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Background

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

Treatment

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

Etiology and Diagnosis

- Causes of epilepsy can be assessed by electroencephalogram (EEG), magnetic resonance imaging (MRI), laboratory testing (for infection, autoimmune conditions, metabolic conditions, and toxic exposures), clinical evaluation, and genetic testing.[4]
- Genetic causes of epilepsy can be assessed by chromosomal microarrays, multi-gene panels, exome sequencing, and genome sequencing. A genetic diagnosis was made in 17%[5] to 24%[6,7] of epilepsy cases.
- Hundreds of genes have been associated with epilepsy across the lifespan of individuals (ranging from early-onset infantile epilepsy to adult-onset epilepsy). Relatively common genes that have actionable results include *ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2,* and *ZEB2*.[8]
- Epilepsy has high genetic heterogeneity and considerable phenotypic overlap between epilepsy conditions. It is not uncommon for a patient with clinical features fitting a certain epilepsy condition to have a genetic diagnosis in a gene not traditionally associated with that condition.

Utility of Genetic Diagnoses

- A genetic diagnosis changed treatment in 12-80% of epilepsy patients including optimal anti-seizure medication, dietary treatment, and epilepsy surgical decisions.[5]
- A genetic diagnosis informs recurrence risk estimations used in family planning.[5,9,10]
- A genetic diagnosis ends diagnostic odysseys that burden families, providers, and payers.[11] A diagnosis was reached 1-8 years earlier in patients who received genetic testing by multi-gene panels or exome sequencing.[11]

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Characteristics of Genetic Epilepsy

- Both focal and generalized epilepsy can have a genetic cause. Focal epilepsy involves abnormal activity in one area of the brain and can cause impaired awareness or loss of consciousness. Generalized epilepsy involves all areas of the brain and includes absence seizures, tonic seizures, atonic seizures, clonic seizures, myoclonic seizures, and tonic-clonic seizures.[2] A genetic cause was identified in 15.8% of patients with focal epilepsy, in 24.3% of patients with generalized epilepsy, and in 24.7% of patients with both generalized and focal epilepsy.[6]
- Earlier age of seizure onset increases the likelihood of a genetic cause.
    - The diagnostic yield of genetic testing is 29.6% in patients with seizure onset within the first year of life, 13.6% for onset between 2-4 years, 7% for onset between 5-10 years, 2.4% for onset between 11-17 years, and 3.7% with onset after 18 years.[12]
    - While the patient's age at seizure onset affects the likelihood of a genetic cause, the patient's age at the time of testing does not.[13]
- Comorbidities including intellectual disability, developmental delay, autism spectrum disorder, and/or encephalopathy increase the likelihood of a genetic cause for epilepsy.[5,6,11,13]
- Drug-resistant epilepsy is more likely to have a genetic cause.[11]
- A family history of epilepsy increases the chance of identifying a genetic cause, however, a lack of family history does not rule out a genetic cause. *De novo* variants were identified in 33.7% of patients with epileptic encephalopathies,[13] and both *de novo* and recessive variants have been noted as significant causes of epilepsy.[11,13]
- Some of the most common genetic causes of epilepsy are summarized below. This is not an exhaustive list due to the significant genetic and phenotypic heterogeneity in epilepsy. There is also considerable genetic and phenotypic overlap between conditions.
    - **Benign Familial Epilepsy**
        - Characterized by cluster seizures and focal motor seizures that evolve to grand mal seizures. EEG is normal. Age of onset is within the first few months of life with remission by age 3.
        - Caused by variants in *PRRT2, SCN2A*, and *SCN8A* (Benign Familial Infantile Epilepsy), *KCNQ2* and *KCNQ3* (Benign Familial Neonatal Epilepsy), *SCN2A* (Benign Familial Neonatal-Infantile Epilepsy). Inheritance pattern is autosomal dominant.
    - **Genetic Epilepsy with Febrile Seizures Plus (GEFS+)**
        - A spectrum of conditions with a combination of febrile, absence, myoclonic, and atonic seizures. EEG shows a normal background with generalized discharges. Age of onset is after 6 months of life with remission by age 5 or early adolescence.
        - Caused by variants in *SCN1A, SCN1B, GABRG2, STX1B* and *SCN9A*. Inheritance patterns include autosomal dominant and autosomal recessive.

