality of life • Medication use • Resource utilization • Treatment related morbidity

Description

Epilepsy is a disorder characterized by unprovoked seizures. It is a heterogeneous condition that encompasses many types of seizures and that varies in age of onset and severity. Many genetic epilepsies are thought to have a complex, multifactorial genetic basis. There are also 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 a single-gene pathogenic variant. Genetic testing is commercially available for a large number of genetic variants that may be related to epilepsy.

Summary of Evidence

For individuals who have infantile- or early-childhood-onset epileptic encephalopathy who receive testing for genes associated with epileptic encephalopathies, the evidence includes prospective and retrospective cohort studies describing the testing yield. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For Dravet syndrome, which appears to have the largest body of associated literature, the sensitivity of testing for SCN1A disease-associated variants is high (≈ 80%). For other early-onset epileptic encephalopathies, the true clinical sensitivity and specificity of testing is not well-defined. However, studies reporting on the overall yield of genetic testing in populations with epileptic encephalopathies and early-onset epilepsy report detection rates for clinically significant variants ranging from 7.5% to 57%. The clinical utility of genetic testing occurs primarily when there is a positive test for a known pathogenic variant. The presence of a pathogenic variant may lead to targeted medication management, avoidance of other diagnostic tests, and/or informed reproductive planning. The evidence is sufficient to determine that the technology results in a meaningful improvement in the net health outcome.

For individuals who have presumed genetic epilepsy who receive testing for genetic variants associated with genetic epilepsies, the evidence includes prospective and retrospective cohort studies describing testing yields. Relevant outcomes are test accuracy and validity, changes in reproductive decision making, symptoms, quality of life, functional outcomes, medication use, resource utilization, and treatment-related morbidity. For most genetic epilepsies, which are thought to have a complex, multifactorial basis, the association between specific genetic variants and the risk of epilepsy is uncertain. Despite a large body of literature on associations between genetic variants and epilepsies, the clinical validity of genetic testing is poorly understood. Published literature is characterized by weak and inconsistent associations, which have not been replicated independently or by meta-analyses. A number of studies have also reported associations between genetic variants and antiepileptic drug (AED) treatment response, AED adverse effect risk, epilepsy phenotype, and risk of sudden unexplained death in epilepsy. The largest number of these studies is related to AED pharmacogenomics, which generally report some association between variants in a number of genes (including SCN1A, SCN2A, ABCC2, EPHX1, CYP2C9, CYP2C19), and AED response. Similarly, genetic associations between a number of genes and AED-related adverse effects have been reported. However, no empirical evidence on the clinical utility of genetic testing for the genetic epilepsies was identified, and the changes in clinical management that might occur as a result of testing are not well-defined. The evidence is insufficient to determine the effects of the technology on health outcomes.

Policy

Genetic testing for genes 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 (see Policy Guidelines) may be considered **medically necessary** if positive test results may:

1. Lead to changes in medication management; AND/OR
2. Lead to changes in diagnostic testing such that alternative potentially invasive tests are avoided;

   AND/OR
3. Lead to changes in reproductive decision making.

Genetic testing for epilepsy is considered **investigational** for all other situations.

Policy Guidelines

Policy Scope

Included Tests/Conditions

This protocol addresses testing for epilepsy that is possibly genetic. The International League Against Epilepsy has classified epilepsy as having underlying genetic cause or etiology when, as best understood, the epilepsy is the direct result of a known or presumed genetic defect and seizures are the core symptom of the disorder and for which there is no structural or metabolic defect predisposing to epilepsy (Berg et al, 2010).

This protocol also addresses the rare epilepsy syndromes that present in infancy or early childhood, in which epilepsy is the core clinical symptom (Dravet syndrome, early infantile epileptic encephalopathy, generalized epilepsy with febrile seizures plus, epilepsy and intellectual disability limited to females, nocturnal frontal lobe epilepsy, and others). Other clinical manifestations may be present in these syndromes, but are generally secondary to the epilepsy itself.

Excluded Tests/Conditions

This protocol 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., neurofibromatosis, tuberous sclerosis) or genetic syndromes associated with cerebral malformations or abnormal cortical development, or metabolic or mitochondrial disorders. Genetic testing for these syndromes may be specifically addressed in other protocols (see Related Protocols).

Testing that is limited to genotyping of CYP450 genes is addressed separately in the Cytochrome P450 Genotyping Protocol.

This protocol does *not* address the use of genotyping for the HLA-B*1502 allelic variant in patients of Asian ancestry prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions. This testing is recommended by the U.S. Food and Drug Administration (FDA) labeling for carbamazepine (FDA, 2014). (See also Background; Pharmacogenomics of Epilepsy).