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- **Early Infantile Epileptic Encephalopathy**, also known as **Ohtahara Syndrome**
  - Characterized by a wide spectrum of seizure types, most commonly focal or generalized tonic seizures or clustered tonic spasms (as many as hundreds per day). EEG shows a burst-suppression pattern. Most individuals have intellectual disability, hypotonia, or spastic quadriplegia. Age of onset is within the first 3 months of life and is lethal in infancy or severely progressive to West Syndrome or Lennox-Gastaut Syndrome in childhood.
  - Caused by variants in *STXBP1* (30%), *KCNQ2* (20%), *SCN2A* (10%), and at least 12 other genes including *SLC25A22*, *CDKL5*, and *ARX*. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Early Myoclonic Encephalopathy**
  - Characterized by focal myoclonic seizures, and isolated or clustered tonic spasms. EEG shows a burst-suppression pattern that can be more distinct during sleep. Prognosis is poor with high mortality and morbidity. Age of onset is within the first 3 months of life.
  - Caused by variants in *SETBP, SIK1, SLC25A22, PIGA,* and *ERBB4*. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Infantile Spasms Syndrome**, including **West Syndrome**
  - Characterized by infantile spasms, developmental delay, and regression. EEG shows hypsarrhythmia. May progress to Lennox-Gastaut Syndrome or other seizure types. Age of onset is 2-12 months, usually around 6 months.
  - Caused by variants in *CDKL5* (10%), *STXBP1* (2%), and at least 46 other genes. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Dravet Syndrome and Dravet-like Phenotypes**
  - Characterized by prolonged hemiconvulsive or generalized febrile seizures for the first year, followed by intractable afebrile seizures, frequent status epilepticus, developmental delay, and possible regression. EEG is normal for the first 1-2 years, then shows generalized and multiform epileptiform abnormalities. Age of onset is 5-16 months, usually around 5-8 months.
  - Caused by variants in *SCN1A* (90%) and at least 12 other genes including *SCN1B, SCN9A, STXBP1, PCDH19, HCN1, GABRA1,* and *CHD2*. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Epilepsy of Infancy with Migrating Focal Seizures (EIMFS)**
  - Characterized by focal seizures that migrate between cerebral hemispheres, severe-to-profound developmental delay, and often regression. EEG can be normal, show multifocal spikes with slow