This protocol also does not address the use of testing for variants in the mitochondrial DNA polymerase gamma (POLG) gene in patients with clinically suspected mitochondrial disorders prior to initiation of therapy with valproate. Valproate's label contains a black box warning related to increased risk of acute liver failure associated with the use of valproate in patients with POLG gene-related hereditary neurometabolic syndromes. FDA labeling states: "Valproate is contraindicated in patients known to have mitochondrial disorders caused by variants in mitochondrial DNA polymerase γ (POLG; e.g., Alpers-Huttenlocher Syndrome) and children under two years of age who are suspected of having a POLG-related disorder" (FDA, 2015).

Medically Necessary Statement Definitions and Testing Strategy

The medically necessary statement refers to epilepsy syndromes that present in infancy or early childhood, are severe, and are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. As defined by the International League Against Epilepsy, these include epileptic encephalopathies, which are electroclinical syndrome associated with a high probability of encephalopathic features that present or worsen after the onset of epilepsy. Other clinical manifestations, including developmental delay and/or intellectual disability may be present secondary to the epilepsy itself. Specific clinical syndromes based on the International League Against Epilepsy classification include:

- Dravet syndrome (also known as severe myoclonic epilepsy in infancy [SMEI] or polymorphic myoclonic epilepsy in infancy [PMEI])
- EFMR syndrome (epilepsy limited to females with mental retardation)

- Epileptic encephalopathy with continuous spike-and-wave during sleep
- GEFS+ syndrome (genetic epilepsy with febrile seizures plus)
- Ohtahara syndrome (also known as early infantile epileptic encephalopathy with burst suppression pattern)
- Landau-Kleffner syndrome
- West syndrome
- Glucose transporter type 1 deficiency syndrome

Variants in a large number of genes have been associated with early onset epilepsies. Some of these are summarized in Table PG1.

Table PG1: Single-Genes Associated With Epileptic Syndromes

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*

<u>Application of Medically Necessary Policy Statement</u>

Although there is not standard definition of epileptic encephalopathies, they are generally characterized by at least some of the following: (1) onset in early childhood (often in infancy); (2) refractory to therapy; (3) associated with developmental delay or regression; and (4) severe electroencephalogram (EEG) abnormalities. There is a challenge in defining the population appropriate for testing given that specific epileptic syndromes may be associated with different EEG abnormalities, which may change over time, and patients may present with severe seizures prior to the onset or recognition of developmental delay or regression. However, for this protocol, the medically necessary policy statement would apply for patients with:

1. Onset of seizures in early childhood (i.e., 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 that would potentially better explain the patient's symptoms.

<u>Testing Strategy</u>

There is clinical and genetic overlap for many of the electroclinical syndromes previously discussed. If there is suspicion for a specific syndrome based on history, EEG findings, and other test results, testing should begin with targeted mutation 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/ 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. In these cases, panels should meet the criteria outlined in the Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders Protocol.

Genetics Nomenclature Update

Human Genome Variation Society (HGVS) nomenclature is used to report information on variants found in DNA and serves as an international standard in DNA diagnostics. It is being implemented for genetic testing medical protocol updates starting in 2017 (see Table PG2). HGVS nomenclature is recommended by HGVS, the Human Variome Project, and the HUman Genome Organization (HUGO).

The American College of Medical Genetics and Genomics (ACMG) and Association for Molecular Pathology (AMP) standards and guidelines for interpretation of sequence variants represent expert opinion from ACMG, AMP, and the College of American Pathologists. These recommendations primarily apply to genetic tests used in clinical laboratories, including genotyping, single genes, panels, exomes, and genomes. Table PG3 shows the recommended standard terminology—"pathogenic," "likely pathogenic," "uncertain significance," "likely benign," and "benign"—to describe variants identified that cause Mendelian disorders.

Table PG2. Nomenclature to Report on Variants Found in DNA

Previous	Updated	Definition
Mutation	Disease-associated variant	Disease-associated change in the DNA sequence
	Variant	Change in the DNA sequence
	Familial variant	Disease-associated variant identified in a proband for use in subsequent targeted genetic testing in first-degree relatives

Table PG3. ACMG-AMP Standards and Guidelines for Variant Classification

Variant Classification	Definition
Pathogenic	Disease-causing change in the DNA sequence
Likely pathogenic	Likely disease-causing change in the DNA sequence
Variant of uncertain significance	Change in DNA sequence with uncertain effects on disease
Likely benign	Likely benign change in the DNA sequence
Benign	Benign change in the DNA sequence