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background activity, or show a burst-suppression pattern. Age of onset is within the first 6 months of life.
    - Caused by variants in *KCNT1* (27%), *SCN2A* (7-25%), and at least 21 other genes. Inheritance patterns include autosomal dominant, autosomal recessive, and X-linked.
- **Lennox-Gastaut Syndrome**
    - Characterized by focal, tonic, atonic, myoclonic, absence, or generalized tonic-clonic seizures, spasms, or nonconvulsive status epilepticus, developmental delay, and cognitive impairment. EEG shows a slow spike-and-wave pattern. Age of onset is 1-8 years, usually between 3-5 years, with rare adult onset.
    - Caused by variants in *ALG13, CACNA1A, CDKL5, CHD2, DNM1, FLNA, GABRB3, GRIN2B, HNPRNU, HNRNPH1, IQSEC1, IQSEC2, KCNQ3, MTOR, SCN1A, SCN2A, SCN8A,* and *STXBP1*. While most variants are *de novo*, the inheritance pattern is autosomal dominant.
- **Epilepsy-Aphasia Spectrum**, including **Landau-Kleffner Syndrome**, **Epileptic Encephalopathy with Continuous Spike-Wave Discharges in Slow Wave Sleep**, and **Atypical Benign Rolandic Epilepsy**
    - Characterized by language impairment, rolandic seizures, focal seizures, atonic seizures, epileptic encephalopathy, mild to severe intellectual disability, and normal to severe developmental delay often with regression. EEG shows a continuous spike-and-wave during slow-wave sleep pattern or centrotemporal spikes that synchronize and increase during sleep. Age of onset is 3-7 years with remission by mid-adolescence.
    - Caused by variants in *GRIN2A* (10-20%). Inheritance pattern is autosomal dominant.
- **Childhood Absence Epilepsy**
    - Characterized by brief, frequent absence seizures. EEG shows an asynchronous, bilateral spike-and-wave pattern. Age of onset is 3-8 years, usually between 5-7 years.
    - Caused by variants in *GABRA1, GABRB3, GABRG2, JRK,* and *CACNA1H*. Inheritance patterns include autosomal dominant and multifactorial.
- **Juvenile Myoclonic Epilepsy**
    - Characterized by myoclonic jerks or seizures, generalized tonic-clonic seizures, and absence seizures. EEG shows a 3-6 Hz generalized polyspike and wave discharge. Age of onset is 12-18 years.
    - Caused by *CACNB4, EFHC1, GABRA1*, and *CILK1*. Inheritance patterns include autosomal dominant, autosomal recessive, and multifactorial.

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- **Familial Temporal Lobe Epilepsy**
  - Characterized by seizures involving one or both temporal lobes, including focal aware seizures, focal impaired awareness seizures, tonic-clonic jerking, and rarely, status epilepticus. EEG shows spikes or sharp waves in the front of the temporal lobe. Age of onset is adolescence or early adulthood.
  - Caused by variants in *GAL, CPA6, RELN, LGI1*, *DEPDC5*, and *MICAL1*. Inheritance patterns include autosomal dominant and multifactorial.
- **Syndromes with epilepsy in addition to other clinical features**
  - The following conditions have clinical features in addition to unexplained epilepsy, and should be included in panel, exome, and genome testing for epilepsy. Targeted testing may be more appropriate for these conditions if there is strong clinical suspicion due to the presence of characteristic clinical features.
    - Glucose Transporter Type 1 Deficiency Syndrome (*SLC2A1*)
    - Angelman Syndrome (*UBE3A*, 15q11-q13 deletion, or uniparental disomy of chromosome 15)
    - Chromosome 1p36 Deletion Syndrome (1p36 deletion)
    - Miller-Dieker Syndrome (17p13.3 deletion)
    - Rett Syndrome (*MECP2*)
    - Ring chromosome 20 (breakage of fusion of chromosome 20)
    - Tuberous Sclerosis Complex (*TSC1*, *TSC2*)
    - Smith Kingsmore Syndrome (*MTOR*)
    - Focal cortical dysplasia (*MTOR, PIK3CA, PTEN, DEPDC5, NPRL2, NPRL3*)

Technical Information:

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

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

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- It is strongly recommended that genetic testing be conducted by a qualified healthcare provider, such as an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor, including test selection, ordering, interpretation, and pre- and post-test counseling.
- Exome/genome sequencing
    - Next-generation sequencing (NGS) is used to assess (1) the coding DNA sequence of all genes, also known as the exome, or (2) both coding and non-coding DNA sequences, also known as the genome.
    - Exome/genome sequencing has higher diagnostic yield and efficiency compared to multi-gene panel sequencing.[5] Exome/genome sequencing can identify variants that may be missed by multi-gene panel testing due to increased coverage of the genome.
    - Genome sequencing has higher diagnostic yield and efficiency compared to exome sequencing.[14] Genome sequencing has more uniform coverage and can identify variants that may be missed by exome sequencing, including deep intronic SNVs, small CNVs, and SNVs in noncoding RNA.[15]
    - A meta-analysis of 40 studies utilizing genetic testing in cohorts ascertained for epilepsy showed that the diagnostic yield of genome sequencing was 48%, exome sequencing was 24%, gene panels was 19%, and chromosomal microarray was 9%.[5]
    - Patients should be evaluated by a Board-Certified or Board-Eligible Medical Geneticist, an Advanced Practice Nurse in Genetics (APGN) credentialed by either the Genetic Nursing Credentialing Commission (GNCC) or the American Nurses Credentialing Center (ANCC), or a provider with expertise in epilepsy to determine if exome/genome sequencing is the most appropriate testing strategy.
    - Exome/genome sequencing may identify secondary findings that are variants associated with diseases other than epilepsy. The American College of Medical Genetics (ACMG) has identified a list of genes with clinically actionable findings that are recommended to report as secondary findings and is updated periodically.[16]
- Multi-gene panel testing
    - NGS is used to assess the coding DNA sequence of a select number of genes.
    - The diagnostic yield of multi-gene panels increases as the number of genes included on the panel increases.[5]
    - Multi-gene panel testing for epilepsy should include but not be limited to at least the following genes: *ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2,* and *ZEB2*.[8]
    - Multi-gene panel tests vary in technical specifications (e.g., depth of coverage, extent of intron/exon boundary analysis, methodology of large deletion/duplication analysis).

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    - Under certain circumstances, technologies used in multi-gene panel testing may fail to identify mutations that might be identifiable through single-gene testing. If high clinical suspicion remains for a particular syndrome after negative multi-gene panel test results, consultation with the testing lab and/or additional targeted genetic testing may be warranted. Ideal sample type may also be considered due to the occurrence of brain tissue-specific mosaicism in epilepsy.
- Single-gene testing
    - Due to significant genetic heterogeneity and large phenotypic overlap, single-gene testing is not recommended for epilepsy unless there is a known familial variant or the patient has additional clinical features distinctive of a particular genetic condition.

Guidelines and Evidence:

The most recent practice guideline on genetic testing for epilepsy was published in 2022, adopted by the National Society of Genetic Counselors (NSGC), and endorsed by the American Epilepsy Society (AES).[17] The guideline recommends genetic testing for individuals of any age with unexplained epilepsy. Both the NSGC and the International League Against Epilepsy Commission of Pediatrics (2015 practice guideline) recommend that genetic testing be conducted by qualified healthcare providers, including test selection, ordering, interpretation, and pre- and post-test counseling.[17,18]

- The *Journal of Genetic Counseling* published a practice guideline for genetic testing and counseling for epilepsy in 2022.[17] The guideline was adopted by the NSGC and endorsed by the American Epilepsy Society, and provides the following two recommendations:
    - "Genetic testing is strongly recommended for all individuals with unexplained epilepsy, without limitation of age, with exome/ge- nome sequencing and/or a multi-gene panel (>25 genes) as first-tier testing followed by chromosomal microarray, with exome/genome sequencing conditionally recommended over multi-gene panel."
    - "It is strongly recommended that genetic tests be selected, ordered, and interpreted by a qualified healthcare provider in the setting of appropriate pre-test and post-test genetic counseling."
- The International League Against Epilepsy Commission of Pediatrics published a practice guideline for the management of infantile seizures in 2015[18] with the following three recommendations:
    - "Genetic screening should not be undertaken at a primary or secondary level of care, as the screening to identify those in need of specific genetic analysis is based on tertiary settings"
    - "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

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care (optimal intervention would permit an extended genetic evaluation) (level of evidence—weak recommendation, level C)"

- Published criteria for epilepsy genetic testing created by a Genetic Testing Advisory Committee in Ontario, Canada in 2018[19] includes:
  - Circumstances where genetic testing is indicated:
    - "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."
  - Circumstances where genetic testing is not indicated:
    - "Recognizable seizure syndrome with benign course"
    - "Childhood epilepsy with centrotemporal 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"

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Criteria:

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

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

Exclusions

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

Other Considerations:

- Ideal sample type should be considered based on the clinical presentation (e.g., if mosaicism is suspected, consider testing brain tissue after focal resection).
- While exome and genome sequencing are similar diagnostic tools in the evaluation of individuals with epilepsy, there are clear technical advantages of genome sequencing that support increased diagnostic yield and efficiencies. As such, if given a choice, genome sequencing is the preferred diagnostic test in individuals who meet the above criteria. Criteria for genome sequencing can be found in the Genome Sequencing for Rare Disease policy.
- Exome/genome sequencing is preferred over multi-gene panel testing due to increased diagnostic yield. If multi-gene panels are used, larger panels are preferred due to increased diagnostic yield. Panels should include at least 24 genes: *ALDH7A1, CACNA1A, CDKL5, CHD2, GABRG2, GRIN2A, KCNQ2, MECP2, PCDH19, POLG, PRRT2, SCN1A, SCN1B, SCN2A, SCN8A, SLC2A1, SLC9A6, STXBP1, SYNGAP1, TCF4, TPP1, TSC1, TSC2*, and *ZEB2.*[8]
- Pre- and post-test counseling by an appropriate provider, such as an American Board of Medical Genetics and Genomics or American Board of Genetic Counseling-certified Genetic Counselor, is strongly recommended.
- Trio samples are preferred for exome/genome sequencing. Use of family trio samples in genomic sequencing analysis helps reduce the time to diagnosis and the rate of uncertain findings, improves the clinical sensitivity and efficiency with

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regard to the interpretation of clinically novel genes, and increases the diagnostic yield of exome/genome sequencing.

- Re-analysis of previously obtained exome or genome sequence has the potential for additional diagnostic yield because of expanding variant databases, as well as periodic novel gene discovery and publication. Re-analysis could be considered prior to additional genomic sequencing, particularly if there has been onset or identification of additional symptoms that broadens the clinical phenotype assessed during the original exome/genome sequencing analysis, and/or there has been a change in the family history that expands the clinical picture, such as the birth or diagnosis of a similarly affected first-degree relative.
- Targeted variant testing is the most appropriate test for a known familial variant in pre-symptomatic individuals.
- Genetic testing has rapidly advanced over the last 20 years. Exceptions to once per lifetime testing may be considered if an individual has previously had negative genetic testing, but technical advances in testing demonstrate significant advantages that would support a medical need to retest or re-analyze data from previous testing.
- Genetic testing for epilepsy in the setting of prenatal genetic diagnosis or screening is not addressed in this policy.
- Rapid genome sequencing, defined as return of preliminary positive results in <7 days and final report in <14 days, may be indicated for critically-ill individuals. Criteria for rapid genome sequencing can be found in the Rapid Genome Sequencing policy.

CPT Codes:

Procedure(s) addressed by this policy:	Procedure Code(s)
Epilepsy genomic sequence analysis panel	81419
Unlisted molecular pathology procedure	81479
Exome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81415
Sequence analysis, each comparator exome (e.g., parent(s), sibling(s))	81416
Genome (e.g., unexplained constitutional or heritable disorder or syndrome); sequence analysis	81425
Sequence analysis, each comparator genome (e.g., parent(s), sibling(s))	81426
Genome (e.g., unexplained constitutional or heritable disorder or syndrome), rapid sequence analysis (e.g., RCIGM Rapid Whole Genome Sequencing; Rady Children's Institute for Genomic Medicine)	0094U

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Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	0212U
Rare diseases (constitutional/heritable disorders), whole genome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator genome (eg, parent, sibling)	0213U
Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, proband	0214U
Rare diseases (constitutional/heritable disorders), whole exome and mitochondrial DNA sequence analysis, including small sequence changes, deletions, duplications, short tandem repeat gene expansions, and variants in non-uniquely mappable regions, blood or saliva, identification and categorization of genetic variants, each comparator exome (eg, parent, sibling)	0215U

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