American College of Medical Genetics and Genomics; AMP: Association for Molecular Pathology

Genetic Counseling

Genetic counseling is primarily aimed at patients who are at risk for inherited disorders, and experts recommend formal genetic counseling in most cases when genetic testing for an inherited condition is considered. The interpretation of the results of genetic tests and the understanding of risk factors can be very difficult and complex. Therefore, genetic counseling will assist individuals in understanding the possible benefits and harms of genetic testing, including the possible impact of the information on the individual's family. Genetic counseling may alter the utilization of genetic testing substantially and may reduce inappropriate testing. Genetic counseling should be performed by an individual with experience and expertise in genetic medicine and genetic testing methods.

Medicare Advantage

In addition to or in place the above policy statements the following statement applies for Medicare Advantage.

Genetic testing for the following genes is unlikely to impact therapeutic decision-making, directly impact treatment, outcome and/or clinical management in the care of the patient with epilepsy and therefore are considered **not medically necessary**: MT-TK, ARX, EPM2A, ALDH7A1, CDKL5, and EFHC1.

Background

Epilepsy

Epilepsy is defined as the occurrence of two or more unprovoked seizures. It is a common neurologic disorder, with approximate 3% of the population developing the disorder over their entire lifespan.[1] The condition is generally chronic, requiring treatment with one or more medications to adequately control symptoms. Seizures can be controlled by antiepileptic medications in most cases, but some patients are resistant to medications, and further options such as surgery, vagus nerve stimulation, and/or the ketogenic diet can be used.[2]

Classification

Epilepsy is heterogeneous in etiology and clinical expression and can be classified in a variety of ways. Most commonly, classification is done by the clinical phenotype, i.e., the type of seizures that occur. The International League Against Epilepsy (ILAE) developed the classification system shown in Table 1[3] that is widely used for clinical care and research purposes (see Table 1).[3] Classification of seizures can also be done on the basis of age of onset: neonatal, infancy, childhood, and adolescent/adult.

Table 1. Classification of Seizure Disorders by Type (condensed from Berg et al, 2010)[3]

Seizures Disorders
Partial (focal seizures)
Simple partial seizures (consciousness not impaired)
With motor symptoms
With somatosensory or special sensory symptoms
With autonomic symptoms or signs
With psychic symptoms (disturbance of higher cerebral function)
Complex partial (with impairment of consciousness)
Simple partial onset followed by impairment of consciousness
Impairment of consciousness at outset
Partial seizures evolving to secondarily generalized seizures
Generalized seizures
Nonconvulsive (absence)
Convulsive
Unclassified seizures

More recently, the concept of genetic epilepsies has emerged as a way of classifying epilepsy. Many experts now refer to "genetic generalized epilepsy" as an alternative classification for seizures that were previously called "idiopathic generalized epilepsies." The ILAE report published in 2010 offers the following alternative classification[3]:

- Genetic epilepsies. These are conditions in which the seizures are a direct result of a known or presumed genetic defect(s). Genetic epilepsies are characterized by recurrent unprovoked seizures in patients who do not have demonstrable brain lesions or metabolic abnormalities. In addition, seizures are the core symptom of the disorder and other symptomatology is not present, except as a direct result of seizures. This is differentiated from genetically determined conditions in which seizures are part of a larger syndrome, such as tuberous sclerosis, fragile X syndrome, or Rett syndrome.
- Structural/metabolic. These conditions have a distinct structural or metabolic condition that increases the likelihood of seizures. Structural conditions include a variety of central nervous system abnormalities such as stroke, tumor or trauma, and metabolic conditions include a variety of encephalopathic abnormalities that predispose to seizures. These conditions may have a genetic etiology, but the genetic defect is associated with a separate disorder that predisposes to seizures.
- Unknown cause. These are conditions in which the underlying etiology for the seizures cannot be determined and may include both genetic and nongenetic causes.

For the purposes of this protocol, the ILAE classification is most useful. The review will focus on the category of genetic epilepsies in which seizures are the primary clinical manifestation. This category does not include syndromes that have multiple clinical manifestations, of which seizures may be one. Examples of syndromes that include seizures are Rett syndrome and tuberous sclerosis. Genetic testing for these syndromes will not be assessed in this protocol, but may be included in separate protocols that specifically address genetic testing for that syndrome.

Genetic epilepsies can be further broken down by type of seizures. For example, genetic generalized epilepsy refers to patients who have convulsive (grand mal) seizures, while genetic absence epilepsy refers to patients with nonconvulsive (absence) seizures. The disorders are also sometimes classified by age of onset.

The category of genetic epilepsies includes a number of rare epilepsy syndromes that present in infancy or early childhood.[1, 4] These are syndromes that are characterized by epilepsy as the primary manifestation, without associated metabolic or brain structural abnormalities. They are often severe and sometimes refractory to medication treatment. They may involve other clinical manifestations such as development delay and/or intellectual disability, which in many cases are thought to be caused by frequent uncontrolled seizures. In these cases, the epileptic syndrome may be classified as an epileptic encephalopathy, which is described by ILAE as disorders in which the epileptic activity itself may contribute to severe cognitive and behavioral impairments above and beyond what might be expected from the underlying pathology alone and that these can worsen over time.[3] A partial list of severe early-onset epilepsy syndromes is as follows:

- Dravet syndrome
- EFMR syndrome (epilepsy limited to females with mental retardation)
- Nocturnal frontal lobe epilepsy
- GEFS+ syndrome (genetic epilepsy with febrile seizures plus)
- EIEE syndrome (early infantile epileptic encephalopathy with burst suppression pattern)
- West syndrome
- Ohtahara syndrome

Dravet syndrome (also known as severe myoclonic epilepsy in infancy or polymorphic myoclonic epilepsy in infancy) falls on a spectrum of SCN1A-related seizure disorders, which includes febrile seizures at the mild end to Dravet syndrome and intractable childhood epilepsy with generalized tonic-clonic seizures at the severe end. The spectrum may be associated with multiple seizure phenotypes, with a broad spectrum of severity; more severe seizure disorders may be associated with cognitive impairment or deterioration.[5] Ohtahara syndrome is a severe early-onset epilepsy syndrome characterized by intractable tonic spasms, other seizures, interictal EEG abnormalities, and developmental delay. It may be secondary to structural abnormalities but has been associated with variants in the STXBP1 gene in rare cases. West syndrome is an early-onset seizure disorder associated with infantile spasms and the characteristic EEG finding of hypsarrhythmia. Other seizure disorders that present early in childhood may have a genetic component but are characterized by a more benign course including benign familial neonatal seizures and benign familial infantile seizures.

Genetics

Most genetic epilepsies are primarily believed to involve multifactorial inheritance patterns. This follows the concept of a threshold effect, in which any particular genetic defect may increase the risk of epilepsy, but is not by itself causative.[6] A combination of risk-associated genes, together with environmental factors, determines whether the clinical phenotype of epilepsy occurs. In this model, individual genes that increase the susceptibility to epilepsy have a relatively weak impact. Multiple genetic defects, and/or particular combination of genes, probably increase the risk by a greater amount. However, it is not well understood how many abnormal genes are required to exceed the threshold to cause clinical epilepsy, nor is it understood which combination of genes may increase the risk more than others.

Early-onset epilepsy syndromes may be single-gene disorders. This hypothesis arises from the discovery of pathologic variants in small numbers of patients with the disorders. Because of the small amount of research available, the evidence base for these rare syndromes is incomplete, and new variants are currently being discovered frequently.[7]

Some of the most common genes that have been associated with genetic epileptic syndromes are listed in Table 2.

Table 2. Selected Genes Most Commonly Associated With Genetic Epilepsy (adapted from Williams and Battaglia, 2013)[1]

Gene	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

For the severe early epilepsy syndromes, the disorders most frequently reported to be associated with single-gene variants include GEFS+ syndrome (associated with SCN1A, SCN1B, GABRG2 variants), Dravet syndrome (associated with SCN1A variants, possibly modified by SCN9A variants), and epilepsy and intellectual disability limited to females (associated with PCDH19 variants). Ohtahara syndrome has been associated with variants in STXBP1 in cases where patients have no structural or metabolic abnormalities. West syndrome is often associated with chromosomal abnormalities or tuberous sclerosis, or may be secondary to an identifiable infectious or metabolic cause, but when there is not an underlying cause identified it is thought to be due to a multifactorial genetic predisposition.[8]

Targeted testing for individual genes is available. Several commercial epilepsy genetic panels are also available. The number of genes included in the tests varies widely, from about 50 to over 450. The panels frequently include genes for other disorders such as neural tube defects, lysosomal storage disorders, cardiac channelopathies, congenital disorders of glycosylation, metabolic disorders, neurologic syndromes and multisystemic genetic syndromes. Some panels are designed to be comprehensive while other panels target specific subtypes of epilepsy Chambers et al (2016) reviewed comprehensive epilepsy panels from seven U.S.-based clinical laboratories and found that between 1% and 4% of panel contents were genes not known to be associated with primary epilepsy.[9] Between 1% and 70% of the genes included on an individual panel were not on any other panel.

Pharmacogenomics

Another area of interest for epilepsy is the pharmacogenomics of antiepileptic medications. There are a wide variety of these medications from numerous different classes. The choice of medications, and the combinations of medications for patients who require treatment with more than one agent, is complex. Approximately one third of patients are considered refractory to medications, defined as inadequate control of symptoms with a single medication.[10] These patients often require escalating doses and/or combinations of different medications. At present, selection of agents is driven by the clinical phenotype of seizures, but has a large trial and error component in many refractory cases. The current focus of epilepsy pharmacogenomics is in identifying genetic markers that identify patients who are likely to be refractory to the most common medications. This may lead to directed treatment that will result in a more efficient process for medication selection, and potentially more effective control of symptoms.

Of note, genotyping for the HLA-B*1502 allelic variant in patients of Asian ancestry, prior to considering drug treatment with carbamazepine due to risks of severe dermatologic reactions, is recommended by the U.S. Food and Drug Administration labeling for carbamazepine.[11] Serious dermatologic reactions, including sometimes fatal dermatologic reactions (including toxic epidermal necrolysis [TEN] and Stevens-Johnson Syndrome [SJS]) may occur in individuals with the HLA-B*1502 allele. HLA-B*1502 is found almost exclusively in patients with ancestry across broad areas of Asia. FDA Labeling on carbamazepine products contains the warning "patients with ancestry in genetically at-risk populations should be screened for the presence of HLA-B*1502 prior to initiating treatment with carbamazepine. Patients testing positive for the allele should not be treated with carbamazepine unless the benefit clearly outweighs the risk."

Regulatory Status

Clinical laboratories may develop and validate tests in-house and market them as a laboratory service; laboratory-developed tests (LDTs) must meet the general regulatory standards of the Clinical Laboratory Improvement Act (CLIA). Commercially-available genetic tests for epilepsy are available under the auspices of CLIA. Laboratories that offer LDTs must be licensed by CLIA for high-complexity testing. To date, the FDA has chosen not to require any regulatory review of this test.

Related Protocols

Cytochrome P450 Genotyping

General Approach to Evaluating the Utility of Genetic Panels

Whole Exome and Whole Genome Sequencing for Diagnosis of Genetic Disorders

Genetic Testing for Developmental Delay and Autism Spectrum Disorder

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References

We are not responsible for the continuing viability of web site addresses that may be listed in any references below.

1. Williams CA, Battaglia A. Molecular biology of epilepsy genes. Exp Neurol. Jun 2013; 244:51-58. PMID 22178301
2. Kwan P, Brodie MJ. Early identification of refractory epilepsy. N Engl J Med. Feb 3 2000; 342(5):314-319. PMID 10660394
3. Berg AT, Berkovic SF, Brodie MJ, et al. Revised terminology and concepts for organization of seizures and epilepsies: report of the ILAE Commission on Classification and Terminology, 2005-2009. Epilepsia. Apr 2010; 51(4):676-685. PMID 20196795
4. Merwick A, O'Brien M, Delanty N. Complex single gene disorders and epilepsy. Epilepsia. Sep 2012; 53 Suppl 4:81-91. PMID 22946725
5. Miller IO, Sotero de Menezes MA. SCN1A-Related Seizure Disorders. GeneReviews. 2007 (updated 2014). PMID 20301494
6. Petrovski S, Kwan P. Unraveling the genetics of common epilepsies: approaches, platforms, and caveats. Epilepsy Behav. Mar 2013; 26(3):229-233. PMID 23103323
7. Helbig I, Lowenstein DH. Genetics of the epilepsies: where are we and where are we going? Curr Opin Neurol. Apr 2013; 26(2):179-185. PMID 23429546
8. Deprez L, Jansen A, De Jonghe P. Genetics of epilepsy syndromes starting in the first year of life. Neurology. Jan 20 2009; 72(3):273-281. PMID 19153375
9. Chambers C, Jansen LA, Dhamija R. Review of commercially available epilepsy genetic panels. J Genet Couns. Apr 2016; 25(2):213-217. PMID 26536886
10. Cavalleri GL, McCormack M, Alhusaini S, et al. Pharmacogenomics and epilepsy: the road ahead. Pharmacogenomics. Oct 2011; 12(10):1429-1447. PMID 22008048
11. Food and Drug Administration (FDA). Label: Tegretol. 2014; http://www.accessdata.fda.gov/drugsatfda_docs/label/2014/016608s099,018281s047,018927s040,020234s030l bl.pdf. Accessed January 17, 2017.
12. Food and Drug Administration (FDA). Depakene (valproic acid) Capsules and Oral Solution, Depakote (divalproex sodium) Delayed Release and Depakote ER (Extended Release) Tablets, Depakote Sprinkle Capsules (divalproex sodium coated particles in capsules), Depacon (valproate sodium) Injection. Safety Labeling Changes Approved By FDA Center for Drug Evaluation and Research (CDER) 2015; http://www.fda.gov/Safety/MedWatch/SafetyInformation/ucm360487.htm. Accessed January 17, 2017.
13. Dyment DA, Tetreault M, Beaulieu CL, et al. Whole-exome sequencing broadens the phenotypic spectrum of rare pediatric epilepsy: a retrospective study. Clin Genet. Jul 2015; 88(1):34-40. PMID 25046240
14. Thevenon J, Milh M, Feillet F, et al. Mutations in SLC13A5 cause autosomal-recessive epileptic encephalopathy with seizure onset in the first days of life. Am J Hum Genet. Jul 3 2014; 95(1):113-120. PMID 24995870
15. GeneTests. https://www.genetests.org/. Accessed January 5, 2017.
16. National Center for Biotechnology Information, Genetic Testing Registry. https://www.ncbi.nlm.nih.gov/gtr/. Accessed January 5, 2017.
17. Hirose S, Scheffer IE, Marini C, et al. SCN1A testing for epilepsy: application in clinical practice. Epilepsia. May 2013; 54(5):946-952. PMID 23586701
18. Mulley JC, Nelson P, Guerrero S, et al. A new molecular mechanism for severe myoclonic epilepsy of infancy: exonic deletions in SCN1A. Neurology. Sep 26 2006; 67(6):1094-1095. PMID 17000989
19. Wu YW, Sullivan J, McDaniel SS, et al. Incidence of Dravet syndrome in a US population. Pediatrics. Nov 2015; 136(5):e1310-1315. PMID 26438699
20. Moller RS, Larsen LH, Johannesen KM, et al. Gene panel testing in epileptic encephalopathies and familial epilepsies. Mol Syndromol. Sep 2016; 7(4):210-219. PMID 27781031

21. Trump N, McTague A, Brittain H, et al. Improving diagnosis and broadening the phenotypes in early-onset seizure and severe developmental delay disorders through gene panel analysis. J Med Genet. May 2016; 53(5):310-317. PMID 26993267
22. Wirrell EC, Shellhaas RA, Joshi C, et al. How should children with West syndrome be efficiently and accurately investigated? Results from the National Infantile Spasms Consortium. Epilepsia. Apr 2015; 56(4):617-625. PMID 25779538
23. Mercimek-Mahmutoglu S, Patel J, Cordeiro D, et al. Diagnostic yield of genetic testing in epileptic encephalopathy in childhood. Epilepsia. May 2015; 56(5):707-716. PMID 25818041
24. Hrabik SA, Standridge SM, Greiner HM, et al. The clinical utility of a single-nucleotide polymorphism microarray in patients with epilepsy at a tertiary medical center. J Child Neurol. Nov 2015; 30(13):1770-1777. PMID 25862739
25. Ottman R, Hirose S, Jain S, et al. Genetic testing in the epilepsies--report of the ILAE Genetics Commission. Epilepsia. Apr 2010; 51(4):655-670. PMID 20100225
26. Go CY, Mackay MT, Weiss SK, et al. Evidence-based guideline update: medical treatment of infantile spasms. Report of the Guideline Development Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. Jun 12 2012; 78(24):1974-1980. PMID 22689735
27. Pellock JM, Hrachovy R, Shinnar S, et al. Infantile spasms: a U.S. consensus report. Epilepsia. Oct 2010; 51(10):2175-2189. PMID 20608959
28. Wilmshurst JM, Gaillard WD, Vinayan KP, et al. Summary of recommendations for the management of infantile seizures: Task Force Report for the ILAE Commission of Pediatrics. Epilepsia. Aug 2015; 56(8):1185-1197. PMID 26122601
29. Epilepsies: diagnosis and management. Clinical guideline 2012; CG137:https://www.nice.org.uk/guidance/cg137/resources/epilepsies-diagnosis-and-management-35109515407813. Accessed January 26, 2016.
30. Ream MA, Mikati MA. Clinical utility of genetic testing in pediatric drug-resistant epilepsy: A pilot study. Epilepsy Behav. Aug 2014; 37:241-248. PMID 25108116
31. National Institute of Neurological Disorders and Stroke (NINDS). NINDS Common Data Elements. Epilepsy. 2017, January 31; https://www.commondataelements.ninds.nih.gov/Epilepsy.aspx#tab=Data_Standards. Accessed February 7, 2017.
32. Tan NC, Berkovic SF. The Epilepsy Genetic Association Database (epiGAD): analysis of 165 genetic association studies, 1996-2008. Epilepsia. Apr 2010; 51(4):686-689. PMID 20074235
33. International League Against Epilepsy Consortium on Complex Epilepsies. Electronic address e-auea. Genetic determinants of common epilepsies: a meta-analysis of genome-wide association studies. Lancet Neurol. Sep 2014; 13(9):893-903. PMID 25087078
34. Epicure Consortium, EMINet Consortium, Steffens M, et al. Genome-wide association analysis of genetic generalized epilepsies implicates susceptibility loci at 1q43, 2p16.1, 2q22.3 and 17q21.32. Hum Mol Genet. Dec 15 2012; 21(24):5359-5372. PMID 22949513
35. Guo Y, Baum LW, Sham PC, et al. Two-stage genome-wide association study identifies variants in CAMSAP1L1 as susceptibility loci for epilepsy in Chinese. Hum Mol Genet. Mar 1 2012; 21(5):1184-1189. PMID 22116939
36. Cordoba M, Consalvo D, Moron DG, et al. SLC6A4 gene variants and temporal lobe epilepsy susceptibility: a meta-analysis. Mol Biol Rep. Dec 2012; 39(12):10615-10619. PMID 23065262
37. Nurmohamed L, Garcia-Bournissen F, Buono RJ, et al. Predisposition to epilepsy--does the ABCB1 gene play a role? Epilepsia. Sep 2010; 51(9):1882-1885. PMID 20491876
38. Kauffman MA, Moron DG, Consalvo D, et al. Association study between interleukin 1 beta gene and epileptic disorders: a HuGe review and meta-analysis. Genet Med. Feb 2008; 10(2):83-88. PMID 18281914
39. Tang L, Lu X, Tao Y, et al. SCN1A rs3812718 polymorphism and susceptibility to epilepsy with febrile seizures: a meta-analysis. Gene. Jan 1 2014; 533(1):26-31. PMID 24076350

40. von Podewils F, Kowoll V, Schroeder W, et al. Predictive value of EFHC1 variants for the long-term seizure outcome in juvenile myoclonic epilepsy. Epilepsy Behav. Mar 2015; 44:61-66. PMID 25625532
41. Kwan P, Poon WS, Ng HK, et al. Multidrug resistance in epilepsy and polymorphisms in the voltage-gated sodium channel genes SCN1A, SCN2A, and SCN3A: correlation among phenotype, genotype, and mRNA expression. Pharmacogenet Genomics. Nov 2008; 18(11):989-998. PMID 18784617
42. Jang SY, Kim MK, Lee KR, et al. Gene-to-gene interaction between sodium channel-related genes in determining the risk of antiepileptic drug resistance. J Korean Med Sci. Feb 2009; 24(1):62-68. PMID 19270815
43. Li SX, Liu YY, Wang QB. ABCB1 gene C3435T polymorphism and drug resistance in epilepsy: evidence based on 8,604 subjects. Med Sci Monit. 2015; 21:861-868. PMID 25799371
44. Lu Y, Fang Y, Wu X, et al. Effects of UGT1A9 genetic polymorphisms on monohydroxylated derivative of oxcarbazepine concentrations and oxcarbazepine monotherapeutic efficacy in Chinese patients with epilepsy. Eur J Clin Pharmacol. Nov 29 2016. PMID 27900402
45. Hashi S, Yano I, Shibata M, et al. Effect of CYP2C19 polymorphisms on the clinical outcome of low-dose clobazam therapy in Japanese patients with epilepsy. Eur J Clin Pharmacol. Jan 2015; 71(1):51-58. PMID 25323806
46. Ma CL, Wu XY, Jiao Z, et al. SCN1A, ABCC2 and UGT2B7 gene polymorphisms in association with individualized oxcarbazepine therapy. Pharmacogenomics. 2015; 16(4):347-360. PMID 25823783
47. Guo Y, Yan KP, Qu Q, et al. Common variants of KCNJ10 are associated with susceptibility and anti-epileptic drug resistance in Chinese genetic generalized epilepsies. PLoS One. 2015; 10(4):e0124896. PMID 25874548
48. Ma CL, Wu XY, Zheng J, et al. Association of SCN1A, SCN2A and ABCC2 gene polymorphisms with the response to antiepileptic drugs in Chinese Han patients with epilepsy. Pharmacogenomics. Jul 2014; 15(10):1323-1336. PMID 25155934
49. Radisch S, Dickens D, Lang T, et al. A comprehensive functional and clinical analysis of ABCC2 and its impact on treatment response to carbamazepine. Pharmacogenomics J. Oct 2014; 14(5):481-487. PMID 24567120
50. Yun W, Zhang F, Hu C, et al. Effects of EPHX1, SCN1A and CYP3A4 genetic polymorphisms on plasma carbamazepine concentrations and pharmacoresistance in Chinese patients with epilepsy. Epilepsy Res. Dec 2013; 107(3):231-237. PMID 24125961
51. Taur SR, Kulkarni NB, Gandhe PP, et al. Association of polymorphisms of CYP2C9, CYP2C19, and ABCB1, and activity of P-glycoprotein with response to anti-epileptic drugs. J Postgrad Med. Jul-Sep 2014; 60(3):265-269. PMID 25121365
52. Haerian BS, Roslan H, Raymond AA, et al. ABCB1 C3435T polymorphism and the risk of resistance to antiepileptic drugs in epilepsy: a systematic review and meta-analysis. Seizure. Jul 2010; 19(6):339-346. PMID 20605481
53. Sun G, Sun X, Guan L. Association of MDR1 gene C3435T polymorphism with childhood intractable epilepsy: a meta-analysis. J Neural Transm. Jul 2014; 121(7):717-724. PMID 24553780
54. Shazadi K, Petrovski S, Roten A, et al. Validation of a multigenic model to predict seizure control in newly treated epilepsy. Epilepsy Res. Dec 2014; 108(10):1797-1805. PMID 25282706
55. Chung WH, Chang WC, Lee YS, et al. Genetic variants associated with phenytoin-related severe cutaneous adverse reactions. JAMA. Aug 6 2014; 312(5):525-534. PMID 25096692
56. He XJ, Jian LY, He XL, et al. Association of ABCB1, CYP3A4, EPHX1, FAS, SCN1A, MICA, and BAG6 polymorphisms with the risk of carbamazepine-induced Stevens-Johnson syndrome/toxic epidermal necrolysis in Chinese Han patients with epilepsy. Epilepsia. Aug 2014; 55(8):1301-1306. PMID 24861996
57. Wang W, Hu FY, Wu XT, et al. Genetic susceptibility to the cross-reactivity of aromatic antiepileptic drugs induced cutaneous adverse reactions. Epilepsy Res. Aug 2014; 108(6):1041-1045. PMID 24856347
58. Bagnall RD, Crompton DE, Cutmore C, et al. Genetic analysis of PHOX2B in sudden unexpected death in epilepsy cases. Neurology. Sep 9 2014; 83(11):1018-1021. PMID 25085640
59. Coll M, Allegue C, Partemi S, et al. Genetic investigation of sudden unexpected death in epilepsy cohort by panel target resequencing. Int J Legal Med. Mar 2016; 130(2):331-339. PMID 26423924

60. Bagnall RD, Crompton DE, Petrovski S, et al. Exome-based analysis of cardiac arrhythmia, respiratory control, and epilepsy genes in sudden unexpected death in epilepsy. Ann Neurol. Apr 2016; 79(4):522-534. PMID 26704558
61. Riviello JJ, Jr., Ashwal S, Hirtz D, et al. Practice parameter: diagnostic assessment of the child with status epilepticus (an evidence-based review): report of the Quality Standards Subcommittee of the American Academy of Neurology and the Practice Committee of the Child Neurology Society. Neurology. Nov 14 2006; 67(9):1542-1550. PMID 17101884
62. Hirtz D, Ashwal S, Berg A, et al. Practice parameter: evaluating a first nonfebrile seizure in children: report of the quality standards subcommittee of the American Academy of Neurology, The Child Neurology Society, and The American Epilepsy Society. Neurology. Sep 12 2000; 55(5):616-623. PMID 10980722
63. Burgunder JM, Finsterer J, Szolnoki Z, et al. EFNS guidelines on the molecular diagnosis of channelopathies, epilepsies, migraine, stroke, and dementias. Eur J Neurol. May 2010; 17(5):641-648. PMID 20298421
64. National Government Services, Inc. (Primary Geographic Jurisdiction - Illinois, New York - Entire State, Connecticut, Massachusetts, Maine, New Hampshire, Rhode Island, Vermont, Wisconsin, Minnesota) Local Coverage Determination (LCD): Molecular Pathology Procedures (L35000), Revision Effective Date for services performed on or after 08/01/2017.